FORMULATION AND EVALUATION OF TABLET IN TABLET OF MAGNESIUM GLYCINE COMPLEX AND VITAMIN D_3 TABLETS

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CERTIFICATE

This is to certify that the investigation described in the dissertation entitled "**FORMULATION AND EVALUATION OF TABLET IN TABLET OF MAGNESIUM GLYCINE COMPLEX AND VITAMIN D_3 TABLETS"**. Submitted by Reg.No:261610401 was carried out in the Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil-626126.

Which is affiliated to the Tamilnadu Dr.M.G.R.Medical University, Chennai, Under the supervision and guidance of **Dr.S.R.Senthilkumar,M.Pharm.,Ph.D.,** Department of Pharmaceutics for the partial fulfillment of degree of MASTER OF PHARMACY IN PHARMACEUTICS.

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This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

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DECLARATION

The work presented in this thesis entitled "**FORMULATION AND EVALUATION OF TABLET IN TABLET OF MAGNESIUM GLYCINE COMPLEX AND VITAMIN D_3 TABLETS**". Was carried out by me in the department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil. Under the direct supervision of **Dr.S.R.SENTHILKUMAR,M.Pharm.,Ph.D.,** Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

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"You will meet more angles on a winding path than on a straight one"

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DEDICATED TO GOD

MY FAMILY AND FRIENDS

ABBREVIATIONS :

mg	Milligram
kg	Kilogram
LDPE	Low Density Poly Ethylene
HDPE	High Density Poly Ethylene
rpm	Revolutions Per Minute
mm	Millimeter
μm	Micro meter
°	Degree
C	Centigrade
RH	Relative Humidity
%	Percentage
BMR	Batch Manufacturing Record
MFR	Master Formula Record
mins	minutes
NMT	Not More Than
NLT	Not Less Than
N	Newton's
Lit	Liter
gm	Gram
Q.C	Quality Control
SOP.	Standard Operating Procedure
QA	Quality Assurance
Wt.	Weight
NA	Not Applicable
&	And
ROW	Rest of World
Mfg.Lic No.	Manufacturing License Number
EHS	Environmental Health and Safety
IHS	In House Specification
Hrs	Hours
SS	Stainless Steel
Tabs	Tablets

Why we prepare tablet in tablet of Magnesium glycine complex and Vitamin D_3

1. Normaly, single Vitamin D_3 tablets are easily degrade in moisture content and temperature. So, overages add 100% then the half life should be 6 months or one year. But in the tablet in tablet formulation, prevent the degradation. Here overages added only 50%. Then the half life become two years.
2. Single vitamin D_3 tablets sometimes leads to side effect, it is prevented by combined with magnesium.
3. Magnesium and vitamin D essential for bone synthesis otherwise intensify to Osteoporosis. Mg is also credited with **stabilizing function** in bone building. If there is no stabilizing function of magnesium during bone synthesis this also degrease in bone density.

INTEX

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Introduction

1.INTRODUCTION

Solid medicaments may be administered orally as powders, pills, cachets, capsules or tablets [1].These dosage forms contain a quantity of drug which is given as a single unit and they are known collectively as solid unit dosage forms, even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug .The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large-scale economic manufacture, have led to a steady decline in the prescribing of powders and pills [2] .Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients [3]. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the Tablet form except where it is difficult to formulate or administer [4].

The advantages of the Tablet dosage form are: They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.

- Cost is lowest of all oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallowing with least tendency for hang-up.
- Sustained release product is possible by enteric coating.
- Objectionable odour and bitter taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage form.
- Product identification is easy and rapid requiring no additional steps when employing an embossed and/or monogrammed punch face [5].

Disadvantages of Tablet dosage form are:

- Difficult to swallow in case of children and unconscious patients.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost [6].

General properties of Tablet dosage forms: A tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.

- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time
- The tablet must be able to release the medicinal agents in a predictable and reproducible manner.
- Must have a chemical stability over time so as not to follow alteration of the medicinal agents [7].

Different types of Tablets

(A) Tablets ingested orally:

- Compressed tablet, e.g. Paracetamol tablet
- Multiple compressed tablet
- Repeat action tablet
- Delayed release tablet, e.g. Enteric coated Bisacodyl tablet
- Sugar coated tablet, e.g. Multivitamin tablet
- Film coated tablet, e.g. Metronidazole tablet
- Chewable tablet, e.g. Antacid tablet [8].

(B) Tablets used in oral cavity:

- Buccal tablet, e.g. Vitamin-c tablet

- Sublingual tablet, e.g. Vicks Menthol tablet
- Troches or lozenges
- Dental cone

(c) Tablets administered by other route:

- Implantation tablet
- Vaginal tablet, e.g. Clotrimazole tablet[9].

(D) Tablets used to prepare solution:

- Effervescent tablet, e.g. Dispirin tablet (Aspirin)
- Dispensing tablet, e.g. Enzyme tablet (Digiplex)
- Hypodermic tablet
- Tablet triturates e.g. Enzyme tablet (Digiplex)

Tablet Ingredients In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients.

Different excipients are:

1. Diluent
2. Binder and adhesive
3. Disintegrents
4. Lubricants and glidants
5. Colouring agents
6. Flavoring agents
7. Sweetening agents [10].

Granulation technology on large scale by various techniques

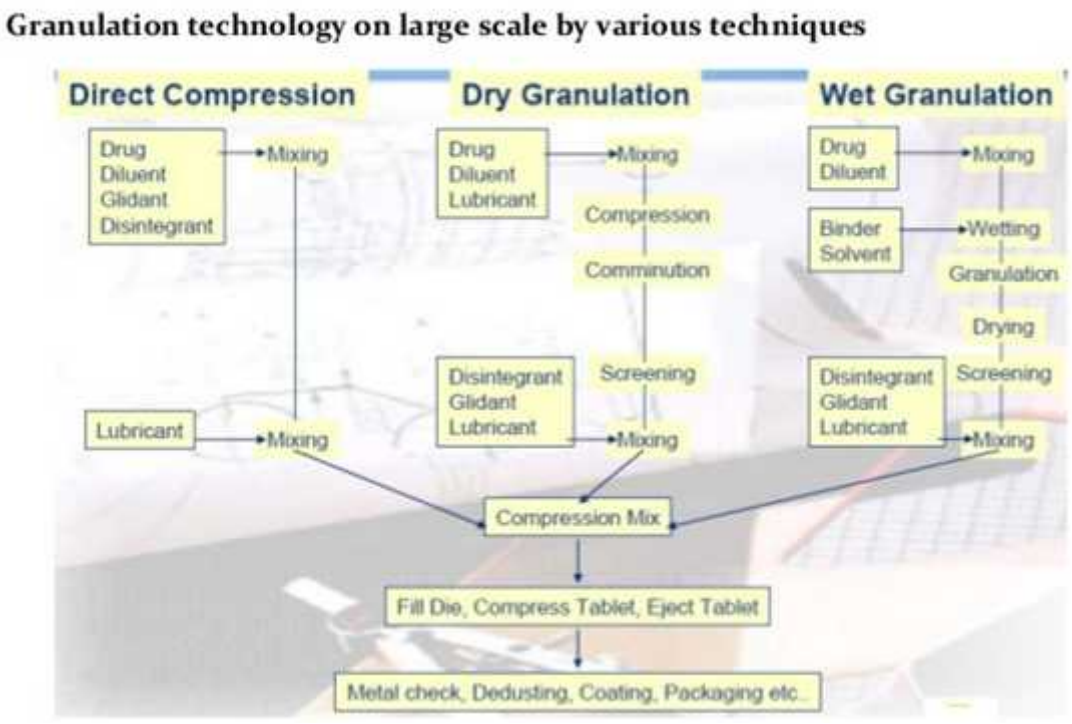


Fig 1:1 Granulation Technology

VITAMIN D3

Vitamin D3(cholecalciferol) is derived from 7-dehyrocholesterol and involved in bone health. Scientists have recognized that, depression, back pain, cancer, both insulin resistance and pre-eclampsia during pregnancy, impaired immunity and macular degeneration are directly linked to the Vitamin D3 deficiency [11].Inadequate Vitamin D3 may cause secondary hyperparathyroidism that increases the risk of osteoporosis and fractures and change the regulatory mechanisms of parathyroid hormone (PTH) [12,13]. Other types of condition such as high blood pressure, fibromyalgia, diabetes, multiple sclerosis, rheumatoid arthritis has been linked to the low levels of Vitamin D3 [14,15]. Vitamin D3

deficiency is responsible psychiatric and neurologic disorders and associated with low mood [16].

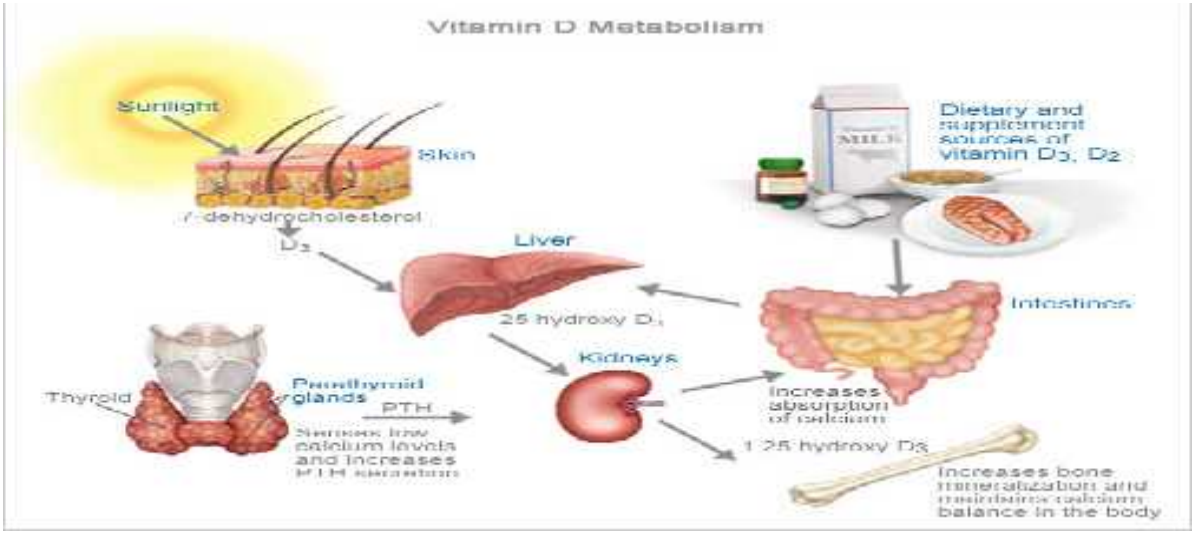


Fig 1:2 Vitamin D metabolism

ORAL TABLETS: Standard compressed tablets e.g. Paracetamol tablet′ Multiple compressed tablets′ I. Compression coated tablet- sugar coated tablet, Film coated tablet, Gelatin coated tablet, Enteric coated tablet II. Layered tablet III. Inlay tablet Targeted tablet[17,18,19].

Fig 1:3 vitamin D Deficiency

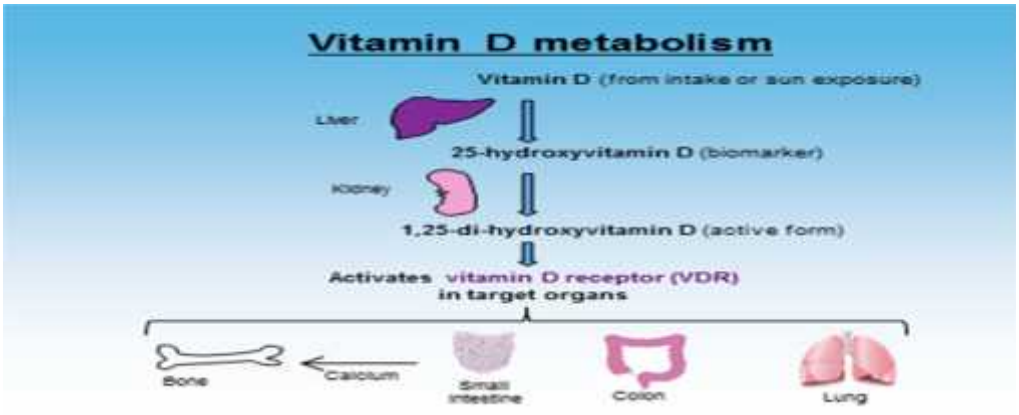


Fig 1:4 Vitamin D Metabolism

I. **Floating tablet II. Colon targeting tablet**

Different types of Tablets:

Tablets ingested orally: 1. Compressed tablet, e.g. Paracetamol tablet 2. Multiple compressed tablet 3. Repeat action tablet 4. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet 5. Sugar coated tablet, e.g. Multivitamin tablet 6. Film coated tablet, e.g. Metronidazole tablet 7. Chewable tablet, e.g. Antacid tablet[20,21,22]. Tablets used in oral cavity: 1. Buccal tablet, e.g. Vitamin-c tablet 2. Sublingual tablet, e.g. Vicks Menthol tablet 3. Troches or lozenges 4. Dental cone [23,24]. Tablets administered by other route: 1. Implantation tablet 2. Vaginal tablet, e.g. Clotrimazole tablet (D)[25,26]. Tablets used to prepare solution: Effervescent tablet, e.g. Dispirin tablet (Aspirin) 2. Dispensing tablet, e.g. Enzyme tablet (Digiplex) 3. Hypodermic tablet 4. Tablet triturates e.g. Enzyme tablet (Digiplex)[27,28].

Tablet-in-tablet technology: Tablets are indeed the most popular solid dosage form for oral administration. One category of tablet formulations that has gained remarkable importance in drug therapeutics owing to various benefits it offers is controlled or modified release formulations[29,30,31] . Although less popular, tablet-in-atablet technology (see Fig 1) gained increased interest in the recent years for creating modified released products[32,33]. It involves the compaction of granular materials around a preformed tablet core using specially designed tableting equipment. Compression coating is a dry process [34,35,36]. This type of tablet (compression coated tablet) has two parts, internal core and surrounding coat [37,38]. The core is small porous tablet and prepared on one turret. After tablet core manufacture it is transferred (centrally positioned) to another slightly larger die that is partially filled with coating powder. More coating powder is filled on the top of the core and compressed again resulting in tablet with in tablet. Mechanically, it is a complex process, as the tablet may be tilted when transferred to the second die cavity. Mostly, the coat is water soluble and disintegrates easily after swallowing, in order to achieve immediate release product. This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved [39,40]. Tablet coating is the key step involved in the manufacturing of tablets having

controlled release, delayed release profiles. The tablet coating have number of advantages like masking odor, taste, color of the drug, providing physical and chemical protection to drug, Protecting drug from the gastric environment. Tablets are usually coated in horizontal rotating pan with coating solution is either directly poured or sprayed on to them. The amount of coating on the surface of a tablet is critical to the effectiveness of the oral dosage form. Recent trends in tablet coating focuses on overcoming disadvantage of solvent based coating. This review concerns with the coating process, equipment's involved, coated tablets evaluation and specialized coating techniques. Tablets are usually coated in horizontal rotating pans with the coating sprayed onto the free surface of the tablet bed. Tablets must have a coating mass that lies within a prescribed range with very little inter-and intra-tablet coating variability. Using the Discrete Element Method (DEM) tablet coating can be simulated on the computer [41,42,43].

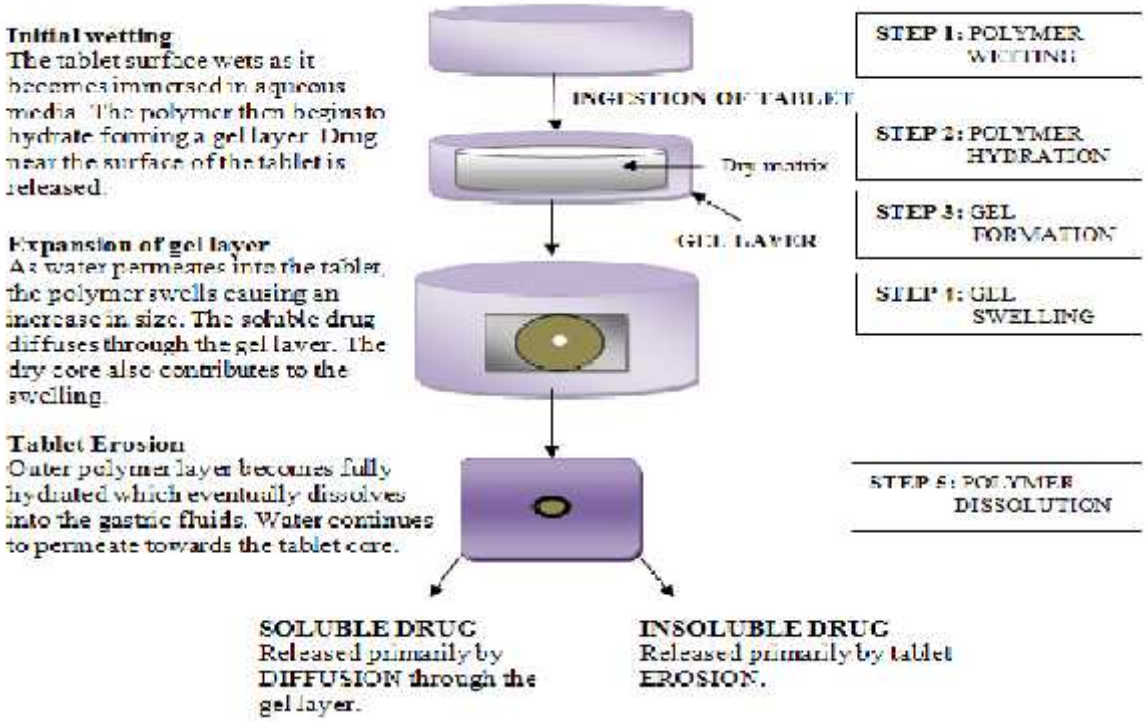


Fig 1:5 Formulation Tablet in Tablet

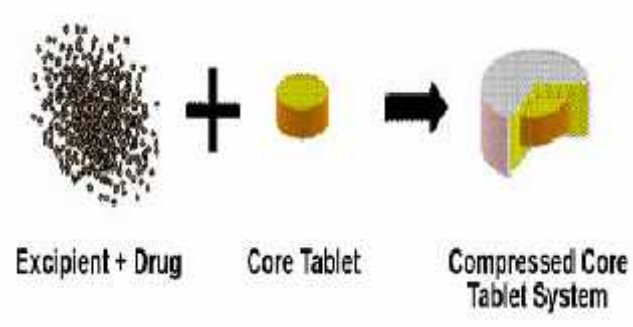


Fig 1:6 Compressed Core Tablet System

Simulation data provide the position, velocity and orientation of each tablet within the coater allowing accurate measurements of the time and orientation that each tablet spends exposed to the coating spray. The blend was compressed on a single punch machine, tablets were subjected to various tests (weight variation, diameter and thickness, hardness, disintegration and assay of the drug) and the results were also in compliance with the official specifications [44, 45,46,47].

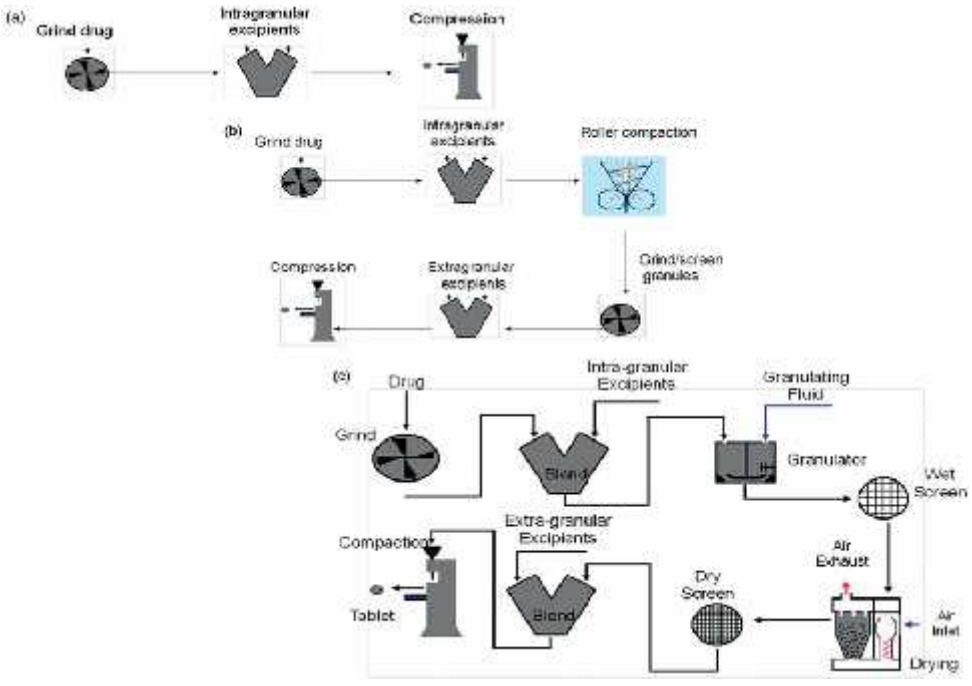


Fig1:7 Tablets Various Compression

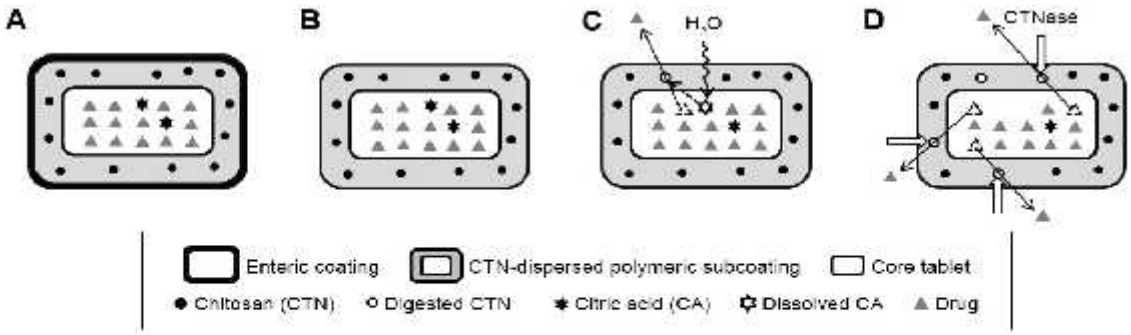


Figure 1 Stepwise illustration of DF-CODES as a platform for colon targeting.
Notes: (**A**) In the stomach, the outermost enteric coating layer inhibits drug release; (**B**) in the small intestine, the inner CTN dispersed polymeric subcoating layer impedes drug release; (**C**) in the colon, water infiltrates the core tablet and dissolves CA, resulting in microclimate acidification and pore generation to some extent; (**D**) in the latter part of the colon, under the influence of microflora, such as CTNase, a number of macroporous channels are formed by enzymatic CTN digestion, thus facilitating drug release.
Abbreviations: DF-CODES, double layer-coated colon-specific drug delivery system; CTN, chitosan; CTNase, chitosanase.

Fig 1:8 Core Tablet Designed

Coating techniques: - Generally three methods are used for tablet coating A) Sugar coating. B) Film coating. C) Enteric coating.

A) Sugar coating:

Sealing/Water proofing: provides a moisture barrier and harden the tablet surface. Sub coating causes a rapid buildup to round off the tablet edges. Grossing/Smoothing: smoothes out the sub coated surface and increases the tablet size to Predetermine dimension. Coloring gives the tablet its color and finished size. Polishing produces the characteristics gloss [48,49].

B) Film coating:

Film coating and the sugar coating share same equipment and the process parameters. There are basically two methods of film coating they are Pan pour methods: Tablets coated by pan pour method subjected to alternate solution application, mixing and drying steps are similar to pan pour sugar coating. This method is relatively slow and relies heavily on the skill of operator. Pan-spray methods: The introduction of spraying equipment was the next evolution in improving

the film coating process allows for automated control of liquid application. Broad flat spray patterns are usually chosen by appropriate nozzle systems [50,51].

Spray dryer: Spray drying is a method of producing a dry powder from a liquid or slurry by rapidly drying with a hot gas [52,53]. This is the preferred method of drying of many thermally-sensitive materials such as foods and pharmaceuticals. A consistent particle size distribution is a reason for spray drying some industrial products such as catalysts. Air is the heated drying medium; however, if the liquid is a flammable solvent such as ethanol or the product is oxygen-sensitive then nitrogen is used. All spray dryers use some type of atomizer or spray nozzle to disperse the liquid or slurry into a controlled drop size spray. The most common of these are rotary disk and single-fluid high pressure swirl nozzles. Atomizer wheels are known to provide broader particle size distribution, but both methods allow for consistent distribution of particle size.[2] Alternatively, for some applications two-fluid or ultrasonic nozzles are used. Depending on the process needs, drop sizes from 10 to 500 µm can be achieved with the appropriate choices. The most common applications are in the 100 to 200 µm diameter range. The dry powder is often free-flowing. The most common type of spray dryers are called single effect. There is a single source of drying air at the top of the chamber (see n°4 on the diagram). In most cases the air is blown in the same direction as the sprayed liquid (co-current). A fine powder is produced, but it can have poor flow and produce a lot of dust. To overcome the dust and poor flow of the powder, a new generation of spray dryers called multiple effect spray dryers have been produced [54].

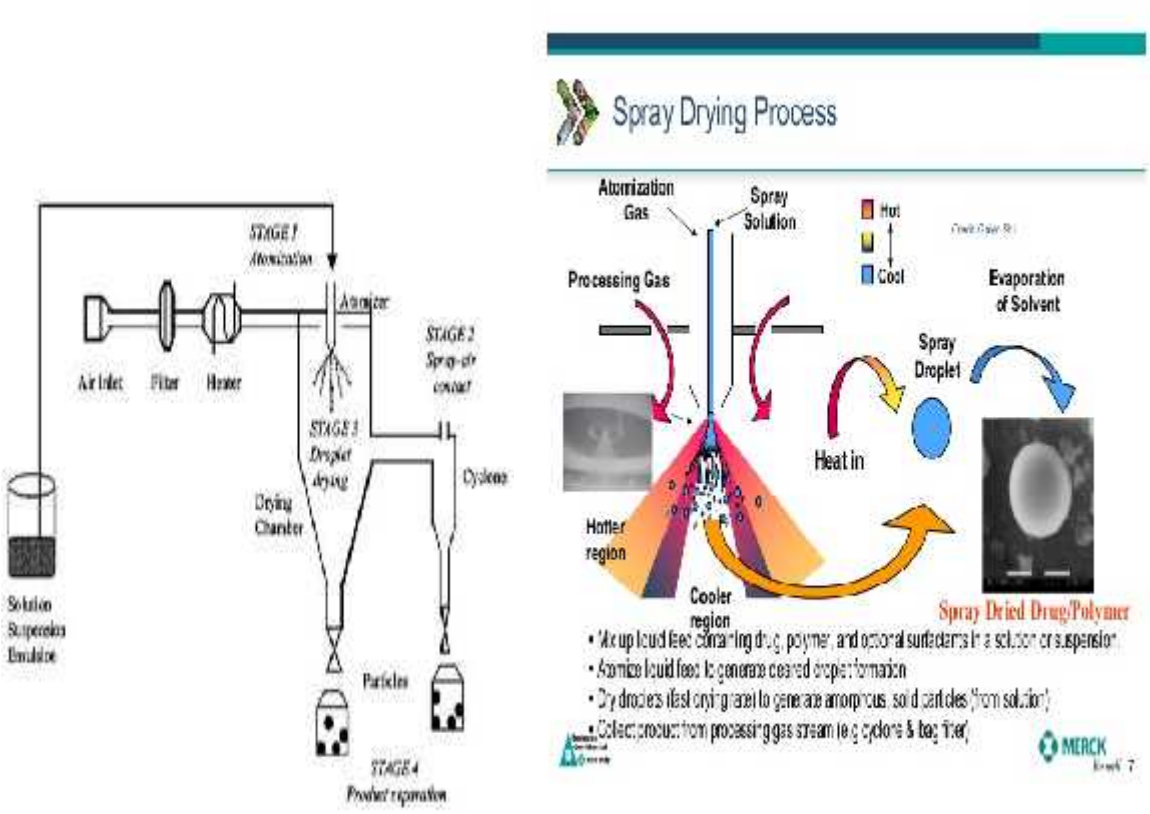


Fig 1:9 Spray Drying Process

Encapsulation method:

Encapsulation relates to technologies which enable to formulate one active compound (or more), inside individualized particles with a specific geometry and properties. Encapsulation defines no size notion • Microencapsulation usually refers to sizes ranging from 1 µm to 1 mm • Nanoencapsulation is used for nanometric sizes but sometimes refers to sizes ranging up to 1 µm or few micrometers. Methods: droplet extrusion (single or multi nozzle device, simple gravity, spinning disk, jet breakage systems, co-extrusion) of a (bio)polymer solution in a gelation bath or in ambient/cold air[55,56,57]. Particles properties (standard): Size range: from 50 µm to 7-8 mm, Final state: wet (can be dried or lyophilized), Active type: liquid, solid; hydrophilic or lipophilic, Active content: up to 400 mg/g (wet), 900 mg/g (dry), Structure: matrix, core / shell (s), (matrix core) / shell [58].

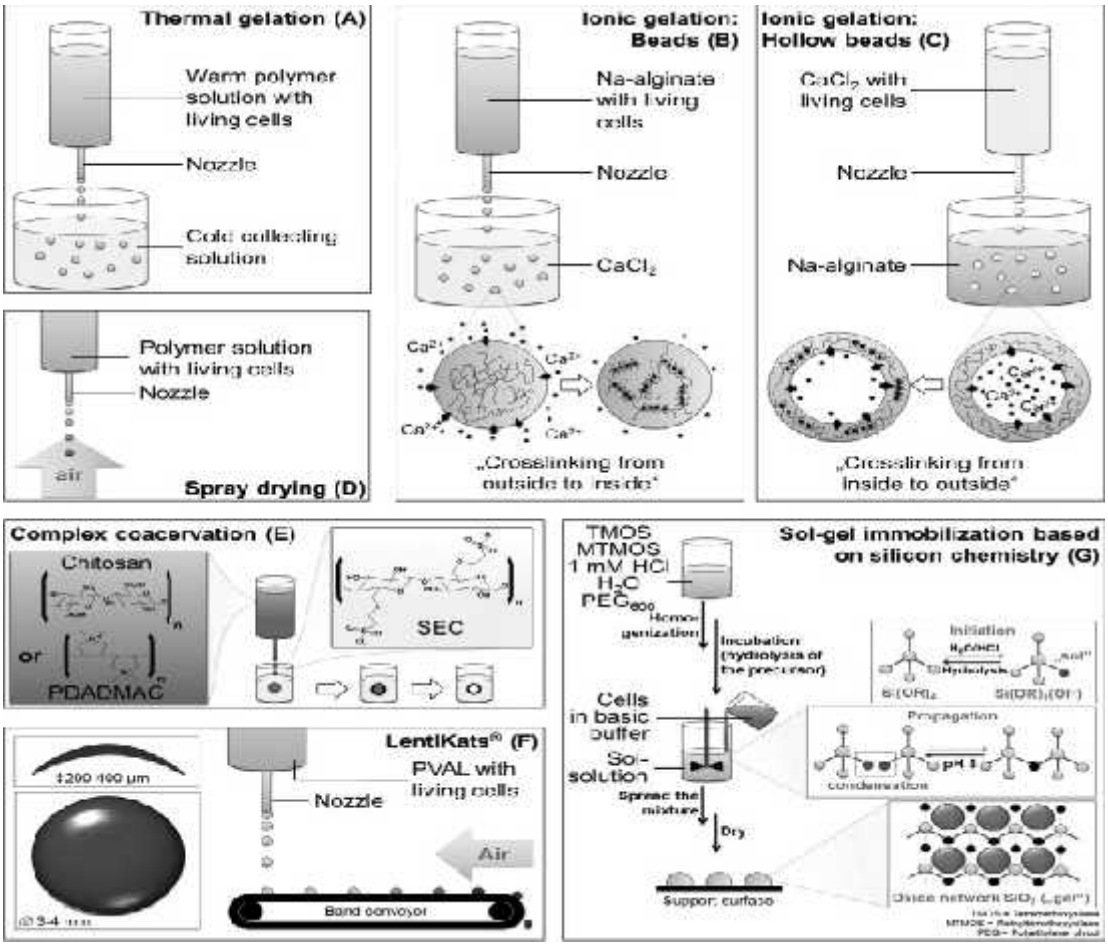


Fig 1:10 Hydrogenation Method

Hydrogenation method:

Hydrogenation – to treat with hydrogen – is a chemical reaction between molecular hydrogen (H_2) and another compound or element, usually in the presence of a catalyst such as nickel, palladium or platinum. The process is commonly employed to reduce or saturate organic compounds. Catalytic hydrogenation has evolved into a key process technology for the manufacture of pharmaceutical and fine chemicals, replacing chemical reduction methods that generate large quantities of waste. According to Roessler [1•], 10 to 20% of chemical reactions in fine chemical synthesis at Roche are catalytic hydrogenations. Catalytic hydrogenations strike a

balance among reaction kinetics, reactor design, catalyst activity and selectivity, process control, mass transfer and mixing. Each of these factors contribute to the performance of hydrogenation processes and their products [59,60,61,62].

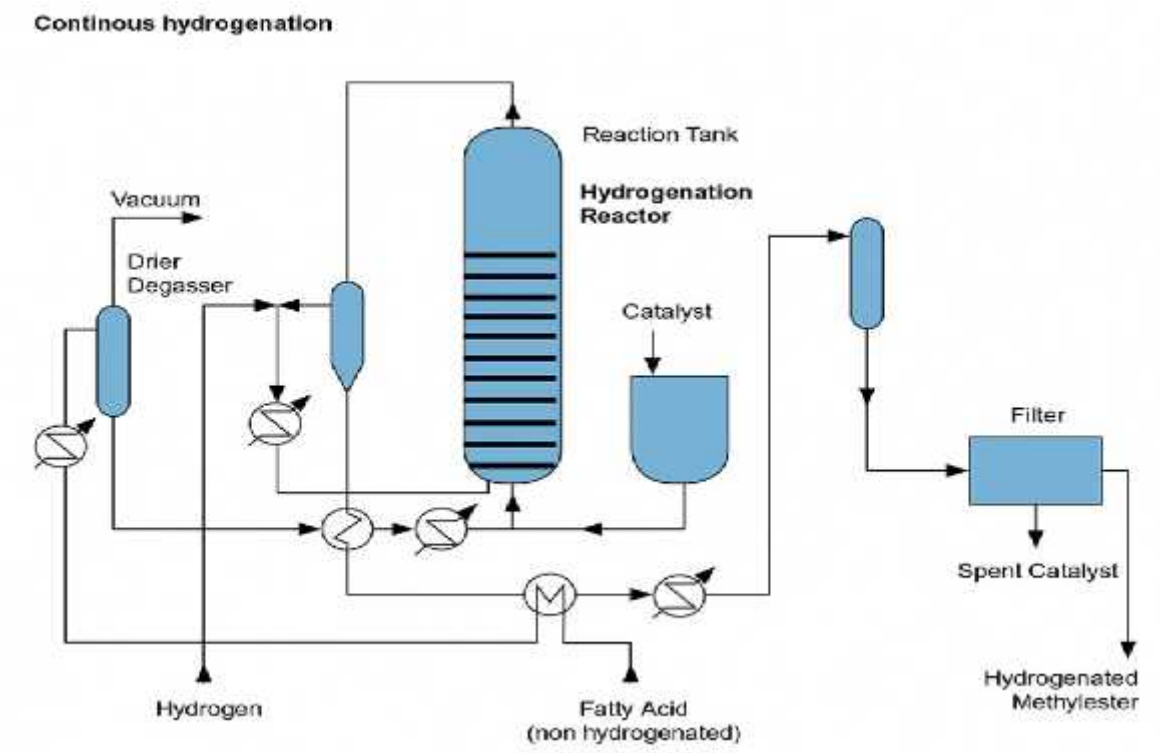
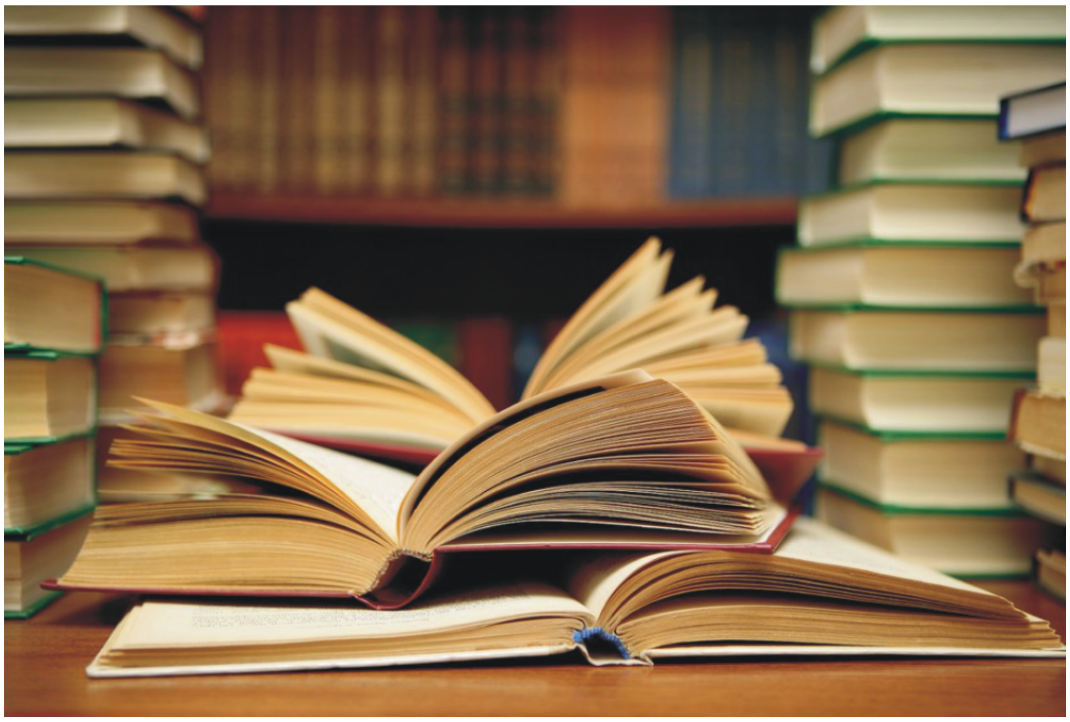


Fig 1:11 Continuous Hydrogenation

Literature Review



2. LITERATURE REVIEW

Y. Ankamma Chowdary, Ramakrishna Raparla, *et al*., (2014) reviewed on the present study, multilayered tablets of pioglitazone hydrochloride 15 mg and metformin hydrochloride 500 mg were prepared in an attempt for combination therapy for the treatment of type 2 diabetes mellitus. Pioglitazone HCl was formulated as immediate release layer to show immediate action by direct compression method using combination of superdisintegrants, namely, crospovidone and avicel PH 102. Crospovidone at 20% concentration showed good drug release profile at 2 hrs. Formulation F13 showed 99.97% of pioglitazone release at 2 hrs in 0.1 N HCl and metformin showed 98.81% drug release at 10 hrs of dissolution in 6.8 pH phosphate buffer. The developed formulation is equivalent to innovator product in view of in vitro drug release profile. The results of all these evaluation tests are within the standards. The procedure followed for the formulation of these tablets was found to be reproducible and all the formulations were stable after accelerated stability studies. Hence, multilayered tablets of pioglitazone HCl and metformin HCl can be a better alternative way to conventional dosage forms.

Karthik Varma V (2016) the study focus on excipients are additive substances used in tablet formulation to improve bulkiness, disintegration, dissolution rate and bioavailability of the drug. The drug and excipient interaction study is carried using Infrared Spectrum to know the stability of excipients and drug.

D.Banerjee, R. Singh *et al .*, (2016) This review on purpose of this study was to formulate Cefpodoxime Proxetil compression-coated tablets for gastroretentive drug delivery. In this the core tablet is formulated to be retained in the stomach for a period of approximately 12 hrs using different polymer blend. The core tablet has half

the amount of the drug and the rest of the drug in the coating layer. This outer layer is so formulated to release its drug content in a period of 15mins so as to achieve the initial burst release and then after 2 hours as the plasma concentration of the drug decreases then the core layer starts releasing its drug content so that the plasma concentration of the drug is maintained in the therapeutic window for the duration of 12 hrs. Thus the dosing interval is increased from 4 hrs to 12hrs. The batches are optimized using the factorial designing. Also the formulation is evaluated for its release profile and compared with the other standard release profiles.

Surya Bhan Singh Rathore, Anshu Sharma, *etal.,*(2013) The present study was an attempt to formulate and evaluate enteric coated tablets for Ilaprazole to reduce the gastrointestinal tract side effects. Four formulations of core tablets were prepared and one who shows rapid disintegration (near around three minutes) was selected for enteric coating. Ilaprazole which have an irritant effect on the stomach can be coated with a substance that will only dissolve in the small intestine. Enteric coat was optimized using two different polymers such as HPMCP 50 and Eudragit L 100 in different concentrations. The prepared tablets were evaluated in terms of their pre-compression parameters, physical characteristics and in-vitro release study. 2.5% seal coating on core tablets was optimized and 9% enteric coating on seal coated tablets was performed using HPMC P 50 (60%), triethyl citrate (10%) and IPA:DCM (60:40) which gives the highest dissolution release profile and f2 value.

Himanshu.K.Solanki *et al.*, (2010) Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation process will improve flow and compression characteristics, reduce segregation, improve content uniformity, and eliminate excessive amounts of fine particles. The results will be improved yields, reduced tablet defects, increased productivity, and

reduced down time. Pharmaceutical products are processed all over the world using the direct-compressing, wet-granulation, or dry granulation methods. Which method is chosen depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can be applied. The objective of present article was to focus on the novel granulation technology.

Singh Deep Hussan*, Roychowdhury Santanu, *et al*.,(2012) this study evaluate enteric coated tablets are solid unit dosage forms which are designed to bypass the stomach and release the drug in small intestine and are meant for oral administration. The word “enteric” indicates small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a coated surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. Materials used for enteric coatings include CAP, CAT, PVAP and HPMCP, fatty acids, waxes, shellac, plastics and plant fibers. The present review describes enteric coating, their ideal properties, benefits and limitation, various polymers used, their chemical structure, criteria for drug selection and mechanism, methods of manufacturing and evaluation of enteric coated tablets. Recently, these have attracted the interest of many formulators due to their advantages over the conventional drug delivery systems as they prolong the dosing intervals and also increase patient compliance. The study provides an overview of the recent advances that have taken place in this arena.

Shrivastava Priyanka and Sethi Vandana., (2013), A Review article on: Superdisintegrants. Disintegration plays a major role in improving the drug activity

and hence increases the patient compatibility. The therapeutic activity of the formulations is obtained by disintegration followed by dissolution. Disintegrants are the substances that causes the rapid disintegration of the capsules or tablets into smaller particles that dissolves more rapidly than in the absence of the disintegrants. On the other hand super disintegrants, as it name suggests superior to disintegrants are the substances which facilitates or increases the disintegration time even at low level ,typically 1-10% by weight relative to the total weight of the dosage unit. This article comprises of study of superdisintegrants which are being used in the formulation to provide safe and effective drug delivery with improved patient compliance.

Amit A. Patel *et al*., (2012), Formulation and evaluation of doxycycline hydrochloride delayed release enteric coated tablets. The present study was undertaken with an aim to formulate doxycycline hydrochloride delayed release tablets. Successful delivery of drugs specifically to the intestine requires the protection of drug from being released in stomach. This drug is universal antibiotic and can be targeted to the specific site of absorption by enteric coating using pH dependant polymers. The present study demonstrates that the doxycycline hydrochloride compression coated tablets could be targeted to intestine using pH dependent polymers. Enteric coating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and acryl-EZE® to achieve 5% weight gain and 9 % weight gain. This was concluded that formulation containing Eudragit L 30 D 55 remain intact in 0.1 N HCl and dissolve fast in pH 6.8 phosphate buffer.and shows better results compare to the formulation containing hypromellose phthalate and cellulose acetate phthalate.

Ahuja Naresh *et al*., (2012), this review on development of hpmcp based aqueous enteric coating polymer. The advantages of an aqueous-based coating system have been recognized. This is derived from the drawbacks of organic solvents, including pollution, explosion hazards and solvent toxicity. Especially, there are risks for operators. For these reasons, water based systems are now gradually being applied instead of organic coating systems. The objective of current study is to develop a HPMCP based enteric coating material which satisfy the need of enteric coating and contains the advantages of aqueous coating material.

Ajit Patil et al., (2011), Formulation and evaluation of enteric coated tablets for azithromycin dihydrate to reduce the Gastrointestinal tract side effects.Three formulations of core tablets were prepared and one whoshows rapid disintegration (below three minutes) was selected for enteric coating . Enteric coat was employed by usingdifferent polymers such as HPMC-55, Eudragit, Ethyl cellulose in different ratios Combination of HPMC-55 and ethylcellulose (10:1.5) exibited better dissolution ,disintegration, hardness and friability properties .This study concluded that enteric coated tablets of azithromycin dihydrate can be prepared by using combination of polymers studied and we can reduce the GI tract side effects.

Tsung Yueh Tsai *et al*., (2011), Effect of diluents on the swelling force of the tablet. The swelling force, especially the swelling force development rate, is a very important parameter in studying the effect of a disintegrant in a tablet. However, a tablet also contains diluents in most cases and the effect of diluents on the swelling force has not been studied. In this study two commonly used diluents, microcrystalline cellulose and calcium phosphate dihydrate, were investigated for their effect on the swelling force with or without a superdisintegrant, Polyplasdone XL. It was found that microcrystalline cellulose alone can develop swelling force

depending on the compression force of the tablet. When combined with Polyplasdone XL, it can significantly change the swelling force of Poly plasdone XL. Their results reveals that Depending on the nature, the diluent can display the swelling force or not. Di-tab doesn't show any swelling force but Avicel shows varied degrees of swelling force depending on the compression force. Avicel alone shows gradual force development. With Di-tab added a plateau appears quickly.

Nobutomo Ikarashi *et al*., (2011), The Laxative Effect of Bisacodyl is attributable to decreased aquaporin-3 expression in the colon induced by increased PGE2 secretion from macrophages. This study was to investigate the role of aquaporin3 (AQP3) in the colon in the laxative effect of bisacodyl. After oral administration of bisacodyl to rats, AQP3, macrophages, cyclooxygenase 2 (COX2), and prostaglandin E2 (PGE2) were examined in the colon. Aquaporins are integral membrane proteins from a larger family of major intrinsic proteins (MIP) that form pores in the membrane of biological cells.Genetic defects involving aquaporin genes have been associated with several human diseases. From the results suggest that bisacodyl may decrease the expression of AQP3 in the colon, which inhibits water transfer from the luminal to the vascular side and leads to a laxative effect.

AppaRao. B *et al*., (2010), Formulation and Evaluation of Aceclofenac Solid Dispersions for Dissolution Rate Enhancement. Aceclofenac is a novel non-steroidal antiinflammatory drug (NSAID) having anti-inflammatory and analgesic properties, and is widely used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, solid dispersions (SDs) of Aceclofenac were prepared using lactose, mannitol and urea to increase its aqueous solubility. Aceclofenac SDs was prepared

in 9:1, 7:3 and 4:1 ratios of the drug to polymer (by weight). In vitro release profiles of all SDs preparations were comparatively evaluated and also studied against pure Aceclofenac. Faster dissolution was exhibited by solid dispersion containing 9:1 ratio of drug: lactose. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity.

Rupesh S. Kamble *et al*., (2010), Formulation and Development Of Enteric Coated Dosage Form Using Ketorolac Tromethamine to reduce the side effects while prolonging its action by using controlled release of oral dosage forms is highly desirable. In the present study direct compression method is used for the preparation of fabricated batches and EudragitL100 is used as coating polymer for enteric coating. In vitro release profiles of batches F1-F4 shows that Ketorolac Tro methamine drug:polymer ratio with Guar gum, Xanthan Gum, Ethyl cellulose and Sodium alginate give 79.32%, 91.52%, 88.35% and 92.19% drug release respectively in 12 hours. In vitro release profile of batches F5-F8 shows 85.21%, 95.52%, 93.50%, 97.24% respectively in 12 hours. In vitro release profile of batches F9-F12 shows that Ketorolac Tromethamine in ratio 1:3 with Guar gum, Xanthan Gum, Ethylcellulose and Sodium alginate gives release of 89.50%, 98.25%, 95.22%, 100.27% respectively in 12hours. And then showed higher increase in phosphate buffer of pH 6.0 up to 12 hours. All these batches follow near zero order kinetics. This indicates that the Guar Gum, Xanthan Gum and Ethyl cellulose and Sodium alginate at minimum concentration is not only able to sustain but also control the drug release.

Tansel Comoglu., (2010), Effects Of Compression Speed And Lubrication On The Compaction Properties Of Some Commonly Used Direct Compression Materials.

This study was to investigate the effects of punch speed and lubrication (with and without the addition of 1% magnesium stearate) on the compaction properties of three different classes of excipients; microcrystalline cellulose (Avicel PH 101), pregelatinized starch (Starch 1500) and dibasic calcium phosphate (Fujicalin) having plastic, elastic and brittle fragmentation characteristics were evaluated. The three different speeds were investigated 10, 50 and 100 mm/sec. From the data observed, plastic materials like Avicel PH 101 form harder tablets at low compression speeds whereas brittle fragmenting materials like Fujicalin were relatively unaffected by compaction speed. Avicel PH 101 gave the hardest tablets at all compression speeds with and without the addition of lubricant. It is concluded that because of its plastic deformation under pressure, Avicel PH 101 perform as a binder whereas both fragmentation and plastic deformation take place in Starch 1500.

V. P. Pandey *et al,.* (2009), Studies On Diluents For Formulation Of Tablets. Tablet remains popular as a dosage form because of the advantages afforded both to the manufacturer (e.g. Simplicity and economy of preparation, stability and convenience in packing, shipping, and dispensing) and the patient (accuracy of dose, compactness, baldness of taste and ease of administration). Tablet formulation may contain diluent to provide better tablet properties such as improved cohesion, direct compression manufacturing and to promote flow properties. In this study, lactose monohydrate, dibasic calcium phosphate (DCP) and microcrystalline cellulose phosphate (MCCP) were studied as diluents in the same quantity for manufacture of chloroquine phosphate tablet using polyvinyl pyrrolidone K-30 (PVP K-30) as binding agent and sodium starch glycolate (S.S.G.) as disintegrating agent. It was concluded that formualtion containing lactose monohydrate as diluent produces 87.12% drug

release in 45 minutes. So lactose monohydrate is considered as suitable diluent for formulating this drug.

Amitava Roy *et al*., (2009), Effects of plasticizers and surfactants on the film forming properties of hydroxypropyl methylcellulose for the coating of diclofenac sodium tablets. In this work, hydroxy propyl methyl cellulose (HPMC) 5cPs, an aqueous soluble polymer was employed for coating diclofenac sodium (DFS) tablets 25 mg for protecting the integrity of the drug yet rendering the drug to release at a faster rate on contact with the gastric environment. The defect free selected formulations were further subjected for studying the effects of surfactants like sodium lauryl sulphate (SLS) and Tween-80 along with the plasticizers. The quality of the aqueous film coats or the plasticizer efficiency in case of PEG-400 is in the order 1.5> 0.5> 1.0% and for PG 1 > 4 > 3% which can be stated on the basis of less incidence of major coat defects like chipping, cracking, orange peel, roughness, blistering, blooming, picking. The quality of aqueous film coat or the surfactant efficiency in case of SLS + PEG-400 is in the order 0.3< 0.5< 0.1% and SLS + PG is in the order 0.5< 0.1< 0.3%. In case of Tween-80 +PEG-400 the order is 0.3 < 0.1% and Tween-80 + PG is in the order 0.3< 0.1< 0.5%. They concluding that tablet coating films made of HPMC 5cPs with the addition of PEG at 1.5% and SLS at 0.3% and films made of HPMC 5cPs with PG at 1% and Tween-80 at 0.3% could be considered as an elegant film forming formulation for solving different coating problems.

European Patent Specification., (1995), Bisacodyl Dosage Form: This subject invention involves pharmaceutical compositions in dosage unit form, for peroral administration of bisacodyl to a human or lower animal having a gastrointestinal tract, with a lumen there through, with a small intestine and a colon with a junction

there between, comprising: (a) a safe and effective amount of rapidly-dissolving bisacodyl means; and (b) a delivery means which completely surrounds and encases the bisacodyl means in the dosage unit form prior to oral administration and which prevents the release of bisacodyl from the dosage form into the lumen of the gastrointestinal tract during transport of the dosage form through the lumen until the dosage form is near the junction between the small intestine and the colon or in the colon, and which then releases the bisacodyl in the lumen near the junction between the small intestine and the colon or within the colon.

Eija Leskinen., (2003), Tablet disintegration: Effects of temperature and pH of aqueous disintegrating fluid and influence of solubility of diluent on the behaviour of superdisintegrants. In the experimental work three grades of lactose were combined with foursuperdisintegrants and tablets were prepared with different porosity levels. Also one hygroscopic and insoluble diluent, sorbitol and dicalcium phosphate dihydrate were used in combination with disintegrants. Disintegration and calorimetric measurements were made in three temperatures with water and simulated gastric and intestinal fluid. Investigations show that superdisintegrants have a greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system. It is concluded that results showed that the choice of tablet excipients can have a great influence in disintegration time. As the dissolution of drug is dependent on the disintegration rate of tablet, it is thus important to pay attention to diluent and disintegrant used in order to achieve the desired availability for the drug.

Rajnikant C.Patel., (2009), Formulation Strategies For Improving Drug Solubility Using Solid Dispersions. The solubility is the biggest challenging aspects for most of the drugs in develpoing the tablets. Solid dispersions have been employed to

enhance the dissolution rates of poorly water - soluble drugs. This work is based on the various solubility enhancement strategies in solid dispersion. The approaches described are fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electro static spinning method and super critical fluid technology and also highlights the potential applications and limitations of these approaches. They concludes solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs.

Eija Leskinen., (2003), Tablet disintegration: Effects of temperature and pH of aqueous disintegrating fluid and influence of solubility of diluent on the behaviour of superdisintegrants. In the experimental work three grades of lactose were combined with foursuperdisintegrants and tablets were prepared with different porosity levels. Also one hygroscopic and insoluble diluent, sorbitol and dicalcium phosphate dihydrate were used in combination with disintegrants. Disintegration and calorimetric measurements were made in three temperatures with water and simulated gastric and intestinal fluid. Investigations show that superdisintegrants have a greater effect on disintegration time in an insoluble system than in a soluble or partially soluble system. It is concluded that results showed that the choice of tablet excipients can have a great influence in disintegration time. As the dissolution of drug is dependent on the disintegration rate of tablet, it is thus important to pay attention to diluent and disintegrant used in order to achieve the desired availability for the drug.

Masaaki Nakahara, Akihiko Kurosaki, *et al...* (2009) have clearly demonstrated the conventional methods for powdering oil-soluble substance mentioning their common drawbacks. They discovered that elution of the same to heat, pressure,

water, or the like, can be prevented by allowing the same to adsorb on a calcium component in an aqueous solution in the presence of surfactant.

Gregory Paul (2007) Dittmar Andrew Irvine Sokolik in their patent application title "Vitamin D content uniformity in pharmaceutical dosage forms" have come up with new dosage forms of vitamin D3 and calcium carbonate having improved content uniformity. The improvements are realized through modifications to the formulation, the raw material specifications, and the process of manufacture [6].

Vladimir Babtsov, Kiryat Shmona, *etal*., (2005) in their patent article "Methods of Microencapsulation" have used excipients like polymethylacrylate, cellulose acetate, polyvinyl alcohol, sodium Lauryl acetate etc in their preparation involving Microencapsulations of water insoluble drugs.

Hahnlein, Wolfgang, *etal*.. (2003) have prepared a dry emulsion preparation of vitamin D3 by homogenizing vitamin D3 in an aqueous solution containing one of more protective colloids for a time and under conditions effective to produce an emulsion containing vitamin D3. They said aqueous solution optionally contains one or more sugars or other additives and drying the mixture optionally in the presence of a coating material, to yield a dry powder.

Yajima and Mizuo (1990) have demonstrated the powdering of vitamin D3 by spray drying a method that involves addition of the vitamins to a solvent and agitation. The solvent is removed and the residue is subjected to powdering. The powdering may be effected by spray drying, drying in vacuum, freeze-drying in drum of other know drying methods. They concluded that when a diluted acid is used as a solvent, the pH Should preferably be adjusted to 3 to 4. On the contrary, when diluted ammonia is used, the pH should preferably adjust to 10-11. Subsequently, vitamins are added.

Makino, Yuji Suzuki*, etal*.., (1996) have introduced a pharmaceutical solid preparation of active form of vitamin D3 of improved stability which comprises of active form of vitamin D3 dispersed in an excipient readily soluble in organic solvent and a basic substance. They also examined the stability and 'residual percentage of active vitamin D3' of the prepared specimen comparing with the control (standard vitamin D3).

Ishii, Kuniaki, Toriumi, *etal*.. (1994) have prepared solid pharmaceutical preparations containing a vitamin D3 derivative. The composition of this preparation consisted of excipients like Mannitol, sugar, Hydroxypropyl cellulose, and a binder polyvinyl pyrrolidone.

Moroi, Masami, *etal*… (1993) have demonstrated the methid, for the preparation of a stable dosage-form of active vitamin D3, which comprises an active vitamin D3 and a stabilizer selected from polyvinylacetal diethylaminoacetate and Hydroxypropylcellulose adding a pharmaceutically-acceptable carrier to the resultant mixture [(12)].

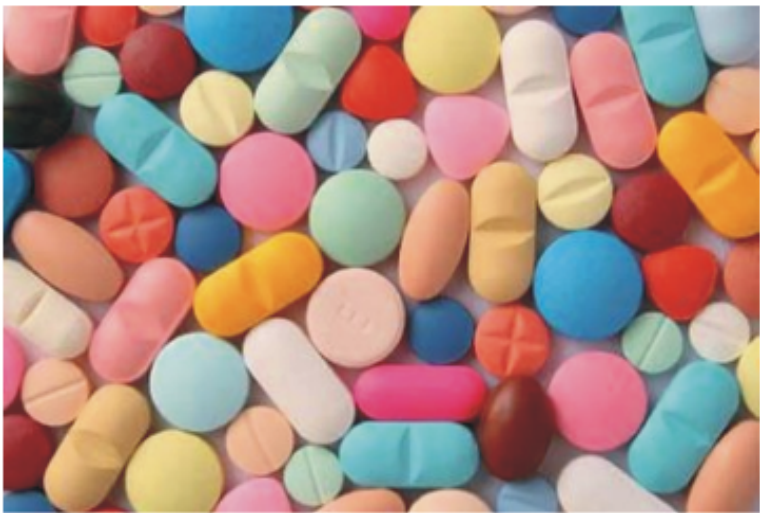
Nemoto, Kaoru, *etal*… (1989) in their patent article "Stabilized active forms of vitamin D3" demonstrated the preparation containing an active form of vitamin D3 which is stabilized by incorporation of an amino acid. They concluded amino acids that do not contain a sulphur atom or an acid amino group in its structure stabilized the vitamin D3.

John M. Ballard, LImin Zhu, *etal*.. (2007) conducted LC-UV profile of a thermally stressed vitamin D3 tablet and concluded that four major degradants formed are identified as the Octanoate and Decanoate esters of D3 and pre-vitamin D3. This observation reinforces the need to be aware of potential interactions when designing

formulations of apparently inert excipients and active pharmaceutical ingredients. They also concluded that even minor drug-excipent reactivity can be significant in the long-term stability of pharmaceutical products due to the stringent quality standards to which pharmaceutical formulations are held.

Semih Otles, Yasar Hisil (1994) have clearly demonstrated the determination of vitamin D3 by high pressure liquid chromatography (HPLC). They estimated the quantity of vitamin D_3 in hen egg and the recovery study of vitamin D3. They finally concluded that HPLC method is rapid simple, sensitive, reproducible and very efficient technique for the determination of vitamin D3 in hen eggs.

DRUG PROFILE



3. DRUG PROFILE

VITAMIN D3

Cholecalciferol, also known as **vitamin D_3** and **colecalciferol**, is a type of vitamin D which is made by the skin, found in some foods, and taken as a dietary supplement.

Chemical Formula	C27H44O
Chemical Name	5Z,7E)-9,10-secocholesta-5,7,10 (19)-trien-3ß-ol
Molecular Weight	384.64
Synonyms	Calciol, CC, Colecalciferol, Colecalciferolum
CAS number	67-97-0
IUPAC Name	(1S,3Z)-3-{2-[(1R,3aS,4E,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-octahydro-1H-inden-4-ylidene]ethylidene}-4-methylidenecyclohexan-1-ol
Absorption	Readily absorbed
Volume of distribution	Not Available
Protein binding	50% to 80%

Indication	For the treatment of vitamin D deficiency or insufficiency, refractory rickets (vitamin D resistant rickets), familial hypophosphatemia and hypoparathyroidism, and in the management of hypocalcemia and renal osteodystrophy in patients with chronic renal failure undergoing dialysis. Also used in conjunction with calcium in the management and prevention of primary or corticosteroid-induced osteoporosis
Pharmacodynamics	cholecalciferol (vitamin D3) is a steroid hormone that has long been known for its important role in regulating body levels of calcium and phosphorus, in mineralization of bone, and for the assimilation of Vitamin A. The classical manifestations of vitamin D deficiency is rickets, which is seen in children and results in bony deformaties including bowed long bones. Deficiency in adults leads to the disease osteomalacia. Both rickets and osteomalacia reflect impaired mineralization of newly synthesized bone matrix, and usually result from a combination of inadequate exposure to sunlight and decreased dietary intake of vitamin D. Common causes of vitamin D deficiency include genetic defects in the vitamin D receptor, severe liver or kidney disease, and insufficient

	exposure to sunlight. Vitamin D plays an important role in maintaining calcium balance and in the regulation of parathyroid hormone (PTH). It promotes renal reabsorption of calcium, increases intestinal absorption of calcium and phosphorus, and increases calcium and phosphorus mobilization from bone to plasma
Mechanism of Action	The first step involved in the activation of vitamin D3 is a 25-hydroxylation which is catalysed by the 25-hydroxylase in the liver and then by other enzymes. The mitochondrial sterol 27-hydroxylase catalyses the first reaction in the oxidation of the side chain of sterol intermediates. The active form of vitamin D3 (calcitriol) binds to intracellular receptors that then function as transcription factors to modulate gene expression. Like the receptors for other steroid hormones and thyroid hormones, the vitamin D receptor has hormone-binding and DNA-binding domains. The vitamin D receptor forms a complex with another intracellular receptor, the retinoid-X receptor, and that heterodimer is what binds to DNA. In most cases studied, the effect is to activate transcription, but situations are also known in which vitamin D suppresses transcription.

	Calcitriol increases the serum calcium concentrations by: increasing GI absorption of phosphorus and calcium, increasing osteoclastic resorption, and increasing distal renal tubular reabsorption of calcium. Calcitriol appears to promote intestinal absorption of calcium through binding to the vitamin D receptor in the mucosal cytoplasm of the intestine. Subsequently, calcium is absorbed through formation of a calcium-binding protein
Metabolism	Within the liver, cholecalciferal is hydroxylated to calcidiol (25-hydroxycholecalciferol) by the enzyme 25-hydroxylase. Within the kidney, calcidiol serves as a substrate for 1-alpha-hydroxylase, yielding calcitriol (1,25-dihydroxycholecalciferol), the biologically active form of vitamin D3

Cholecalciferol was first described in 1936. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. The wholesale cost in the Costa Rica is about 2.15 USD per 30 ml bottle of 10,000 IU/ml. In the United States treatment costs less than 25 USD per month.

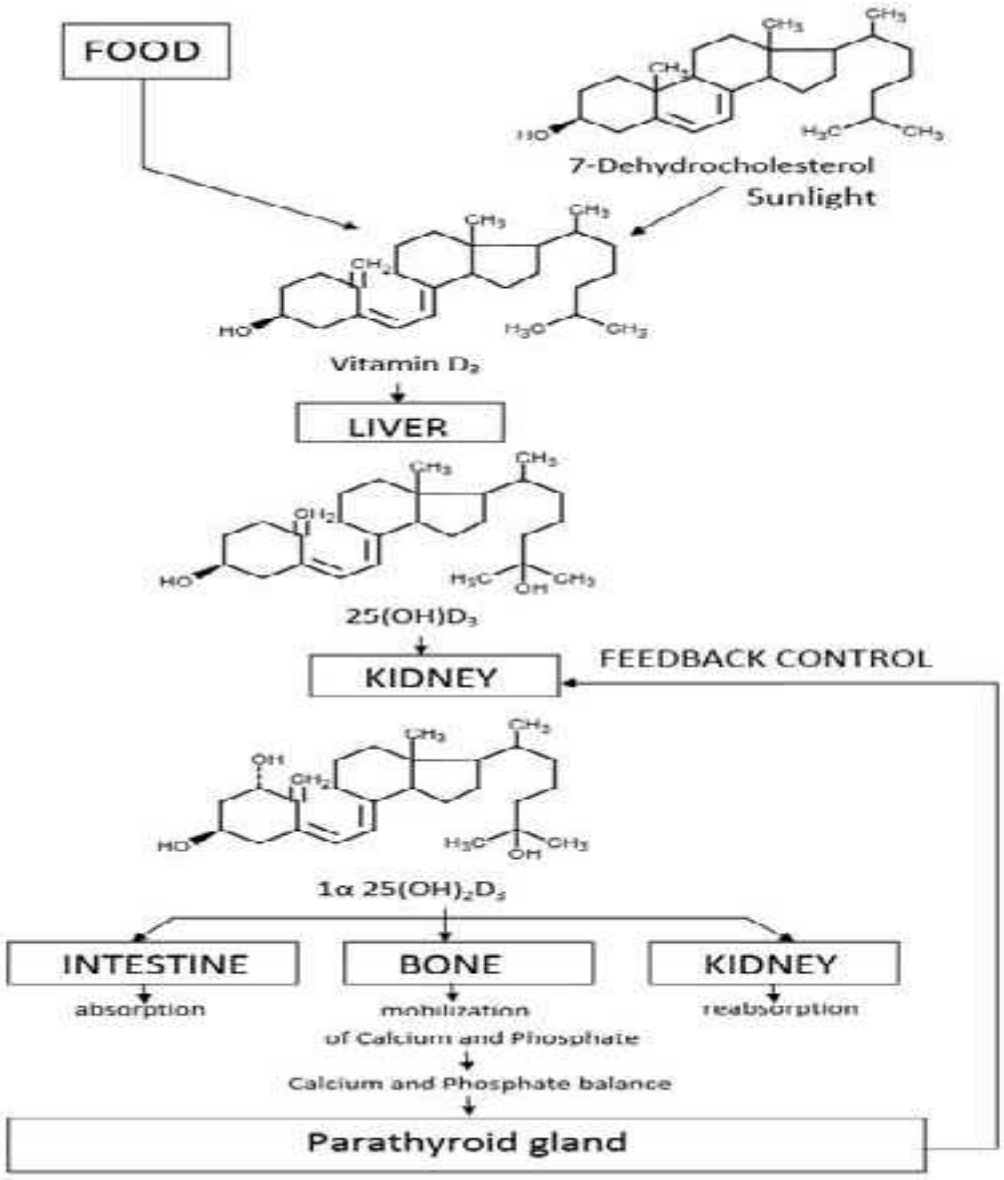


Fig: 12 The three steps in the synthesis and activation of vitamin D_3 are regulated as follows:

- Cholecalciferol is synthesized in the skin from 7-dehydrocholesterol under the action of ultraviolet B (UVB) light. It reaches an equilibrium after several minutes depending on the intensity of the UVB in the sunlight - determined by latitude, season, cloud cover, and altitude - and the age and degree of pigmentation of the skin.
- Hydroxylation in the endoplasmic reticulum of liver hepatocytes of cholecalciferol to calcifediol (25-hydroxycholecalciferol) by 25-hydroxylase is loosely regulated, if at all, and blood levels of this molecule largely reflect the amount of cholecalciferol produced in the skin combined with any vitamin D_2 or D_3 ingested.
- Hydroxylation in the kidneys of calcifediol to calcitriol by 1-alpha-hydroxylase is tightly regulated: it is stimulated by parathyroid hormone and serves as the major control point in the production of the active circulating hormone calcitriol (1,25-dihydroxyvitamin D_3).

MAGNESIUM GLYCINE COMPLEX

Magnesium glycine complex is a mineral supplement advised nowadays to treat low amounts of magnesium in the blood. Magnesium is an essential micronutrient which plays a key role in the functioning of muscles, nerves, heart and bones.

Table 3:1 Magnesium glycine complex

S.No	Magnesium glycine complex
1.	Magnesium
2.	Lead
3.	Arsenic
4.	Mercury
5.	Cadmium

Magnesium glycinate is often used because it is the best-absorbed form of magnesium.

Table 3:2 Magnesium glycine complex

Name	**Magnesium Glycinate**
Chemical Formula	$C_4H_8MgN_2O_4$
IUPAC Name	magnesium(2+) ion bis(2-aminoacetate)
Type	• Small Molecule
Description	• Magnesium glycinate is a magnesium salt of glycine that is available as dietary supplements as a source of magnesium. It is used in the treatment of magnesium deficiency.
CAS number	14783-68-7
Synonyms	Not available

- In Osteoporosis: Magnesium plays a role in the development of healthy bones, and people with higher levels of magnesium may have a higher bone mineral density. This is important in helping to reduce the risk of bone fractures and osteoporosis.

EXCIPIENT PROFILE

EXCIPIENT PROFILE

POVIDONE K30

Synonyms : polyvinylpyrrolidone (PVP) , polyvidone

Description : Povidone occurs as a fine, white to creamy white colored, odourless oral most odourless, hygroscopic powder.

Functional category : It is used as a binder in many pharmaceutical tablets and used in many technical applications with various roles such as an adhesive, additive, and emulsifier. It also has disinfectant properties.

Applications In Pharmaceutical Formulation Or Technology

Povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydro-alcoholic solutions.

CROSPOVIDONE

Synonyms : Poly vinyl pyrolidone, crospovidone,povidone

Chemical name : C6H9NO

Descriptions : White color fine powder, tasteless, odourless

Functional categories : Disintegrating agents

Solubility : Insoluble in PVP, Soluble in water

Melting point : 150^0c

Stability and storage condtions : Stored in a well closed container in a cool place.

MICROCRYSTALLINE CELLULOSE

Non-proprietary : BP/ JP /USPNF : Microcrystalline cellulose

PhEur : Cellulosum microcristallinum

Synonyms : Avicel PH, Celexe, Cellulose gel, Celphere, Ceolus KG, Crystalline cellulose, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, and Vivapur.

Chemical Name : Cellulose.

Description : Colour : White.

Nature : Crystalline powder composed of porous particles.

Typical Properties : Angle of repose : 49° for Ceolus KG.

Density (bulk) : 0.337 gm/cm3.

Functional Category : Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Table 3:3 Applications MCCPpH102 in Pharmaceutical Formulation

Use	Concentration
Adsorbent	20–90
Adherent	5–20
Capsule binder/diluents	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

COLLOIDAL SILICON DIOXIDE:

Non-proprietary Names : BP : Colloidal anhydrous silica

PhEur : Silica colloidalis anhydrica

USPNF : Colloidal silicon dioxide

Synonyms : Aerosil, Cab-O-Sil, Cab-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, Wacker HDK.

Chemical Name : Silica

Description : Colour: Bluish-White.

Nature : Nongritty amorphous, particle size: 15 nm.

Typical Properties : Acidity/alkalinity: pH = 3.5–4.4 (4% w/v aqueous dispersion) Bulk Density : 0.029–0.042 g/cm3 Carr's index : 35.52% Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid, soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Functional Category : Adsorbent, Anticaking agent, Emulsion stabilizer, Glidant, Suspending agent, Tablet disintegrant, Thermal stabilizer, Viscosity-increasing agent.

Talc Synonyms : Talcum powder, Soaprock, Talc, French chalk, Steatite Chemical

Formula : $Mg_3Si_4O_{10}(OH)_2$

Descriptions : Colorless

Functional categories : Lubricant

Solubility : **I**nsoluble in water, slightly soluble in dilute mineral acids

Melting point : 1500^0c

Molecular weight : 379.259 g/mol

MAGNESIUM STEARATE

Synonyms : Dolomol, Magnesium Stearate

Chemical formula : $Mg(C_{18}H_{35}O_2)_2$

Descriptions : White color

Functional categories : Lubricant

Molecularweight : 591.27 g/mol

Solubility : Soluble in Water, Slightly Soluble in Benzene

Melting point : $88{\cdot}5^0$C

AIM & OBJECTIVES

4. AIM AND OBJECTIVES

AIM :

Aim of present study is investigated formulation development and evaluate of Vitamin D3. Research is focused to improve the stability of the drug by changing the production process meant for the treatment of rickets, familial hypophosphatemia and hypoparathyroidism, and in the management of hypocalcemia and renal osteodystrophy in patients with chronic renal failure undergoing dialysis,calcium in the management and prevention of primary or corticosteroid-induced osteoporosis.

OBJECTIVES :

- To formulate development and evaluate food drug product of Vitamin D3
- To study the disintegration time and coating technology of tablet.
- To study the stability of the formulated drug.

The **Pharmaceutical Formulation** objectives which were destined to achieve during the work are:

- Stability of the tablet with good physical strength with long period of time.
- Tablets with optimum content of active pharmaceutical ingredients without variation in the content unit/tablet.


Materials
and
Methods

5. MATERIAL AND METHOD

Table No 5:1 List of materials:

S.No	Raw Materials	Manufacture
1.	Cholecalciferol Vitamin D3	Spansules pharmatech
2.	Magnesium Glycine Complex	Coral Calcium
3.	Mannitol	Shandong Tianl
4.	Sodium Starch Glycolate	Amishi Drugs/J.R. Pharma
5.	Microcrystaline Cellulose	Amit hydrocolloids/Akash Pharma
6.	Povidone	Jiaozuo Yuanhai/Boai NKY Pharmaceuticals
7.	Povidone	Jiaozuo Yuanhai
8.	Crospovidone	JH Nan hang
9.	Microcrystalline Cellulose	Juku orchem/Amishi
10.	Colloidal silicone di oxide	Cabot Sanmar/ Henan Xunyu Chemical
11.	Talc	Gangotri/ Neelkanth
12.	Erythrosine Lake	Neelikon Foods dyes
13.	Brilliant Blue Lake	Neelikon Foods dyes
14.	Isopropyl Alcohol	Deepak Fertilizers/ Lee Chang Yuang
15.	Methylene Chloride	Chemplast/Gujarat Fluoro Chemicals

Table No 5:2 Equipment used for formulation

S.NO	EQUIPMENT	MAKE
1.	Laminar Air Flow – Dispensing booth	Micro Flow
2.	Electrical Balance	LCGC
3.	Vibro Sifter – 1 & 2	Gem Pharma Machineries
4.	Paste Preparation Kettle	Gem Pharma Machineries
5.	Ribbon Mixture	Gem Pharma Machineries
6.	Rapid Mixer	Gem Pharma Machineries
7.	Tray Drier	Gem Pharma Machineries
8.	Fluid Bed Drier	Gem Pharma Machineries
9.	Multi mill	Gem Pharma Machineries
10.	Mobile Loader	Gem Pharma Machineries
11.	Compression Machine – 16/27 station	Cadmach Machinery
12.	Tablet in Tablet Compression Machine	Cadmach Machinery
13.	Tablet De–Duster – 1,2&3	Fluid Pack
14.	Analytical Balance	LCGC
15.	Disintegration Apparatus	Electro Lab
16.	Friability Apparatus	Electro Lab
17.	Hardness Tester	In Lab
18.	Digital Vernier Caliber – 1,2&3	Mitutoyo
19.	Tap Density Apparatus	Electro Lab
20.	IR Moisture Analyser	LCGC
21.	Manual Coating Machine	Gem Pharma Machineries

22.	Auto Coater	Neo Cota
23.	Colloid Mill	Gem Pharma Machineries
24.	Tablet Inspection Conveyor	Gem Pharma Machineries
25.	Metal Detector	United Engineering

Pre-formulation studies:

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of dosage forms. Pre-formulation studies yield necessary knowledge to develop suitable formulation. It gives information needed to define nature of drug substance and provide a dosage form. Hence, the following pre-formulation studies were performed for the obtained sample of drug.

- Organoleptic evaluation
- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Hausner's ratio
- Solubility studies

Organoleptic evaluation:

The organoleptic property of

- Color
- Taste
- Odor
- Flavor

Angle of repose:

The angle of repose is the maximum angle of a stable slope determined by friction, cohesion and the shapes of the particles. When bulk granular materials are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density surface area, and coefficient of friction of the material. Material with a low angle of repose forms flatter piles than material with a high angle of repose [63].

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed blend is allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation,

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

θ = angle of repose

h = height of pile

r = radius of pile

Table No 5:3 Flow property of angle of repose:

S.No	Flow property	Angle of repose
1.	Excellent	25-30
2.	Good	31-35
3.	Fair	36-40
4.	Passable	41-45
5.	Poor	46-55

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to granulated cylinder or through volume measuring apparatus into cup [64].

Bulk density = M/V_0

Where, M = Mass of the powder

V_0 = bulk volume of the powder.

Limits: It has been stated that the bulk density values having less than 1.2g/cm^3 indicates good packing and values greater than 1.5g/cm^3 indicates poor packing.

Tapped density:

A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achived by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed [65].

Tapped density = M/V_r

Where,

M = Mass of the powder

V_r = final tapping volume of the powder

Compressibility index and Hausner ratio:

The compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows[66],

Compressibility index = 100 × tapped density/bulk density

Hausner ratio = tapped density/bulk density.

Solubility studies :

The solubility of Vitamin D3 in solvents was observed to decrease in the order of Propan-1-ol > Ethanol > Ethyl Ethanoate > Propan-2-one > Methanol > Ethanenitrite [67].

Compressed Tablet

Description:

Blue coloured, caplet shaped film coated tablets with plain on both sides

Weight Variation:

Twenty tablets were selected randomly and the average weight was determined using an electronic balance. Tablets were weighed individually and compared with the average weight [68].

Thickness test:

Ten tablets were selected randomly and thickness was assessed using a Vernier caliper/screw gauge.

Diameter:

It also dimensionally described & controlled. Tablet diameter can be measured for six tablets by Dial caliper [69].

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport [70].

Friability of the tablets was determined using Roche friabilator at 25 rpm/min for 4 min. the device subjects the tablet to the combined effect of abrasion and shock in

a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Twenty tablets were weighed and loss in weight (%) was calculated. The friability (F) is given by the formula,

%Friability =[(W1-W2)100]/W1

Where,

W1 : weight of tablet before test,

W2 : weight of tablet after test

Disintegration study:

The disintegration test determines whether dosage forms such as tablets, capsules, suppositories disintegrate with in prescribed time when placed in a liquid medium under the prescribed experimental conditions.

Disintegration is defined as the state in which no residue of the unit under test remains on the screen of the apparatus or if a residue remains it consists of fragments of disintegrated parts of tablet component part such as insoluble coating of tablets.

Disintegrants are agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule “slugs” into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture

penetration and dispersion of the tablet matrix. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release.

Disintegrants are an essential component to tablet formulations. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action [71].

There are three methods of incorporating disintegrating agents into the tablet:

A. Internal Addition (intragranular)
B. External Addition (extragranular)
C. Partly Internal and External.

Assay :

Magnesium Glycine Complex Equivalent to Elemental Magnesium By Titration

Preparation of Ammonium chloride solution $_{p}$H 10.0 :

Dissolve 5.4g of ammonium chloride in 20ml of water, add 35ml of 10M ammonia solution and dilute to 100ml with water.

Preparation of 2M Hydrochloric acid solution :

Dilute 17ml of hydrochloric acid to 100ml with water.

Preparation of 0.05M Disodium Edetate :

Dissolve 18.6g of disodium 50dentate in 500ml of water and dilute to 1000ml with water.

Standardization of 0.05M Disodium EDTA :

Dissolve 0.100g of calcium carbonate in granules in 3ml of hydrochloric acid and add 100ml of water add 30ml of Ammonium chloride Buffer Ph 10 and add 5mg of Erichrome black T Titrate with the 0.05M disodium edentate solution until the violet-pink colour changes to Blue colour.

Each ml of disodium edentate is equivalent to 5.0169 mg of CaCo3.

Blank :

Add 5ml of water then add 5ml of 2M Hydrochloric acid into a 250 ml conical flask and mix well. Add 150 of water then add 5ml of ammonium chloride solution Ph 10.0 and add 5mg of Erichrome black T. Heat to water bath about 40^0c for 5 min then titrate at this temperature with 0.05M Sodium edentate, until the colour changes to permanent blue.

Sample preparation:

Weigh 20 tablets and transfer to mortar pestle triturate into fine powder. Accurately weigh and transfer the sample equivalent to 25mg of Magnesium into a 250ml conical flask add 5ml of water then add 5ml of 2m Hydrochloric acid and sonicate for 15 minutes. After sonication add 150ml of water then add 5ml of ammonium chloride solution pH 10.0 and add about 5mg of Erichrome black T. Heat to water bath about 40^0c for 5 min then titrate at this temperature with 0.05M Sodium edentate, until the colour changes to permanent blue [72].

Note: 1ml of 0.05M Sodium edtate is equivalent to 1.215mg of Mg.

Calculation:

Titre value (sample – blank) × Eq.wt factor × Required Molarity/Weight taken in mg × Actual Molarity ×Average weight of the tablet in mg

= /mg/tablet

% of lable claim = mg/tablet/lable claim in mg × 100

Vitamin D3 by HPLC (UV/PDA Detector) :

Mobile phase & Diluent: Methanol

Blank :

Pipette out 5ml of Dimethyl sulfoxide into a 100ml volumetric flask and make to volume with diluent.

Standard Preparation :

Accurately weigh about 20mg of vitamin D3 (100 IU/ mg) into a dried 100 ml amber colour volumetric flask, add 5ml of Dimethyl sulfoxide and sonicate for 15 minutes at below 25^0c, then add 30ml of Methanol sonicate for 10 minutes at bellow 25^0c and make up to the volume with diluent. Filter the solution through 0.45µm nylon membrane filter.

Sample preparation :

Weigh 20 tablets and transfer to mortar pestle, triturate into fine powder. Accurately weigh and transfer the sample Equivalent to 2000 IU of vitamin D3 into a dried 100 ml amber colour volumetric flask, add 5ml of Dimethyl sulfoxide and sonicate for 15 minutes at below 25^0c, then add 30ml of Methanol sonicate for 10 minutes at bellow

25^0C and make up to the volume with diluent. Filter the solution through 0.45µm nylon membrane filter.

Chromatographic condition

Column : Intsil C18 (250 *4.6mm) 5µm or equivalent

Flow Rate : 1.5ml/minute

Injection volume : 50µl

Column Oven Temperature : 45^0c

Sample Temperature :5^0C

Wavelength : 264 nm

Run time : 15 minutes

Procedure

Separately inject equal volumes (about 50 µl) of the blank, standard preparation and sample preparation into the chromatograph, record the chromatograms, and measure the response of major peak.

Evaluation of system suitability

Chromatograph the standard preparation and the peak responses as directed under the procedure. The test is not valid unless,

a) The tailing factor for vitamin D3 peak in the standard should not be more than 2.0.
b) The number of theoretical plates for vitamin D3 peak should not be less than 2000.

c) The relative standard deviation for the area of vitamin D3 peak for replicate injection of standard preparation should not be more than 2.0%.

Calculation :

Vitamin D3

AT×WS×100×P/AS×100×WT×100 ×AW×100 = IU/TABLET

% lable claim = IU/tablet / LC × 100

Where,

AT : Average area of vitamin D3 peak from sample preparation

AS : Average area of vitamin D3 peak from standard preparation

WS : weight of Vitamin D3 working standard in mg

WT : weight of the sample in mg

P : percentage purity of vitamin D3 working standard as is basis

LC : Label claim in mg

Aw : Average weight of the tablet in mg

Dissolution studies:

As per USP dissolution is not required for oil soluble Vitamins (Vitamin A, D, E, K). Dissolution Test Requirements for Nutritional Supplements

Specifications are provided in *USP 23,* Supplement 9.USP classifications. Table I lists the dissolution test requirements and references for the six USP classes of vitamins, minerals, and vitamins with minerals.

Table No 5:4

USP Classifications with respective dissolution test requirements and references.

Class	Dissolution
I. Oil-soluble vitamins	Not required
II. Water-soluble vitamins	One index vitamin; folic acid if present
III. Water-soluble vitamins with minerals	One index vitamin and one index element; folic acid if present
IV. Oil- and water-soluble vitamins	One index water-soluble vitamin; folic acid if present
V. Oil- and water-soluble vitamins with minerals	One index water-soluble vitamin and one index element; folic acid if present
VI. Minerals	One index element

6. FORMULATION DEVELOPMENT

Table No 6:1 Inner tablet:

S.No	INGREDIENT	CATEGORY
1.	Cholecalciferol	Pharmaceutical active ingredient

Table No 6:2 Outer tablet:

S.No	INGREDIENT	CATEGORY
1.	Magnesium Glycine Complex	Best absorbed form of Magnesium

Table No 6:3 Excipients list for IT formulation:

S.NO	Excipients	Category
1.	Micro Crystalline Cellulose	Suspending agent
2.	Povidone	Adhesive
3.	Iso Propyl Alcohol	Dissolving oils
4.	Crospovidone	Disintegrating agent
5.	Colloidal silicon di oxide	Anti-caking
6.	Talc	Glidant
7.	Magnesium Stearate	Anti-adherent
8.	Instacoal white	Pigments
9.	Erythrosine lake	Cherry pink
10.	Brilliant blue lake	Reddish blue powder
11.	Methylene chloride	Volatile liquid

Table No 6:4 Excipients for OT formulation:

S.No	Excipients	Category
1.	Micro crystalline cellulose	Anti-caking
2.	Sodium starch glycolate	Disintegrant
3.	Povidone	Adhesive
4.	Iso propyl alcohol	Dissolving oils
5.	Crospovidone	Disintegrant
6.	Micro crystalline cellulose	Anti-caking
7.	Colloidal silicone di oxide	Anti-caking
8.	Talc	Glidant
9.	Magnesium stearate	Anti-adherent
10.	Instacoat white	Pigments
11.	Erythrosine lake	Cherry pink
12.	Brilliant blue lake	Reddish blue powder
13.	Iso propyl alcohol	Anti-septic
14.	Methelene chloride	Volatile liquid

Different batches of Vitamin D3 tablet (F1to F5)were prepared with varying concentrations of different formulation ingredients according to Table. The amount required for formulation is given for following Table.

Table No 6:5 Formulation for IT formulation:

S.No	Name of the Materials	F – 1 (kg)	F – 2 (kg)	F - 3 (kg)	F – 4 (Kg)	F – 5 (kg)
1.	Cholecalciferal	0.15	0.150	0.150	0.150	0.150
2.	Mannitol	0.165	0.165	0.165	0.165	0.165
3.	Micro crystalline Cellulose	0.065	0.075	0.025	0.045	0.035
4.	Povidone	0.015	0.015	0.015	0.015	0.015
5.	Iso Propyl Alcohol	0.15	0.15	0.15	0.15	0.15
6.	Crospovidone	0.0075	0.0175	0.0325	0.0125	0.0225
7.	Colloidal silicon di oxide	0.004	0.004	0.004	0.004	0.004
8.	Talc	0.004	0.004	0.004	0.004	0.004
9.	Magnesium Stearate	0.003	0.002	0.004	0.004	0.004
10.	TOTAL	80.00	80.00	80.00	80.00	80.00
11.	Instacoal white	0.0139	0.0139	0.0139	0.0139	0.0139
12.	Erythrosine lake	0.0004	0.0004	0.0004	0.0004	0.0004
13.	Brilliant blue lake	0.00025	0.00025	0.00025	0.00025	0.00025
14.	Iso propyl alcohol	0.095	0.095	0.095	0.095	0.095
15.	Methylene chloride	0.178	0.178	0.178	0.178	0.178

Table No 6:6 Formulation for OT formulation:

S.No	Name of the Materials	F – 1 (kg)	F – 2 (kg)	F - 3 (kg)	F – 4 (Kg)	F – 5 (kg)
1.	Magnesium glycine complex	6.25	6.25	6.25	6.25	6.25
2.	Micro crystalline cellulose	0.4	0.7	0.2	0.4	0.5
3.	Sodium starch glycolate	0.225	0.225	0.225	0.225	0.225
4.	Povidone	0.25	0.25	0.25	0.25	0.25
5.	Iso propyl alcohol	3.1875	3.1875	3.1875	3.1875	3.1875
6.	Crospovidone	0.255	0.305	0.295	0.275	O.265
7.	Micro crystalline cellulose	0.04	0.03	0.07	0.05	0.06
8.	Colloidal silicone di oxide	0.05	0.06	0.02	0.04	0.04
9.	Talc	0.03	0.03	0.03	0.03	0.03
10.	Magnesium stearate	0.08	0.08	0.08	0.08	0.08
11.	TOTAL	1520.00	1520.00	1520.00	1520.00	1520.0
12.	Instacoat white	0.2706	0.2706	0.2706	0.2706	0.2706
13.	Erythrosine lake	0.012	0.012	0.012	0.012	0.012
14.	Brilliant blue lake	0.006	0.006	0.006	0.006	0.006
15.	Iso propyl alcohol	1.4375	1.4375	1.4375	1.4375	1.4375
16.	Methelene chloride	2.67	2.67	2.67	2.67	2.67

Manufacturing process:

Inner part:

Step 1: Sifting:

1. **Intra Granular:** Sift total dispensed quantity of Vitamin D3, Mannitol and Microcrystalline Cellulose through 40-mesh (420μm) sieve and collect into separate clean double LDPE poly bags & appropriately labeled.
2. **Extra Granular:** Sift total dispensed quantity of Crospovidone, Colloidal Silicon Dioxide and Talc through 40-mesh (420μm) sieve and collect into separate clean double LDPE poly bags & appropriately labeled.
3. Sift total dispensed quantity of Magnesium Stearate through 40-mesh (420μm) sieve and collect into separate clean double LDPE bag and appropriately labeled.

Step 2 : Binder solution preparation :

Solution: In a suitable stainless steel vessel fitted with stirrer, add Isopropyl Alcohol and start continuous stirring with required RPM to form a vortex. Add total dispensed quantity of PVP slowly into the vortex to get clear solution.

Step 3 : Granulation :

Load total sifted quantity of Intra Granular part of Vitamin D3, Mannitol and Microcrystalline Cellulose into the Ribbon Mixer and mix for 10 minutes in Clockwise direction.

1. Add the binder solution slowly for 2-3 minutes into the above Ribbon mixer and granulated.
2. If required add additional quantity of Isopropyl Alcohol and mix it for further 3minutes to get the uniform wet mass.
3. Collect the above wet mass in a Trays and fixed into Tray Drier. Start drying the granules at 35 - 40°C (inlet temperature) to reach the moisture content of 6.0 to 8.0%.
4. Check the moisture content of granules by using moisture balance at 60°C. If the granules not reach the moisture limit (6.0 - 8.0 %), dry the wet mass until the granules reach the above moisture limit. Shuffle the granules at every 15minutes.

Table No 6:7 Blending & Lubrication

Blending & Lubrication	Description Assay	White to Off white colored granular powder. Each 80 mg of Lubricated Blend Contains: Vitamin D3 IP : 1200IU	After Completion of lubrication

Pass the above semi dried granules through Vibro sifter using 16 # mesh sieve.

1. Collect the sieved granules in Tray Drier trays and fixed into Tray Drier. Start drying at 35-40°C (inlet temperature) to the granules reach the moisture content of 1.0 to 1.5%.
2. Pass the dried granules through Vibro sifter using 20 # mesh and oversized granules are milled through multi mill using 1.5 mm screen at required speed at forward direction and again sifted the milled granules through 30 # mesh
3. Collect the sifted dried granules into IPC bin lined with double poly bag.

Step 4 : Blending and Lubrication :

1. Add Crospovidone, Colloidal Silicon Dioxide and Talc(extra granular) into the Ribbon Mixer containing dried and sized granules and blend for 10 minutes.
2. Add Magnesium stearate (Lubrication part) into the above Ribbon Mixerand mix for 5 minutes.

Collect samples from different location of HDPE container lined with poly bag and ensure the content uniformity of the drug through process validation protocol. Until required for tableting, the bulk lubricated Blend is stored in a secure holding area NMT 25°C and RH should be not more than 60%.

Step 5 : Compression : (Inner Tablet)

1. Set the compression machine with 5.5 mm Plain, Circular shape standard concave punches and dies (Refer –annexure MFR: FD: 012: A1/00).
2. Charge the lubricated blend into hopper to allow the compression machine and start the machine.
3. Check the product for all quality parameters as per In-process Specifications.

4. Set the compression machine and continue the compression after setting all the quality parameters.
5. Pass the compressed tablets through de-duster and collect the tablets in clean bulk container lined with double polythene bag.
6. Record all the details in the BMR – In-process Check Record.
7. The core tablets are then transferred to quarantine bulk hold area till reported for Coating.

Step 6 : Preparation of coating solution and coating process:
(Manual Coating Pan)

1. Disperse separately dispensed quantity of Instacoat White, Erythrosine Lake & Brilliant Blue Lakein and Isopropyl Alcohol in a suitable SS vessel. Stir well at 500-1200 RPM by means of Remi stirrer or 10-40 Hertz in Solution Preparation Vessel for about 5 minutes. Then add Methylene chloride and Stir well for about 25 minutes at required RPM. Then passed the above solution through colloid mill at required RPM and again stir the solution for about 20 minutes at 500-1200 RPM. Filter the solution through muslin cloth. Record the stirring time & Mixing speed. Carry out the film coating process.
2. Transfer the totalquantity of the core tablet into the coating pan and pre heat the tablet bed by using warm air at 35-50°C. Transfer the coating solution to solution tank, attach the spray gun and connected with peristaltic pump. Continue stirring of coating solution at slow speed throughout the process.

Table No 6:8 Processing Parameters

S.NO	PROCESS PARAMETERS	LIMIT
1	Pan	Manual Coating Pan-36”
2	Pan speed	2–8 RPM
3	Quantity charged	3,00,000tabs(24.00 kg)
4	Inlet temperature	35°C -50°C
5	Bed Temperature	35 – 50°C
6	Atomization pressure	1.4 to 4.2 kg/cm^2
7	RPM of peristaltic pump	12 - 50 RPM
8	Spray rate	40-100 g/min (per gun)

3. Switch on the mains and start the pan. Record RPM of pan, inlet temperature, spray gun air pressure, RPM of peristaltic pump, & spray rate.
4. Spray the coating solution over the rolling tablets at a constant rate, while running the Coating pan machine continuously, in order to cover the surfaces of tablets uniformly.
5. Based on observed average weight of core tablets, weight gain required for 2.8 to 3.2 % (Target 3.0%).Record the film-coating time in BMR.
6. If weight gain achieved between 2.80% to 3.20% stop pump and spray unit. Keeps the pan rotating with heating at 50°C for 15 minutes.
7. Then Switch off the heater at pan speed 1 RPM for 30 mins. After completion of coating, remaining coating solution to be destroyed.
8. Unload the film-coated tablets into suitable HDPE containers lined with double poly bags. Labelled the HDPE container properly.

Outer part:

Step 1: Sifting

1. **Intra Granular:** Sift dispensed quantity of Magnesium Glycine Complex, Microcrystalline Cellulose and sodium Starch Glycolate through 40-mesh (420μm) sieve and collect into separate clean double LDPE poly bags & appropriately labeled.
2. **Extra Granular:** Sift dispensed quantity of Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide and Talc through 40-mesh (420 μm) sieve and collect into separate clean double LDPE poly bags & appropriately labeled.
3. Sift dispensed quantity of Magnesium Stearate through 40-mesh (420 μm) sieve and collect into separate clean double LDPE bag and appropriately labeled.

Step 2: Binder solution preparation:

1. **Solution**: In a suitable stainless steel vessel fitted with stirrer, add Isopropyl Alcohol and start continuous stirring with required RPM to form a vortex. Add total dispensed quantity of PVP slowly into the vortex to get clear solution.

Step 3 : Granulation

1. Load total of Intra Granular part of Magnesium Glycine Complex, Microcrystalline Cellulose and sodium Starch Glycolate into the Rapid mixer granulator and mix for 15 minutes with slow impeller.
2. Add the binder solution slowly for 3-6 minutes with slow impeller,

   No Chopper into the above Rapid mixer granulator.

3. If required add additional quantity of Isopropyl Alcohol and mix it for further 2-3 minutes.
4. Collect the above wet mass in a Fluid Bed Drier bowl fix into Fluid Bed Drier. Start the air drying to vanish the Isopropyl Alcohol.
5. Then start the steam supply and dry the granules at 50-60°C (inlet temperature) to reduce the Moisture content to 6.00 to 8.00%. Moisture content checked by using moisture analyser at 105°C temperature
6. Pass the above dried granules through Vibro sifter using 16# mesh sieve. Oversized granules are milled through multi mill using 2.0 mm screen at required speed at forward direction, Again sifted the milled granules through 20 # mesh.
7. Collect the sieved and milled granules in a Fluid Bed Drier bowl fix into Fluid Bed Drier. Start the steam supply and dry the granules at 50-60°C (inlet temperature) to get granules 1.50 to 2.50 %. Moisture content checked by using moisture analyser at 105°C temperature
8. Collect the sifted dried granules into IPC bin with silica gel desiccant between the two black poly bags.

Step 4 : Blending and lubrication :

Transfer the dried granules **&** sifted extra granular and lubrication materials into blending area.

1. Transfer the granules into the Octagonal Blender. Add Microcrystalline Cellulose, Crospovidone, Colloidal Silicon Dioxide and Talc (extra granular) into the Octagonal Blender. Its containing dried and sized granules and blend for 10 minutesat 10 RPM.

2. Add Magnesium stearate (Lubrication part) into the above Octagonal Blender then mix for 5 minutes at 10 RPM.

Collect samples from different location of HDPE container lined with poly bag and ensure the content uniformity of the drug through process validation protocol.Until required for tableting, the bulk lubricated Blend is stored in a secure holding area NMT 25°C and RH should be not more than 60%.

Table No 6:9 Specifications Blending & Lubrication

Stage	Checks	Specifications	Frequency/ Method
Blending & Lubrication	Description Assay	White to Off white colored granular powder. Each 1520 mg of Lubricated Blend Contains: Magnesium Glycine Complex Eq. to Elemental Magnesium: 250 mg	After Completion of lubrication

Step 5 : Compression: (Tablet in Tablet)

1. Set the compression machine with 22.0 x 10.50 mm Plain, Caplet shape standard concave punches and dies (Refer –annexure MFR: FD: 012: A1/00).
1. Charge the lubricated blend into hopper to allow the blend into punch cavity. Then charge the inner coated tablet into the hopper which is available separately in the machine and allow the inner tablet blend filled cavity and proceed the compression.
2. Check the product for all quality parameters as per In-process Specifications.
3. Set the compression machine and continue the compression after setting all the quality parameters.
4. Pass the compressed tablets through de-duster and collect the tablets in clean bulk container lined with double polythene bag.
5. Record all the details in the BMR – In-process Check Record.
6. The tablets in tablet are then transferred to quarantine bulk hold area till reported for Coating.
7. Maximum Hold time 15 days of core tablet to be evaluated through Hold time study protocol.

Step 6 : P reparation of Coating solution & coating process :

1. Disperse separately dispensed quantity of Instacoat White, Erythrosine Lake&Brilliant Blue Lakein and Isopropyl Alcohol in a suitable SS vessel. Stir well at 500-1200 RPM by means of Remi stirrer or 10-40 Hertz in Solution Preparation Vessel for about 5 minutes. Then add Methylene chloride and Stir well for about 25 minutes at required RPM. Then passed the above solution through colloid mill at required RPM and again stir the solution for about 20

minutes at 500-1200 RPM. Filter the solution through muslin cloth. Record the stirring time & Mixing speed. Carry out the film coating process.

2. Transfer the quantity of tablet in tablet into the coating pan and pre heat the tablet bed by using warm air at 35-50°C. Transfer the coating solution to solution tank, attach the spray gun and connected with peristaltic pump. Continue stirring of coating solution at slow speed throughout the process.
3. Switch on the mains and start the pan. Record RPM of pan, inlet temperature, spray gun air pressure, RPM of peristaltic pump, & spray rate.
4. Spray the coating solution over the rolling tablets at a constant rate, while running the Coating pan machine continuously, in order to cover the surfaces of tablets uniformly.
5. Based on observed average weight of core tablets, weight gain required for 2.8 to 3.2 % (Target 3.0%). Record the film-coating time in BMR.
6. If weight gain achieved between 2.80% to 3.20% stop pump and spray unit. Keeps the pan rotating with heating at 50°C for 15 minutes.
7. Then Switch off the heater at pan speed 1 RPM for 30 mins. After completion of coating, remaining coating solution to be destroyed.

Table No 6:10 Processing Parameters

S.No	Process Parameters	Limit
1	Pan	Auto Coater-48”
2	Pan speed	2–8 RPM
3	Quantity charged	75,00,000tabs (120.18 kg)
4	Inlet temperature	35°C -50°C
5	Bed Temperature	35 – 50°C
6	Atomization pressure	1.4 to 4.2 kg/cm^2
7	RPM of peristaltic pump	12 - 50 RPM
8	Spray rate	40-100 g/min (per gun)


Results
&
Discussion

7. RESULT AND DISCUSSION

PREFORMULATION STUDIES:

The overall objective of preformulation studies is to generate useful information to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

Table: 7.1 Saturation solubility:

S No.	Medium	Solubility
1	Methanol	Soluble
2	Water	Insoluble
3	7.4 phosphate buffer	Soluble

Calibration curve

Table : 7.2 Calibration curve

S.NO	Calibration (µg)	Absorbance
1	0	0
2	5	0.104
3	10	0.271
4	15	0.459
5	25	0.648

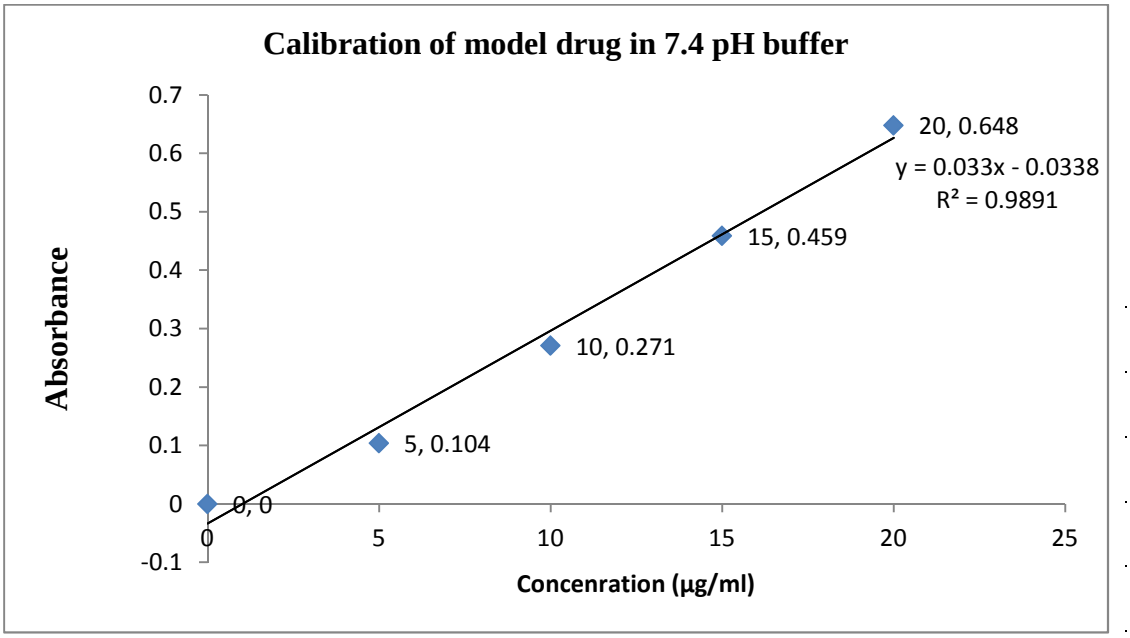


Fig 7:1 Calibration curve

Table no 7:1 Preformulation Studies of IT Powder

Formulation	Angle of Repose Mean ± SEM	Bulk density Mean ± SEM	Tapped density Mean ± SEM	Carr's index Mean ± SEM	Hausners ratio Mean ± SEM
F_1	21.87 ± 0.99	0.59± 0.18	0.66 ± 0.87	14.99 ± 0.09	1.95 ± 0.34
F_2	20.14 ± 0.48	0.51 ± 0.65	0.62 ± 0.23	13.78 ± 0.15	1.80 ± 0.87
F_3	22.65 ± 0.11	0.50 ± 0.09	0.66 ± 0.62	13.26 ± 0.65	1.98 ± 0.65
F_4	21.09 ± 0.99	0.51 ± 0.98	0.64 ± 0.45	14.76 ± 0.33	1.54 ± 0.23
F_5	23.65 ± 0.54	0.53 ± 0.87	0.61 ± 0.54	14.43 ± 0.51	1.33 ± 0.98

All values are expressed as mean ± SEM for six determinations

Table No 7:2 Physical Parameters of IT formulation: (before coating)

Formulation	Weight Variation(mg)	Hardness test(kg/cm^2)	Thickness test(mm)	Diameter (mm)	Friability %
F_1	81.23 ± 0.99	3.9 ± 0.14	2.56 ± 0.23	5.40± 0.66	0.4%
F_2	80.60 ± 0.98	4.1 ± 0.54	2.43 ± 0.87	5.36± 0.32	0.5%
F_3	81.02 ± 0.54	4.0 ± 0.33	2.54± 0.99	5.34± 0.87	0.4%
F_4	81.99 ± 0.33	4.3 ± 0.21	2.44± 0.11	5.45± 0.54	0.4%
F_5	80.80 ± 0.98	4.7 ± 0.87	2.51± 0.66	5.48± 0.33	0.5%

All values are expressed as mean ± SEM for six determinations

Table No 7:3 Physical Parameters of IT formulation: (after coating)

Formulation	Weight Variation(mg)	Thickness test (mm)	Diameter (mm)
F_1	82.43 ± 0.18	2.62 ± 0.87	5.48 ± 0.78
F_2	82.42 ± 0.65	2.54 ± 0.11	5.44 ± 0.11
F_3	82.41 ± 0.87	2.61 ± 0.24	5.43 ± 0.54
F_4	82.40 ± 0.77	2.56 ± 0.28	5.51 ± 0.87
F_5	82.40 ± 0.82	2.59 ± 0.99	5.53 ± 0.65

All values are expressed as mean ± SEM for six determinations

Table no 7:4 Drug content

S.NO	Formulation	Drug content uniformity (%)
1	F_1	91.20%
2	F_2	91.67%
3	F_3	93.80%
4	F_4	97.40%
5	F_5	96.23%

Table no 7:5 Preformulation Studies of OT Powder

Formulation	Angle of Repose Mean ± SEM	Bulk density Mean± SEM	Tapped density Mean ± SEM	Carr's index Mean ± SEM	Hausners ratio
F_1	22.91 ± 0.587	0.58 ± 0.06	0.67 ± 0.09	13.32 ± 0.10	1.15 ± 0.11
F_2	23.76 ± 0.453	0.58 ± 0.05	0.64 ± 0.11	13.99 ± 0.95	1.10 ± 0.11
F_3	21.01 ± 0.867	0.61 ± 0.11	0.67 ± 0.12	14.32 ± 0.47	1.07 ± 0.17
F_4	23.81 ± 0.767	0.59 ± 0.07	0.65 ± 0.09	15.56 ± 0.97	1.09 ± 0.15
F_5	23.08 ± 0.437	0.58 ± 0.09	0.66 ± 0.04	14.87 ± 0.48	1.11 ± 0.05

All values are expressed as mean ± SEM for six determinations

Table No 7:6 Physical Parameters of OT formulation :

Formulation	Weight variation	Hardness test (kg/cm^2)	Thickness (mm)	Diameter (mm)	Friability %
F_1	1621 ± 0.12	4.2 ± 0.12	6.81 ± 0.04	10.52 ± 0.14	0.5%
F_2	1625 ± 0.23	4.1 ± 0.14	6.81 ± 0.05	10.49 ± 0.24	0.4%
F_3	1619 ± 0.09	4.1 ± 0.54	6.78 ± 0.02	10.50 ± 0.05	0.5%
F_4	1624 ± 0.10	4.6 ± 0.61	6.80 ± 0.01	10.50 ± 0.62	0.4%
F_5	1622 ± 0.41	4.7 ± 0.71	6.80 ± 0.03	10.51 ± 0.71	0.5%

All values are expressed as mean ± SEM for six determinations

Table No 7:7 Physical Parameters of OT formulation: (after coating)

Formulation	Weight variation	Thickness test	Diameter
F_1	1634 ± 0.32	4.1 ± 0.04	10.67 ± 0.22
F_2	1636 ± 0.54	4.5 ± 0.05	10.58 ± 0.53
F_3	1632 ± 0.34	4.6 ± 0.14	10.61 ± 0.12
F_4	1633 ± 0.87	4.9 ± 0.62	10.57 ± 0.75
F_5	1635 ± 0.98	4.9 ± 0.71	10.59 ± 0.53

All values are expressed as mean ± SEM for six determinations

Table No 7:8 Disintegration Time (min)

S.NO	Formulation	Disintegration time (min)
1	F_1	7.43 ± 0.53
2	F_2	8.87 ± 0.22
3	F_3	7.53 ± 0.05
4	F_4	6.32 ± 0.32
5	F_5	7.76 ± 0.71

Table No. 7:9 Dissolution profile of formulation of Vitamin d3 tablet

Time	Dissolution Test F_1	Dissolution Test F_2	Dissolution Test F_3	Dissolution Test F_4	Dissolution Test F_5
0	0	0	0	0	0
10	28.25	23.95	28.25	30.21	31.41
20	65.33	47.93	45.33	58.99	55.33
30	84.24	71.65	76.88	78.96	79.25
45	87.23	84.89	85.25	92.47	91.45

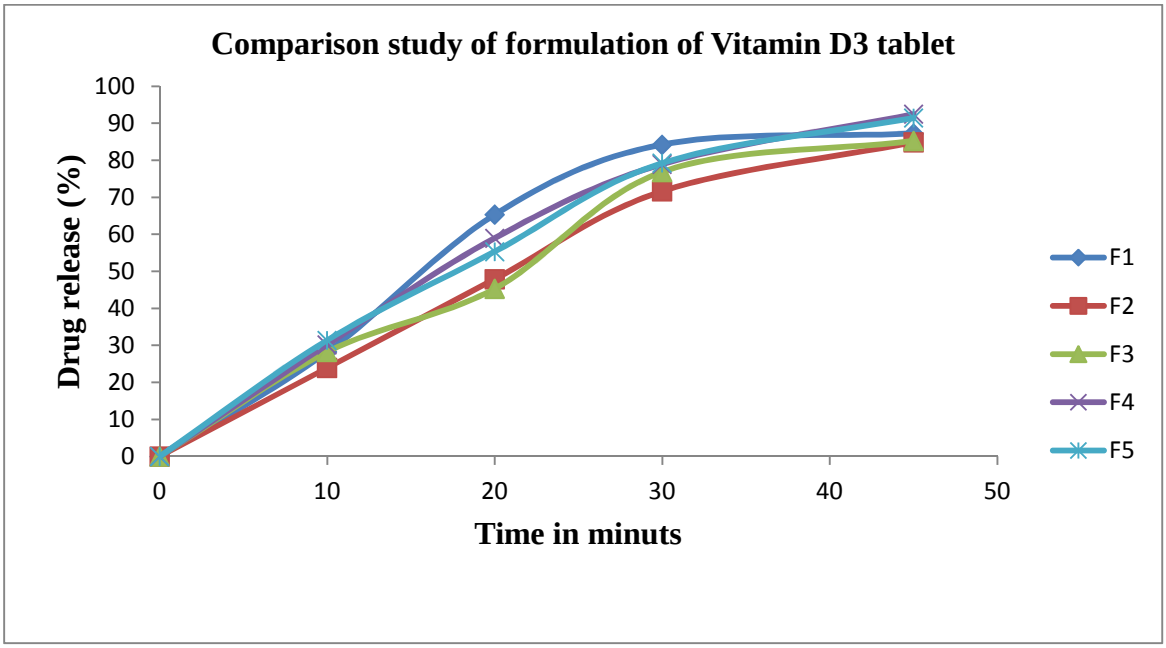


Fig 7:2 Dissolution profile of formulation of Vitamin D3 tablet

Assay: Method:E:\PROJECTS\AD_INS_006\2016\October\Method\ Cholicalciferol tablet

Assay & UOC.met Sequence: \PROJECTS\AD_INS_006\2016\October\Sequence\ Cholicalciferol tablet Assay & UOC.seq Acquired:18-10-2016 13:06:28 (GMT +05:30)

Printed Time:18-10-2016 15:37:32

(GMT +05:30) Sample ID:Standard

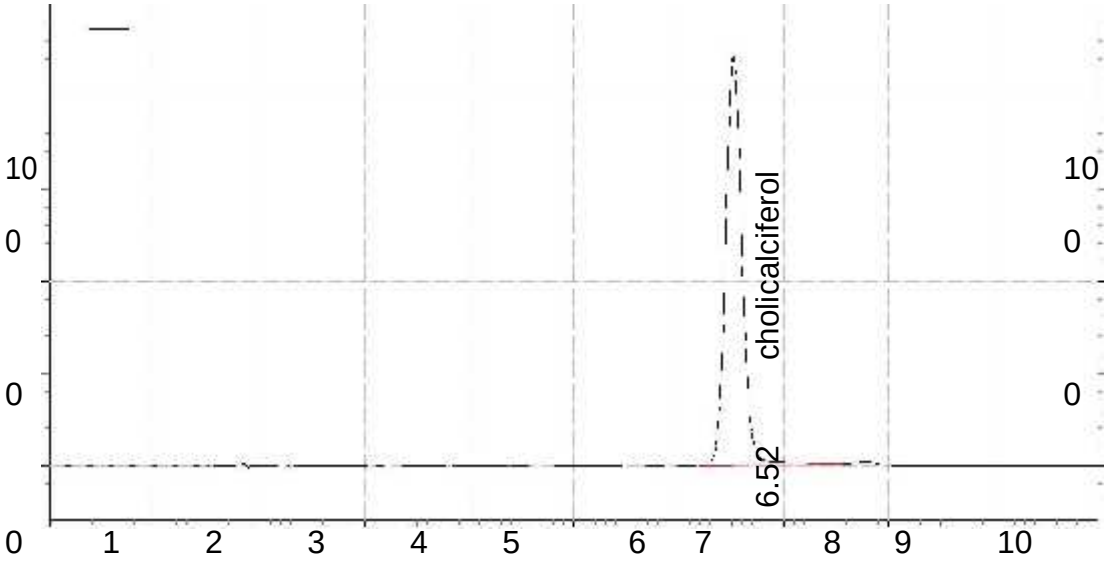
Assay

Injection

volume:20µl

Vial no:42

Cloumn ID: AD/LCCN/124



Wet granulation process was used to prepare the magnesium Carbonate and vitamin D3 tablets by using different types of excipients used. Tablet properties were evaluated by performing various tests. The result of weight variation test was + 0.54% and -1.43%. The weight variation test is alternative to content uniformity test that assure the therapeutic utility. Weight variation test is an also an indicator of variations in the drug content. Standards and specifications have given in Pharmacopoeias that provide permissible limits for weight variation. Result of width and thickness was 6.2 mm respectively. The result of hardness was 10 kg (permissible limit is not less than 4.0 kg) which meet the permissible limit. Friability test indicates the mechanical strength. According to Pharmacopoeia friability for compressed tablet is not more than 1.0%. The result of magnesium and Vitamin D3 tablet was 0.14%. After physical tests the tablets were subjected to chemical tests. Assay, disintegration and tests were carried out for evaluation of chemical properties. Availability of a drug for dissolution and absorption is determined by evaluation of disintegration. The result showed that tablets took 5 minutes to

disintegrate (permissible limit is not more than 15 minutes). Content of Cholicalciferol was determined by HPLC method and the result was 243.4 IU (permissible limit is 180.0 IU -330.0 IU). The Calcium content was assayed by Titrimetric Method and result was 432.07 mg (permissible limit is 450.0 mg -550.0 mg).From the above data it was found that Vitamin D_3 formulation (F_4), the %drug release was found to be 92.47% at 45 mins time.

8. STABILITY STUDIES

Quality guidelines known as ICH guidelines have established a series of guidelines acceptable to multiple countries for the drug approval process. (ICH Guidelines) It is a normal practice to study the stability of pharmaceutical preparations at accelerated conditions of temperature and humidity, the experimental findings which can be transformed into reliable shelf life or expiry date by adopting certain assumptions or criterions (Cannorset al.1979). In comparison to conventional preparations Pharmaceutical product represents number of unique problems when quality and stability are considered. To ensure proper reproducibility, proper control is essential an important part of quality control is to ensure the chemical stability of final product during storage product. Present study is an attempt to study accelerated stability of Vitamin D3 tablet in tablets, these have been prepared using time tested pharmaceutical ingredient in optimum concentration which includes Vitamin D_3 tablet in tablet formulation.

METHODS

The present work on “Accelerated Stability study of Suppliment” was undertaken to standardize and study the stability profile of Vitamin D_3 tablet in tablet formulation. The study was done at accelerated temperature and humidity conditions, i.e. accelerated stability study taking ICH guidelines as reference. The ten tablets were randomly collected. Enough blisters in duplex were kept in humidity chamber at 40^0 ±2^0 c and 70 ± 5% RH humidity. Required blisters were withdrawn after one, two, three and six month in triplicate for analysis. The main ingredient of Vitamin D_3 tablet in table formulation initial sample 1, 2, 3 and 6 month of storage at accelerated conditions of temperature and humidity. For evaluation different parameters were taken that were organoleptic evaluation, identification tests, Average weight test, disintegration test, dissolution test. Samples were tested at the time of their release of batch and after 1st, 2nd, 3rd and 6th month of storage.

Table No 8:1 Results of different parameters used for Accelerated Stability study data of selected Vitamin D3 tablet in tablet formulations subjected to study as per ICH guidelines (3month at 40°C ± 2°C and 75%RH ± 5% RH). At predetermined time intervals of 1, 2, 3 and 6 month.

Days	Formulation	Colour and Odour	pH	Weight variation test	Friability test	Hardness test	Thickness test	Disintegration test (sec)	Assay	Solubility	Dissolution test
0 Day	F -1	No change	6.7	1641	0.96%	No change	4.4%	4.00min	95.82%	No change	Good
	F -2	No change	6.4	1643	1.01%	No change	4.5%	3.45min	96.21%	No change	Good
	F -3	No change	6.8	1642	1.5%	No change	4.5%	4.54min	97.11%	No change	Good
	F -4	No change	6.6	1644	1.5%	No change	4.3%	4.12min	96.01%	No change	Good
	F -5	No change	6.3	1644	0.9%	No change	4.2%	4.34min	95.22%	No change	Good
60 Days	F -1	No change	6.6	1642	1.01%	No change	4.4%	4.00min	94.82%	No change	Good
	F -2	No change	6.0	1645	0.9%	No change	4.6%	3.45min	96.37%	No change	Good
	F -3	No change	6.3	1643	1.5%	No change	4.2%	4.54min	96.23%	No change	Good
	F -4	No change	5.9	1644	0.9%	No change	4.1%	4.12min	94.19%	No change	Good
	F -5	No	6.7	1641	1.01%	No change	4.2%	4.34min	96.23%	No change	Good

		change									
90 Days	F -1	No change	6.5	1645	1.5%	No change	4.4%	4.00min	93.21%	No change	Good
	F -2	No change	5.9	1644	0.9%	No change	4.2%	4.15min	94.7%	No change	Good
	F -3	No change	6.2	1645	1.01%	No change	4.1%	4.24min	96.58%	No change	Good
	F -4	No change	5.9	1643	1.5%	No change	4.3%	5.52min	95.19%	No change	Good
	F -5	No change	6.4	1644	0.9%	No change	4.4%	5.34min	94.34%	No change	Good

No visible physical and chemical changes observed in any one the product during storage period**. Vitamin D^3 tablet in tablet** formulation conducted Color and Odour, pH, Wight variation test, Friability test, Hardness test, Thickness test, Disintegration test (sec), Assay, Solubility, Dissolution test all the product should be stable in the **Accelerated** storage period of 6 month.


Conclusion

9. SUMMARY AND CONCLUTION

The present research work is design and evaluate tablet in tablet of Magnesium and Vitamin D3 tablets (250 mg/1200 IU). Vitamin D is important for bone structure. If there is too little Vitamin D available not enough calcium reaches the blood through the intestinal walls. Magnesium & vitamin D essential for bone synthesis otherwise intensify to Osteoporosis. Mg is also credited with stabilizing functions in bone building. If there is no stabilizing function of Mg during bone synthesis, this also decrease bone density. The term Osteoporosis already indicates a lack of calcium in the bones. Mg & vitamin D rich diet can help to bring calcium back to where it belongs. All the formulations were evaluated for physical characteristics, disintegration, *in vitro* disintegration study and stability. Following conclusions have been made from the present study.

Preformulation studies:

The pre-formulation study carried out that angle of repose, bulk density, tapped density, compressibility, Hausner ratio. The results were clearly shown. Manufacturing process is lengthy but in the formulated product shows greater stability with adding less overages.

Evaluation of Designed Formulations:

Post formulation studies

Physical characterization of all the lubricated blends were carried out and found to have good flow properties. The **physical characteristics** of all the blended formulations were satisfactory.

The tablets prepared with the plain polymer mixture combination were found to have desired limits of hardness and thickness and complies to weight variation and within the official limits of friability. The drug release for formulation F_4 was found to be 91.34% at the end of 45 mins. The prepared tablets were evaluated for Weight variation, Hardness, Friability, Disintegration time, Drug content and The prepared tablets evaluated for **Assay, weight variation, thickness and Disintegration time** were found to be within the official limits. The ***in vitro*** **disintegration studies** were performed for all the **IT and OT formulations.** The in vitro dissolution tests. The results were clearly shown. Accelerated Stability studies were also done for optimized formulation F_4, F_5 and the results were found satisfactory. This research work proven formulation tablet in tablet F_4 of shows good stability compared with other 4 formulation.

Conclusion:

The results Vitamin D3 tablet in tablets of evaluation of different batches were done. The HPLC assy study shows that there was drug content final tablet. The weight variation limited tablets was found maximum up to ± 1.2 % RSD. Hardness was found to be within 3.0 to 4.0 kg/cm2 which limit friability within 0.7% only. The evaluation results of F_4 batches were found to be satisfactory within limit and the **disintegration time (4min).** the same ratio the formulation F_4 gave 92.47% drug release at 45 mins time point. The drug Contents was found to be within limits nd all tablets were passing the dispersion test. Vitamin D3 tablet in tablets of optimized all batch were of satisfactory stability during 3 months of accelerated stability studies.

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Thank you