Ph.D. THESIS

MODIFICATION OF NATURAL HYDROPHILIC POLYMERS FOR USE IN PHARMACEUTICAL FORMULATIONS

By

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DECLARATION

*"*I certify that this work has not been accepted in substance for any degree, and is not concurrently being submitted for any purpose, other than that of the PhD thesis being studied at the University of Greenwich. I also declare that this work is the result of my own investigations except where otherwise identified by refer*ences and that I have not plagiarised another's work".*

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ABSTRACT

MODIFICATION OF NATURAL HYDROPHILIC POLYMERS FOR USE IN PHARMACEUTICAL FORMULATIONS

The introductory chapter of this doctoral thesis provides an overview of the salient properties of pharmaceutical excipients, chitin, metal silicates and sugar alcohols in order to give a scientific background/context to the research subject matter reported in subsequent chapter of the thesis.

When chitin is used in pharmaceutical formulations processing of chitin with metal silicates is advantageous, from both an industrial and pharmaceutical perspective, compared to processing using silicon dioxide. Unlike the use of acidic and basic reagents for the industrial preparation of chitin-silica particles, co-precipitation of metal silicates is dependent upon a simple replacement reaction between sodium silicate and metal chlorides. When co-precipitated onto chitin particles, aluminum, magnesium, or calcium silicates result in non-hygroscopic, highly compactable, and disintegrable compacts. Disintegration and hardness parameters for co-processed chitin compacts were investigated and found to be independent of the particle size. Capillary action appears to be the major contributor to both water uptake and the driving force for disintegration of compacts. The good compaction and compression properties exhibited by the chitin–metal silicates were found to be strongly dependent upon the type of metal silicate co-precipitated onto chitin. In addition, the inherent binding and disintegration abilities of chitin–metal silicates are useful in pharmaceutical applications when poorly compressible and/or highly non-polar drugs need to be formulated.

The influence of the lubricant magnesium stearate (MgSt) on the powder and tablet properties of chitin-Mg silicate co-precipitate was examined and compared with lubricated Avicel® 200 and Avicel-Mg silicate co-precipitate. Crushing strength and disintegration-time studies were conducted in order to evaluate tablet properties at different compression pressures. Lubrication of chitin-Mg silicate powder with MgSt was evaluated using a high speed rotary tablet press. The compactability and disintegration time of chitin-Mg silicate are unaffected by the possible deleterious action of up to 2% (w/w) MgSt. The deleterious effect of MgSt on Avicel® 200 compaction was found to be minimized when magnesium silicate was co-precipitated onto Avicel® 200. Lubrication of chitin-Mg silicate with MgSt does not enhance particle agglomeration, whereas the opposite is the case for Avicel® 200; the foregoing was ascertained by measurements of the fixed measured bulk density, constant powder porosity using Kawakita analysis and by the absence

of variation in particle size distribution in the presence of up to 5% (w/w) MgSt. In the case of chitin-Mg silicate tablets the ejection force was greatly reduced at a compression speed of 150,000 tablet/h at a MgSt concentration of 0.5% (w/w) when compared with the unlubricated powder. The physical properties and drug dissolution profile of ibuprofen tablets were found to be unaffected when chitin-Mg silicate was lubricated up to 5% (w/w) with MgSt. Optimal drug dissolution was attained for gemfibrozil tablets using 3% (w/w) MgSt when compared to a reference (LOPID® tablets).

A co-processed excipient was prepared from commercially available crystalline mannitol and α-chitin using direct compression as well as spray, wet and dry granulation. The effect of the ratio of the two components, percentage of lubricant and particle size on the properties of the prepared co-processed excipient has been investigated. α-Chitin forms non-hygroscopic, highly compactable, disintegrable compacts when co-processed with crystalline mannitol. The compaction properties of the co-processed mannitol-chitin mixture were found to be dependent upon the quantity of mannitol added to chitin, in addition to the granulation procedure used. Optimal physicochemical properties of the excipient, from a manufacturing perspective, were obtained using a co-processed mannitol-chitin (2:8 w/w) mixture prepared by wet granulation (Cop-MC). Disintegration time, crushing strength and friability of tablets produced by Cop-MC, using magnesium stearate as a lubricant, were found to be independent of the particle size of the prepared granules. The inherent binding and disintegration properties of the compressed Cop-MC are useful for the formulation of poorly compressible, low and high strength active pharmaceutical ingredients. The ability to co-process α-chitin with crystalline mannitol allows chitin to be used as a valuable industrial pharmaceutical excipient.

The preparation and characterization of the performance of a novel excipient for use in the development of oro-dispersible tablets (ODT) has also been undertaken. The excipient consists of α-chitin and crystalline mannitol. The physical properties (disintegration and wetting times, crushing force and friability) of the ODTs produced depend on the ratio of chitin and mannitol, in addition to the processing techniques used for excipient preparation. The excipient with optimal physicochemical properties was obtained at a chitin: mannitol ratio of 2:8 (w/w) produced by roll compaction (Cop-CM). Differential scanning calorimetry (DSC), Fourier-transform infrared (FT-IR), X-ray powder diffraction (XRPD) and scanning electron microscope (SEM) techniques were used to characterize the Cop-CM, in addition to characterization of its powder and ODT dosage forms. The effect of particle size distribution of the Cop-CM was investigated and found to

have no significant influence on the overall tablet physical properties. The compressibility parameter (a) for Cop-CM was calculated from a Kawakita plot and found to be significantly higher (0.661) than that of mannitol (0.576) due to the presence of the highly compressible chitin (0.818). Montelukast sodium and domperidone ODTs, produced using Cop-CM**,** displayed the required physicochemical properties. The exceptional binding, fast wetting and super-disintegration properties of Cop-CM, in comparison with commercially available co-processed ODT excipients, results in a unique multi-functional base which can successfully be used in the formulation of oro-dispersible and fast immediate release tablets.

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DEDICATION

This thesis is dedicated to my wife:

HALA NAZZAL (B.Sc.; M.Sc.)

My children:

BARA'A, MOHAMMAD & BASHAR

And my parents

CONTENTS

Publications/Conference Presentations

Published Reviews in Monographs

(1) "Chitin", **Nedal H. Daraghmeh**, Babur Z. Chowdhry, Stephen A. Leharne, Mahmoud M. Al Omari, andAdnan A. Badwan: in Profiles of Drug Substances, Excipients, and Related Methodology, **36**, 35-102, 2011; Ed: H. G. Brittain (Elsevier Inc.)

(2) "Magnesium Silicate", Iyad Rashid, **Nedal H. Daraghmeh**, Mahmoud M. Al Omari, Babur Z. Chowdhry, Stephen A. Leharne, Hamdallah A. Hodali, and Adnan A. Badwan, in: Profiles of Drug Substances, Excipients, and Related Methodology, **36**, 241-285, 2011; Ed: H. G. Brittain, (Elsevier Inc.).

Published Research Articles

(1) "Characterization of Chitin-Metal Silicates as Binding Superdisintegrants", Iyad Rashid, **Nedal Daraghmeh**, Mayyas Al-Remawi, Stephen A. Leharne, Babur Z. Chowdhry, Adnan Badwan, Journal of Pharmaceutical Sciences, **98** (12), 4887–4901, 2009 (**Chapter 2**).

(2) "Characterization of the Impact of Magnesium Stearate Lubrication on the Tableting Properties of Chitin-Mg Silicate as a Superdisintegrating Binder When Compared to Avicel® 200", Iyad Rashid, **Nedal Daraghmeh**, Mayyas Al-Remawi, Stephen A. Leharne, Babur Z. Chowdhry, Adnan Badwan, Powder Technology, **203** (3), 0 609-619, 2010 (**Chapter 3**).

(3) "Preparation and Characterization of a Novel Co-Processed Excipient of Chitin and Crystalline Mannitol", **Nedal Daraghmeh**, Iyad Rashid, Mahmoud M. H. Al Omari, Stephen A. Leharne, Babur Z. Chowdhry, and Adnan Badwan, AAPS Pharm. Sci. Tech. **11** (4) 1558-1571, 2010 (**Chapter 4**).

Research Manuscripts Submitted

(1)"A Novel Oro-Dispersible Tablet Base: Characterization and Performance", **Nedal Daraghmeh**, Babur Z. Chowdhry, Stephen A. Leharne, Mahmoud M.H. Al Omari, Adnan A. Badwan, Submitted: J. Pharm. Sci., (2012) (**Chapter 5**).

Manuscripts in Preparation (2012)

(1) "Chitin the Pharmaceutical Disintegrant: A Review (Polymers)

(2) "Chitin/Magnesium Silicate Co-Precipitate as a Pharmaceutical Formulation Aid for Enhancement of Drug Properties" (AAPS PharmSciTech)

Conference Presentations (Posters)

(1) "Preparation and Characterization of a Novel Co-Processed Excipient of Chitin and Crystalline Mannitol"

5th International Granulation Workshop, Lausanne, Switzerland: 20-22 June, 2011 and

11th Eurasia Conference on Chemical Sciences: 6-10 October, 2010; the Dead Sea–Jordan

(2) "Characterization of Chitin-Metal Silicates as Binding Superdisintegrants".

22nd of December, 2009; University of Jordan.

(This poster won the Hisham Hijjawi award for Applied Sciences (Industry & Energy Sector))

(3) "The Effect of Metal Silicates on the Binding and Disintegration Properties of Chitin"

(4) "Chitin/Magnesium Silicate Co-Precipitate as a Pharmaceutical Formulation Aid for Enhancement of Drug Properties"

Posters 3 and 4 were presented at Excipientfest Europe: 17–18 June, 2008; Cork, Ireland.

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

Symbol	Description
$NHCOCH_3$	Acetamide
HCOOH	Acetic acid
API	Active pharmaceutical ingredient
ATP	Adenosine triphosphate
α-	Alpha-
UTP	α-D-hexose-1- phosphate uridylyltransferase
AlCl3	Aluminium chloride
$Al_2(SiO_3)_3$	Aluminum silicate
NH_2	Amine
NH_4NO_3	Ammonium nitrate
Å	Angstrom
BD	Bulk density
β-	Beta-
Cop-MC	Co-processed mannitol-chitin (2:8 w/w) mixture prepared by wet granulation
Cop-CM	Co-processed chitin-mannitol (2:8 w/w) mixture produced by roll compaction
$CaCO_3$	Calcium carbonate
$CaCl_2$	Calcium chloride
$CaCl_2 2H_2O$	Calcium chloride dihydrate
$Ca(SCN)_2.4H_2O$	Calcium cyanate tetrahydrate
$Ca(NO_3)_2.4H_2O$	Calcium nitrate tetrahydrate
$CaSiO_3$	Calcium silicate
CO_2	Carbon dioxide
C=O	Carbonyl
$(C_8H_{13}NO_5)_n$	Chitin
CSD	Colloidal silicon dioxide
Crospovidone	Cross-linked polymer of N-vinyl-2-pyrrolidinone
Da	Dalton
DBCP	Dibasic calcium phosphate
DBCH	Dibutyrylchitin
DSC	Differential scanning calorimetry
DMAc/LiCl	N,N-Dimethylacetamide/Lithium chloride
DMF	N,N-Dimethylformamide
DC	Direct compression
Domp	Domperidone
EP	European patent
EDTA	Ethylene di-amine tetra-acetic acid
FDA	Food and Drug Administration
FCC	Food Chemical Codex
FTIR	Fourier- transform infra-red
γ-	Gamma-
GRAS	Generally recognized as safe
HPLC	High performance liquid chromatography
HCl	Hydrochloric acid
HF	Hydrofluoric acid
H_2O_2	Hydrogen peroxide
OH-	Hydroxyl
HPC	Hydroxypropylcellulose

Symbol	Description
HPMC	Hydroxypropylmethylcellulose
ICH	International conference of harmonization
IPEC	International Pharmaceutical Excipients Council
JECFA	The Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives
LOQ	Limit of quantitation
$MgCl_2$	Magnesium chloride
$MgCl_2.6H_2O$	Magnesium chloride hexahydrate
$Mg(NO_3)_2.6H_2O$	Magnesium nitrate hexahydrate
MgO	Magnesium oxide
$MgSiO_3$	Magnesium silicate
MgSt	Magnesium stearate
LD_{50}	Median toxic dose; "Lethal Dose, 50%"
MCC	Microcrystalline cellulose
Monte	Montelukast sodium
NF	National Formulary
NMR	Nuclear magnetic resonance
ODT	Oro-dissolving tablets/Oro-disintegrating tablets
O-3 MD	O-3-Methylmethyldopa impurity
KCl	Potassium chloride
KOH	Potassium hydroxide
PGS	Pregelatinized starch
RH	Relative impurity
RSD	Relative standard deviation
RC	Roll compaction
RSC	Rosuvastatin calcium
SEM	Scanning electron microscope
SMCC	Silicified microcrystalline cellulose
SiO_2	Silicon dioxide
NaCl	Sodium chloride
NaOH	Sodium hydroxide
$Na_2HPO_4.12H_2O$	Sodium hydrogen phosphate dodecahydrate
Na_2SiO_3	Sodium metasilicate
H_2SO_4 /H_3PO_4	Sulphuric acid/Phosphoric acid
TD	Tapped density
3D	Three dimensional
UV	Ultra-violet
USP	United States Pharmacopiea
UTM	Universal testing machine
UDP-N-acetylglucosamine	Uridinediphosphate-N-acetyl-glucosamine
V	Voltage
WG	Wet granulation
WHO/FAO	World Health Organization/Food and Agriculture Organization of the United Nations
XRPD	X-Ray Powder Diffraction Spectroscopy

Introduction

1.1 Pharmaceutical Excipients

The International Pharmaceutical Excipients Council (IPEC) defines excipients as: "Substances, other than the active pharmaceutical ingredient (API) in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use" [1]. Ideally, excipients should not produce any pharmacological action, or adversely impact drug product quality, safety, or efficacy [2]. Recently, researchers have reached the conclusion that excipients are not inactive and have a substantial impact on the manufacture, quality, safety, and efficacy of the API in a dosage form [3]. Furthermore, variability in the performance of an excipient (both batch to batch within a single manufacturer as well as between batches from different manufacturers) is a key determinant of dosage form performance and consistency. Excipients are now known to have numerous, defined functional roles in pharmaceutical dosage forms [3]. These include:

- modulating the solubility and bioavailability of the API,
- enhancing the stability of the API in the dosage form,
- contributing to the maintenance of a preferred polymorphic form or conformation of the API(s),
- pH and osmotic pressure modifiers,
- acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders and tablet disintegrants, and
- preventing aggregation or dissociation.

Excipients can be obtained from different sources (natural, animal, vegetable, semi-synthetic, or synthetic) using different production technologies to be used for different functions and applications [3, 4]. Excipients are classified into different categories based on their function (e.g., diluent/filler, binder, disintegrant, glidant, lubricant, etc.) and they normally fulfill various performance characteristics and specifications (e.g., bulk density, particle size distribution, surface area, polymorphic form, water content etc.) depending on their uses in formulations, manufacturing processes, and the intended

dosage form [4, 5, 6]. The definitions of different excipient categories used in solid dosage form formulations are illustrated in Table 1.1.

Table 1.1 Classification of excipients according to their functions.

Excipient Function	Definition
Fillers/Diluents	Fillers are added to increase the bulk of the formulation i.e. fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Fillers make it possible for the final product to possess the proper volume for patient handling.
Binders	Some pharmaceutical ingredients require a binder for tabletting. This provides the cohesiveness necessary for bonding during tablet compression. Binders are usually starches, sugars, cellulose or a modified cellulose (such as microcrystalline cellulose, hydroxypropyl cellulose), lactose, or sugar alcohols like xylitol, sorbitol or maltitol. Binders can be used in dry (solid state) form or dissolved in solution.
Disintegrants	Usually added for the purpose of ensuring that compressed tablets break apart when placed in an aqueous medium.
Lubricants	Prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals like talc or silica, and fats, metal stearate like magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatine capsules.
Glidants	Glidants are used to promote powder flow by reducing inter-particle friction and cohesion. Glidants, in some cases, occur in solution form due to the weight variation problems during tablet compression and capsule filling as a result of improving the powder flowability. Generally, materials that are good glidants are poor lubricants.

Excipients play a pivotal role in the processing, stability, safety, and performance of solid dosage forms. Therefore, the critical excipient properties that can influence product performance need to be evaluated and controlled to ensure that consistent product performance is achieved throughout the product's life cycle [7, 8]. An overview of some dosage form parameters affected by excipients is given in Table 1.2.

Table 1.2 Dosage form parameters affected by excipients.

Dosage form parameter	Effect of excipients
Stability	Residual moisture content/adsorbed moisture on excipient surface protects API from hydrolytic degradation.
Processability	• Surface area, surface free energy, crystal defects, and deformation potential affect compressibility and machine ability for high speed tabletting machines with reduced compression dwell times. • Particle size distribution and shape affect flow properties, efficiency of dry mixing processes, and segregation potential. • Compressibility, flowability, and dilution potential affect the choice of direct compression as a manufacturing process.
Performance	Cohesive and adhesive properties, surface free energy, and water uptake behavior affect disintegration and dissolution behavior.

Generally, pharmaceutical excipients have to meet special requirements including [4]:

- physiological inertness,
- acceptance by regulatory authorities,
- physical and chemical stability,
- commercial availability at pharmaceutical grade and standards,
- being relatively inexpensive, and
- their approval as a food additive if it is intended for use in dietary supplements and vitamin products.

Table 1.3 lists some of the commercially available excipients, exploited for their different functionalities, commonly used in solid dosage formulations [9].

Table 1.3 Commonly used excipients in solid dosage formulations.

Material	Trade name	Company	Function
Mannitol	Pearlitol	Roquette/ USA	Filler
Lactose monohydrate	Pharmatose	DMV Pharma / Netherlands	Filler
Microcrystalline cellulose	Avicel PH	FMC Biopolymer / USA	Filler
Starch	C*PharmGel	Cerestar / France	Filler/Disintegrant
Croscarmelose sodium	Ac-Di-Sol	FMC Biopolymer / USA	Disintegrant
Sodium starch glycolate	Explotab	JRS Pharma LP / USA	Disintegrant
Cross-linked polyvinylpyrollidone	Polyplasdone XL	ISP / USA	Disintegrant
Pregelatinized starch	Starch 1500	Colorcon / UK	Disintegrant/Binder
Low substituted hydroxypropylcellulose	L-HPC	Shin-Etsu Chemical / Japan	Disintegrant/Binder/ Filler
Hydroxypropylcellulose	Klucel	Aqualon /USA	Binder
Poly(vinylpyrollidone)	Kollidon	PASF corp./USA	Binder
Sodium stearyl fumarate	Pruv	JRS Pharma LP/USA	Lubricant
Magnesium stearate	Magnesium Stearate	Mallinckrodt Baker/ USA	Lubricant
Purified talc	Altalc	Luzenac America/USA	Lubricant/Glidant
Colloidal silicon dioxide	Aerosil	Degussa Ltd / UK	Glidant

1.2 Preparation Techniques for Solid Dosage Forms

Development of solid dosage forms, more specifically tablets, involves major alternative processing methodologies including wet granulation (low shear wet granulation, high shear wet granulation or fluid-bed granulation), dry granulation (slugging or roller compaction) or direct compression (DC) [8, 10]. The detailed processing steps involved in each of the three processing methods are explained in Figure 1.1 [4]. These processing methods share the following common problems [8]:

- product weight variation due to poor flow properties,
- problems in content uniformity during mixing, due to wide differences in density and particle size distribution,
- loss of excipient compressibility due to wet granulation and repeated compaction cycles in dry granulation, or excessive usage of lubricants and poorly compressible ingredients in the formulation, and
- poor disintegration of product due to excessive addition of binders.

The use of high speed tabletting machines and the increasing shift in the processing of tablets towards direct compression have, together, led to aggravating these problems.

1.2.1 Wet Granulation [4, 11]

Granulation is the process of collecting particles together by creating bonds between them. When the required homogeneity, compactibility or flowability of powder cannot be obtained by simple mixing, the ingredients must be granulated prior to compression. There are several reasons for using granulation processes (wet / dry) including the following:

- improving powder flowability,
- improving content uniformity of APIs in dosage form to assure consistency of dosing,
- improving the bioavailability of some APIs,
- taste masking of poor taste APIs / improvement in palatability,
- materials densification,
- compactability and compressibility enhancement of the APIs,
- drug release control,
- reduction of dust, and
- improvement in tablet physical properties

Wet granulation is a process in which a liquid binder is added to the powder mixture and agitation is used to form granules.

1.2.1.1 Advantages

- Improvement of cohesiveness and compressibility of powders; hence the tablet compressibility is improved.
- Drugs exhibiting a high dose and poor flowability and/or compressibility; their flowability and cohesion for compression will be improved by wet granulation.
- The uniformity and distribution of soluble, low dosage drugs and colour additives can be obtained, especially if these materials are distributed in the granulation solution. Also it prevents segregation of components of a homogeneous powder during processing and transfer.
- The dissolution rate of insoluble drugs can sometimes be improved by wet granulation.

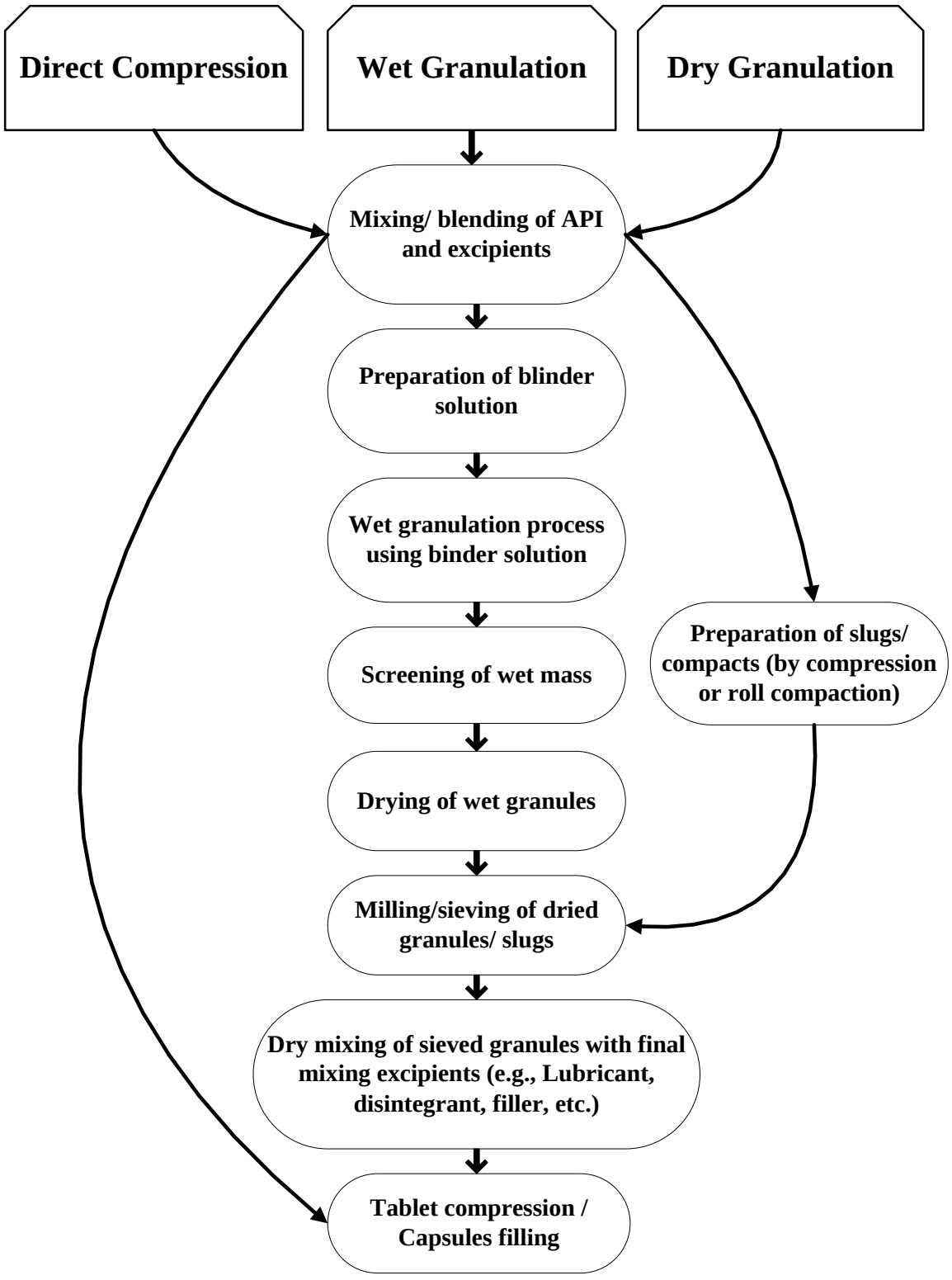


Figure 1.1 Comparison of steps involved in the different processing techniques for solid dosage form preparations.

1.2.1.2 Limitations

The main disadvantage of wet granulation is its cost because of the space, time and equipment involved. For the following reasons, the process is labour intensive.

- Long processing steps are involved and a relatively large space is needed for the preparation area.
- Different types of expensive equipment are required.
- It is time consuming, especially for the granulation and drying steps.
- The manufacturing yield is much lower when compared with direct compression processing techniques because of the material losses in multi-step processes.
- There is a greater possibility of cross-contamination, as there are many steps involved compared to direct compression.
- Drug release is slower, sometimes due to stronger binding.
- Many process variables including mixing, granulation, drying, granule sizing and final mixing are involved in the validation of the manufacturing process which is required to insure the consistency of the process.
- Additional testing (e.g, gas chromatography) is required for residual solvents when non-aqueous granulation is performed.

1.2.2 Dry Granulation [12, 13]

Dry granulation is used to form granules without using a liquid solution or it refers to the process of densification via roller compaction, followed by gravity milling/screening to give the required particle size distribution. This process is used when the product is sensitive to moisture and heat. Commonly, dry granulation processes can be conducted using slugging tooling via tablet compression machinery or by using other specialized machines such as a roller compactor.

1.2.2.1 Advantages

- Overcomes poor physical properties of API (particle size, shape).
- Improves the flowability, content uniformity, and compaction properties of powders.
- Dry granulation equipment offers a wide range of pressure and roll types to attain proper densification.
- The process cycle is often reduced and equipment requirements are minimized; thus the cost is reduced.

1.2.2.2 Limitations

- Dry granulation often produces a higher percentage of fines or non-compacted products, which can affect the quality or create yield problems in the tablet produced.
- Requires drugs or excipients with cohesive properties.
- Longer processing time when compared to direct compression process which may compromise compactibility.

1.2.3 Direct compression [11, 14]

This method is used when a group of ingredients can be blended and compressed into tablets without any of the ingredients having to be changed. Powders that can be blended and compressed are commonly referred to as direct compression excipients.

1.2.3.1 Preparation methods of direct compression excipients

Direct compression excipients can be produced by different technelogies. The advantages, limitations and main features of the methods are listed in Table 1.4.

Table 1.4 Methods used to prepare direct compression excipients.

Method	Advantages and limitation	Examples
Chemical modification	-Relatively expensive -Toxicological data required -Time consuming	Ethyl cellulose, methylcellulose, and sodium carboxymethyl cellulose from cellulose, lactitol
Physical modification	Relatively simple and economical	Dextrates of compressible sugar, sorbitol
Grinding and/or sieving	Compressibility may alter because of changes in particle properties such as surface area and surface activation	Pharmatose® 150M, Pharmatose® 100M, Pharmatose® 50M, Capsulac® 60, PrismaLac® 40
Crystallization	Import flowability to excipient but not necessarily self-binding properties, require stringent control on possible polymorphic conversions and processing conditions	β-lactose, dipac
Spray drying	Spherical shape and uniform size gives spray-dried materials good flowability- poor re- workability	Spray dried lactose, Avicel PH, TRI-CAFOS® S, Advantose 100 maltose powder. FlowLac® 100, Pharmatose® DCL 11
Granulation/ agglomeration	Transformation of small particle, cohesive, poorly flowable powders into flowable and directly compressible powders	Granulated Lactitol, Tablettose® 70, Tablettose® 80
Dehydration	Increased binding properties by thermal and chemical dehydration	Anhydrous α-lactose

1.2.3.2 Advantages and limitations of direct compression processes

In direct compression the manufacturing cycle is much shorter and the product yield is much higher than wet or dry granulation techniques. Less manufacturing steps and machines are involved in direct compression, resulting in a reduction in the processing costs. Regarding the product quality, the most significant advantage is that processing is performed in the absence of moisture and heat. The critical issue in direct compression formulations is the choice of excipients involved (e.g. the compressibility and flowability of the fillers/binders). The particle size distribution, strength, compactability and the physical properties of the API also play an important role in using this process. The critical issues, advantages and limitations which may occur in direct compression processes are outlined in Table 1.5.

Table 1.5 Critical issues, advantages and limitations of direct compression.

Critical Issues	Advantages	Limitations
Flowability	Cost effective production	Segregation, problems in the content uniformity of the API
Compressibility and compactibility	- Better stability of API - Retains compactibility of materials	Tablet weight variation due to poor flow properties
Dilution potential	Faster dissolution rate	Low dilution potential
Reworkability (reprocessing)	Less wear and tear of punches	Re-workability
Stability	Simple process validation	High content of poorly compressible APIs
Controlled particle size	Lower microbial contamination	Lubricant sensitivity

Direct compression excipients, especially fillers and binders, are mostly common excipients modified using special procedures to improve their flow properties and compressibility. The physical and chemical properties of this special type of excipient are of significant importance when they are manufactured or involved in formulation design. Many factors are involved in the selection of a suitable, direct compression excipient which is to be used in tablet formulation including powder characteristics, solubility, stability, compatibility, flowability, compressibility and cost. Examples of some commercially available direct compression excipients are listed in Table 1.6 [9, 15].

Table 1.6 Examples of commercially available direct compression excipients.

Excipient	Brand Name (Manufacturer, country)
Lactose	Tablettose (Meggle, Germany), pharmatose (DMV, the Netherland), fast-flo lactose (Foremost)
Microcrystalline cellulose/cellulose	Avicel PH (FMC, USA), Emcocel (Edward mendell, USA, Vivacel (JRS, USA)
Mannitol	Mannogem 2080 (SPI Polyols, France), Sorbidex P (Cerestar, USA)
Starch	Starch 1500 (Colorcon, USA Spress B820 (GPC, USA) Era Tab (Erawan, Thialand), Purity (National starch, USA), pharm DC 93000 (Cerestar, USA)
Di-calcium phosphate	Emcompress (JRS, GmbH), A-Tab and Di-Tab (Rhodia, USA)
Tri-calcium phosphate	Tri-Tab (Rohodia, USA)
Sorbitol	Neosorb 60 (Roquette, France) sorbogem (SPI polyols, France), sorbidex P (Cerestar, USA)
Sucrose	Di-pac (American sugar company, USA), NuTab (ingredient technology Inc., USA)
Dextrose	Emdex (Edward mendell, USA)
Lactitol	Finlac DC (Danisco, USA), Lacty-TAB (Purac, USA)
Xylitol	Xylitab (Danisco, USA)
Maltodextrin	Maltrin (Grain Processing Corp, USA)
Powdered Cellulose/Cellulose	Elcema (Allchem Pharma, UK)
Calcium sulphate	Destab (Particle Dynamics, USA)
Calcium lactate penta-hydrate Calcium lactate tri-hydrate	Puracal DC (Purac, USA) Puracal TP (Purac, USA)
Aluminium hydroxide	Barcroft (SPI Polyols, France)

1.3 Co-Processed Excipients [8, 16]

There are three possible procedures by which a new excipient can be developed:

- new chemical entities as excipients,
- new grades of already existing excipients, and
- new combinations of existing excipients.

Additionally, regulatory expectations of safety and toxicity properties ensure that new chemical entities being developed as excipients undergo various stages of scrutiny, which is a lengthy and costly process. Furthermore, the excipient is required to undergo a phase of generic development which shortens the market exclusivity period. Accordingly, modification of the physicochemical properties of existing excipients has been the most successful strategy to produce new functional excipients.

The introduction of high-speed tablet compression machines and the shift in tablet manufacturing toward direct compression process have encouraged the search for new excipients meeting special requirements. Tablet formulators have recognized that single component excipients do not always provide the requisite performance to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. In response to these deficiencies, they have relied on increasing numbers of combination excipients introduced by excipient manufacturers into the commercial market (Table 1.7). Combination excipients fall into two broad categories.

1.3.1 Physical mixtures

Physical mixtures are simple admixtures of two or more excipients typically produced by short duration low shear processing. They may be either liquids or solids and are generally used for convenience rather than for facilitating the manufacturing process or improving the resultant pharmaceutical product. Examples of such physical mixtures include immediate release film coating powders for dispersion that reduce the time required to prepare film coating suspensions and to minimize colour variation of the final product. Such physical mixtures are not appropriate for consideration for National Formulary (NF) monographs because the individual components are isolated (distinct and intact) before mixing; i.e., the manufacturing process for each of the individual components has been taken to completion, and consequently these components can be adequately controlled before mixing.

1.3.2 Co-processed excipients

Co-processed excipients can be defined as a combination of two or more excipients that possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients. Co-processing of excipients was introduced in the pharmaceutical industry in the late 1980s, by e.g. co-processing MCC and calcium carbonate followed by “Cellactose” (Meggle, Germany) in 1990, a co-processed combination of cellulose and lactose, and silicified microcrystalline cellulose (SMCC) in 1996, a co-processed product of MCC and colloidal silicon dioxide (CSD).

Table 1.7 Commercially marketed co-processed direct compression excipients.

CO-PROCESSED EXCIPIENTS	TRADE NAME	MANUFACTURER	ADVANTAGES/FUNCTION
Lactose monohydrate (93%), Kollidon ®30 (3.5%), and Kollidon ®CL (3.5%)	Ludipress®	BASF AG. Ldwigshafen, Germany	Lower hygroscopicity, good flow ability, tablet hardness independent of machine speed
Lactose monohydrate (96.5%) and Kollidon ®30 (3.5%)	Ludipress LCE	BASF AG, Ludwigshafen, Germany	Lower hygroscopicity, higher tablets hardness
α-Lactose monohydrate (75%) and cellulose powder (25%)	Cellactose® 80	Meggle GmbH &, Co. KG, Germany	Highly compressible, good mouth feel, better tabletting at low cost
α-Lactose monohydrate (75%) and MCC (25%)	MicroceLac ®100	Meggle GmbH &, Co. KG, Germany	Capable of formulating high-dose small tablets with poor flowability
α-Lactose monohydrate(85%) and maize starch (15%)	starLac™	Roquette, Lestrem, France	Good flow, optimized disintegration, excellent tablet hardness
Anhydrous β-lactose (95%) and lactitol (5%)	Pharmatose® DCL-40	j. Rettenmaier & Sohne GmbH & Co. KG, Germany	High compatibility, superior flow properties, low lubricant sensitivity
Silicified microcrystalline cellulose (SMCC) [microcrystalline cellulose (MCC) 98% and colloidal silicon dioxide (CSD) (2%)]	ProSolv HD ®90, ProSolv SMCC ®50, ProSolv SMCC ®90	FMC Biopolymer, Newark, Delaware, U.S.A.	High compatibility, high intrinsic flow, good blending properties, reduced sensitivity to wet granulation, better tablet hardness
MCC and guar gum	Avicel® CE-15	FMC BioPolymer, Netwark, Delaware, U.S.A.	Less grittiness, reduced tooth packing, minimal chalkiness, creamier mouth feel, improved overall palatability
MCC and carboxymethylcllulose sodium	Avicel ®RC-581, RC-591, CL-661	FMC BioPolymer, Netwark, Delaware, U.S.A.	Viscosity regulator and modifier , thixotropic characteristics, heat and freeze-thaw stable, long shelf-life stability, lengthy hydration times eliminated, stable in the 4-11 pH range
MCC and calcium phosphate	Celocal ®	FMC BioPolymer, Netwark, Delaware, U.S.A.	Direct compression excipient
MCC (65%) and calcium carbonate (35%)	Vitacel ®VE-650	FMC BioPolymer, Netwark, Delaware, U.S.A.	Direct compression, encapsulation
MCC and carrageenan	LustreClear ™	FMC BioPolymer, Netwark, Delaware, U.S.A.	Efficient tablet-coating with short hydration time prior to coating and fast drying time
Mannitol 85%, crospovidone 10%, sorbitol 5%, silicon dioxide <1%.	Pharmaburst ™ B2	SPI Pharma TM, Inc., New Castel , U.S.A/	High compactibility, high loading in small diameter tablets, smooth mouth feel, rapid disintegration
Mannitol 84%, crospovidone 16%, silicon dioxide <1%	Pharmaburst ™ C1		
Fructose (95%) and starch (55)	Advantose™ FS Fructose	SPI Pharma TM, Inc., New Castel , U.S.A/	Excellent flow, good compressibility, tablets hold shape well, but are very chewable

Table 1.7. (continued)

CO-PROCESSED EXCIPIENTS	TRADE NAME	MANUFACTURER	ADVANTAGES / FUNCTION
MCC, mannitol	Avicel HFE102	FMC, USA	High compatibility, superior flow properties, low lubricant sensitivity
Xylitol, carboxymethyl cellulose sodium	XyliTab	Danisco Sweeteners, Finland	Artificial sweeteners for medical purposes
Vinylacetate, vinylpyrollidone	Plasdon S-630 (Copovidone)	ISP, USA	Excellent tablet binder, matrix polymer for solid dispersions and film former for topical applications
Sucrose (97%) and dextrin (3%)	Di-Pac ®	American Sugar Co, New York, U.S.A.	Direct compression excipient
Calcium carbonate, starch	Barcroft CS 90	SPI Pharma, France	Directly compressible calcium carbonate
Aluminium hydroxide, magnesium hydroxide, sorbitol and mannitol	Barcroft AHMN		A free flowing, highly reactive, and directly compressible antacid powder
Calcium carbonate (70%) and sorbitol (30%)	Formaxx ®CaCO3 70	Merck KGaA, Darmstadt, Germany.	High compressibility, excellent taste masking, free flow, superior content uniformity, controlled particle size distribution
Calcium carbonate, acacia	Carbofarma GA10	Resinas industrials, S.A., Argentina	Directly compressible calcium carbonate
Calcium carbonate, maltodextrin	Carbofarma GM11		
Polyhydric sugar alcohol (75%), proprietary silicate salt (25%)	PanExcea MC200G	Malinkrodt Baker/USA	High performance rapid disintegrating direct compression excipient for oro-dissolving tablets formulation.
MCC (89%), hydroxypropylmethyl cellulose (HPMC) 2% and crospovidone (9%)	PanExcea MHC300G		High performance excipient for immediate release formulation

Co-processing is typically performed using some form of specialized manufacturing process such as high shear dispersion, granulation, spray drying, or melt extrusion. It is the one of the most widely explored and commercially utilized method for the preparation of direct compression excipients. Co-processing offers the following main advantages.

- Provides a single excipient with multiple functionalities.
- Produces a product with added value related to the ratio of its functionality against price.
- Improved compressibility and flow properties. Better dilution potential can be obtained where co-processed excipient possess a higher dilution potential than a physical mixture of its constituent excipients (dilution potential is defined as the amount of an active ingredient that can be satisfactorily compressed into tablets along with the direct compression excipient at a minimum possible weight).
- Allows the development of superior excipients by keeping functionality and removing undesirable properties, which helps in faster product development.
- Improvement in organoleptic properties (e.g., a co-processed excipient of MCC and guar gum, designed for providing chewable tablets with reduced grittiness and tooth packing, minimal chalkiness, better mouth feel, and improved overall palatability).
- Provides more robust tablets at low compression force. Co-processing of mannitol with sorbitol results in excipients with stronger binding capacity. This permits the packaging of orally dissolving tablets (ODTs) in conventional HDPE bottles, eliminating the need for specialized packaging where significant cost reduction can be achieved.
- Reduces product cost due to improved functionality and fewer test requirements compared to individual excipients.
- Provides intellectual benefits in terms of proprietary combinations, specific for in-house use.
- Co-processing is another way that new excipients are coming to market without undergoing the rigorous safety testing of a completely new chemical entity.

Co-processed excipients development generally starts by designing the following factors.

- The selection of the excipients to be combined and their targeted proportion.
- The selection of the preparation method to obtain an optimized product with the desired physicochemical parameters.
- Optimization of the preparation method to assure process reproducibility and product quality and functionality.

An overview of the co-processing methodology is shown in Figure 1.2.

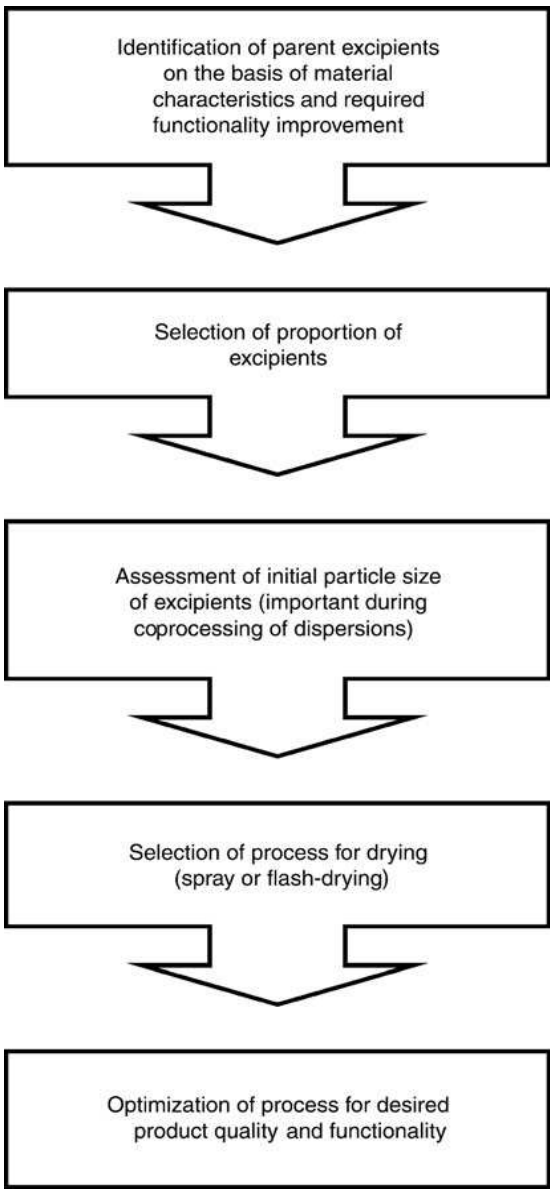


Figure 1.2 Co-processing methodology.

1.3.3 Role of Material Characteristics in Co-Processing [8, 17]

Material science plays a significant role in altering the physico-mechanical characteristics of excipients, especially with regard to their compression and flow properties. The solid materials can be classified according to their response towards applied mechanical force into three categories (Table 1.8): elastic, plastic and brittle (Figure 1.3.A).

Table 1.8 Material classification according to their response to applied mechanical force.

Material classification	Description
Elastic	Any change in shape is completely reversible, and the material returns to its original shape upon release of applied stress.
Plastic	Permanent change in the shape of a material due to applied stress, e.g., MCC, corn starch, and sodium chloride.
Brittle	Rapid propagation of a crack throughout the material on application of stress, e.g., sucrose, mannitol, sodium citrate, lactose, and di-calcium phosphate.

The predisposition of a material to deform in a particular manner depends on its lattice structure; in particular whether weakly bonded lattice planes are inherently present. In definitive terms, most of the materials cannot be classified distinctly into individual categories. Pharmaceuticals exhibit all three characteristics, with one of them being the predominant response, thus making it difficult to clearly demarcate the property favorable for compressibility. Compression refers "to a reduction in the bulk volume of materials as a result of displacement of the gaseous phase". Stages involved in the bulk reduction of powdered solids are shown in Figure 1.3.B. There are four stages encountered during compression:

(I) initial repacking of particles,

(II) elastic deformation of the particles until the elastic limit (yield point) is reached,

(III) plastic deformation and/or brittle fracture then predominate until all the voids are virtually eliminated, and

(IV) compression of the solid crystal lattice then occurs.

At the onset of the compression process, when the powder is filled into the die cavity, and prior to the entrance of the upper punch into the die cavity, the only forces that

exist between the particles are those that are related to the packing characteristics of the particles, the density of the particles and the total mass of the material that is filled into the die (Figure 1.3.B.I).

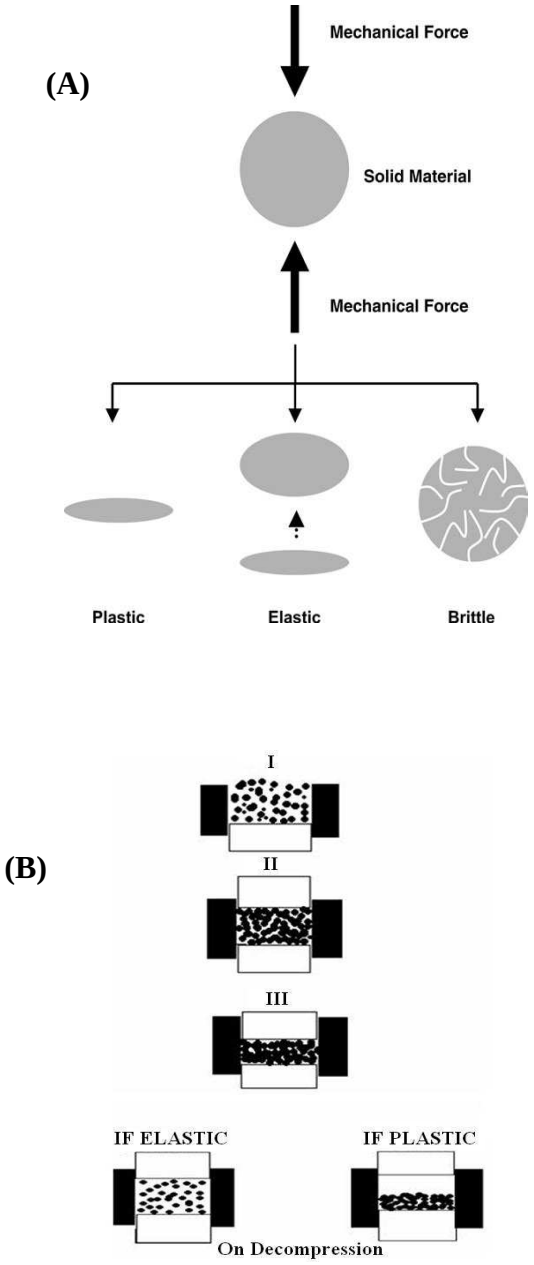


Figure 1.3 (A) Material classification on the basis of deformation behavior in the presence of an applied mechanical force, (B) stages involved in compression (I-III) and decompression.

Packing characteristics of a mass of dry powder are determined, in large part, by the characteristics of the individual particles. When external mechanical forces are applied to a powder mass, there is usually a reduction in volume due to closer packing

of the powder particles and, in most cases, this is the main mechanism of initial volume reduction (Figure 1.3.B.II). However, as the load increases, rearrangement of particles becomes more difficult and further compression leads to some type of particle deformation (Figure 1.3.B.III). If on removal of the load (decompression), the deformation is, to a large extent, reversible (behaves like rubber) then the deformation is said to be "elastic". All solids undergo elastic deformation, to some extent, when subjected to external forces. In some groups of powdered solids, an elastic limit is reached, and loads above this level result in deformation not immediately reversible on the removal of the applied force. Bulk volume reduction, in such cases, results from plastic deformation and/or viscous flow of particles, which are squeezed into the remaining void spaces. This mechanism predominates in materials in which the shear strength is less than the tensile or breaking strength. Plastic deformation is believed to create the greatest number of clean surfaces. Because plastic deformation is a time dependent process a higher rate of force application leads to the formation of less new clean surfaces and thus results in weaker tablets. Furthermore, since tablet formation is dependent on the formation of new clean surfaces, high concentrations or over mixing of materials that form weak bonds result in weak tablets (e.g, over mixing the granules with magnesium stearate may produce weak tablets due to the formation of weak bonds and easily wet surfaces). Conversely, in materials in which the shear strength is greater than the tensile strength, some particles may be preferentially fractured, and the smaller fragments then help to fill up the adjacent air spaces. This is most likely to occur with hard, brittle particles and is known as "brittle fracture"; sucrose behaves in this manner. The ability of a material to deform in a particular manner depends on the lattice structure; in particular whether weakly bonded lattice planes are inherently present. Brittle fracture creates clean surfaces that are brought into intimate contact by an applied load. Irrespective of the behavior of large particles, small particles may deform plastically via a process known as "microsquashing", and the proportion of fine powders in a sample may therefore be significant.

Co-processing offers an interesting tool for altering these physico-mechanical properties of excipients. It is generally conducted using plastic and brittle excipients. In this regard cellactose is an appropriate example which involves co-processing of 75% lactose (a brittle material) with 25% cellulose (a plastic material). Use of this particular combination prevents the storage of excessive elastic energy during

compression, resulting in a small amount of stress relaxation and a reduced tendency for capping and lamination. However, examples at the other extreme also exist, e.g., silicified microcrystalline cellulose (SMCC) which contains a large amount of microcrystalline cellulose (MCC) (a plastic material) and a small amount of colloidal silicon dioxide (CSD) (a brittle material). These two cases exemplify the fact that co-processing is generally performed by using a combination of materials possessing plastic deformation and brittle fragmentation characteristics.

Particle properties have a direct influence on excipient functionalities such as the potential for dilution, disintegration, and lubrication. Therefore, when developing a new excipient particle design must be taken into consideration. The role of particle engineering, by varying various particle properties, in achieving the desired excipient functionalities is shown in Table 1.9.

Table 1.9 Particle properties influencing excipient functionality.

Particle property	Affected excipient functionality
Particle size	Flowability, content uniformity, compressibility, disintegration, dissolution rate
Particle size distribution	Segregation potential
Particle shape	Flowability, content uniformity, compressibility
Particle porosity	Compressibility, disintegration, dissolution rate
Surface roughness	Flowability, segregation potential, dilution potential, lubricant sensitivity

1.3.4 Characterization of Co-Processed Excipients [8, 14, 18]

Formulations are developed by characterizing particles, powders, and compacts of API and excipients. Such characterization is associated with some predictive tools and allows formulators to understand the important physical, chemical, and mechanical properties of materials and thus design robust formulations at a relatively low cost and to achieve acceptable exposure in clinical studies.

The improvement in performance due to co-processing is the driving force for the introduction of excipients into the market. The absence of any chemical reaction between individual ingredients in the co-processed excipient must initially be

analytically demonstrated and over the proposed storage period of the co-processed excipient using different analytical techniques (e.g. X-ray powder diffraction spectroscopy (XRPD), Fourier-transform infra-red (FTIR) spectroscopy, differential scanning calorimetry (DSC), scanning electron microscope (SEM), etc.). The performance and functionality of the developed co-processed excipient should be evaluated using different testing procedures to prove the added value over the individual components properties. Table 1.10 presents the important parameters involved in the evaluation of co-processed and direct compression excipients.

Table 1.10 Parameters involved in the evaluation of co-processed and direct compression excipients**.**

Property	Related parameters	Comments
Tablet characteristics	Lubricant sensitivity	Lubricant, especially metal stearates, reduce the tensile strength (due to reduction of inter-particle bonding) and/or make the API hydrophobic and thereby prolong the disintegration time or decreases it on long, intensive mixing. The material undergoing plastic deformation is more susceptible to the negative effect of lubricant.
	Re-workability (re-processing)	This is the ability to reprocess a defective batch. Re-workability is influenced by the deformability of the directly compressible adjuvant on initial compression.
	Tensile strength, friability, and disintegration time	These are important parameters for the quality control of tablets. The mechanical properties of a tablet are the consequence of consolidation and expansion phenomenon. The increase in particle surface contact promotes a greater propensity for increased bonding. Tablets should have sufficient tensile strength to hold the API intact at the lowest compression force. Simultaneously it should give low friability and desired disintegration time.
	Dilution potential and loading capacity	High dilution potential is desirable to produce tablets with less weight. Compressibility and flowability of the drug has a strong influence on it.
Others parameters such as moisture absorption or stability upon storage can be used to compare the performance of directly compressible excipients.		
Powder Characteristics (Flow-ability)	Angle of repose, Carr's index (Compressibility index) and Hausner's ratio	• Carr's index (C) is an indication of the compressibility of a powder. It is calculated by the formula: $C = 100\ V_T - V_B / V_T$, where V_B is the bulk volume of a given mass of powder, and V_T is the tapped volume of the same mass of powder. • Hausner's ratio (H) is an indication of powder flowability and it is measured by the ratio: tapped density / bulk density. • Angle of repose (θ) is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. ($\theta = \tan^{-1} h/r$) where, h = height of the cone, r = radius of the cone base According to US pharmacopeia 31, General chapter <1174 >, angle of repose (25-30°) indicates excellent flow, and 31-35° indicate good flow. Carr's index ≤10 indicates excellent flow whereas 11-15 indicates good flow. Hausner's ratio less than 1.0-1.11 indicates excellent flow, whereas 1.12–1.18 indicates good flow. Good flowability of powder is needed for content uniformity and less weight variation in final tablets.
	Bulk density/Tapped density	• Bulk density is defined as the mass of a powder divided by the bulk volume and has units of gm/cm ^{3}. • Tapped density is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. The bulk density of a powder mainly depends on particle size distribution, particle shape and the tendency of particles to adhere together. The bulk and tapped density values influence the ability of the material to undergo compression and the final volume of the tablets.
	Particle size distribution - Mean particle size - Percentage fines	The angle of repose and Hausner's ratio are based on the ability of a mass of powder to flow. The flowability of the direct compression excipient is influenced by particle size and shape. Fine powder retards the flow, whilst particles with uniform size and shape exhibit better flow than irregular particles of the same size and shape.

Property	Related parameters	Comments
Powder Characteristics (Compressibility)	Heckle and Kawakita equations	A direct compression excipient should exhibit an acceptable pressure-volume profile (compressibility). Heckle and Kawakita equations are most widely used to assess material compressibility. The slope, k, of the Heckle plot gives a measure of the plasticity of a compressed material and the reciprocal of k is known as the yield value (Py). The yield value reflects the deformability of the material; soft, ductile powders have a lower yield value, the agglomerates with low yield value can be plastically deformed as a result of the rebinding of smaller primary crystals. Low values of Py (steep slope) reflect low resistance to pressure, good densification and ease of compression. A large slope value indicates the onset of plastic deformation at relatively low pressure. $\mathbf{In}\left[\frac{1}{1-D}\right]$ **=kP+A (Heckel Equation)** where, D is the relative density of a powder compact at pressure P. The constant k is a measure of the plasticity of a compressed material. The constant A is related to the die filling and particle rearrangement before deformation and bonding of the discrete particles. The Kawakita equation is used to study powder compression using the degree of volume reduction, C. The basis for the Kawakita equation for powder compression is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of the pressure term and the volume term is a constant: **$C = [V_0 - V/V_0] = [abP/1 + bP]$ (Kawakita Equation)** where, C is degree of volume reduction, V_0 is the initial volume; V is the volume of powder column under the applied pressure P. The a value is the material's minimum porosity before compression while b relates to plasticity of the material. The smaller a value for the granules indicates good packing even without tapping. The large value of b indicates rapid packing velocity of the powder or agglomerates. The reciprocal of b defines the pressure required to reduce the powder bed by 50%. The equation above can be rearranged in linear form as: **$P/C = P/a + 1/ab$** The expression of particle rearrangement could be affected simultaneously by the two Kawakita parameters a and b. The combination of these into a single value, i.e. the product of the Kawakita parameters a and b, may hence be used as an indicator of the expression of particle rearrangement during compression.
	Functionality	Co-processed excipient can involve APIs using different processing techniques including direct compression, wet or dry granulation to assess the capability of the co-processed excipient to maintain and preserve its superior properties and functionality.
	Moisture Uptake (Hygroscopicity)	Moisture uptake is an important characteristic of pharmaceutical powders. Many pharmaceutical excipients can sorb atmospheric moisture. Moisture has a significant impact on the physical stability, chemical stability, flowability, and compactibility of powder excipients and formulations (e.g., moisture-sensitive APIs formulation). Water sorption and equilibrium moisture content depend upon the atmospheric humidity, temperature, surface area, and exposure, as well as the mechanism for moisture uptake [17].

1.4 Special Types of Excipients (Oro-Dissolving Tablets) [19, 20]

Oro-dissolving tablets (ODTs) are solid dosage forms containing medicinal substances that disintegrate rapidly in the oral cavity and disperse in the saliva without the need for water. In April 2007, the Food and Drug Administration (FDA) issued draft guidance, Guidance for Industry: Orally Disintegrating Tablets [21]. The definition considers ODTs to be solid oral preparations that disintegrate rapidly in the oral cavity with an in vivo disintegration time of approximately 30 seconds or less, when based upon the USP disintegration test method. Besides convenience of intake the advantage of this dosage form is fast bioavailability of the active ingredient. The mechanism behind the disintegration of ODTs is illustrated in Figure 1.4.

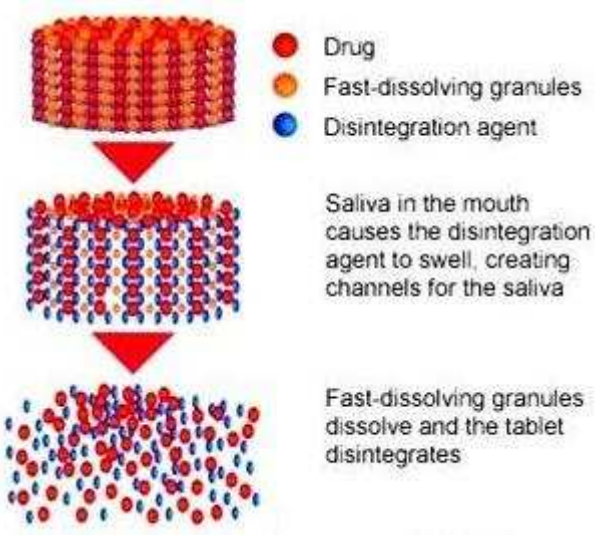


Figure 1.4 Mechanism of disintegration of ODTs.

Orally disintegrating tablets offer all the advantages of solid dosage forms and liquid dosage forms together with special advantages, including the following.

- ODTs are solid dosage forms which provide good stability, accurate dosing, easy manufacturing, small packaging size and easy to handle by patients.
- No risk of obstruction of dosage form, which is beneficial for traveling patients who do not have access to water.
- Easy to administer for pediatric, geriatric, mentally retarded and psychiatric patients.

- Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.
- Medication as a "bitter pill" has changed because of acceptable mouth feel properties produced by the use of flavors and sweeteners in ODTs.
- Bioavailability of drugs that are absorbed from the mouth, pharynx, and oesophagus is increased.
- Pre-gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability.

Some challenges may be faced when developing and designing ODT solid dosage forms including the following.

- Achieving rapid disintegration of tablets.
- Avoiding an increase in tablet size.
- Obtaining sufficient mechanical strength for tablets.
- Minimizing or avoiding residue in mouth.
- Protecting tablets from moisture.
- Good package design (necessary because of low tablet hardness).
- Compatibility of API with taste masking technology.
- Overcoming undesirable API properties.

Several technologies are commonly used by the manufacture of ODTs (Table 1.11). These technologies differ in their methodologies and the ODTs produced vary in their properties such as:

- mechanical strength, wetting and disintegration time of tablets
- taste and mouth feel
- swallow-ability
- drug dissolution in saliva
- bioavailability
- stability

The most common procedures are lyopholization (freeze drying) and direct compression.

Table 1.11 Technologies used in ODT preparations.

Innovator/ Dosage form	Technology	Technology Basic	Drug marker	Marketed product/Indication
(CIMA Labs) Direct compression tablet	**Durasolv**	Conventional direct compression tablets containing API, filler, disintegrant, flavourings, sweeteners, colorants and lubricant.	Alamo	Fazaclo (clozapine) / Antipsychotic
			AstraZeneca	Zomig-ZMT (zolmitriptan) / Migraine
			Organon	Remeron, SolTabs (mirtazapine)/ Depression
		Conventional direct compression tablets containing API, filler, disintegrant, flavourings, sweeteners, colorants and lubricant.	Schwarz Pharma	Fluxid (famotidine) / Duodenal ulcers
	Orasolv	Conventional direct compression tablets containing API, filler, disintegrant, flavourings, sweeteners, colorants and lubricant.		NuLev (hyoscyamine sulfate) / Irritable bowel
				Parcopa (carbidopa, levodopa) / Parkinson's disease
			Wyeth	Alvert (loratadine) /Allergy
(Ethypharm/BMS) Compressed tablet	**Flash Tab**	A direct compression tablets consist of Eudragit-microencapsulated API and effervescent couple	Bristol-Myers Squibb	Excedrin, QuickTabs (acetaminophen, caffeine) / Headache
(Yamanouchi) Compressed molded tablet	**WOWTAB (Without water)**	API is mixed with a low mouldability saccharide (lactose, mannitol, maltose and maltilol) and granulated with a high mouldability saccharide and compressed into tablet	Pfizer	Benadryl, Fastmelt (diphenhydramine citrate, pseudoephedrine HCL / Allergy and sinus
(Cardinal Health) Lyophilized (Freeze-dried) wafer	**Zydis**	A Zydis tablet is produced by lyophilizing (freeze-drying) the API in a matrix usually consisting of gelatin. Amorphous porous structure is formed that can dissolve rapidly. Freeze drying technique has demonstrated improved absorption and increase in bioavailability of APIs.	Eli Lilly	Zyprexa, Zydis (olanzapine) / Schizophrenia
			GlaxoSmithKline	Zofran ODT (ondansetron) / Nausea and vomiting
			Janssen	Risperdal, M-Tab (risperidone)/Schizophrenia
			Merck	Maxalt-MLT (rizatriptan benzoate) / Migraine
			Schering-Plough	Claritin, Resitags (loratadine) / Allergy
				Clarinex. Reditabs (desloratadine) / Allergy
(Biovail) Floss-based tablet technology	**Flash Dose**	A sugar-based tablet matrix prpared in a procedure similar to that used in the preparation of cotton candy usind high temperature called 'Floss' is used to mask the bitter taste of API.	Reckitt Benckiser Healthcare (UK) Ltd	Nurofen meltlet/ NSAIDs

However, the number of fillers/binders that can be used for ODT formulations is limited because these bulk excipients have to fulfil special requirements, such as being soluble in water, having a pleasant sweet taste and mouth feel, as well as being rapidly dispersible.

Direct compression ODT formulations usually contain the API, diluents/fillers, disintegrants, lubricants, flavourings, sweeteners and colorants. The most commonly used bulk excipients for the development of this kind of formulations are sugar based excipients such as dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness in addition to other favourable characteristics which improve the performance and impart taste masking property of ODTs [22].

No single excipient can fulfil the requirements of all ODT formulations. A popular way to enhance disintegration properties is the addition of a super-disintegrant, such as croscarmelose sodium, sodium starch glycollate and crospovidone. Table 1.12 shows the most commonly used excipients/fillers for the preparation of ODTs.

Table 1.12 Commonly used excipients in ODT preparations.

Excipient	Manufacturer	Manufacturer Website
PanExcea MC200G	Mallinckrodt Baker / USA	http://www.mallbaker.com/panexcea/
Isomalt galenIQ-720	BENEO-Palatinit GmbH (Germany)	http://www.beneo-palatinit.com/en/Pharma_Excipients/galenIQ/galenIQ_Grades/
Isomalt galenIQ- 721		
Ludiflash	BASF / Switzerland	http://www.pharma-ingredients.basf.com/Ludiflash/Home.aspx
Pharmaburst ™	SPI / FRANCE	http://www.spipharma.com/default.asp?contentID=588
Pharmafreeze™		
Mannitol (Mannogem)		
Lactose Spry Dried (Fast-Flu)	Foremost / USA	http://www.foremostfarms.com/Commercial/Dairy-Ingredients/Pharmaceutical-Grade-Lactose.php

1.5 Chitin: A Solid Dosage Form Excipient [23]

Lack of the amine group "NH_2" makes chitin almost chemically inactive. In addition, the availability of chitin as the second most naturally abundant material, after cellulose, allows its use as an excipient in processing solid drug dosage forms. This facilitates its use with other common excipients, namely microcrystalline cellulose (MCC), lactose, starch, and calcium hydrogen phosphate. Consequently, chitin is a natural hydrophilic polymer wherein chemical modification and co-processing can be carried out to prepare multi-functional excipients.

1.5.1 Chemical names and structural formula of chitin (CAS No.:1398 -61-4)

"Chitin" and "chiton" (a marine animal) both derive from the same Greek word meaning "tunic", referring to the protective shell. Chitin is a white, hard, inelastic, nitrogenous polysaccharide found in the outer skeletons of crabs and lobsters as well as in the internal structures of other invertebrates. Chitin $(C_8H_{13}NO_5)_n$ is, β-(1,4)-2-acetamido-2-deoxy-D-glucopyranose, poly-N-acetyl-D-glucosamine [poly (D-GlcNAc)], β-1, 4-poly-N-acetyl-D-glucosamine, poly-(β1-4)-N-acetyl-glucosamine, poly-(acetyl amino glucose), β- (1,4)-2-acetamido-2-deoxy-D-glucose, 2-acetamido-2-deoxy-D-glucose, β-(1,4)-2-amino-2-deoxy-D-glucose, poly-(N-acetyl-1,4-β-D glucopyranosamine), fully acetylated chitosan. Chitin has a monomer molecular weight of 203.19 and average molecular weight ranging from 1.0 to 2.5 million Da. The variation in the molecular weight is a function of the extent of N-acetylation. The chemical structure of the monomeric unit of chitin is shown in Figure 1.5. The elemental composition of fully acetylated chitin is: carbon: 47.29%, hydrogen: 6.45%, nitrogen: 6.89% and oxygen: 39.37%.

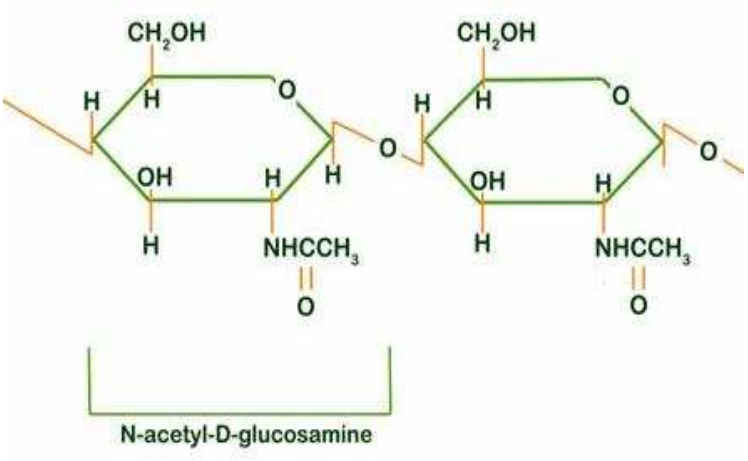


Figure 1.5 Chemical structure of chitin showing its monomer: N-acetyl-D-glucosamine [24].

1.5.2 Preparation of chitin

Crude chitin is isolated from the outer skeletons of crustaceans, molluscs or invertebrate animals, insects and certain fungi. Commercially, crab and shrimp shells are the major sources of chitin. Crustacean shells consist of 30-40% protein, 30-50% calcium carbonate and 20-30% chitin, but also contain pigments of a lipidic nature such as carotenoids. These components have to be quantitatively removed to obtain pure chitin necessary for biological applications. Several published methods for the extraction of chitin from crustacean shells in addition to enzymatic preparation are summarized in Table 1.13.

Table 1.13 Methods for the preparation of chitin [25-28].

Method	Procedure
Method 1	Crude chitin is washed with water, dried at room temperature and cut into small pieces, then treated with acid (HCl, HNO_3, H_2SO_4, CH_3COOH, or HCOOH) (demineralization), followed by alkali using NaOH at 105-110^oC (deproteinization). The decolouration is performed by refluxing in ethanol or by using oxidizing or bleaching agents (e.g. $KMnO_4$, NaOCl and H_2SO_4).
Method 2	Crude chitin is washed with water, dried at room temperature and cut into small pieces, then soaked for 3 days in 10% NaOH solution (freshly prepared and degassed every day at room temperature). The obtained solid is then treated with 95% ethanol to clean the pigment products. The white protein free-residue is then suspended in 37% HCl at 20°C for 4 hours. The solid is filtered and washed with water, ethanol and ether.
Method 3	The shells are partially digested with an organic acid, followed by 2N HCl for 5 hours at room temperature. The decalcified shells are shaken for 18 hours with 90% formic acid at room temperature and then filtered. The solid is washed with water and treated for 2.5 hours with 10% NaOH solution on a steam bath. The suspension is then filtered, washed with water, ethanol and ether.
Method 4	Decalcification with EDTA at pH 10 at room temperature for 2 or 3 weeks. Large cuticle fragments of the crab Cancer parugus are reacted slowly (2 or 3 weeks) with EDTA at pH 9.0. The solid is then further treated with EDTA at pH 3, extracted with ethanol for pigment removal and with ether for the removal of lipids. The protein is removed with formic acid (98-100%) followed by treatment with hot alkali.
Method 5	Decalcification with EDTA at pH 10 at room temperature, followed by digestion with a proteolytic enzyme such as tuna proteinase at pH 8.6 and 37.5ºC, or papain at pH 5.5-6.0 and 37.5ºC or a bacterial proteinase at pH 7.0 and 60ºC for over 60 hours. The remaining protein (~5%) is removed by treatment with sodium dodecylbenzensulfonate or dimethylformamide.
Method 6	Decalcification is carried out by a simple treatment with 1.4N HCl at room temperature in a plastic or wooden container. After completion of the decalcification treatment, proteins are removed using papain, pepsin or trypsin. This method is simple and suitable for the mass production of chitin with little deacetylation.
Method 7	The shell wastes are treated with hot 1% Na_2CO_3 solution followed by dilute HCl (1-5%) at room temperature, and then 0.4% Na_2CO_3 solution
Method 8	Hydrolysis of protein present in the shell followed by digestion of $CaCO_3$. The shells are treated with hot 5% NaOH, followed by cold NaOCl and then with warm 5% HCl.
Method 9	Trehalose is hydrolyzed with the enzyme trehalase, followed by phosphorylation with ATP/enzyme hexokinase to form glucose-6-phosphate, which is transformed to fructose-6-phosphate in the presence of the enzyme glucose phosphate isomerase. Amination occurs in the presence of glutamine amino-transferase and the amino acid glutamine to form α-D-glucosamine-6-phosphate. Acetylation by acetyl-CoA in the presence of the enzyme glucosamine-6- phosphate-N-acetyl transferase causes the formation of N-acetylglucosamine-6-phosphate. The latter rearranges via the enzyme phosphoacetylglucosamine mutase to form N-acetylglucosamine-1-phosphate, which is converted to uridinediphosphate-N-acetyl glucosamine (UDP-N-acetylglucosamine) via the enzyme uridinediphosphate-N-acetylglucosamine pyrophosporylase and UTP. The final product, chitin, is produced via the enzyme chitin synthesase by the loss of UDP (Figure 1.6).

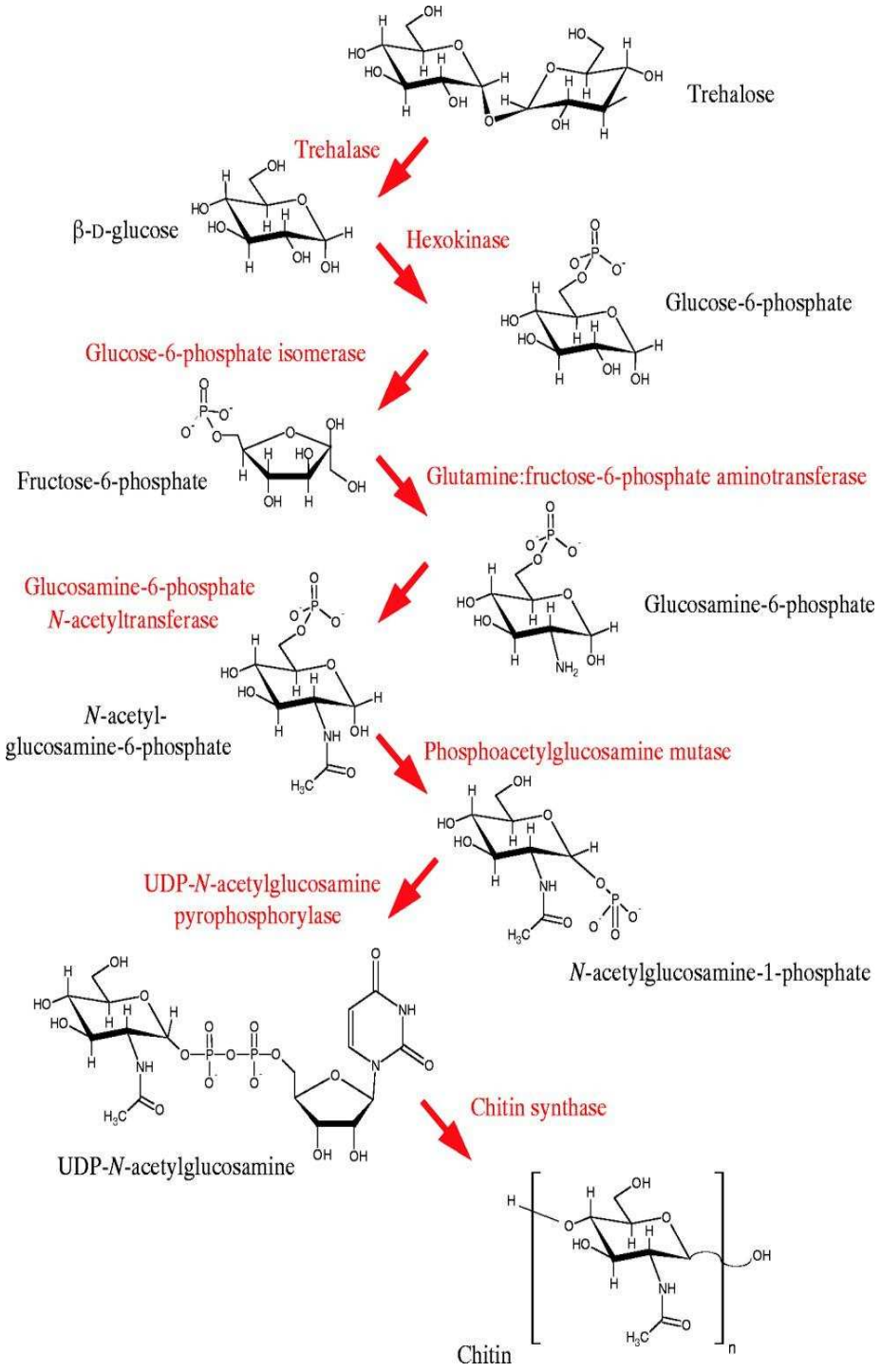


Figure 1.6 Biosynthesis of chitin [26].

1.5.3 Deacetylation of chitin (chitosan preparation)

The most important derivative of chitin is chitosan obtained by partial deacetylation of chitin in the solid state under alkaline conditions or by enzymatic hydrolysis in the

presence of a chitin deacetylase. The ratio of 2-acetamido-2-deoxy-D-glucopyranose to 2-amino-2-deoxy-D-glucopyranose moieties determines the identity of the product i.e. chitin or chitosan. Published methods used for the production of chitosan from chitin are summarized in Table 1.14.

Table 1.14 Methods used for the deacetylation of chitin to form chitosan [26, 27, 29, 30].

Method	Procedure
Method 1	40% NaOH solution is added to chitin and refluxed under nitrogen at 115°C for 6 hours. The cooled mixture is then filtered and washed with water until the washings are neutral to phenolphthalein. The crude chitosan is purified as follows. It is dispersed in 10% acetic acid and then centrifuged for 24 hours, to obtain a clear supernatant liquid. The latter is treated drop-wise with 40% NaOH solution and the white flocculent precipitate formed at pH 7. The precipitate is then recovered by centrifugation, washed repeatedly with water, ethanol and ether and the solid collected and air-dried (Figure 1-7).
Method 2	Fusion with solid KOH at very high temperature in a nickel crucible under nitrogen atmosphere. The melt is poured carefully into ethanol and the precipitate washed with water to neutrality.
Method 3	Heating in 40% NaOH solution at 115 ºC for 6 h under nitrogen. After cooling, the mixture is filtered and washed with water until neutral. This method does not include a purification step.
Method 4	Kneading with NaOH and liquid paraffin in a 1:1:10 ratio, and stirred for 2 h at 120°C. The mixture is poured into cold water, filtered and thoroughly washed with water.
Method 5	Steam heating with a solution containing 50% KOH, 25% EtOH (96%) and 25% mono-ethylene glycol. The temperature of the system is 120°C. The obtained chitosan is filtered, washed with water until neutral, and then dried at moderate temperatures.
Method 6	Recovery of shell proteins, sodium acetate and calcium carbonate in addition to chitosan as commercial pure products. The extraction procedure includes different reaction and crystallization steps.
Method 7	The fungal order mucorales contains chitosan as a cell wall component. Absidia coerula a member of this class is readily cultured on nutrients (e.g. glucose or molasses) and the cell wall material recovered by simple chemical procedures.

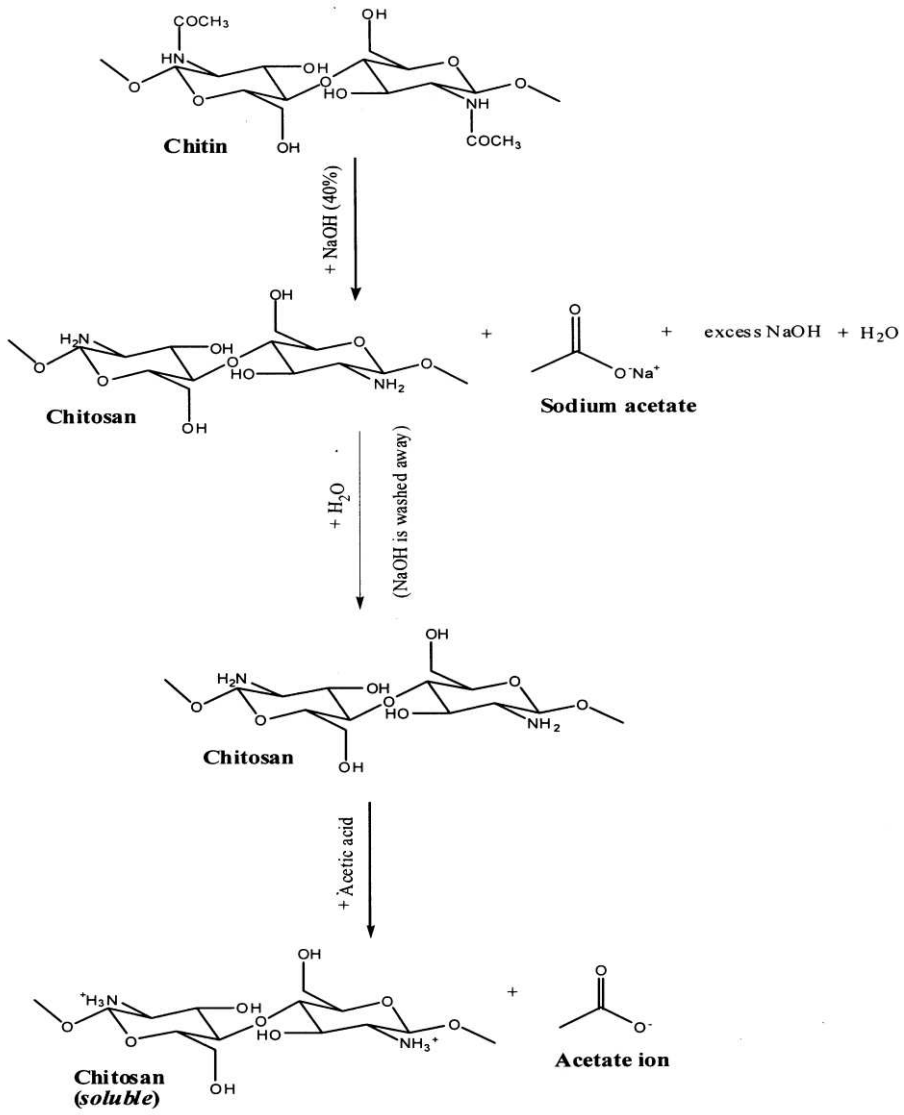


Figure 1.7 Scheme for the deacetylation of chitin [29].

1.5.4 Hydrolysis products of chitin (oligomers)

Chitin is hydrolyzed to form smaller oligosacharides by different methods including acetolysis using acetic anhydride/H_2SO_4, hydrolysis with HCl/sonolysis under ultrasound irradiation or fluorohydrolysis using anhydrous HF (Figure 1.8). Enzymatic hydrolysis is a useful method for the preparation of monomers from chitin and chitosan because the yield of monomers is greater by enzymatic hydrolysis than by acid hydrolysis. The enzyme chitin deacetylase hydrolyzes the acetamido group in the N-acetylglucosamine units of chitin and chitosan, thus generating glucosamine

units and acetic acid (Figure 1.9).

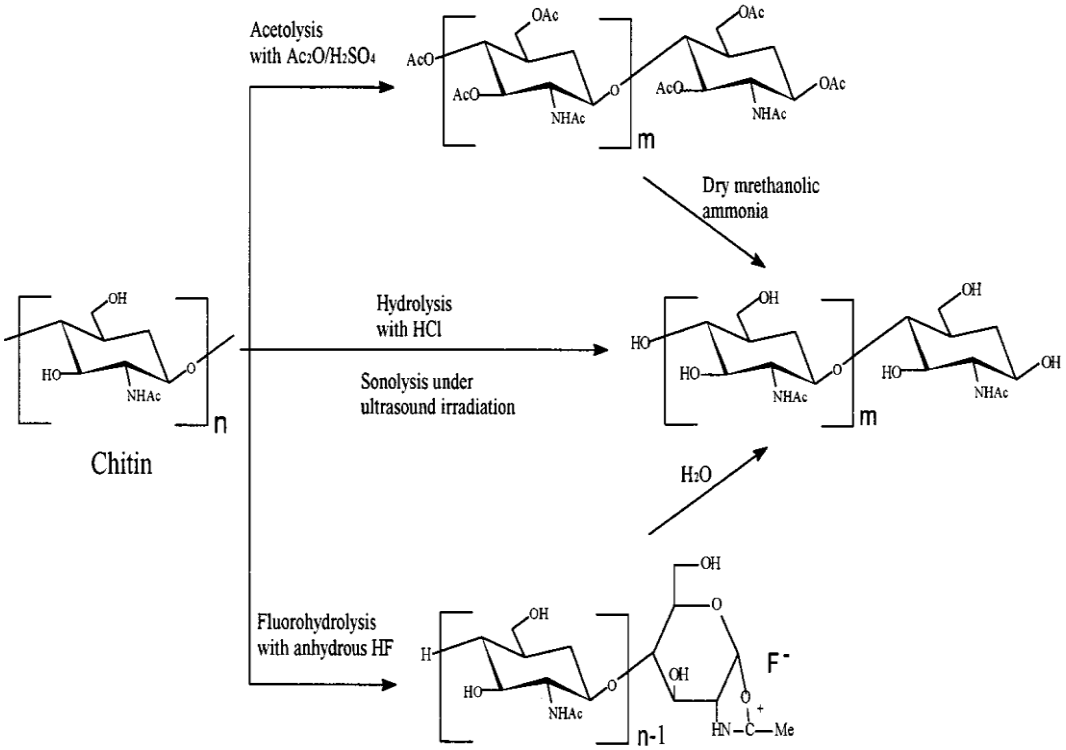


Figure 1.8 Mechanisms for the acid hydrolysis of chitin [31].

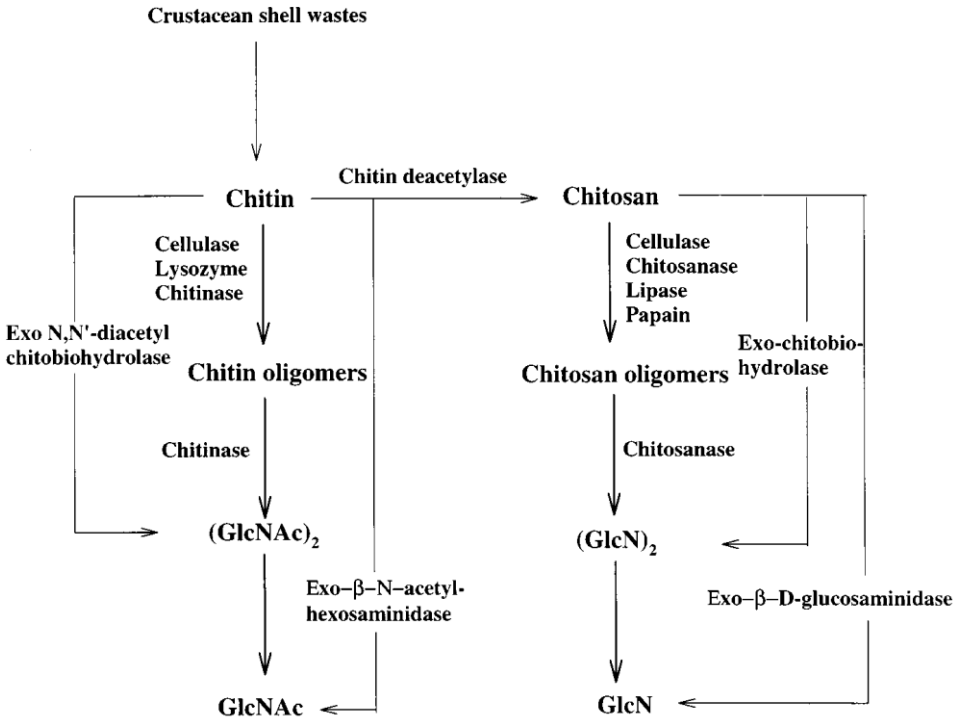


Figure 1.9 Enzymatic hydrolysis of chitin and chitosan into their monomers [31].

1.5.5 Other derivatives

Carboxymethyl chitin (CM-chitin), as a water-soluble anionic polymer, is the second most studied derivative of chitin after chitosan. The carboxymethylation of chitin is undertaken in a similar manner to that of cellulose. Chitin is treated with monochloracetic acid in the presence of concentrated NaOH. The same cellulose derivatization procedure can be used to prepare hydroxypropylchitin, which is a water-soluble derivative used for artificial lachrymal drops. Fluorinated chitin, N- and O-sulfated chitin, (diethylamino) ethylchitin, phosphoryl chitin, mercaptochitin and chitin carbamates have also been reported and described in the literature. Similar chemical modifications (e.g. etherification and esterification), as for cellulose, can be performed for chitin. Chitin can be used in blends with natural or synthetic polymers; it can be cross-linked by the reagents used for cellulose (e.g, epichlorhydrin and glutaraldehyde) or grafted in the presence of ceric salt or after selective modification. Another chitin derivative dibutyrylchitin (DBCH) is prepared from krill chitin by esterification with butyric anhydride in the presence of perchloric acid. DBCH can be used in fibre spinning. DBCH fibres have been manufactured from a polymer solution in ethyl alcohol by extrusion.

1.5.6 Physical characteristics of chitin

1.5.6.1 Solubility

Table 1.15 Solubility of α-chitin in different solvents and solvent mixtures at room temperature [32-34].

Solvent/Solvent mixture	Solubility
Water	i
Dilute acids	i
Dilute and concentrated alkalies	i
Alcohol	i
Organic solvents	i
Concentrated HCl, H_2SO_4 or H_3PO_4, anhydrous HCOOH	s (with depolymerization)
N,N-dimethylacetamide (DMAc)/5% LiCl	s
Dinitrogen tetroxide/N,N-dimethylformamide (DMF)	s
Fluoroisopropanol/hexafluoroacetone	s
N,N-dimethylacetamide/N-methyl-2-pyrrolidone/LiCl	s
N-methyl-2-pyrrolidone/5% LiCl	s

i and s represent insoluble and soluble, respectively

The dissolution mechanism of α-chitin in DMAc/5% LiCl (Table 1.15) can be attributed to the formation of a weak complex between Li^+ ions and the carbonyl oxygens of the DMAc, which solvates the polyelectrolyte formed between the Cl^- ions and labile proton groups (OH and $NHCOCH_3$) of the chitin chain, disrupting the extensive intra- and inter-molecular hydrogen bonds of the crystalline sheet structure of α-chitin.

Table 1.16 shows the effect of different solvent mixtures containing methanol, ethanol and anhydrous and hydrate forms of calcium and magnesium salts.

Table 1.16 Solubility of α-chitin in various calcium and magnesium salt-alcohol solutions [32-34].

Solvent System	**Solubility***
Saturated anhydrous $CaCl_2$-methanol	p.s.
Saturated $CaCl_2.2H_2O$-methanol	s
Saturated $CaCl_2.2H_2O$-ethanol	p.s.
Saturated $MgCl_2.6H_2O$-methanol	i
100%(w/v) $Ca(NO3)_2.4H_2O$-methanol	i
100%(w/v) $Mg(NO3)_2.6H_2O$-methanol	i
200%(w/v) $Ca(SCN)_2.4H_2O$-methanol	p.s

*0.5g chitin was stirred in 50 mL of each solution at room temperature; s, p.s. and i represent soluble, partially soluble and insoluble, respectively.

By comparing the solubility of α- and β-chitins (although the later exists in a crystalline hydrated structure, which is much looser than that of the α-chitin), β-chitin shows lower solubility due to the penetration of water between the chains of the lattice. Based upon data for chitin-solvent interactions and solubility mechanisms, β-chitin starts gelling at a lower concentration than α-chitin. Table 1.17 shows the solubility of chitin and structurally related compounds in a saturated $CaCl_2.2H_2O$-methanol solvent system.

Table 1.17 The solubility of α-/β-chitins and structurally related compounds in a saturated $CaCl_2.2H_2O$-methanol solvent system [32-34].

Material	Solution (g/100 mL)	Solubility*
α-Chitin	2.00	s
β-Chitin	1.25	t
Chitosan	5.00	i
Bacterial cellulose	0.15	g
O-Acetylated chitin	1.25	t
Nylon-6	5.00	s

*s, t, g, and i represent soluble, turbid or gelation, gelation and insoluble, respectively.

1.5.6.2 Chitin Morphology

The morphology of α-chitin was determined using a Quanta-200 3D scanning electron microscope (SEM) operated at an accelerating voltage of 1200 V. The sample (0.5 mg) was mounted onto a 5×5 mm silicon wafer affixed via graphite tape to an aluminium stub. The powder was then sputter-coated for 105 s at a beam current of 20 mA/dm^3 with a 100 Å layer of gold/palladium alloy. The SEM images in Figure 1.10 show the highly porous structure of α-chitin in addition to the high particulate surface area.

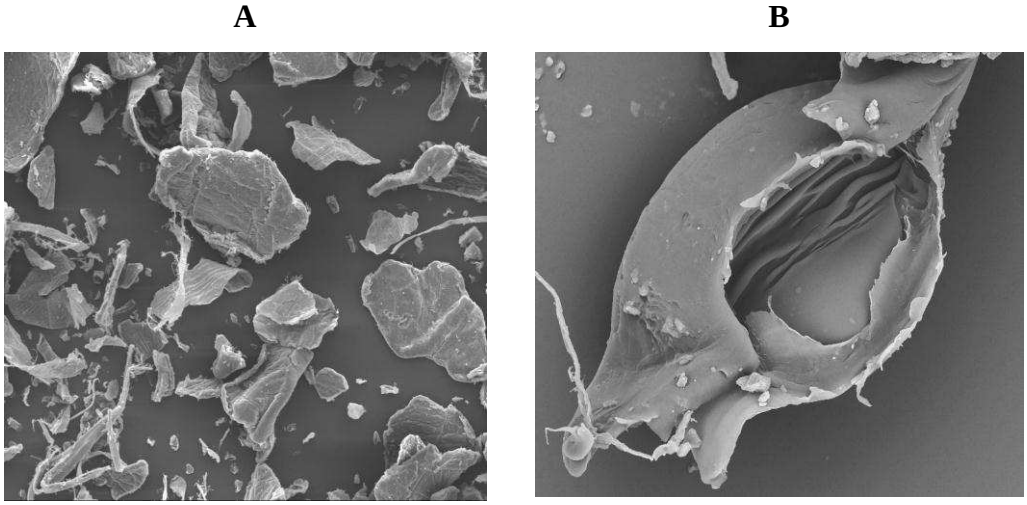


Figure 1.10 SEM images of α-chitin, at magnifications of (A) x160 and (B) x1600 [35].

1.5.6.3 Chitin polymorphs and their sources

Chitin is isolated from the exoskeletons of crustaceans (e.g, crabs, lobsters, crayfish, shrimp, krill, barnacles), molluscs or invertebrate animals (e.g, squid, octopus, cuttlefish, nautilus, chitons, clams, oysters, scallops, geoducks, mussels, fossils, snails), insects (e.g. ants, scorpions, cockroaches, beetles, spiders, brachiopods) and certain fungi. Commercially, crab and shrimp shells are the major sources of α-chitin whereas squid is the source of β-chitin. There are three polymorphic forms of chitin: α, β and γ. They differ in the arrangement of chains in the crystalline phase. The most abundant and stable form is α-chitin, which displays orthorhombic crystals. The crystallographic parameters for α- and β-chitin are shown in Table 1.18. The neighboring sheets in α- and β-chitin are connected by hydrogen bonds via C=O and N-H groups. In addition, each chain has intra-molecular hydrogen bonds between the neighboring sugar rings (C=O and OH groups on C-6 and a second hydrogen bond between the OH- group on C-3 and the ring oxygen) (Figure 1.11). The differences among chitin polymorphs are due to the arrangement of the chains in the crystalline regions. α-Chitin has a structure of anti-parallel chains, β-chitin has intra-sheet hydrogen-bonding resulting in parallel chains and γ-chitin, being a combination of α- and β-chitin, has both parallel and anti-parallel structures. Because of these differences each chitin polymorph differs in specific properties. The poor solubility of chitin is a result of the close packing of chains and its strong inter- and intra-molecular bonds between the hydroxyl and acetamide groups. On the other hand, β-chitin lacks these inter-chain hydrogen bonds; therefore it swells readily in water and it is more prone to N-deacetylation than α-chitin.

Table 1.18 Crystallographic parameters for α-and β-chitin [36, 37].

Compound	a (nm)	b (nm)	c (nm)	γ(°)	Space group
α-Chitin	0.474	1.886	1.032	90.0	$P2_12_12_1$
β-Chitin	0.485	0.926	1.038	97.5	$P2_1$

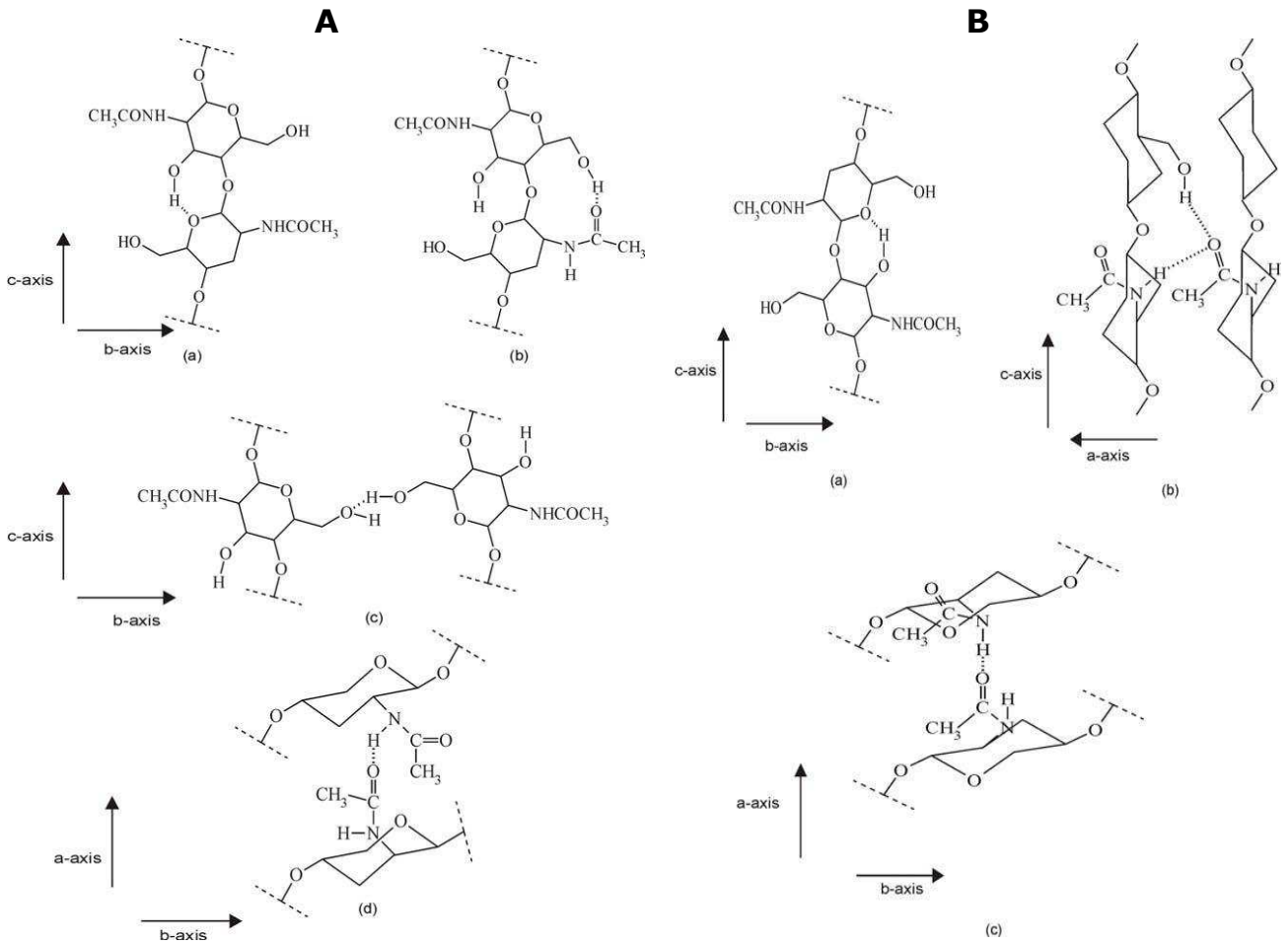


Figure 1.11 Modes of hydrogen bonding in (A) α-chitin: (a) intra-chain C(3′) OH···OC(5) bond; (b) intra-chain C(6_1)OH···O=C(7_1) bond; (c) inter-chain C($6'_1$)O···HOC(6_2) bond; (d) inter-chain C(2_1)NH···O=C(7_3) and (B) β-chitin: (a) intra-chain C(3′)OH···OC(5) bond; (b) inter-chain C(2_1)NH···O=C(7_3) bond and C($6'_1$)OH···O=C(7_3) bond (ac plane projection); (c) inter-chain C(2_1)NH···O=C(7_3) bond (ab plane projection) [36,37].

The seafood industry produces in excess of 3.5 million tonnes of solid waste each year and with this figure rising, there is a subsequent waste disposal issue. Chitin is mainly used as a raw material to produce chitin-derived products such as chitosans, chitin/chitosan derivatives, oligosaccharides and glucosamine. An increasing number of useful products derived from chitin continue to attract commercial development. The large number of patents filed involving chitin-derived products reflects the commercial expectations for these products. An estimated 75 % of chitin produced is used to manufacture products for the nutraceutical market. Currently the major

driving force in the market is the increasing sales of glucosamine as a dietary supplement. Approximately 65% of the chitin produced is converted into glucosamine, nearly 25% is converted into chitosans, about 9% is used to produce oligosaccharides and approximately 1% is used in the production of N-acetylglucosamine. Table 1.19 shows the estimated global price of high purity chitin, mannitol and different pharmaceutical grades of microcrystalline cellulose and microcrystalline cellulose related products.

Table 1.19 Estimated global market prices of some pharmaceutical excipients [35].

Item	Pharmaceutical Application	Price* in USD/Kg
Chitin (high purity powder grade)	Tablet/ capsule filler and disintegrant	8-15
D-Mannitol (Crystalline)	Tablet/ capsule filler	5-15
Microcrystalline Cellulose PH 200	Direct compression excipient for tablet/ capsule formulation	6-10
Silicified Microcrystalline Cellulose	Direct compression excipient for tablet/ capsule formulation	21-27
AVICEL HFE 102 NF (Mannitolized Microcrystalline Cellulose)	Direct compression excipient for tablet/ capsule formulation	10-15

* The price range is dependent on the quantity supplied, grade and supplier.

1.5.6.4 Chitin stability

Chitin is a stable compound, incompatible with oxidizing agents. In the solid state under alkaline condition (e.g, NaOH, KOH, heat at about 120^{o}C) or by enzymatic hydrolysis in the presence of a chitin deacetylase, it hydrolyses to form the deacetylated degradation product chitosan. It was found that the presence of urea in basic media and at low temperature (-20^{o}C) had little effect on chitin structure and that urea is of benefit to the stability of chitin solution. Under acidic conditions including acetolysis with acetic anhydride/H_2SO_4, hydrolysis with HCl/sonolyses under ultrasound irradiation and fluorohydrolysis with anhydrous HF or by using the enzyme chitin deacetylase, it forms smaller oligosaccharides. The effect of hydrogen peroxide on the stability of chitin by microwave radiation was investigated, it was suspended in water, and 30% hydrogen peroxide was added in quantities to achieve H_2O_2 concentrations of 1%, 5%, 9% and then subjected to 600 W microwave

radiation for 10 to 30 min. The results indicated that chitin degradation with hydrogen peroxide in a microwave field caused significant changes in the molecular weight and the chemical structure of the polymer in a short period (up to 30 min). The limiting viscosity numbers of the degradation products were from 15 to 83% lower than those of the initial chitin.

1.5.6.5 Biodegradability and toxicology

Chitin is a biodegradable material and undergoes biodegradation by enzymes such as lysozyme and chitinase. In-vivo studies show that lysozyme plays an important role in the degradation of chitin to produce mostly soluble oligomers such as N-acetylglucosamine upon hydrolysis. Chitin is not believed to present a significant health risk. Also no risk to humans is expected when products containing chitin are used according to label directions. Chitin is structurally closely related to the active ingredient chitosan (poly-D-glucosamine), which shows no toxicity in mammals, and is approved by the FDA as a food additive. The LD_{50} for the intravenous administration of chitin is 50 mg/Kg in rats.

1.5.6.6 Chitin/ chitin derivatives applications

Chitin and its derivatives have been used in different applications including the food, medical, pharmaceutical, agriculture and biotechnology industries. Table 1.20 illustrates some of these applications.

Table 1.20 Examples of applications of chitin and its derivatives [34, 38].

Fields	Chitin and Chitosan	Chitin and chitosan oligomers
Food	Antimicrobial agent preservative agent Edible film	Antimicrobial agent preservative agent
Pharmaceutical	Protective effect on bacterial infection Antitumor agents Immunopotentiating agent Carrier for drug delivery system	Protective effect on bacterial infection Antitumor agents Immunopotentiating agent
Medical	Accelerator for wound healing Artificial skin Fiber for absorbable sutures	
Nutritional	Dietary fiber Hypocholesterolemic agent Antihypertensive agent	Hypocholesterolemic agent Calcium absorption accelerator in vitro
Biotechnological	Carrier for immobilized enzymes and cells Porous bead for bioreactors Resin for chromatography Membrane material	
Agricultural	Seed coating preparation Activator of plant cells	Activator of plant cells
Others	Coagulant for wastewater treatment processing plants Removal of heavy metal from wastewater Cosmetics material	

1.5.6.7 Chitin in the pharmaceutical industry

Because chitin is a non-toxic material biodegradable material, it is attractive for use in a wide variety of applications.

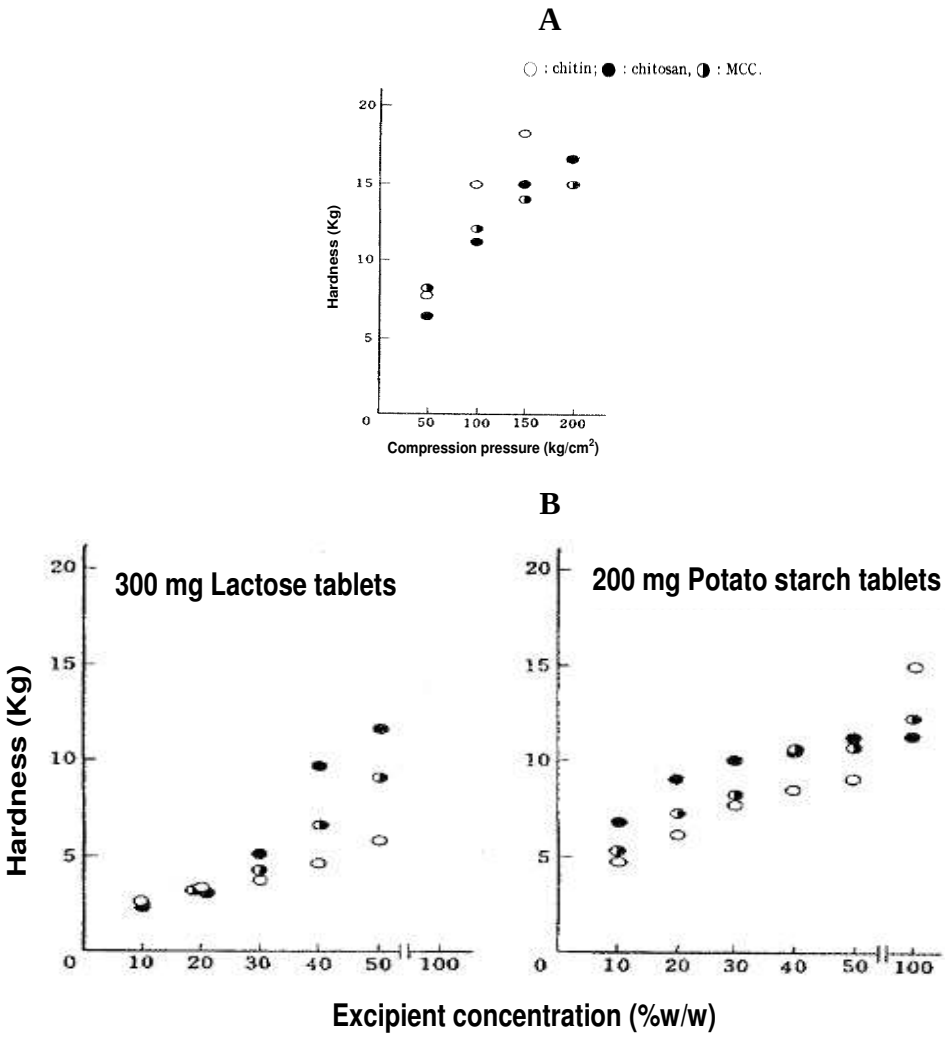
1.5.6.8 Chitin as a tablet/capsule disintegrant

Chitin is well known as a disintegrant in pharmaceutical solid dosage formulations in tablets to facilitate their break up or disintegration after oral administration. Chitin, as a disintegrant, can be used at the 2 – 20% (w/w) level.

1.5.6.9 Chitin as a tablet diluent and disintegrant

A study was undertaken of directly compressed tablet matrices containing chitin or chitosan in addition to lactose, microcrystalline cellulose (MCC) or starch formulation. Using lactose/chitin, lactose/chitosan, and lactose/MCC tablet hardness increases with the addition of chitin, chitosan and MCC as shown in Figure 1.12.A. Comparing the hardness of starch/MCC tablets with that of starch/chitin, there was no

statistical difference at 10 and 30% (w/w) addition. The hardness of the tablets containing chitin, chitosan and MCC is increased by increasing the compression force (Figure 1.12.B). This study also shows that the hardness of chitin tablets is greater than that of chitosan due to the structural rigidity of chitin, attributed to the acetylamino groups. Results suggest that chitin and chitosan can be used as direct compression diluents. Rapid disintegration time was obtained for tablets produced from lactose/chitin, lactose/chitosan, lactose/MCC, potato starch/chitosan and potato starch/ MCC below a certain concentration level of excipient (chitin, chitosan and MCC), as shown in Figure 1.12.C.



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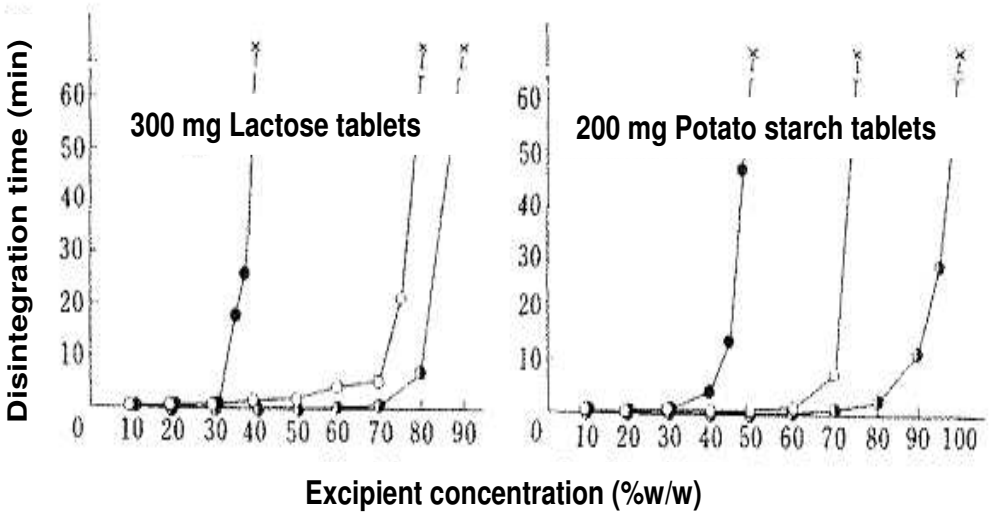

Figure 1.12 A) Relationship between tablet hardness and applied compression pressure, B) relationship between the tablet hardness and concentration of used excipient and C) relationship between tablet disintegration time and concentration of excipient (x: disintegration was not completed within 60 min) [39,40].

1.5.6.10 Directly compressed tablets containing chitin or chitosan in addition to mannitol

Mannitol is not a compressible material. The addition of chitin, chitosan and MCC improves the compressibility of mannitol. The measured hardness for the tablets composed of mannitol/chitin, mannitol/chitosan and mannitol/MCC increased with increase in the concentration of chitin, chitosan or MCC (Figure 1.13). Chitin, chitosan and MCC should be added at a level >20% w/w in order to improve the compressibility of mannitol tablets. The relationship between the disintegration time of tablets and the concentration of chitin chitosan or MCC excipients added to mannitol were investigated. Results showed that all tablets obtained disintegrate within 1 minute except for those containing 80% w/w chitosan [23].

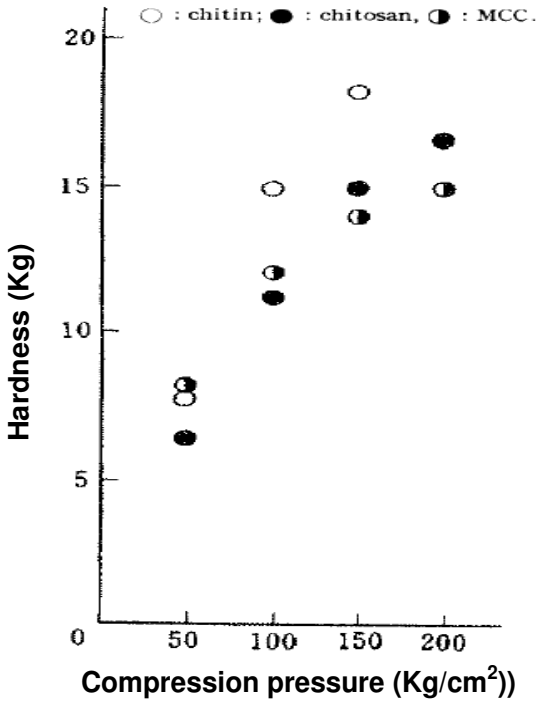

Figure 1.13 The relationship between the tablet hardness and excipient concentration [40].

The compactibility of chitin and chitosan were evaluated by investigating the relationship between applied compression pressure and obtained tablet crushing strength (Figure 1.14). Chitin and chitosan exhibited almost identical compression pressure-crushing strength profiles, being clearly more compressible than DBCP and PGS. MCC showed the highest tablet crushing strength values (highest slope of the curve). Table 1.21, shows the compression and friction properties (tensile strength, net work, compactibility and R-value) of the chitin and chitosan in comparison with the commercially available reference excipients at an applied compression pressure of 94 Mpa. The tensile strength and compactibility values for microcrystalline cellulose (MCC) were the highest among the others, while chitin and chitosan presented similar results of these parameters, and dibasic calcium phosphate (DBCP) the lowest values. The excipients exhibited the same order with the present parameters as was found with the compression profiles. MCC, chitin and chitosan presented the highest R-values. The magnitude of this effect conformed to the following descending rank order: MCC, chitosan, chitin, pregelatinized starch (PGS) and DBCP. Chitin and chitosan were found to be potential co-excipients for direct compression applications.

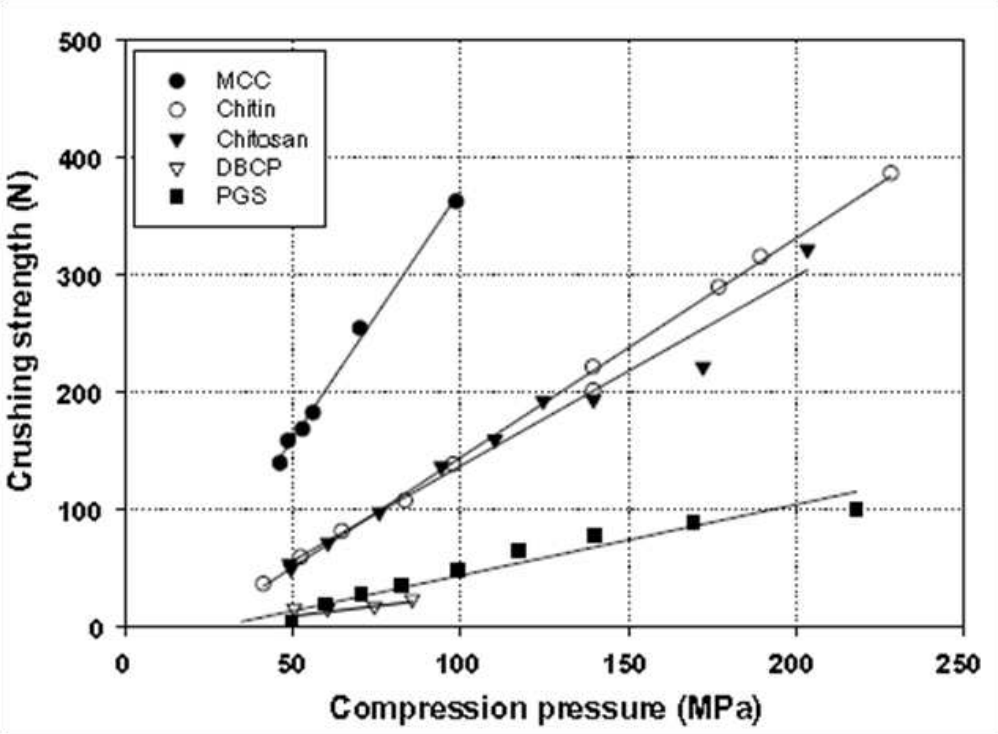

Figure 1.14 Effect of compression pressure on the crushing strength of chitin, chitosan and direct compressed reference tablets [41].

Table 1.21 Compression and compaction properties of chitin, chitosan and direct compression reference excipients [41].

Material	Tensile strength (Mpa)	R-value [1]	W_{net} (J)	Compactibility [2] (Mpa/J)
Chitin	64.91	0.919	4.31	15.06
Chitosan	60.19	0.921	3.74	16.10
MCC (Avicel PH 102®)	146.87	0.920	5.45	26.93
DBCP (Emcopress®)	8.96	0.679	2.62	3.41
PGS (Starch 1500)	18.16	0.726	3.18	5.72

[1] R-value is the lubrication coefficient.

[2] Compactibility is calculated from the ratio between tensile strength and network "W_{net}".

1.4.6.11 Co-processed tablet excipient composed of chitin and silicon dioxide

Chitin is a water-insoluble hydrophilic polymer that can absorb water and function as a disintegrant. Due to the unacceptable flow and compression properties of chitin, co-precipitation with silicon dioxide was used to provide a new excipient with excellent flow, compaction and disintegration properties when compared to the

individual components or commercially available direct compression fillers and disintegrants. The optimal composition of the co-processed excipient contains a silicon concentration of about 50 % w/w.

1.6 Synthetic Metal Silicates [8, 42]

Synthetic metal silicates are non toxic materials widely used in food and pharmaceutical industry. Synthetic metal silicates i.e. “brittle materials” are good candidates for preparing co-processed excipients when combined with chitin, a “plastic material”.

1.6.1 Synthetic Magnesium Silicate [43]

Magnesium silicate (silicic acid, magnesium salt) is a compound of magnesium oxide and silicon dioxide. Magnesium silicate occurs as an odourless and tasteless, fine, white coloured slightly hygroscopic powder that is free from grittiness. Magnesium silicate is used in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. Orally administered magnesium silicate is neutralized in the stomach to form magnesium chloride and silicon dioxide; some magnesium is absorbed. Magnesium silicate is listed in GRAS and accepted for use as a food additive in Europe. It is included in the FDA regulation part 182 “Substances generally recognized as safe” sub-part C as anti-caking agents. Also, in part 169 “Food dressings and flavourings” Subpart B – requirements for specific standardized food dressings and flavourings.

1.6.1.1 Structural formula and composition

Magnesium silicate is a compound of magnesium oxide and silicon dioxide; it is the magnesium salt of silicic acid containing an unspecified amount of water. Many natural silicate minerals are formed under aqueous conditions by reactions which are hypothesized to proceed via "protosilicate" intermediates, gels of hydrated oxides which, in the absence of structural information, have been described as $xMgO.ySiO_2.zH_2O$. The molecular formula may be expressed as $MgSiO_3.xH_2O$, Figure 1.15.

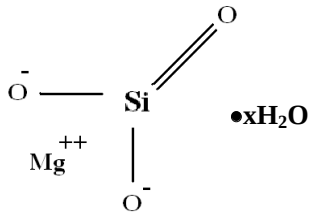

Figure 1.15 A schematic of the structure of magnesium silicate [44].

The USP/NF and JP state that the assay of magnesium silicate should be expressed as the percentages of magnesium oxide (MgO) and silicon dioxide (SiO_2). Table 1.22 shows the acceptance criteria for the content of magnesium silicate, as reported in the USP/NF and JP.

Table 1.22 Acceptance criteria of content of magnesium oxide and silicon dioxide in magnesium silicate [45, 46].

Component	**Content**	
	USP/NF	**JP**
MgO (%)	≥ 15.0*	≥ 20.0
SiO_2 (%)	≥ 67.0*	≥ 45.0
MgO (%)/SiO_2 (%)	2.50 – 4.50*	2.2 – 2.5

*Calculated on the basis of ignition.

1.6.1.2 Methods of preparation of synthetic magnesium silicate

I) Precipitation Method

The most common route for the synthesis of magnesium silicate is via the precipitation reaction between a soluble metal silicate (e.g. sodium orthosilicate, sodium metasilicate or potassium silicate) and a soluble magnesium salt (magnesium sulphate, nitrate, or chloride). The aqueous suspension of the precipitate is filtered and the collected solid washed and dried. The physical properties and magnesium oxide (MgO) content of the precipitated magnesium silicate depend on the type of magnesium salt, sequence of addition of magnesium salt and metal silicate, type and concentration of dispersion modifiers (e.g. non-ionic surfactants, NaOH), and experimental conditions. Regardless of the type of soluble metal silicates used, they are subject to the same molecular speciation in aqueous solution resulting in a mixture

of monomeric tetrahedral ions, oligomeric linear or cyclic silicate ions and polysilicate ions. Sodium metasilicate, an example of a soluble metal silicate, can be prepared in anhydrous form, or with water of crystallisation as the penta- or nonahydrate. It is readily soluble in water.

The dissolution process of sodium silicate consists of its hydration with the formation of NaOH. Sodium orthosilicate hydrolyzes according to equation 1:

$$Na_4SiO_4 + H_2O \rightarrow 2NaOH + Na_2SiO_3 \quad (1)$$

The hydrolytic dissociation is particularly strong with sodium metasilicate (equations 2 and 3):

$$2Na_2SiO_3 + H_2O \rightarrow Na_2Si_2O_5 + 2NaOH \quad (2)$$

$$Na_2SiO_3 + H_2O \rightarrow NaHSiO_3 + NaOH \quad (3)$$

Sodium silicate reacts with ions in solution (e.g. magnesium) forming nearly insoluble magnesium silicates. The effectiveness of sodium silicate on precipitation of Mg^{2+} ions when a bulk solution with magnesium chloride added to deionized water is shown in Figure 1.16. It can be seen that the ion concentration of Mg^{2+} decreases rapidly with the addition of sodium silicate.

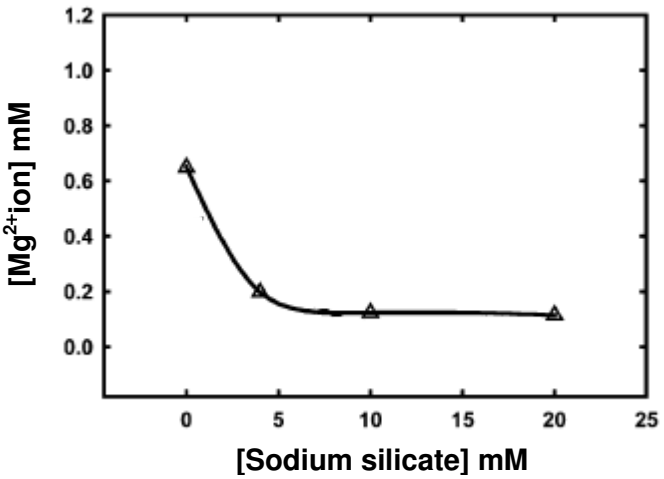

Figure 1.16 Concentration of Mg^{2+} ions, in deionized water, as a function of sodium silicate concentration (pH 8.5) [47].

II) Hydrothermal Precipitation Method

A hydrothermal solution is a multi-component system containing compounds of Na,

K, Si, Ca, Mg, Al, Fe, Cl, S, O, C, B, Li, As, Cu, Zn, Ag, Au, and other elements in ionic and molecular forms; Si is usually present at high concentrations. Silica, together with other compounds, passes into this hydrothermal solution due to the chemical interaction of water with aluminosilicate minerals of rocks of hydrothermal fields at a depth in regions of thermal anomalies at high temperatures and pressures. At temperatures of 250–300°C, silicon occurs in solution predominantly in the form of individual molecules of silicic acid, H_4SiO_4. As a consequence, such an aqueous solution becomes supersaturated with respect to solutions of amorphous silica in pure water. When metal cations (e.g. Ca^{2+}, Mg^{2+} and Co^{2+}) are introduced into the solution, some of these ions are sorbed by the surface of colloidal particles resulting in neutralization of the negative surface charge. Bridging bonds, with the participation of coagulating ions, are formed between the surfaces of particles which results in coagulation and precipitation of colloidal silica. The material precipitated by metal ions has an amorphous structure of metal silicate. After high-temperature calcination at 900^{o}C, the amorphous samples prepared upon addition of magnesium sulfate or cobalt sulfate (with simultaneous alkalization to pH 12.4) have a crystalline structure of forsterite (Mg_2SiO_4) or cobalt silicate (Co_2SiO_4), respectively.

III) Mechano-chemical Dehydration Method

An amorphous phase can be formed as a result of the reaction of amorphous SiO_2 with magnesium hydroxide. The solid-state reaction between $Mg(OH)_2$ and SiO_2 begins at the contact points between these dissimilar particles. Mechano-chemical dehydration and amorphization of $Mg(OH)_2$ are substantially enhanced by grinding with SiO_2. In the mixture, enhanced mechano-chemical dehydration of $Mg(OH)_2$ is explained by assuming the following complex processes take place: intimate mixing, agglutination at the contact points of dissimilar particles promoted by the higher affinity of silica over magnesia towards hydroxyl groups and initiation of simultaneous solid-state reactions. Since magnesium hydroxide is a strong base and silicic acid is a weak acid, acid-base neutralization ensues. A possible reaction mechanism involves the release of excess water from the silicic acid which makes the surface of the magnesium hydroxide more alkaline. This leads to the dissolution of silica at the contact points, resulting in precipitation of amorphous magnesium

silicate. Thus the reaction between the two ingredients and dehydration results in a precursor of magnesium silicate in an amorphous state.

1.6.1.3 Solubility characteristics

Magnesium silicate is practically insoluble in ethanol (95%), ether and water. It is readily decomposed by mineral acids.

Table 1.23 shows the total amount of Mg and Si (mg/50 mL) dissolved in various aqueous solutions (H_2O, HNO_3, HCl, H_3PO_4, and NaOH), which reflects the solubility of magnesium silicate in these solvents. The experiment was performed by the addition of about 0.5 g of magnesium silicate to 50 mL of solution at room temperature (25°C) followed by incubation for 24 hours with intermittent shaking. The total amount of Mg and Si was measured using an ICP_{seq}-7500 spectrometer.

Table 1.23 The total amount of Mg and Si dissolved (mg/50 mL) in various solutions at 25°C [48].

Solvent	**H_2O**	**HNO_3**			**HCl**			**H_3PO_4**	**NaOH**
Conc. (M)	-	0.1	1.0	3.0	0.1	1.0	3.0	0.1	1.0
Conc. of Mg and Si dissolved in (mg/50 mL)	0.0	5.0	12.0	20	4.0	10.0	16.0	0.0	0.0

Magnesium silicate displays low solubility in acids of up to 3 M concentration; above this concentration it partially dissolves. It is dissociated in acids forming magnesium ions and silicic acid in what is referred to as “acid leaching” of silicates (equation 4):

$$MgSiO_3 + H^+ \rightarrow HSiO_3^- + Mg^{2+} \quad (4)$$

Figure 1.17 shows the conditional solubility product of magnesium silicate as a function of pH (at an initial ion concentration of 1 mM). The region above the curve represents a system of higher concentration product where bulk magnesium silicate precipitation is anticipated. The higher the solution pH is the lower the conditional solubility product, and the higher the propensity for magnesium to be precipitated.

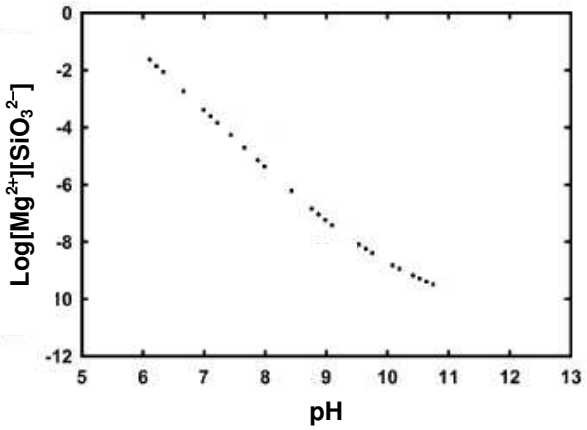

Figure 1.17 Conditional solubility product of magnesium silicate (initial ion concentration of 1 mM) as a function of pH [48].

Solubility-pH diagrams for Mg^{2+}-SiO_3^{2-} can be constructed to show the relationship between Mg^{2+} precipitation and solution pH. For a given solution system, if the magnesium ion concentration is above the solubility product limit, the formation of magnesium silicate is anticipated, and is governed by equation 5:

$$MgSiO_{3(s)} \rightarrow Mg^{2+}_{(aq)} + SiO_3^{2-}{}_{(aq)} \quad K_{sp} = 4\times10^{-12} \quad (5)$$

where K_{sp} is the corresponding solubility product constant, which defines the solubility limit.

According to the USP/NF, the pH of magnesium silicate (10% aqueous dispersion) is 7.0–10.8. The pH of magnesium silicate is controlled by the degree to which magnesium is released from the surface when it comes into contact with water. The basicity of magnesium silicate is mainly attributed to the magnesium oxide present.

1.6.1.4 Surface active sites (adsorption and absorption)

The surface of magnesium silicate is composed of free hydroxyl groups (silanol groups); the most reactive groups on the surface. They provide the sites for the physical adsorption of organic particles and can easily react, chemically, with multiple substituents. Being substituted with new atom groups, they provide potential for surface modification. The surface composition of magnesium silicate is illustrated in Figure 1.18.

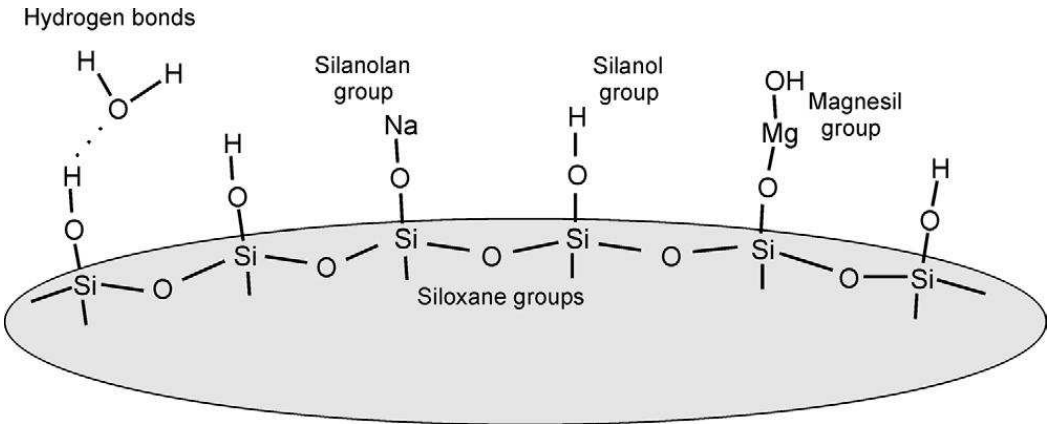

Figure 1.18 Schematic of the functional groups on the surface of magnesium silicate [48].

The concentration of active acidic and basic sites of synthetic magnesium silicate (Magnesol XL) is an important physicochemical characteristic which determines its impact on adsorption performance.

1.6.1.5 Specific surface area, pore volume, and pore size

The specific surface area, pore volume, and pore size (ASAP 2010, Micromeritics Instruments, USA), of synthetic magnesium silicate resulting from the precipitation reaction of sodium metasilicate and a magnesium salt are dictated by the type of metal salt, the non-ionic surfactant introduced, and the type of silane pro-adhesive compounds used in the course of precipitation. Generally, the precipitated magnesium silicate manifests a relatively high BET specific surface area. The highest values of specific surface area occur with magnesium silicate produced from magnesium sulphate and magnesium nitrate (Table 1.24). The lowest value is obtained from magnesium chloride in the presence of Rokanol K3. The situation is analogous to when the surface is modified using a silane coupling agent. As is the case for non-ionic surfactants, the presence of silane decreases the specific surface area. Pore volume and pore diameter are not affected by the presence of both reagents. The type and amount of silane exerts no significant effect on the specific surface area, pore volume or mean pore diameter of precipitated magnesium silicate (Table 1.25).

Table 1.24 Physicochemical properties of unmodified and modified magnesium silicates [49].

Precipitating agent	Amount of non-ionic surfactant	Modifying agent	Amount of modifying agent (wt./wt.)	Specific surface area BET (m^2/g)	Pore volume (cm^3/g)	Average pore diameter (nm)
$MgCl_2$	-	-	-	411	0.80	5.5
	5 wt/wt % of Rokanol K3	-	-	197	0.67	6.3
	5 wt/wt % of Rokanol K7	-	-	356	0.61	7.9
$Mg(NO_3)_2$	-	-	-	474	0.83	5.5
	5 wt/wt % of Rokanol K3	-	-	347	0.87	6.2
	5 wt/wt % of Rokanol K7	-	-	470	0.98	7.3
$MgSO_4$	-	-	-	408	0.73	5.5
	5 wt/wt % of Rokanol K3	-	-	433	0.85	5.6
	5 wt/wt% of Rokanol K7	-	-	453	0.79	5.2
$MgSO_4$	-	U-15 silane	3	401	0.68	5.2
	-		5	384	0.67	5.2
	-		10	332	0.63	5.2
$MgSO_4$	-	U-15 silane	3	384	0.64	4.8
	5 wt/wt % of Rokanol K3		5	376	0.64	4.9
	5 wt/wt % of Rokanol K3		10	364	0.67	4.8

Rokanol K3 and K7 are non-ionic surfactants (oxyethylenated unsaturated fatty alcohols, of the general formula $RO(CH_2CH_2O)nH$ $R=C_{16\text{-}22}$, where $n_{av}=3$ or $n_{av}=7$, respectively). U-15 is silane pro-adhesive compound (N-2-aminoethyl-3-aminopropyltrimethoxysilane).

Table 1.25 Physicochemical properties of unmodified magnesium silicate and magnesium silicate modified with silane coupling agents [50].

Modifying agent	Amount of modifying agent (w/w)	Specific surface area BET (m^2)	Pore volume (cm^3/g)	Mean pore diameter (nm)
--	-	515	0.80	5.3
3-Isocynatepropyltrimethoxysilane	3	536	0.84	5.4
	5	511	0.76	5.0
	10	503	0.76	5.0
3-Thiocyanatepropyltrimethoxysilane	3	506	0.79	5.2
	5	539	0.83	5.4
	10	528	0.81	5.4
N-Phenyl-3-isocynatepropyltrimethoxysilane	3	519	0.85	5.6
	5	496	0.80	5.6
	10	486	0.77	3.4

1.6.1.6 Particle morphology

A scanning electron microscope (SEM) image of magnesium silicate prepared from solutions of magnesium sulphate and sodium meta-silicate is shown in Figure 1.19. The SEM image shows the presence of large primary agglomerates and numerous secondary agglomerates. In addition, numerous primary particles of small diameter

are observed. Primary particles exhibit a smooth surface and no sharp edges are observed. On the other hand, primary agglomerates of small diameter exhibit a tendency to acquire/exhibit spherical shapes.

Figure 1.19 SEM photograph of magnesium silicate [51].

1.6.2 Preparation of Synthetic Calcium Silicate/ Synthetic Aluminium Sodium Silicate *(Precipitation Method)*

Synthetic calcium silicates, aluminum silicates and magnesium silicates can be prepared from the reaction of the aqueous solution of sodium metasilicate with the corresponding water soluble metal salt (e.g., chloride, sulphate, etc.). This reaction produce varying contents of sodium oxide, aluminium oxide and silicon dioxide.The preparation procedure is shown in Figure 1.20. The content ranges of the oxides after ignition are described in Tables, 1.22 & 1.26.

Table 1.26 Composition of synthetic calcium silicate and synthetic aluminum sodium silicate **[43, 52].**

Parameter	Wt %	
	Aluminium sodium silicate	Calcium Silicate
SiO_2	42 – 85	50 – 95
Na_2O	0.2 – 22	<4.0
Al_2O_3	0.2 – 36	--
CaO	--	1 – 35
Sulphates	< 1	n.a.
Fe_2O_3	< 0.1	< 0.1
Trace oxides	< 0.1	< 0.1

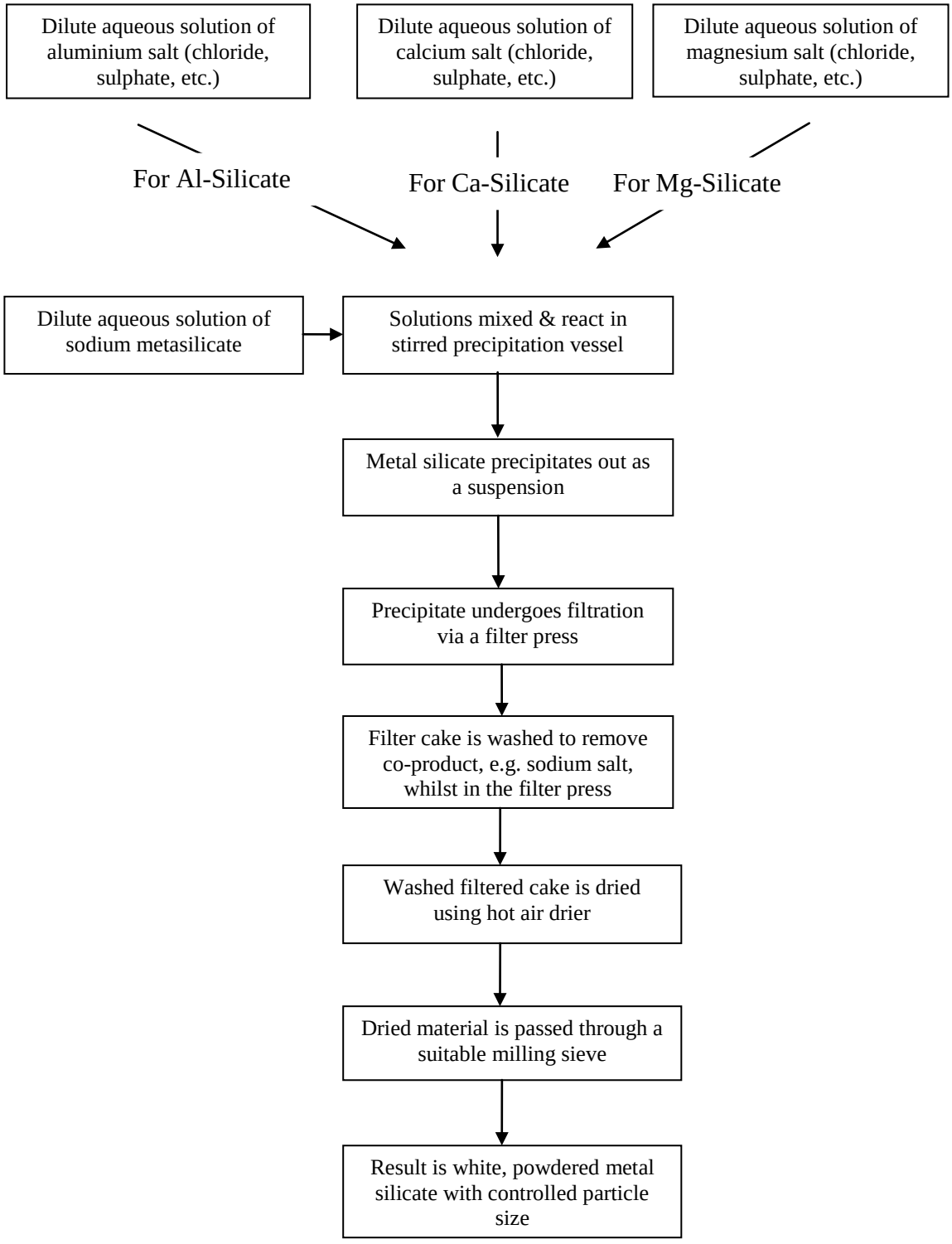

Figure 1.20 Preparation procedures for synthetic amorphous metal silicates (wet method) [52].

1.6.3 Stability and Incompatibilities

In general, metal silicates are classified as stable compounds (Table 1.27). Magnesium silicate exposed to temperatures of 750^{o}C transforms from amorphous form to the magnesium silicate minerals enstatite ($MgSiO_3$) and forsterite (Mg_2SiO_4). When the temperature reaches 1100^{o}C and above, others polymorphs (protoenstatite and clinoenstatite) are formed. Magnesium silicate in its solid state should be stored in a well-closed container in a cool, dry place. When magnesium silicate is stored in double-distilled, deionised water for 6 months at 85^{o}C, it maintains its amorphous structure with some improvement in the order and maintains its chemical entity. Magnesium silicate is readily decomposed by mineral acids. Magnesium silicate may decrease the oral bioavailability of drugs such as mebeverine hydrochloride, sucralfate, and tetracycline, via chelation or binding, when they are taken together. The dissolution rate of folic acid, erythromycin stearate, paracetamol, and chloroquine phosphate, may be retarded by adsorption onto magnesium silicate. Antimicrobial preservatives, such as parabens, may be inactivated by the addition of magnesium silicate

1.6.4 Biodegradability and Toxicity

Orally administered magnesium silicate is neutralized in the stomach to form magnesium chloride and silicon dioxide; some magnesium is absorbed. Caution should be used when greater than 50 meq of magnesium is given daily to patients with impaired renal function, owing to the risk of hypermagnesemia. Reported adverse effects include the formation of bladder and renal calculi following the regular use, for many years, of magnesium silicate as an antacid. It is not explosive, flammable, or combustible. It is a mild irritant to eyes, skin, and respiratory passages. It is not classified as dangerous under EU Directive 67/548/EEC. In the EEC, magnesium silicate is a permitted food additive according to directive 95/2/EC (E 553a). The essential physical and chemical properties in addition to toxicological profiles of magnesium silicate, calcium silicate, and aluminium sodium silicate are summarized in Table 1.27.

Table 1.27 Physicochemical properties and toxicological profile of magnesium silicate, calcium silicate, and aluminium sodium silicate [43, 52].

Test	Synthetic magnesium silicate	Synthetic aluminum sodium silicate	Synthetic calcium silicate
PHYSICO-CHEMICAL PROPERTIES			
CAS Number	1343-88-0	1344-00-9	1344-95-2
Chemical structure	$MgO.SiO_2.nH2O$	$Na_2O.SiO_2.nH2O$/ $Al_2O_3.SiO_2.nH2O$	$CaO.SiO_2.nH2O$
Form	Solid powder		
Melting Point [°C]	Approx. 1910 (m)	Approx. 1700	
Partition Coefficient (log P_{ow})	Not relevant (inorganic , non-lipophilic substance)		
Water Solubility (Saturation) [mg/l] (m)*	Insoluble in cold and hot water	Approx. 68 – 79 at 20 °C, pH ~9 (Sum of soluble SiO_2, Na and Al ions)	Approx. 260 at 20 °C, pH ~9.7 (Sum of soluble SiO_2, Na and Ca ions)
pH (m)*	7– 10.8	5 – 11	7 – 11
ENVIRONMENTAL FATE and PATHWAY			
Photo-degradation	Stable in water and air		
Stability in Water	Stable: ion exchange processes possible		
Stability in Soil	Stable: silicates = soil components; ion exchange processes possible		
Biodegradation	Not applicable, inorganic substance		
Bioaccumulation	Not bio-accumulating due to inherent substance properties		
ECOTOXICOLOGY			
Acute/Prolonged Toxicity to Fish	Not a known pollutant	96h LL_0=10000 mg/l (limit test)	No data: analogy
Acute Toxicity to Aquatic Invertebrates	Not a known pollutant	No data: analogy	
Toxicity to Aquatic Plants, e.g. Algae	Not a known pollutant	72h NOEL= 10000 mg/l	No data: analogy
TOXICOLOGY			
Acute Oral Toxicity	On rabbit: LD_{50} >10000 mg/kg	LD_{50} >5000 mg/kg	
Acute Inhalation Toxicity	Slightly hazardous	No data: analogy	
Acute Dermal Toxicity	On albino rabbit: LD_{50} >10000 mg/kg	LD_{50} >5000 mg/kg (limit test)	No data: analogy
Primary Irritation (skin, eye)	On rabbit: primary irritation index 0.80, no erythema (skin redness)	Not irritating	No data: analogy
Sensitization	No data		
Repeated Dose Toxicity (inhalation)	Causes damage to lungs	No data: analogy	
Repeated Dose Toxicity (oral)	No substance-related abnormalities in rat: NOAEL(6 months) = ~9000 mg/ kgbw	Chronic: no data: analogy no gross signs of toxicity in rat and mouse, no death: NOAEL (14 d) >5000 mg/kgbw	No gross signs of toxicity in rat, no death NOAEL (2 years) = approx. 5000 mg/kgbw

Table 1.27 (continued)

Test		Synthetic magnesium silicate	Synthetic aluminum sodium silicate	Synthetic calcium silicate
Genetic Toxicity in Vitro				
A.	Bacterial Test (Gene mutation)	Not mutagenic	No data: analogy	Not mutagenic
B.	Non-Bacterial In-Vitro Test (Gene Mutation)	Not mutagenic	No data: analogy	No data: analogy
C.	Non-Bacterial In-Vitro Test (Chromosomal Aberration)	Not mutagenic	No data: analogy	Not mutagenic
Genetic Toxicity in-Vivo		Not mutagenic	No data: analogy	Not mutagenic
Carcinogenicity (inhalation)		Inconclusive	No data	
Carcinogenicity (oral)		Not carcinogenic in rat and mouse	No data: analogy	Not carcinogenic in rat
Carcinogenicity (intrapleural)		No data: analogy	Not carcinogenic in rat	No data: analogy
Toxicity to Fertility		No effects in limited study in rat	No data: analogy	
Developmental / Teratogenicity		No adverse effects in rat, mouse, rabbit and hamster	No adverse effects in rat, mouse, rabbit and hamster	No adverse effects in rat, mouse, and hamster
Photo-degradation		Stable in water and air		
Stability in Water		Stable: ion exchange processes possible		
Stability in Soil		Stable: silicates = soil components; ion exchange processes possible		
Biodegradation		Not applicable, inorganic substance		
Bioaccumulation		Not bio-accumulating due to inherent substance properties		

1.6.4 Applications

Due to their inert nature and non-toxic properties, metal silicates are widely used in different applications including cosmetics, pharmaceuticals, foods, chromatography, rubber, paints, paper and plastic industries (Table 1.28).

Table 1.28 Applications of metal silicates in various industries [43, 52].

Industry	Function
Pharmaceutical	Synthetic magnesium silicate is used in oral pharmaceutical formulations and food products as a glidant and an anti-caking agent while calcium silicate is widely use as filler and disintegration promoter in tablet formulation [53]. Other uses of metal silicates can be summarized as follows. • Magnesium silicate and aluminium silicate are used in anti-acid, anti-ulcer and anti-obesity preparations. • Magnesium silicate is used as a component of anti-epileptic drugs, in the treatment of alimentary intoxication, indigestion and in the inflammatory conditions of the small intestine. • In topical preparations, magnesium silicate is used as anti-fungal agent. • Magnesium sodium silicates are used in cosmetics especially in toothpastes, gels, facial creams, body washes, cosmetic creams, sunscreens, shampoo, and blush. • Magnesium sodium silicate is also used in treatment of acne and function as facial moisturizer. • Arginine silicate (The reaction product of arginine and magnesium silicate) is highly soluble in water and can be used as source of the essential amino acid arginine and as a source of silicate, both of which exert anti-atherosclerotic effects and also promotes bone and cartilage formation in mammal.
Food	Metal silicates function as a carrier for fragrances or flavors. They are also used in beer and wine clarification. In animal feed, synthetic amorphous silica and silicates serve as carriers and anti-caking agents in vitamins and mineral premixes. Synthetic magnesium silicate and calcium silicate are used as bleaching agent in animal and vegetable oils production. It is also used in the production of confectionery as an anti-adhesive and anti-caking agent (molding powder or a component of anti-glitter paste). As far as whiteness is concerned, the white color of magnesium silicate may easily compete with titanate based pigments, which eliminates partially or totally the use of titanium dioxide.

Table 1.28 (continued)

Industry	Function
Rubber and Silicones	Magnesium silicate, calcium silicate and aluminum silicate are used as reinforcing fillers for many non-staining and colored rubber and silicones products.
Paints	Magnesium silicate and aluminum silicate can be used as filler and pigment in dispersive paints.
Chromatography	Magnesium silicate is used as an adsorbent in affinity chromatography.
Paper	Magnesium silicate and aluminium silicate are used as filler in paper manufacturing to improve printability and opacity that result in glossy paper used in most magazines.
Insecticide, micro biocide & fungicide	Magnesium silicate has been used against juvenile and adult store product pests, predominantly exerting their lethal activity on juvenile and adult forms by sorption of the cuticular lipid layer, thus causing dehydration of the insects.
Cements	Cement is made by forming a calcium silicate product from limestone and clay minerals in a kiln which requires very hot temperatures, releasing high levels of CO_2 as it burns. Most low carbon cements on the market are based on magnesium silicate, which takes less energy to heat.
Other uses	• Sodium silicate together with magnesium silicate is used in muffler repair and fitting paste. When dissolved in water, both sodium silicate, and magnesium silicate form a thick paste that is easy to apply. When the exhaust system of an internal combustion engine heats up to its operating temperature, the heat drives out all of the excess water from the paste. The silicate compounds that are left over have glass like properties, making a temporary brittle repair. • Highly dispersed magnesium silicates can be used as polymer fillers or active adsorbents. • Magnesium silicate is an amphoteric compound with a huge specific area capable of absorbing either acid or alkali metal catalyst. It is an efficient refining and purifying agent in the production of polyols for its excellent depicking, deodorizing, potassium ion absorbing effects and function as filter medium. In addition it is used as an adsorbent to regenerate frying oils and purify biodiesel. • Magnesium silicate, aluminium silicate and calcium silicate are used as filler and pigment extender in fingernail lacquers and in plastic industries.

1.7 Sugar Alcohols

Sugar alcohols are brittle materials having unique physicochemical properties. They are ideal candidates for the co-processing with chitin to produce an excipient with improved physical properties. Sugar alcohols are carbohydrates which are also called "polyols". Part of their chemical structure resembles sugar, and part of it resembles alcohol hence the name is sugar alcohol. Examples of common sugar alcohols are mannitol, maltitol, sorbitol, isomalt, and xylitol. They occur naturally in plants (sorbitol is extracted from corn syrup and mannitol from seaweed), but they are mostly manufactured from sugars and starches. Sugar alcohols are not completely absorbed by the body like sugars. Because of this, the blood sugar impact of sugar alcohols is less and they provide fewer calories per gram [54, 55].

Table 1.29 Comparison of the properties of sugar and sugar alcohols.

Ingredient	Sweetness (relative to sucrose) %	Glycemic Index (GI)	Cal/g	Derived from
Sucrose (sugar)	100	60	4	Plant sources (sugar beets, sugar cane,..)
Hydrogenated Starch Hydrolysate	33	39	2.8	Partial hydrolysis of starch
Maltitol	75	36	2.7	High maltose corn syrup
Xylitol	100	13	2.5	D-xylose
Isomalt	55	9	2.1	Sucrose
Sorbitol	60	9	2.5	Glucose
Lactitol	35	6	2	Lactose
Mannitol	60	0	1.5	Fructose
Erythritol	70	0	0.2	Glucose

Additionally, sugar alcohols don't induce tooth decay as sugars do, so are often used to sweeten chewing gum. Sugar alcohols have fewer calories than sugar, and most of them are less sweet than sugar except for xylitol which have the same sweetening factor [54]. The glycemic index is an indicator of how a food is likely to affect blood sugar (Table 1.29).

1.7.1 Mannitol: sugar alcohol with added functionality

Mannitol is a naturally occurring six-carbon sugar alcohol or polyol (Figure 1.21) [56]. It is the most abundant polyol in nature occurring in bacteria, yeasts, fungi, algae, lichens and several plants like pumpkins, celery, onions, grasses, olives and mistletoe. Mannitol **(**$C_6H_{14}O_6$**)** is widely used in pharmaceutical formulations and food products [57]. In pharmaceutical preparations it is primarily used as a diluent in tablet

formulations, where it is water soluble, non-hygroscopic (Can be used with moisture-sensitive active ingredients) and produces a sweet, smooth, cool taste and it can be advantageously combined with other direct compression excipients.

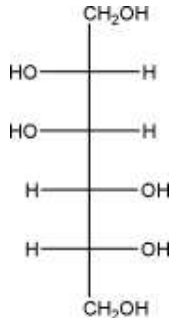

Figure 1.21 Chemical structure of mannitol [56].

In ODT formulation, the direct compression grade of mannitol is prefered to obtain a fast disintegrating hard tablets withstand processing and transportation. Specially treated directly compressible, spray-dried, or granulated mannitol excipients have been designed to meet these needs. Figure 1.22, shows the scanning electron microscopic images of granular, powder and spray dried mannitol.

Processing of treated mannitol (Figures 1.22.a and 1.22c) produced under defined manufacturing conditions give them a highly porous and friable external particle structure. Upon compression, the particles break into finer particles, which fill the interstitial spaces between larger porous particles which give harder ODTs using direct compression at low pressure.

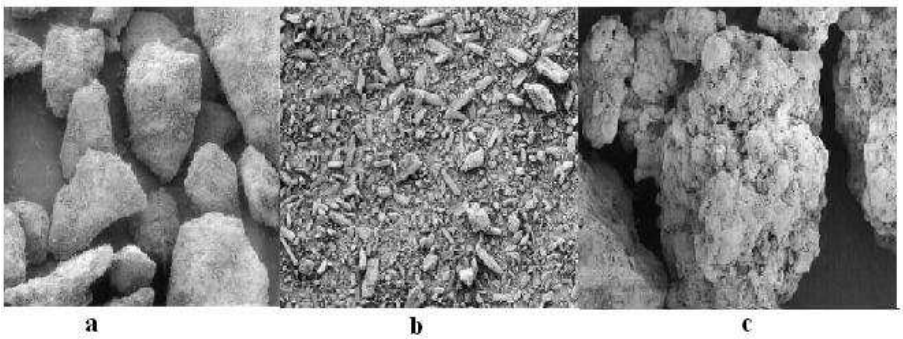

Figure 1.22 SEM images of a) granular mannitol, b) mannitol powder and c) spray-dried mannitol [56].

Untreated crystalline mannitol has some limitations including the poor aqueous solubility, bad flowability and the high friability of tablets obtained. Figure 1.23, shows the water solubility of mannitol in comparison with other excipients.

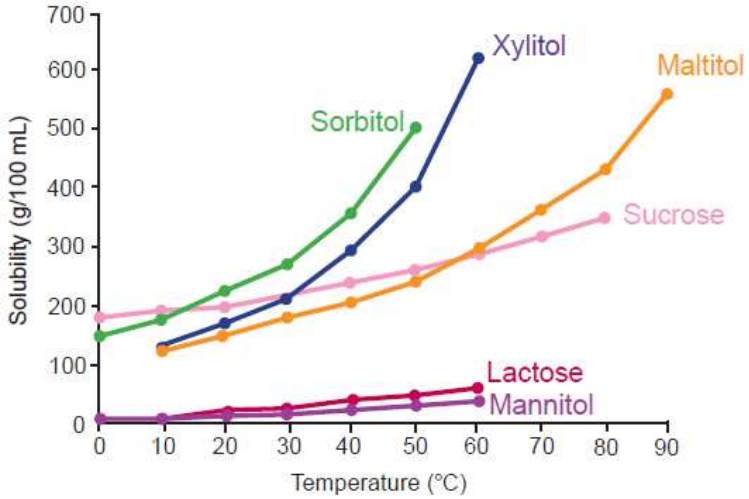

Figure 1.23 The aqueous solubility of mannitol versus other excipients [58].

Figures 1.24, 1.25 and 1.26 show the physical properties of different types and grades of mannitol.

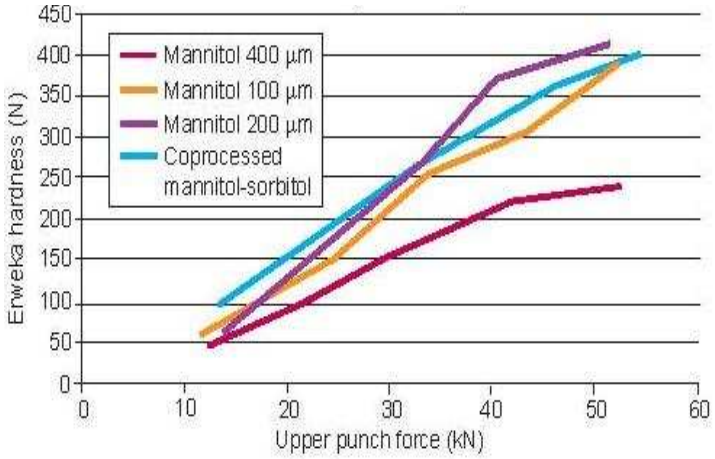

Figure 1.24 Tablet compression profiles of different grades of mannitol [58].

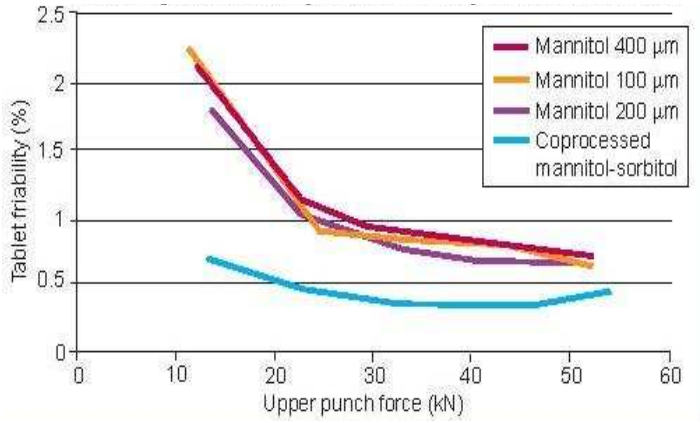

Figure 1.25 Friability versus compression profile for different grades of mannitol [58].

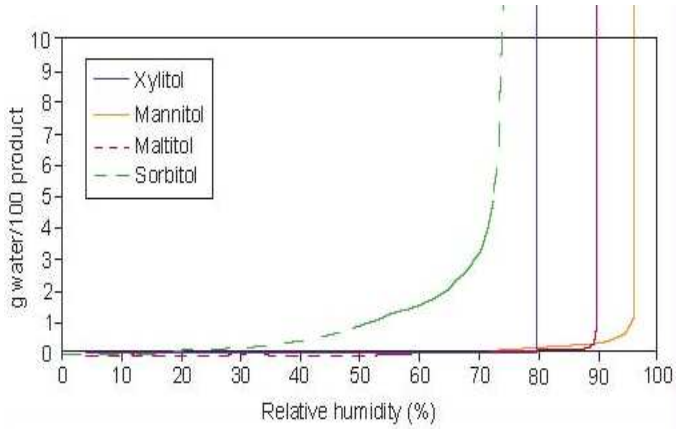

Figure 1.26 Moisture sorption profiles of different sugar alcohols at 20°C [58].

One major limitation of most currently marketed ODTs is their requirement for special and expensive packaging to protect them during transportation and handling. Furthermore, the consumer must follow specific instructions to remove fragile tablets from specialized blister packs to ensure added protection and to retain the quick dispersibility of the tablets even after exposure to unfavorable humidity and temperature conditions. These challenges could be addressed by [58]:

- Using binders with the mannitol powder may increase the disintegration time of the ODT and accordingly disintegrant(s) should be added to reduce the disintegration time.
- Co-processing of mannitol with other excipients or material is a way to create an excipient that exhibits a flowability and compressibility. Additionaly, the slow disintegration properties of mannitol can be significantly improved by the right selection of the co-processing candidate.

1.7.1.1 Toxicology

Mannitol is GRAS listed material. The use of mannitol in food is permitted by FDA food additive regulations (21 CFR 180.25). The Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) has reviewed the safety data and concluded the safety of mannitol. JECFA has allocated an acceptable dietary intake of 0-50mg/kg. Mannitol has monographs in the United States Pharmacopoeia/National Formulary (USP/NF), as well as the various pharmacopoeias around the world. In addition, mannitol is included in the Food Chemical Codex (FCC) [56, 59].

1.8 Project: Hypothesis, Aims and Work Plan

1.8.1 Hypothesis

In powder form, chitin is a highly compressible material due to the presence of pores on the surface and it is a well known disintegrant for tablet formulation [42]. However, chitin is not compactible. It would be beneficial, therefore, to form inclusion complexes of guest material inside the chitin pores to improve its compactibility without affecting its disintegration properties.

1.8.2 Aims

Improvements in the compaction properties of chitin by co-processing with a guest material could be verified as follows:

- co-processing of chitin with metal silicates, by incorporating the metal silicate inside the chitin pores, could produce a multi-functional super-disintegrant (excipient that can achieve fast disintegration while preserving the binding properties of the tablets).

- by examining the effect of lubricant on powder compaction of co-processed chitin-metal silicate excipients.

- co-processing of chitin with mannitol (as an example of a compound representing a non-hygroscopic inert excipient) could result in a universal multi-functional excipient that could be used with metal-incompatible active pharmaceutical ingredients.

1.8.3 Work Plan

(I) To study the physicochemical properties, performance and applications of the co-precipitates of chitin and metal silicates prepared according to European patent (EP1997480) invented by the Jordanian Pharmaceutical Manufacturing CoLtd (Chapters 2&3). This work covers the following aspects.

- Preparation of a solid in solid dispersion of metal silicate within the chitin pores. The procedure followed was that in European Patent (EP1997480), by dispersing the chitin polymer and an appropriate quantity of monovalent

silicate in sufficient quantity of water or a mixture of water and solvent(s). Precipitation of the mineral silicate within the structure of the polymer can be achieved by the addition of a divalent or trivalent chloride solution to form a solid in solid dispersion of mineral silicate within the chitin high surface pores. The divalent or trivalent chloride solution can be magnesium chloride, calcium chloride, aluminum chloride, etc.

- Preparation of different grades of the silicate-chitin material (different salts) with respect to the particle size and physical properties. In addition to study the effect of these properties on the performance of this material.
- Characterization and identification of the obtained chitin silicates (different salts) using different analytical techniques such as scanning electron microscopy, x-ray powder diffraction, powder flow analysis, FTIR spectroscopy, NMR, etc.
- Investigate the prepared co-precipitated excipient properties including the compactibility, flowability and density.
- Testing the physical properties of the tablet formulations containing the co-precipitated excipient such as compressibility, granules flowability and disintegration properties will be evaluated in comparison with reference formulations containing commercially available super-disintegrants such as sodium starch glycolate, pregelatinized starch, PVP-XL and croscarmelose sodium.
- Designing tablet formulations containing the co-precipitated chitin-metal silicate excipient using different techniques including, direct compression, wet and dry granulation. The co-processed excipient functionality, compatibility with APIs and compression profiles of the tablets produced will be evaluated.
- Determination of the recommended working range(s) of the silicate-chitin material, which can be used in solid state pharmaceutical formulations in order to attain the optimal function as a super-disintegrant and pharmaceutical aid in tablet formulation.
- Investigate the effect of lubricant on the overall physical properties of the co-precipitated chitin-metal silicate excipient.

(II) To study the physicochemical properties, performance and applications of the co-processed excipients consisting of chitin and mannitol prepared according to the European patent (EP2384742) invented by the Jordanian Pharmaceutical Manufacturing CoLtd (Chapters 3 & 4) This work covers the following aspects.

- Preparation of a co-processed excipient consisting of chitin and mannitol by following the procedure as in the European Patent (EP2384742). Two types of excipients were prepared according the formentioned patent including: i) a multifunctional immediate release tablet base (Chapter 4) and ii) an ODT multifunctional base (works as disintegrant, binder, filler) (Chapter 5).
- Optimizing the ratio of chitin and mannitol within the co-processed excipient and selecting the proper processing technique to be used.
- Characterization and identification of the prepared co-processed excipients using different analytical techniques such as scanning electron microscopy, x-ray powder diffraction, powder flow analysis, FTIR spectroscopy, NMR, etc..
- Characterization of the obtained excipients regarding the physical properties including flowability, compressibility, functionality, disintegration and wetting properties.
- Evaluation of the tablets prepared from the co-processed chitin-mannitol excipients.
- Studying the applications of the obtained co-processed excipients in tablet formulation containing different APIs.

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CHAPTER TWO

2. CHARACTERIZATION OF CHITIN–METAL SILICATES AS BINDING SUPER-DISINTEGRANTS

2.1 Introduction

There is increasing interest in exploring new commercial uses for chitin, a polymer which is normally regarded merely as a waste product from, for example, the sea food industries. This is due to the fact that, next to cellulose, chitin is the most abundant polysaccharide on earth [1]. In relation to the pharmaceutical industry; chitin has been reported to play different roles in tablet formulations, for example, as an excipient for direct compression and as a disintegrant [2, 3]. However, for many pharmaceutical formulations there is a need to improve compression properties in order to make them acceptable to the formulator [4, 5]. Recently, chitin was modified by precipitation of silicon dioxide on its surface [6]. The foregoing concept was based upon the high water absorption capacity and surface modification properties of silicon dioxide when co-processed with polymers [7, 8]. Co-precipitation of silicon dioxide onto chitosan or chitin particles resulted in high mechanical strength of compacts with super-disintegration properties [6]. When modified in this manner, tablet disintegration was characterized by superior water uptake and penetration, with no gelling hindrance effects; this makes silicon dioxide different from other known super-disintegrants. However, there are disadvantages associated with silicon dioxide polymer preparations. For example, co-precipitation of colloidal silicon dioxide onto chitin or chitosan particles involves the use of large volumes of concentrated hydrochloric acid and sodium hydroxide solutions not to mention high temperature [6, 9]. This imposes a high cost burden during industrial processing. Furthermore, the disintegration properties of chitin–silica powder are strongly dependent on its compactability. Finally, the chitin–silica particles are highly hygroscopic at humidity conditions above 70% RH. Such drawbacks necessitated an exploration of the use of an alternative industrial processing strategy. We hypothesized that metal silicates could represent a suitable alternative to silicon dioxide. In fact, metal silicates have been tested as disintegration promoters (Rxcipients FM 10001 application bulletin). Specifically, the use of amorphous synthetic calcium silicate (Rxcipients FM10001) has been advocated; one reason for calcium silicate's potential as a fast disintegrant may be its

highly porous nature. It has been found that the combined use of calcium silicate, in concentrations up to 30% (w/w), with super-disintegrants, provides acceptable tablet hardness whilst concomitantly allowing rapid tablet disintegration; in less than 30 s in the mouth [10]. The combined use of chitin and metal silicate could fulfill the dual role of superdisintegrant and filler in pharmaceutical formulations. However, it is well documented that commercially available super-disintegrants lose their function as disintegrants when their concentration exceeds certain limits (3–15%, w/w) [9]. Therefore, their use as fillers or binders in solid dosage form formulations could be deleterious. Chitin exhibits super-disintegration properties that depend, mainly, upon a high water uptake rate, [3] so it can be presented over a higher concentration range compared to other commercial super-disintegrants without affecting the disintegration properties [6, 9]. However, chitin shows poor powder compressibility [11].

Ultimately, the combination of one of the most abundant naturally occurring polymers with metal silicates could represent a practical and invaluable choice of an industrial excipient in terms of disintegration and compaction properties. In this regard, if co-precipitation is the desired methodology to ensure an effective distribution of silicon dioxide onto chitin particles, then replacing silicon dioxide with an insoluble metal silicate should be considered. Indeed poor (aqueous) solubility is a useful property for a disintegrant and it just so happens that this is a general characteristic of most metal silicates, except for sodium silicate [12, 13]. Therefore, it was hypothesized that by carrying out a simple chemical displacement reaction, that is, by adding a soluble salt of the appropriate metal to a sodium silicate solution in which chitin particles are suspended, an insoluble metal silicate could be produced. Thus, chitin particles could provide the surface on which metal silicate precipitation takes place. The work reported herein aims to test such an assumption as well as to characterize the resulting co-precipitates produced using different metal silicates and its utilization as a super-disintegrant and a single component additive in immediate release tablets.

CHAPTER TWO

2.2 Experimental

2.2.1. Materials

Chitin (200 mm, JBICHEM, Shanghai, China), Avicel® 200 (FMC BioPolymer, Philadelphia, PA), $Na_2SiO_3.5H_2O$ (BDH, Poole, England), $AlCl_3.6H_2O$ (MERCK KGaA, Darmstadt, Germany), $MgCl_2.6H_2O$ (SIGMA Chemical Co, St. Louis, MO), $CaCl_2.2H_2O$ (ACROS Organics, Geel, Belgium), paracetamol (Sri Krishna Pharmaceutical Ltd, Hyderabad, India), metformin HCl (Hercules Plaza, Wilmington, DE), mefenamic acid (Shinpoong Pharma, Seoul, Korea), PonstanTM Forte 500 mg tablets (Chemidex Pharma Ltd, Surrey, UK). All reagents used were of analytical grade.

2.2.2 Methods

2.2.2.1. Preparation of Metal silicate-Chitin powder

Into three separate solutions, each containing 10.0 g of sodium silicate dissolved in 400 mL of deionized water, 7.5, 10, and 11.5 g of chitin were suspended under stirring conditions. Respectively, 6.0 g of aluminium chloride, 9.6 g of magnesium chloride, 6.9 g of calcium chloride were added to stochiometrically react with sodium silicate to produce suspended particles of the insoluble metal silicate that co precipitated onto chitin. The particles were filtered out using 20-25 μm filter papers (ALBET 135, Quantitative, Barcelona, Spain) then washed with deionized water until the filtrate conductivity, measured using a conductivity meter (METTLER TOLEDO MPC227, Greifensee, Switzerland), was less than 20 μS. The product was dried in the oven at 90ºC for 3 hours, and finally passed over a mesh of 425μm size and kept for further testing and characterizations of the obtained material. The final Al, Mg, and Ca silicate mass content was fixed at 32% (wt/wt).

2.2.2.2 FT-IR Spectroscopy

Infrared spectroscopy was used to follow the molecular interaction between chitin and the metal silicates. For Fourier transform infrared spectroscopy (Perkin–Elmer, Buckinghamshine, UK), Al silicate, Mg silicate, Ca silicate, their corresponding

co-precipitates with chitin particles, a physical mixture of chitin and magnesium silicate, with a Mg silicate content of 32% (w/w), and chitin were all separately mixed with dried KBr (1%, w/w). Then a small portion of the mixture was compressed in a 15 mm dye at 1×10^5 kPa to yield a transparent disk. The disk was mounted in the instrument beam for spectroscopic examination.

2.2.2.3. X-ray diffraction

The XRPD patterns of Al, Mg, and Ca silicates, their corresponding chitin particle co-precipitates chitin, a physical mixture of chitin and magnesium silicate at a Mg silicate content of 32% (w/w), and chitin, were all investigated using an X-ray diffractometer (Philips PW 1729 X-Ray Generator; Philips, Eindhoven, the Netherlands). XRPD spectra were acquired on a Scintag Pad V X-ray Powder Diffractometer using CuKα radiation on a $\theta - 2\theta$ goniometer equipped with a germanium solid-state detector, using acquisition conditions of 35 kV and 30 mA. Scans were typically obtained from 10 to 70 2θ, with step size or integration range of 0.05θ, and a count time of 5 s.

2.2.2.4. Scanning electron microscopy

Chitin and chitin–Mg silicate samples were mounted on aluminum stubs and then coated with gold by sputtering at 1200 V, 20 mA for 105 s using a vacuum coater. A FEI Quanta 200 3D SEM (FEI, Eindhoven, The Netherlands) instrument was used.

2.2.2.5 Water penetration rate

Chitin-Mg silicate and Avicel® 200 were separately poured into graduated cylinders. In order to visualize and measure the water penetration into the samples, 50 mL of 0.1% (wt/vol) of sunset yellow solutions were prepared and added on top of each of the chitin-Mg silicate and Avicel® 200 samples. The penetration rate was calculated by measuring the speed of water in mL/min penetrating the samples column. This method was validated upon changing the dye concentration (0.1-1%), dye solutions added volume (10-100 mL) and the samples volume (50-200 mL). This test was performed at the following powder particle size of 125, 300, 710, 1400 μm for chitin-

Mg silicate and Avicel® 200. In order to obtain different particle size of Avicel® 200 (particle size was 180 μm) and chitin-Mg silicate (particle size of 425 μm), initially each powder was compressed into 12 mm circular tablets and then the tablets were crushed in a dry granulator (Erweka TG IIS) coupled to a Erweka AR 400 multipurpose motor (Erweka GmbH, Heusenstamm, Germany) to obtain granules with a particle size < 2.00 mm. Finally, the slugs were ground manually, using a pestle, over separate sieves of mesh particle size 125, 300, 710, 1400 μm.

2.2.2.6 Chitin-Mg silicate hygroscopicity

Different samples of chitin–Mg silicate (initial weight of 2.0 g) were stored in desiccators containing saturated salt solutions at room temperature for a week. The media compositions were set according to the Handbook of Chemistry and Physics [14]. Samples were stored in desiccators under equilibrium conditions for one week. The percentage gain in weight compared to the original weight was measured for each humidity setting.

2.2.2.7 Water infiltration rate

Infiltration of water into the chitin, chitin-Mg silicate, Mg silicate, and Avicel® 200 powders at tap density was performed in capillary rise experiments [15]. Each powder was poured into a glass tube supported by a clamp attached on top of a beaker containing a reservoir of water. The water was once more dyed with sunset yellow solution to visualize the ascending water from bottom to top of the tube. A glass wool was placed at the bottom of the tube to allow water to pass while supporting the powder. The tube was lowered in the beaker up to the point that the fluid level reached the top of the glass wool. Time zero was chosen when the liquid first meets the powder. The infiltration rate was calculated by measuring the speed of ascending water in mL/min penetrating the samples column from bottom to top.

2.2.2.8. Particle size influence on disintegration and hardness measurements of chitin-Mg silicate

Chitin-Mg silicate granules were initially produced by co precipitation and then ground manually (using a pestle) over separate sieves, after drying, of mesh particle

size 1400 μm, 425 μm, and 125 μm. Each of the three powder samples of specific particle size was subjected to compression using a single punch tableting machine (Manesty, Merseyside, UK) at the compression forces 30, 35, 40, 45, and 50 KN, in which a 12 mm circular punch was fitted, producing tablets of 400 mg weight. Tablet hardness and disintegration time were examined for all tablets produced at each compression force. Tablet hardness was measured using a hardness tester (Copley, Nottm Ltd, Therwil, Switzerland), whereas disintegration time was measured using a disintegration tester (Caleva, Dorset, UK). The average hardness and disintegration readings of 10 tablets were considered for each particle size at the specific compression force.

2.2.2.9 Mass content influence of metal silicates on tablet hardness and disintegration time

For chitin-Al silicate samples preparation: 7.5, 11.2, 15, 22.6, and 30.1 g of chitin were respectively suspended in five separate solutions, each containing 10 g of sodium silicate dissolved in 400 mL of deionized water. 6 g of aluminum chloride were added to each of the chitin suspensions to ensure complete precipitation of Al silicate. The method was repeated using same concentration of sodium silicate separate solutions containing 10, 15, 20, 30, and 40 g of chitin for chitin-Mg silicate and 11.5, 17.2, 23, 34.6 g of chitin for chitin- Ca silicate preparations. 9.6 g of magnesium chloride and 6.9 g of calcium chloride were respectively added to each of the chitin suspensions. All the resulted chitin-metal silicate suspensions were filtered out, washed with deionized water, dried in the oven at 90ºC for 3 hours, and finally passed over a mesh of 425μm size. All the samples produced were compressed using the single punch tabletting machine in which a 12 mm circular punch was fitted, producing tablets of 400 mg weight. Tablet hardness and disintegration time were measured for each tablet. An average of 10 tablets was considered for each test. The percentage content of metal silicate for the prepared samples was calculated as follows: 32, 23.9, 19.0, 13.5, 10.5 % (wt/wt).

2.2.2.10. Characterization of the compression process of chitin–metal silicate

Chitin, chitin-Al silicate, chitin-Mg silicate (at the Mg silicate contents of 13, 19, 24,

32 % (wt/wt) in the chitin-Mg silicate compacts) and chitin-Ca silicate were separately compressed by direct compressing using the universal testing machine (UTM, RKM 50, PR-F system, ABS Instruments Pvt., Ltd., Leipzig, Germany). This was achieved without lubrication of the upper and lower punches as well as the die. The punch speed was fixed at 10 mm/min. Different compression forces from 80 to 390 MPa were applied. Three tablets were prepared to ensure reproducibility. The tablets were flat, round of 12 mm diameter and 400 mg weight.

The compression behavior of the samples was evaluated using the Kawakita analysis of powder compression data. The Kawakita equation (Equation 1) is used to study powder compression using the degree of volume reduction, C. The basis for the Kawakita equation for powder compression is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of the pressure term and the volume term is a constant [16]:

$$C = [V_0 - V/V_0] = [abP/1 + bP] \quad (1)$$

Where, C is degree of volume reduction, V_0 is the initial volume, V is the volume of powder column under the applied pressure P. The constant, a is the material's minimum porosity before compression while the constant b relates to the material's plasticity. The reciprocal of b defines the pressure required to reduce the powder bed by 50% [17, 18]. The equation above can be re arranged in linear form as:

$$P/C = P/a + 1/ab \quad (2)$$

The expression of particle rearrangement could be affected simultaneously by the two Kawakita parameters a and b. The combination of these into a single value, i.e. the product of the Kawakita parameters a and b, may hence be used as an indicator of the expression of particle rearrangement during compression [19].

2.2.2.11. Formulations using chitin-Mg silicates

The composition and the type of formulation process (direct compression and wet granulation) of formulas containing paracetamol, metformin HCl, and mefenamic acid are listed in Table 2.1. Formulas F1, F3, F4, F6, and F7 were formed by direct compression, whereby the lubricant was initially passed through a 200 µm sieve, all the other components were mixed using an Erweka mixer (Erweka AR 400,

Heusenstamm, Germany), then passed through a 0.8 mm sieve and finally the lubricant was added to the mixture. For the case of wet granulation, purified water was used as the granulating fluid of formulations F2 and F5 using a graduated measuring cylinder. The wetted granules were passed through a 2.5 mm sieve. The granules were dried in a hot-air oven at 40 °C for 1 hour. The dried granules were passed through a 0.8 mm sieve. Finally, the lubricant (magnesium stearate) was added to the mixture. All formulas were compressed using a single punch tabletting machine (Manesty F3 single stroke tablet press, West Pharmaservices Ltd, Dorset, UK) in which a 13 mm shallow concave punch was fitted. Compression was carried out using a load of 40 KN.

Table 2.1 Composition of paracetamol, metformin HCl, and mefenamic acid tablets formulations.

Formula No.	Drug	Manufacturing Process	Active Ingredient (mg)	Chitin-Mg Silicate Quantity (mg)	Calcium Silicate Quantity (mg)	Magnesium Stearate Quantity (mg)
1	Paracetamol	Direct Compression	500	385	--	2
2	Paracetamol	Wet Granulation	500	385	--	2
3	Paracetamol	Direct Compression	500	--	358	2
4	Metformin HCl	Direct Compression	500	375	--	5
5	Metformin HCl	Wet Granulation	500	375	--	5
6	Metformin HCl	Direct Compression	500	--	375	5
7	Mefenamic Acid	Direct Compression	500	470	--	3
8	Ponstan® Forte 500 mg	--	500	--	--	--

For hardness and disintegration testing, an average of 20 tablets from each formula was considered using the hardness and disintegration testers respectively. For drug dissolution, an average of 8 tablets was considered using the USP specifications of the

dissolution media and apparatus for each drug [20]. Ponstan™ Forte 500 mg tablets were used for comparison purposes with formula F7 of mefenamic acid with respect to hardness, disintegration and dissolution in its designated USP media

2.3 Results and Discussion

Metal ions react with silicate ions and form insoluble metal silicates [21]. Accordingly, co-precipitation of Al, Mg and Ca silicate followed the following reactions:

$$2AlCl_3 + 3Na_2SiO_3 \longrightarrow Al_2(SiO_3)_3 + 6NaCl$$

$$MgCl_2 + Na_2SiO_3 \longrightarrow MgSiO_3 + 2NaCl$$

$$CaCl_2 + Na_2SiO_3 \longrightarrow CaSiO_3 + 2NaCl$$

Consequently, the soluble sodium silicates changed to larger molecules of metal silicates that precipitated onto chitin. The pH of the compacts (5% (w/v) aqueous dispersion) resulting from the co- precipitation of Ca, Mg, and Al silicates onto chitin particles was measured as 10.5, 8.5, and 6.0 respectively. All these metal silicates are composed of silicon dioxide (K_{sp} of 10^{-3} in water) linked randomly to the metal oxide which has a degree of solubility that depends on the type of metal. In water, these metal oxides are characterized by the solubility product constant K_{sp} of metal hydroxide which has the values of $5.0x10^{-6}$, $6.0x10^{-12}$, and $3.0x10^{-34}$ for Ca, Mg, and Al hydroxides respectively. The K_{sp} for the $Al(OH)_3$ is the lowest of all, thus the acidic nature of Al silicate is mainly attributed to the silicon dioxide which is very slightly soluble in water and acidic in nature. Alternatively, Ca and Mg silicates basicity is mainly attributed to the metal Ca and Mg oxides present [22, 23]. The nature of chitin-metal silicate association resulting from the co-precipitation process was investigated using FTIR and x-ray diffraction analysis.

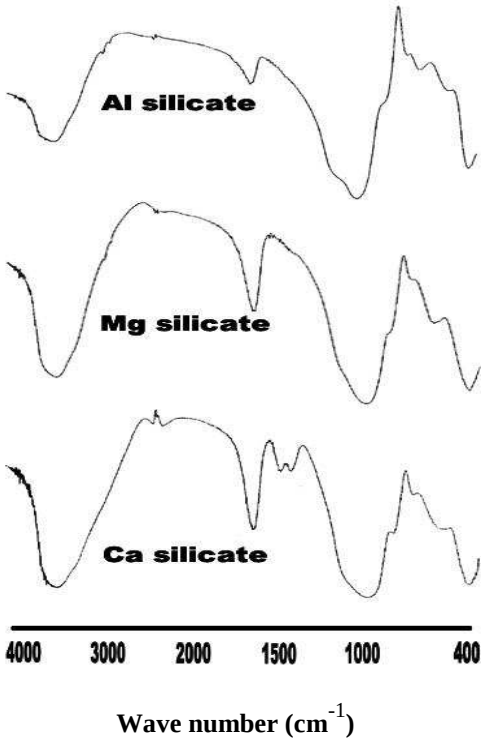

Figure 2.1 FTIR of Al, Mg, Ca silicates prepared by precipitation of the metal silicates through replacement reaction of sodium meta-silicate with the metal chlorides.

Infrared spectra of the prepared precipitates of Al silicate, Mg silicate, and Ca silicate are shown in Figure 3.1. All these metal silicates showed common IR features with respect to the absorption band at 1039 cm^{-1} which is due to a Si-O-Si symmetrical stretching vibration. In addition, the Si-O bending vibration of the metal silicate can be observed at 432 cm^{-1} in the spectrum. The other bands in the spectrum around 654 cm^{-1} and 3450 cm^{-1} are probably associated with various metal-O modes and water molecules, respectively [24]. However, Ca silicate had two distinctive bands in the 1400-1480 cm^{-1} region that can be assigned to the O-H bending mode [25] .These two bands were not present in the Al and Mg silicates. In general, the cation electropositivity and ionic radius play important roles in the stretching and bending modes, respectively [26]. On the other hand, chitin (Figure 2A) showed split absorption bands at 1660 and 1620 cm^{-1} corresponding to the amide I region (C=O stretching) and an absorption band at 1560 cm^{-1} corresponding to the amide II region (N-H bending vibrations) [27].

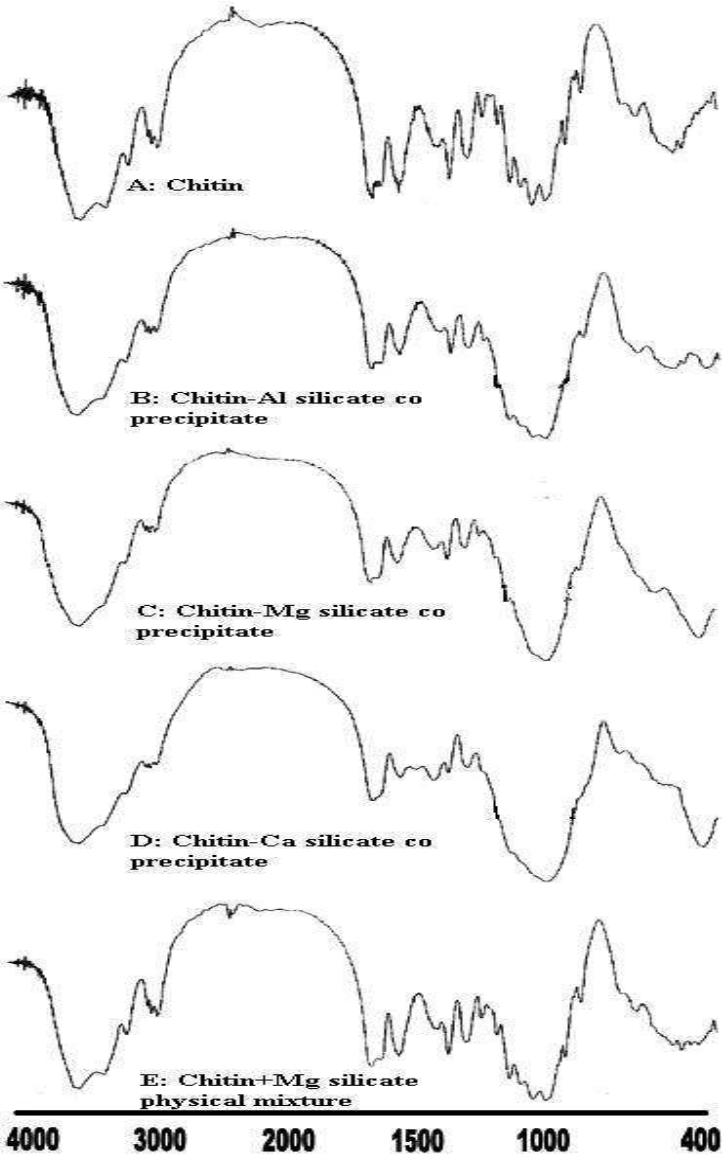

Figure 2.2 FTIR of chitin, chitin-metal (Al, Mg, Ca) silicate co-precipitates, and chitin-Mg silicate physical mixture.

All these bands were identical in both chitin and chitin-metal silicate co-precipitates on the one hand (Figures 2.2B, C, & D for chitin-Al, Mg, and Ca co precipitates respectively), and chitin-Mg silicate physical mixture (taken as an example of a chitin-metal silicate) on the other (Figure 2.2E). This suggests no chemical reactivity is present between chitin and all the tested metal silicates when the later underwent co-precipitation. The difference between the co-precipitate (Figures 2.2B, C, & D)

and the physical mixture (Figure 2.2E) could be clearly demonstrated by the sharpness of the peaks of the physical mixture and the broadness of the peaks of the co-precipitate. It seems that this difference is related to the precipitation of Mg silicate onto the chitin surface. The silanol groups, which are known to have a hydrogen bonding potential with some substances, [28] present on the surface of Mg silicate could attribute to the broadening of IR peaks of both chitin and Mg silicate for the co precipitate. Generally, the impact of hydrogen bonding is to produce significant band broadening and to lower the mean absorption frequency [29]. The investigated chitin-metal silicates co precipitates and their physical mixtures were tested using x-ray diffraction in order to evaluate the role of co precipitation on crystallinity. The x-ray diffraction patterns of synthetic Al, Mg, and Ca silicates produced by the reaction of sodium silicate with their corresponding metal salts are presented in Figure 2.3. In general, the term 'silicate' refers to crystalline materials with known composition. However, Al and Mg silicates clearly showed amorphic characters with broad peaks all over the diffraction pattern range. A fairly more ordered pattern was noticed for Ca silicate, which showed a distinctive broad peak at 30º *2θ*. This suggests that Ca silicate could have a little more than a two-dimensional short-range order [30]. Such crystallographic diversities of metal silicates could be attributed to the fact that different alkaline cations favor different structures. More specifically, the crystalline lattice structure of different metal silicates is dependent upon the type, size and atomic weight of the metal cation which defines the orientation of the metal-O-Si domains [31]. Hence, the resulted amorphous patterns of the tested metal silicates could be a result of the predominance of metal-O-Si bonds, rather than phase separated metal oxide/SiO_2 mixtures [32].

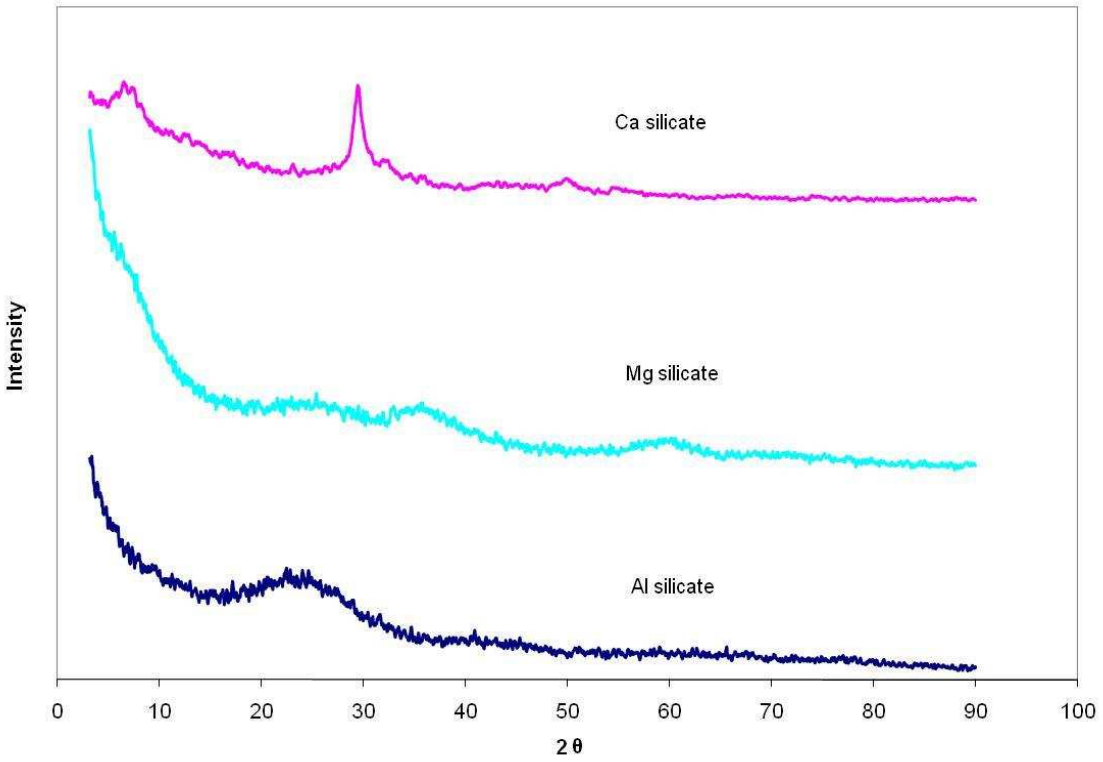

Figure 2.3 X-ray powder diffraction results for Al, Mg, Ca-silicate precipitates.

This difference was crucial for the proper choice of amorphous metal silicates instead of the natural crystalline silicates with regard to the mechanical strength of the complex compacts. In this perspective, naturally occurring metal silicates, specifically phyllosilicates, are generally brittle and of weak binding capacity. Alternatively, they would represent improper candidates when used as pharmaceutical fillers in solid dosage forms. Such weakness could be theoretically attributed to the crystalline lattice structure of metal silicates as they are composed of stacks of individual silicate layers held together by weak van der Waals forces resulting in gap spacing between the layers [33, 34]. On the other hand, chitin (Figure 2.4) displayed six broad peaks at 9.4°, 12.9°, 19.3°, 23.5°, 26.9° and 39.8°, which are likely caused by polycrystalline domains or disturbed crystal structure [35]. Such domains originate from the anti-parallel arrangement of chitin molecules in the α form which is stabilized by a high number of hydrogen bonds formed within and between the molecules [36].

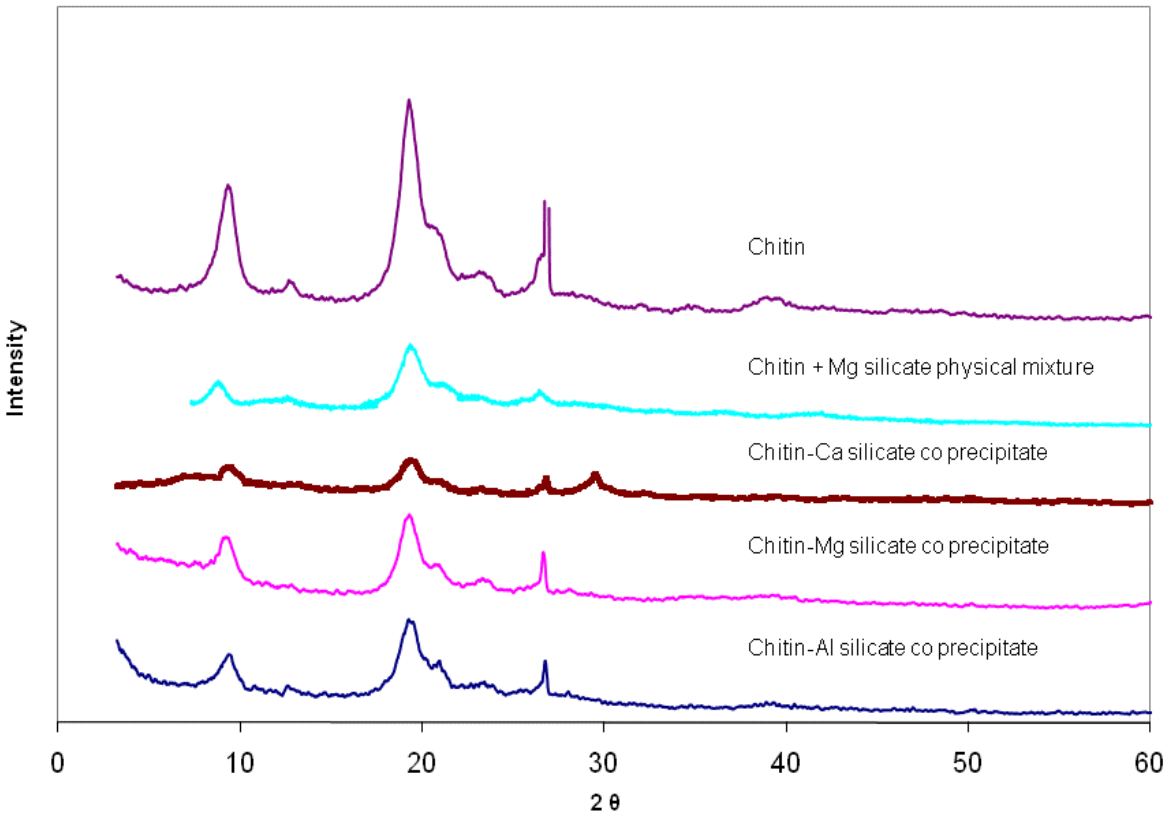

Figure 2.4 X-ray powder diffraction spectra for chitin-metal (Al, Mg, Ca) silicate co-precipitates, chitin Mg silicate physical mixture, and chitin.

Co-precipitation of the metal silicates onto the chitin particles did not alter the position of the amorphous domains of both chitin and metal silicates, as shown in Figure 2.4. However, there was a decrease in the peak intensities of chitin in all the chitin-metal silicates diffraction patterns when compared to that of chitin. This could be attributed to dilution effect caused by the content of metal silicates in the complex. Similarly, the x-ray diffraction patterns of chitin and magnesium silicate (taken as an example for demonstration) physical mixtures prepared using a magnesium silicate content of 32% (wt/wt) showed no alteration in the amorphous domain positions. In addition, there were no noticeable differences with regard to the x-ray diffraction patterns between the co precipitate and the physical mixtures in the case of chitin-Mg silicate. This further demonstrates the physical association between chitin and metal silicates.

The chitin–metal co-precipitate was screened, after drying and sieving the powder, by SEM and compared with the original chitin powder, as shown in Figure 2.5. Chitin, Figure 2.5.A, had changed its native structure from thin smooth, flat surface structure, with folded edges, to three-dimensional compacts with the metal silicate co precipitate, Figure 2.5.B for chitin-Mg silicate. Figure 2.5.C shows a larger view of chitin-Mg silicate indicating the presence of inter-particulate voids and channels.

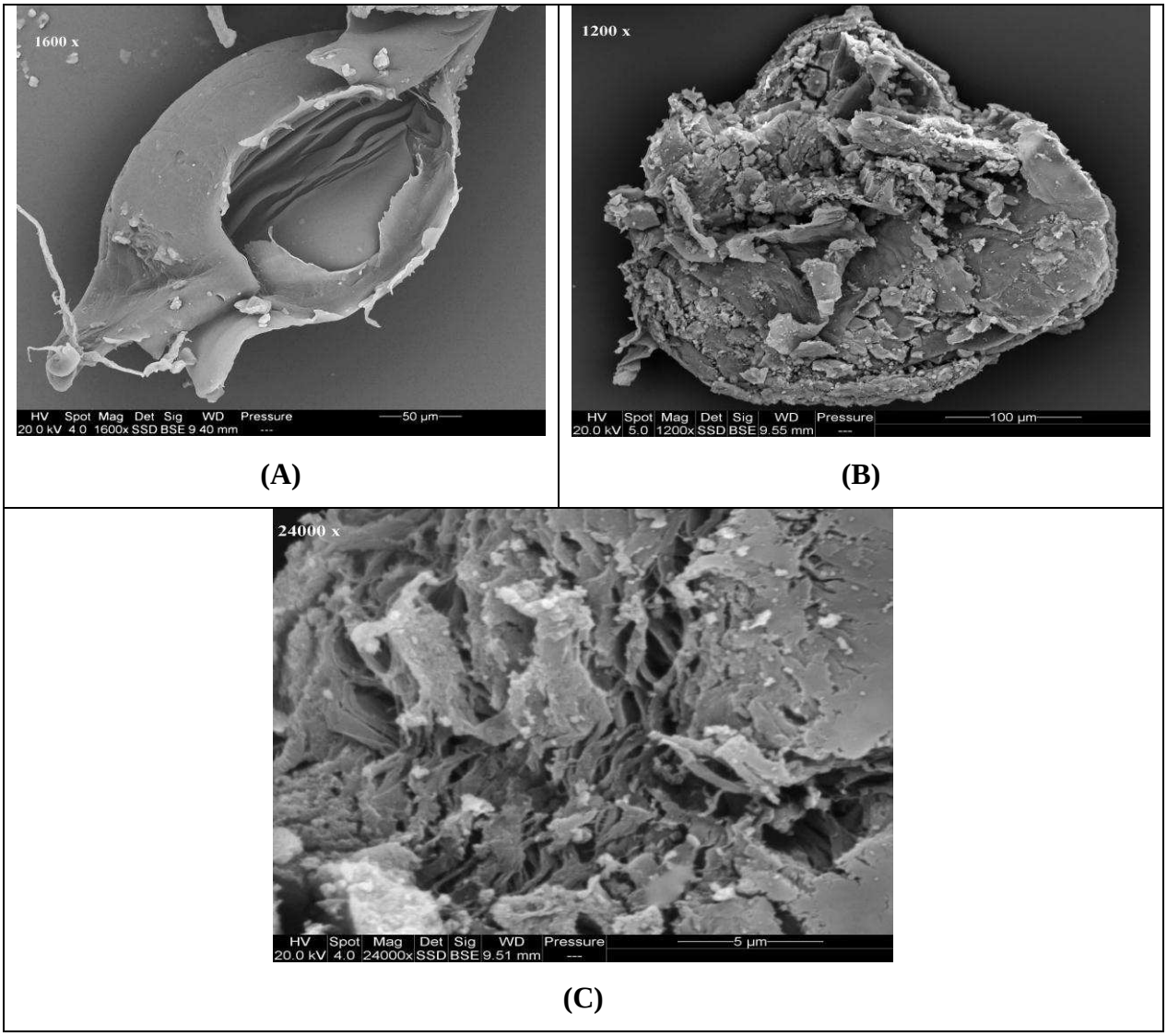

Figure 2.5 SEM of chitin (A), chitin-Mg silicate co-precipitate (B) and (C).

The disintegration mechanism of chitin-metal silicates was investigated by examining the water uptake driving force of the powder. This was achieved by performing water penetration rate and water infiltration experiments for chitin-Mg silicate as a demonstrating example of chitin-metal silicate co precipitate.

Water penetration rate of chitin-Mg silicate at different particle size was carried out and compared with Avicel® 200 at the same particle size (Figure 2.6). The choice of using Avicel® 200 was based upon its free allowance to water passage without any hindrance caused by gelling. Water penetration rate increased from 20 to 30 mL/min with decreasing the particle size from 1400 μm to 125 μm of chitin-Mg silicate, whereas the water penetration rate of Avicel® 200 increased from 7 mL/min to 18 mL/min with increasing the particle size from 125 μm to 1400 μm. Generally, increasing a powder particle size allows larger voids between particles, thus higher penetration rates as in the case of Avicel® 200. This case was the opposite for chitin-Mg silicate. It seems that the voids between the particles have a little significance to increase the passage of water amongst them. In spite of its high water penetration rate, Figure 2.6 demonstrates that chitin-Mg silicate was found to be slightly hygroscopic. Polymers with a higher moisture uptake capacity will be expected to be more prone to accelerate tablet disintegration.

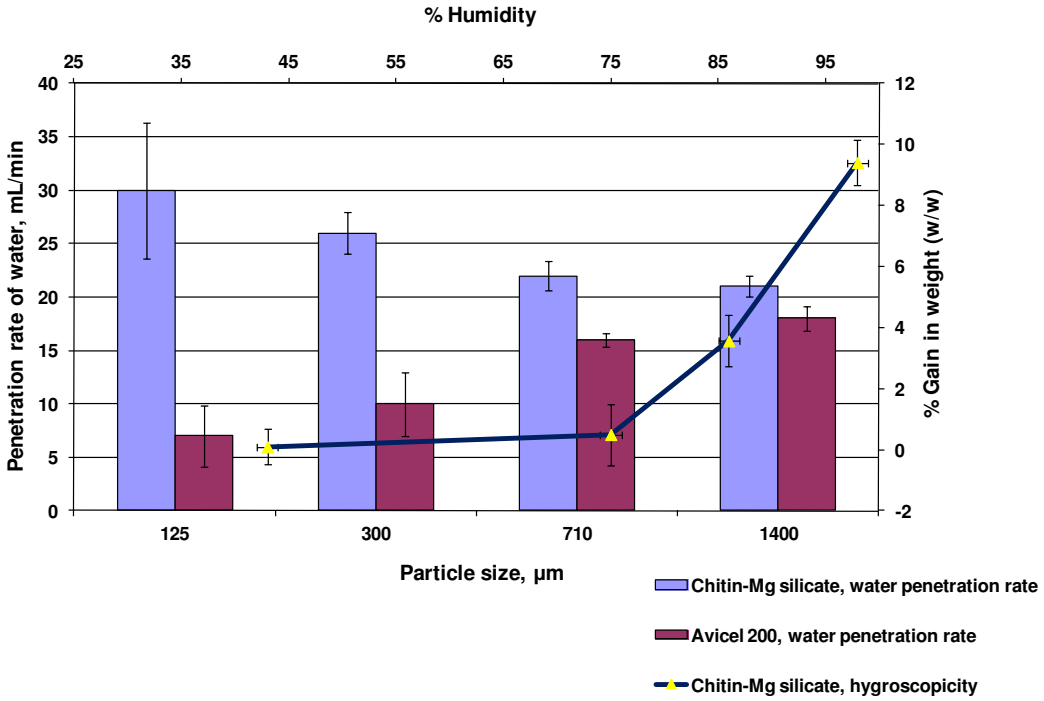

Figure 2.6 Water penetration rate of chitin-Mg silicate and Avicel® 200 as function of particle size (primary axis). Hygroscopicity of chitin-M silicate co-precipitate performed using standard salt solutions of differer humidity conditions stored inside desiccators at room temperature for week (secondary axis). Error bars presented as ± RSD.

The hygroscopicity measured for chitin-Mg silicate (Figure 2.6) clearly indicated that chitin-Mg silicate only gained maximum moisture content up to 9.4% of its initial weight at the 98% humidity condition. Water infiltration through capillary rise experiment gave a clearer explanation to such behaviour when chitin-Mg silicate, chitin, Mg silicate, and Avicel® 200 were allowed to come in contact with water from the bottom side across a glass wool pledget. Capillary action seemed to have a major contribution to the water uptake of chitin-Mg silicate (a measured rate of 0.145 mL/min) and almost similar to chitin (a measured rate of 0.15 mL/min). This indicates that the capillary action is mainly contributed to chitin as the rate was measured to be 0.015 mL/min for Mg silicate. Avicel® 200, which showed a significant water penetration (Figure 2.6), had no significant capillary action which was almost similar to Mg silicate. This may suggest that decreasing the particle size of chitin-Mg silicate

(Figure 2.6) may have increased the water uptake through capillary action. As the particle size was decreased more intra particulate voids may have come into contact with each other giving rise to more capillary channels (see Figure 2.5.C for illustration) for water to penetrate.

This investigation was further illustrated when studying tablets hardness versus compression force for varying powder particle sizes; 125 μm, 425 μm, 1400 μm (Figure 2.7). Generally, a reduction in particle size is associated with an increase in tablet mechanical strength. This increase is attributed to an increase in the surface area available for inter-particulate attractions, as the particles become smaller [37]. However, when chitin-Mg silicate was used, it was found that varying the particle size had no effect in increasing the mechanical strength of the tablets produced. Generally, for materials with a fragmentation tendency, such as dibasic calcium phosphate dihydrate and saccharose, the mechanical strength of the tablet seems to be almost independent on particle size [38]. This could be the case for the chitin-metal silicate particles which undergo fragmentation, as will be illustrated later, at early compression stages which normally lead to a limited effect on tablet tensile strength when varying the particle size.

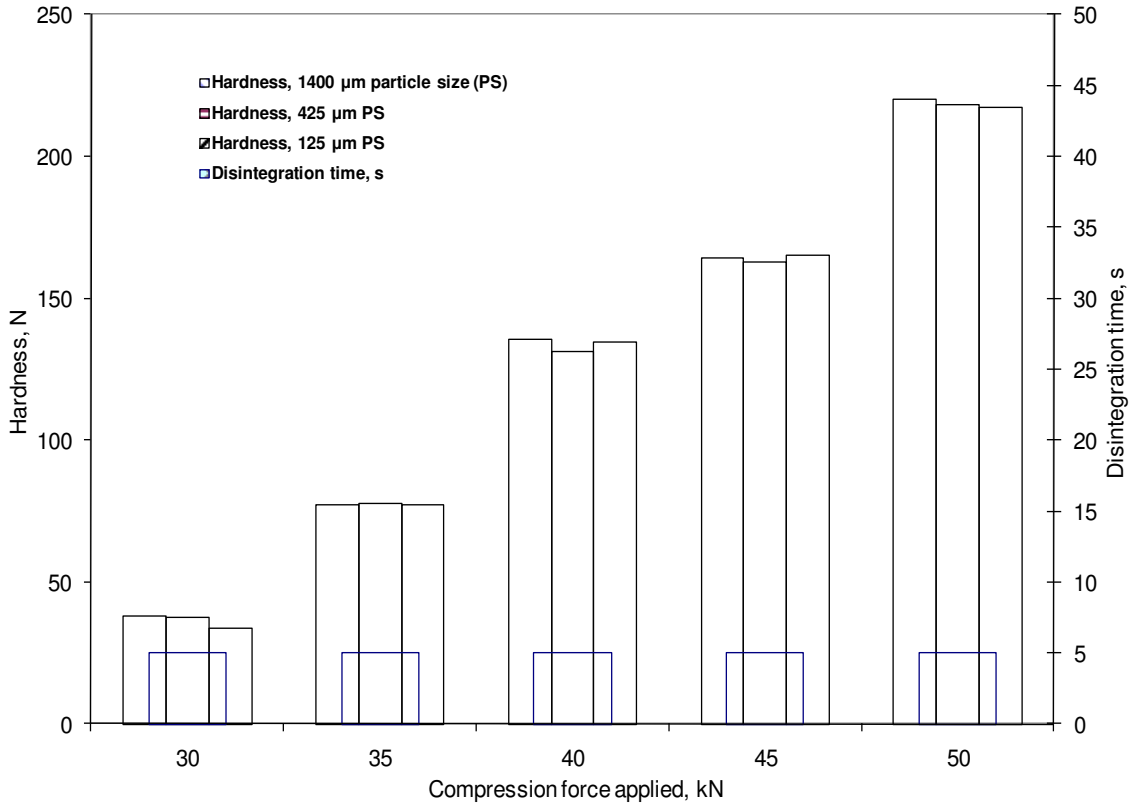

Figure 2.7 Hardness and disintegration time as a function of compression force for different particle size of chitin-Mg silicate co-precipitate. Tablets were 12 mm in diameter and 400 mg weight.

With respect to tablets disintegration, chitin-Mg silicate, as shown in Figure 2.7, showed a unique and distinctive characteristic whereby disintegration was independent upon particle size and tablet hardness. Chitin-Mg silicate tablets, produced from initial powder particle sizes of 125 µm, 425 µm, and 1400 µm at compression forces between 30-50 KN for each particle size, showed a superior disintegration time, i.e. no longer than 5 seconds. This was achieved for tablet hardness values ranging from 40-220 N. Once more, this may suggest that capillary action was the dominant mechanism for disintegration irrespective of tablets tensile strength. Therefore, the inter-particulate voids, as previously mentioned, would have remained intact and unchanged through varying the powder particle size and the compression force.

Processing chitin with metal silicates was found to cause alterations to chitin's powder compressibility and compactability**.** Regarding powder compactability, metal

silicates within the chitin-metal silicate complex have demonstrated an effective mean to establish hard tablets while maintaining super-disintegration power, as could be deduced from Figure 2.7. In the absence of metal silicates, chitin showed a maximum tablet hardness of 73 N at a compression force of 50 KN. Increasing the content of metal silicates resulted in an increase in tablet hardness (at the same compression force) which followed the pattern shown in Figure 2.8 for Al, Mg, and Ca silicate-chitin compacts. All types of chitin-metal silicates tablets showed a sharp increase in the compaction properties (tablets hardness >140 N) while maintaining a low disintegration time (<10 seconds) when the metal silicate content was increased up to 30% (wt/wt). Above this value, the increase in tablet hardness values became slower whereas disintegration time increased sharply to values greater than 7 minutes for all the chitin-metal silicates compacts. Pure metal silicates (100% metal silicate content in Figure 2.8) showed good compaction properties but disintegration was slow (about 10 minutes for all chitin-metal silicates). This behaviour could, in a way, justify the hypothesis that the optimum metal silicate content in chitin-metal silicates should not exceed 30% (wt/wt) in order to maintain good compaction and super disintegration characteristics. Figure 2.8 further indicates that the tensile strength of chitin-metal silicates compacts was dependant upon the type of metal cation. The increasing hardness of compacts was as follows: chitin-Al silicate > chitin-Mg silicate > chitin-Ca silicate.

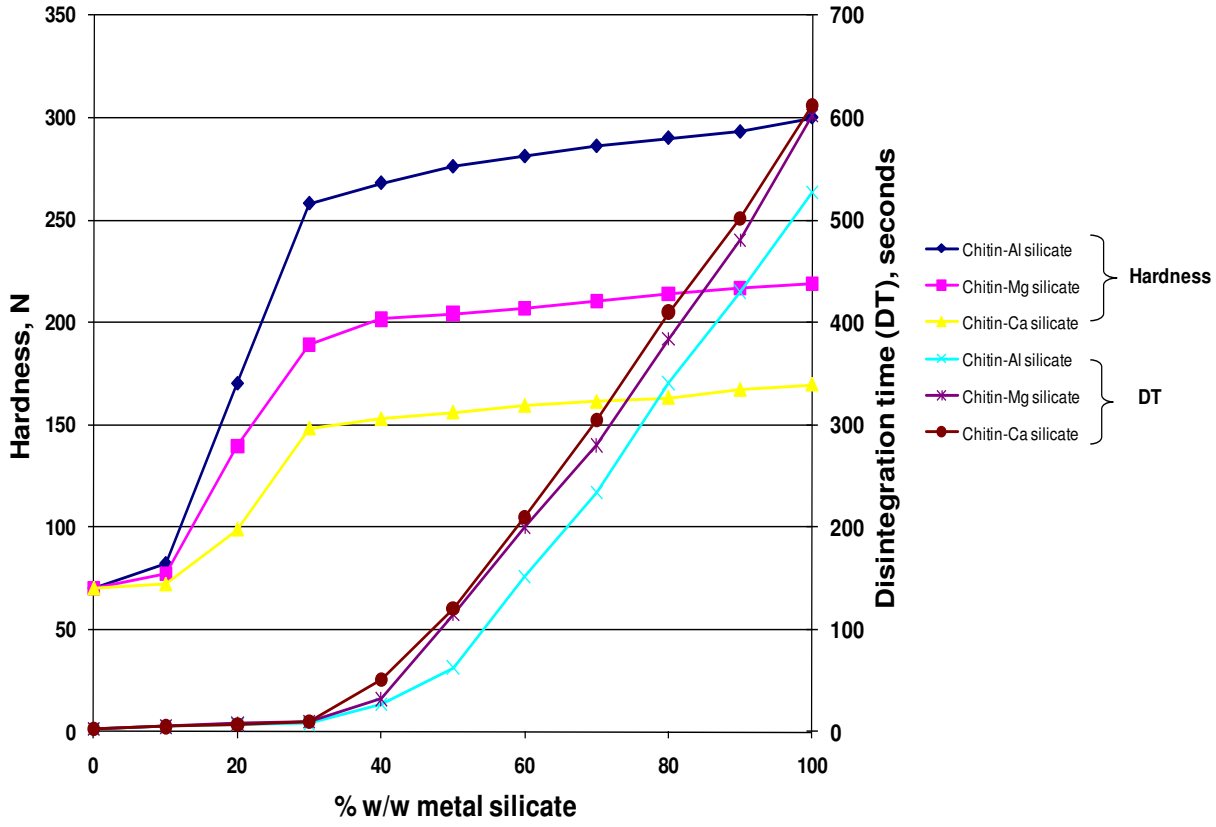

Figure 2.8 Hardness and disintegration time as a function of chitin-metal (Al, Mg, and Ca) silicate content. Tablets were 12 mm in diameter and 400 mg weight.

The trend of increase in compacts mechanical strength is mainly attributed to the compacts porosity. Generally, tablets of low porosity will have a high mechanical strength [39]. The incorporation of metal silicates onto the chitin particles through the co precipitation process has established some modifications to the physical properties of the chitin powder. This will be clearly demonstrated by powder compressibility analysis of various chitin-metal silicates. Early investigation of the Heckel plots indicated non-log-linearity of compression data. Therefore, Heckel analysis was not adopted in this work as it may result in misinterpretation to the estimated intercept and slope parameters. Therefore, the Kawakita analysis was adopted instead in order to linearize the compression data.

Figures 2.9 and 2.10 show representative Kawakita plots for chitin-Mg silicate at different concentrations of Mg silicate and for the three investigated types of metal silicates in the chitin-metal silicates powders.

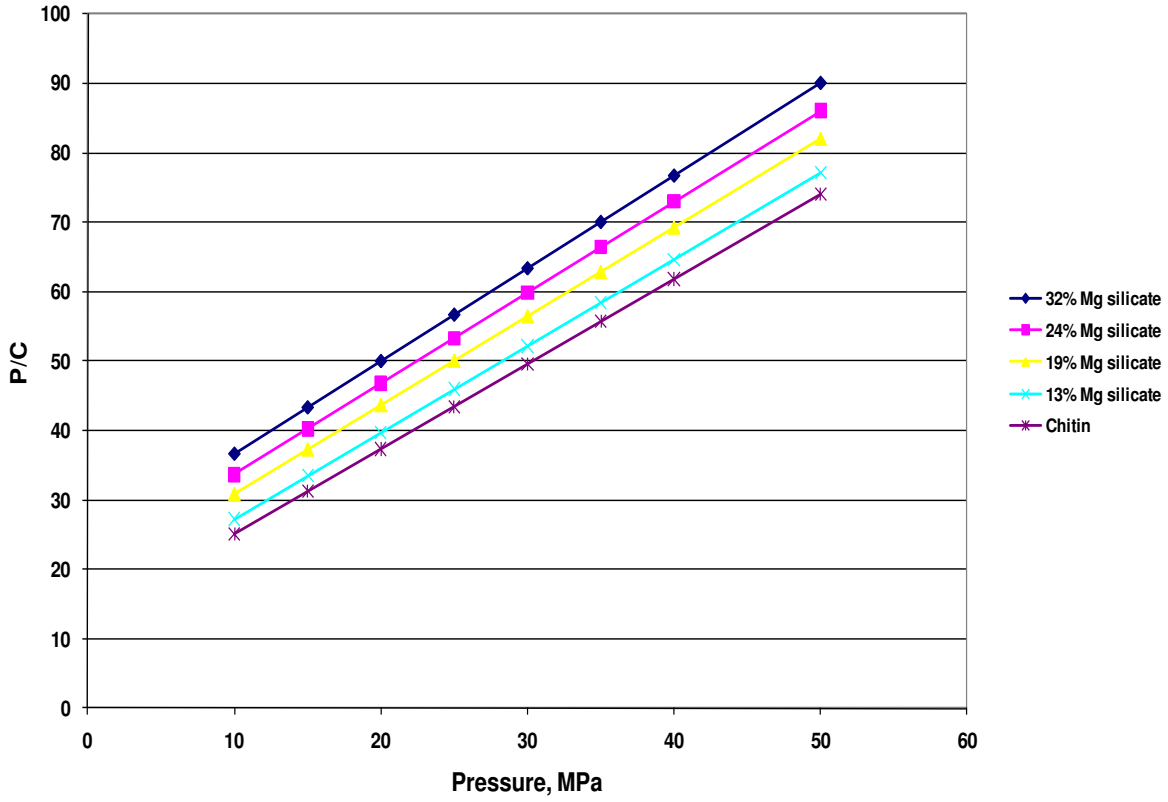

Figure 2.9 Kawakita plots for different concentrations of Mg silicate in the chitin-Mg silicate co precipitate. Tablets were 12 mm in diameter and 400 mg weight.

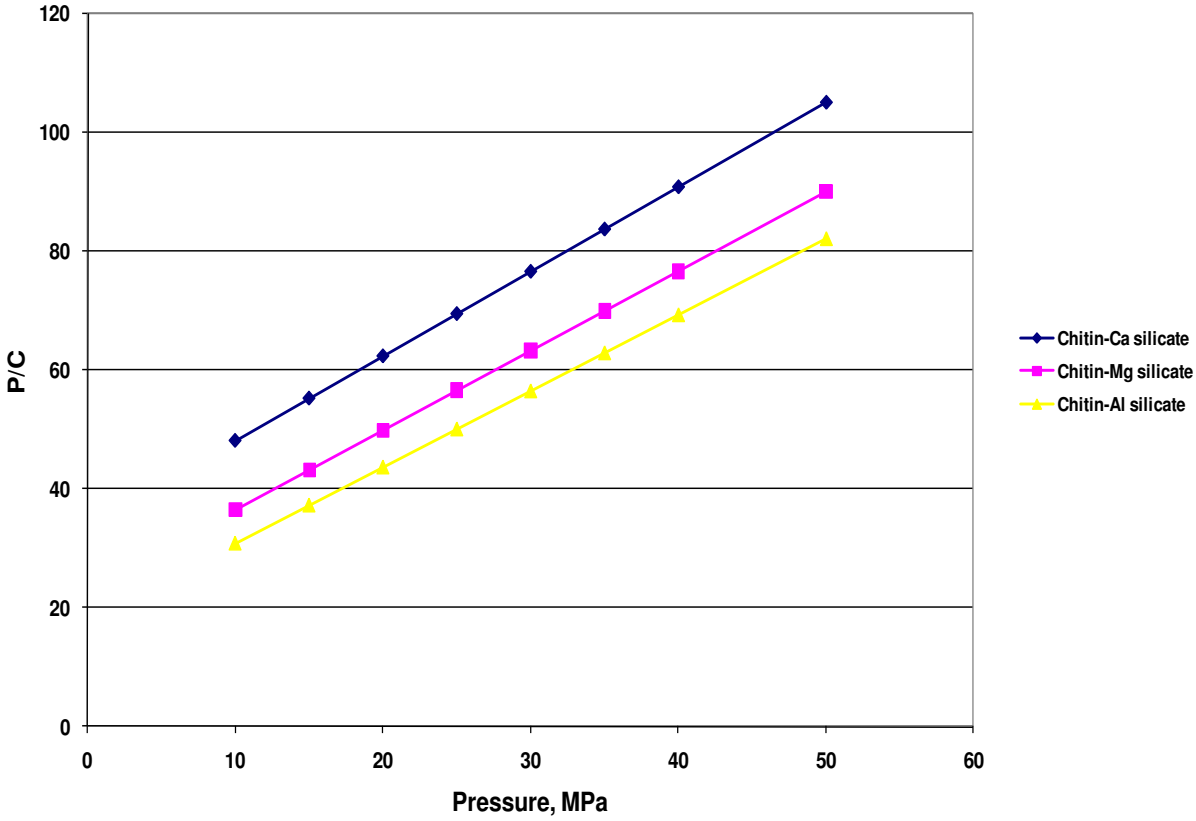

Figure 2.10 Kawakita plots for chitin-metal (Al, Mg, Ca) silicate co precipitates. Tablets were 12 mm in diameter and 400 mg in weight.

From the the data in the plots, the Kawakita constants a and 1/b are listed in Table 2.2. In terms of a constant, chitin showed the highest compressibility (highest a value). Increasing the Mg silicate content from 13% to 32% (%wt/wt) lowered the a value and therefore compressibility was decreased. In terms of metal type, chitin-Al silicate had the highest compressibility followed by chitin-Mg silicate which in turn was higher than chitin-Ca silicate.

Values of 1/b, which are an inverse measure of the amount of plastic deformation occurring during the compression process increased with increasing the Mg silicate content. This implies that increasing the Mg silicate content exhibited a lower degree of total plastic deformation during the compression process. Hence, it would appear that chitin exhibited a faster onset of plastic deformation during compression. On the other hand, chitin-Al silicate had a higher degree of plastic deformation than chitin-Mg silicate whereas chitin-Ca silicate showed the lowest degree. The product ab,

which is a measure of the extent of particle rearrangement, is shown in Table 2.2.

Table 2.2 Kawakita parameters for different concentrations of Mg silicate precipitates in the chitin-Mg silicate co precipitate and for chitin-metal (Al, Mg, Ca) silicate co precipitates.

Material	Metal silicate (% wt/wt)	Kawakita Parameters		
		a	1/b	ab
Chitin	0	0.82	10.60	0.077
Chitin-Mg silicate	13	0.80	11.86	0.067
Chitin-Mg silicate	19	0.77	14.00	0.055
Chitin-Mg silicate	24	0.76	15.68	0.048
Chitin-Mg silicate	32	0.75	17.37	0.043
Chitin-Al silicate	32	0.78	14.82	0.052
Chitin-Ca silicate	32	0.70	23.89	0.029

It appears that the degree of particle rearrangement of chitin decreased with increasing the Mg silicate content. This may imply that the metal silicate precipitated onto the chitin particles may have reduced the surface micro-irregularities of chitin and facilitated particle rearrangement during the densification phase of compaction. On the other hand, chitin-Ca silicate showed the lowest degree of rearrangement (Table 2.2). It appears that chitin-Ca silicate had the highest degree of packing. Such a trend could be correlated to the fact that chitin-Ca silicate had the highest true density (1.766) of all the examined chitin-metal silicates.

Finally, the good compaction characteristics provided by chitin-metal silicates was tested for their binding capabilities, disintegration time, and drug dissolution over poorly compressible drugs such as paracetamol and metformin HCl as examples of hydrophilic drugs and mefenamic acid as an example of a hydrophobic drug. Direct compression and wet granulation processing formulations were tested for the hydrophilic drugs. In addition, the performance of formulas containing paracetamol and metformin HCl drugs directly compressed with Ca silicate was tested (see Table 2.1). Results are summarized in Table 2.3.

Table 2.3 Hardness, disintegration, and dissolution results for the paracetamol, metformin HCl, and mefenamic acid tablets formulations.

Formula *	Hardness (N)	Disintegration Time (Sec)	Dissolution (% Drug Release at times 10, 20 min)
F1	103	44	91, 100
F2	118	48	86, 100
F3	144	261	67, 86
F4	98	41	94, 100
F5	112	50	90, 100
F6	159	336	75, 96
F7	126	84	60, 90
F8	131	300	42, 71

* See Table 2.1.

The dilution capacities (percentage of incompressible material) of paracetamol and metformin HCl were 58.1% (wt/wt) and 56.8% (wt/wt), respectively, for direct compression and wet granulation formulas containing chitin-Mg silicate as the investigated binder. Hardness values for F1, F2, F4, and F5 (see Table 2.4) indicated high binding capabilities with less than a minute of disintegration time for all the formulas. Full drug release (% assay measured) was attained at the 20 minute dissolution of both drug formulas. When Ca silicate was included in the paracetamol and metformin HCl formulas (same drug dilution capacities as F1 and F4) as a filler in direct compression mode (see F3 and F6 in Table 2.4), tablets displayed higher hardness values with much higher disintegration time. This may indicate that metal silicates functionality as disintegration promoters necessitated the presence of other superdisintegrants (chitin in this case) to enhance tablet disintegration.

The performance of chitin-metal silicates was evaluated in formulations with mefenamic acid as a model hydrophobic drug. Mefenamic acid was reported to be soluble in alkali hydroxides [40]. Direct compression of mefenamic acid with chitin-Mg silicate at the dilution capacity of 51.7% (wt/wt) resulted in hard tablets and 90% drug release within 20 minutes of dissolution. In comparison with PonstanTM Forte

500 mg, as the commercial drug reference, percentage drug release at the 20 minutes dissolution was much lower (71%). Therefore, the use of chitin-Mg silicate of alkaline nature (pH 8.5 for 5% w/v aqueous dispersion) could improve the solubility of mefenamic acid while maintaining intact physical properties of the tablets produced. For example, disintegration time of the mefenamic acid formula, F7, was even lower than PonstanTM Forte (F8) in which it was reported to compose of lactose, maize starch, sodium lauryl sulphate, and pregelatinized starch as fillers, binders, and disintegrants in addition to croscarmellose as the superdisintegrant [41]. Formula F7 was composed of one excipient, in addition to mefenamic acid and the lubricant, which enhanced better binding, disintegration, and dissolution properties to the tablets produced

2.4 Conclusions

Co-precipitation of a metal silicate on chitin particles offers industrial potential for use as a single filler which has binding as well as super-disintegration properties and can be used in directly compressed tablets or in wet granulation methodologies. The co-precipitation process causes physical adsorption of the metal silicates onto chitin particles as illustrated by the SEM data without any chemical interaction as evidenced by the IR and XRPD analysis. The good disintegration property of the highly non-hygroscopic product is most likely to be related to capillary action. Disintegration and binding properties were found to be independent of particle size and compression force applied. The final pH of the complex, the mechanical strength of the tablets produced, and the powder compressibility and plasticity were all found to be dependent on the identity of the metal silicate. Pharmaceutical applications using formulations containing paracetamol, metformin HCl, and mefenamic acid indicated the good binding and disintegration abilities of chitin–metal silicates with poorly compressible and/or non-polar drugs.

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CHAPTER THREE

3. CHARACTERIZATION OF THE IMPACT OF MAGNESIUM STEARATE LUBRICATION ON THE TABLETING PROPERTIES OF CHITIN-MG SILICATE AS A SUPERDISINTEGRATING BINDER WHEN COMPARED TO AVICEL® 200

3.1 Introduction

Solid dosage forms, e.g. tablets and capsules, are the most popular and preferred drug delivery systems. Tablet dosage forms are mainly composed of the API/APIs (active pharmaceutical ingredient) and excipients [1]. Excipients include diluents, binders, disintegrants, glidants and lubricants; the latter i.e. lubricants are usually added in the final stages of mixing of the formulation components prior to compression. The main function of lubricants is to prevent adhesion of compacts to the surface of the punches and dies, used in pharmaceutical manufacture, thus facilitating their ejection from the die cavity [2]. Furthermore, the presence of lubricants in formulated powder mixtures reduces inter-particulate friction leading to improved flow properties [3]. Such effects are mainly attributed to the ability of lubricants to be distributed as a surface film on the base/carrier material [2]. Magnesium stearate (MgSt) is the most widely used lubricant in pharmaceutical formulations [4]; the amount used is assessed during the early stages of pharmaceutical formulation development, and does not usually exceed 2% of the total powder weight used in tablet manufacturing [5]. In the case of MgSt the surface area per unit mass of powder mixture can be as high as 20% (w/w), depending on the other ingredients present in the pharmaceutical formulation [6]. In spite of the importance of lubricants in solid dosage forms, problems can occur when lubricants are added to excipient/API mixtures. The compaction and/or disintegration time of binders, fillers, and disintegrants has been reported to be negatively affected by the presence of lubricants [7]. The possible deleterious effects of MgSt have been attributed to the formation of a hydrophobic lubricant film on the surface of formulation component particles resulting, effectively, in a physical barrier [8]. Hence, the binding properties of the particles are altered and the wettability of the tablet ingredient particles will be negatively affected. This can result in retardation of water penetration into tablets and thereby cause delayed dissolution of the API, as the pore surfaces in the tablets become more hydrophobic [9, 10]. A decrease in crushing

strength is manifested in compacts made from microcrystalline cellulose (Avicel® 200) when concentrations of MgSt exceeding 2% (w/w) are used [11]. In addition, the physico-chemical effects of MgSt are dependent on the mixing time of the lubricant with the formulation components due to the redistribution of the lubricant on the mixture of particles [10]. Use of pregelatinized starch (Starch® 1500), calcium sulphate dihydrate, and amylase resulted in a large decrease in crushing strength, accompanied by an increase in mixing time with the lubricant [12]. The extent of lubricant sensitivity is dependent on a large number of factors, such as the nature and physico-chemical properties of the lubricant and other tablet ingredients. Therefore, in order to limit lubricant sensitivity, these factors must be considered in determining the optimal level of lubricant(s) in a formulation. In this regard, minimal effect of lubricant on powder compaction was reported for dicalcium phosphate dihydrate particles due to the very irregular surface of the excipient preventing the formation of a continuous film on blending with MgSt [13]. Moreover, low lubricant sensitivity is displayed by materials (for example brittle materials such as dicalcium phosphate dihydrate and β-lactose) which undergo high levels of fragmentation upon powder compression [14]. In addition, the presence of other formulation components can influence the film formation properties of lubricants and thereby minimize the deleterious effects of the lubricant. For example, mixing of excipient particles with MgSt and colloidal silica (Aerosil 200) can significantly suppress the negative effect of the lubricant on the interaction between lubricated particles [15].

Processing of chitin with silica products offers significant advantages for the exploitation of multifunctional excipients in the pharmaceutical industry. For example, chitin-metal silicate co-precipitates have, recently, been reported to be useful excipients, with appropriate binding and disintegration characteristics, when compared to conventional super-disintegrants and fillers [16, 17, 18]. However, the impact of chitin-metal silicate lubrication with MgSt has not been reported, especially in cases where MgSt causes undesirable changes in tablet properties (as described above). In the current investigation, the compaction and disintegration properties of chitin-metal silicates at different concentrations of MgSt are reported. Comparison with lubricated and unlubricated microcrystalline cellulose and its co-precipitated form with magnesium silicate are also examined. In addition, the effect of MgSt on

the ejection force of chitin-Mg silicate and on the dissolution profiles of ibuprofen and gemfibrozil (as model drugs exhibiting poor compactability/water solubility) formulated with chitin-Mg silicate are evaluated.

3.2 Experimental

3.2.1 Materials

Chitin (measured 50th percentile diameter d(0.5) = 216 µm, JBICHEM, Shanghai, China), Avicel® 200 (measured d(0.5) = 201 µm, FMC BioPolymer, Philadelphia, PA, USA), calcium hydrogen orthophosphate $CaHPO_4$ (CHO) (measured d(0.5) = 203 µm after being passed through a 250 µm mesh sieve and collected on a 200 µm mesh sieve, BDH Laboratory Supplies, Poole, UK), $Na_2SiO_3.5H_2O$ (BDH, Poole, UK), $MgCl_2.6H_2O$ (SIGMA Chemical Co, St. Louis, MO, USA), MgSt (d(0.5) = 3.1 µm, Mallinckrodt Corporation, Raleigh, NC, USA), ibuprofen powder (d(0.5) = 82.5 µm, Sigma, St. Louis, MO, USA), gemfibrozil powder (of a wide particle size distribution from 40 to 300 µm with a d(0.5) = 110 µm, Zhejiang Excel Pharmaceutical Co., Ltd., Zhejiang, China), and Lopid 600 mg gemfibrozil tablets (batch number: 0212027, expiry date: 01/2010, manufactured by Goedecke AG, Freiburg, Germany under license from Parke-Davis, Pontypool, Gwent, U.K) were used. All reagents used were of analytical grade.

3.2.2. Methods

3.2.2.1 Preparation of chitin-magnesium silicate and Avicel-magnesium silicate powders

Into a solution containing 10.0 g of $Na_2SiO_3.5H_2O$ (dissolved in 400 mL of deionized water), 10 g of chitin or Avicel® 200 were suspended under stirred conditions. 9.6 g of $MgCl_2.6H_2O$ was added to stoichiometrically react with sodium silicate to produce suspended particles of the magnesium silicate, which co-precipitated onto chitin or Avicel® 200. The particles were filtered using 20-25 µm filter papers (ALBET 135, Quantitative, Barcelona, Spain) then washed with deionized water until the filtrate conductivity, measured using a conductivity meter (METTLER TOLEDO MPC227, Greifensee, Switzerland), was less than 20 µS. The product was dried in an oven at

90ºC for 3 h, passed through a 250 µm mesh sieve, collected on a 200 µm mesh sieve and kept for further testing and characterization. If it is assumed that 1 mol of $Na_2SiO_3.5H_2O$ reacts, stoichiometrically, with 1 mol of $MgCl_2.6H_2O$ to produce 1 mol of $MgSiO_3$, the final magnesium silicate mass content is calculated to be 32% (w/w).

3.2.2.2. Tablet compression, crushing strength and disintegration testing

100.0 g of six powder blends of chitin-Mg silicate or Avicel® 200 or $CaHPO_4$ or Avicel-Mg silicate physically mixed with MgSt at concentrations of 0.25, 0.5, 1.0, 2, 5, and 10% (w/w) were prepared. Mixing was performed manually in a 2L Mini-blend v-blender (GlobePharma, New Brunswick, NJ, USA). The v-blender was operated at 30 rpm for a period of 5 min. Each of the powder samples was subjected to compression using a single 12 mm circular punch tableting machine (Manesty, Merseyside, UK) at compression pressures of 156, 182, 208, 234 MPa. Tablet weight was fixed at 400 mg. The crushing strength of the compacts was used to study the compactibility of the manufactured tablets. By measuring crushing strength, it is possible to compare results obtained for tablets formulated with different ingredients/compositions or under different compaction pressures. Crushing strength was calculated using the measured maximum force, F (N), which was applied diametrically to fracture the tablet, using a hardness tester (Copley, Nottm Ltd, Therwil, Switzerland). The crushing strength, σ, was calculated using the following equation [19]:

$$\sigma = \frac{2F}{\pi dL} \qquad (1)$$

where d (m) is the tablet diameter and L is the tablet thickness (m). The average crushing strength of 10 tablets was recorded for each sample. Using the tablet hardness measurement equipment, tablets were subjected to a diametrical compression test after they had been allowed to remain at room temperature for 24 h in a desiccator. Disintegration times were measured for chitin-Mg silicate, Avicel®

200, and Avicel-Mg silicate tablets produced using a disintegration tester (Caleva, Dorset, UK) in accordance with the USP 31 disintegration procedures for uncoated tablets. Comparison of disintegration times between different materials was carried out for tablets (12 mm diameter) compressed to reach a fixed crushing strength value of 0.6 MPa (equivalent to the maximum crushing strength for Avicel® 200 at 10% (w/w) MgSt concentration).

3.2.2.3. Compression data acquisition and analysis

Unlubricated and lubricated chitin-Mg silicate and Avicel® 200 samples, at MgSt concentrations of 1 and 5% (w/w) for the lubricated samples, were separately compressed by direct compression using a universal testing machine (UTM, RKM 50, PR-F system, ABS Instruments Pvt., Ltd., Leipzig, Germany). The punch speed was fixed at 10 mm/min. Different compression pressures from 10 to 70 MPa were applied. Three tablets were prepared to ensure reproducibility. The tablets were flat, 12 mm in diameter and 400 mg in weight. Bulk density was determined using a weighed 100 mL cylinder and a volumeter (Erweka GmbH, Heusenstamm, Germany). 20 g of the powder was gently filled into the cylinder. Bulk volume was read and bulk density calculated, as the average of five measurements.

The powder compression behaviour of the samples was evaluated using Kawakita analysis which was performed on three preparations of chitin-Mg silicate powder and on three Avicel® 200 samples. All the tested samples were unlubricated and lubricated (1 and 5% w/w) with MgSt. The Kawakita equation describes powder compression using the degree of volume reduction, C [20]:

$$C = \left[\frac{V_0 - V}{V_0}\right] = \frac{abP}{1 + bP} \qquad (2)$$

V_o is initial volume and V is the volume of the powder column under an applied pressure, P. The constant a is the minimum porosity of the material before compression while the constant b relates to the plasticity of the material. The

reciprocal of b defines the pressure required to reduce the powder bed volume by 50% [21, 22]. Equation (2) can be rearranged in linear form as:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad (3)$$

Particle rearrangement can be affected simultaneously by the two Kawakita parameters a and b. The combination of these into a single value, i.e. the product of the Kawakita parameters a and b, may be used as an indicator of particle rearrangement, and hence the powder packing density during compression. The average P/C values and their relative standard deviation at compression pressures between 10-70 MPa of the three tested un-lubricated and lubricated preparations and samples were ascertained.

3.2.2.4. Particles sized distribution analysis

The particle size distribution of chitin, chitin-Mg silicate, Avicel® 200, and Avicel-Mg silicate at MgSt concentrations of 0, 0.5, 1, and 5% (w/w), in the powder phase, was measured (Malvern Mastersizer 2000; Malvern, Worcestershire, UK), using dry powder, in the 0.02 µm to 2000 µm range. The instrument is equipped with a Scirocco 2000 unit as the dry powder feeder, with compressed air to transport the particles. The optimum air pressure was set at 0.1 bar, which ensured no breakup of agglomerates; the foregoing was verified by repeating the measurement five times for the same sample collected at the end of each run. Moreover, reproducibility was tested for three powder samples of chitin and Avicel 200 and for different preparations of chitin-Mg silicate and Avicel-Mg silicate. Three diameter values were used to characterize the particle population: d (0.1) 10^{th}, d (0.5) 50^{th}, and d (0.9) 90^{th} percentile diameter, respectively. The average of fifteen particle size distribution measurements for each powder and the percentage relative standard deviation for the d (0.9) were recorded.

3.2.2.5. Specific surface area

A gas sorption analyzer (Nova 2000, Quantachrome Co., Syosset, NY, USA) capable of measuring surface areas from 0.01 to more than 2,000 m^2/g was employed to obtain nitrogen vapor adsorption isotherms at 77 K. Chitin, chitin-Mg silicate, Avicel® 200,

and Avicel-Mg silicate samples were heated to 60°C while being purged under a stream of pure nitrogen. Purging was continued for 24 h prior to analysis and the experiments were undertaken in duplicate.

3.2.2.6. Scanning electron microscopy

Chitin-Mg silicate and Avicel® 200 samples at MgSt concentrations of 0 and 5% (w/w) were mounted on aluminum stubs and then coated with gold by sputtering at 1200 V and 20 mA for 105 sec using a vacuum coater. Samples were examined using a FEI Quanta 200 3D SEM (FEI, Eindhoven, Netherlands)

3.2.2.7. Compression of chitin-Mg silicate using a high speed tablet press

The procedure used to prepare chitin-Mg silicate in section 2.2 was scaled up using $Na_2SiO_3.5H_2O$ (2.5 kg), deionized water (100 L), chitin (2.5 kg), and $MgCl_2.6H_2O$ (2.4 kg). Stirring was carried out using a vertical mixer (Wuxi Mingzhou Environment Protection Machinery & Equip Factory, Jiangsu, China) in a 100 L stainless steel container The magnesium silicate suspension was filtered out using a filter fabric (Varun Tex, Inc., Madhya Pradesh, India) fitted on top of a 100 L empty container. Washing, drying, and sieving of the filter cake was carried out as described in section 2.2. The preparation was repeated until 10 kg of chitin-Mg silicate were produced. A 5 kg batch of the prepared chitin-Mg silicate was compressed using a Fette P2100 rotary tablet press (Fette, Schwarzenbek, Germany) into which 43 circular punches (12 mm) were fitted. Compression was carried out without MgSt at press speeds of 30,000, 50,000, 100,000, and 150,000 tablets / hr. A compression trial with MgSt was carried out at a press speed of 150,000 tablets / hr. The ejection force displayed on the instrument panel was recorded. Stickiness was visually observed on the upper and lower punches. 60 tablets were randomly taken out, weighed, tested using disintegration (10 tablets) and tensile strength (10 tablets) testers, and visually observed for the appearance of any surface cracking.

3.2.2.8. Dissolution testing of ibuprofen and gemfibrozil tablets

The effect of MgSt on the dissolution profile of ibuprofen tablets composed of 400 mg ibuprofen and 300 mg of either of the following excipients: chitin-Mg silicate,

Avicel® 200, and Avicel-Mg silicate was examined. The excipients were either lubricated with 1 or 5% (w/w) MgSt, or unlubricated. Excipients were physically mixed with ibuprofen and directly compressed into 13 mm circular tablets (700 mg tablet mass) using a single punch tableting machine at a compression pressure of 182 MPa. Five tablets were used for each dissolution profile test. The dissolution media was composed of phosphate buffer (pH 7.2). USP Apparatus II was used at a paddle rotary speed of 50 rpm. For dissolution studies of gemfibrozil, the tablets were composed of 600 mg gemfibrozil directly mixed with 224.5 mg of chitin-Mg silicate and 25.5 mg of MgSt (3% w/w) followed by direct compression into 13 mm circular tablets (850 mg tablet weight) using a single punch tableting machine at a compression pressure of 182 MPa. Five tablets were used for each dissolution profile test. The dissolution media was composed of a phosphate buffer (pH 7.5). USP Apparatus II was used at a paddle rotary speed of 50 rpm.

3.3 Results and Discussion

3.3.1. Effect of magnesium stearate concentration on the crushing strength of chitin and Avicel co-processed with magnesium silicate

The effects of the lubricant MgSt on powder compression for chitin-Mg silicate, Avicel® 200, calcium hydrogen orthophosphate and Avicel-Mg silicate are shown in Figure 3.1. The data show a general trend of decrease in tablet crushing strength as the amount of MgSt added to powder blends increases. However for blends composed of chitin-Mg silicate there is no significant change in crushing strength for MgSt compositions up to 2% (w/w). We therefore see no evidence for a decrease in tablet crushing strength when the MgSt concentration is increased up to 2% (w/w) for the chitin-Mg silicate and MgSt blends (Figure 3.1). This contradicts the general notion that tablet crushing strength decreases with increase in the MgSt concentration. For example, it has been reported that for a cyclodextrin/calcium silicate/MgSt tablet formulation, as the concentration of MgSt is increased above 1.5% (w/w), the crushing strength of an optimized fast disintegrating tablet formulation decreases [23]. In addition to the concentrations of MgSt normally used, Figure 3.1 includes two

extreme concentrations, i.e. 5 and 10% (w/w) of MgSt. The aforementioned concentrations of MgSt were included for the purpose of determining the extent of any deleterious effect of MgSt on the compaction of chitin-Mg silicate powder. It is clear, from the data in Figure 3.1 that the crushing strength of the compacts made of chitin-Mg silicate decreases to almost half of the values recorded for the compacts containing 0-2% (w/w) MgSt. Nevertheless, the addition of MgSt, up to 5 or 10% (w/w), to chitin-Mg silicate powder still results in hard tablets with crushing strength values reaching 2.0 MPa at a compression pressure of 234 MPa. Hence, chitin-Mg silicate is able to accommodate up to 10% (w/w) of MgSt and still maintain intact solid tablets.

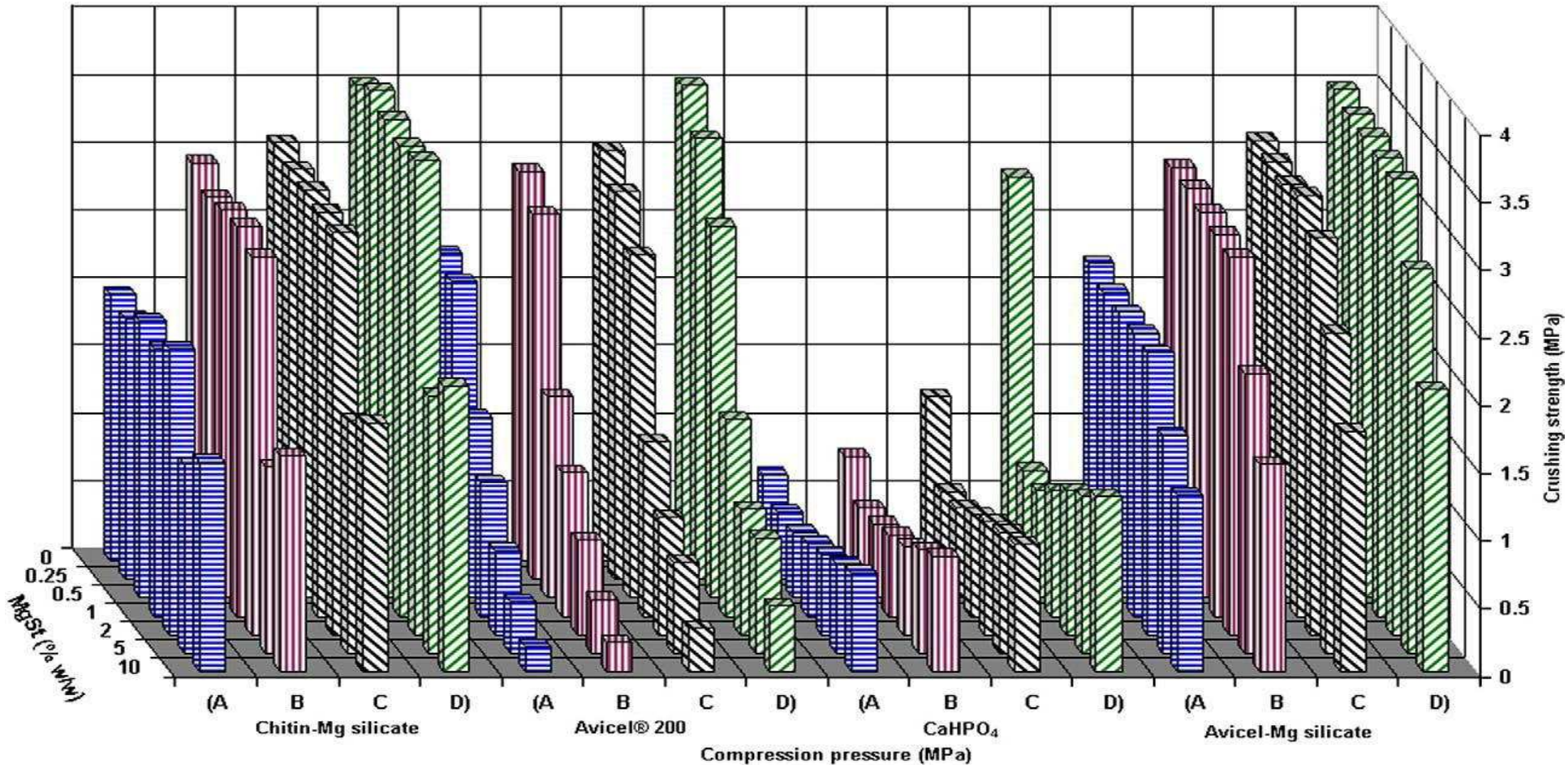

Figure 3.1 Effect of MgSt concentration on tablet crushing strength of chitin-Mg silicate, Avicel ®200, calcium hydrogen orthophosphate, and Avicel-Mg silicate co-precipitates at different compression pressures. Tablets, 12 mm in diameter and weighing 400 mg each were used. A, B, C, and D represent compression pressures of 156, 182, 208, 234 MPa, respectively.

The importance of this finding is clearly demonstrated when MgSt is added to separate powders of Avicel® 200 and $CaHPO_4$. The data in Figure 3.1 illustrate the fact that when MgSt is added to microcrystalline cellulose or $CaHPO_4$, the resultant tablet crushing strength decreases. For example, in the case of MgSt concentrations of 0.25, 0.5, 1.0 and 5% (w/w), there was a 6, 48, 63, and 86% decrease, respectively, in tablet crushing strength of Avicel® 200 compacts at a compression pressure of 182 MPa. However, the percentage decrease in tablet crushing strength for lubricated $CaHPO_4$ was 31, 29, 22, and 16% for the 0.25, 0.5, 1.0 and 5% (w/w) MgSt concentrations, respectively, at a compression pressure of 182 MPa. It is generally accepted that MgSt has a more negative effect on the crushing strength of tablets constituted of deformable materials (e.g. Avicel® 200) than brittle ones (e.g. $CaHPO_4$). Brittle materials are more likely to fracture and fragment during compaction. As more fresh surfaces, not covered by lubricant particles, are generated, they tend to bond together. Film formation on deformable particles, on the other hand, weakens the bonding of the granules as there are less fresh surfaces formed during compaction [14]. Therefore, the sensitivity of $CaHPO_4$ to MgSt was less when compared to Avicel® 200; especially at MgSt concentrations greater than 0.5% (w/w). However, it is noted that the percentage decrease in tablet crushing strength for lubricated $CaHPO_4$ undergoes a significant decrease with increasing MgSt content. This behavior is suggested to be a typical example of the combination of brittle (e.g. $CaHPO_4$) and plastic (e.g. MgSt) materials which plays a significant role in altering the physico-mechanical characteristics of a material [24, 25]. Optimum tableting performance is generally achieved by using such a combination which produces a synergistic effect; thus improving functionalities such as compaction performance, flow properties, lubricant sensitivity etc. Therefore, the small increase in tensile strength (detected mostly at the 10% (w/w) MgSt concentration for all working pressures in the data shown in Figure 3.1 and in particular for the mixtures compressed at 234 MPa) encountered with $CaHPO_4$ as the mass of MgSt was increased is, presumably, a result of a combination of $CaHPO_4$ as a

brittle material, with magnesium stearate as a plastic material.

In performing the same powder compaction tests for lubricated Avicel® 200 on which magnesium silicate was co-precipitated, powder sensitivity appeared to be insignificant. This was evident from the lower decrease in tablet crushing strengths, up to MgSt concentrations of 2% (w/w), when compared to Avicel® 200. Moreover, the data in Figure 3.1 illustrates the finding that lubricated Avicel-Mg silicate maintains highly compactable tablets at MgSt concentrations of 2 and 5% (w/w). Hence, the low lubricant sensitivity of chitin-Mg silicate is likely to be due to the presence of Mg silicate co-precipitated on chitin particles. Arguably, this behavior resembles the improved lubricant sensitivity of coprocessed silicified microcrystalline cellulose (Prosolv®). Prosolv® is microcrystalline cellulose containing 2% (w/w) colloidal silicon dioxide. Tablets prepared with Prosolv have been reported to maintain crushing strength profiles when MgSt (0.5% w/w) was added [26].

3.3.2. Effect of magnesium stearate concentration on the disintegration time of chitin and Avicel co-processed with magnesium silicate

Comparison of the influence of composition on disintegration time between chitin-Mg silicate, Avicel® 200, and Avicel-Mg silicate at the 0, 0.25, 0.5, 1.0, 2, 5, and 10 % (w/w) MgSt (Figure 3.2) is only possible for tablets with the same crushing strength (in MPa). Since the maximum possible crushing strength attained for lubricated Avicel® 200 was recorded as 0.6 MPa, and since the disintegration time for chitin-Mg silicate is independent of crushing strength [18], disintegration time testing was carried out up to this value of crushing strength for all the tested materials. Although short disintegration times are often associated with tablets with poor crushing strength, this crushing strength range was used to in order to fairly examine the contribution of lubrication on the tablets' disintegration time. The hydrophobic character of MgSt appears to have little effect on chitin-Mg silicate powder; whereas in the case of Avicel® 200 the influence of the lubricant on its disintegration time is, by comparison, distinctly noteworthy (Figure 3.2). The super-disintegration power of chitin-Mg silicate is retained at a MgSt concentration of 2% (w/w). Above this concentration, disintegration did not exceed a maximum time of 5 min at 10% (w/w) concentration of MgSt. Even though tablet crushing strength values

for Avicel® 200 decreased, due to the presence of MgSt, the disintegration time remained high. The results for the 5 and 10% (w/w) concentrations of MgSt clearly demonstrate the hydrophobic hindrance of the lubricant coat towards water penetration, as tablets disintegrated within 17 and 30 min, respectively.

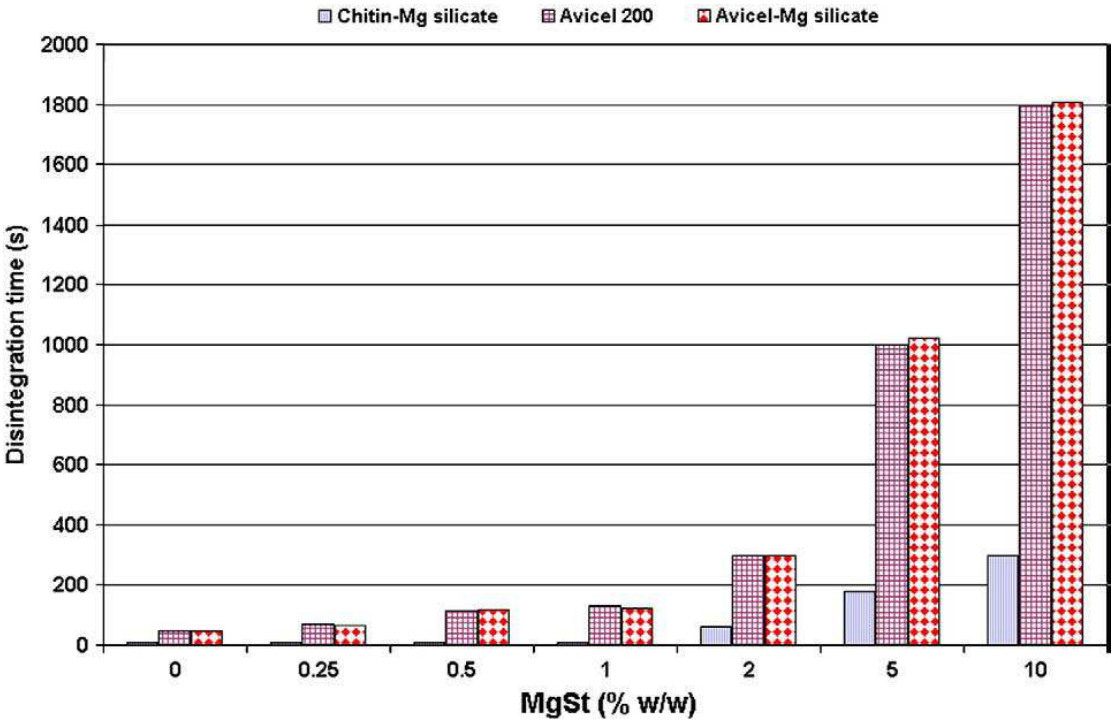

Figure 3.2 Effect of MgSt concentration on the disintegration time of chitin-Mg silicate, Avicel® 200, and Avicel-Mg silicate tablets. Tablets were 12 mm in diameter and 400 mg in weight, compressed to reach a fixed crushing strength value of 0.6 MPa.

On the other hand, the data shown in Figure 3.2 indicates that modification of Avicel® 200 with Mg silicate co-precipitate does not decrease the long disintegration time encountered with lubricated Avicel® 200 when the former is also lubricated. The aforementioned finding gives more credence to the use of chitin-magnesium silicate, when disintegration time and drug dissolution are significant parameters in formulations. The difference in disintegration time between tablets formulated with chitin-Mg silicate or Avicel® 200 highlights the difference in particle-particle (MgSt-excipient) distribution (as will be discussed below).

3.3.3. Compressibility analysis of chitin and Avicel co processed with magnesium silicate

In order to attain an understanding of the effects of lubricant on powder compression, at the particulate level, it was important to carry out Kawakita plot analysis (Table 3.1) of the two plastically deforming materials chitin-Mg silicate (Figure 3.3) and Avicel® 200 (Figure 3.4).

Table 3.1 Kawakita parameters for lubricated (with MgSt) and unlubricated chitin-Mg silicate and Avicel® 200.

Magnesium Stearate (%,w/w)	Slope	Intercept	a	ab	b	1/b
	Chitin-Mg silicate					
0	1.33	23.217	0.74	0.043	0.05757	17.37
1	1.34	9.6623	0.74	0.103	0.138963	7.19
5	1.35	8.5486	0.73	0.116	0.158669	6.30
	Avicel® 200					
0	1.49	11.899	0.66	0.084	0.125767	7.95
1	1.37	12.707	0.72	0.078	0.10798	9.26
5	1.40	18.592	0.71	0.0537	0.075307	13.27

The choice of the Kawakita plot is based on the fact that different densification changes from the bulk density state to compressed state of powders, on the assumption of e.g. the appearance of agglomerates, will directly influence the powder volume reduction upon compression. For chitin-Mg silicate, the insignificant change in the value of the constant a for the unlubricated chitin-Mg silicate, at MgSt concentrations of 1 and 5% (w/w), indicates that chitin-Mg silicate shows no change in compressibility. Theoretically, the constant, 'a' is the minimum porosity of a material before compression. Therefore, the porosity of chitin-Mg silicate remains unchanged for the unlubricated powder and at the 1 and 5% (w/w) concentrations of MgSt.

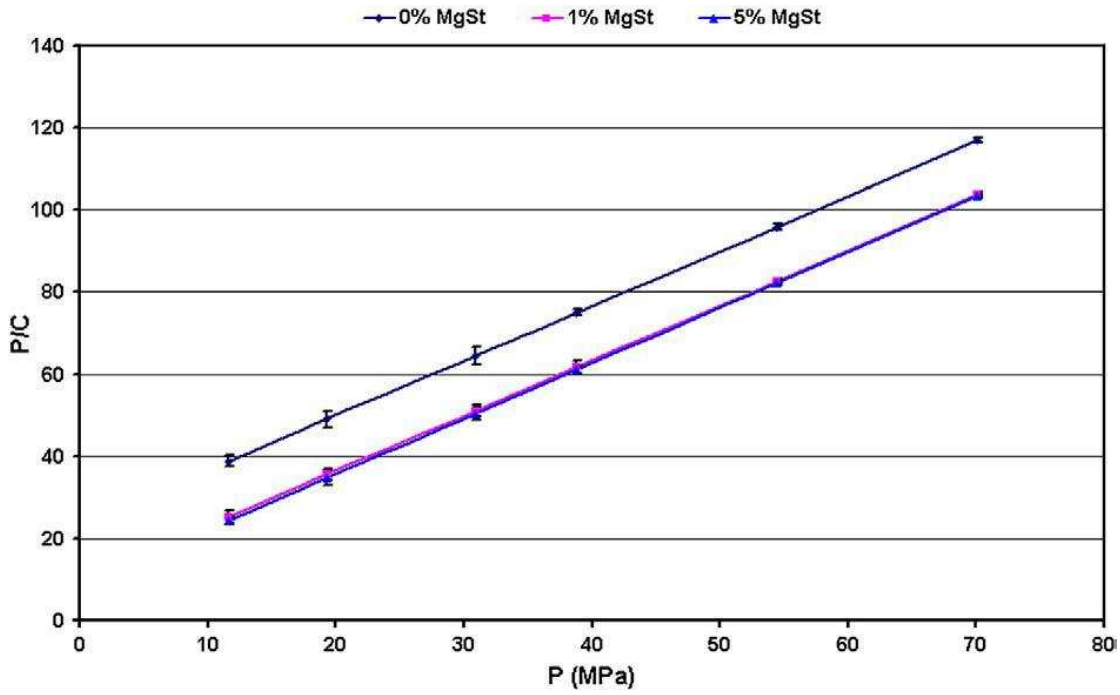

Figure 3.3 Kawakita plots for unlubricated (0% w/w) and lubricated (1%, 5% w/w) chitin-Mg silicate with MgSt. Tablets were 12 mm in diameter and 400 mg in weight.

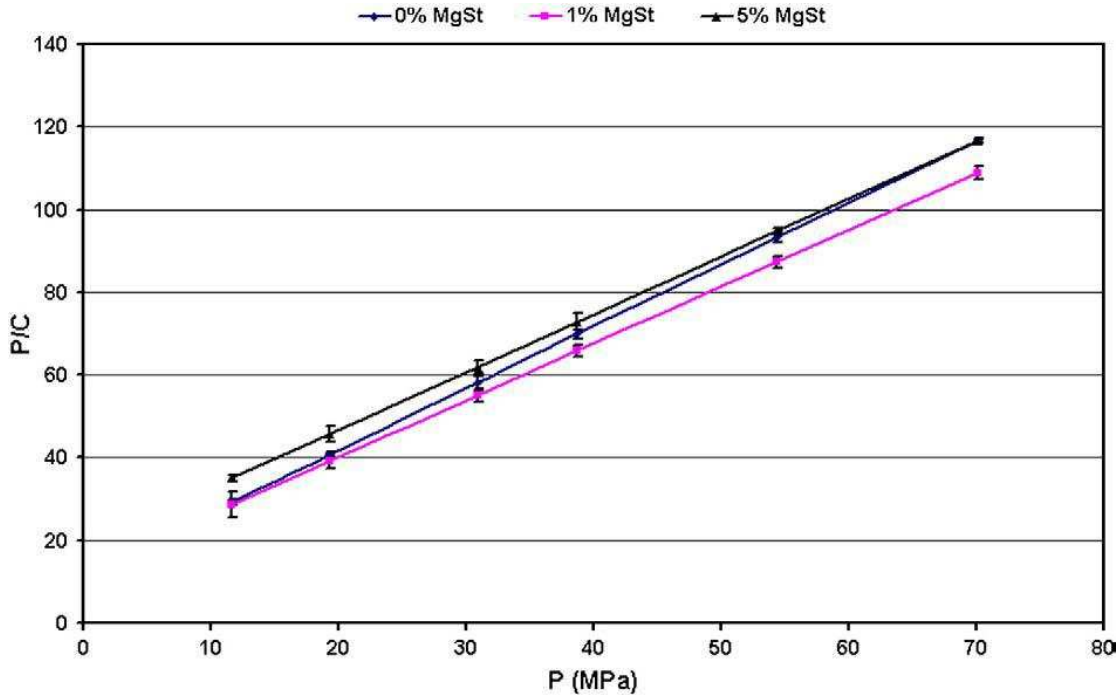

Figure 3.4 Kawakita plots for unlubricated (0% w/w) and lubricated (1%, 5% w/w) Avicel® 200 with MgSt. Tablets were 12 mm in diameter and 400 mg in weight.

The foregoing result can be accounted for by the lack of change in bulk density of chitin-Mg silicate (illustrated in Table 3.2) and indicates that the initial particle size remains unchanged for both lubricated and unlubricated chitin-Mg silicate.

Table 3.2 Physical parameters for unlubricated and lubricated chitin, chitin-Mg silicate, Avicel® 200 and Avicel-Mg silicate powders.

Excipient	Magnesium Stearate (%, w/w)	Bulk density (g/mL)	Particle size distribution (μm)				Specific surface area (m^2/g), %RSD
			d(0.1)	d(0.5)	d(0.9)	% RSD	
Chitin	0.0	0.17	70.7	216.6	418.6	0.46	48.80, 1.70
	0.5	0.17	72.5	217.5	416.4	0.37	43.81, 1.29
	1.0	0.17	71.3	217.9	413.5	0.51	37.94, 1.90
	5.0	0.18	60.6	218.9	414.6	0.38	29.52, 1.08
Chitin-Mg silicate	0.0	0.32	50.8	206.8	392.3	0.37	17.60, 1.48
	0.5	0.32	49.0	207.0	388.0	0.34	22.60, 1.27
	1.0	0.33	37.1	202.6	394.3	0.43	20.30, 1.41
	5.0	0.33	15.9	202.1	391.4	0.41	20.90, 1.35
Avicel® 200	0.0	0.35	74.2	201.6	367.4	0.45	0.78, 3.20
	0.5	0.41	76.5	217.3	596.4	0.51	0.53, 3.80
	1.0	0.43	83.2	220.4	648.9	0.36	0.54, 3.31
	5.0	0.41	36.5	204.9	439.6	0.44	0.58, 3.90
Avicel-Mg silicate	0.0	0.41	74.1	201.0	383.2	0.41	21.20, 1.29
	0.5	0.41	60.7	206.9	394.7	0.39	18.20, 1.76
	1.0	0.41	45.6	209.2	397.0	0.48	18.32, 1.21
	5.0	0.41	32.8	212.3	406.3	0.38	19.80, 1.13

On the other hand, Avicel® 200 exhibits an increase in the a value, i.e. a higher increase in porosity, when MgSt is added at concentrations of 1 and 5% (w/w); thus highlighting the increase in particle size when Avicel® 200 is subjected to lubrication. It should be noted that the minimum porosity attained (maximum particle size before compression)

for Avicel® 200 was recorded for the powders in the order: lubricated Avicel® 200 (1% (w/w) MgSt> lubricated Avicel® 200 (5% (w/w) MgSt) > unlubricated Avicel® 200 (this trend in particle size will be examined further throughout the discussion).

Values for the product ab, which is a measure of the extent of particle rearrangement during compression, are shown in Table 3.1. The degree of particle rearrangement of chitin-Mg silicate increases with increasing MgSt content. Generally, particle rearrangement is determined by the flow of smaller particles into the voids between larger particles; therefore it would be expected that the presence of a lubricant would minimize inter-particle friction and facilitate particle slippage. Apparently, from the elevation shift (downward in this case) of the gradient of the data for the lubricated, when compared to unlubricated, chitin-Mg silicate (Figure 3.3), at any fixed pressure value, the degree of volume reduction (C) increases when MgSt is added to chitin-Mg silicate; allowing improved consolidation behavior. This, presumbably, brings the particle surface areas into closer proximity as new surface and denser compacts are formed. However, this was not the case for Avicel® 200 which, when lubricated, produced a decreased level of particle rearrangement as shown by the decreased ab values (Table 3.1) for the 1 and 5% (w/w) MgSt concentrations. On the other hand, the elevation of the gradient of the data for the 5% (w/w) lubricated Avicel® 200 is shifted (upward in this case) when compared to unlubricated Avicel® 200 (Figure 3.4) indicating a decrease in volume reduction of the Avicel, when lubricated to this extent. It is hypothesized, from the a and ab values, that for Avicel® 200 the degree of particle-particle interaction increases when lubricated with MgSt. The foregoing suggestion is in agreement with the data of Faqih et al., [27] who reported an improvement in powder flow properties of microcrystalline cellulose due to the presence of coarse particles of Avicel agglomerates when MgSt was present at a concentration of 0.25% (w/w). In the case of chitin-Mg silicate, a similar effect of lubricant was not observed.

Values of 1/b, which are an inverse measure of the amount of plastic deformation

occurring during the compression process, decrease with increasing MgSt content (Table 3.1) for chitin-Mg silicate (i.e. increase in plasticity). But, the plasticity of Avicel decreases with increasing MgSt content (increasing 1/b values in Table 3.1). The increased level of chitin-Mg silicate particle rearrangement, accompanied by its increased level of plasticity upon lubrication, indicates an increased tendency for particle fragmentation during compaction. The extent of particle fragmentation will have a considerable influence on susceptibility to lubrication [28]. Generally, the bonding properties of a highly fragmenting material seem not to be significantly affected upon lubrication as clean, lubricant-free surfaces are created by fragmentation [14]. Nevertheless, lubricated Avicel® 200 (which showed a decreased level of particle rearrangement and plasticity) may undergo a decreased number of surface contact points between the compressed particles upon fragmentation. The extent of this decrease was highly significant at 5% (w/w) MgSt concentration resulting in the lowest powder volume reduction and the lowest tablet crushing strength values. Such behavior is the most likely reason for the weakness of lubricated Avicel® 200 compacts compared to lubricated chitin-Mg silicate. The aforementioned hypothesis is further supported by the b values in Table 3.1. The constant b is inversely related to the yield strength of the particles and the higher the value of b, the greater the total plastic deformation occurring during compression [29]. Total plastic deformation creates more contact points for inter-particle bonding [30]. Thus, higher b values indicate high tablet crushing strength. It is clear, from the data presented in Table 3.1, that lubricated chitin-Mg silicate has higher b values when compared with Avicel® 200.

3.3.4. Particle size distribution, bulk density, and specific surface area measurements of unlubricated and lubricated chitin and Avicel co-processed with magnesium silicate

Evidence for the lack of change in particle size of chitin-Mg silicate, when lubricated with MgSt, is illustrated in Table 3.2. The measured d (0.5) and d (0.9) values for chitin-Mg silicate particle size remain almost unchanged at MgSt concentrations of 0.5, 1, and 5% (w/w), respectively, when compared to unlubricated chitin-Mg silicate. The same behavior occurs for the d (0.5) and d (0.9) values of lubricated and unlubricated chitin. For Avicel® 200, there is an increase in the d (0.5) values at 0.5 and 1% (w/w) MgSt concentrations; reaching a maximum of 220 µm (at the 1% (w/w) lubricant concentration). In addition, at the same lubricant concentrations (0.5 and 1% w/w), the d (0.9) values for lubricated Avicel® 200 indicate the presence of larger particles, reaching a particle size of 649 µm (at 1% w/w lubricant concentration). This is evidence for the presence of Avicel agglomerates at these concentrations of MgSt. However, at the 5% (w/w) lubricant concentration, Avicel® 200 undergoes a decrease in the d(0.5) and d (0.9) values (205 µm and 440 µm, respectively) when compared to Avicel® 200 lubricated with MgSt at the 0.5 and 1% (w/w) concentrations (Table 3.2). Nevertheless, agglomerates, albeit to a lesser extent when compared to the 0.5% lubricant concentration sample, may still be present as indicated by the d(0.9) value of 440 µm. The differences in particle size distribution are reflected in the measured bulk densities for the unlubricated and lubricated chitin, chitin-Mg silicate and Avicel® 200 (Table 3.2). The bulk densities of chitin and chitin-Mg silicate, when lubricated with MgSt, remain almost unchanged; similar to the particle size distribution behavior. Whereas, Avicel® 200 shows an increase in bulk density when lubricated with MgSt, thereby indicating the contribution of the formed agglomerates to the increase in powder bulk density; as more particles result in more mass occupying the same volume.

The effect of co-precipitated magnesium silicate on particle size distribution and bulk density was examined for Avicel® 200. It is evident from the fixed bulk density and the slight increase in the d (0.9) values for lubricated Avicel-Mg silicate compared to

lubricated Avicel® 200 (Table 3.2) that magnesium silicate minimizes the adhesion potential of lubricated Avicel® 200. Therefore, the increase in particle size of Avicel® 200 can be correlated to the cohesive tendency of MgSt to enhance particle agglomeration [31]. The most probable mechanism, for lubricated Avicel® 200, starts by partial filling of particle cavities, then quasi-total filling of cavities, and, finally, the formation of a peripheral layer of varying composition around the particles [32]. The particle size distribution results, Table 3.2, illustrating such agglomeration were measured at a MgSt concentration of 1% (w/w) added to Avicel® 200. However, at higher concentrations (in this case 5% w/w) of MgSt, the interaction favors de-agglomeration. At the 5% (w/w) MgSt concentration, agglomerates reach a critical size where an equilibrium occurs between breakdown and size increase of the agglomerates [32]. The absence of an increase in particle size distribution for the lubricated chitin-Mg silicate, in the presence of MgSt, indicates the absence of agglomeration. This conclusion is based on the assumption that chitin-Mg silicate has a higher uptake capacity for MgSt inside its cavities before forming the peripheral layer around the particles. Such an assumption is based on the fact that chitin and its derivates (like chitosan) are well characterized by their high absorption capacities for fatty acid materials (e.g. MgSt). In this context, it should be noted that chitin does not necessarily need to be converted to chitosan in order to absorb/adsorb fatty acids [33].

The decrease in the crushing strength values of lubricated Avicel® 200, the observed agglomeration and lack of agglomeration for lubricated Avicel® 200 and chitin-Mg silicate, respectively, are theoretically considered to be related to their interaction with MgSt. This hypothesis is based upon the physical, chemical and geometric properties of the particles. For example, the agglomeration of particles when lubricated with MgSt is related to the electrostatic charging of particles during blending of dry powders [28, 34]. In this regard, it is suggested that the cohesive characteristics of MgSt may enable MgSt auto-agglomerates to stick to oppositely charged particles and thus form larger

agglomerates of high MgSt content. In relation to the foregoing statement, the physicochemical properties of the chitin surface are important. The surface of chitin has been reported to possess a greater tendency for the adsorption of highly hydrophobic materials compared to materials of low hydrophobicity. It has also been suggested that the difference is likely to be due to partitioning of the compounds into the chitin particles and not due to adsorption at the surface of the particles [33]. Therefore, the distribution of MgSt on the surface of Avicel (as a peripheral layer) will not be the same as that on the surface of chitin or chitin-Mg silicate; most probably because of their high adsorption or partitioning tendencies towards MgSt. With regard to geometric structure, Ohta et al. [35] suggested that the deleterious effect of MgSt on tablet hardness cannot be attributed to the hydrophilic structure of silica particles but to the geometric structure which they defined as a three-dimensional property such as porosity, particle size and specific surface area. They concluded that the increase in tablet hardness of lubricated Avicel® PH-101 with MgSt was due to the presence of hydrophilic porous silica of high surface area. This explains the role of co-precipitated magnesium silicate onto chitin or Avicel particles in minimizing the deleterious effect of MgSt on tablet hardness. Such an assumption is based on the fact that synthetic magnesium silicate has a highly porous structure [36]. Studies reported by Late et al. [23] lend support to this idea by hypothesizing that the combined use of calcium silicate (Rxcipients FM 1000®) with superdisintegrants, provides acceptable tablet hardness whilst concomitantly allowing rapid tablet disintegration; in less than 30 seconds in the mouth. Furthermore, the co-precipitated synthetic magnesium silicate has a high adsorption capacity for fatty acids (MgSt in this case) [36, 37]. This is due to the presence of the negatively charged silanol groups (≡Si−OH) as the most active groups on the surface; they normally provide the site for physical adsorption of organic particles [38], more specifically those which carry a positive electrostatic charge e.g. MgSt [39]. Hence, the lack of agglomeration of chitin-Mg silicate could be correlated to the peripheral layer formation of MgSt in a different

manner than for Avicel® 200 particles. This is due to the fact that chitin and Mg silicate have adsorption/absorption tendencies for MgSt. As stated earlier, MgSt can partition inside chitin particles. In addition, the minimal extent of aggregation and decrease in tablet crushing strength values for Avicel-Mg silicate particles accounts for the role of magnesium silicate in hindering peripheral layer formation.

The extent of MgSt distribution onto particle surfaces can be correlated with their specific surface areas, illustrated in Table 3.2, since surface coverage is related to the geometric structure of the particles [35]. Chitin exhibits a high specific surface area (48.8 m^2/g) when compared to Avicel® 200 (0.78 m^2/g) in spite of a similar particle size (Table 3.2). When chitin is lubricated with MgSt, the particles undergo a decrease in specific surface area from that of unlubricated particles, but this parameter (for unlubricated and lubricated chitin) remained significantly higher than that for unlubricated and lubricated Avicel® 200 (Table 3.2). This suggests that chitin has a highly porous structure giving rise to more surface area for MgSt distribution than is the case for Avicel® 200. Co-precipitation of magnesium silicate onto chitin particles results in a decrease in the specific surface area (17.6 m^2/g) compared to chitin, but it still remains ~23 times higher than Avicel® 200 (specific surface area of 0.78 m^2/g). Upon lubrication with MgSt (at concentrations of 0.5% and 5.0% w/w), the specific surface area of Avicel® 200 decreases, as expected, due to the coverage of the micro-irregular surface by the added lubricant. However, it would be hard to judge the extent of this decrease for different lubricant concentrations as Avicel particle size varies at all concentrations of MgSt (Table 3.2). In the case of chitin-Mg silicate, lubrication caused no significant alteration in the high specific surface areas found for the chitin-Mg silicate particles (Table 3.2). This finding further confirms the high uptake capacity of the particles towards coverage with MgSt. Finally, co-precipitation of magnesium silicate on Avicel particles results in a higher specific surface area (21.2 m^2/g) when compared to Avicel® 200 (0.78 m^2/g), as illustrated in Table 3.2. Upon lubrication with MgSt, at 0.5 and 5.0% (w/w), the

measured specific surface area did not change significantly from that for unlubricated Avicel-Mg silicate. This explains the lower reduction in crushing strength values of lubricated Avicel-Mg silicate when compared to lubricated Avicel® 200 (Figure 3.1) as the surface of Avicel-Mg silicate provides more contact area upon compression than Avicel® 200.

In summary the high lubricant uptake capacity of chitin-Mg silicate, due to its high surface area, displays minimal (if any) agglomeration as indicated by the particle size distribution. This is confirmed by the lack of change in values of a but increased ab values obtained from the Kawakita analysis. On the other hand, the relatively low surface area of Avicel® 200 results in complete coverage with MgSt giving rise to an increased level of agglomeration, as indicated by the increased a and decreased ab parameter values from the Kawakita analysis. The change in particle size, therefore, contributes to the change in particle behavior towards compression. Theoretically, the tensile strength of agglomerates decreases with increase in particle size [40]. Therefore, the observed decrease in the tablet crushing strength, for Avicel® 200 when lubricated with MgSt, can be correlated to its tendency towards agglomeration.

3.3.5. Scanning electron microscopy of lubricated and unlubricated chitin and Avicel co processed with magnesium silicate

Particle shape and size were examined using scanning electron microscopy (Figure 3.5). When comparing the surface of chitin powder, Figure 3.5.A, with the surface of chitin-Mg silicate, Figure 3.5.B, it is clear that chitin undergoes a change in topography from a flat, smooth surface to a more irregular three dimensional compact. The addition of MgSt did not change the visual appearance of chitin-Mg silicate particles when observed at the same magnification level (Figure 3.5.C). However, for Avicel® 200 particles visually observed at the magnification level of 400x (Figure 3.5.D) can only be clearly observed at a lower magnification level of 200x (Figure 3.5.E). In other words, a reduced depth of focus was used to visualize large particles (agglomerates). Therefore, the massive particle of Avicel® 200 in Figure 3.5.D could be an agglomerate of more than one particle.

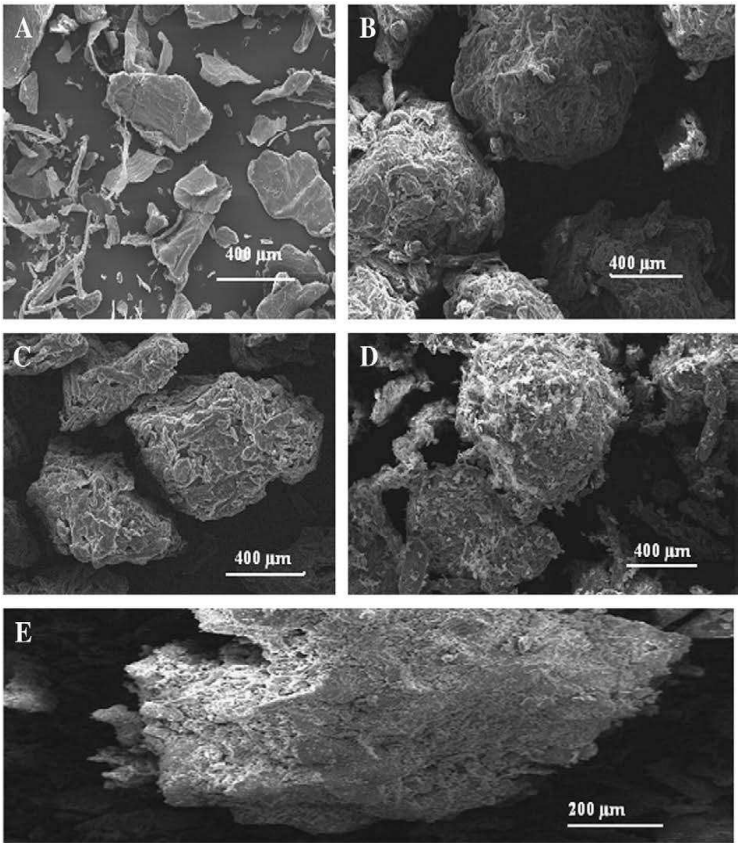

Figure 3.5 SEMs of un-lubricated chitin (A), un-lubricated chitin-Mg silicate (B), lubricated particles of chitin-Mg silicate up to 5% (w/w) MgSt (C), un-lubricated Avicel® 200 (D), and lubricated Avicel® 200 up to 5% (w/w) MgSt (E).

3.3.6. Performance of chitin-Mg silicate on the high speed tablet press machine and the role of MgSt

The performance of a batch of chitin-Mg silicate powder on the Fette high speed tableting machine was tested. The output parameters are shown in Table 3.3. At all the Fette press speeds, used in steps 1-4 in Table 3.3, no stickiness was observed on the lower and upper surfaces of the punches. This is further quantitatively indicated by the constant weight of the tablets. Tablet crushing strength and disintegration time remained relatively constant at all press speeds. With respect to the ejection force values, these typically increased with increasing press speed. Fortunately, they still remained below the maximum acceptable limit of 300 N in tablet compression [41].

Table 3.3 Effect of Fette P2100 tablet press compression speed on unlubricated and lubricated (up to 0.5% w/w with MgSt) ejection force for chitin-Mg silicate, stickiness to the punches, tablet crushing strength, disintegration time, appearance of cracks and tablet weight. Tablets were 12 mm circular.

Step	Action	Speed, tablet/hr	Force applied (kN)	Ejection Force, (N)	Stickiness	Tablet crushing strength, (MPa)	Tablet disintegration time, (s)	Cracks	Tablet average weight, (mg)
1	-	30,000	9.9	140	No stickiness	1.5-2.1	12	Exist	640±2
2	Increase Fette speed	50,000	8.1	182		1.5-2.0	12	Exist	640±3
3	Increase Fette speed	100,000	9.6	242		1.2-1.5	12	Exist	640±4
4	Increase Fette speed	150,000	9.6	278		1.5-1.8	12	Exist	640±5
5	With Mg stearate, 0.5% (w/w)	150,000	10.7	53		1.5-2.1	12	None	640±3

However, the appearance of surface cracks was the major defect observed. Crack formation is usually caused by the shear stress generated by die-wall friction during ejection of the tablets [42]. To reduce die-wall friction, MgSt was applied (step 5 in Table 3.3) to the formula at a concentration of 0.5 % (w/w). It is clear from the data presented in Table 3.3 that MgSt plays a significant role in reducing die-wall friction and thus eliminating the development of cracks.

3.3.7. Dissolution of ibuprofen and gemfibrozil tablets formulated by direct compression with chitin and Avicel co-processed with magnesium silicate

The extent of MgSt sensitivity was investigated in relation to the dissolution profile of two model drugs: ibuprofen and gemfibrozil. In addition to their poor compressibility, the two drugs were chosen because of the high cohesive characteristics of their bulk powders. Therefore, they may require high concentrations of MgSt in order to overcome such behavior [43]. However, this could negatively affect the crushing strength of the tablets. In the case of ibuprofen using lubricated (1% and 5% w/w) and unlubricated chitin-Mg

silicate, Avicel® 200, and Avicel-Mg silicate results in the drug dissolution profiles shown in Figure 3.6.

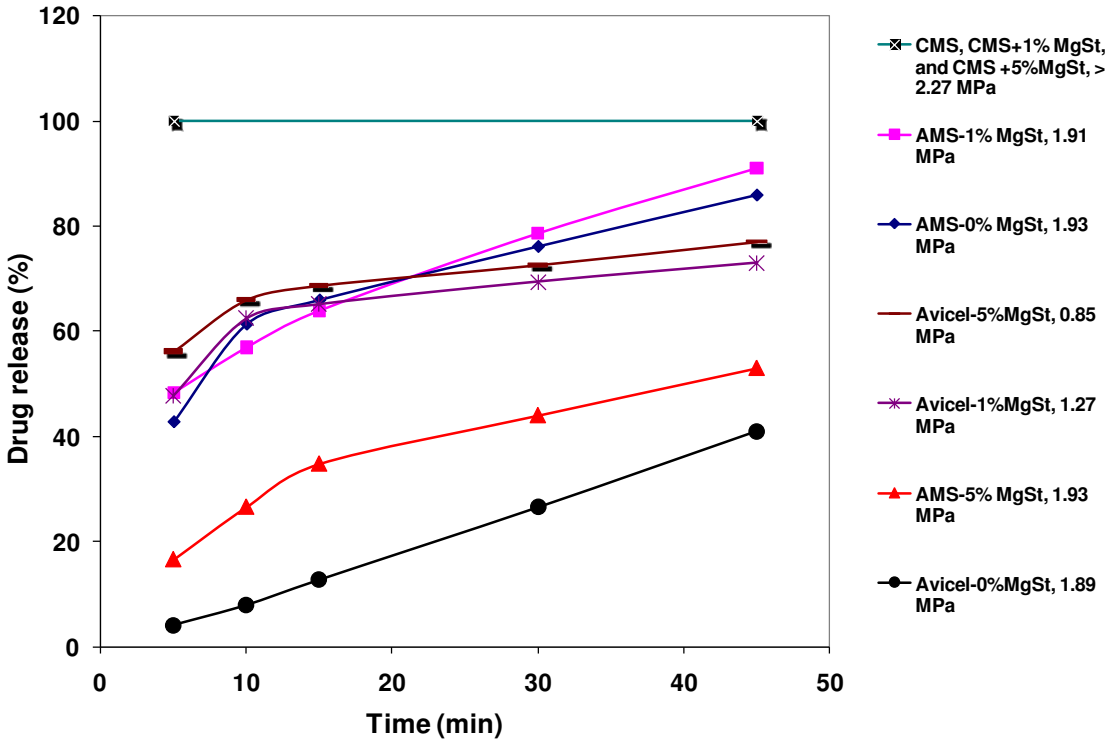

Figure 3.6 Dissolution profiles for ibuprofen (400 mg strength) tablets formulated with unlubricated and lubricated (1% and 5%, w/w) chitin-Mg silicate (CMS), Avicel®, and Avicel-Mg silicate (AMS) using physical mixing and direct compression. MgSt was used as the lubricant. Tablets (700 mg) were 13 mm in diameter and compressed at 182 MPa. Tablet crushing strength values are included in the legend for each specific powder.

It is clear from the data shown that ibuprofen tablets (400 mg strength) containing lubricated and unlubricated chitin-Mg silicate exhibit full drug release within 5 min of dissolution time. The measured tablet crushing strength remained almost unchanged for the lubricated and unlubricated tablets (around 2.27 MPa). This finding indicates that the fast drug release of ibuprofen tablets is unaffected by lubricated chitin-Mg silicate, which maintains its super-disintegration and tensile strength powers when lubricated. Ibuprofen tablets, with an average crushing strength value around 2.0 MPa, containing unlubricated Avicel® 200 showed slow drug release (Figure 3.6). But, when Avicel® 200 was lubricated with 1 and 5% (w/w) MgSt the tablet crushing strength values decreased to

1.27 and 0.85 MPa, respectively. Thus faster dissolution profiles result, as expected, from weak crushing strength tablets. When Avicel® 200 was replaced by Avicel-Mg silicate co-precipitate, the tablet lubricant sensitivity towards decreased crushing strength values was minimized, as the ibuprofen tablets retained a crushing strength of 1.93 MPa. This was achieved for the 1 and 5% (w/w) concentrations of MgSt within the Avicel-Mg silicate powder. With regard to drug dissolution, ibuprofen drug release was almost unaffected when 1% (w/w) MgSt was used. However, when 5% (w/w) MgSt was used, drug dissolution was found to be slower as the tablets maintained their high crushing strength values, but with slower disintegration time (as indicated in Figure 3.2).

In the case of gemfibrozil (a lipophilic drug), the data in Figure 3.7 shows that gemfibrozil (600 mg) tablets containing chitin-Mg silicate and 3% (w/w) of MgSt display a similar dissolution profile to the Lopid tablets when the later is used as a reference. According to the United States Patent 5726201, Lopid tables are composed of calcium stearate and talc (both as lubricants) at the percentages of 1.9 and 2.8 (%w/w) respectively. Therefore, the importance of such dissolution similarity finding lies in the fact that in a formulation containing chitin-Mg silicate (as filler, binder, and disintegrant) together with a water insoluble and highly hydrophobic active ingredient (gemfibrozil), a high concentration of MgSt can be safely used to attain the desired dissolution profile.

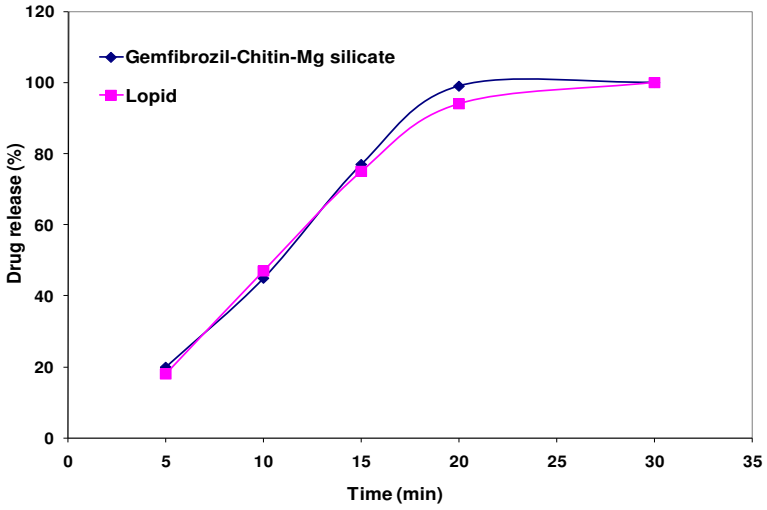

Figure 3.7 Dissolution profile of gemfibrozil (600 mg strength) tablets formulated with chitin-Mg silicate by physical mixing and direct compression. The lubricant (MgSt) concentration was 3% (w/w). Tablets (850 mg) were 13 mm in diameter and, compressed at 182 MPa. Lopid tablets (600 mg strength and 850 mg weight) were used as a reference.

3.4 Conclusions

Magnesium silicate co-precipitated on chitin and Avicel provides advantageous formulation processing, by minimizing the deleterious effects of MgSt. The addition of MgSt as a lubrication aid did not show a significant variation in disintegration, dissolution, and crushing strength of compacts made from chitin-Mg silicate. Such variation was clearly observed when a comparison was made with Avicel® 200. This may be attributed to the high surface area and porous structure of chitin and Mg silicate. In this respect, co-precipitation with magnesium silicate changes Avicel® 200 into a less lubricant sensitive excipient, whilst the disintegration time remains high. Unlike Avicel® 200, lubrication with MgSt shows improved powder consolidation behavior and powder properties for chitin-Mg silicate with no effect on particle size distribution. MgSt proved to be highly efficient in lowering the ejection force and eliminating the appearance of surface cracks in chitin-Mg silicate tablets, at high compression speeds. A slight deleterious effect of MgSt was evident when two hydrophobic drugs were prepared in compacts made from chitin-Mg silicate.

Despite the fact that the studies reported in this chapter have shown that chitin-metal silicates can be used as efficient multifunctional excipients, it is important to note that some active pharmaceutical ingredients (APIs) are chemically incompatible with metal ions [44-46]. Therefore, in order to be able to use such APIs another multifunctional excipient based on mannitol, which is a common tablet excipient, and chitin is proposed and has been investigated. The results of such studies are reported in Chapters 4 and 5 of this thesis.

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CHAPTER FOUR

4. PREPARATION AND CHARACTERIZATION OF A NOVEL CO-PROCESSED EXCIPIENT OF CHITIN AND CRYSTALLINE MANNITOL

4.1 Introduction

In the pharmaceutical industry, solid dosage formulations require different types of excipients to be added to the active pharmaceutical ingredient(s) in order to facilitate manufacturing and to achieve the required physicochemical properties (e.g. flowability, compressibility, disintegration, dissolution, stability, etc.). Excipients are incorporated in formulations using different techniques such as direct compression, wet or dry granulation as well as spray or freeze drying [1].

Single-component excipients do not always provide the requisite performance/physicochemical properties to allow certain active pharmaceutical ingredients to be formulated or manufactured adequately. As a result, drug formulation scientists have relied on excipients used in combination and often introduced commercially by excipient manufacturers. Such combinations fall into two broad categories: physical mixtures and co-processed excipients. Co-processed excipients are combinations of two or more excipients that possess performance advantages that cannot be achieved using a physical admixture of the same combination of excipients [2]. The use of different co-processed excipients has been investigated to overcome deficiencies arising from single-component excipients and existing formulations [3-5]. For example, a co-processed excipient containing microcrystalline cellulose (MCC; Avicel PH 102) and mannitol was prepared by wet granulation with hydroxypropyl cellulose (HPC) using high-shear mixing [3]. The prepared excipient exhibited the necessary characteristics of pharmaceutical filler compared with co-processed lactose and calcium phosphate-containing formulations. Both lactose and calcium phosphate can give rise to physical and chemical problems (e.g. the Maillard reaction) [3]. A novel co-processed excipient has been prepared by spray drying the aqueous slurry of MCC and mannitol to provide a system with reduced lubricant sensitivity, higher compactibility and a lower tablet ejection force profile, relative to its individual components or the physical mixture. The prepared co-processed excipient exhibited reduced reactivity towards actives and is

particularly useful as a binder for tablet formulations processed by direct compression [4].

In order to overcome the problem of the loss in compressibility of MCC when used in wet granulation formulations, silicon dioxide particles have been integrated with MCC particles using a spray-drying process [5]. The co-processed excipient shows better flowability, compressibility and disintegration properties compared to commercially available MCC or a physical mixture of MCC and silicon dioxide, specifically in wet granulation formulations. However, using the aforementioned co-processed excipients in tablet formulations needs a disintegrant to enhance the disintegration and subsequent release of the active pharmaceutical ingredients from the tablets [5].

There is increasing interest in exploring new commercial uses for chitin, a polyglucosamine, which can exist in three polymorphic forms: α, β and γ; the most abundant naturally occurring polymorph is α-chitin. Of the three polymorphic forms, α-chitin has the highest compressibility [6]. Chitin is natural, non-toxic, non-allergenic, anti-microbial, and biodegradable material and as such does not present any known health risks [7, 8]. The compactibility values of α-chitin powder are very similar to those of MCC and significantly higher when compared to dibasic calcium phosphate or pregelatinized starch. This is because chitin is less plastic and more elastic than microcrystalline cellulose, as well as being more plastic and elastic than dibasic calcium phosphate [9].

Recently chitin has been used to prepare different co-processed excipients with a range of metal silicates and silicon dioxide [10, 11]. The excipients obtained offer formulations with the requisite physical properties (e.g. non-hygroscopic, highly compactable, and highly disintegrable). As a result of such modifications, tablet disintegration is characterized by superiority in water uptake and penetration, with no gelling hindrance effects [11]. Furthermore, chitin can be used at higher concentrations than commercially available superdisintegrants without negatively affecting the disintegration properties [10,11]. It is reported that commercially available superdisintgrants loose their function, as disintegrants, when their concentration exceeds certain limits (3-15% w/w); thereby excluding their use as fillers or binders in solid dosage formulations [12].

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present

in small quantities in almost all vegetables. An acceptable daily intake of mannitol has not been specified by the World Health Organization (WHO) since the amount consumed as a sweetening agent is not considered to represent a hazard to health. Mannitol is widely used in pharmaceutical formulations and as such it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is water soluble, non-hygroscopic and produces a semi-sweet, smooth, and cool taste [13]. Because of its low hygroscopicity, mannitol is potentially an excellent excipient since it is compatible with the majority of active pharmaceutical ingredients. However, crystalline mannitol is excessively friable, leading to the formation of fine particles that are particularly detrimental to its flow properties. In addition, because of its compact crystal structure, mannitol obtained by crystallization from water exhibits poor solubility. This slow dissolution rate is a major disadvantage and thus restricts its use in pharmaceutical formulations [14]. Recently, novel pharmaceutical formulations containing both α-chitin and crystalline mannitol have been developed in order to eliminate such disadvantages [15]. It is expected that such formulations will result in the co-processed excipient displaying no adverse effect on human health, because the proposed novel co-processed excipient is produced in the absence of any chemical reactions between the individual components [2]. As a result the combination of chitin with mannitol (a non-hygroscopic inert material) may offer a valuable and practical industrial choice as an excipient in terms of disintegration and compaction properties [15].

The majority of commercially available co-processed excipients are produced by spray-drying [16], which is a costly and complicated technique. In the present work, an easily useable, dry or wet granulation procedure is expected to be advantageous for preparing a co-processed excipient from crystalline mannitol and α-chitin that can be used as a multi-purpose superdisintegrant, filler and binder in solid dosage formulations. From an industrial perspective, the production of co-processed excipients using classical techniques results in a less expensive method of manufacturing compared to spray drying. Further, the machines used in such technique are practically available in almost every industrial facility. Consequently, the use of such technique would not imply any further costing to the manufacturer. The studies reported herein aim to test the foregoing assumption and to characterize and optimize the composition and preparation procedure

for mannitol/α-chitin mixtures. The overall properties, functionality and applications of the co-processed mixture are also investigated.

4.2 Experimental

4.2.1. Materials

Commercial chitin, average molecular mass 1000 KD and degree of acetylation about 0.96, was obtained from Zhejiang Jiande Biochemical, (China). Crystalline grade D-mannitol (Pearlitol), with a mean particle size of 160 μm, was obtained from Roquette (France). Purified water of British Pharmacopeia grade was obtained from the Jordanian Pharmaceutical Manufacturing Co. (Jordan). Co-spray dried microcrystalline cellulose with D-mannitol (Avicel® HFE 102) was obtained from FMC BioPolymer (Germany); magnesium stearate from Mallinckrodt (USA) and Opadry OY-1350 film coat from Colorcon (UK). All the active ingredients used were of pharmaceutical grade. These included: amlodipine besylate (Matrix Lab., India), methyldopa (Xinshiji pharma, China) and rosuvastatin calcium (Bicon, India). Aldomet® 250 tablets (Merck & CO., Inc), Norvasc® 10 tablets (Pfizer Inc.) and Crestor® 20 tablets (AstraZeneca UK Limited) were obtained from a market in Jordan. All other reagents used were of analytical grade.

4.2.2. Methods

4.2.2.1. Preparation of Co-Processed Mannitol-Chitin

Three co-processed mixtures (each 1 kg) of mannitol and chitin of different ratios (1:9, 2:8, and 3:7, w/w) were prepared using different processing techniques i.e. direct mixing, as well as spray, wet and dry granulation.

Direct mixing

The components of each mixture were individually passed through a 710 μm mesh sieve (Fritsch, Germany) and then mixed together for 5 min at 10 rpm using a 7.5 liter cubic blender equipped with a motor drive machine (Erweka, Germany).

Dry granulation

The three mixtures prepared by direct mixing were compacted using a roll compactor equipped with DPS type rolls (TFC-labo, Vector Corporation, USA), set at about 5 MPa roll pressure, 4 rounds/minutes roll speed and 20 rounds/minutes screw control speed. The compacted powder was collected and sieved through a 710 μm sieve using a milling machine equipped with a motor drive machine. Finally the granules were mixed for 5 min at 10 rpm using a 7.5 liter cubic blender equipped with a motor drive machine.

Spray granulation

A 20% (w/v) aqueous mannitol solution was prepared. Chitin was passed through a 710 μm sieve and fluidized in a fluid bed granulator vessel (Strea 1, Niro Aeromatic, Germany) using an air pressure and drying temperature of 1.5 bar and 60 °C, respectively. The appropriate volumes of mannitol solution (0.5, 1, and 1.5 liter for 1:9, 2:8, and 3:7 (w/w) mannitol-chitin mixtures, respectively) were sprayed into the fluidized chitin at a spray rate of 5 mL/min. The granules were then sieved and mixed using the same parameters as for the dry granulation procedure.

Wet granulation

Different mannitol solutions (6, 12 and 16% w/v) were prepared by dissolving the required quantity of mannitol to be used to prepare the mannitol-chitin mixtures (1:9, 2:8 and 3:7 w/w ratio, respectively) in sufficient amount of water to achieve a suitable granulation end point. The sieved chitin was placed in granulation pan (Erweka, Germany) and granulated with the mannitol solution using a mixing speed of 200 rpm. The wet mass was passed through a 9.5 mm sieve. Granule drying was performed at 60 °C using a drying oven (UT6200, Heraeous, Germany). The granules were sieved and mixed using the same procedures as used for the dry granulation procedure.

4.2.2.2 Characterization of Cop-MC

Fourier transform infrared spectroscopy (FT-IR)

FT-IR measurements were undertaken using an FT-IR instrument (Paragon 1000, Perkin Elmer, UK) using thin pellets containing 1 mg of each sample dispersed in 100 mg of KBr. The spectra were recorded at room temperature as an average of 30 scans, in the 400–4000 cm^{-1} range with a spectral resolution of 1 cm^{-1}. In order to minimize the effects of traces of CO_2 and water vapour from the atmosphere of the sample compartment, the spectrometer was purged with N_2.

X-ray powder diffractometry (XRPD)

The XRPD profiles were measured using an X-ray diffractometer (PW1729, Philips, Holland). The radiation was generated using a CoK_α source and filtered through Ni filters; a wavelength of 1.79025 Å at 40 mA and 35 kV was used. The instrument was operated over the 2θ range of 5-60^o. The range and the chart speed were set at 2×10^3 cycles/sec and 10 mm/2θ, respectively.

Scanning-electron microscopy (SEM)

Sample morphology was determined using a scanning electron microscope (Quanta 200 3D, FEI, Eindhoven/Netherland) operated at an accelerating voltage of 1200 V. The sample (0.5 mg) was mounted onto a 5×5 mm silicon wafer affixed via graphite tape to an aluminum stub. The powder was then sputter-coated for 105 s at a beam current of 20 mA/dm^3 with a 100 Å layer of gold/palladium alloy.

4.2.2.3 Testing of the Cop-MC Containing Tablets

The compressed tablets containing Cop-MC were tested for crushing strength (6D, Schelenuiger tester, Germany), disintegration (2T31, Erweka tester, Germany) and friability (Erweka tester, Germany) following the general tests in the British Pharmacopeia [17].

4.2.2.4 Physical and Chemical Properties of Cop-MC

Bulk density and particle size distribution

The bulk density and particle size distribution were measured using a powder volumeter (SVM, Tapped volumeter, Erweka, Germany) and a powder particle size analyzer (Vibratory sieve, shaker analysette 3PRO and 1000 to 63 μm sieves, Fritsch, Germany), respectively.

pH and water content measurements

The pH of a 5% (w/v) aqueous dispersion and powder water content were measured using pH meter (Seven-multi pH-meter, Mettler, Switzerland) and titrator (DL38, Karl Fischer Titrator, Mettler, Switzerland), respectively.

Hygroscopicity

Samples (each 2.5 g) were stored in desiccators containing water saturated salt solutions at room temperature (20°C) for 10 and 14 days. The media compositions were set according to the Handbook of Chemistry and Physics [18] to obtain relative humidity's (RHs) of 52, 62, 75, 84 and 95% using $Ca(NO_3).4H_2O$, NH_4NO_3, NaCl, KCl and $Na_2HPO_4.12H_2O$, respectively. The samples were withdrawn after a fixed time period and stored at 20°C for 1 and 24 hr before weighing and calculating the percentage gain in weight from the original weight under the different RH conditions.

4.2.2.5 Influence of Particle Size on Compression Characteristics

Samples of Cop-MC were passed through either 710 μm or 853 μm sieves and individually dry-mixed with 0.5% w/w magnesium stearate for 3 minutes and then compressed using a single punch tabletting machine (SFS, Chadmach machinery, India) at different crushing strength values of: 30, 50, 70, 90, 110, 130 and 150 N, using a 9 mm circular punch to produce tablets of 180 mg weight. The disintegration time and friability were measured at each tablet crushing strength point. Avicel® HFE 102 NF was treated in the same way and used as a reference.

4.2.2.6 Effect of Lubricant Quantity on Tablet's Physical Properties

Samples of Cop-MC were physically mixed for 3 minutes with different percentages of magnesium stearate (0.25 - 5% (w/w)) in a 7.5 liter cubic blender equipped with a motor drive machine. The powder was compressed at an adjusted upper punch scale of 25 KN, in which a 8 mm circular punch was fitted and tablet weight was fixed at 180 mg. The disintegration time and friability were measured.

4.2.2.7 Functionality

To study the functionality of the Cop-MC tablets of rosuvastatin calcium (RSC) were prepared by different procedures including direct mixing as well as dry and wet granulation. The tablets contained RSC (7.6% w/w), Cop-MC (91.7% w/w) and magnesium stearate (0.7% w/w). For the direct mixing procedure (Formula 1), RSC and Cop-MC were first mixed for 2 min and then magnesium stearate was added and further mixed for another 3 minutes. For the dry granulation procedure (Formula 2), RSC (7.6% w/w), Cop-MC (25% w/w, intra-granular) and magnesium stearate (0.2% w/w) were compacted with a DP roll type using 10 MPa roll pressure, 3 rounds/minutes roll speed and 43 rounds/minutes screw control speed, and then passed through a 710 μm sieve. The remaining amount of Cop-MC (66.7% w/w) was added and mixed for 2 minutes; magnesium stearate (0.5% w/w) was added. The preparation was further mixed for 2 minutes. For the wet granulation procedure (Formula 3), RSC (7.6% w/w) and Cop-MC (35% w/w, intra-granular) were granulated with 50% (w/v) ethanol solution, dried at 60^{o}C, and then passed through 710 μm. The remaining amount of Cop-MC (56.7%) was added and mixed for 2 minutes; magnesium stearate (0.7%) was then added and the preparation mixed for a further 2 minutes. The three formulations were compressed at 290 mg tablet weight, for which 10 mm shallow concave punches and dies were used. Dissolution testing [19] (DT80; Erweka tester, Germany) was performed according to the U.S. Food and Drug Administration published dissolution method [20] for rosuvastatin calcium tablets. The percentage release of rosuvastatin calcium was determined spectrophotometrically (Du-650i UV/Visible spectrophotometer, Beckman, USA) by measuring the absorbance at a λ_{max} of 240 nm.

4.2.2.8 Compressibility of the Cop-MC (Kawakita Equation)

Cop-MC was compressed using a universal testing machine (RKM 50, PR-F system, ABS Instruments, Germany) equipped with 12 mm round, flat face upper and lower punches as well as dies. The punch speed was fixed at 10 mm/min. Different compression forces from 80 to 390 MPa were applied. Three tablets were prepared to ensure reproducibility. Compression was carried out at 400 mg tablet weight. The compression behavior of the samples was evaluated using Kawakita analysis. The Kawakita equation (Equation 1) is used to study powder compression using the degree of volume reduction, C. The basis for the Kawakita equation for powder compression is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of the pressure term and the volume term is a constant [21]:

$$C = \frac{(V_o - V)}{V_o} = \frac{abP}{(1 + bP)} \qquad (1)$$

where V_o is the initial volume and V is the volume of powder column under an applied pressure, P. The constants a and b represent the minimum porosity before compression and plasticity of the material, respectively. The reciprocal of b defines the pressure required to reduce the powder bed by 50% [22, 23]. Equation 1 can be re-arranged in linear form as:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \qquad (2)$$

The expression for particle rearrangement can be affected simultaneously by the two Kawakita parameters a and b. The combination of these into a single value, i.e. the product of the Kawakita parameters a and b, may hence be used as an indicator of particle rearrangement during compression [24].

4.2.2.9 Compatibility Study of Cop-MC with Methyldopa

Differential scanning calorimetry (DSC 25, Mettler Instruments, Switzerland) can be used for a wide range of pharmaceutical applications ranging from the characterization of

materials to the evaluation of drug excipient interactions via the appearance, shift, or disappearance of endothermic or exothermic peaks [25-27]. DSC was used to study the compatibility of the methyldopa active pharmaceutical ingredient in a tabletted dosage form with Cop-MC and magnesium stearate (Formula 4). The tablets were packed in either open or closed glass containers and stored at 40°C/75% RH for a 6 month period. The reference formula was prepared without methyldopa according to Formula 4 using the same composition ratio of excipients. All the samples were tested before and after storage, under defined conditions. DSC samples were hermetically sealed in aluminum pans and scanned over a range temperature of 0 to 300°C at a rate of 5°C/min. The instrument was calibrated using indium and the calorimetric data was analyzed using STAR software (version 9).

4.2.2.10 Applications

The Cop-MC was used to formulate methyldopa and amlodipine besylate active ingredients into a tabletted dosage form; tablets were prepared using direct mixing. The methyldopa formulation (Formula 4) comprised the active ingredient (63.3% in its hydrated form), Cop-MC (32.8%), and magnesium stearate (0.6%). Tablets were film-coated using Opadry OY-1350 (Colorcon-UK) coating material (3.3%) and sufficient water as solvent. The amlodipine besylate formulation (Formula 5) comprised the active ingredient (7.0% as besylate), Cop-MC (92.5%), and magnesium stearate (0.5%). 10 mm shallow concave and 8 mm flat face beveled edge punches were used for tabletting the methyldopa and amlodipine besylate containing formulations, respectively. Tablets of Formulas 4 and 5 were tested for crushing strength, disintegration and dissolution. Methyldopa tablets (250 mg) were further tested for their stability after being stored at 40^{o}C/75% RH for 6 months using HPLC instrument equipped with a P1000 pump and a UV1000 detector (TSP/USA). A stability indicating and validated HPLC method was used to determine methyldopa, O-3-methylmethyldopa (synthetic impurity) and other related compounds [28]. A mixture of 50% (v/v) aqueous methanol and 1% (v/v) perchloric acid (350:650 v/v) was used as the mobile phase and an octyl silane column as the stationary phase (Lichrosphere 100 RP-8, 250×4 mm, 10 μm). UV detection at 230

nm, a flow rate of 1 mL/min and a 20 μL injection loop were used. The HPLC method was initially tested for system suitability (i.e. peak symmetry, repeatability, and resolution) and for validation parameters (i.e. specificity, recovery, stability in solution, linearity and limit of quantitation (LOQ)) according to USP guidelines [29]. The stored tablet samples in addition to methyldopa active ingredient (as a reference) were packed in either open or close amber glass bottles. Aldomet® 250 and Norvasc® 10 tablets were used as reference materials for comparison purposes. The U.S. FDA published dissolution method [20] for amlodipine besylate tablets was adopted for the dissolution analysis. The dissolution method states the use of USP apparatus II (Paddle), 75 rpm speed, 500 mL of 0.01N hydrochloric acid as the dissolution medium and 10, 20, 30, 45 and 60 min sampling times. The dissolution testing of methyldopa tablets were performed according to the United States Pharmacopeia (USP 32), following the methyldopa tablet official monograph [30]. The dissolution system states the use of USP apparatus II (Paddle), 50 rpm speed and 900 mL of 0.1N hydrochloric acid as the dissolution medium. The percentage release of amlodipine besylate and methyldopa was determined spectrophotometrically by measuring the absorbances at λ_{max} of 250 (1^{st} derivative) and 280 nm, respectively.

4.3 Results and Discussion

4.3.1 Co-Processed Mannitol-Chitin with Low Lubricant Sensitivity

Lubricant sensitivity is the ratio of the un-lubricated to the lubricated compactibility of the tablet formulation. Addition of lubricant reduces the heat produced and tablet ejection force during compression, which is related to the reduction in inter-particulate interaction during compaction; as a result powder compactibility is decreased. Lubricant sensitivity also refers to the reduction in interaction between the plastically deforming particles in the powder, due to the addition of lubricant, which leads to a reduction in tablet crushing strength [31].

Chitin powder exhibits poor flow and produces fragile tablets upon compression, while pure crystalline mannitol displays undesirable compaction properties and results in tablet capping. To obtain the optimal ratio of co-processed mannitol-chitin mixture**,** three different ratios of mannitol: chitins were used: 10:90, 20:80 and 30:70 (w/w). These mixtures were prepared by different processing techniques i.e. direct mixing, dry, spray and wet granulation. The prepared granules were lubricated using different weight fractions of magnesium stearate ranging from 0.25% to 5.0% (w/w). The mixtures were compressed at 25 kN scale of the upper punch and the tablets obtained were tested for crushing strength, friability and disintegration time. The results indicate that improvements in the physical properties of mannitol and chitin mixtures follow the order: wet and spray granulation > dry granulation > direct mixing. The mixtures prepared by direct mixing have unacceptable physical properties (e.g. poor powder flow, powder non-uniformity (segregation), friable and low crushing strength tablets). Additionally, the results indicate that the properties of mannitol/chitin mixtures are improved by dry granulation but they were still not optimal. Moreover it was noted that friability was sensitive to the fraction of magnesium stearate added. As a result, excipients produced by direct mixing and dry granulation methods were no longer used since the addition of active ingredients having critical properties (e.g. poor flow, incompressible, fragile, etc) could have a negative impact on compressed tablets.

The main objective thus became to find the most appropriate mixture that could be used

to overcome the poor flow and weak compressibility of its components. The method of integrating two components is an important factor in obtaining a suitable mixture that is needed to act as a diluent for the active ingredient.

From the preliminary results physical mixing and direct compaction of the two components proved unsatisfactory; consequently spray and wet granulation were used to produce the new excipient, whereby the properties of the two components are able to overcome poor flow and compression properties. In addition the compatibility of the mixture towards lubrication sensitivity was tested.

In the case of spray and wet granulations, the physical properties were improved with respect to the mannitol: chitin ratio used in the following order: 2:8 > 3:7 > 1:9 (w/w mannitol/chitin). The mixtures prepared using ratios of 1:9 and 3:7 (w/w) showed relatively high friability and sensitivity to the weight fraction of magnesium stearate added as a lubricant. The optimal ratio with respect to physical properties improvement is the 2:8 (w/w) ratio (mannitol: chitin). All the physical properties at this ratio prepared using dry granulation as well as spray and wet granulation in comparison with co-processed microcrystalline cellulose (Avicel HFE 102) as a reference are shown in Figure 4.1.

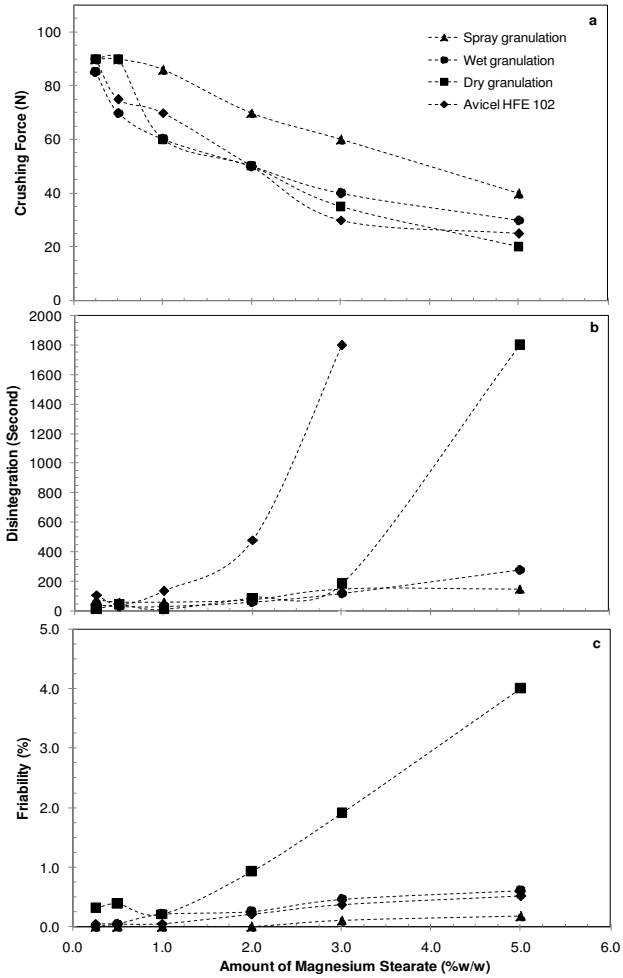

Figure 4.1 Plots of the physical properties (crushing strength, disintegration time and friability) of the co-processed mannitol-chitin mixture prepared by different granulation techniques versus the amount of magnesium stearate added.

It is clear from the data presented in Figure 4.1 that the physical properties of mixtures prepared by spray and wet granulation are not very sensitive to the amount of magnesium stearate added due to the presence of folding (e.g. high surface area) (Figure 4.2), while those prepared by dry granulation and Avicel HFE 102 are relatively sensitive to the lubricant content.

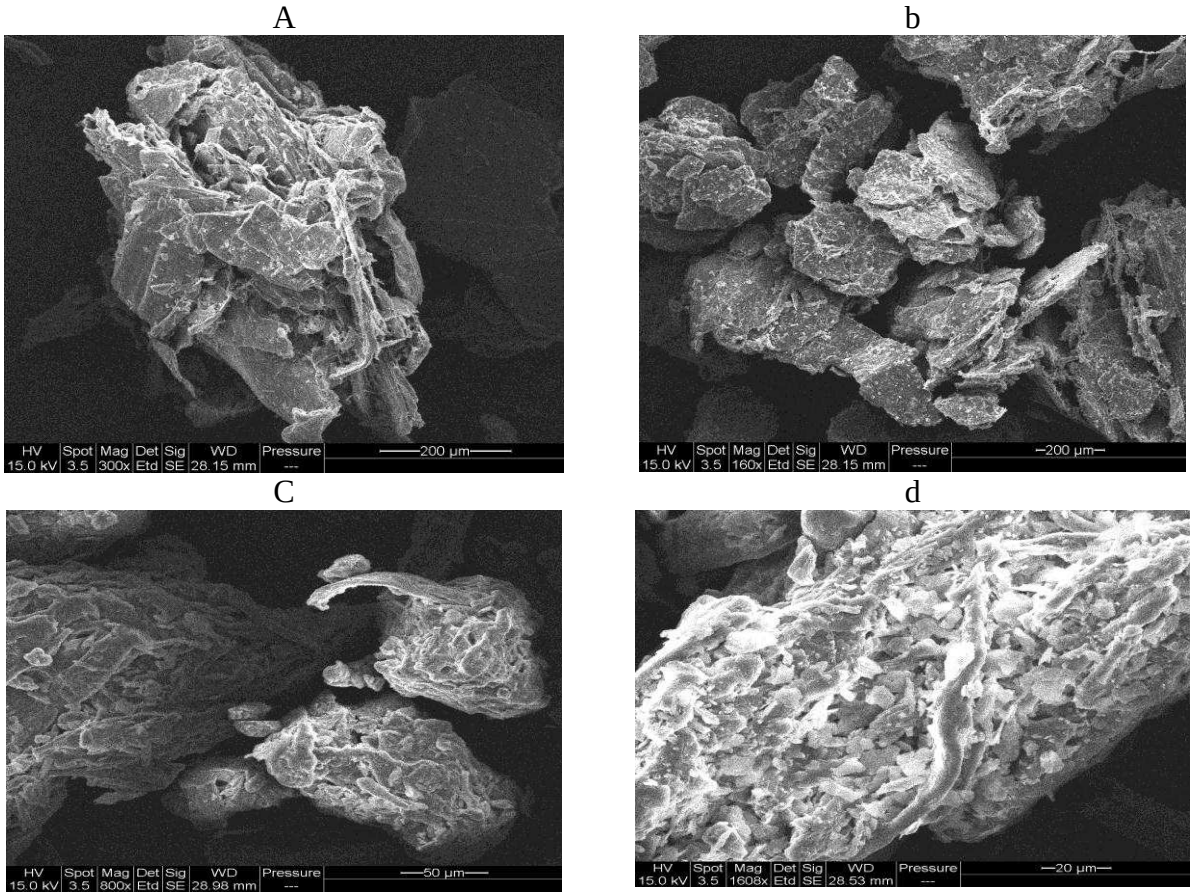

Figure 4.2 SEM images of Cop-MC lubricated with **(a)** 0.5% and **(b)** 3.0% (w/w) magnesium stearate; Avicel HFE 102 powder lubricated with **(c)** 0.5% and **(d)** 3.0% (w/w) magnesium stearate.

For further investigation, the mixture prepared by wet granulation was used and the other preparations were excluded because from a manufacturing process perspective, the former is conventional and more practical compared with using spray granulation and/or compaction.

4.3.2 Characterization of Cop-MC

4.3.2.1 Fourier Transform Infrared Spectroscopy (FT-IR)

The FT-IR spectra of mannitol, chitin, the corresponding 2:8 physical mixture and Cop-MC are shown in Figures 4.3a, 4.3b, 4.3c and 4.3d, respectively. It is clear that the FT-IR spectra of the physical mixture of mannitol and chitin (Figure 4.2c), is almost a

superposition of the FT-IR profile contributed by mannitol and chitin. The dominance of the principal bands of chitin in the physical mixture is a result of its high percentage in the mixture (80%, w/w). The FT-IR spectra of Cop-MC (Figure 4.2d) showed almost the same bands as the physical mixture, which suggests the absence of any detectable chemical interaction and the formation of a new solid phase, as shown by scanning electron microscopy.

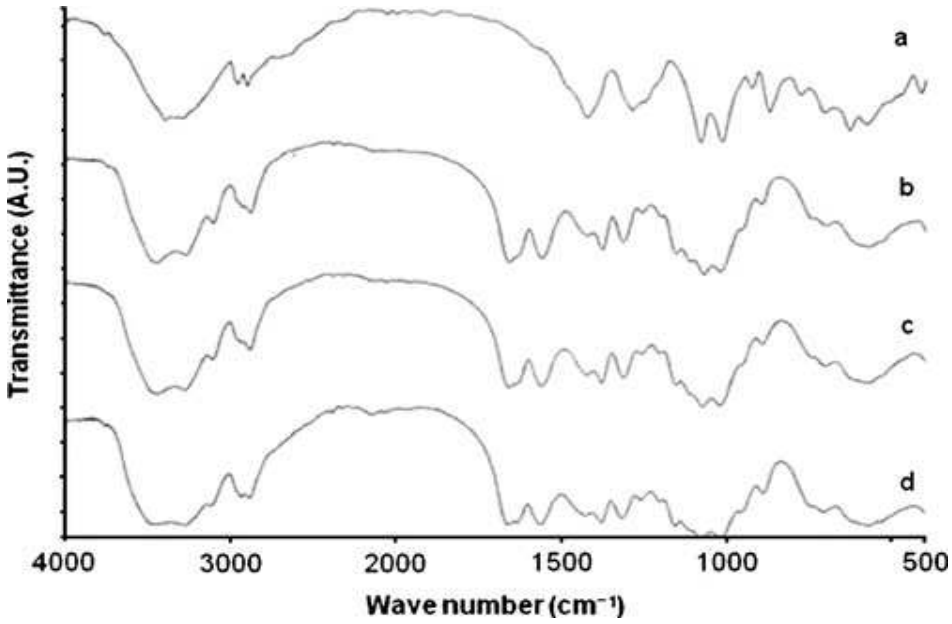

Figure 4.3 FT-IR spectra of **(a)** mannitol, **(b)** chitin, **(c)** physical mixture of mannitol-chitin (2:8, w/w), and **(d)** Cop-MC.

4.3.2.2 X-Ray Powder Diffractometry (XRPD)

Figures 4.4a, 4.4b, 4.4c and 4.4d show the XRPD profiles of mannitol, chitin, the corresponding 1:1 physical mixture and Cop-MC, respectively.

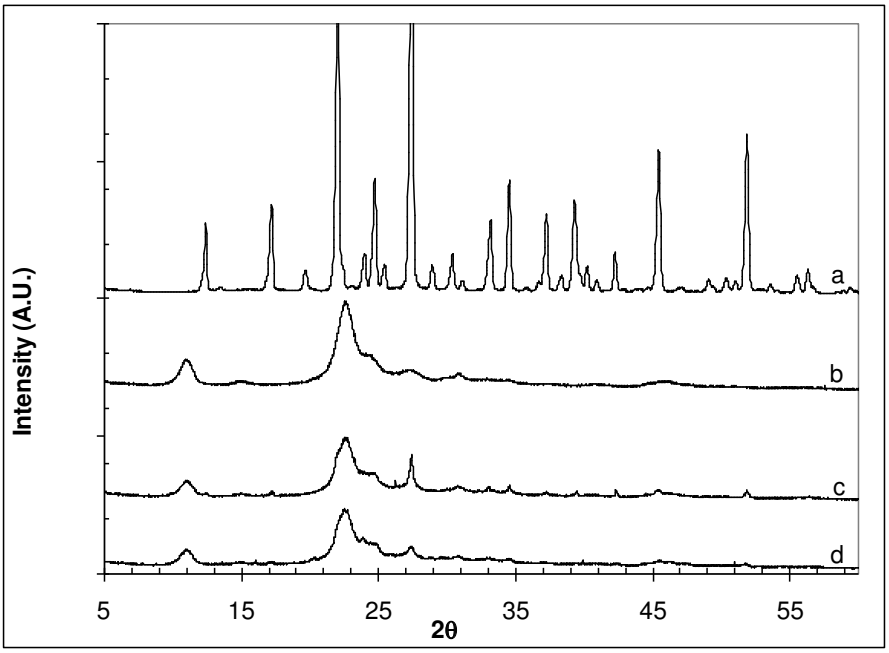

Figure 4.4 XRPD profiles of **(a)** mannitol, **(b)** chitin, **(c)** physical mixture of mannitol-chitin (2:8, w/w), and **(d)** Cop-MC.

It is clear that the XRPD pattern of the physical mixture of mannitol and chitin is almost a superposition of the patterns contributed by mannitol and chitin. In contrast, the diffraction pattern of Cop-MC showed a reduction in the principal diffraction peaks apparent in the XRPD patterns of the physical mixture, which suggests the formation of a new solid phase.

4.3.2.3 Differential Scanning Calorimetry (DSC)

Figure 4.5 shows the thermal behavior of all samples investigated by DSC.

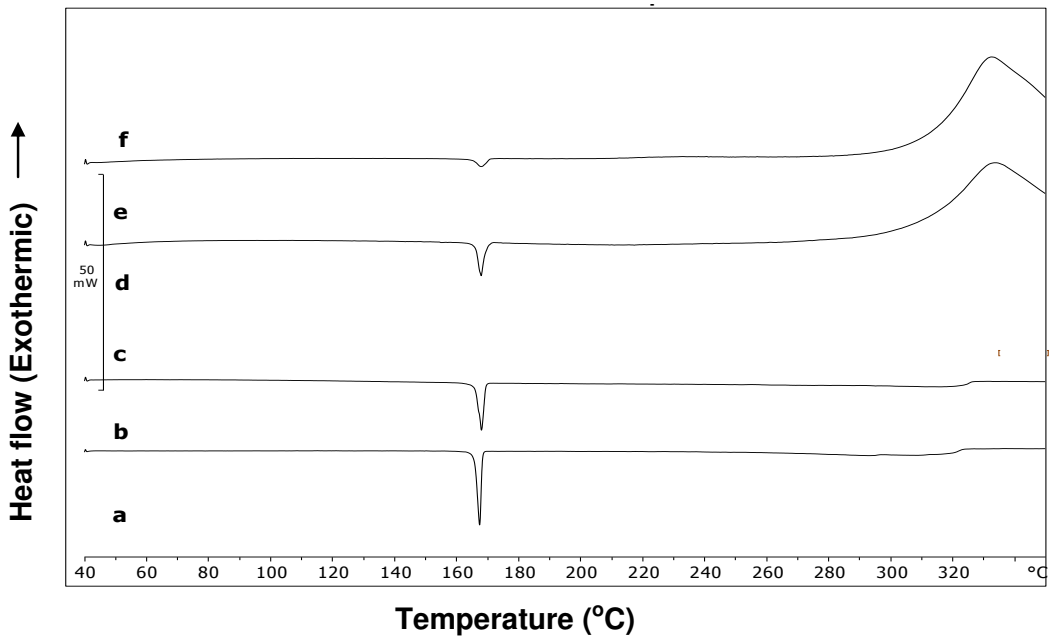

Figure 4.5 DSC thermograms of **(a)** chitin, **(b)** mannitol, **(c)** treated mannitol, **(d)** non treated physical mixture of mannitol-chitin (2:8, w/w), **(e)** treated physical mixture of mannitol-chitin (2:8, w/w) and **(f)** Cop-MC.

Mannitol exhibits an endothermic peak at about 167°C (Figure 4.5a), which is retained with high intensity in the physical mixture of mannitol and chitin (Figure 4.5c), but a significant reduction in the intensity of the mannitol peak in the thermogram of the Cop-MC occurs (Figure 4.5d) indicating that some of the mannitol is sequestered in the chitin pores.

4.3.2.4 Scanning-Electron Microscopy (SEM)

SEM was used to investigate particle surface morphology (Figure 4.6). When comparing the surface of chitin (Figure 4.6b) with the surface of the Cop-MC prepared using wet granulation (Figure 4.6d), it is apparent that its native structure has changed from a smooth, flat surface structure, with folded edges, to three-dimensional compacts for the Cop-MC. This folding in the surface of the co-processed chitin creates a bigger surface area which can accommodate a larger quantity of lubricant.

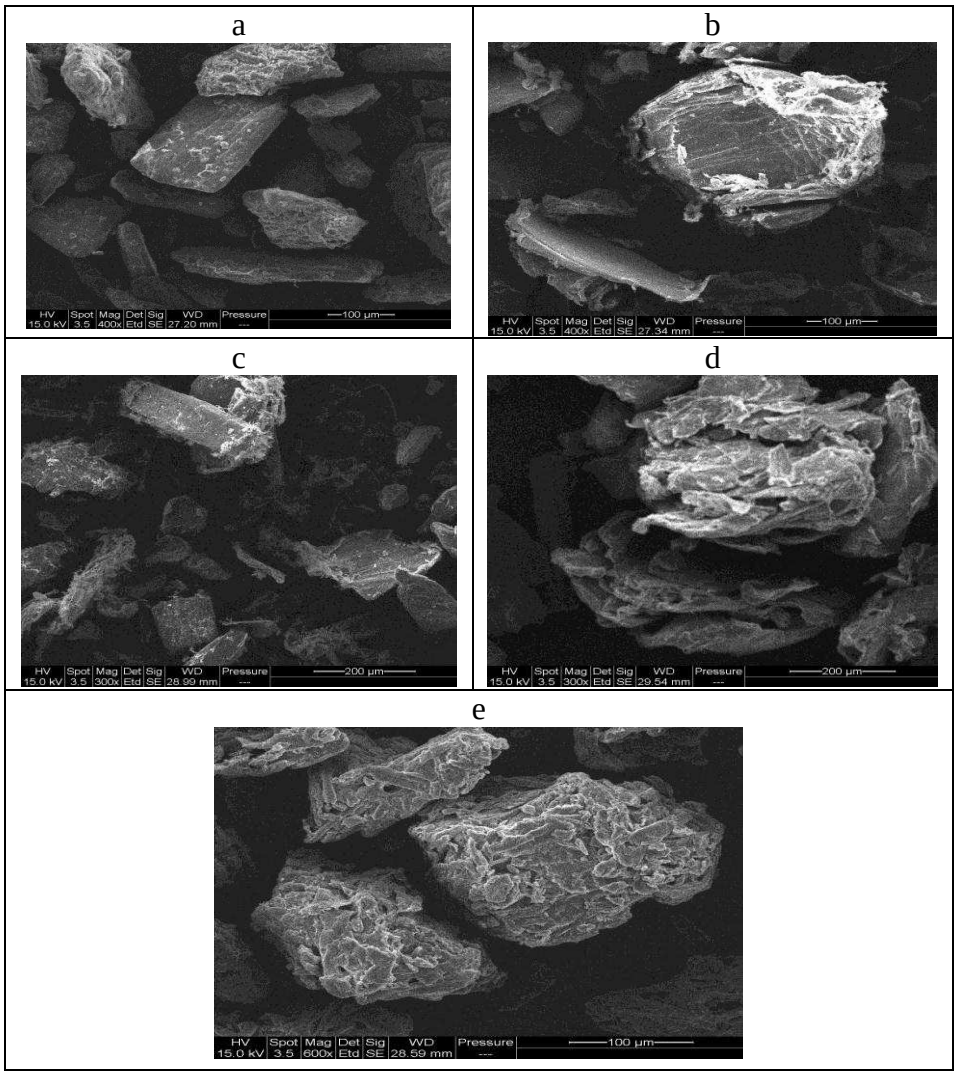

Figure 4.6: SEM images of **(a)** mannitol, **(b)** chitin, **(c)** physical mixture of mannitol-chitin (2:8, w/w), **(d)** Cop-MC and **(e)** Avicel HFE 102.

Figure 4.6e shows the surface of chitin-mannitol indicating the presence of inter-particulate voids and channels. Figure 4.6c shows the surface of the AVICEL HFE 102, which exhibits a smaller surface area due to the solid surface and the absence of folded edges. This is the major reason underlying the clear increase in the disintegration time and reduction in the crushing strength of the tablets containing AVICEL HFE 102, as a result of increasing the quantity of magnesium stearate present. It is evident that the Cop-MC excipient is not chemically altered; consequently it was used in further work.

4.3.3 Physical Properties of Cop-MC

Some of the physical properties of the mixture prepared by wet granulation and sized using two different sieves 710 μm and 853 μm (corresponding to mesh sizes of 22 and 18, respectively) were measured. These two sieves were selected in order to obtain Cop-MC with particle size distributions capable of improving solid formulation characteristics. Generally, in direct compression formulation, excipient flowability and compaction performance are critical; therefore excipients used for such applications should exhibit narrow particle size distributions with moderate-to-coarse particle size (e.g. 100 to 200 μm) [32]. The granules obtained have a bulk density of 0.2-0.3 g/cm^3 with particle size distributions of 20%, 45% and 30% in the range of < 180, 180 – 355, > 355 μm, respectively.

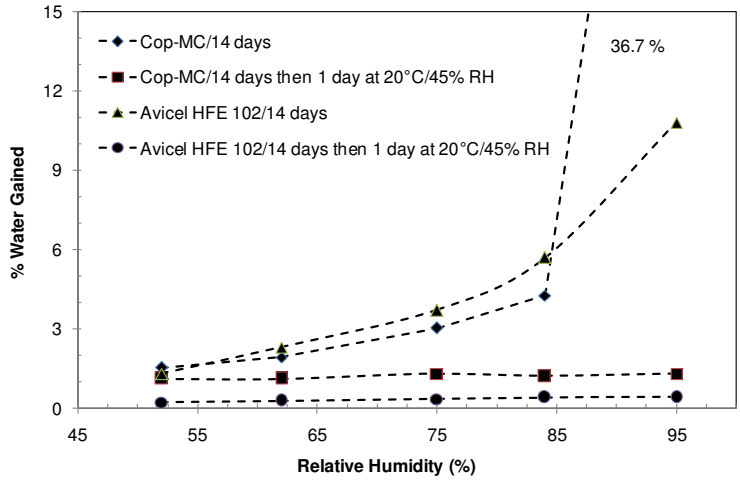

Figure 4.7 The water gained by Cop-MC and Avicel HFE 102 kept in an open container at different relative humidities and 20^{o}C.

The pH of a 5% (w/v) aqueous dispersion is 7-8 and a water content of about 6% w/w. Cop-MC was found to be slightly hygroscopic with a high moisture uptake capacity, but only under extremely high humidity conditions (95% RH). This is expected and explains the fast disintegration of the tablets in aqueous media. The data from the water gain vs. relative humidity plots (Figure 4.7) clearly indicates that the Cop-MC absorbs a moisture content that is up to 37% of its initial weight at 95% RH, but it loses most of this moisture after equilibration at ambient conditions of 20^{o}C and 45% RH for a day.

4.3.4 Effect of Particle Size on Tablet Disintegration Time, Crushing Strength and Friability

The disintegration time and friability versus the crushing strength for the tablets prepared using Cop-MC powders passed through either 710 μm or 853 μm sieves are shown in Figure 4.8. Generally, a reduction in particle size is associated with an increase in tablet mechanical strength. The increase in mechanical strength of the tablets is attributed to an increase in the surface area available for inter-particulate attraction, as the particles become smaller [33]. However, when Cop-MC was used it was found that varying the particle size had a minimal, or no, effect in increasing the mechanical strength of the tablets produced. Generally, for materials with a tendency to fragment, the mechanical strength of a tablet appears to be independent of particle size [34]. This is likely to be the case for the Cop-MC particles which undergo fragmentation at an early stage of compression; this normally results in a limited effect on tablet crushing strength when varying the particle size. With respect to tablet disintegration, the Cop-MC, as evidenced by the data in Figure 4.8, showed a unique and distinctive characteristic whereby disintegration was independent of particle size and tablet crushing strength. Tablets, produced from Cop-MC powders passed through either 710 μm or 853 μm sieves at an upper bunch compression scale of 37-42 kN for each particle size, showed a superior disintegration time, ranging from 5-145 seconds. This was achieved for tablet crushing strength values ranging from 30-150 N, which suggests that capillary action is the dominant mechanism for disintegration irrespective of the tablet crushing strength. Therefore, the inter-particulate voids within the chitin particle structure in the Cop-MC, as previously ascertained by scanning-electron microscopy, remain intact and unchanged by varying the powder particle size and tablet crushing strength.

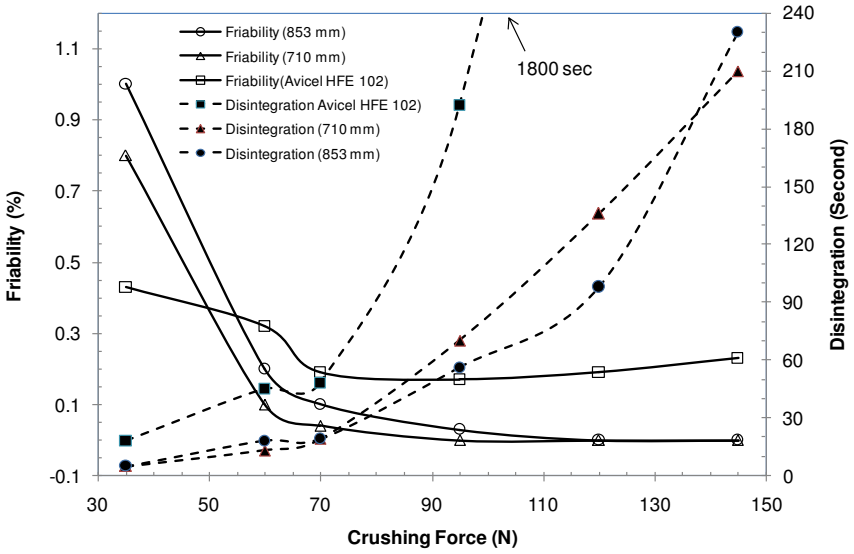

Figure 4.8 Effect of Cop-MC particle size on tablet crushing strength, disintegration time and friability. The tablets were 9 mm in diameter and 180 mg in weight. All samples were lubricated with 0.5% (w/w) magnesium stearate

Processing chitin with mannitol was found to cause alterations in chitin powder compressibility and compactibility**.** Regarding powder compactibility, mannitol within the Cop-MC mixture provides an effective means of obtaining hard tablets with low friability while maintaining its super disintegration power, as deduced from the data in Figure 4.8. While with the mannitolized microcrystalline cellulose (Avicel HFE 102), it can be clearly observed that increasing the tablet crushing strength results in a significant increase in disintegration time.

4.3.5 Kawakita Analysis (Compressibility)

Initial investigations of mannitol, chitin and Cop-MC using Heckel analysis indicated non-log-linearity of compression data. Therefore, Heckel analysis was not adopted in this work as it may result in misinterpretation of the estimated intercept and slope parameters of the Heckel plots [10]. Therefore, in the present work, Kawakita analysis was adopted to linearize the compression data. Figure 4.9 displays representative Kawakita plots for mannitol, chitin and Cop-MC. The Kawakita constants a, b, ab and 1/b were calculated from the intercept and slope of the plot (Table 4.1).

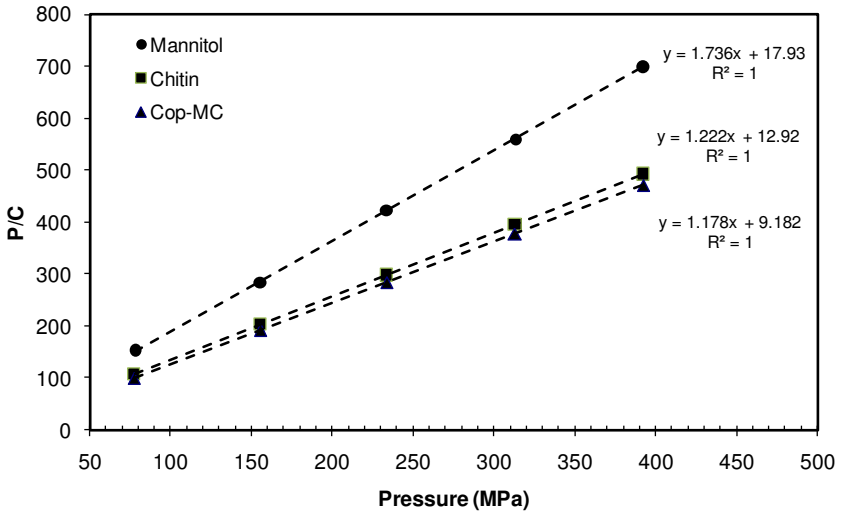

Figure 4.9 Kawakita plot for mannitol:chitin (20:80) Prepared by a wet granulation procedure. Tablets were 12 mm in diameter and 400 mg in weight.

Table 4.1 Kawakita Parameters.

Material	Kawakita parameters					
	Slope	**Intercept**	**a**	**ab**	**b**	**1/b**
Mannitol	1.736	17.932	0.576	0.0558	0.0968	10.330
Chitin	1.223	12.927	0.818	0.0774	0.0946	10.570
***Cop-MC**	1.178	9.182	0.849	0.1089	0.1283	07.795

***C**o-processed mannitol-chitin (2:8 w/w) mixture

The constant (a), which represents the compressibility, is nearly the same for chitin and the Cop-MC (a = 0.818 and 0.849, respectively) and is relatively low for mannitol (a = 0.576). Co-processing of chitin with mannitol has no significant increase in the compressibility of chitin. This is because mannitol (20% of the Cop-MC content) occupies only a limited area of the large surface pores of chitin. These pores are responsible for the decrease in the volume of chitin powder upon compression [35]. The value of the constant (1/b) for Cop-MC (7.795), which is an inverse measure of the amount of plastic deformation occurring during the compression process [36], indicates that the presence of mannitol increases the plastic deformation of chitin. The higher degree of plastic deformation of Cop-MC during compression is most probably due to (a) the formation of intermolecular hydrogen bonding between the plastically deformed

adjacent particles within the chitin particles and (b) the presence of moisture within the porous structure of chitin, which enforces the formation of hydrogen bonds and gives Cop-MC high crushing strength values upon compaction and also acts as an internal lubricant [37].

The relatively high value of ab for Cop-MC (0.1089), which is a measure of the extent of particle rearrangement, indicates that, in the presence of mannitol, chitin exhibits a high degree of packing during tablet compression. This implies that co-processing reduces the surface micro-irregularities of chitin and facilitates particle re-arrangement during the densification process of compaction. As a result, co-processing of chitin with mannitol has positively improved the compression characteristics of chitin as shown by Kawakita analysis.

4.3.6 Application

4.3.6.1 Functionality

The functionality of Cop-MC was investigated by employing different processing techniques (dry granulation, wet granulation and direct compression) for the preparation of tablet dosage forms. Rosuvastatin calcium (RSC), a drug indicated for primary hypercholesterolaemia, was selected as a model for this study. RSC is a hydrophobic drug reported to be soluble and stable in the presence of the pH modifier tri-basic calcium phosphate as one of the excipients used in the tablet matrix [38]. Crestor® 20 tablet commercial drug product was used as a reference. These tablets are composed of lactose and microcrystalline cellulose as fillers, tri-basic calcium phosphate as alkalinizer and stabilizer in addition to crospovidone as the disintegrant [38, 39]. Therefore, the use of Cop-MC under neutral/alkaline conditions (pH of 7.0-8.0) is a suitable choice for RSC tablet formulation [40-41]. The direct compression procedure for RSC with Cop-MC at a dilution capacity of 7.6% (w/w) resulted in hard tablets with more than 90% drug release within a 10 min time interval. The disintegration times for the RSC tablets prepared by the three different procedures and Crestor® 20 tablets were similar and lie in the 120-160 sec range. The uncoated tablets of RSC, obtained by using the three different methods of preparation, have crushing strength values in the range of 90-120 N and friability values

of 0.1-0.3%. The foregoing results indicate that the Cop-MC has an improved compressibility, whether utilized in direct compression, dry granulation or wet granulation formulations. Thus implying that Cop-MC can be used as a single excipient acting as filler, binder and disintegrant in tablet formulations.

Some applications using Cop-MC as the only filler, binder and superdisintegrant were also investigated. Two antihypertensive agents, amlodipine besylate (which is a 1,4-dihydropyridine calcium channel blocker) and methyldopa (L-3-(3,4-dihydroxyphenyl)-2-methylalanine" an aromatic-amino acid decarboxylase inhibitor), were selected as model drugs for this study as they have special requirements in tablet formulation design. Due to the high strength and weak compactibility of methyldopa powder, difficulties in the formulation of this active ingredient can occur e.g. capping (i.e. "layering") of the tablets during ejection in tabletting processing. In addition, the particle size and shape of the active ingredient have a major impact on the tablet compaction and binding properties during compression. Usually these unfavorable characteristics mean that a granulation procedure has to be used for the preparation of the tablets [42]. This is because direct compression procedures cannot overcome the aforementioned characteristics by using sufficient quantities of suitable fillers, binder and disintegrant while maintaining a low tablet weight. The 355 mg film coated Aldomet 250 tablets contain calcium disodium edetate, cellulose powder, anhydrous citric acid, colloidal silicon dioxide, ethyl cellulose, guar gum and magnesium stearate in the tablet core and D&C Yellow 10, hydroxypropyl methylcellulose, anhydrous citric acid, iron oxide, propylene glycol, talc, and titanium dioxide for tablet coating [43]. On the other hand, lactose is incompatible with amlodipine besylate (Maillard reaction) due to the presence of a primary amine group in its chemical structure [44]. Therefore to achieve the required binding, while maintaining other tablet physical properties, a multi-excipient system is employed in the originator product "Norvasc® 10 tablets" using a high dilution factor for the amlodipine besylate. The 400 mg tablets of Norvasc® 10 contain microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycollate and magnesium stearate [38]. The performance of Cop-MC in a direct compression formulation containing a poorly compressible high strength drug, such as methyldopa, and a low strength drug, such as amlodipine besylate, were investigated. The

binding and super-disintegration properties, in addition to drug dissolution rate of the tablets prepared, were examined and the results are summarized in Table 4.2. Direct compression techniques were used to prepare the tablets in which Cop-MC was used as the only binder, filler and disintegrant. Crushing strength values of the tablets obtained from both formulations showed high internal binding and fast disintegration time. Full drug release was obtained at 10 min dissolution time for both drugs. This indicates that Cop-MC functions as a binding, disintegration and dissolution promoter. However, it is worth mentioning that although methyldopa tablets showed super-disintegrating characteristics this did not have an influence on their coating using an aqueous coating system.

Table 4.2 Physical properties of rosuvastatin 20 mg, methyldopa 250 mg and amlodipine 10 mg tablets.

Tested Parameter		Rosuvastatin 20 tablets				Methydopa 250 tablets		Amlodipine 10 tablets	
		Formula 1	**Formula 2**	**Formula 3**	**Crestor**	**Formula 4**	**Aldomet**	**Formula 5**	**Norvasc**
Weight (mg)		290			315	450	355	200	400
Shape (mm)		Round shallow biconvex of 9 mm diameter			Pink round of 9 mm diameter	Round shallow biconvex of 9 mm diameter	Round shallow biconvex of 9 mm diameter	Round flat faced beveled edged of 8.mm diameter	Elongated octagon flat faced beveled edged
Crushing force (N)		119	120	120	*	140	*	110	112
Friability (%)		0.35	0.11	0.30	*	0.25	*	0.15	0.24
Disintegration time (Seconds)		120	160	120	180	35	120	30	10
Dissolution (%)	10 min	91	96	96	82	99	101	97	95
	20 min	91	95	97	88	101	102	98	98
	30 min	92	96	96	92	101	101	97	99

* Not performed as the tablets are film coated

4.3.6.2 Stability of Active Ingredients in the Presence of Cop-MC

The DSC thermogram obtained for the initial analysis of pure methyldopa (Figure 4.10h) shows an endothermic peak at about 124.5°C which corresponds to the loss of water of crystallization (sesqui-hydrate). The exothermic decomposition peak observed at about 300°C is assigned to the melting of methyldopa. The DSC thermograms (Figsure 4.10f and 4.10g) of a pure methyldopa sample stored for 6 months at 40°C/75% RH, in open and closed containers, showed an absence of secondary peaks corresponding to impurities. The splitting obtained in the endothermic peak of the loss of the hydrate in the 120-130°C temperature range is most likely to be due to different melting patterns of the sesqui-hydrate in the methyldopa structure.

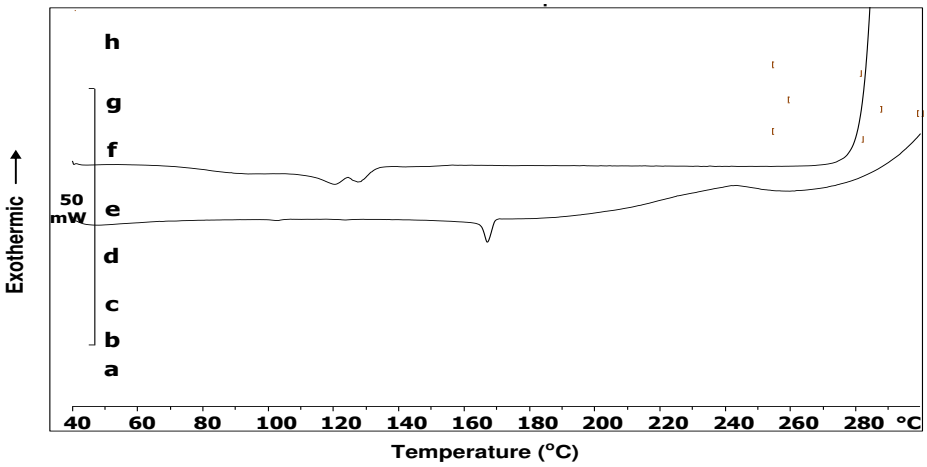

Figure 4.10 DSC scans of methyldopa 250 mg tablets (Formula 4) **(a)** after 6 months at 40°C/75% RH–close amber glass bottles, **(b)** after 6 months at 40°C/75% RH–open amber glass bottles, **(c)** initial analysis, **(d)** reference formula (without active ingredient) at 40°C/75% RH–close amber glass bottles, **(e)** reference formula (without active ingredient) at 40°C/75% RH–open glass amber bottles, **(f)** methyldopa at 40/75% RH–close amber glass bottles, **(g)** methyldopa at 40°C/75% RH–open amber glass bottles and **(h)** methyldopa initial analysis.

The DSC thermograms of Formula 4 (without active ingredient) samples (Figures 4.10d and 4.10e) stored for 6 months at 40°C/75% RH in open and closed containers showed only one endothermic peak obtained at about 167°C, which corresponds to mannitol. The DSC scan of the samples of methyldopa 250 mg tablets (Formula 4) analyzed initially (Figure 4.10c) and the samples stored at 40°C/75% RH in closed (Figure 4.10a) and open

amber glass bottles (Figure 4.10b) for 6 months, showed superimposition whereby no secondary peaks were obtained upon storage under the accelerated conditions of temperature and humidity (40°C/75% RH).

Mixing methyldopa with Cop-MC lowers the decomposition peak temperature of methyldopa from 300°C to 270 °C; this can be attributed to the interaction of two different crystalline structures; such an interaction does not affect the stability of methyldopa as indicated by the absence of new/additional DSC peaks (Figures 4.10-a, b and c) [45]. The absence of new/additional peaks is an indication of the thermal stability and compatibility of methyldopa in the tablet matrix containing Cop-MC.

The DSC study performed on methyldopa 250 mg tablets (Formula 4) was further supported by a HPLC study.

Table 4.3 Stability data for α-methyldopa 250 mg film coated tablets at 40°C/75% RH.

Product	Period (months)	Assay (%) <5.0%+ from initial	Impurities Profile (%)		% Drug release			
			O-3 MD* ≤ 1.0%	Total (1.0%)	5 min.	10 min.	15 min	20 min
Methyldopa	Initial	99.6	0.01	0.19	--	--	--	--
	6/close	102.2	0.01	0.22	--	--	--	--
	6/open	99.6	0.01	0.21	--	--	--	--
Formula 4	Initial	99.4	0.01	0.18	95.6	99.5	100.5	100.8
	1/close	97.7	0.01	0.20	92.2	98.5	101.5	102.1
	1/open	98.1	0.02	0.16	75.4	92.6	96.1	98.0
	2/close	97.4	0.01	0.17	92.9	97.6	100.0	100.2
	2/open	99.9	0.02	0.16	75.8	97.8	100.5	101.1
	3/close	98.4	0.01	0.22	92.0	98.9	99.8	102.4
	3/open	98.6	0.01	0.17	79.2	96.8	99.5	100.0
	6/close	99.2	0.01	0.16	89.3	96.4	98.4	99.8
	6/open	98.2	0.01	0.31	88.2	95.5	98.3	99.4
Aldomet 250	Initial	100.9	0.01	0.14	91.6	101.2	102.1	101.9
	6/close	97.8	0.01	0.29	83.4	94.7	99.1	100
	6/open	98.0	0.01	0.27	57.1	77.5	90.0	95.3

*O-3 MD represents O-3-methylmethyldopa impurity.

+ According to ICH guideline for stability testing of new drug substances and products [39].

HPLC was used to investigate the chemical stability and compatibility of the tablets containing methyldopa and Cop-MC**,** according to Formula 4. The HPLC method was initially validated before use and the results showed a good separation between methyldopa and O-3-methylmethyldopa related compound (the resolution R_1 is more than 3) and the relative standard deviation of replicate injections is less than 2%. In addition,

analyses of samples obtained from a stress-testing study (0.1N NaOH, 0.1N HCl, and 0.3% H_2O_2 at 25^oC for 10 days) in solution indicated that the HPLC method is stability indicating by a significant decrease in percentage assay of methyldopa in the basic media and in the presence of hydrogen peroxide as oxidizing agent (35% and 89% w/w, respectively). The accuracy of the method was investigated by testing 6 different sample preparations containing methyldopa at two different concentrations (5 and 25 mg/100 mL) for measuring the percentage impurities and percentage assay, respectively. The percentage recovery and RSD for 6 replicates are within the range of 98.1 to 102.9% and 0.3 to 1.4%, respectively. The method is linear over a concentration range of 1.3–50.0 mg/100 mL with an r^2 value of > 0.999. The LOQ value is 0.7 mg/100 mL. Table 4.3 shows the analytical data obtained for methyldopa 250 mg tablet (Formula 4) samples stored in open and close amber glass bottles at 40°C/75% RH for 6 months. Pure methyldopa and Aldomet® 250 tablets were treated in the same manner and analyzed as a reference for this study. No significant decrease in the assay of methyldopa 250 tablets according to Formula 4 was observed upon storage under the accelerated condition of temperature and humidity (40°C/75% RH).

Co-processing of α-chitin with crystalline mannitol significantly improves the performance and functionality of both components. This offers a potential use of this co-processed additive as a single tablet excipient displaying super-disintegrating properties.

The mechanical strength of the tablets and lubricant sensitivity were found to be dependent upon the mannitol content and the processing technique used in the preparation of the co-processed excipient.

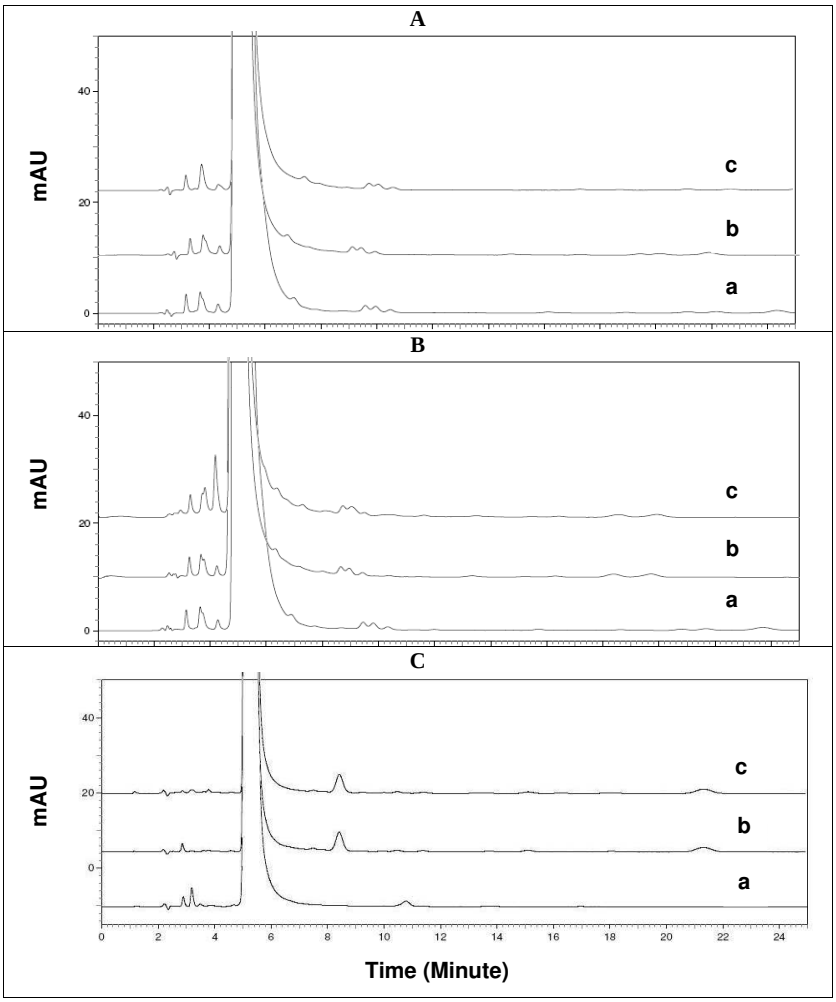

Figure 4.11 HPLC chromatograms of **(A)** methyldopa, **(B)** methyldopa 250 mg tablets (Formula 4) and **(C)** Aldomet 250 mg tablets. Where **(a)** is the initial chromatogram (no incubation), and **(b)/(c)** after 3 and 6 months incubation at 40^{o}C/75% RH, respectively in closed containers.

A small increase in the total impurities for samples of Formula 4, stored in open amber glass bottles at 40°C/75% RH for 6 months, was observed when compared to the samples stored in closed amber glass bottles and Aldomet® 250 tablets (Table 4.3, Figure 4.11).

4.4 Conclusions

The functionality of the Cop-MC is not affected by the tablet preparation procedure whether it is direct mixing or dry/wet granulation. Utilization of Cop-MC, as an excipient, in tablet formulations containing active pharmaceutical ingredients, offers excellent chemical stability, binding and disintegration properties.

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CHAPTER FIVE

5. A NOVEL ORO-DISPERSIBLE TABLET BASE: CHARACTERIZATION AND PERFORMANCE

5.1 Introduction

Tablets are widely used in medication due to their convenience with respect to self-administration and ease in manufacturing [1]. To improve the performance, functionality and quality of pharmaceutical tablets, various excipients are used in their preparation [2]. However, pediatric, geriatric and mentally ill patients experience difficulties in swallowing conventional tablets, which leads to poor patient compliance. To overcome this deficiency, oro-dispersible tablet (ODT) formulations have been developed [3, 4]. In the European Pharmacopoeia, an ODT is defined as a tablet to be placed in the mouth where it disperses rapidly before being swallowed in less than 3 minutes [5], while the FDA consider it as a solid oral preparation that disintegrates rapidly in the oral cavity with an in vivo disintegration time of approximately 30 seconds or less [4]. ODTs are advantageous due to their administration without water, rapid onset of action and improved bioavailability [6, 7]. Various ODT technologies including Orasolv/DuraSolv (by direct compression (DC)), Zydis (by freeze drying), FlashTab (Eudragit-microencapsulation and effervescent couple), FlashDose (cotton candy process) and WowTab (compression moulding process) have been patented [8, 9]. ODTs are highly friable, due to their compaction at lower crushing force compared to conventional tablets, resulting in rapid disintegration; therefore they are commonly packed in special packaging materials [10]. A high level of super-disintegrant (up to 20% w/w) is usually used in ODT preparations to enhance their disintegration properties. Additional excipients including a suitable filler, binder, lubricant, sweetener and color may be added to improve product properties [6, 11].

Mannitol, in crystalline, granulated, or spray dried form, is commonly used in ODT tablet formulations due to its sweet cool taste, compatability with a range of active pharmaceutical ingredients (APIs), non-hygroscopicity, and the fact that its metabolism does not increase blood sugar levels [12-14]. Unlike crystalline mannitol, spray dried mannitol is highly compactible, non-friable, and quick dissolving, which facilitates it use in DC formulation which facilitate its use in ODTs. Furthermore, crystalline mannitol is

widely used in wet granulation (WG) processes due to its low cost and availability [15-17]. α-Chitin plays several important roles in tablet formulations because it is non-toxic, non-allergenic, anti-microbial, non-reactive and biodegradable. Its disintegration power is mainly dependent upon a high water uptake rate. Therefore, chitin can be used over a higher concentration range than many commercially available disintegrants without negatively affecting other tablet properties. However, chitin powder shows poor compactibility. α-Chitin is the most abundant form among the three identified polymorphs of chitin (α-, β- and γ-). It is the second most abundant polysaccharide on earth after cellulose [18, 19].

Co-processing of pharmaceutical excipients is performed using specialized manufacturing processes such as spray drying or melt extrusion in order to produce a single excipient with multiple functionalities. In addition co-processing can be utilized for improving the undesirable physico-mechanical properties of excipients and their performance and is generally undertaken by using a combination of plastic and brittle excipients [20]. For example, chitin, a plastic material, has been successfully used to prepare different excipients via co-processing with diverse brittle materials including mannitol, metal silicates and silicon dioxide [21-23]. In all cases co-processing was achieved by incorporating the brittle material (≤ 30% w/w) inside the pores of chitin (≥ 70% w/w) using an aqueous vehicle. The result of the foregoing studies showed that the extremely large surface pores of chitin were not fully accommodated by the guest materials and thus chitin preserved its functionality as a disintegrant. Moreover, the co-processed excipients obtained displayed enhanced physical properties, functionality and performance (e.g. no-hygroscopicity and highly compactable/disintegrable) [21-23]. Recently, a European patent (EP2384742) describing a novel co-processed single excipient comprising different ratios of chitin and mannitol has been published [24]. This novel co-processed excipient offers a valuable and practical industrial choice in terms of super-disintegration and compaction properties of tablet dosage forms. Furthermore, an article describing the characterization and application of such a novel co-processed excipient in immediate release tablet formulations has been reported in the literature [23]. In the aforementioned study, the tablets prepared by using the co-processed excipient chitin-mannitol (80:20 w/w) and different APIs displayed excellent chemical stability,

binding, and disintegration properties.

The advantage of using chitin and mannitol in conventional tablets [23] proofs the use of such combination in ODT formulation. Due to the ease of manufacturing, ability to produce fast disintegration / dissolving properties and the ability of producing hard tablets makes this a target to test the suitability to offer an excipient base for ODTs. Roll compaction (RC) or WG may then be used to prepare the excipient using mannitol and chitin. The studies reported herein aim to test the foregoing hypothesis and to characterize the excipient obtained by using a higher ratio of mannitol to chitin than used in the previous work [23] by applying RC and WG techniques. The functionality, loading capacity, compatibility and applications of the obtained excipient with different APIs are also reported.

5.2 Experimental

5.2.1 Materials

α-Chitin of average molecular weight 1000 KD, degree of acetylation of about 0.96 and a mean particle size of 90 µm (Zhejiang Jiande Biochemical, China) and D-mannitol (Pearlitol), crystalline grade, with a mean particle size of 160 µm (Roquette, France) were used Purified water of British pharmacopeia grade, Mannogem EZ and Pharmaburst C1 (SPI, France), Isomalt galenIQTM 721 (BENEO-Palatinit GmbH (Germany), PanExcea MHC200G (Avantor Performance Materials, Inc./USA), sodium stearyl fumarate (JRS, USA) and Crospovidone (Polyplasdone XL) with an average particle size of 110 – 140 (ISP, USA) were also used. All active pharmaceutical ingredients employed i.e., montelukast sodium (Matrix Lab., India), domperidone (Xinshiji pharma, China) and metronidazole (Hubei Max Pharma, China) were of pharmaceutical grade. All other excipients and reagents used were of pharmaceutical or analytical grades, respectively.

5.2.2 Methods

5.2.2.1 Preparation of Co-Processed Mannitol-Chitin Excipient

Three co-processed mixtures (each 1 kg) of chitin and mannitol of different ratios (1:9, 2:8 and 3:7 w/w) were prepared using different processing techniques i.e., direct mixing,

RC and WG.

Direct mixing

The three mixtures were separately passed through a 1000 μm mesh sieve (Fritsch, Germany) and then mixed for 5 min at 10 rpm using a 1 liter cubic blender equipped with a motor drive machine (Erweka, Germany).

Roll compaction

The three mixtures prepared by direct mixing were compacted using a roll compactor equipped with DPS type rolls (TFC-labo, Vector Corporation, USA), set at about 5 MPa roll pressure, 4 rounds/minutes roll speed and 20 rounds/minutes screw control speed. The compacted powders were collected and passed through either the 710 μm or 1000 μm sieves using a milling machine equipped with a motor drive machine. Finally the granules were mixed for 5 min at 10 rpm using a 1 liter cubic blender equipped with a motor drive machine.

Wet granulation

350, 450 and 550 ml of 14.5% (w/v) of aqueous mannitol solutions were used as granulating agents to prepare the chitin-mannitol mixtures (1:9, 2:8 and 3:7 w/w ratio, respectively). The sieved chitin and the remaining quantity of mannitol were placed in granulation pans (Erweka, Germany) and granulated with the mannitol solution using a mixing speed of 150 rpm. The wet masses were passed through a 9.5 mm sieve. Drying was performed at 60°C using a drying oven (UT6200, Heraeous, Germany). The granules were passed through the 1000 μm sieve and mixed using the same procedures as used for the RC preparation.

5.2.2.2 Characterization of co-processed chitin-mannitol (Cop-CM)

Fourie-transform infrared spectroscopy (FT-IR)

FT-IR measurements were undertaken using an FT-IR instrument (Paragon 1000, Perkin

Elmer, UK) by means of thin pellets containing 1 mg of each sample dispersed in 100 mg of KBr. The spectra were recorded at room temperature as an average of 30 scans, in the 400–4000 cm^{-1} range with a spectral resolution of 1 cm^{-1}. In order to minimize the effects of traces of CO_2 and water vapour from the atmosphere of the sample compartment, the spectrometer was purged with nitrogen.

X-ray powder diffractometry (XRPD)

The XRPD profiles were measured using an X-ray diffractometer (PW1729, Philips, Holland). The radiation was generated using a CoK_α source and filtered through Ni filters; a wavelength of 1.79025 Å at 40 mA and 35 kV was used. The instrument was operated over the 2θ range of 5-60^o. The range and the chart speed were set at 2 × 103 cycles/sec and 10 mm/2θ, respectively.

Differential scanning calorimetry (DSC)

Samples (~ 5mg) were hermetically sealed in aluminum pans and scanned over a range temperature of 0–300°C at a rate of 5°C/min (DSC 25, Mettler Instruments). The instrument was calibrated using indium and the calorimetric data were analyzed using STAR software (version 9)

Scanning-electron microscopy (SEM)

The morphology of the samples were determined using a scanning electron microscope (Quanta 200 3D, FEI, Eindhoven/Netherland) operated at an accelerating voltage of 1200 V. The sample (0.5 mg) was mounted onto a 5×5 mm silicon wafer affixed via graphite tape to an aluminum stub. The powder was then sputter-coated for 105 s at a beam current of 20 mA/dm^3 with a 100 Å layer of gold/palladium alloy.

Angle of repose

Angle of repose (q) was determined using the funnel method [25]. The sample blends were poured through a funnel that could be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and then q was calculated using

the formula:

$$q = \tan^{-1} h/r \quad (1)$$

Particle size

The particle size distributions for all samples were measured by using a Malvern Mastersizer 2000 instrument (Malvern Instruments Ltd, Worcestershire, UK). Approximately 5 mL of powder was used for each measurement. The air pressure was set at 2.0 bar, and the feed rate was set at 50%. The particle size distributions D10, D50 and D90 were recorded. Each sample was measured 3 times.

Bulk density (BD) and tapped density (TD) [25]

Approximately 100 mL of powder was gently poured into a tarred graduated cylinder and the initial volume and weight of the material recorded. The graduated cylinder is placed on a tap density tester and the final volume is recorded after 200 taps. BD and TD are calculated by dividing the initial and final volume of powder by the weight of powder, respectively.

Water content

The water content of the powders was measured using a DL38, Karl Fischer Titrator (Mettler Toledo-Switzerland).

Hygroscopicity

Samples (2.5 g) were stored in desiccators containing water saturated salt solutions at room temperature (20°C) for 10 and 14 days. The media compositions were set according to the Handbook of Chemistry and Physics [26] to obtain relative humidity's (RHs) of 52, 62, 75, 84 and 95% using $Ca(NO_3).4H_2O$, NH_4NO_3, NaCl, KCl and $Na_2HPO_4.12H_2O$, respectively. The samples were withdrawn after a fixed time period and kept at 20°C for 1 and 24 hr before weighing and calculating the fractional gain in mass compared to the original mass under the different RH conditions.

2.2.3 Physical and chemical properties of tablets prepared from Cop-CM

Crushing force, disintegration and friability

The crushing force (6D, Schelenuiger tester, Germany), disintegration (2T31, Erweka tester, Germany) and friability (Erweka tester, Germany) were performed following the general tests in the British Pharmacopeia [27].

Influence of particle size on tablet properties

Samples of Cop-CM powders were passed using either 710 μm or 1000 μm sieves and individually mixed with 1.0% (w/w) of sodium stearyl fumarate as a lubricant and then compressed using a single punch tabletting machine (SF3, Chadmach Machinery, India) at different crushing force values of 30, 50, 70, 90, 110, 130 and 150 N, using a 10 mm circular punch to produce tablets of 250 mg weight. The disintegration time and friability were measured at each tablet crushing force point. Some of the commercially available ODT bases (Pharmaburst C1, Isomalt galenIQ^{TM} 721, Mannogem EZ and PanExcea MHC 200G) in addition to Mannogem EZ and 3% crospovidone, Isomalt galenIQ^{TM} 721 and 3% crospovidone powders were lubricated using 1% w/w sodium stearyl fumarate and used as reference materials.

Moisture uptake studies

Moisture uptake studies were conducted in order to assess the physical stability of the ODTs composed of Cop-CM base. Twenty tablets were kept in a desiccator over calcium chloride at 37°C for 24 hours. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 14 days. The required humidity was achieved by the use of saturated sodium chloride solution at the bottom of the desiccators for 72 hours. Tablets were weighed and the fractional increase in mass was recorded [26].

Wetting time

A piece of tissue paper (8 cm in diameter), folded twice was placed in a Petri dish (8.5 cm in diameter) containing 6 ml of water. One tablet was carefully placed on the surface

of the tissue paper and allowed to wet completely [26]. The time required for the water to reach the upper surface of the tablet was recorded as the wetting time.

Loading capacity

A study was undertaken to measure the impact of the API load on the performance of the Cop-CM as tablet excipient. Tablets were prepared by DC using a SF3 single punch tablet press machine equipped with D-type tooling. The seven experiments were performed using Cop-CM and metronidazole, containing, 0%, 10%, 30%, 50%, 70, 90 and 100% (for comparison) of metronidazole lubricated with 0.3% sodium stearyl fumarate. The prepared tablets were circular in shape with a diameter of 12 mm and a mass of 500 mg. Tablets from each experiment were evaluated for crushing force and disintegration time.

Functionality

To investigate the functionality of the Cop-CM, two API model as small strength tablets were studied including montelukast sodium (Monte) and domperidone (Domp). The tablets for the two APIs were prepared by DC, RC as well as WG methods. The Monte and Domo tablets contained 1.77% and 3.4% of API and 94.7% and 93.1% of Cop-CM, respectively. In addition, both APIs formulations contained strawberry powder (2.0%), aspartame (0.5%) and sodium stearyl fumarate (1.0%). For the DC experiments, Monte and all excipients, except sodium stearyl fumarate, were first mixed for 2 min and then sodium stearyl fumarate was added and further mixed for another 2 min.

For the RC procedure, Monte (1.77% w/w), Cop-CM (25% w/w, intra-granular) and sodium stearyl fumarate (0.6% w/w) were compacted by employing a DP roll type compaction using 10 MPa roll pressure, 3 rounds/minutes roll speed and 43 rounds/minutes screw control speed and then passed through a 1000 μm sieve. The remaining amount of Cop-CM was added and mixed for 2 min followed by the addition of sodium stearyl fumarate (0.4% w/w). The powder was then further mixed for 2 min.

For the WG procedure, Monte (1.77% w/w) and Cop-CM (35% w/w, intra-granular) were granulated with 50% (w/v) ethanol in water, dried at 60^{o}C, and then sieved using the

1000 μm sieve. The remaining amount of Cop-CM was added and mixed for 2 min; sodium stearyl fumarate (1%) was then added and mixed for a further 2 min. The same procedures were repeated for Domp. The prepared mixtures for each API were compressed at 300 mg tablet weight, for which 10 mm shallow concave punches and dies were used. Dissolution tests (DT-80; Erweka tester, Germany) for Monte and Domp were performed according to the U.S. Food and Drug Administration [28, 29] and British Pharmacopeia [30] published dissolution methods. The released fraction of Monte and Domp were determined spectrophotometrically (Du-650i UV/Visible spectrophotometer, Beckman, USA) by measuring the first derivative absorbance modes at 290 nm for Monte and absorbance mode at 280 nm for Domp.

Compressibility

Mannitol, chitin and Cop-CM powder samples were compressed using a universal testing machine (RKM 50, PR-F system, ABS Instruments, Germany) equipped with 12 mm round, flat face upper and lower punches as well as dies; punch speed was fixed at 10 mm/min. Different compression forces from 80 to 390 MPa were applied. Three tablets were prepared to ensure reproducibility. Compression was carried out at 400 mg tablet weight. The compression behavior of the samples was evaluated using Kawakita analysis. [31-34].

Stability studies

Monte and Domp tablets prepared by DC were packed in aluminum/aluminum strips and stored at 25^{o}C/60% RH and 40°C/75% RH for 24 and 6 months, respectively. At different interval times, tablets were withdrawn and tested for dissolution and content of API and its related substances by stability-indicating and validated HPLC methods [35-37]. The HPLC instrument was equipped with a P1000 pump and a UV1000 detector (TSP/USA). For Monte tablets, a mixture of acetate buffer (0.385% ammonium acetate in water adjusted with acetic acid to pH 3.5) and methanol (15:85, v/v) was used as the mobile phase and an octadecylsilyl silica column as the stationary phase (250 × 4 mm, 10 μm). UV detection at 254 nm, a flow rate of 1 mL/min, and 20-μL injection volumes of the test solutions (0.2 mg Monte/ml of 70% ethanol) were used. While for Domp tablets,

methanol and 0.5% ammonium acetate in water were used as the mobile phases A and B, respectively. A linear gradient elution with a flow rate of 1.5 ml/min was programmed as follows: time 0 min: 30, 70, time 10 min: 100, 0, and time 12 min: 100, 0 for mobile phases A and B, respectively. A based-deactivated, end capped L7 column was used as the stationary phase (Hypersil C8 BDS, 100×4.6 mm, 3 μm). UV detection at 280 nm and a 10-μL injection volume of the test solutions (5 mg Domp/ml of 0.1 M HCl in 50% ethanol) were employed. The HPLC method was initially tested for system suitability (i.e., peak symmetry, repeatability, and resolution) and for validation parameters (i.e., specificity, recovery, stability in solution, linearity, and limit of quantitation (LOQ)) according to USP guidelines [37].

5.3 Results and Discussion

5.3.1 Selection of process and ratio for co-processed chitin-mannitol excipient

In order to select the optimal ratio and process for co-processed excipient preparation, three different ratios of chitin and mannitol (10:90, 20:80 and 30:70 w/w) and three different processing techniques i.e., direct mixing, WG and RC were used. The prepared excipients were lubricated with sodium stearyl fumarate (1.0% w/w) and compressed at different tablet crushing forces (50 – 150 N). The tablets obtained were tested for friability, disintegration and wetting times versus the corresponding crushing forces. The preliminary results of the aforementioned experiments indicated that direct mixing and WG were unsuitable, because the mixtures prepared by direct mixing displayed unacceptable physical properties (e.g. poor flow and powder non-uniformity). The difference in bulk densities of chitin (~0.2 g/cm^3) and mannitol (~0.5 g/cm^3) is the reason underlying such unacceptable physical properties. In the case of WG, the tablets suffered from capping and high disintegration times due to the penetration of the dissolved mannitol into the chitin pores. Such penetration did not allow the pores to act as as functional compression and disintegration enhancers. However, RC gave reasonable results. The data in Figure 5.1 shows the effect of crushing force on the friability, disintegration and wetting times of tablets produced. Up to a crushing force of 90 N, all chitin: mannitol ratios showed acceptable physical properties (low friability and fast disintegration and wetting times). While at crushing forces above 90 N, the excipient

prepared by using a chitin: mannitol ratio of 1:9 showed capping upon tablet compression due to an insufficient amount of chitin, responsible for improving the compressibility. Using ratios of chitin: mannitol of 2:8 and 3:7 (w/w) over all the investigated range of crushing forces produced tablets with acceptable physical properties. However, a ratio of chitin and mannitol of 2:8 (w/w) was chosen in order to obtain beneficial mannitol taste properties and to reduce the amount of insoluble chitin in ODT preparations.

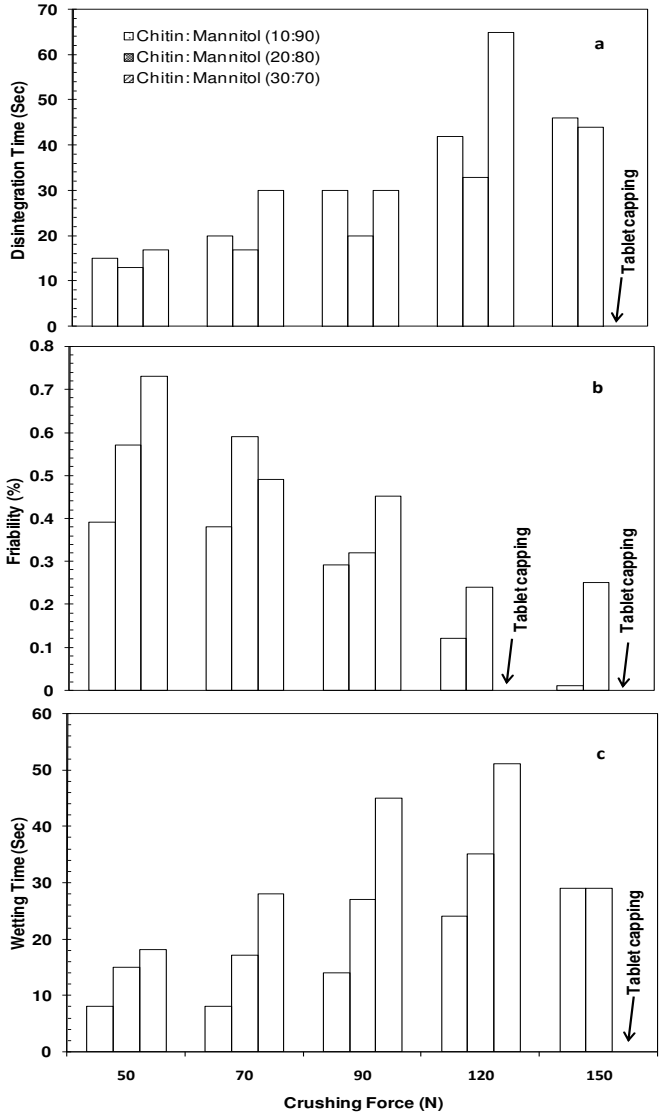

Figure 5.1 Plots of the crushing force (N) versus (**a**) disintegration time, (**b**) friability, and (**c**) wetting time for compacted mixtures prepared using different ratios of chitin and mannitol (1:9, 2:8, and 3:7 w/w). Tablets were 10 mm in diameter and 250 mg in weight. All powders were lubricated using 1% (w/w) sodium stearyl fumarate.

5.3.2 Characterization of Cop-CM Powder

The FT-IR spectra of chitin, mannitol, the corresponding physical mixtures and co-processed excipients (Cop-CM) are presented in Figure 5.2.

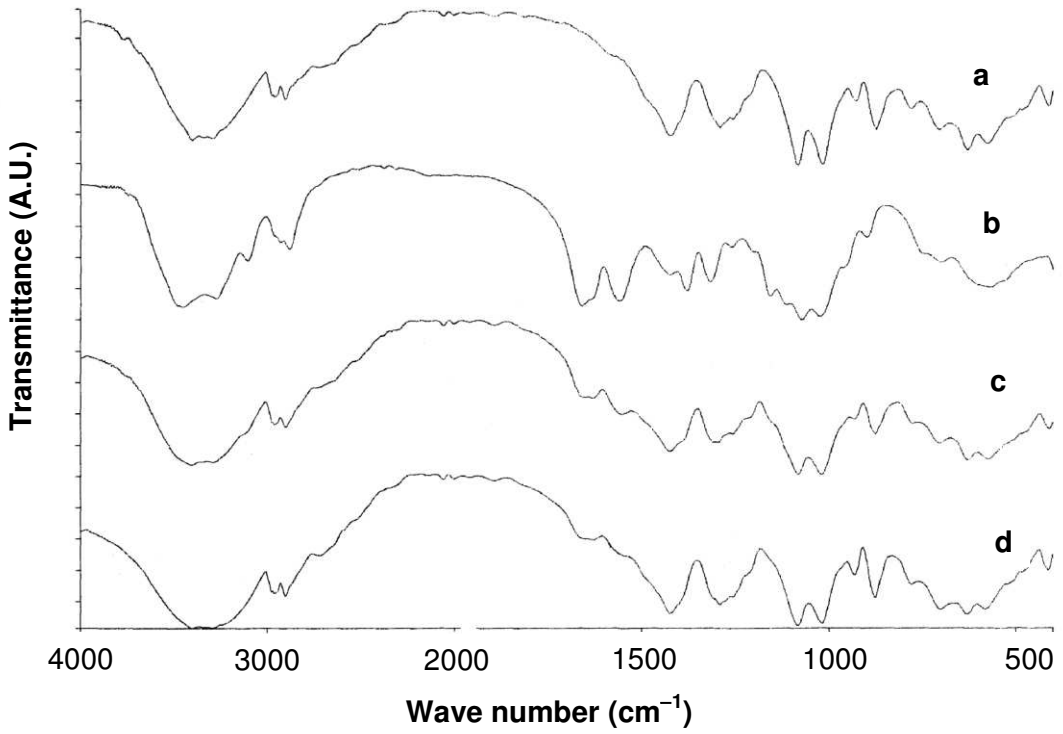

Figure 5.2 FT-IR spectra of (**a**) mannitol, (**b**) chitin, (**c**) physical mixture of chitin-mannitol (2:8, w/w), and (**d**) Cop-CM.

It is clear that the FT-IR of the physical mixture of chitin and mannitol (Figure 5.2c) is a superposition of the vibrational band profiles contributed by chitin and mannitol (Figures 5.2a and 5.2b). The dominance of the principal bands of mannitol in the physical mixture is a result of its high fractional composition in the mixture (80% w/w). The two bands in the 1550-1660 cm^{-1} range corresponding to the chitin amide I and II vibrational modes (Figure 5.2a) persist in the spectra of the physical mixture and Cop-CM, while the remaining bands are due to mannitol. The absence of any shift in the FT-IR bands of the Cop-CM (Figure 5.2d), in comparison with the bands of the physical mixture (Figure 5.2c), suggests the absence of chemical interaction due to the use of RC to form

the co-processed excipient Cop-CM.

Further analysis of the Cop-CM by XRPD (Figure 5.3) and DSC (Figure 5.4) techniques showed the same results, where the signals corresponding to mannitol are dominant due to its high percentage and crystallinity. The absence of new signals or shift in the patterns indicates the absence of formation of a new crystal form or chemical interaction.

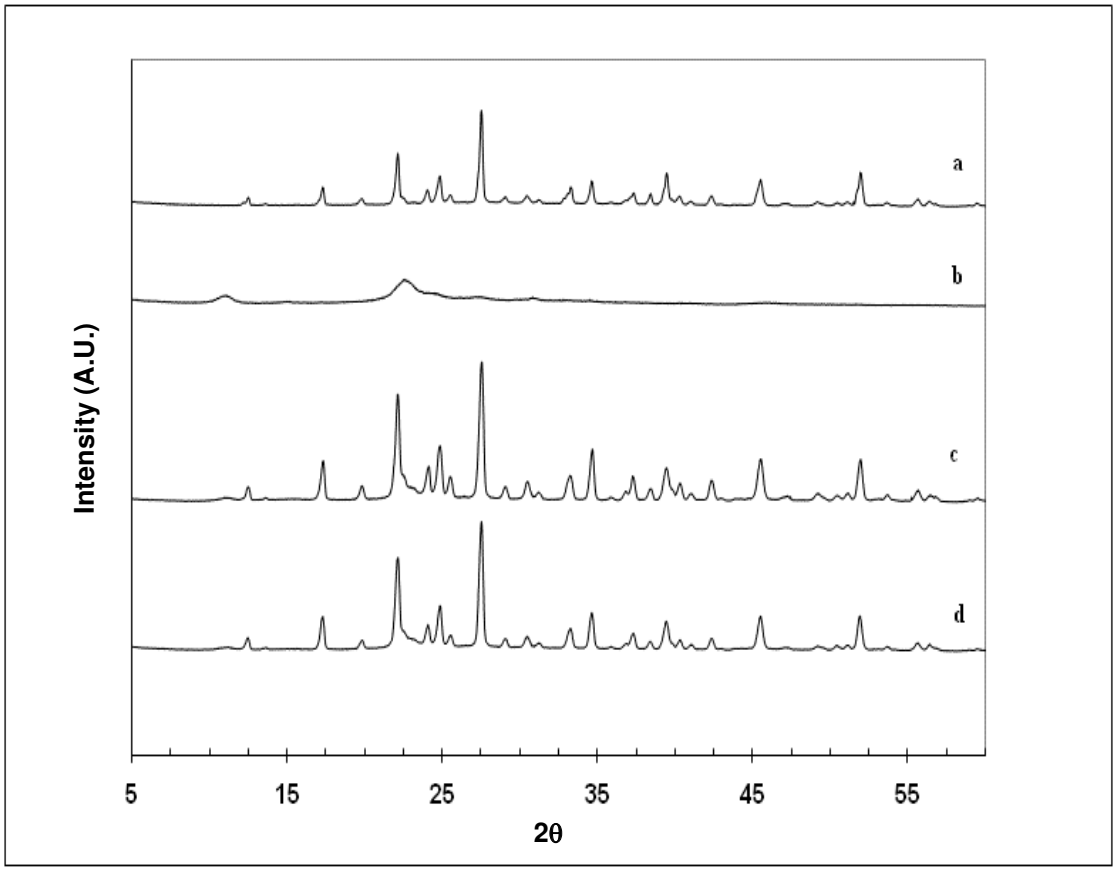

Figure 5.3 XRPD profiles of (**a**) mannitol, (**b**) chitin, (**c**) physical mixture of chitin-mannitol (2:8, w/w), and (**d**) Cop-CM.

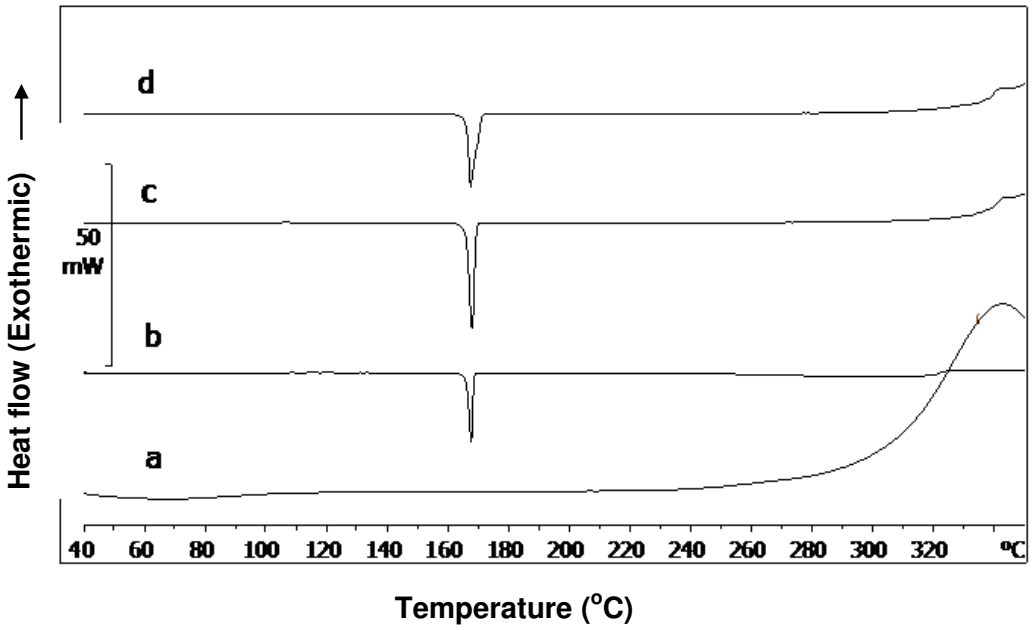

Figure 5.4 DSC thermograms of (**a**) chitin, (**b**) mannitol, (**c**) physical mixture of chitin-mannitol (2:8, w/w) and (**d**) Cop-CM.

SEM was used to investigate particle surface morphology (Figure 5.5). When comparing the particle shape of mannitol (Figure 5.5a) with that of the Cop-CM (Figure 5.5d), it is apparent that it has changed from rectangular rod granules to three-dimensional dense compacts for the Cop-CM.

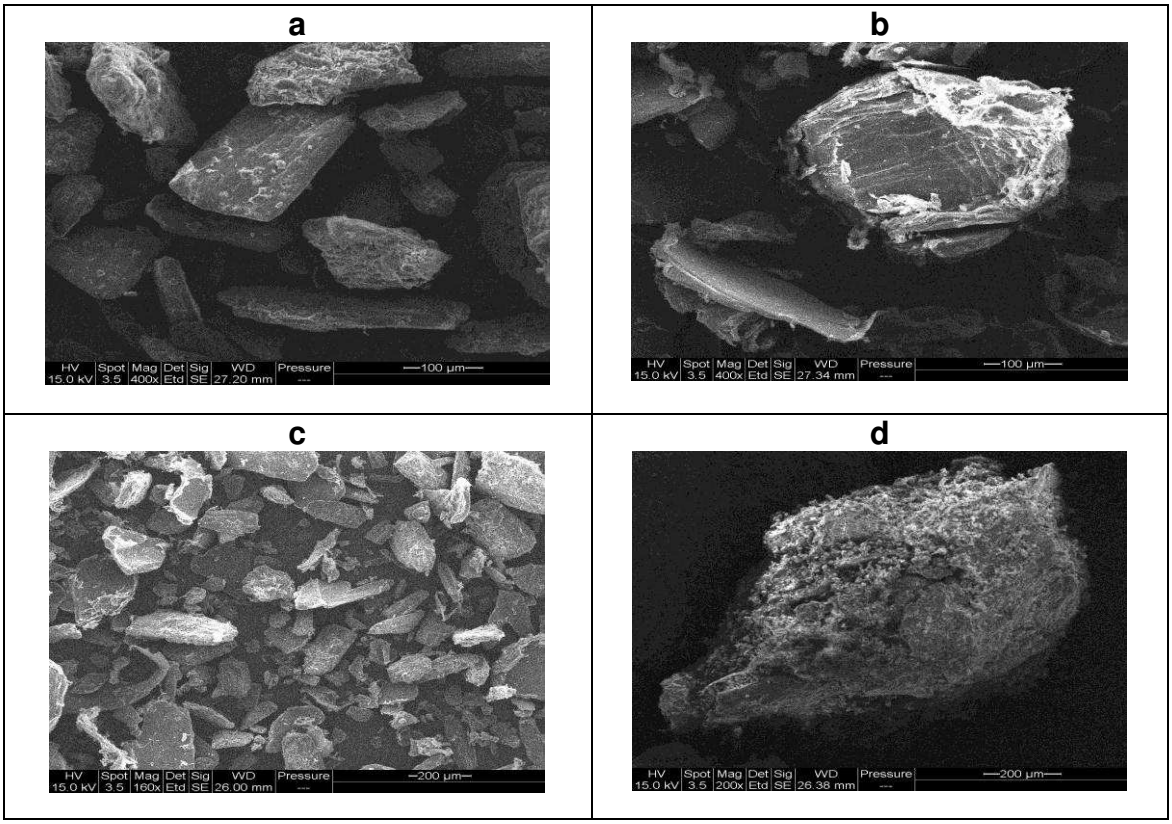

Figure 5.5 SEM images of (**a**) mannitol, (**b**) chitin, (**c**) physical mixture of chitin-mannitol (2:8, w/w), and (**d**) Cop-CM.

5.3.3 Physical Properties of Cop-CM Powder

The physical properties of the Cop-CM powders passed through two different mesh size sieves (710 and 1000 μm) were evaluated. The two powders have a water content of about 1.5% w/w (DL38, Karl Fischer Titrator, Mettler, Switzerland) and a bulk density of 0.5-0.55 g/cm^3 (SVM, Tapped volumeter, Erweka, Germany). The pH of a 5% (w/v) aqueous dispersion is in the range 6-8. The particle size distribution (D10, D50 and D90) of Cop-CM is given in Table 5.1.

Table 5.1 The physical properties of Cop-CM.

Parameter	Value
Water content (w/w%)	1.5
pH	6.0 – 8.0
Bulk density (gm/ml)	0.50-0.55
Tapped density (gm/ml)	0.55-0.65
Particle size distribution: - Milling through 710µm - Milling through 1000µm	 D10: 5 µm; D50: 145 µm; D90: 496 µm D10: 7 µm; D50: 170 µm; D90: 584 µm
Hausner's ratio	1.13
Carr's index	11.86
Angle of repose	32°

Particle size and shape are critical parameters in powder characterization, particularly in DC formulations affecting powder performance, packing, consolidation, flowability and compaction. It is one of the prime considerations in selecting excipients to develop and optimize a pharmaceutical formulation. Ideally, DC excipients should exhibit narrow size distributions with moderate-to-coarse particle size, having a mean particle size of 100 to 200 µm [38]. In ODT formulation, the control of particle size is essential for the water insoluble excipients to minimize the grittiness feeling during the tablet administration. Best results are obtained when using smaller particle size for insoluble excipients. Another critical parameter for the DC excipient is the bulk density which can be used to describe the packing behavior of granules [38]. Cop-CM powder passed through 710 µm mesh size has a mean particle size of about 215 µm. A higher bulk density is advantageous in tabletting because of a reduction in the powder-fill volume of the die. Cop-CM powder sieved through 1000 µm mesh size has a bulk density of about 0.52 gm/mL and a tapped density of 0.59 gm/mL.

On the other hand, Hausner's Ratio (H) is an indirect index of ease of powder flow. It is calculated by using the formula, [25]

$$H = \mathrm{TD}/\mathrm{BD} \qquad (2)$$

The simplest method of measurement of free flow of a powder is compressibility; an

indication of the ease with which material can be induced to flow is given by Carr's Index (I) which is calculated using the formula:

$$I = 100 \times (TD - BD)/ TD \quad (3)$$

Hausner's ratio of 1.0-1.11 indicates excellent flow whereas values of 1.12–1.18 indicate good flow, while Carr's index of ≤10 indicates excellent flow, whereas I values of 11-15 indicate good flow. (Generally lower Hausner's ratio and Carr's Index values represent better flow).

The density change before and after tapping calculated as % compressibility (Carr's index) is an indicator of how fast granules can flow to their highest packing. The Carr's index calculated from the density data showed a value less than 12, and Hausner's ratio of less than 1.13 indicating further the good flowability, which is an important factor for DC powders. Good flowability of powder is needed for content uniformity and less weight variation in final tablets. According to US Pharmacopeia 31, General Chapter <1174 >, angle of repose (25-30°) indicates excellent flow, and 31-35° indicate good flow. The Hausner`s ratio, Carr`s index and the angle of repose values for Cop-CM powder are shown in Table 5.1. From the data obtained, Cop-CM powder showed a good flow-ability and compressibility.

5.3.3.1 Moisture Uptake by Cop-CM

The data in Figure 5.6 shows the water uptake by Cop-CM and commercial ODT bases (Phrmaburst C1, Isomalt 721, and Mannogem EZ) at 25^{o}C and different relative humidities.

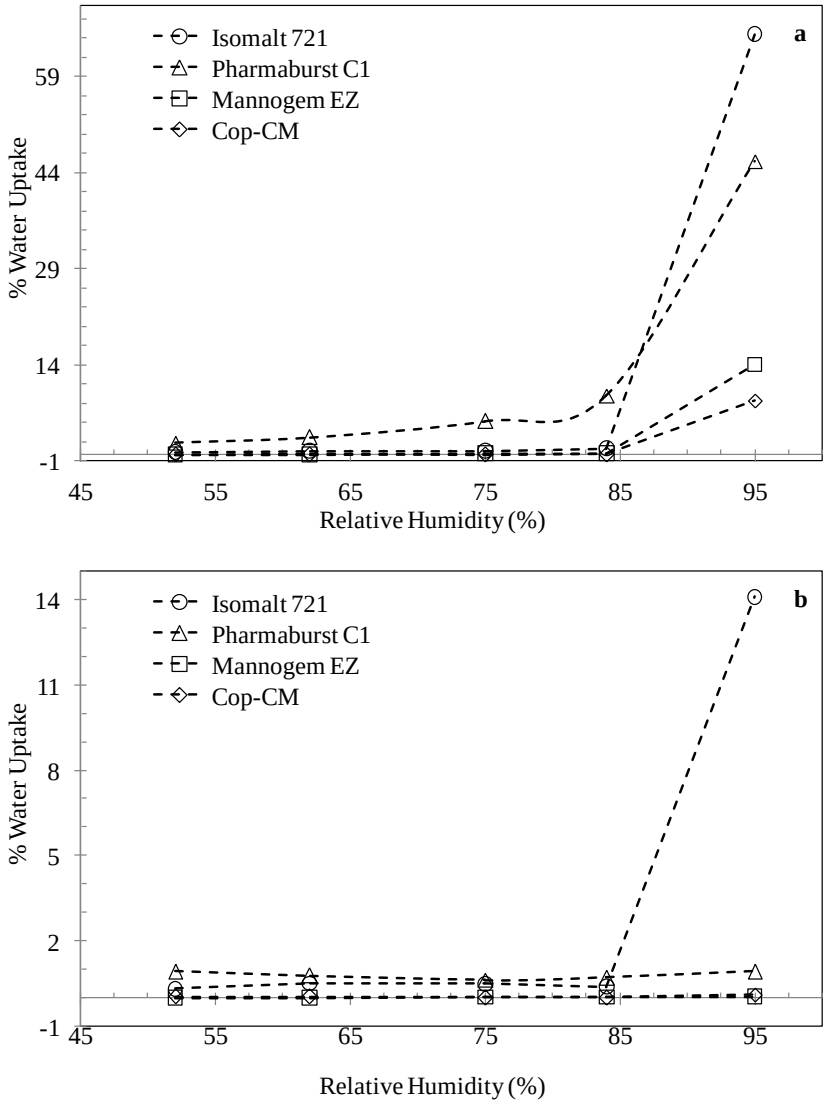

Figure 5.6 The water uptake by Cop-CM in comparison with some commercially available ODT bases after incubation at 25°C and different relative humidity's (**a**) for 2 weeks and (**b**) after equilibration at 25°C/45% relative humidity for one further day.

Up to 84% relative humidity for 2 weeks, all bases, except Pharmaburst C1, showed insignificant increase in water uptake (Figure 5.6a). However, following equilibration for 1 day at 25°C/45% relative humidity, Pharmaburst C1 lost the excess water absorbed (9%) to reach only 0.7% (Figure 5.6b). At high relative humidity (95%), the water uptake follows the order: Cop-CM (8%) < Mannogem EZ (14%) < Pharmaburst C1 (46%) < Isomalt galenIQ™ 721 (66%). Following equilibration for 1 day at 25°C/45% relative

humidity, all bases except Isomalt galenIQ^{TM} 721 lost the excess water absorbed to give values less than 1% (Figure 5.6b). While it is about 14% for Isomalt galenIQ^{TM} 721 which is most probably due to partial dissolution of Isomalt at high relative humidity. This difference in water uptake of different bases is due to the difference in their components and their morphology (e.g. crystalline versus amorphous). The roller compaction of large amount of mannitol (80% w/w) with chitin results in the coverage of the outer surface of chitin with mannitol; therefore, the Cop-CM powder was clearly non-hygroscopic due to the very minimal water uptake of mannitol.

5.3.3.2 Hygroscopicity of Tablets Prepared from Cop-CM

The water adsorption study was conducted for tablets prepared from Cop-CM at 75% relative humidity and room temperature. Results indicate that the tablets prepared from Cop-CM do not sorb water (less than 0.4% w/w). It is advantageous in the pharmaceutical industry to have non-hygroscopic ODT preparations, as this will reduce the cost of the expensive package which is usually used to obtain the required protection against moisture.

5.3.3.3 Compression Profile of Tablet Prepared from Cop-CM

Data for the friability, disintegration and wetting times versus the corresponding crushing force for tablets prepared using Cop-CM powders passed through either the 710 μm or 1000 μm sieves are shown in Figure 5.7. Generally, a reduction in particle size is associated with an increase in tablet mechanical strength. The increase in mechanical strength of the tablets is directly reflected in its physical properties (crushing force, disintegration time, friability, wetting time, etc.) and attributed to an increase in the surface area available for inter-particulate attraction [39]. However, when Cop-CM was used it was found that varying the particle size had no impact on the tablet's mechanical strength. The mechanical strength of the tablets prepared from materials with a tendency to fragment, such as mannitol, dibasic calcium phosphate dihydrate and saccharose appear to be independent of particle size [40]. This could be the case for the Cop-CM particles which contain excess amount of mannitol (80% w/w) and undergo

fragmentation [41] at the early stages of compression, thereby causing a minimal effect on tablet mechanical strength when varying the particle size.

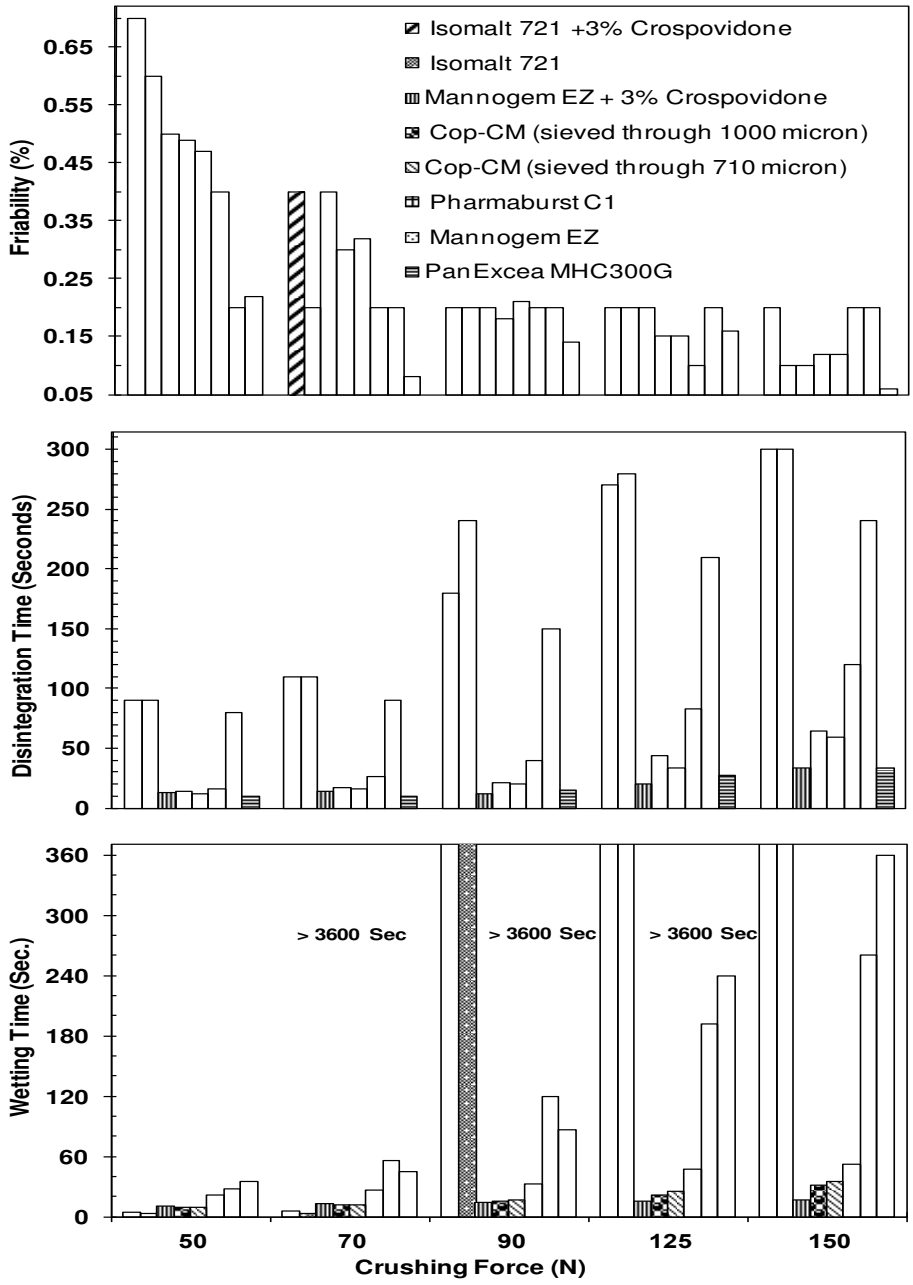

Figure 5.7 Plots of the crushing force (N) versus (**a**) disintegration time, (**b**) friability, and (**c**) wetting time for tablets prepared from Cop-CM powders passed through either 710 μm or 1000 μm sieves in comparison with commercially available bases. The tablets were 10 mm in diameter and 250 mg in weight. All samples were lubricated with 1% (w/w) sodium stearyl fumarate.

The disintegration time of ODTs is generally less than one minute and actual disintegration time that patients expect is less than 30 seconds. The general compendial method of performing disintegration tests for ODTs is not capable of detecting such a very short disintegration time. The wetting time of the ODT is another important test, which gives an insight into the disintegration properties of the tablet. Lower wetting time indicates a quicker disintegration of the tablet [42]. With respect to tablet disintegration, the Cop-CM showed a unique characteristic whereby tablet disintegration time was independent of particle size and tablet crushing force (Figure 5.7). Tablets produced from Cop-CM powders passed through either the 710 μm or 1000 μm sieves, at an upper punch compression scale of 16-20 kN for each particle size, showed a superior disintegration time ranging from 11.5 to 59 seconds and from 14 to 64 seconds, respectively. This was achieved for tablet crushing force values ranging from 50-150 N. By increasing the crushing strength from 50 to 150 N, the wetting time of the tablet was only increased from 9 to 35 seconds. This suggests that capillary action is the dominant mechanism for the disintegration of Cop-CM which is irrespective of the tablet crushing force [23]. In addition, the inter-particulate voids within the chitin particles in the Cop-CM, as previously mentioned, remain intact and unchanged after using the RC procedure with mannitol and by varying the powder particle size. Regarding powder compressibility, chitin within the Cop-CM mixture provides an effective means of obtaining hard tablets with low friability while persisting in its fast disintegration and wetting properties, as can be concluded from the data shown in Figure 5.7.

Four commercially available ODT excipients were used for comparison purposes including, Isomalt galenIQ^{TM} 721, Mannogem EZ, Pharmabust EZ and PanExcea MHC200G. The data in Table 5.2 shows the function and composition of these excipients. Crospovidone (a cross-linked polymer of N-vinyl-2-pyrrolidinone is often used at concentrations up to 5.0% and is commonly used as an effective disintegrant in tablet formulations) is used at 3% w/w level in both Isomalt galenIQ^{TM} 721 and Mannogem EZ powders [11]. Both PanExcea MC200G and Pharmaburst C1 already contain disintegrant in their compositions (calcium silicate and crospovidone, respectively).

Table 5.2 Function and composition of used ODT excipients.

Trade Name	Composition	Manufacturer	Advantages & Function
PanExcea MC200G	Mannitol (75%), calcium silicate (25%). Particle size: 50% (103µm)	Avantor Performance Materials, Inc./USA http://www.avantormaterials.com/	High performance, rapid disintegration, direct compression excipient for oro-dissolving tablets formulation
Mannogem™ EZ	Spray dried direct compression mannitol Particle size: 60% (75-150µm)	SPI Pharma TM, Inc., New Castel , U.S.A http://www.spipharma.com	Assist in formulating difficult to use non-hygroscopic ODT containing fine APIs
Pharmaburst™ C1	Mannitol 84%, crospovidone 16%, silicon dioxide <1%		High compactibility, high loading in small diameter tablets, smooth mouth feel, rapid disintegration
Isomalt galenIQ-721	1-O--D-glucopyranosyl-D-mannitol dehydrate and 6-O--D-glucopyranosyl-D-sorbitol (1:3) Particle size: 90% (360µm), 50% (220 µm)	BENEO-Palatinit GmbH (Germany) http://www.beneo-palatinit.com/en/Pharma_Excipients/galenIQ/galenIQ_Grades/galenIQ721/	Highly soluble agglomerated spherical isomalt for fast dissolving and very fast disintegrating direct compression tablet preparations

In order to obtain a tablet crushing force range of 50-150 N, upper punch compression scales of 25.5 to 29.5 kN were applied to all excipients except for PanExcea in which case a scale range from 39-42 kN was applied. For all reference excipients used, increasing the crushing force from 50 to 150 N resulted in the disintegration and wetting time of the tablets increasing linearly. The friability of the tablets was found to be within the limit (less than 0.7% for Isomalt galenIQ^{TM} 721+3% crospovidone) at the lower crushing force (50 N). With increasing tablet crushing force, the friability was significantly reduced (less than 0.2%). At 50 N tablet crushing force value, the reference excipients except for Mannogem EZ and Isomalt galenIQ^{TM} 721 (with and without crospovidone) gave a disintegration time of less than 30 seconds. In addition, the wetting time for all reference excipients was less than 30 seconds at the same crushing force. The data in Figure 5.7 clearly shows that by increasing the tablet crushing force, the disintegration times and wetting times were increased accordingly. Only, Isomalt galenIQ^{TM} 721 plus crospovidone and PanExcea MC200G tablets showed a short disintegration time (less than 33 seconds) at the highest crushing force (150 N), whereas for the other excipients a disintegration time range of 120-300 seconds were observed. At a tablet crushing force of 150 N, only pharmaburst C1 and Mannogem EZ plus crospovidone showed a short wetting time of less than 60 seconds (52 and 16 seconds, respectively).

It can be clearly observed that with Cop-CM**,** the increasing in tablet crushing force up to 150 N does not significantly affect both disintegration and wetting times. This property is extremely advantageous where very fast disintegrating hard tablets can be prepared using Cop-CM and simply packed in traditional packaging materials. This prevents the need of a special type of packaging to avoid the breakage of the tablets during removal from the package. Mannogem^{TM} EZ + 3% crospovidone combination has showed similar behavior to Cop-CM at high tablets crushing forces. At 150 N tablet crushing force, PanExcea MHC300G has preserved the very short disintegration time, while the tablet wetting time was significantly increased. On the otherwise, Pharmaburst C1 behave in a different manner, where by increasing the tablet crushing force to 150 N the disintegration time was relatively high (> 2 min), while the tablets wetting time was not significantly affected.

5.3.3.4 Powder Compressibility

The Kawakita equation (Equation 4) is used to study powder compression using the degree of volume reduction, C. The basis for the Kawakita equation for powder compression is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of the pressure term and the volume term is a constant [31]:

$$C = \frac{(V_o - V)}{V_0} = \frac{abP}{1+bP} \qquad (4)$$

Where, V_o is the initial volume and V is the volume of powder column under an applied pressure, P. The constants a and b represent the minimum porosity before compression and plasticity of the material, respectively. The reciprocal of b defines the pressure required to reduce the powder bed by 50% [32, 33]. Equation 4 can be re-arranged in linear form as:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \qquad (5)$$

The expression for particle rearrangement can be affected simultaneously by the two Kawakita parameters a and b. The combination of these into a single value, i.e. the product of the Kawakita parameters a and b, may hence be used as an indicator of particle rearrangement during compression [34]. Figure 5.8 shows the Kawakita plots for mannitol, Cop-CM and chitin.

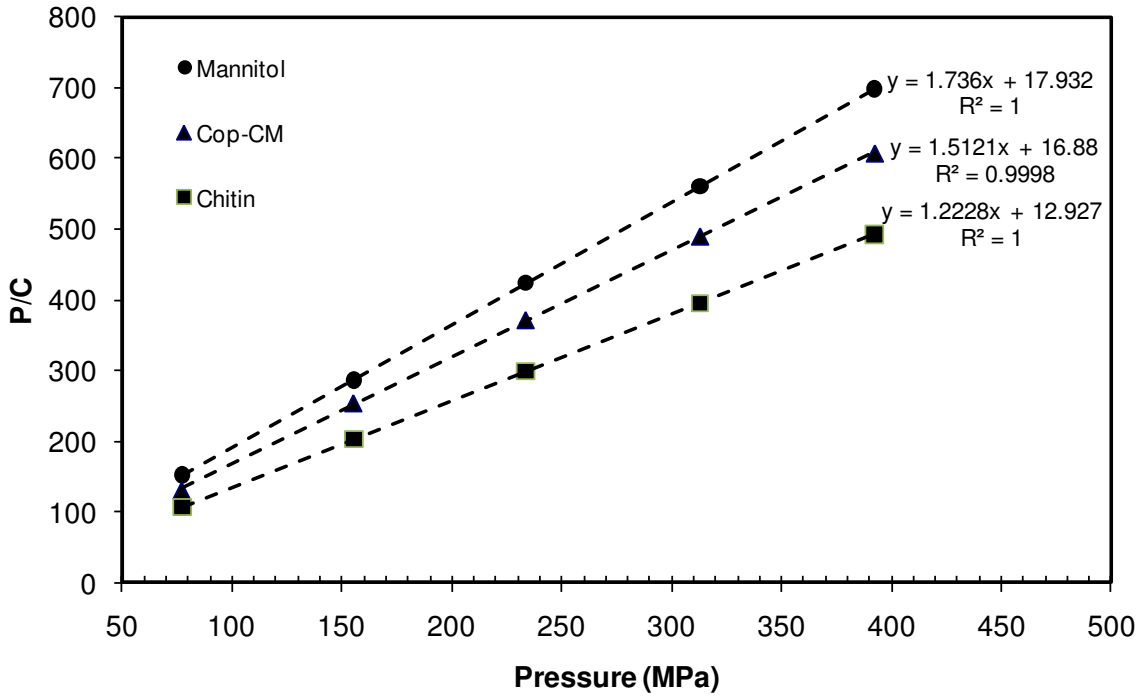

Figure 5.8 Kawakita plot for Cop-CM. Tablets were 12 mm in diameter and 400 mg in weight.

The Kawakita constants a, b, ab and 1/b were calculated from the intercept and slope of the plots (Table 5.3).

Table 5.3 Kawakita parameters for mannitol, chitin and Cop-CM.

Material	Kawakita parameters					
	Slope	**Intercept**	**a**	**ab**	**b**	**1/b**
Mannitol	1.736	17.932	0.576	0.0558	0.0968	10.330
Chitin	1.223	12.927	0.818	0.0774	0.0946	10.570
Cop-CM*	1.512	16.880	0.661	0.0592	0.0896	11.164

*Cop-CM represents the co-processed chitin-mannitol (2:8 w/w) mixture

The constant a, which represents the compressibility, is the highest for chitin (a = 0.818) and this is due to the high internal surface pores. The compressibility of Cop-CM is significantly higher than mannitol alone (a = 0.661 and 0.576, respectively) and this is ascribed to the addition of the chitin to mannitol. This result emphasizes the fact that although the mannitol constitutes 80% of the Cop-CM content, using RC techniques in

the preparation of the Cop-CM keeps the large chitin surface pores active and unoccupied because mannitol physically adheres at the outer chitin surfaces.

The increase in the ab value for Cop-CM (0.0592), which is a measure of the extent of particle rearrangement, indicates that the addition of chitin has improved the degree of particle rearrangement and packing during tabletting. The 1/b parameter is an inverse measure of the amount of plastic deformation occurring during the compression process [22, 43]. Generally, the low value of 1/b is a reflection of the soft nature of the material and that the material is readily deformed plastically under pressure [44].

Chitin is a highly porous material and forms intermolecular hydrogen bonds between adjacent plastic deformed chitin particles. The presence of moisture within the porous structure of chitin enforces the formation of hydrogen bond bridges which increase the internal binding upon compaction. Therefore, the use of a smaller amount of chitin (20%) with mannitol within the Cop-CM decreases plastic deformation during compression [22, 45].

5.3.3.5 Loading Capacity

The loading capacity of Cop-CM excipient was studied by using metronidazole as a model for an incompressible material. Compressing metronidazole alone (100% as a reference) gives rise to tablets with low mechanical strength and long disintegration time. However, the effect of increasing the weight ratios of Cop-CM/metronidazole from 0/500 to 500/0 (wt/wt) on these properties were investigated. The results indicated that by increasing the quantity of the Cop-CM in the matrix, the compactability is significantly improved and the disintegration time is decreased as shown Figure 5.9. As a result Cop-CM is capable to accommodate poorly compressible APIs with high loading capacity without significantly affecting the physical and mechanical properties.

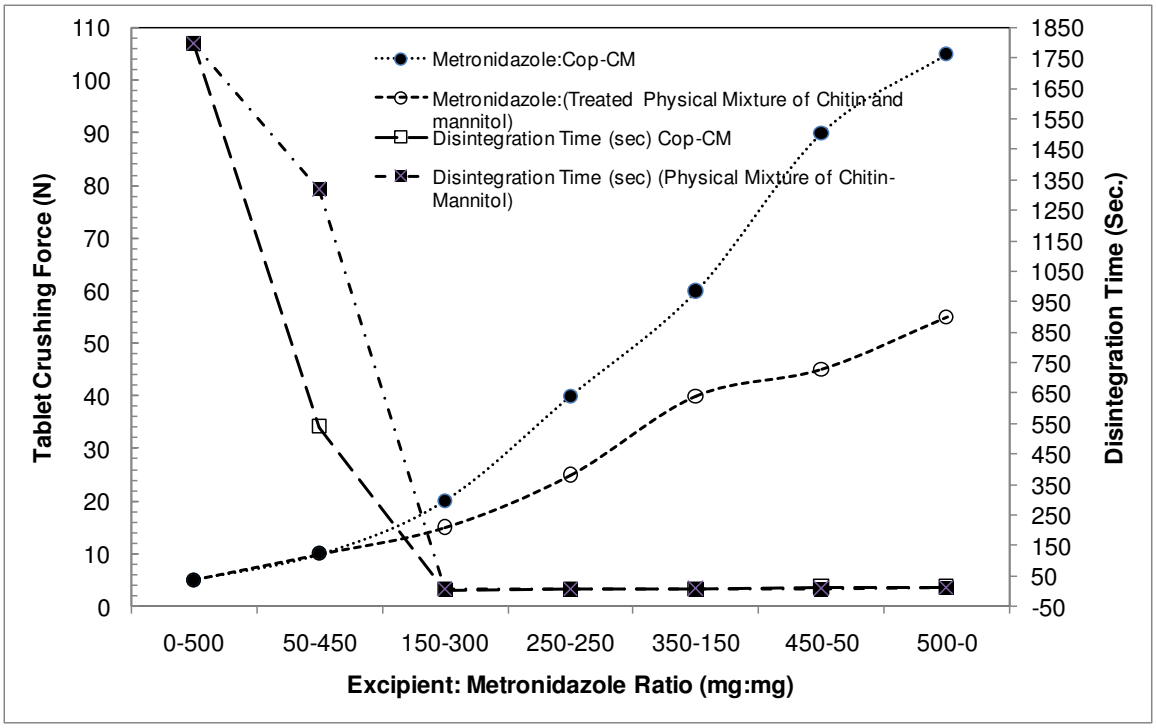

Figure 5.9 Relationship between tablet crushing force and disintegration time at different Cop-CM: metronidazole ratios using a physical mixture of chitin-mannitol (2:8, w/w) as a reference. Data are represented as the mean of n = 10.

5.3.3.6 Functionality

The functionality of the Cop-CM as an excipient was investigated by examining different processing techniques including DC, RC and WG to prepare tablets. The three formulations containing Cop-CM and low strength APIs (Monte and Domp) were investigated. The performance and mechanical properties of the prepared tablets were examined and the results are summarized in Table 5.4.

Table 5.4 Composition and physical properties of Monte and Domp ODTs.

Materials	Composition (% w/w)					
	Monte			Domp		
API	01.77			03.40		
Cop-CM	94.73			93.10		
Strawberry powder flavor	02.00			02.00		
Aspartame	00.50			00.50		
Sodium stearyl fumarate	01.00			01.00		
Tablet Physical Properties	**Tablet preparation process**					
	DC	**RC**	**WG**	**DC**	**RC**	**WG**
Crushing force (N)	70 – 80			60 – 70		
Friability (%)	0.25	0.32	0.30	0.18	0.29	0.37
Disintegration time(sec)	20	30	20	26	20	28

The tablets obtained from all the processing techniques showed high internal binding (crushing force: 60-80 N and friability: < 0.4%) and fast disintegration times (≤ 30 sec). The results indicate that Cop-CM is compressible and preserved its functionality whether utilized in DC, RC or WG formulations. Hence, it can be used as a multi-functional base (binder, filler and disintegrant) in ODT formulations.

5.3.3.7 Stability Studies

The stability of Monte and Domp tablets prepared by RC procedures in the functionality section was investigated. Tablets were packed in aluminum/aluminum blisters and incubated at 25^{o}C and 40^{o}C/75% relative humidity for different periods of time and then tested by HPLC methods. The HPLC method was initially tested for system suitability (i.e., peak symmetry, repeatability, and resolution) and for validation parameters (i.e., specificity, stability in solution, linearity and limit of quantitation (LOQ)) according to USP and ICH guidelines [37, 46]. The HPLC results showed a good separation between the APIs and their related impurities. Also the methods were found to be suitable for stability studies, i.e., the resolution, tailing factors and injection repeatability are within

the acceptable criteria. In addition, analysis of samples obtained from stress-testing studies in solutions (0.1N NaOH, 0.1N HCl, and 0.3% H_2O_2) indicated that the HPLC methods are stability indicating. The methods were linear over the range of ±50% of the target concentrations with r^2 of > 0.99. The LOQ values are within 0.08 – 0.4 and 0.05 – 0.14 (w/w %) for Monte and Domp tablets, respectively.

As shown in the data in Table 5.5, no significant decrease in the potency of Monte and Domp tablets occurred upon storage at 40°C/75% RH for 6 months. Monte is liable to oxidation by heat [35] forming Monte S-oxide; however, under shelf-life conditions the degradation content of this product is within the limit (2.0%). Domp tablets display excellent stability when the fraction of impurities does not exceed 0.1% after 6 months incubation at 40°C/75% RH. Both products showed fast disintegration (< 30 sec) and a drug release (> 90%) before and after incubation at 40°C/75% RH indicating the absence of formulation ageing (Table 5.5).

Table 5.5 Stability data for Monte and Domp tablets.

Product	**Compound/Limit**	**Percentage (w/w)**			
		25°C		**40°C/75% RH**	
		Initial	**24 months**	**3 months**	**6 months**
Monte	Monte/90% - 110%	99.4	104.8	102.8	98.2
	Monte S-oxide/≤2.0%	0.9	1.1	3.4	3.6
	Monte cis-isomer/≤0.5%	0.1	0.5	0.1	0.1
	Any other≤0.4%	0.0	0.2	0.1	0.1
	Total impurities≤3.0%	1.0	2.0	3.6	3.8
Domp	Domp/95%-105%	100.1	-	100.7	101.4
	Any other/≤0.25%	0.06	-	0.04	0.04
	Total impurities/≤0.5%	0.2	-	0.1	0.1

CHAPTER FIVE

5.4 Conclusions

Co-processing of crystalline mannitol with α-chitin by RC offers an excellent multi-functional base for ODT formulations. The novel excipient displayed fast disintegration and wetting properties over a wide range of tablet crushing force values in comparison with commercially available ODT bases. Regardless of the preparation method (DC, WG or DG), the functionality of the novel excipient was preserved. Moreover, the excipient can accommodate a high amount of API without affecting its functionality. Utilization of the novel excipient in ODT containing active pharmaceutical ingredients, offers very fast disintegration and wetting rates, excellent chemical stability and binding properties. Consequently, the use of expensive packaging materials for ODT can be eliminated as the tablets are not prone to breakage when used by patients.

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CHAPTER SIX

6. SUMMARY AND FUTURE WORK

6.1 Summary

The hypothesis that, despite being highly porous and displaying low compactibilty, guest molecules such as metal silicates or mannitol can be accommodated in the chitin pores via relatively simple co-processing procedures has been proved by the work reported in this thesis. The foregoing was clearly shown by the high compactibility and crushing force data obtained for the pharmaceutical tablets prepared by using the chitin-metal silicates and chitin-mannitol co-processed excipients. Additionally it is to be noted that the tablets maintained their high crushing force and internal binding; the fast disintegration and wettability characteristics were also preserved. The functionality, compatibility and stability of the co-processed chitin excipients were also investigated and evaluated using problematic active pharmaceutical excipients. The results obtained showed the multi-functionality and suitability of the prepared excipients in improving the physical and chemical properties of the prepared tablets.

6.1.1 Characterization of Chitin–Metal Silicates as Binding Super-Disintegrants

The modification of chitin (a plastic material), as a selected hydrophilic polymer, using different metal silicates (brittle materials) e.g., aluminium, calcium and magnesium has resulted in the production of a non-hygroscopic multifunctional excipient with superior super-disintegration and binding properties. The interaction of chitin with metal silicate excipients does not involve a chemical interaction, as shown by analysis of IR and XRPD data. Disintegration and binding properties for the tablets produced using this excipient were also found to be independent of particle size and applied compression force. Aluminium obviously cannot be used because of e.g. neuronal toxicity. Calcium increases the pH of the resulting chitin-metal silicate excipient to a pH of 10.5 which is not suitable for most APIs, as it is highly basic. Therefore magnesium silicate was the best candidate amongst the metal silicates for co-processing with chitin. The functionality of the chitin-Mg silicate co-processed excipient was assessed by formulating different APIs including paracetamol, mefenamic acid and gemfibrozil using direct compression as well as wet and dry granulation preparation techniques. Chitin-Mg silicate preserved its

functionality, whereby it's binding and superdisintegration properties remained unaffected by high concentrations of poorly compressible APIs using different preparation methods. The physical properties and drug dissolution profile of the ibuprofen/chitin-Mg silicate tablet matrix were found to be unaffected even when 5% (w/w) lubrication was performed using a powerful lubricant such as MgSt. Also similar drug dissolution was attained for gemfibrozil tablets using 3% (w/w) MgSt when compared to a reference (LOPID® tablets). This indicates that lubrication has a minimal effect on the chitin-metal silicate tablet matrix.

6.1.2 Characterization of the Impact of Magnesium Stearate Lubrication on the Tabletting Properties of Chitin-Mg Silicate as a Super-Disintegrating Binder When Compared to Avicel® 200

Lubricants are vital excipients in tablet formulation. Magnesium stearate is one of the most widely used excipients due to its high melting point, efficiency and economy. Magnesium stearate reduces tablet hardness and prolongs drug release due to its hydrophobicity. Thorough mixing of an active pharmaceutical ingredient with magnesium stearate may result in some sort of interaction and thus the ability of powder to form tablets is time dependent. Therefore, investigations were conducted to study the effects of lubrication on the functionality and performance of chitin-metal silicates. As a model, chitin-Mg silicate was selected from amongst the other metal silicates and magnesium stearate was used as a lubricant. Avicel® 200 (commercially available microcrystalline cellulose with an average particle size of 180 µm) was used as the direct compression reference excipient. Microcrystalline cellulose is similar in chemical structure to chitin, where the acetyl group of chitin is replaced with a hydroxyl moiety. The co-precipitation of magnesium silicate on chitin and Avicel® was clearly beneficial in minimizing the deleterious effects of MgSt. The addition of MgSt as a lubrication aid did not show a significant variation in disintegration, dissolution, and crushing strength of compacts made from chitin-Mg silicate. Such variation was clearly observed when a comparison was made with Avicel® 200. This is due to the smooth irregular, folded particle shape of chitin which results in a high surface area capable of holding/adsorbing a high amount of lubricant in its surface pores. Co-precipitation with magnesium silicate

changes Avicel® 200 into a less lubricant sensitive excipient with regard to compaction and binding properties, whilst the disintegration time of tablets prepared remains high.

6.1.3 Preparation and Characterization of a Novel Co-Processed Excipient of Chitin and Crystalline Mannitol

Chitin is well known as a disintegrant and filler in tablet and capsule formulation because of its unique properties (chemically inactive, naturally abundant, biodegradable, non-toxic material). α-Chitin is a highly compressible material due to its high surface porous structure, but the compaction and binding properties of chitin need to be improved. Mannitol, a water soluble sugar alcohol, was used in order to improve the binding properties of chitin. It is a non-hygroscopic material commonly known as a "potential excipient" since it is compatible with the majority of pharmaceutical active ingredients. Unfortunately, crystalline mannitol is friable with limited flow properties and poor solubility when compared to lactose and other sugars. A small amount of mannitol (< 30% w/w) was physically co-processed with chitin using different methods. The wet granulation processing of chitin and mannitol mixture (80:20) resulted in a non-hygroscopic valuable multi-functional excipient in terms of disintegration and compaction properties. The tablets prepared from the Cop-MC displayed a fast disintegration time while maintaining their superior binding properties. Different APIs were incorporated in tablets consisting of Cop-MC and the lubricant. Results showed the high stability of the APIs in a Cop-MC matrix.

6.1.4 A Novel Oro-Dispersible Tablet Base: Characterization and Performance

ODT tablets need to exhibit rapid disintegration/dissolving effects; therefore high levels of superdisintegrants (up to 10-20 % (w/w)) are usually added to achieve this target. Accordingly ODTs are packed in unit dose special type blisters due to their low hardness and high friability. Additional excipients including filler, binder, lubricant, sweetener, and colouring material can be added to improve the "*elegance"* and identification of the ODTs. Mannitol is widely used in ODT formulations because of its unique properties (non-hygroscopic, sweet, smooth and cool taste feel). Therefore it was advantageous, for a material like mannitol to be combined with a highly porous disintegrant/filler such as

chitin via a physical co-processing methodology to improve its compaction and disintegration properties. Roll compaction was found to be a suitable preparation method, where optimal physical properties were obtained for the co-processed excipient. Co-processed mixtures of chitin (20 and 30% w/w) with mannitol show excellent binding properties, fast disintegration and wetting properties upon tablet compression. Further studies were performed on the co-processed mixture of mannitol and chitin at a ratio of 80:20 (Cop-CM), including functionality, compression profile, hygroscopicity and loading capacity. Results indicate that the non-hygroscopic excipient is functional when different tablet preparation procedures are used by maintaining the overall excellent physical properties of the tablets produced. The disintegration and wetting properties of Cop-CM are not significantly affected by increasing the crushing force of the tablets which allow the formulator to produce hard ODTs with fast disintegration and wetting times. The foregoing will permit the use of blister packaging without the need for specialised packaging procedures.

6.2 Future Work

Metal silicates, via co-precipitation in the pores and surface of chitin are potentially useful single multifunctional excipients. The co-processed excipient acts as both a binder and filler while maintaining its superdisintegrating properties and it was successfully used in formulating hard tablets with super-disinitegration properties.

Among the sugar alcohols, crystalline mannitol was used for co-processing with chitin because of its inert and unique properties. Two different excipeints were prepared by the co-processing of chitin with mannitol. The first excipient (Cop-MC) was developed with 80% w/w chitin where it can be used successfully used as multifunctional excipient in the preparation of immediate tablet dosage form. The second excipient (Cop-CM) was designed with 80%w/w mannitol to serve as a multifunctional ODT base.

The following research is aimed at providing recommendations for further work, based on results and observations obtained from co-processing chitin with mannitol and metal silicates. It is important to investigate the modification of chitin properties using materials other than silicates and mannitol to obtain additional co-processed excipients which can can be used in a wide spectrum of pharmaceutical applications and dosage forms in terms

of physical properties, suitability and compatibility. Other sugar alcohols including sorbitol, erthritol, xylitol, maltitol and lactitol need to be investigated for their suitability in formulating fast disintegrating and chewable tablets.

6.2.1 Determination of Degree of Deacetylation in Chitin

Most of the methods available for the analysis of degree of deacetylation of chitin are complicated and time consuming (e.g, NMR, XRPD, mass spectroscopy, differential scanning calorimetry and FTIR). However, the aforementioned instruments are not always available. In addition most of the current methods rely upon the degradation of chitin and this may lead to incorrect results. Therefore, the non-aqueous potentiometric titration of the reactive amine groups of chitin may be possible using saturated calcium chloride di-hydrate in methanol as a solvent. In addition the spectrophotometric method could have potential using the same solvent system by acquiring 1^{st} derivative spectra.