FORMULATION AND EVALUATION OF METHYLPHENIDATE HYDROCHLORIDE EXTENDED RELEASE CAPSULES-40mg

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register Number: 26111001

UNDER THE GUIDANCE OF

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CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND EVALUATION OF METHYLPHENIDATE HYDROCHLORIDE EXTENDED RELEASE CAPSULES-40mg"** submitted to **THE TAMILNADU DR. M. G. R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree **Master of pharmacy in Pharmaceutics** is a bonafide research work done by **Register Number: 26111001** under my Guidance in the Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-600 097 during the academic year 2012-2013.

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This is to certify that the thesis titled **"FORMULATION AND EVALUATION OF METHYLPHENIDATE HYDROCHLORIDE EXTENDED RELEASE CAPSULES 40mg"** is submitted by **Ms. AGOLLU MONISHA,** Reg.No:**26111001,** Department of Pharmaceutics, **C L BAID METHA COLLEGE OF PHARMACY**, Chennai in partial fulfillment of the requirement for the degree of **M.Pharmacy (Pharmaceutics)** is a bonafied record work carried out by her under my supervision. The contents of this thesis, in full or in parts have not been submitted to any institute or university for the award of any degree or diploma.

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DECLARATION

I hereby declare that the thesis entitled **"FORMULATION AND EVALUATION OF METHYLPHENIDATE HYDROCHLORIDE EXTENDED RELEASE CAPSULE-40mg"** has been originally carried out by me under the supervision and guidance of **Dr. P. THILEK KUMAR M.Pharm.Ph.D.,**(Industrial guide) and **Mr. T. Udaya kumar. M.pharm.,**(Institutional Guide) Asst.Professor,Department of Pharmaceutics, C.L.Baid Metha college of Pharmacy,Chennai-97 during the academic year 2012-2013.

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NOMENCLATURE

%	Percentage
Conc	Concentration
Hr	Hour
Min	Minute
µg/ml	Microgram/millilitre
Sec	Seconds
API	Active pharmaceutical ingredient
g/ml	gram/millilitre

ABBREVIATIONS

ADHD	Attention Deficit Hyper Active Disorder
API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
CNS	Central Nervous System
CR	Controlled release
DSC	Differential Scanning Colorimetry
ER	Extended Release
EC	Ethyl Cellulose
FTIR	Fourier Transformer Infrared Spectroscopy
GIT	Gastro Intestinal Tract
HPMC	Hydroxy Propyl Methyl Cellulose
HPLC	High Performance Liquid Chromatography
HPC	Hydroxy Propyl Cellulose
ICH	International Conference On Harmonisation
IPA	Iso Propyl Alcohol
MC	Methyl Cellulose
MUPS	Multiple Unit Particulate System
MEC	Minimum Effective Concentration
MPH	Methylphenidate
PVP	Poly Vinyl Pyrrolidone
PEG	Poly Ethylene Glycol
SR	Sustained Release
UV	Ultra Violet
USP	United State Pharmacopoeia

LIST OF TABLES

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Last but not the least I wish to express my deepest sense to respect and love to my parents and sisters for their constant support and encouragement throughout.

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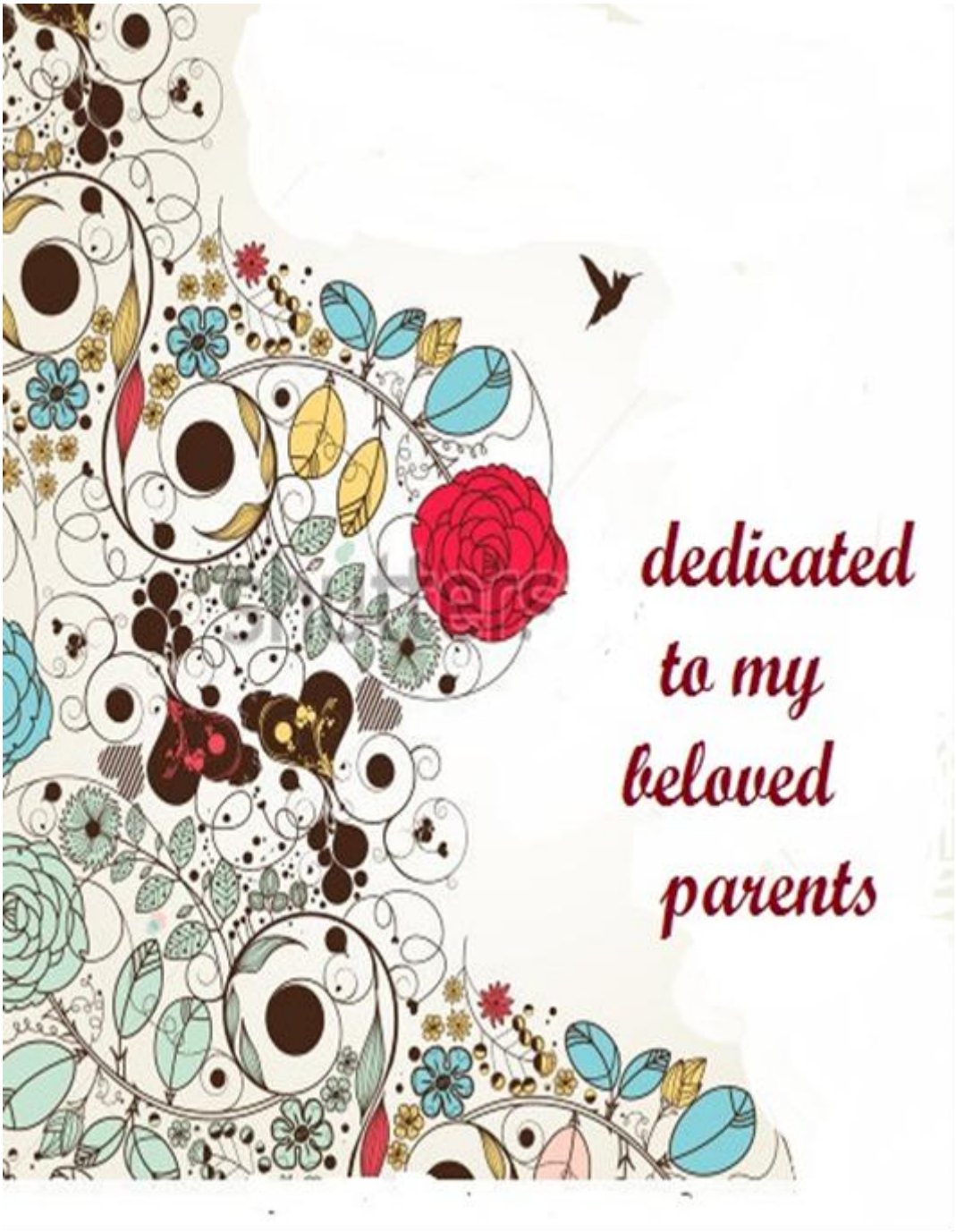
dedicated
to my
beloved
parents

INTRODUCTION

1.1 Drug delivery system

The treatment of acute diseases or chronic illness was achieved by delivery of drugs to patients from many years. These drug delivery systems include tablets, injectables, capsules, suspensions, creams, ointments, liquids and aerosols. Nowadays these drug delivery systems are widely used. The term drug delivery system can be defined as techniques which are used for getting therapeutic agents inside the human body.[1]

An ideal drug delivery system must contain two pre requisites. [2]

1. It deliver the drug at a rate dictated by the needs of the body over the period of treatment.
2. Spatial targeting to specific sites.

These prerequisites provide a need for modified drug release technologies, which can improves the therapeutic efficacy and safety of a drug by particular temporal and spatial placement in the body, thereby decreasing both size and number of doses required.[2]

1.2 Conventional drug delivery

Conventional drug therapy requires periodic doses of therapeutic agents. These systems are formulated to produce maximum stability, activity and bioavailability. For many drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs possess solubility problems. In that cases, a method of continuous administration of drug is required to maintain fixed plasma levels. To overcome these problems, modified drug delivery systems were introduced.

These delivery systems have number of advantages over traditional systems such as improved efficiency, minimum toxicity and improved patient convenience. The main aim of modified drug delivery systems was to improve the effectiveness of drug therapies. [3]

1.3 Modified release dosage forms

Modified release dosage forms can be defined as one for which the release characteristics of time course and location are chosen to accomplish therapeutic or convenience objectives, which were not offered by conventional dosage forms. Mostly, modified release dosags forms were orally administered tablets and capsules. Several types of modified release dosage forms are available.[4]

They include:

1.3.1 Delayed release dosage forms

1.3.2 Extended release dosage forms

1.3.1 Delayed release dosage forms [5]

Delayed-release dosage forms are the systems which were formulated to release the active ingredient after predetermined time at a predetermine location. E.g. when the dosage form reaches the small intestine (enteric-coated dosage forms) or the colon (colon-specific dosage forms).

These delayed release systems are used to protect the drug from degradation in the low pH acidic environment of the stomach or to protect the stomach from irritation by the drug. In these cases drug release should be delayed until the dosage form has reached the small intestine. Often polymers are used to achieve this aim. The dosage form (for example, a tablet or the granules before tableting) can be coated with a suitable polymer. The polymer dissolves as a function of pH, so when the dosage forms travels from the low-pH environment of the stomach to the higher-pH environment of the small intestine, the polymer coat dissolves and the drug can be released.

The two types of delayed release systems are:

1.3.1.a. Intestinal release systems

1.3.1.b. Colonic release systems

1.3.1.a. *Intestinal release systems*

A drug may be enteric coated for intestinal release for several known reasons such as to prevent gastric irritation, prevent destabilization in gastric pH.

1.3.1.b. Colonic release systems

Drugs are poorly absorbed through colon but may be delivered to such a site for two reasons.

a. Local action in the treatment of ulcerative colitis and

b. Systemic absorption of protein and peptide drugs

The most commonly used pharmaceutical delayed release solid oral dosage forms today include tablets, capsules, granules and pellets.

1.3.2 Extended release dosage forms [6]

Extended release dosage forms were designed to achieve a prolonged therapeutic effect by continuously releasing the drug over an extended period of time after administration of a single dose. Extended release dosage form allows at least two fold reduction in dosage frequency as compared to that drug presented in conventional dosage forms.

Ex: controlled release, sustained release.

1.3.2.1. Controlled release drug delivery systems (CRDDS)

More precisely, controlled delivery can be defined as

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4. Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system was usually designed to delivered the drug at particular rate. Safe and effective blood levels were maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release was based on the desired therapeutic concentration and the drug's pharmacokinetics.

1.3.2.2 Sustained release dosage forms

It is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug''. Sustained release technologies can improve the therapeutic efficacy and safety of a drug by precise temporal and spatial placement in the body, thereby reducing both the size and number of doses required. Furthermore, the possibility of repeating successful drugs, coupled with the increasing expense in bringing new drug entities to market, has been instrumental in generating interest in sustained-release dosage forms.

The aim of oral sustained release dosage forms is to achieve a prolonged therapeutic effect by continuously releasing medicament over an extended period of time after administration of a single dose. Sustained release constitutes any dosage form that provides medication over an extended time period. In general, the Sustained release dosage form is to maintain therapeutic blood or tissue level of drug for a prolonged period usually accomplished by attempting slow first order fashion. In recent years sustained release dosage forms continuous to draw attention in the field of research for improved patient compliance and decreased incidence of adverse drug reaction.

The sustained release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug". Once the maximum level is reached, the amount of drug in the body decrease slowly, so it will take longer to drop below the therapeutic range.

The terms sustain or controlled drug release incorporates the element of prolongation of duration of drug action as well as the drug predictability and reproducibility in drug release kinetics. Polymeric sustained

drug delivery systems offer numerous advantages when compared with conventional dosage forms, including improved efficacy, reduced toxicity, and improved patient compliance.

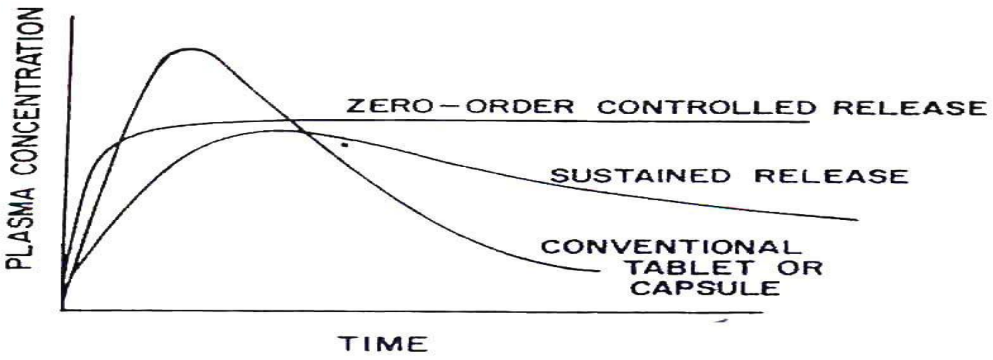

Figure 1: Plasma drug concentration –time profiles

1.3.2.3Advantages of extended release dosage form [7]

- Improved patient compliance and convenience because of less frequent drug administration.
- Reduction in fluctuations in steady state blood levels and therefore, better control of disease condition and reduced intensity of local or systemic side effects.
- For high potency drugs, due to better control of plasma levels increased safety margins can be achieved.
- total amount of dose administered should be reduced through maximum utilization of drug.
- Because of improved therapy, shorter treatment periods, less frequent dosing and reduction in personnel time to dispense, administer and monitor patients health care costs was reduced**.**
- Sustained blood levels; the size and frequency of dosing are determined by the pharmacokinetic and pharmacodynamic

property of drug. The use of extended release products may maintain therapeutic concentration over prolonged period.

- Using of extended release products avoids the high initial blood concentration, which may causes many adverse effect,side effects like nausea, local irritation, haemodynamic changes etc are decreased.

1.3.2.4 Disadvantages of extended release dosage form [8]

- Dose dumping causes toxicity
- Increased cost.
- Unpredictable and often poor *in vitro- in vivo* correlation.
- Upon fast release of total drug (mechanical failure, chewing or masticating, alcohol intake) may causes risks like side effects or toxicity .
- Epithelial lining (lodging of dosage forms) can be damaged due to local irritation.
- Need for additional patient education and counseling.
- Increased potential for first- pass clearance.

1.3.2.5Ideal candidate for Extended/Controlled release drug delivery systems[9-11]

The desired biopharmaceutical characteristics of drugs to be used for the development of per oral controlled release dosage forms are:

Molecular weight	:	< 1000 mg
Solubility	:	0.1 mcg/ml
P^{ka}	:	> 0.1% to 1 % at pH 1 to 7.8
Apparent partition coefficient	**:**	0.5 to 2.0

General absorbability	:	From all GI segment
Stability	:	Stable in GI environment

Release should not be influenced by pH and enzymes.

Less protein binding

To evaluate whether a drug is viable candidate or not for the design of per oral CR formulation, one must consider the following pharmacokinetic parameters of the drug.

Elimination half-life	:	Preferably between 0.5& 8 hours
Total body clearance	:	Should not be dose dependent
Elimination – rate constant	:	Required for the design
Absolute bioavailability	:	Should be 75% or more
Absorption rate	:	Must be greater than release rate

Therapeutic concentration

The lower the c_{ss} and smaller the v_d the lesser was the amount required.

Apparent volume of distribution (V_d)

The larger the apparent volume of distribution v_d and Minimum Effective Concentration (MEC), the larger will be the dose size needed. The maximum dose to be incorporated into a per oral Controlled release (CR) formulations is about 500mg. The smaller the v_d , the easier is incorporation of drug in to dosage form.

1.3.2.6 Candidates unsuitable for Extended-Release Dosage Forms[12]

- Short elimination biological half-life

  E.g. Penicillin G, Furosemide
- Long elimination biological half life (>12hr)

  E.g. Diazepam, Phenytoin
- Narrow therapeutic index

  E.g. Phenobarbital, Digitoxin.
- Not effectively absorbed into the lower intestine.

  E.g. Riboflavin, Ferrous salts.
- Large doses (>1g):

  E.g, Sulphonamides.

1.3.2.7 Controlled Release Formulations [13]

Types of Controlled Release Systems:

Matrix type tablets

- Hydrophobic and hydrophilic matrices.
- Plastic matrices
- Ion exchange resins
- Co-precipitates and solid dispersions.

Film-Coating Tablets

- ❖ Diffusion-controlled membrane
- ❖ Osmotic pumps
- ❖ Floating Tablets
- ❖ Swellable Tablets
- ❖ Mucoadhesive Tablets
- ❖ Complexation
- ❖ Cyclodextrins
- ❖ Pharmaceutical adhesives.

Multiple-Unit Tablets

II Capsules

1.Hard gelatin capsules

2.Soft elastic capsules

3.Floating capsules

III Micro granules/spheroids

IV Beads

V Pellets

VI Emulsions

VII Suspensions

VIII Liposomes

IX Microrparticles

X Nano particles

1.4 Pellets[14,15]

Pharmaceutical pellets were agglomerates of fine powdered particles or bulk drugs and excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm (ideal size for oral administration) obtained from diverse starting materials utilizing different processing techniques and conditions.[14]

1.4.1 Desirable properties of pellets

Uncoated pellets

- Uniform spherical shape and smooth surface
- Optimum size, between 600 and 1000mm
- Improved flow properties.
- High physical strength and integrity
- Good hardness & low friability
- High bulk density
- Ease and superior properties for coating
- Reproducible packing of beds and columns.

Coated pellets

- Maintain all of the above properties
- Contains active ingredient to keep the size of the final dosage form within reasonable limits
- Have desired drug release characteristics.

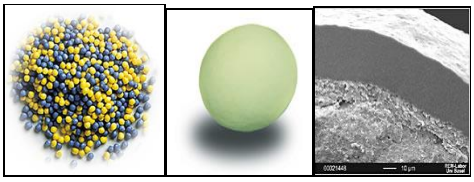

Figure 2: 1. Pellets, 2. Perfect pellet, 3. Coated pellet

Advantages of pellets

- The smooth surface and the uniform size of the pellets allows uniform coating not only in each pellet but also from batch to batch.Controlled release rate can be obtained by coating of pellets with various drugs.
- For immediate release products, large surface area of pellets achieve better distribution.
- Chemically incompatible products can be formulated into pellets and administered in a single dose by encapsulating them.
- The beads or granules of different thickness of coatings are mixed in the desired proportions to give the desired effect.
- The rate of release from the drug or contents depends on thickness of the coated particles.
- Improved appearance of the product and the core was pharmaceutically elegant.
- Pellets can be divided into required dosage strengths without process or formulation changes and also allows the combined delivery of two or more bioactive agents that may or may not be chemically compatible, at the same site or at different sites within the git tract. They will offer high degree of flexibility in the design and development of oral dosage form like suspension, tablet and capsule.
- Small pellets with the mean diameters below 0.5 mm are most suitable for compression into rapidly disintegrating tablets. Such pellets can be produced by direct pelletization methods.

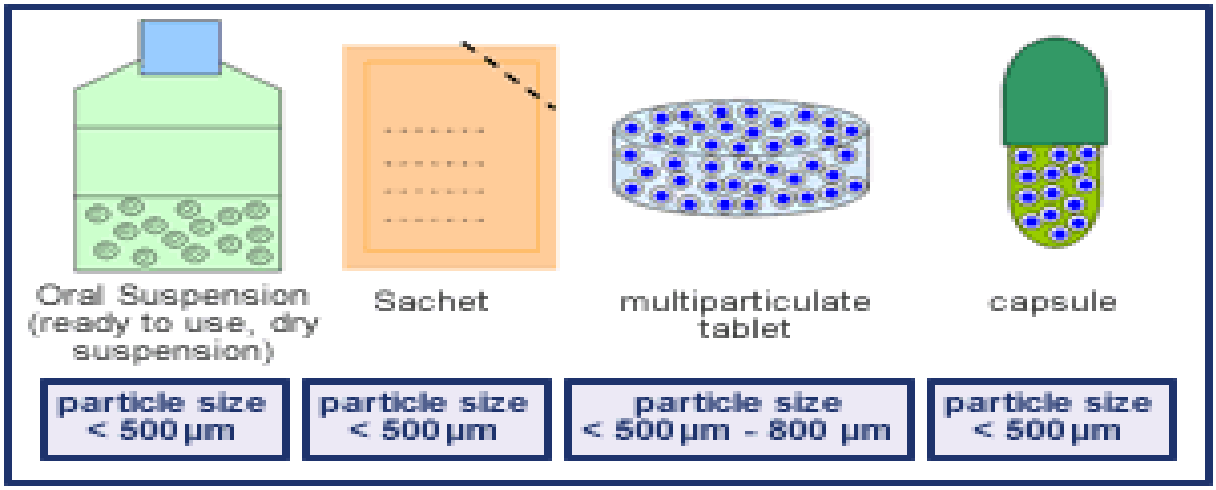

Figure 3: Flexibility of pellets in development of dosage forms

Disadvantages of pellets

- The manufacturing of (MUPS)multiple unit dosage forms was more complicated and expensive.
- The filling of pellets into gelatin capsules was difficult to accomplish, especially in the case where different subunits were involved.

1.4.2 Theory of pellet formation and growth

1.4.2.1 Stages in pellet formation and growth [16,17]

Formation and growth of pellets can be divided into four stages.

- Pendular state
- Funicular state Capillary state
- Droplet state

Pendular state

The initial step in process was the bringing liquid binder into contact with powder particles and attempt to distribute this liquid evenly throughout the fluidized particles. This leads to formation of initial agglomerates and the stage nucleation stage.

When liquid was added in the powder mixture, part of void space in a randomly packed material was filled with a liquid, forming lens-like rings

(Liquid bridges) at the contact points between the particles forming agglomerates. The number of contact points of any particle was a function of the distribution and surface geometry of the adjacent particles.

This state, where the ratio of the liquid to the void volume is low is called pendular state. Mutual attraction of particles was brought about by surface tension of the liquid and the negative suction pressure was generated at the liquid bridges.

Funicular state

Like pendular state, in funicular state also liquid bridges containing gas and pores filled with liquid were present but here the liquid forms a continuous phase and pockets of air were dispersed throughout the agglomerate .

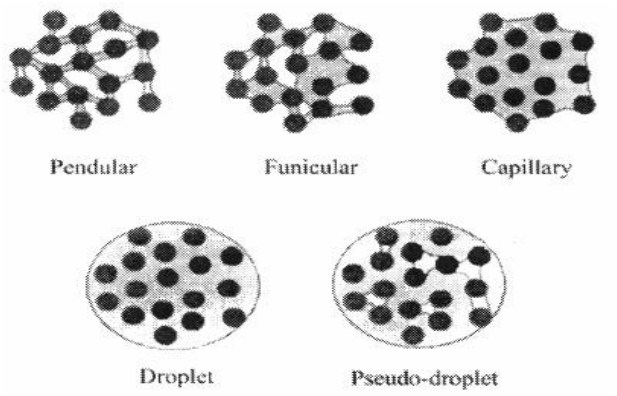

Figure 4: Different formal spatial structures of liquid-bound agglomerates.

Capillary state:

The capillary state was reached when all the void spaces in agglomerate was fully occupied by liquid but the quantity of liquid was not sufficient enough to surround the agglomerate. Capillary pressure and interfacial forces create strong bonds between the particles, which can disappear if the liquid gets evaporated.

Droplet state

In this state, the liquid completely envelopes the agglomerate. The primary particles were held together only by the surface tension of the droplet. There was no interparticle capillary bonding and this situation almost never happens in fluid beds.

1.4.2.2 Elementary Growth Mechanism [18]

The most classified pelletization process involves three consecutive regions nucleation, coalescence and layering, abrasion transfer.

Nucleation

Nucleation occurs whenever a powder is wetted with liquid and presents first stage of the pellets growth. The primary particles accumulate to form three-phase air-water-liquid nuclei and attached together by liquid bridges which are pendular in nature. The size, rate and extent of nuclear formation was influenced by size,viscosity,moisture content,wettability and processing conditions.

Nucleation was followed by a transition phase with two major mechanisms, coalescence and layering.

Coalescence

Coalescence phase was characterized by formation of large-sized particles by random collisions of nuclei containing excess of moisture. Although the number of nuclei was reduced, the total mass of the system remains unchanged during this step.

Layering

This process involves successive addition of fines and fragments on surface of nuclei. The number of nuclei remained to be same but the total mass of nuclei in the system increases due to increasing particle size as a function of time. The fragments and fines formed during the process of particle size reduction due to attrition, breakage and shatter, are picked up by large pellets. Layering continues until the number of favourable collisions decreases rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth was reached.

Abrasion transfer

Which involves the transfer of materials from one granule formed to another without any preference in either direction. Particles will experience a change in size as long as the conditions that lead to the transfer of material exist but not change in the total number or mass of the particles.

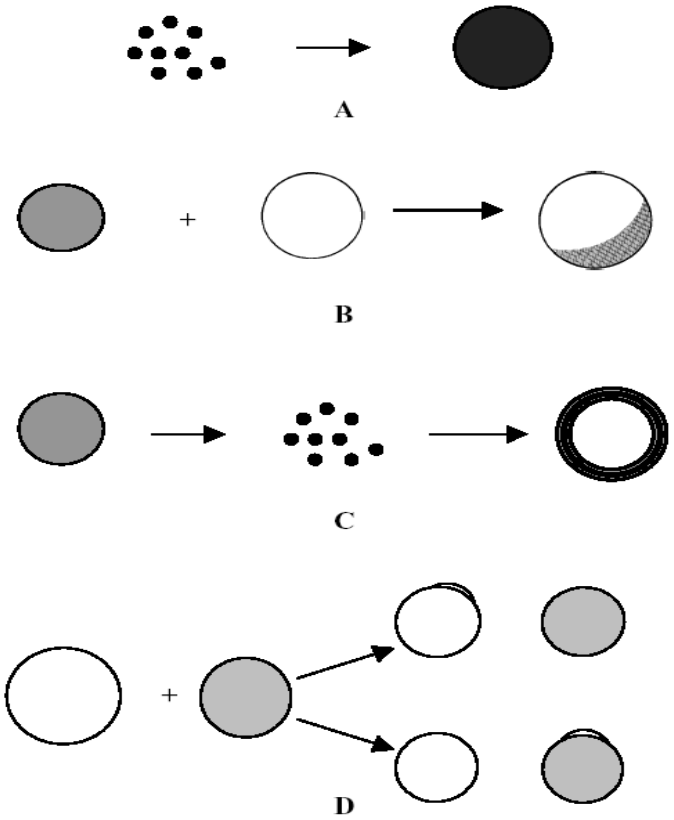

Figure 5: Pellet growth mechanisms. A. Nucleation, B. Coalescence, C. Layering and D. Abrasion transfer

1.4.3 Pelletization techniques

Pelletization was an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets.Release mechanism and release rate from coated pellets depends on film microstructure .This depends on coating technique.There are several manufacturing techniques for production of spherical pellets.[18,19,20]

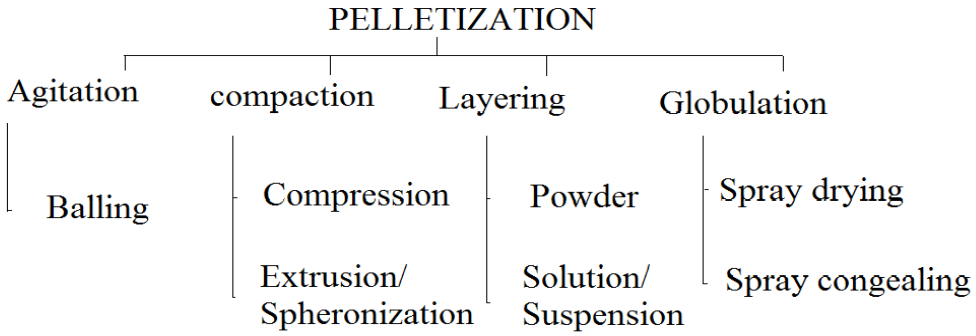

Figure 6: Different pelletization techniques

1.4.3.1 Agitation

Balling

Fine particles are formed upon the addition of appropriate quantities of liquid, to spherical particles by a continuous rolling or tumbling motion. Pans, discs, drums, or mixers were used to produce pellets by the balling.

1.4.3.2 Compaction

a. Compression

Mixtures of API and excipients were compacted under pressure to produce pellets of appropriate shape and size.

b. Extrusion – Spheronization

This was a multistep process invented by Nakahara, in 1964.It involves dry mixing of the API with excipients, granulation of wetted mix, extrusion of the wet mass, transfer of the mass to spheronizer to get spherical shape and drying of the wetted mass in a dryer finally at the end screening of mass to obtain required particle size.

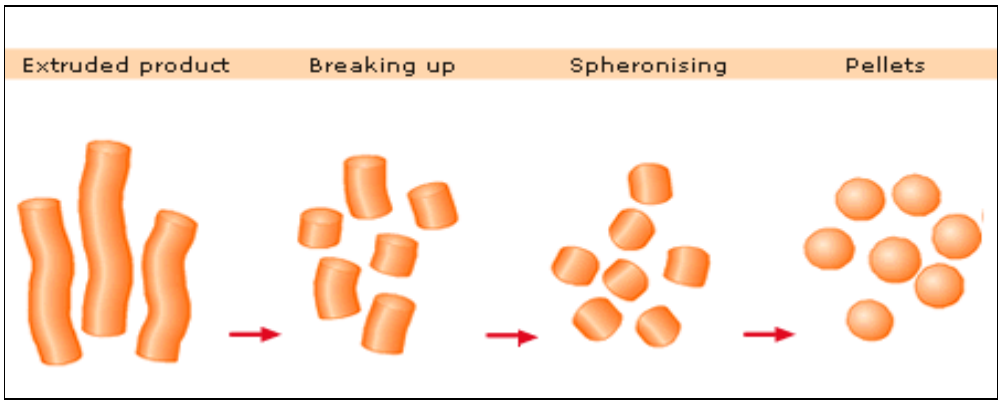

Figure 7: Principle of Extrusion – Spheronization process

1.4.3.3 Layering

In this process, drug was deposited onto seed materials in powder, solution or suspension form and leads to heterogeneous pellets with an inner core region and an outer shell region of a different composition. This process was classified into three types- direct pelletization, solution or suspension layering and powder layering.

a. Direct pelletization

This process leads to formation of homogeneous pellets with microscopically uniform structure.Direct pelletization was mainly performed in high shear mixers and fluidized bed equipment.

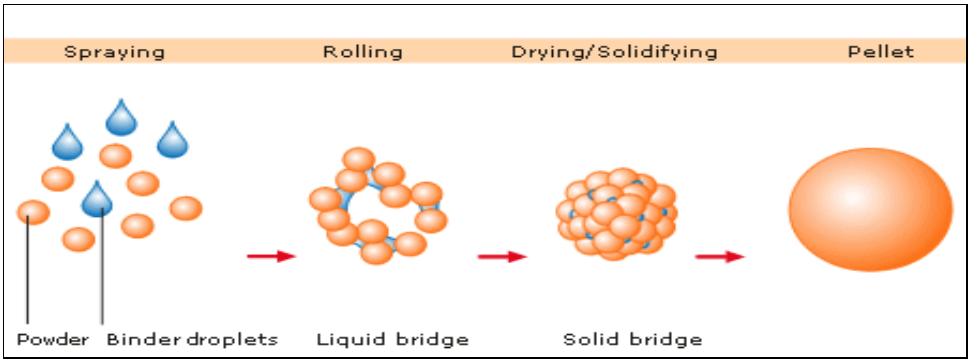

Figure 8: Principle of direct pelletizing process

b. Powder Layering

It involves the deposition of successive layers of dry powder of drug or excipients or both, on previously formed nuclei or cores with the aid of binding liquid . Equipment used was tangential spray/centrifugal/rotary fluidized bed granulator.

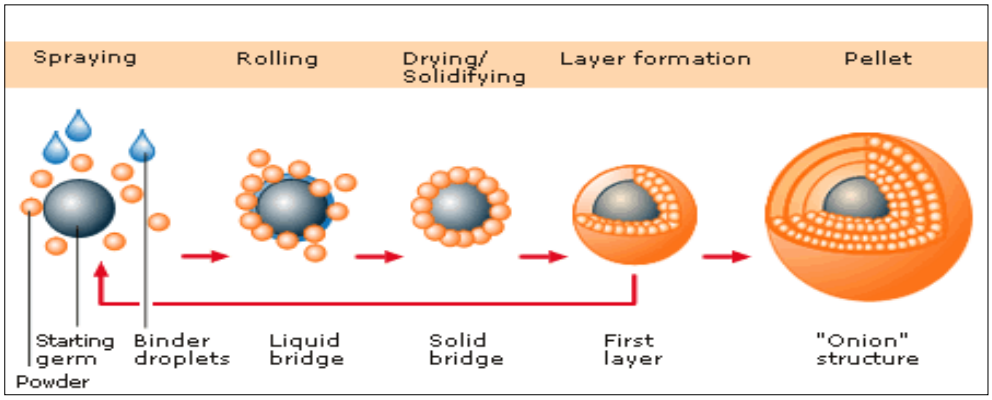

Figure 9: Principle of Powder layering procedure

c. Solution/Suspension layering

In the case of Solution/Suspension layering, growth of pellets involves deposition of successive layers of solution and/or suspension of drug substance and binders on preformed nuclei, which may be inert seed, crystal or granule. The drug was dissolved or suspended in the binding liquid, with or without the binder. Droplets of the binding liquid spread on the surface of the nuclei. Liquid evaporates and the dissolved substances crystallizes out during drying and the formed capillary forces draw the particles towards each other and towards the inert seed, forming solid bridges.

In suspension layering, particles have low solubility and are bonded by solid bridges formed from the hardening binder i.e., that high concentration of binder was needed. In this process fines were produced as a result of attrition or spray drying, especially when the process was not optimized.Starter seeds usually used are sugar spheres containing of a sugar-starch mix or recently MCC pellets and the pure drug crystals were used. The most common configuration used was Wurster, bottom spray coater.

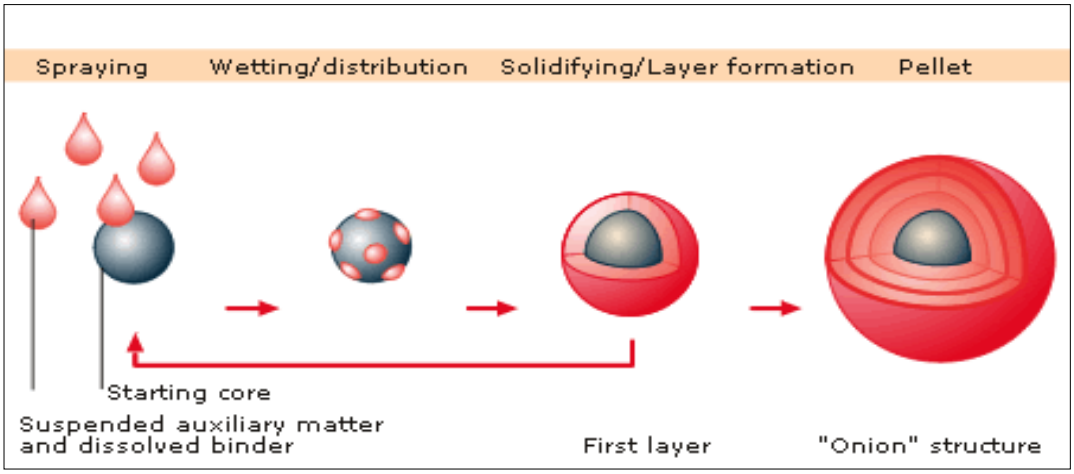

Figure 10: Principle of Solution and Suspension layering process

1.4.3.4Coating equipment

Conventional coating pan

In this technique the granules were placed in the coating pan and the coating solution was sprayed on the granules by atomizer with pressure.

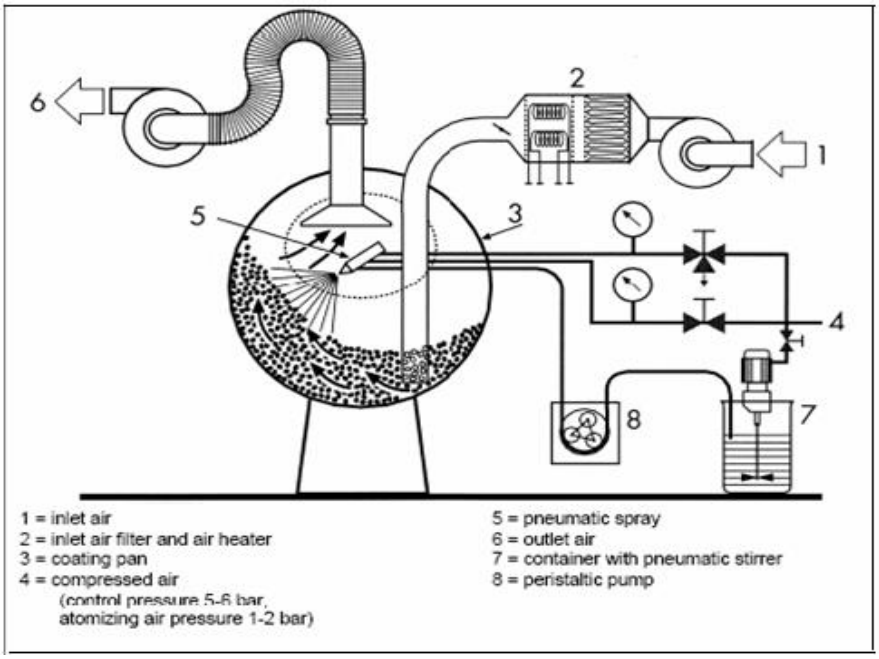

Figure 11: Conventional coating pan

Fluidized Bed Processing

a. Hot air pushes beads into coating column..

b.While moving through the column, beads were sprayed with coating solution.

c.As beads circulate through the bed, the coating solution dries and leaves a layer of solids on the bead.[18]

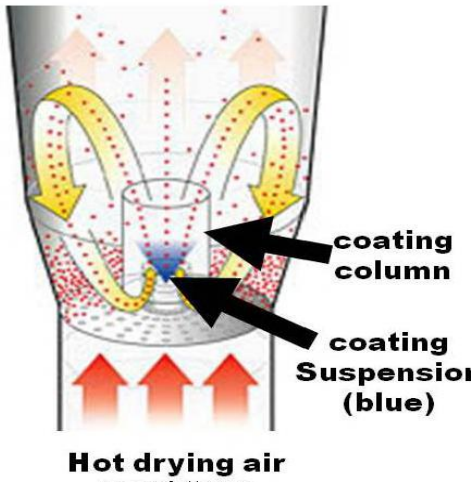

Figure 12: Fluidized bed processing

1.4.3.4 Globulation

Globulation or droplet includes spray drying and spray congealing.

a. Spray drying

Drug particles in solution or in suspension form are sprayed, with or without excipients, into a hot stream of air to generate dry and highly spherical particles. It was generally employed to improve the dissolution rates and bioavailability of poorly soluble drugs.

b. Spray congealing

In this process drug was allowed to melt, disperse, or dissolve in hot melts of gums, waxes, fatty acids, etc., and was sprayed into an air chamber where the temperature was below the melting points of the formulation

components, to provide spherical congealed pellets under appropriate processing conditions.

1.4.4 Pelletization equipment [21]

The production of heterogeneous pellets and particle coating was carried out in top spraying or different types of bottom spraying fluidized bed equipment.

1.4.4.1 Fluidized Bed Processor (FBP)

A fluidized bed system was a unique process for uniform, continuous and coating of granulates, pellets and powders. Aqueous or organic coatings can be applied. Coating and drying takes place in same machine.

Principle of operation

In FBP, particles are fluidized and the coating fluid was sprayed on and dried. Small droplets and a low viscosity of the spray medium ensure an even product coating.

Advantages of fluidized bed processor

- All-in-one process from powder coating to simple drying.
- Unique technology that combines spray behavior with optimum media delivery and easy cleaning.
- Uniform, continuous product coating. Aqueous or organic coatings can be done. Coating and drying take place in same machine. In terms of the coating process and the filling and emptying of the machine can be carried out in complete isolation and without product spreading into the environment.

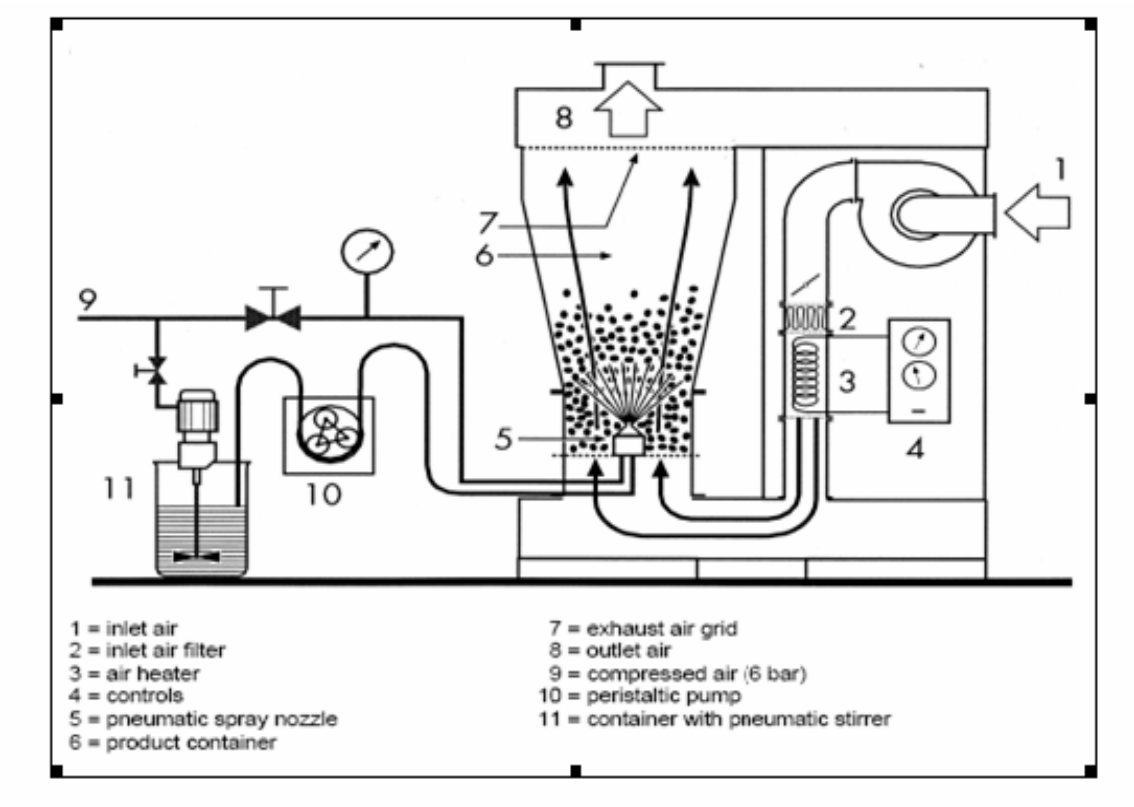

Figure 13: Fluidized bed processor

1.4.4.2 Types of fluid bed systems

- Top spray
- Bottom spray
- Tangential spray

Top spray coating

The binder solution was sprayed into the fluid bed from above against the air flow (counter current) by using nozzle. Air volume was adjusted to have the center of the particle stream very close to the nozzle. Drying takes place as the particles to move upwards in the air flow. It was preferred for taste masking coating , additionally suitable for the application of hot melt coating.

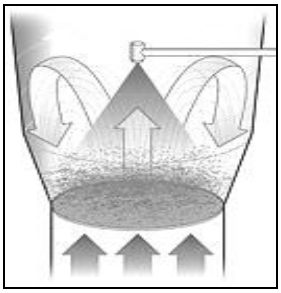

Figure 14: Top spray

Bottom spray coating

The process was suitable for pellet suspension coating or film/sugar coating, particularly useful for a control release active ingredients. In this process, a complete sealing of the surface was achieved with a low usage of coating substance. Convection was created through the strong force from bottom toward top. The granules will fell down and then sucked into the coating column again, while bottom spray gun will spray towards top to achieve coating purpose. As the particles continues moving upwards, pellets were dried and fall outside of the Wurster tube back towards the base plate.Used for application of modified release coatings to a variety of multi particulates and was also suitable for drug layering when the drug dose was in the low to medium range.

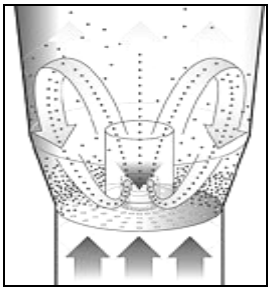

Figure 15: Bottom spray

Tangential spray coating (Rotor pellet coating)

In this process the cores were placed on the turntables and hot air was blown upward between the turntables and the granulation area. The passage of air causes the cores to roll on the turntables. At the same time, the coating solution was sprayed on the rolling cores through the pump and spray gun.

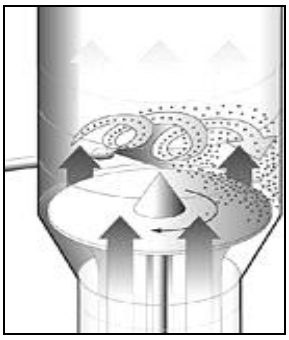

Figure 16: Tangential spray

This process involves simultaneous coating and drying of the cores, layer after layer, till it achieves the required coating thickness or granule size.

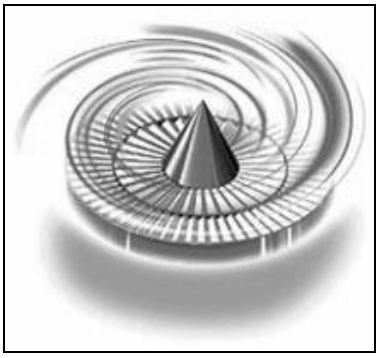

Figure 17: Spin flow of rotation plate in tangential spray coating

1.4.5 Excipients for pellets [18]

Excipients were added to pharmaceutical dosage forms to produce satisfactory delivery of drug to the intended site, to impart favourable characteristics to the dosage form. Since pellets were administered orally, excipients used in the pellets are typically the same as those used in tablet or capsule formulations.

Filler	MCC, Starch, Sucrose, Lactose, Mannitol
Binder	Gelatin, HPC, HPMC, MC, PVP, Sucrose, Starch
Lubricant	Calcium stearate, Glycerin, PEG, Mg stearate
Separating agent	Kaolin, Talc, Silicon dioxide
Disintegrant	Alginates, Croscarmellose sodium
pH adjuster	Citrate, Phosphate, Meglumine
Surfactant	Polysorbate, Sodium lauryl Sulphate
Spheronization enhancer	MCC , Sodium carboxy methyl cellulose
Glidant	Talc, Starch, Magnesium stearate
Release modifier	Ethyl cellulose, Carnauba wax, Shellac

Table 1: Examples of commonly used excipients

1.4.6 Coating of pellets[21,22]

Coating can be applied for the following reasons:

- For masking of the taste, odor or color of drug.
- To provide physical and chemical protection to the drug.
- To control the release characteristics of the drug.
- To protect the drug from gastric environment.
- To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibility or to provide sequential drug release.
- To provide pharmaceutical elegance by using of specific color.

Types of Coating

- Sugar coating
- Film coating
- Enteric coating
- Extended release coating

1.5 Capsules [23]

Capsules are solid dosage forms in which the drug or a mixture of drugs was enclosed in hard or soft gelatin capsules. These shells are made up of gelatin and are intended for oral administration. These are available in various sizes, shapes and capacity.

Advantages of capsules

1.Ease of use because they are smooth, slippery and easy to swallow.

2.Bitter taste and unpleasant odored drugs can be masked by keeping in a capsule.

3.As produced in large quantities it was economic, attractive and available in wide range of colors.

4.Minimum excipients required.

5.Unit dosage form.

Disadvantages of capsules

1. Not suitable for highly soluble materials like potassium chloride, potassium bromide and ammonium chloride, etc.

2.Not suitable in case of highly Efflorescent or Deliquescent materials.

3.Special conditions were required for storage.

1.5.1 Types of capsules

1. Hard gelatin capsules
2. Soft gelatin capsules

1.5.1.1 Hard gelatin capsules

These sizes are designed by in numbers.

S.No	Size of capsules	Volume in ml	Fill weight in mg
1	000	1.37	615-1370
2	00	0.95	430-950
3	0	0.68	305-680
4	1	0.50	225-500
5	2	0.37	165-370
6	3	0.30	135-300
7	4	0.21	95-210
8	5	0.13	60-130

Table 2: Capsules sizes and their fill weights

1.5.1.2 Soft gelatin capsules

These are classified depending upon the sizes and capacities.

The number represents capacities in minims

a. Round-1,2,3,4,,5,6,7,8,9,28,40,40T,80T and 90T.

b. Oval-1,2,3,4,,5,6, 7..5,10,12,16,20,40,60,80,85 and 110.

c. Oblong-3,4,5,6,8,9.5,11,14,16,20,90 and 360.

d. Tube-5,6,8,17.5,30A,30B,35,45,55,65,90,160,250,320 and 480.

e. Misc-6, 17, 30, 35, 60 and 80.

1.5.2 Capsules Standards and limits:

1. Description: It should comply with specifications of product.

2.Content of active ingredient: *Limit:* 90 to110% of label claim or as per In house limit.

3.Uniformity of weight

Average weight of capsules content	Percentage deviations allowed
less than 300mg	10%
300mg or more	7.5%

Table 3: Content uniformity limits

4. Standard length for hard gelatin capsules in mm

Size	Cap	Body
0	10.68-11.68	18.22-19.22
1	9.51-10.51	16.22-17.22
2	8.67-9.67	14.84-15.84
3	7.73-8.73	12.98-13.98
4	6.97-7.97	11.840-12.84

Table 4 :Capsules lock length in mm.

iv. Disintegration test

a. **Hard gelatin capsules:** Disintegration time should not be more than 45 min.

b. **Soft gelatin capsules:** Disintegration time should not be more than 60 min.

c. Enteric capsule: Acidic media –should not disintegrate in 2hrs and in alkaline medium capsules shall disintegrate within 30 min.

6. Microbial limits: Total microbial count, not more than 1000%gram of the capsules shell. One gram of capsules shall be free from E.coli and Salmonella.

7. Loss on drying: Between 12.5% and 16% detrained on 0.3 gram of shell by drying in oven at 105^0C for 4 hrs or to constant weight.

1.5.3 Evaluation tests for capsules [24]

The various evaluation tests for capsulesare as follows.

1. Stability tests

2 .Invariability tests

3. Disintegration test

4. Dissolution test

5. Moisture permeation test

1. Stability tests

Stability tests for capsules are performed to know the integrity of gelatin capsule shell and for determining the shelf life of capsules.

Stability tests include:

A.Shell integrity test

B. Determination of shelf life

A. Shell integrity test:

This test is performed to find out the integrity of capsule shells.

Relative humidity	Temperature	Type of container
80%	Room temperature	Open
-	40^0C	Open
-	40^0C	Tightly closed

Table 5: specifications for shell integrity test.

Method:

The capsules which are to be tested and the standard capsules are placed in one of the above conditions for the two weeks with periodic examination. The gross and the net changes occurring in them are as follows.

i.The standard capsule shells kept at the room temperature and 80% RH become more soft, sticky and swollen.

ii. The test capsules kept under the same conditions undergo the following changes:

- Gross changes include colour fading, discolouration, disintegration, leaking and turning brittle or soft.
- Net changes include loss of volatile ingredients, grooves growing darker and wider and a little change in colour of the shell.

B. Determination of shelf life

Shelf life of packed capsules is determined under normal conditions.

2. Invariability tests

The invariability in the medicaments packed in the capsule shells can be determined by performing the following tests.

a.Weight variation test
b.Content uniformity test

a. Weight variation test

Weight variation test for hard gelatin capsules

- Individually weigh twenty filled capsules and determine their average weight.
- Calculate the weight variation of every capsule against the average weight.
- If the variation exceeds ± 10%, then determine the actual weight of the medicament separately and compare it with the overall average weight.
- If the overall average weight of 2-6 capsules differ by ±10% to ±25%, then repeat the same procedure with 40 more capsules.
- When 60 capsules are taken for test, only six capsules can differ from the overall average weight more than 10%. In no case they should differ more than ±25%.

Weight variation test for soft gelatin capsules

- Individually weigh 10 filled capsules.
- Empty the contents of the capsules by washing with suitable solvents.

- Allow the solvents to evaporate from the contents at room temperature for about half-an- hour. Take necessary steps to prevent the uptake or/ and loss of moisture.
- Net contents are calculated by weighing the empty capsule shell separately.
- Finally, the contents of therapeutically active ingredient are determined from the outcome of the assay directed in the individual monograph in pharmacopeia.

b. Content uniformity test

At first, 10 capsules are assayed individually to determine the percentage purity of the active ingredient. 9 out of these 10 capsules should be within the range of 85-115%.in case 1-3 capsules are outside the standard range, then additional tests are performed on the remaining 20 capsules. The net result of the 30 capsules assayed should prove that atleast 27 capsules are within the desired extremes i.e. between 85 and 115 % and no capsule is beyond the stated range i.e., between 75 and 125%.

3. Disintegration test

Disintegration test is carried out in the disintegration test apparatus. A capsule is placed in every glass tubes is positioned in the beaker containing the required fluid such that all the capsules dip properly. The apparatus is then operated for specified time. The capsule passes the disintegration test when none of the drug particles remain on the mesh/wire screen i.e., the capsule must disintegrate and all the particles must pass through the mesh within the time specified in the monograph. However, the insoluble coating particles or the soft mass without palpable core are exempted.

Note: If one or two capsules do not disintegrate in the specified time, then the test is repeated with 12 more capsules. The net result of 18 capsules tested for disintegration should prove that at least 16 are disintegrated within the specified time.

According to USP, the disintegration time of capsule is 45 min.

4.Dissolution test

The USP has mentioned about seven different apparatus designs for dissolution testing. Among these, apparatus-1 and apparatus-2 are of primary importance.

When one capsule is tested, the amount of dissolved drug in the solution is calculated as a percentage of the amount of dissolves active ingredient (P) specified in the individual monograph.

When more than one capsule are being tested, the dissolution test is carried out through three stages.

Stage 1 T1:

Test six capsules and are accepted if each of them is not less than the monograph specified limit +5% i.e., P+5%.

Stage 2 T2:

If the dosage form fails the T1, then additional six capsules should test. The result is acceptable if the average of the 12 capsules is greater than or equal to P, and none of them is less than P-15%.

Stage 3 T3:

If capsule still fails the test, then additional 12 capsules should test and are accepted if the average of all the 24 is greater than or equal to P, if not more than two are less than P-15% and none of them is less than P-25%.

5. Moisture permeation test

For performing this test, one capsule in the single unit container or the unit dose container is packaged along with the dehydrated pellets, which have the property of changing colour in the presence of moisture. The packaged capsule is then placed for a certain period of time in an atmosphere of known humidity. Any change in the colour of dehydrated pellets reveals the absorption of moisture. The weight of this test capsule is then compared with the weights of

the capsules under test. The difference in weights gives the amount of moisture absorbed.

1.6 Attention deficit hyperactive disorder (ADHD) [25]

The definition of ADHD based on mal adaptively high levels of impulsivity, hyperactivity and inattention. They are all based on observations about how children behave, 'impulsivity' signifies premature and thoughtless actions, 'hyperactivity' a restless and shifting excess of movement, and 'inattention' is a disorganized style preventing sustained effort.

1.6.1 Common problems associated with ADHD

It was very common for the core problems of ADHD in children to present together with other developmental impairments and/or mental health problems. There are many non-specific problems that were observed in ADHD were motor tics, mood swings, unpopularity with peers, clumsiness.

Young and adult people shows some problems,which are self-harm, a predisposition to road traffic accidents, substance misuse, delinquency, anxiety states and academic underachievement, similarly they are not in themselves grounds for the diagnosis and may result either from ADHD or from other causes.

1.6.2 Changes with age

The problems associated with ADHD appear in different ways at different ages, as the individual matures and as the environmental requirements for sustained self-control increase. Hyperactivity in a pre-school child, during the school years an affected child may make excess movements during situations where calm was expected. During adolescence hyperactivity was present as excessive fidgetiness rather than whole body movement. In adult life it may be a sustained inner sense of restlessness and inattention.

1.6.3 Course of the disorder

Onset

The core behaviors of ADHD were typically present from before the age of 7 years, but at all ages presentation as a problem was very variable. Mild forms need not be impairing at all. Extreme forms are considered to be harmful to the individual's development. While both teachers and parents can find it hard to deal with or live with a hyperactive child, their tolerance and ability to cope may determine whether the hyperactivity was presented as a problem. Children with hyperactivity rarely ask for help themselves. Inattention without hyperactivity often was not present as a problem even though an inattentive child may have a marked cognitive impairment. The presentation to the clinician therefore depends on a complex blend of the skills and tolerance of adults surrounding the child and the qualities of the children themselves.

Course and impairment

The core problems of ADHD and the associated features can persist over time and impair development in children. Several studies have followed diagnosed schoolchildren over periods of 4 to 14 years, all have found that they tend to show, by comparison with people of the same age who have not had mental health problems, persistence of hyperactivity and inattention, poor school achievement and a higher rate of disruptive behaviour disorders.

Longitudinal population studies have shown that hyper active impulsive behaviour was a risk for several kinds of adolescent maladjustment . Lack of friends, work and constructive leisure activities were prominent and affect the quality of life. Severe levels of hyperactivity and impulsivity also make children more likely to develop an antisocial adjustment and more likely to show personality dysfunction or substance misuse in later adolescence and adult life. Although ADHD symptoms persist in the majority of cases, it was important to remember that many young people with ADHD will make a good adjustment to adulthood and be free of mental health problems.

1.6.4 Diagnosis

Diagnostic systems and criteria

The most commonly used criteria for the diagnosis of both children and adults are those provided in DSM-IV-TR and in ICD-10.

The DSM criteria break down symptoms into two groups: inattentive and hyperactive-impulsive. Six of the nine symptoms in each section must be present for a 'combined type' diagnosis of ADHD. If there are insufficient symptoms for a combined diagnosis then predominantly inattentive (ADHD-I) and hyperactive (ADHD-H) diagnoses are available. The ICD uses a different nomenclature, the same symptoms were described as part of a group of hyperkinetic disorders of childhood, and inattention, hyperactivity and impulsivity must all be present, so only 'combined-type' ADHD qualifies.

DSM-IV-TR criteria for attention deficit hyperactivity disorder

1. Either A or B.

A. Inattention – Six or more symptoms persisting for at least 6 months to a degree that was maladaptive and inconsistent with developmental level.

- Failure of close attention to details and makes careless mistakes in schoolwork, work, or other activities.
- Lack of attention in tasks or play activities.
- Often should not listen when spoken to directly.
- Often should not follow on instructions; failed to finish schoolwork, chores or workplace duties (not due to oppositional behaviour or failure to understand instructions).
- Difficulty in organising tasks and activities
- Often avoids, dislikes, or was reluctant to do tasks needing sustained mental effort.
- Often loses things necessary for tasks or activities.
- Is often easily distracted by extraneous stimuli.
- Is often forgetful in daily activities.

B. Hyperactivity-impulsivity – 6 or more symptoms persisting for at least 6 months to a degree that was maladaptive and inconsistent with developmental level.

Hyperactivity

- Often fidgets with hands or feet or squirms in seat.
- Often leaves seat in classroom or in other situations where remaining seated was expected.
- Often runs or climbs excessively where inappropriate (feelings of restlessness in young people or adults).
- Often had difficulty in playing or engaging in leisure activities quietly.
- Was often 'on the go' or often acts as if 'driven by a motor'.
- Talks excessively.

Impulsivity

- Often burst out with answers before questions was completed.
- Often had difficulty in awaiting turn.
- Often interrupts or intrudes on others (for example, butts into conversations or games).

2. Some hyperactive-impulsive or inattentive symptoms which causes impairment were present before age 7 years.

3. Some impairment from symptoms was present in two or more settings (for example, at school or work and at home).

4. There must be the clear proof of significant impairment in social, school or work functioning.

5. The symptoms do not happened only during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder. The symptoms were not better accounted for by another mental disorder (for example, mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).

1.7 Psychostimulants [26]

Psychostimulants were the most commonly used medications for the treatment of ADHD in college students and are helpful in greater than 70% of students with ADHD.Nearly an equal percent of students with ADHD can respond to medications in the methylphenidate group or the amphetamine group of drugs. Some persons who can't tolerate or respond well to drugs from 1 group

will respond better when given a medication from the other class of psychostimulants.

Methylphenidate

Methylphenidate (MPH), a Schedule II medication, has been a standard part of ADHD treatment. The mechanism of action of MPH was believed to be its ability to increase the levels of both the norepinephrine and dopamine neurotransmitters by increasing release into the extraneural space and blocking uptake.

Amphetamines

Initially amphitamines were used primarily for the hyperkinetic behavior of minimal brain dysfunction but later they are used to help with the full ADHD spectrum of distractibility, hyperactivity, and impulsivity. As with MPH, amphetamines were believed to have a clinical benefit primarily because they increases the levels of the neurotransmitters dopamine and norepinephrine, block their uptake, and increase their release. Adderall mixture of salts of both d and l amphetamine in 75%:25% ratio was superior to the d enantiomer dextroamphetamine alone. The onset of clinical effects from Adderall assumed to be less abrupt than with Methylphenidate, and the effects were of slightly longer duration. Methamphetamine (Desoxyn) was a psychostimulant approved for the management of ADHD, but it was considered to be less effective behaviorally in ADHD than the d and l- amphetamine preparations. It was also considered to have a higher risk for abuse than the other psychostimulants. It was not recommended for use in the college setting or for other adults.

Bupropion

Bupropion was an antidepressant medication of racemic mixture that was sometimes used for ADHD. It has been approved by the Food drug administration for use as an antidepressant in children, adolescents, and adults, it was not classed as a psychostimulant. Postulated pharmacologic mechanisms of action included was inhibition of the uptake of neurotransmitters serotonin, dopamine, and norepinephrine. The effects may be weaker than those from the psychostimulants.

Literature Review

1.Hara *et al.*,[27](2011) A pharmaceutical patch with superior stability of a drug (methylphenidate), skin permeability of a drug during use of patch, and methylphenidate bioavailability is provided. A patch comprises a support and an adhesive layer formed on at least one surface of the support, wherein the adhesive layer contains methylphenidate and/or a salt thereof, polyisobutylene and a liq.plasticizer. The liq.plasticizer preferably has an HLB value of 1.0-3.3. Thus, a patch was prepared by applying to a polyethylene terephthalate release liner a compound containing methylphenidate blend with an adhesive containing polyisobutylene of two mol.wts (55,000 and 4,00,000) and polybutene as a tackifier, and iso-prpalimitate as a liq.plasticizer.The methylphenidate patch showed good stability even under harsh preservation conditions at 60,high drug permeation rate through human skin, and methylphenidate bioavailability of 66.4%.

2.Abdhul Althaf.s *et al.*,[28](2011) The present study was conducted to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Ambroxol pellets to present it in the form of capsules (Modified release capsules). To achieve this goal various prototype formulation trails were taken and evaluated with respect to the various quality control such as dissolution, assay, acid resistance and moisture content. The active pharmaceutical ingredient Ambroxol was subjected to preformulation study, and the results obtained with selected excipients showed good compatibility with Ambroxol. Ambroxol coated pellets were formulated by using commercially available pellets and Ambroxol coated pellets were filled by capsule filling machine. The stability of the capsules and pellet was determined by conducting "Accelerated stability testing" in 40°C ± 2°C / 75% ± 5%RH, 30ºC ± 2 ºC/ 65% ± 5% RH and 25±2°C/60±5% RH conditions for 1 month. Finally, after the duration, the product was analyzed for content and dissolution study. By the

stability studies, the formulated Ambroxol modified release capsules and pellets proved to be stable throughout the period of the storage.

The Ambroxol modified release pellets were loaded in size 4 capsules. It showed good results in formulation of stable dosage. Modified release pellets have minimum volume in size, greater surface area and more surface of disintegration time for pellets in capsules. Small volumes of pellets enter into the systemic circulation very fast.Moreover no accumulation of drug in the body occurs.

3.Fleshner-Barak *et al.*,[29](2010) The present invention provides a pharmaceutical composition for use in a dosage form for oral administration to a patient. The composition expands upon contact with gastric fluid and promotes retention of the dosage form in the patient's stomach for a prolonged period of time. The dosage forms may be used advantageously in the treatment of Parkinson,s disease with levodopa and hyperactivity and attention deficit disorder with methylphenidate. Thus, tablets containing 10% methylphenidate and Klucel LF,starch,MCC,SSG, and mg.stearate were prepared and coated with a composition containing Et.cellulose,urea,and tri-Et citrate in ethanol. Tablets can adhere to GRDS and burst release of drug takes place.

4.) Kotta Kranthi Kumar *et al.*,[30](2010)In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities. There are so many oral delivery systems in that one of the advance techniques is Pellatization. Indomethacin extended release capsules prepared by pellatization method that the indometahcin is coated on inert sugar spheres by using povidoneK-30 as a binder solutions and Hydroxypropylmethylcellose, Ethyl cellose coating agents used for extended release action. The prepared capsules were evaluated for content uniformity weight variation, in-vitro disintegration time, assay, and in-vitro drug release study. All the formulation exhibited assay, content uniformity with in the range given in USP. Dissolution studies revealed that formulations containing Cross povidone-k 30 2.31gm

coating agent Hydroxypropylmethylcellose, 0.312gm of ethyl cellose 0.216gm Showed 100% of drug release, at the 12th hour. The concentration of coating agents Hydroxtpropylmethycellose and Ethyl cellose had an effect on in-vitro drug release had the same drug release profile when compare with US dissolution parameters, and reference drug release. Thus, the capsules apart from fulfilling all official and other specifications and exhibited higher rate of drug release.

5.Parmindersingh *et al.*,[31](2009) Passive and electrically assisted transport (iontophoresis) of Methylphenidate from aqueous Methylphenidate hydrochloride solutions across excised human skin were studied. Based on in-vitro flux data, the daily dose of 15-40mg Mph delivery can be achieved using current denisity of 0.5mA/cm2 with minimum transport area. Iontophoresis significantly enhanced protonated methylphenidate transport as compared with passive delivery.

6.Russell Schachar *et al.*, [32] (2008) Pharmacodynamics of multilayer release methylphenidate(once per day) with IR methylphenidate(twice per day) or placebo in patients with attention deficit /hyperactivity disorder were compared.MLR MPH showed equivalent improvments in behavioral and cognitive measures and has a duration of effect at least as long as that of IR MPH given twice daily and side effects are reduced with MLR MPH.

7.Robert L. Findling *et al.*, [33] (2008) Efficacious and well-tolerated medications are available for the treatment of attention deficit/hyperactive disorder (ADHD). Stimulants such as Methylphenidate and amphetamines are the most widely used medications approved by the US Food and Drug administration for the treatment of ADHD in children. Many studies have reported the long term efficacy and tolerability of immediate release formulations of MPH. The disadvantage of such formulations include the need for multiple daily dosing and a potential for abuse. An extended release formulation of dexomethylphenidate and mixed

amphetamine salts has been reported to be well tolerated and efficacious. The non stimulant atomoxetine has been well tolerated, although it may not be as effective as stimulants.

8.Kim TW *et al.*, [34] (2007) Studied a drug containing polymeric dispersion was applied onto nonpareil sugar spheres (18/20 mesh) using a fluid-bed spray coater. Eudragit RS30D was selected as the polymeric coating material. Melatonin used as model drug. The release behaviors of the coated sugar spheres were investigated in gastric fluid (pH 1.4) for 2h,and then continuously in intestinal fluid (pH 7.4) for 14h.The release rate of coated sugar spheres decreased with increasing coating levels. The solvent (ethanol) in the coating dispersions significantly decreased the release of the drug due to the good dispersion of the low solubility melatonin in the polymeric films. The polymer (PVP) and drug contents in the coating dispersions did not affect the release rate. The release profiles were drastically changed according to the type and concentration of plasticizers used.

9.Hardy IJ *et al.*, [35] (2007) studied modulation of drug release kinetics from HPMC matrix tablets using PVP. The study presents a simple, cost effective and elegant solution for achieving a range of predictable release profiles from linear to bimodal for a water-soluble drug (Caffeine) form HPMC matrices through the inclusion of PVP. Mechanistic studies using gel rheology,excipient dissolution and near infrared microscopy are presented which shows the modulation of drug release

10.Harris Shoaib M *et al.*, [36] (2006) studied the evaluation of drug release kinetics from Ibuprofen matrix using HPM**C.** Different dissolution models were applied to evaluate drug release mechanism and kinetics. The drug release data fit well to the Higuchi expression. Drug release mechanism as a complex mixture of diffusion, swelling and erosion.

11.Devane *et al.*, [37] (2006) The invention relates to a multiparticulate modified release composition that, upon administration to patient, delivers at least one

active ingredient in a bimodal or multimodal manner. Multiparticulate modified release composition comprised (i) an immediate release component containing Methylphenidate Hydrochloride, Microcrystalline cellulose ,lactose ,povidone and (ii) a modified release matrix containing Methylphenidate Hydrochloride, Microcrystalline cellulose, Eudragit RS and povidone. The bioavailability of Methylphenidate Hydrochloride was evaluated in a human crossover based,fasted healthy volunteers dosed with 20mg Methylphenidate Hydrochloride composition. The plasma profile was equal similar to the control which consisted of two 10mg doses of IR given twice at a 4h interval.

12.W.Brayan Staufer *et al.*, [38] (2005) Studied that, Methylphenidate (MPH), a Schedule II medication, has been a standard part of ADHD treatment for the past four decades. MPH shares common effects and side effects with the other stimulant medications. The mechanism of action of MPH is believed to be its ability to increase the levels of both the norepinephrine and dopamine neurotransmitters by increasing release into the extraneural space and blocking uptake. Clinical effects of immediate release forms of MPH may be noticed within 30 to 40 minutes, and maximum blood levels are reached in 1.5 to 2 hours. Taking this medication with meals delays absorption slightly, which may mitigate some of the side effects. Absorption from the regular tablets is maximized when the medication is taken with a high-fat meal. Most of the drug is metabolized to ritalinic acid and excreted through the kidneys.

13.Cho Sun Hang *et al.*, [39] (2004) The present invention relates to a sustained release drug delivery system composed of a water insoluble polymer, and more particularly, to a sustained release drug delivery system comprising: a crystalline core material; an active ingredient layer which is formed on an outer surface of the crystalline core material and comprises a pharmacologically active ingredient and a water insoluble polymer; and a sustained release layer .

14.M. Dopfner Ph.D. *et al.*, [40] (2004) This investigation was conducted to assess the efficacy and the duration of action of a new extended-release formulation of methylphenidate (MedikinetR retard) as a once-daily treatment for children with

attention-deficit hyperactivity disorder (ADHD). *Meth*od was a randomized,double-blind, crossover multicenter study with three treatment conditions: once-daily extended-release methylphenidate, twice-daily immediate-release methylphenidate and placebo. Once a day extended-release methylphenidate was not different from the same dose of twice daily immediate-release methylphenidate. These data provide support for the benefit of this novel, once-daily methylphenidate preparation in the treatment of ADHD. The longer duration of action of Medikinet Retard has the potential to simplify psychostimulant treatment, thus reducing dose diversion and eliminating the need for in-school administration.

15.Yanfeng Wang *et al*., [41] (2004) Evaluated the in vitro dissolution and in vivo absorption of d,l-threo-methylphenidate (MPH) from a novel bimodal release formulation (Ritalin LA capsule) compared with an immediate-release formulation (Ritalin IR tablet) in healthy volunteers. The bimodal release formulation contains 50% of the dose in the immediate-release (IR) beads and 50% in polymethacrylate-coated, delayed-release (DR) beads. The rate and extent of oral absorption of MPH were evaluated based on the overall Cmax, Tmax and AUC values, as well as the Cmax, Tmax and AUC values for each individual peak of the bimodal plasma concentration-time profile. The in vivo absorption-time profile was also examined by deconvolution. Ritalin LA formulation demonstrated bimodal plasma concentration– time profiles with two peak concentrations observed at 2 and 6 h post dose, mimicking that of Ritalin IR tablets given 4 h apart. Deconvolution results showed that the absorption of MPH was biphasic, with a rapid absorption phase between 0 to 2 h, and a somewhat slower second absorption between 3-6 h, consistent with the in vitro bimodal release characteristics of Ritalin LA formulation.

16.Scott *et al*., [42] (2003) Studied the use of psycho stimulants to treat attention deficit/ hyperactivity disorder has been controversial for a number of reasons. Methylphenidate produces behavioral effects associated with abuse potential as assessed by traditional assays. Neuropharmacologic data suggest that

Methylphenidate has pharmacokinetic properties that reduce its abuse potential as compared with other stimulant drugs of abuse, such as cocaine.

17.Evdokia S. Korakianiti *et al.*, [43] (2000) Studied the optimization of the pelletization process in a fluid bed rotor granulator using experimental design. This study examined the effect of rotor speed, amount of water sprayed, and atomizing air pressure on the geometric mean diameter and geometric standard deviation of pellets produced in a fluid bed rotor granulator using a 2^3 factorial design and an optimization technique. The size of the pellets was found to be dependent on the amount of water added, while an increase in rotor speed decreased their size. Both factors were found to be statistically significant ($P<0.05$). The effect of atomizing air pressure on pellet size was statistically significant.

18.Ranjani V Nellore *et al.*, [44] (1998) Developed model extended-release matrix tablet formulations for Metoprolol tartrate. Different grades of HPMC K4M, K15M, K100M and K100LV were used.Three granulation processes were employed for the preparation of tablets. In vitro drug release testing was performed in pH 6.8 phosphate buffer using USP apparatus type II at 50 rpm. The study results suggested that HPMC K100LV can be used as the hydrophilic matrix polymer and fluid-bed granulation as the process of choice for further evaluation of critical and noncritical.

19.G.M.Clarke *et al.*, [45] (1995) Studied the comparative gastrointestinal transit of pellet systems of varying density. The purpose of this study was to examine the gastrointestinal transit of multiple unit formulations of densities 2.0 and 2.4 g cm^{-3}, comparing both with a control formulation of density 1.5 g cm^{-3}. The result of these studies have indicated that for densities up to 2.4 g cm^{-3} there is no difference in gastrointestinal transit of pellets of size 1.18-1.4 mm to that of a standard control multiple unit formulation of density 1.5 - 1.7 g cm^{-3}.

20.M.F.Saettone *et al.*, [46] *(1995)* Studied the effect of different polymer plasticizer combinations on 'in vitro' release of theophylline from coated pellets. The present investigation evaluated the influence of different plasticizer/polymer combinations on theophylline (TH) release from pellets coated with latex aqueous dispersions of ethyl cellulose (EC) or acrylic polymers (ACR). The plasticizers, present in the coating films in amounts ranging from 8 to 30%, were acetylated monoglycerides (AMG), diethyl phthalate (DEP), dibutyl phthalate (DBP) and dibutyl sebacate (DBS). The release profiles of TH from the coated pellets were influenced by the type and amount of plasticizer and of coating material, and by the ratio polymer-plasticizer. For both types of coating, the drug release rate decreased with increasing plasticizer content. A correlation was found between the permeability coefficients (Pwv) to water vapour of free films, having the same composition as those used for coating, and drug release.

Aim and Objective

Aim of the present investigation was to develop the formulation of Methylphenidate Hydrochloride extended release pellets using pelletisation technique.

The objective of the study was to clarify the effect of different polymers like Ethyl cellulose N-45, PVP k30, PEG6000 and HPMC E5 on dissolution properties of the drug.

The optimized formulation was subjected to evaluation tests and stability studies.

Drug Profile [47,48]

❖ Methylphenidate Hydrochloride

A central nervous system(CNS) stimulant most commonly used in the treatment of attention-deficit disorders in children and for narcolepsy.

Description

White to off-white powder

Synonyms

d-Methylphenidate HCl, Methyl phenidyl acetate, Methylphenidate HCl, Methylphenidate hydrochloride, Methylphenidatum, Methylphenidylacetatehydrochloride, metilfenidat hydrochloride

IUPAC Name

Methyl 2-phenyl-2-(piperidin-2-yl)acetate hydrochloride

Chemical Formula

$C_{14}H_{19}NO_2$.Hcl

Category

CNS stimulant

BCS

class I

Structure:

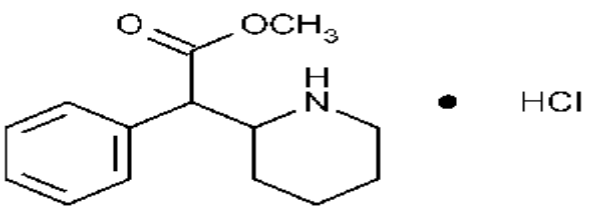

Figure:18 Methylphenidate Hydrochloride

Molecular Weight: 269.77 g/mol

Melting Point: 214-226^{o}C

Solubility:

It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.

Pharmacokinetics

Absorption

Absorbed readily in a biphasic manner. It reaches peak absorption approximately in two hours for the first phase and five hours for the second phase. Bioavailability is low (approximately 30%).

Distribution

Binding to plasma proteins was low (10%-33%). The volume of distribution was 2.65±1.11 L/kg for d-methylphenidate and 1.80±0.91 L/kg for l-methylphenidate.

Metabolism

Methylphenidate was metabolized primarily by de-esterification process in to ritalinic acid (α-phenyl-2-piperidine acetic acid, PPAA), which has little to no pharmacologic activity.Site of metabolism was liver.

Excretion

After absorption, Methylphenidate was mainly excreted as ritalinic acid(a de-esterified product) by urine , 78 to 97% of the dose was excreted in the urine and 1 to 3% in the feces.

Elimination half-life: 2.4 hours in children and 2.1 hours in adults.

Pharmacodynamics

Pharmacology

Methylphenidate was a central nervous system stimulant used most commonly in the treatment of attention-deficit disorders in children and for narcolepsy. Its mechanisms appear to be similar to those of dextro amphetamine.

Mechanism of action

Methylphenidate blocks reuptake of dopamine and norepinephrine in central adrenergic neurons by blocking dopamine transport or carrier proteins. Methylphenidate acts at the brain stem arousal system and the cerebral cortex and causes increased sympathomimetic activity in the central nervous system.It may results in alteration of serotonergic pathways via changes in dopamine transport.

Dosage

5-30 mg twice a day or up to 60mg per day

Toxicity

Symptoms of overdose include Vomiting, Agitation, Tremors, Hyperreflexia, Muscle twitching, Convulsions (may be followed by Coma), Euphoria, Confusion, Hallucinations, Delirium,Diaphoresis, Sweating, Flushing, Headache, Hyperpyrexia, Tachycardia,Alopecia,Loss of appetite, Palpitations, Cardiac arrhythmias, Hypertension, Mydriasis, and Dryness of mucous membranes.

Partition Coefficient

log P =2.25

Dissociation Constant

pka=8.77

Purity: ≥98%.

Therapeutic Class

- Dopamine uptake Inhibitors
- Adrenergic uptake Inhibitors
- Central Nervous System Stimulants

Storage

Store in air tight containers, Protect from sun light and moisture, at a temperature below 40^{o}C.

Indication

For use as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity.

Special Populations

Age

The pharmacokinetics of Methylphenidate was examined in 18 children with ADHD between 7 and 12 years of age. Fifteen of these children were between 10 and 12 years of age. The time until the between peak minimum, and the time until the second peak were delayed and more variable in children compared to adults.

After a 20-mg dose of Methylphenidate, concentrations in children were approximately twice the concentrations observed in 18 to 35 year old adults. This higher exposure was almost completely due to the smaller body size and total volume of distribution in children, as apparent clearance normalized to body weight was independent of age.

Gender

There were no apparent gender differences in the pharmacokinetics between male and female adults when Methylphenidate was administered.

Renal Insufficiency

Renal insufficiency was expected to have minimal effect on the pharmacokinetics of methylphenidate since less than 1% of a radio labeled dose was excreted in the urine as unchanged compound.

Hepatic Insufficiency

Hepatic insufficiency was expected to have minimal effect on the pharmacokinetics of methylphenidate since it was metabolized primarily to ritalinic acid by nonmicrosomal hydrolytic esterases that are widely distributed throughout the body.

Drug-Drug Interactions

Carbamazepine- Carbamazepine may decrease the effect of methylphendiate.

Cyclosporine-Methylphenidate increases the effect and toxicity of cyclosporine

Guanethidine- Methylphenidate may decrease the effect of guanethidine.

Isocarboxazid- Possible hypertensive crisis with this combination.

Phenelzine -Possible hypertensive crisis with this combination .

Precautions*:*

Methylphenidate has high potential for abuse due to its pharmacological similarity to Cocaine and Amphetamines.

Excipients profile

1.Sugar spheres[49]

Nonproprietary names

Sugar Spheres USPNF, EP,BP

Synonyms

Non-pareil, non-pareil seeds, Nu-Core, Nu-Pareil PG, sacchari sphaerae, sugar seeds, Suglets.

Category

Tablet and capsule diluent.

Applications

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained-release formulations.

Description

White free flowing granule

Bulk Density

1.57–1.59 g/cm3 for Suglets less than 500 mm in size,

1.55–1.58 g/cm3 for Suglets more than 500 mm in size.

Loss on Drying: 4%

Solubility

solubility in water varies according to the sucrose-to-starch ratio. The sucrose component was freely soluble in water, whereas the starch component was practically insoluble in cold water.

Stability and storage

Sugar spheres are stable when stored in a well-closed container in a cool, dry place.

2 Poly ethylene glycol- 6000 [50]

Nonproprietary Names

BP: Macrogol

JP: Macrogol 6000

Ph. Eur: Macrogols

USPNF: Polyethylene glycol

Synonyms

Carbowax, Carbowax Sentry, Lipoxol, Lutrol E, PEG, PluriolE, polyoxyethylene glycol.

Chemical Name

a-Hydro-o-hydroxy poly (oxy-1,2-ethanediyl)

Empirical Formula

$HOCH_2$ (CH_2OCH_2)m CH_2OH where "m" represents the average number of oxy ethylene groups.

Functional Category

Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.

Applications

Plasticizer, Tablet Binder, Suspending agent, Emulsifying agent, Suppository base, Disintegrant.Mol wt above 6000 can be used as Lubricants.

Solubility

Soluble in acetone, dichloromethane, ethanol (95%), and methanol. They are slightly soluble in aliphatic hydrocarbons and ether.

Description

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free flowing milled powders.

Density

1.15–1.21 g/cm3 at 25^0C

Stability and Storage Conditions

Polyethylene glycols are chemically stable in air and in solution, Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

Incompatibilities

Incompatible with some coloring agents.

Safety

Polyethylene glycols were widely used in a variety of pharmaceutical formulations. Generally, they are regarded as nontoxic and nonirritant materials.

PEG 6000 was a solid grade. It is used as plasticizer. When it was used along with coating material it avoids rupture of film. Hence PEG 6000 was selected as plasticizer.

3.Poly vinyl pyrrolidone (PVP K30)[51]

Nonproprietary Names BP : Povidone

JP : Povidone

Ph Eur: Povidone

USP : Povidone

Synonyms

E1201, Kollidon, Plasdone, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], poly vidone, polyvinyl pyrrolidone, PVP, 1-vinyl-2-pyrrolidinone polymer.

Chemical Name

1-Ethenyl-2-pyrrolidinone homo polymer

Empirical formula

$(C_6H_9NO)_n$

Molecular Weight: 50 000

Structural formula:

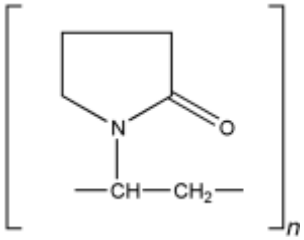

Figure:19 Structural Formula of PVP K30

Category:

Disintegrant, dissolution enhancer, suspending agent, tablet binder.

Description:

Occurs as a fine, white to creamy-white colored, odorless or almost odorless, spheres.

pH:

3.0–7.0 (5% w/v aqueous solution).

Density (bulk):

0.29–0.39 g/cm^3

Density (tapped):

0.39–0.54 g/cm^3

Density (true):

1.180 g/cm^3

Melting point:

150^{0}C.

Applications:

Use	Concentration (%)
Carrier for drugs	10-25%
Carrier for drugs	Up to 5%
Dispersing agent	Up to 5%
Eye drops	2–10%
Suspending agent	Up to 5%
Tablet binder, Tablet Diluent, or Coating agent	0.5-5%

Table:6 Applications of PVP K30

Solubility:

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water, practically insoluble in ether, hydrocarbons, and mineral oil.

Stability and storage:

Darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It should be stored in an airtight container in a cool, dry place.

Incompatibilities:

Compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

4.Ethyl cellulose N-45[52]

Nonproprietary Names:

BP: Ethylcellulose

PhEur: Ethylcellulose

USP-NF: Ethylcellulose

Synonyms:

Aquacoat ECD, Aqualon, Ashacel, E462, Ethocel, ethylcellulosum, Surelease.

Chemical Name:

Cellulose ethyl ether

Empirical Formula:

$C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)n$ $C_{12}H_{23}O_5$

Molecular Weight:

n can vary to provide a wide variety of molecular weights.

Solution viscosity:

EC N-45 :41 to 49

Structural formula:

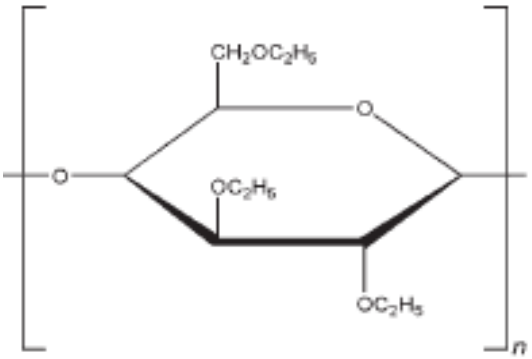

Figure :20 Structural Formula of Ethyl Cellulose

Category:

Coating agent, Flavoring agent, Tablet Binder, Tablet Filler, Viscosity increasing agent.

Applications:

Table:7 Applications of Ethyl Cellulose

Use	Concentration (%)
Microencapsulation	10.0–20.0
Controlled-release tablet coating	2.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

Description:

Ethyl cellulose was a tasteless, free-flowing, white to light tan-colored powder.

Density (bulk):

0.4 g/cm3

Solubility:

Ethyl cellulose was practically insoluble in glycerin, propylene glycol, and water.Ethyl cellulose that contains less than 46.5% of ethoxyl groups was freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethyl cellulose that contains not less than 46.5% of ethoxyl groups was freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Stability and storage:

Ethyl cellulose was a stable, slightly hygroscopic material. Ethyl cellulose was subjected to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. Ethyl cellulose should be stored at a temperature not exceeding 328C (908F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Ethyl cellulose was used as modified release polymer. It acts as matrix and retards drug release from the dosageform. Drug release mechanisam was modified when Ethyl Cellulose was used. 2.0-20% of ethyl cellulose can use as

controlled release polymer. Hence Ethyl Cellulose was selected as controlled release polymer.

*5.*Isopropyl alcohol[53]

Synonyms

Diethyl cardinal, IPA, isopropanol, petrohol 2-propanol.

Empirical formula

C_3H_8O

Molecular weight

60.1

Description

It was a clear color less, mobile, volatile, flamable, liquid with a characteristic spirituous odour resembling that of a mixture of ethanol and acetone; it has a slight bitter taste.

Functional categories

Disinfectant, solvent.

Solubility

Miscible with benzene, chloroform, ethanol (95%), ether, and water.

Melting point

88.5 ^{o}C.

Flash point

11.7 ^{o}C (closed cup),10 ^{o}C (open cup).

Moisture content

0.1-13%w/w commercial grades-13%w/w.

Stability and storage conditions

Stored in well-closed container in a cool and dry place.

Applications

Used in lotions, used as a solvent both for tablet film coating and granulation. Topical disinfectant.

6. Anhydrous sodium acetate[54]

Nonproprietary Names

BP: Sodium Acetate Trihydrate
JP: Sodium Acetate Hydrate
PhEur: Sodium Acetate Trihydrates
USP: Sodium Acetate

Synonyms

Acetic acid, sodium salt, E262, natrii acetas trihydricus, sodium ethanoate.

Chemical Name

Sodium acetate anhydrous

Empirical Formula

$C_2H_3NaO_2$

Molecular Weight

82.0

Category

Antimicrobial preservative, buffering agent, flavoring agent, stabilizing agent.

Applications

Sodium acetate is used as part of a buffer system when combined with acetic acid in various intramuscular, intravenous, topical, ophthalmic, nasal, oral, otic, and subcutaneous formulations.

Stability and Storage Conditions

Sodium acetate should be stored in airtight containers.

Incompatibilities

Sodium acetate reacts with acidic and basic components. It will react violently with fluorine, potassium nitrate, and diketone.

7. Acetic acid [55]

Nonproprietary Names

BP: Glacial Acetic Acid

JP: Glacial Acetic Acid

PhEur: Acetic Acid, Glacial

USP: Glacial Acetic Acid

Synonyms

Acidum aceticum glaciale, E260, ethanoic acid, ethylic acid, methane carboxylic acid, vinegar acid.

Chemical Name

Ethanolic acid

Empirical Formula

$C_2H_4O_2$

Molecular Weight

60.05

Functional Category

Acidifying agent.

Applications

Glacial and diluted acetic acid solutions are widely used as acidifying agents in a variety of pharmaceutical formulations and food preparations. Acetic acid is used in pharmaceutical products as a buffer system

when combined with an acetate salt such as sodium acetate. Acetic acid is also claimed to have some Antibacterial and Antifungal properties.

Description

Glacial acetic acid occurs as a crystalline mass or a clear, colorless volatile solution with a pungent odor.

Solubility

Miscible with ethanol, ether, glycerin, water, and other fixed and volatile oils.

Stability and Storage Conditions

Acetic acid should be stored in an airtight container in a cool, dry place.

Incompatibilities

Acetic acid reacts with alkaline substances.

8.Talc[56]

Nonproprietary Name

BP-Purified Talc

JP-Talc

PhEur-Talc

USP-Talc

Synonyms

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; MagsilOsmanthus; Magsil Star; powdered talc;purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name

Talc

Empirical Formula

$Mg_6(Si_2O_5)_4(OH)_4$.

Functional Category

Anti caking agent; Glidant; Tablet and Capsule Diluent; Tablet and Capsule Lubricant.

Applications in Pharmaceutical Formulation or Technology :

Talc was once widely used in oral solid dosage formulations as a Lubricant and Diluent, although today it was less commonly used. Talc was also used as a Lubricant in tablet formulations in a Novel powder coating for Extended-Release pellets;and as an adsorbant.

Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder.

Moisture content

Talc absorbs insignificant amounts of water at 258^0C and relative humidities up to about 90%.

Storage Conditions

Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Incompatible with quaternary ammonium compounds.

9.Hypromellose[57]

Nonproprietary Names

BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

Synonyms

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

Chemical Name

Cellulose hydroxypropyl methyl ether

Molecular Weight

10 000–1 500 000

Functional Category

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsion stabilizer; extended-release agent; film-forming agent; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

Applications in Pharmaceutical Formulation

Hypromellose is widely used in Oral, Ophthalmic, Nasal and Topical pharmaceutical formulations.In oral products, Hypromellose is primarily used as a Tablet Binder(1) in Film-coating(2–7) and as a matrix for use in Extended Release tablet formulations(8–12) Concentrations between 2% and 5% w/w may be used as a Binder in either Wet- or Dry-granulation processes.

Description:

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

Stability and Storage Conditions:

Hypromellose powder is a stable material, although it is hygroscopic after drying. should be stored in a well-closed container, in a cool, dry place.

Incompatibilities:

Hypromellose is incompatible with some oxidizing agents.

Plan of the Work

The plan of study of the work is as follows.

- Collection of Literature review.
- Preformulation study of drug and excipients.
- Compatibility study of drug with excipients.
- Formulation setup.
- Formulation of Controlled release Methylphenidate Hydrochloride pellets.
- Filling of drug pellets into capsules No.1
- Evaluation tests

Evaluation tests for drug loaded pellets:

  - Physical Description
  - Sieve Analysis
  - Bulk Density
  - Moisture content
  - Compressibility Index
  - Hausner ratio

Evaluation tests for capsules containing pellets:

  - Weight variation test
  - Content uniformity
  - Lock length
  - *In-Vitro* drug release profile

- Stability studies.

MATERIALS AND METHODS

4.1List of Materials:

INGREDIENTS	MANUFACTURER
Methylphenidate Hydrochloride	Sun Pharma,Mumbai.
Sugar Spheres(#20-#25)	Arun Pharma,Cambodia.
Ethyl Cellulose N-45	Colorcon,North America.
PVP k30	ISP Pharma,California.
PEG6000	Clarient,Columbia.
HPMC E5	Shin-Etsu,Japan.
Talc	Luzenac pharma,Europe.
IPA	Rf Cl Ltd,New Delhi.
Purified water	RA Chem,Hyderabad.

Table 8: List of Materials

4.2List of eqiupments:

EQUIPMENT	MANUFACTURER
Weighing balance	Sartorius (LA120S, TE 2145),Bangalore.
Weighing balance	Essae DS-852,Bangalore.
Mechanical stirrer	REMI Electrotechnik RQ1291D,Mumbai.
Tapped density apparatus	Electro lab (ETD-1020),Mumbai.
Fluidised Bed Processor	Pharmatech UFBM-3,Maharashtra.
Dissolution test system	Electrolab ED2AL,Mumbai.
UV Spectrophotometer	Shimadzu UV2450,Singapore.
pH meter	Eutech Cyberscan-100,USA.
Automatic capsule filling machine	Rimek formulations,Gujarat.
HPLC	Shimadzu LC-2010C,Singapore.
FTIR	Shimadzu,Singapore.

Table 9: List of equipments

4.3. Methodology

4.3.1. Preformulation studies [58]

Preformulation study 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 form.

Objective and Scope

The overall objective of Preformulation study is to generate information useful to the formulation development for a stable and bioavailable dosage forms.

The use of Preformulation parameters is to maximize the chances in formulating an acceptable, safe, efficient and stable product.[59]

Characterization of Methylphenidate Hydrochloride

Physical Appearance

The appearance of the API is done by visual observation. Results of physical appearance are mentioned in 5.1.1.[60]

DSC study[61]

The study of phase transitions between the various solid states is important to the pharmaceutical and other industries.Measurements using DSC have become a popular way of studying the thermal reactions of solids. Differential scanning calorimetry (DSC) monitors heat effects associated with phase transitions and chemical reactions as a function of temperature and is a very informative method in physical characterization of a compound. In DSC, the difference in heat flow to the sample and a reference at the same temperature, is recorded as a function of temperature. The reference is an inert material such as alumina, or just an empty aluminum pan. The temperature of both the sample and reference are increased at a constant rate. Since the DSC is at constant pressure, heat flow is equivalent to enthalpy changes:

$$(dq/dt)p = dH/dt$$

Here dH/dt is the heat flow measured in mcal sec. The heat flow difference between the sample and the reference is:

$$\Delta dH/dt = (dH/dt)sample - (dH/dt)reference$$

The endothermic transition upon heating from a crystalline solid to the liquid state. This process is also called fusion. The enthalpy of melting is the heat energy required for melting, i.e. for breaking down the crystalline lattice. This is calculated by integrating the area of the DSC peak on a time basis. A sharp well defined melting peak corresponds to at well-defined crystal structure. Changes in melting temperature and energy gives information about, for instance, content of amorphous material. Thus, the melting endotherm can be used for determination of purity of the sample.The DSC study of Methylphenidate Hydrochloride was carried out for the determination of melting point.Results was mentioned in Fig:21

Solubility studies [62]

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently the therapeutic efficacy of the pharmaceutical product. The solubility of a material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period until equilibrium is achieved. Results of solubility studies are mentioned in 5.1.1.

4.3.2 Physical drug excipients compatibility studies [63]

Compatibility studies were carried out to study the possible interactions between Methylphenidate Hydrochloride and other inactive ingredients.

Procedure:

The compatibility studies were carried out by taking a mixture of drug and excipients. A part of mixture can be exposed to different storage conditions like 40^{o}C±2^{o}C / 75% RH ±5% and control samples were to be kept at 2-8 ^{o}C. They were tested with respect to their physical and chemical aspects. These samples were collected at regular intervals and subjected to FT-IR. Results of drug and excipients compatibility studies are mentioned in Table 12.

S.No.	Storage Condition	Samples packed in	Sampling Periods in Months
1	Accelerated 40 ^{o}C±2 ^{o}C /75% RH ±5%	3 Double polythene bags	1M,2M,3M
2	Refrigeration 2-8^{o}C	1 Double polythene bag + 1 glass vessel	1M,2M,3M

Table :10 Conditions for compatibility studies

4.3.3. Analytical Method Development

a. Calibration curve of Methylphenidate Hydrochloride in pH 0.01N HCl acetate buffer

The analytical method development for Methylphenidate hydrochloride was performed for the determination of absorption maxima of the drug and quantification of pellets prior proceeding for the experiment. Methylphenidate hydrochloride is scanned in the respective medium of pH 0.01N acetate buffer for its absorption maxima and was found that Methylphenidate hydrochloride exhibited maximum absorption at 210.0 nm.

- 100mg of Methylphenidate hydrochloride was added to 100ml of 0.01N pH acetate buffer.
- 10 ml was taken from the above solution and diluted to 100ml with the same pH 1.2 (0.01N HCl) acetate buffer. This is referred as primary stock solution.
- From the primary stock solution, serial dilutions wre performed to give a concentrations of 10, 20, 40, 60,80,100mcg/ml.
- Solutions were analysed by UV-Spectrophotometer at a λ max of 210nm.
- The absorbances of respective solutions were determined at 210 nm against (0.01N Hcl) buffer as the blank. The experiment was repeated six times in the same medium and a calibration curve was determined from the mean value. From this data, the standard curve of Methylphenidate was obtained by plotting absorbance on Y-axis against concentration on X-axis. Results of standard graph are mentioned in Table 13& Fig 28.

b. Calibration Curve of Methylphenidate Hydrochloride in 6.8 pH Phosphate Buffer

- 100mg of Methylphenidate hydrochloride was added to 100ml of 6.8pH phosphate buffer.
- 10 ml was taken from the above solution and diluted to 100ml with the same phosphate buffer. This was referred as primary stock solution.
- From the primary stock solution, serial dilutions were performed to give a concentrations of 10, 20, 40,60,80,100 mcg/ml
- Solutions were analysed by UV-Spectrophotometer at a λ max of 210nm.
- The absorbances of respective solutions were determined at 210 nm against 6.8pH buffer as the blank. The experiment was repeated six times in the same medium and a calibration curve was determined from the mean value. From this data, the standard curve of Methylphenidate was obtained by plotting absorbance on Y-axis against concentration on X-axis. Results of standard graph are mentioned in Table 14 & Fig 29.

4.3.4 Method of manufacture

Fluidized bed process:

Raw material dispensing

Accurately weighed quantities of raw materials and measured quantities of solvents were dispensed and transferred to manufacturing area.

Drug solution preparation

- PEG 6000 was dissolved in specific amount of water under stirred conditions. To this solution, PVP K30 was added and stirred under same conditions until a clear solution was obtained. Then Methylphenidate Hydrochloride was added under same stirred conditions until get a clear solution.

Drug Loading

- Weighed quantity of sugar spheres were loaded onto FBP, and drug solution was coated onto sugar spheres.

Coating Solution Preparation

- Solution-1:Ethyl Cellulose N-45 was dissolved in specific quantity of IPA under stirred conditions.
- Solution-2:PEG6000 and HPMC E5 was dissolved in specific quantity of water under stirred conditions.
- Now the solution-2 was added to EC solution under stirring and was continued until a clear solution was obtained. Finally talc was added and stirred.

Controlled Release Coating

- The dried pellets were loaded onto FBP and coated with controlled release coating solution.

Capsule Filling

- The weight of pellets equivalent to 381mg Methylphenidate Hydrochloride were filled into hard gelatin capsules of size.1 by capsule filling machine.

Process Control Parameters

Spray Gun:	Umang
Spray Type:	Bottom spray
Spray Rate:	5ml/min
Spray Pump RPM:	1-3 RPM
Inlet Temperature:	50 °C
Bed Temperature:	47 °C
Outlet Temperature:	38 °C
Air Pressure:	0.7 Kg/cm^2

4.3.5 Formulation development

S.No.	Ingredients	Quantity(%w/w)							
		F 1	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 7**
1	Sugar Spheres(#20-#25)	83.85	83.47	83.1	82.8	82.9	82.33	82.86	82.86
2	Methylphenidate Hydrochloride	10.5	10.5	10.5	10.5	10.5	10.5	10.5	10.5
3	PVP K30	3	3	3	3	3	3	3	3
4	PEG 6000	0.5	0.6	0.7	0.8	0.8	0.8	0.5	0.5
5	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Controlled release coating									
6	Ethyl cellulose N-45	1.5	1.75	2.0	2.0	2.0	2.5	2.3	2.3
7	HPMC E5	0	0	0	0.2	0.1	0.125	0.115	0.115
8	PEG 6000	0.15	0.175	0.2	0.20	0.2	0.25	0.23	0.23
9	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
10	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
11	Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table:11 Comparison of Trial Batches

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4.3.6 Evaluation of pellets[64]

Evaluation tests for drug loaded pellets:

a.Physical Description

b.Sieve Analysis

c.Bulk Density and Tap density

d.Moisture content

e.Compressibility Index

f.Hausner ratio

Evaluation tests for capsules containing pellets:

a. Weight variation test
b. Content uniformity

c. Lock length

d. In-Vitro drug release profile

Evaluation tests for Drug Loaded Methylphenidate pellets:

a.Physical description:

0.5g of pellets were transferred into a dry Petri dish or dispensed on a white card. Observed the content visually. Results of physical description are mentioned in page 92.

b. Sieve analysis:

The particle size of the pellets after drug loading was evaluated by mechanical sieving using a series of sieves with aperture size 1, 0.85, 0.71, 0.60mm. A sample load of 100g was placed on the sieve and shaken by mechanical shaker. The weight of pellets retained on each sieve were determined and mean particle size have been determined. Results of sieve analysis are mentioned in page 92.

c. Bulk density and Tap density:

Bulk density was determined by USP method-I. 20g of pellets was taken and poured into a measuring cylinder. Bulk volume of pellets was noted.

Bulk density= Mass of pellets/ Bulk Volume.

Tap Density is determined with tap density tester, by placing a graduated cylinder containing a known mass of pellets in it, which is then operated for a fixed number of taps (500). Results of Bulk density and Tap density are mentioned in Table 15.

Tapped density= Mass of pellets/ Tapped Volume.

d. Water content by KF Titration:

30ml of methanol was taken in a clean, dried Karl Fischer titration flask and titrated with KF reagent until the end point to neutralize the free water. Methylphenidate pellets were powderd finely. Accurately weighed quantity of 0.5gm of sample is transferred to the titration flask and dissolved by stirring and titrate with KF reagent to the end point and percentage water content was calculated by following formula. Results of water content are mentioned in Table 16.

% Water Content = V×F×100/W×100

Where,

V = Volume of KF reagent consumed by sample

F = Factor for KF reagent

W = Weight of sample in grams.

e. Compressibility index :

It is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the flow able it is. A material having values of less than 20-30% is defined as the free flowing material.

CI=TBD-LBD/TBDx100

Where

TBD=Tapped bulk density LBD=Loose bulk density.

f. Hausner's ratio:

It indicates the flow properties of powder and is measured by the ratio of tapped density to bulk density. Results of Hausner's ratio are mentioned in table 15.

Hausner's ratio=Tapped density/Bulk density

Evaluation tests for capsules containing pellets

a. Weight variation test

20 intact capsules were selected randomly and weighed and average weight is calculated. Individual weight of each capsule is determined. According to USP, none of the individual capsule weight should be less than 90% and more than 110% of the average weight. Results of weight variation test are mentioned in Table 17.

b. Lock length

The lock length can be determined by vernier callipers. The empty capsule cap and body were measured individually to know the lock length of the capsule. Results of lock length are mentioned in Page 94.

c. Content uniformity by HPLC [65]

According to USP, 30 intact capsules were selected, of which 10 are assayed. 9 of 10 capsules should be within the potency range of 85%-115%. The potency of 10th capsule should not exceed the range of 75-125%. Results of Content uniformity are mentioned in Table 17.

Reagents:

Anhydrous sodium acetate: A.R Grade

Acetic acid: A.R Grade

Acetonitrile: HPLC Grade

Methanol: HPLC Grade

Preparation of buffer solution

Acetate buffer-Accurately weighed and transferred about 1.64 g of anhydrous sodium acetate into a beaker containing 900 ml of water and mixed. Adjusted pH with acetic acid to 4.0, diluted with water to 1000 ml, and mixed.

Preparation of mobile phase

Filtered and degassed mixture of Methanol, Acetonitrile, and Acetate buffer (4:3:3) was prepared.

Preparation of standard solution

Accurately weighed and transferred 20mg of Methylphenidate Hydrochloride working standard into a 100ml of volumetric flask, added 70ml of Mobile phase and sonicated, dissolved, diluted to volume with Mobile phase and mixed. Transferred 10ml of this solution to 20ml volumetric flask and diluted to volume with Mobile phase. Filtered the solution through 0.45 Nylon filter paper.

Preparation of Sample Solution

Accurately weighed and transferred the pellets equivalent to about 20mg of Methylphenidate Hydrochloride into a 100ml volumetric flask. Added about 70ml of mobile phase and sonicated for 15min with intermittent shaking. Diluted to volume with mobile phase. Transferred 10ml of this solution into a 20ml volumetric flask and diluted to the volume with mobile phase.

Chromatographic Conditions

Column : Kromosil 60, CN 250×4.6 mm, 5µm or equivalent.
Flow Rate : 1.5 ml/min
Wave Length : 210 nm
Column Temperature : 25°C
Injection Volume : 50µl
Run Time : 10minutes.

System Suitability

The percentage relative standard deviation for six replicate injection of standard solution is not more than 2.0

Procedure

Separately injected equal volumes (about 50 µL) of the Standard preparation and sample solution into the chromatograph, recorded the chromatograms, and measured the responses for the major peaks. Calculated the quantity, in mg, of Methylphenidate hydrochloride in the portion of pellets taken by the formula.

$$\%\text{Drug Content} = \frac{A_T}{A_S} \times \frac{W_S}{W_T} \times \frac{10}{10} \times \frac{100}{100} \times \frac{20}{20} \times p \times 100$$

$$\%\text{ of labeled amount} = \frac{\%\text{ of Methylphenidate Hydrochloride}}{\text{Label claim}} \times 100$$

Where,

A_T = Area count of Methylphenidate Hydrochloride Peak in sample solution.

As = Average area of Methylphenidate Hydrochloride peak in sample solution.

W_S = Weight of Methylphenidate working standard taken in mg.

W_T = Weight of the sample taken in mg.

P = Purity of Methylphenidate working standard used.

d. In vitro dissolution by HPLC [66]

In vitro drug release studies were carried out using an USP type I dissolution test apparatus at 75rpm for 2 hrs in 0.01N Hcl acetate buffer (500 ml) maintained at 37°C ± 0.5°C and 10 ml of sample was withdrawn and analyzed.

Then, the dissolution medium was replaced with pH 6.8 phosphate buffer (500 ml) and tested for drug release for 8 hrs at same temperature and same rotation speed. At all the time points of 0.5,1,3,6,8 and 10,each 10 ml of the samples were withdrawn, and analyzed. The results of invitro dissolution was mentioned in table18.

Preparation of Standard:

Transferred about 20mg of Methylphenidate Hydrochloride, accurately weighed, to a 50ml volumetric flask added 20ml of methanol, sonicated to dissolve and diluted with methanol to volume and mix. Transferred 5.0ml of this solution to a 50ml volumetric flask, diluted with medium to the volume and mixed. Filtered the solution through Nylon filter paper.

Sample Preparation:

The parameters of dissolution apparatus were set as mentioned above and a capsule is placed in each dissolution vessel containing pellets equivalent to 380.95mg Methylphenidate Hydrochloride and the dissolution apparatus was operated. 10ml of the sample solution was withdrawn from each vessel at the end of the time point.10 ml of withdrawn sample is transferred to 25ml volumetric flask and made up to the volume with dissolution medium.

Procedure:

Separately injected 50µl of standard solution (six injections) and sample solution into the chromatographic system. Recorded the chromatograms and measured the peak responses.

Calculation:

% labeled amount of Methylphenidate dissolved

$$= \frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{5}{50} \times \frac{500}{W_T} \times \frac{P}{\text{label Claim in \%}} \times 100$$

where,

A_T = Area of Methylphenidate Hydrochloride in sample solution

A_S = Area of Methylphenidate Hydrochloride in standard solution

W_S = Weight of Methylphenidate in working standard(mg)

W_T = Weight of sample taken (mg)

P = Purity of Methylphenidate Hydrochloride working standard taken in mg.

4.3.7. DISSOLUTION PROFILE COMPARISON USING SIMILARITY AND DISSIMILARITY FACTORS

f1=Dissimilarity factor

f2=Similarity factor

A dissolution profile can characterize the product more precisely than a single point dissolution test. It helps to assure similarity in product performance and signals bioequivalence. The factor f1 is proportional to the average indifference between two profiles, where as factor f2 inversely proportional to the average squared indifference between two profiles. The factor f2 measures the closeness between two profiles, FDA has set a public standard of f2 value between 50-100 to indicate similarity between two profiles. It was calculated by the following formulae.

$f1 = \Sigma D\ (1/\ \Sigma t)\ 100$

$f2 = 50 \times \ln\{1/\surd 1+\Sigma\ (Rt-Tt)^2\}$

4.3.8 Stability studies

Stability studies are an integral part of the drug development program and are one of the most important areas in the registration of pharmaceutical products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re-test periods and shelf lives to be established.

Stability assessment starts with studies on the substance to determine degradation products, degradation pathway. In these type of studies the pellets are stored in suitable containers and stability study is conducted as per

ICH guidelines. The product is analyzed at intervals for various parameters which may include assay of active ingredient, measurement of known degradation products, hardness, disintegration time, dissolution time, appearance, etc., Stability studies have been conducted at following conditions. Results of stability studies are mentioned in Table:12..

Storage conditions:

40 ºC ± 2 ºC /75%RH ± 5%, 25 ºC ± 2 ºC /60% RH ± 5%

Packs:

Capsules containing pellets have been packed into blister packages.

Period:

Initial, 1, 2 and 3 months.

RESULTS AND DISCUSSIONS

Preformulation studies

5.1. API Characterization

Appearance

Methylphenidate Hydrochloride was a white to off white powder.

Solubility

The drug, Methylphenidate Hydrochloride was freely soluble in Water.

DSC study

These studies shows the characteristic peaks of Methylphenidate Hydrochloride.

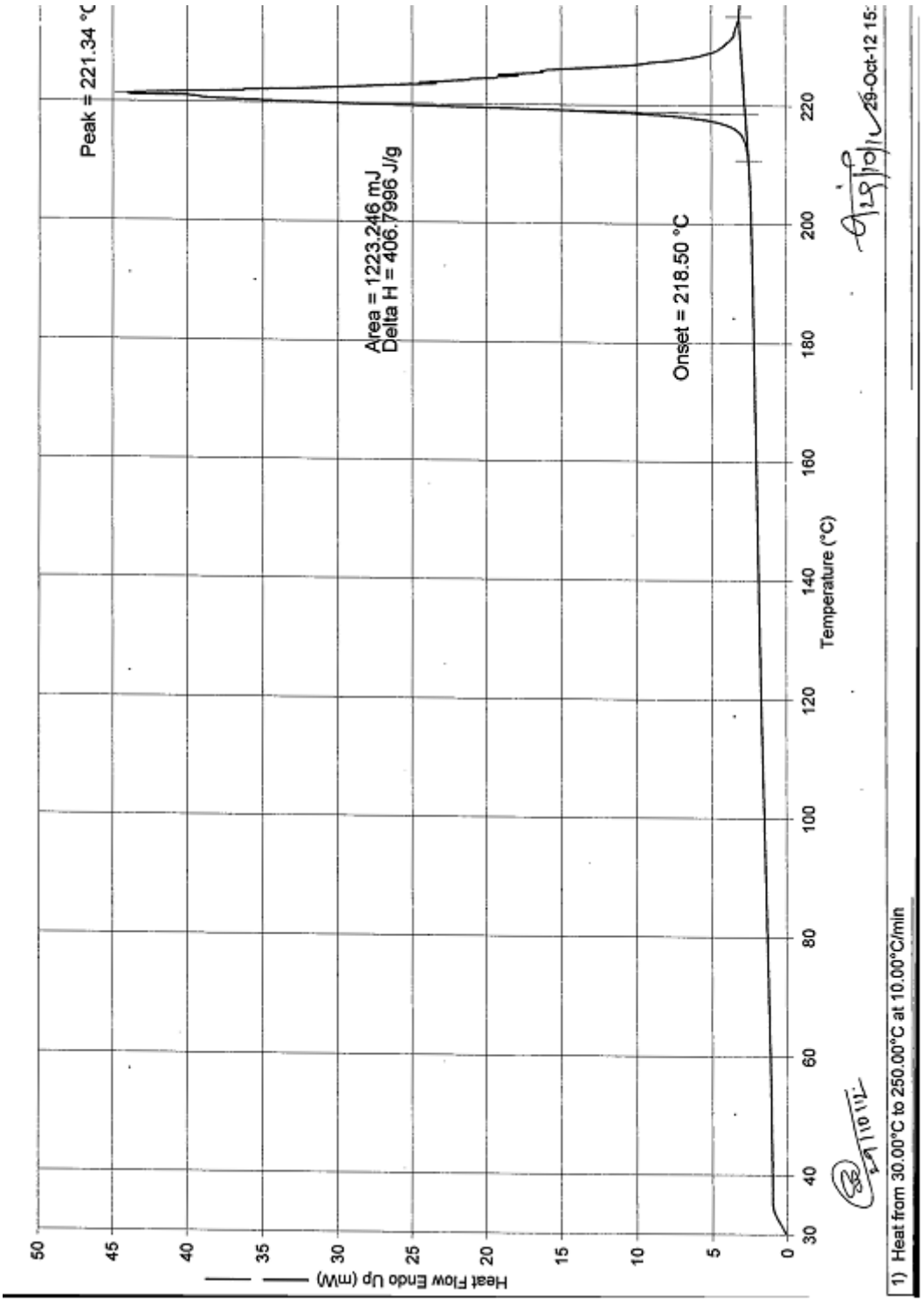

Figure:21 DSC graph

5.2 Drug excipient compatibility study

Physical observation:

Physical observation of sample was done every week for any color change or lumps formation and flow, storing at 40^{o}C/ 75% RH

S. No.	Composition details	Observations			
		Storage condition / Duration			
		Initial	40^{o}C/ 75%RH		
			1Month	2Month	3Month
1	Methylphenidate Hydrochloride alone	White to off White powder	NCC	NCC	NCC
2	Methylphenidate Hydrochloride + Sugar spheres	White to off White powder	NCC	NCC	NCC
3	Methylphenidate Hydrochloride + PEG 6000	White to off White powder	NCC	NCC	NCC
4	Methylphenidate Hydrochloride + Polyvinyl pyrrolidone k30	White to off White powder	NCC	NCC	NCC
5	Methylphenidate Hydrochloride+ Ethyl Cellulose N-45	White to off White powder	NCC	NCC	NCC
6	Methylphenidate Hydrochloride+ HPMC E5	White to off White powder	NCC	NCC	NCC

Table :12 Drug excipients compatibility study

NCC:No change in color

5.3.FT-IR Spectroscopy:

Methylphenidate hydrochloride, PVP K30, HPMC E5, are subjected to FT-IR spectroscopy. The FT-IR spectrums are interpreted and the functional groups C-H-2900cm^{-1}, C=O- 1740cm^{-1}(stretching) are identified in Methylphenidate hydrochloride. The functional groups C-N, C-O-1330cm^{-1}(stretching), N-H-1530cm^{-1}(bending) are observed in PVPK30. The following functional groups are identified in HPMC E5 polymers O-H-1330cm^{-1}, C-H-2960cm^{-1}(stretching), C=C - 1680cm^{-1}. From the spectrum of drug and excipient mixture, no interaction of drug and polymers have been observed.

FTIR Spectra for Methylphenidate Hcl:

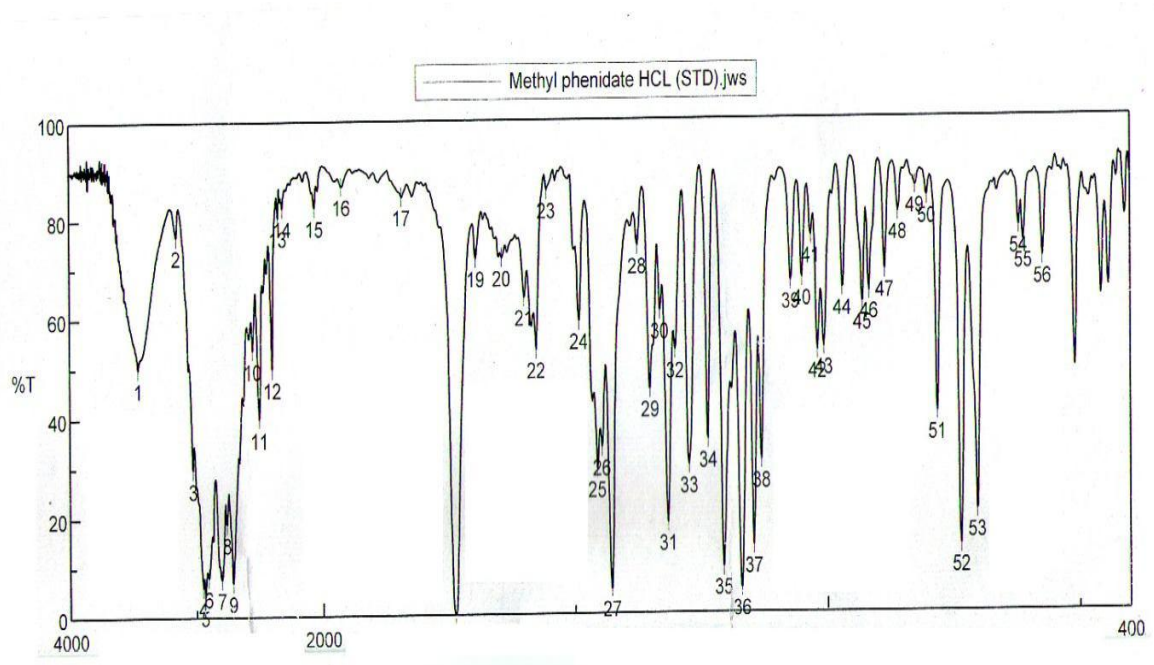

Figure :22 FTIR Spectra of Methylphenidate Hydrochloride

FTIR Spectra for PEG-6000:

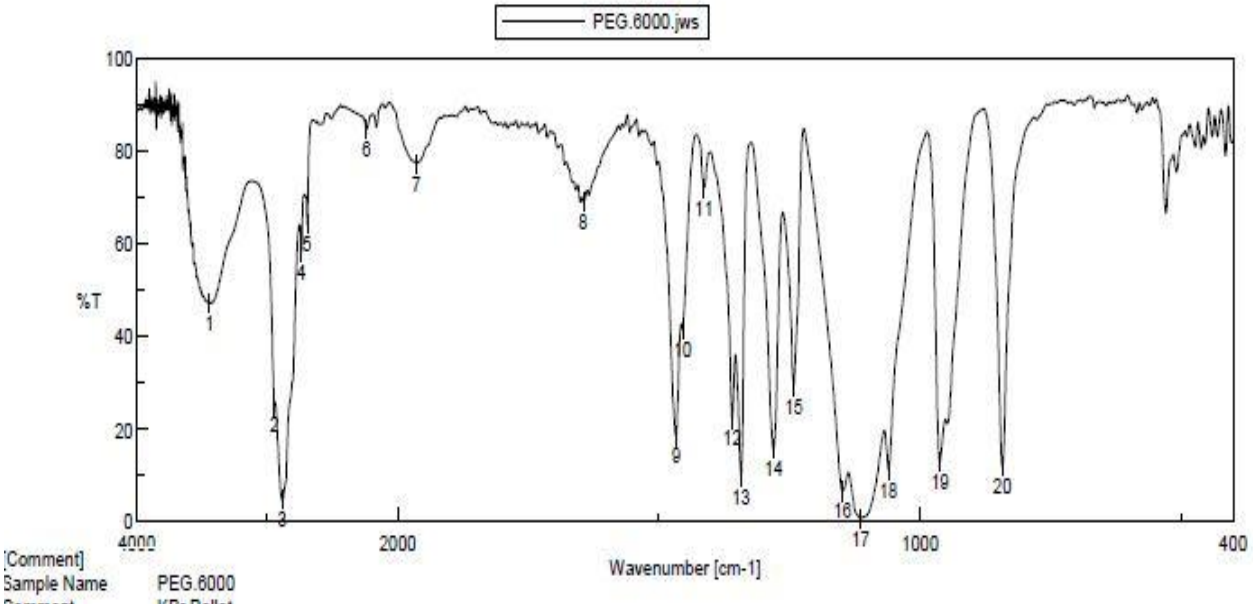

Figure :23 FTIR Spectra of PEG-6000

FTIR Spectra for PVPK-30:

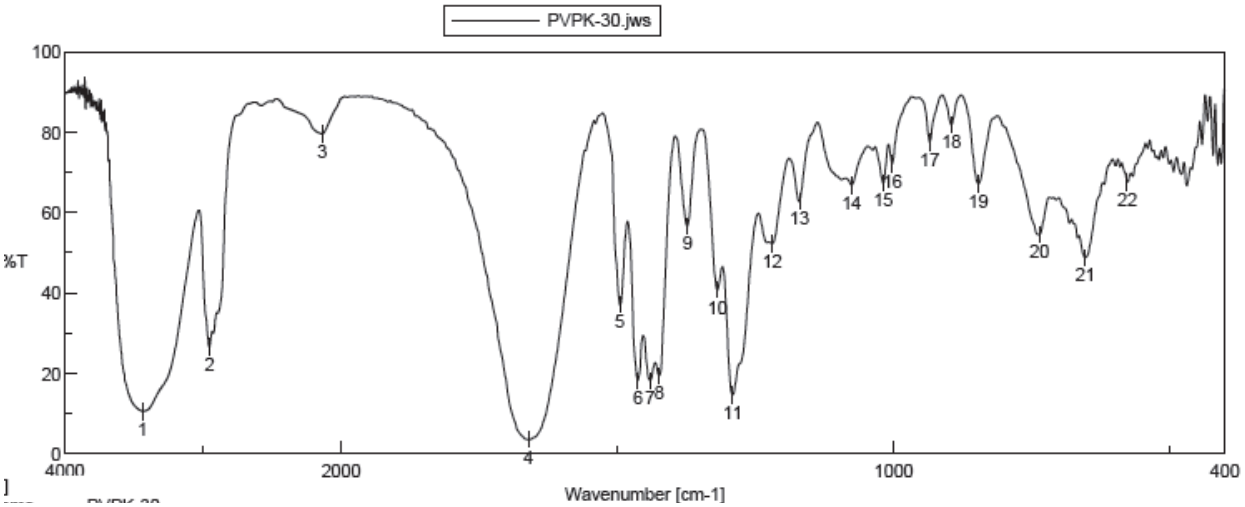

Figure :24 FTIR Spectra of PVPK-30

FTIR Spectra for Ethyl cellulose N-45:

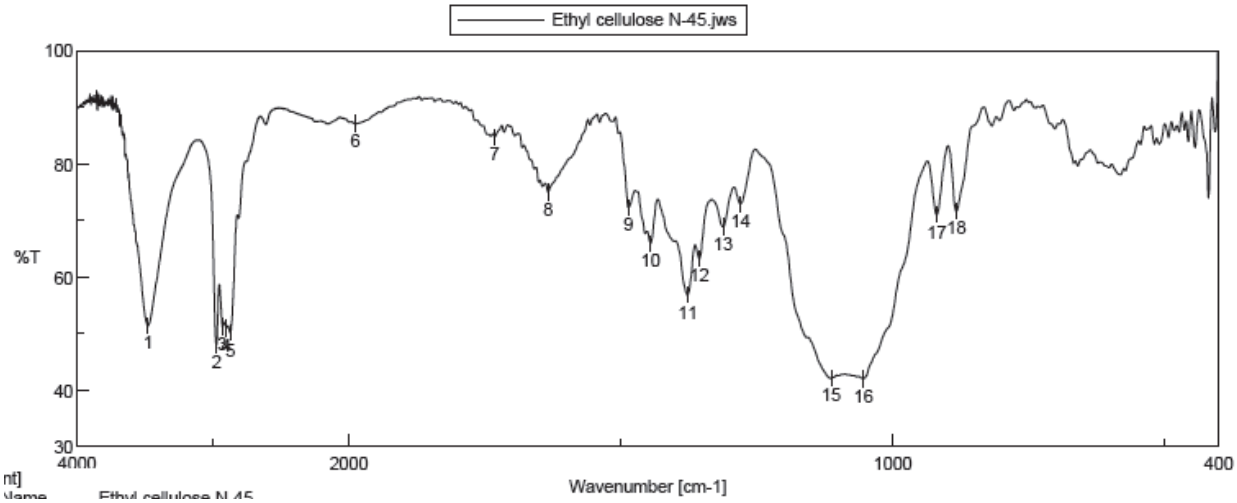

Figure:25 FTIR Spectra of Ethyl cellulose N-45

FTIR Spectra for HPMC E5:

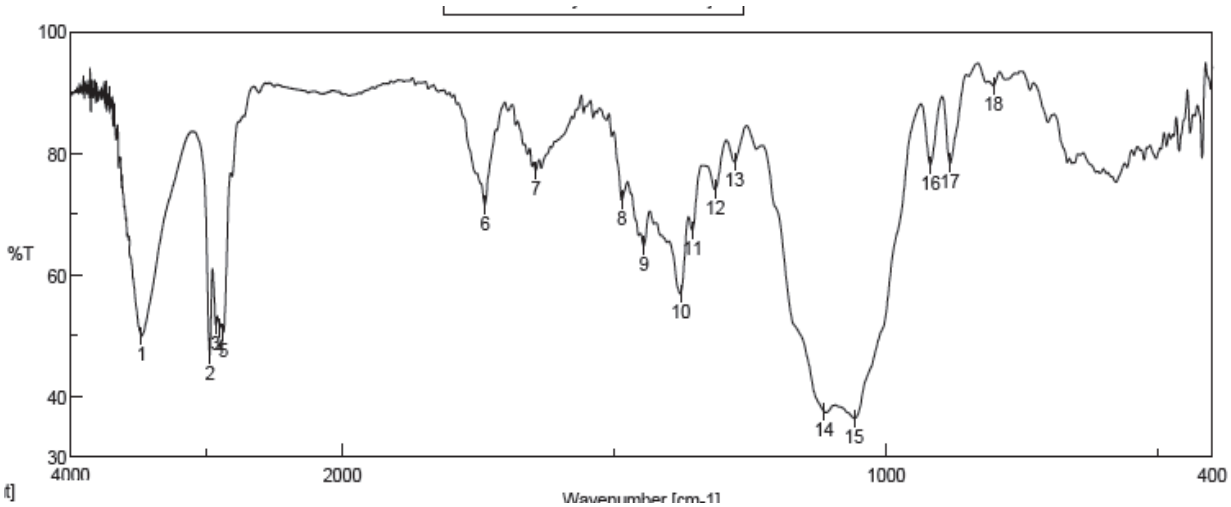

Figure: 26 FTIR Spectra for HPMC E5

FTIR Spectra for Physical mixture:

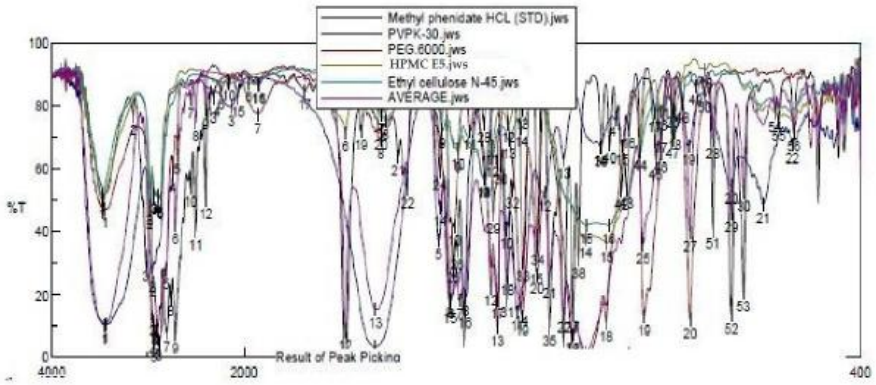

Figure :27 FTIR Spectra of Physical mixture

5.4Analytical Method Development:

a. Calibration Curve of Methylphenidate Hydrochloride in pH 0.01N Hcl acetate buffer at λ_{max} 210.0 nm

Concentration (µg/mL)	Absorbance
10	0.113
20	0.206
40	0.457
60	0.585
80	0.751
100	0.899

Table:13 calibration of Methylphenidate Hcl in 0.01N Hcl acetate buffer

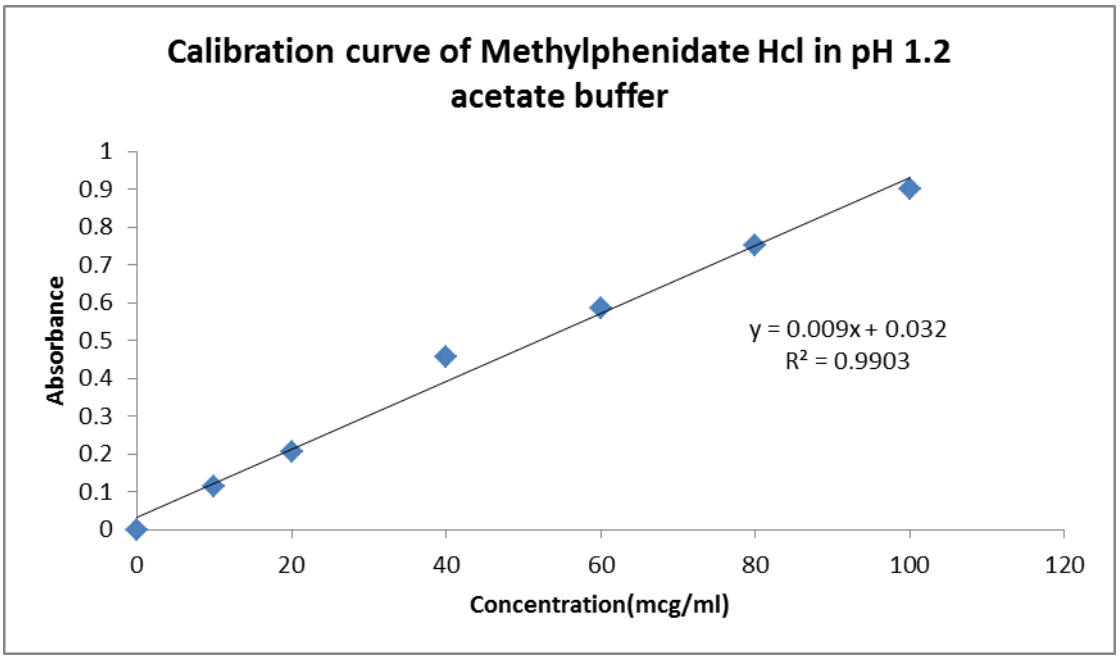

Figure:28 calibration curve of Methylphenidate Hcl in 0.01N Hcl acetate buffer

b. Calibration Curve of Methylphenidate Hydrochloride in 6.8 pH Phosphate Buffer at λ_{max} 210.0 nm:

Concentration (µg/mL)	Absorbance
10	0.126
20	0.218
40	0.391
60	0.611
80	0.757
100	0.921

Table:14 calibration of Methylphenidate Hcl in 6.8pH phosphate buffer

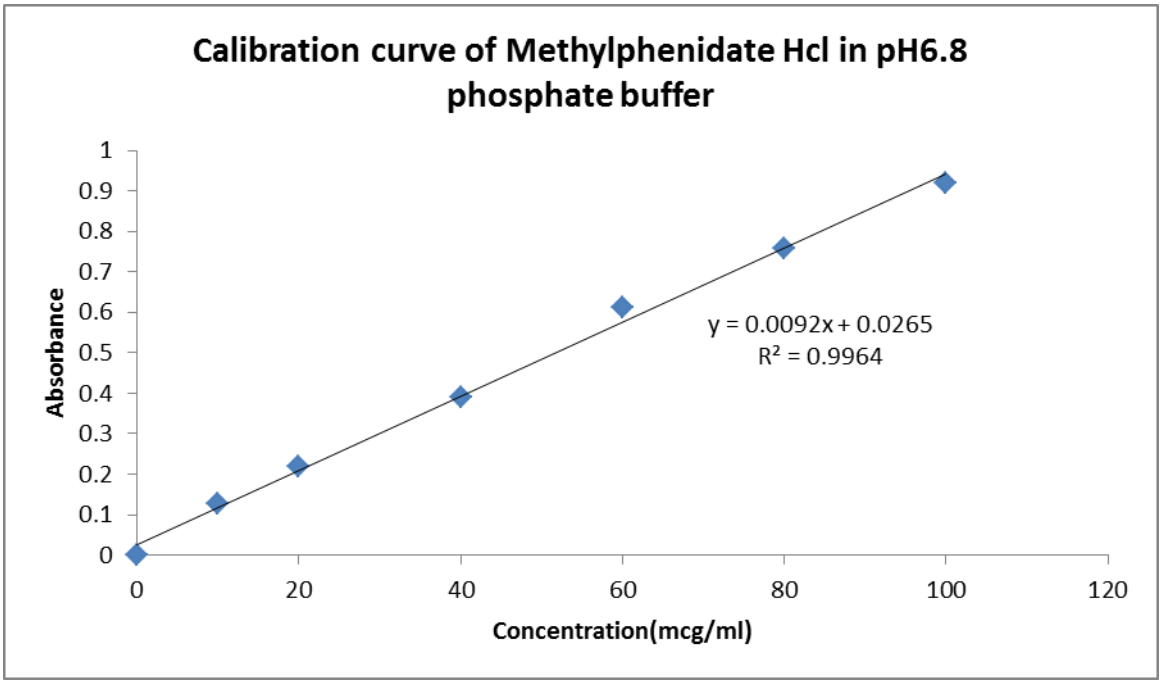

Figure:29 calibration curve of Methylphenidate Hcl in 6.8pH phosphate buffer

5.5.Evaluation of drug loaded pellets:

Physical description:

0.5g of pellets were transferred into a dry petri dish or dispensed on a white card. The contents were observed visually. It was found that Methylphenidate Hydrochloride is a white to off white powder.

Sieve analysis:

All the Methylphenidate Hydrochloride formulations were tested for particle size by sieve analysis using mechanical sieve shaker. The size of pellets (841-1190µm) was found to be within the range of standard sieves. All the pellets are passed through sieve no.16 easily and retained on sieve no.20.

S. No	Formulation	Bulk Density (gm/ml)	Tap Density (gm/ml)	Hausner ratio:
1	F 1	0.66 ± 0.03	0.69 ± 0.02	1.04
2	F 2	0.64 ± 0.03	0.67 ± 0.03	1.04
3	F 3	0.66 ± 0.04	0.69 ± 0.04	1.04
4	F 4	0.64 ± 0.04	0.67 ± 0.03	1.04
5	F 5	0.65 ± 0.03	0.68 ± 0.02	1.04
6	F 6	0.67 ± 0.04	0.71± 0.03	1.00
7	F 7	0.66 ± 0.03	0.69 ± 0.05	1.04

Table :15 Bulk density and Tap density

% Moisture content: It has been determined by KF Titration Method

S. No	Formulation	% Moisture Content
1	F 1	1.98
2	F 2	1.95
3	F 3	1.8
4	F 4	1.73
5	F 5	1.63
6	F 6	1.42
7	F 7	1.5

Table :16 % Moisture content

5.6. Evaluation of capsules containing pellets:

Weight variation & drug content:

Capsules containing Methylphenidate formulations have shown the average weight & drug content uniformity in the range of 453.5-455.9 & 98.3%-100.5%.

S.No	Formulation	Average Weight (mg)	%Drug Content
1	F 1	453.5 ± 3.6	98.5 ± 0.2
2	F 2	454.2 ± 5.8	99.7 ± 0.3
3	F 3	454.7 ± 4.5	100.1 ± 0.2
4	F 4	455.3 ± 3.5	99.5 ± 0.4
5	F 5	454.6 ± 3.2	98.3 ± 0.3
6	F 6	454.3 ± 4.5	99.7 ± 0.4

7	F 7	455.9 ± 4.6	99.9 ± 0.2

Table : 17 Weight variation

Weight variation profile:

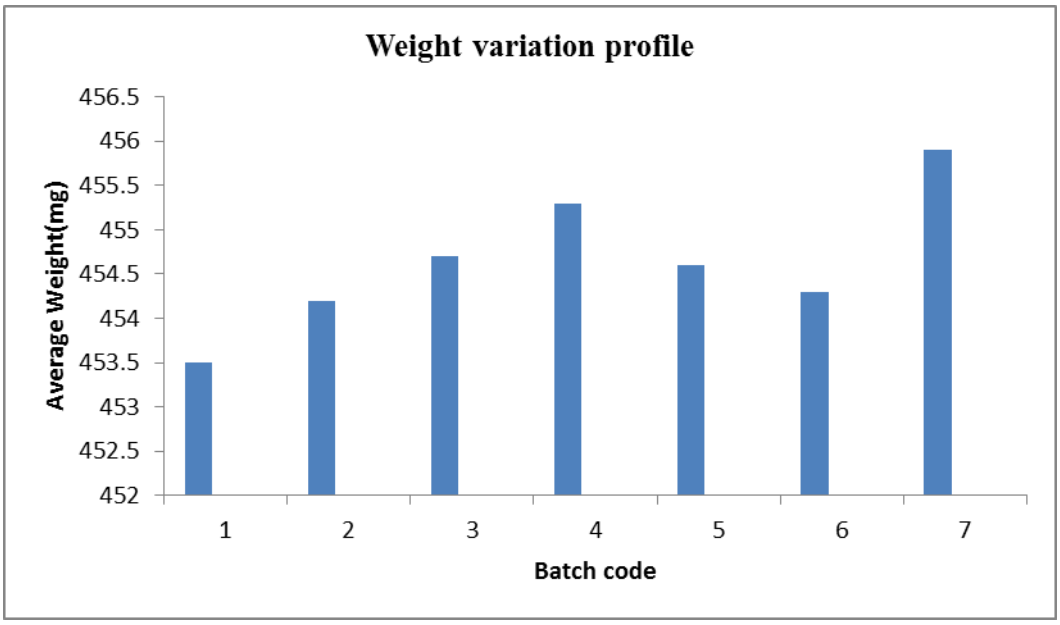

Figure:30 Weight variation profile of 7 formulations

Lock length:

Empty capsule cap length and width: 10.2mm, 6.58mm

Empty capsule body length and width: 16.82mm, 6.5mm

Filled capsule length and width: 19.22, 6.8mm

Lock length of the capsules containing pellets was found to be 7.8mm

Assay by HPLC

HPLC Chromatogram for Blank

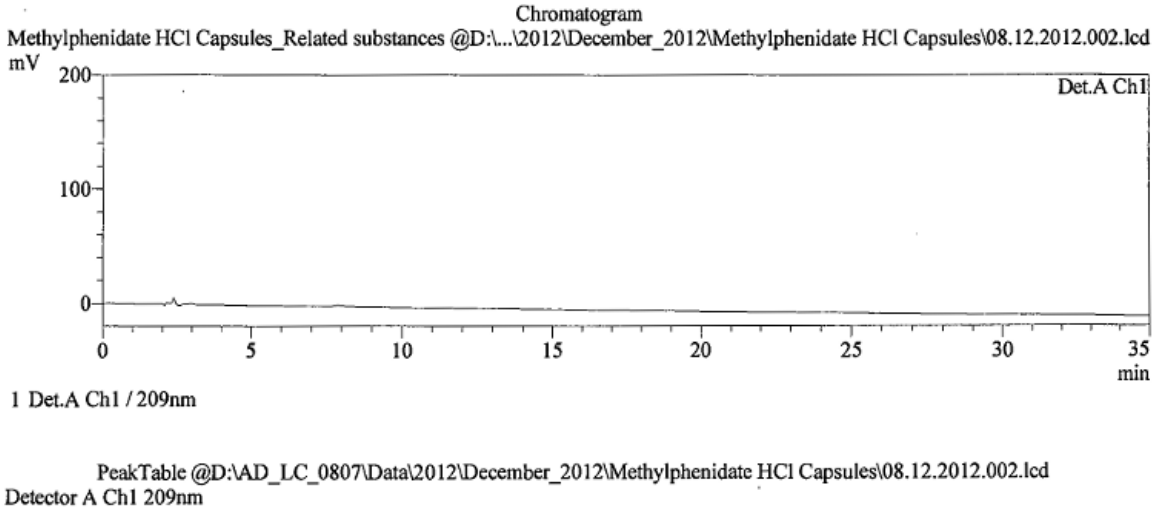

Figure:31 HPLC Chromatogram for Blank

HPLC Chromatogram for Standard

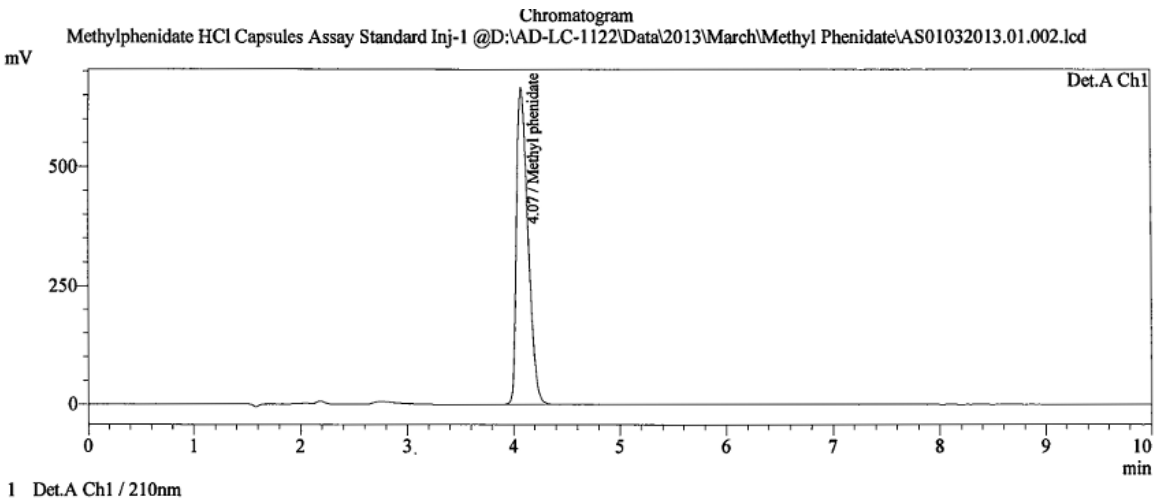

Figure:32 HPLC Chromatogram for Standard

HPLC Chromatogram for Optimised Formulation F7:

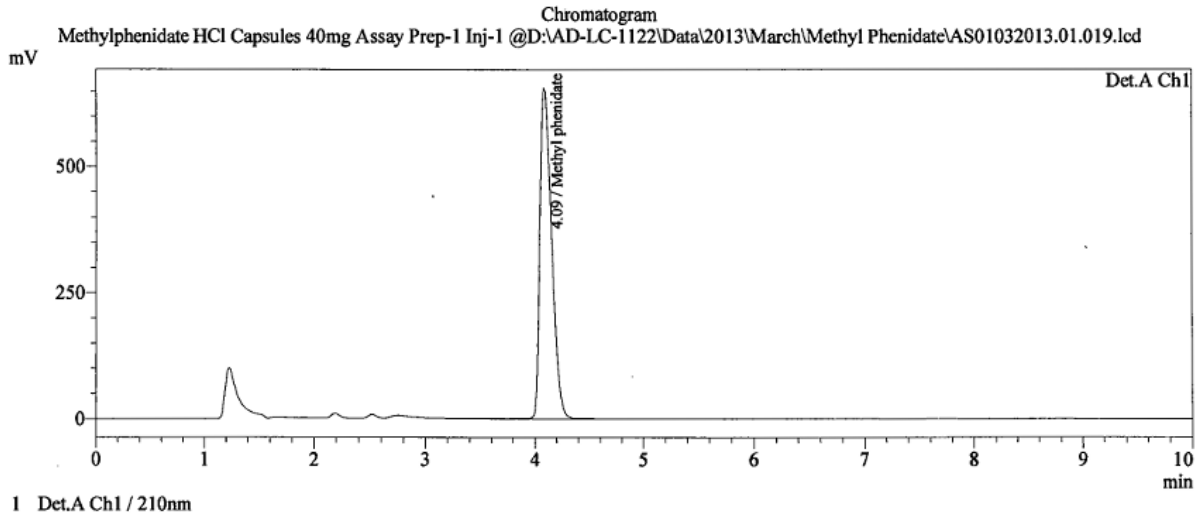

Figure:33 HPLC Chromatogram for optimized formulation F7.

***In-Vitro* Drug release profile:**

Dissolution by HPLC:

Stage:1

Medium : 0.01N Hcl acetate buffer

Volume : 500ml

Apparatus : Basket(USP-I)

RPM : 75

Time : 2hours

Temperature : 37±0.5°C

Stage:2

Medium : 6.8pH phosphate buffer

Volume : 500ml

Apparatus : Basket(USP-I)

RPM : 75

Time : 8 hours

Temperature : 37±0.5^0 C

S.No	Time (hrs)	Cumulative % Drug release								
		Innovator Drug	F1	F2	F3	F4	F5	F6	F7	F8
1	0.5	27.4	36.3	32.8	28.8	40.8	35.8	22.5	24.1	24.2
2	1	37.9	59.9	54.3	50.3	62.3	57.3	46.1	46.5	46.6
3	3	56.3	74.6	71.2	67.3	79.5	76.1	65.3	65.6	65.1
4	6	68.2	81.7	76.3	72.0	84.1	81.2	73.9	74.2	74.4
5	8	84.6	85.3	80.2	76.9	88.4	84.9	81.2	83.5	83.7
6	10	92.5	89.0	83.4	79.4	96.4	94.5	90.2	93.9	93.8
f2 Values (Similarity factor)			43.4	48.7	51.2	39.5	44.4	50.6	61.1	61.1

Table :18 Comparative dissolution data

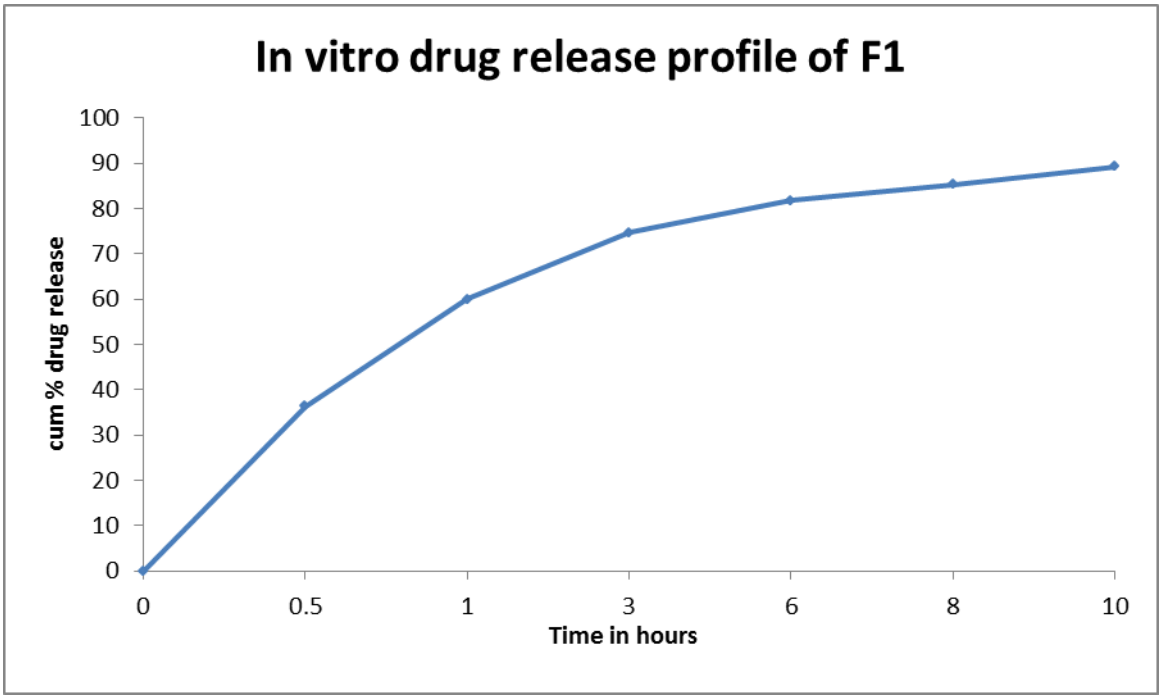

Figure :34 In Vitro drug release profile of F1.

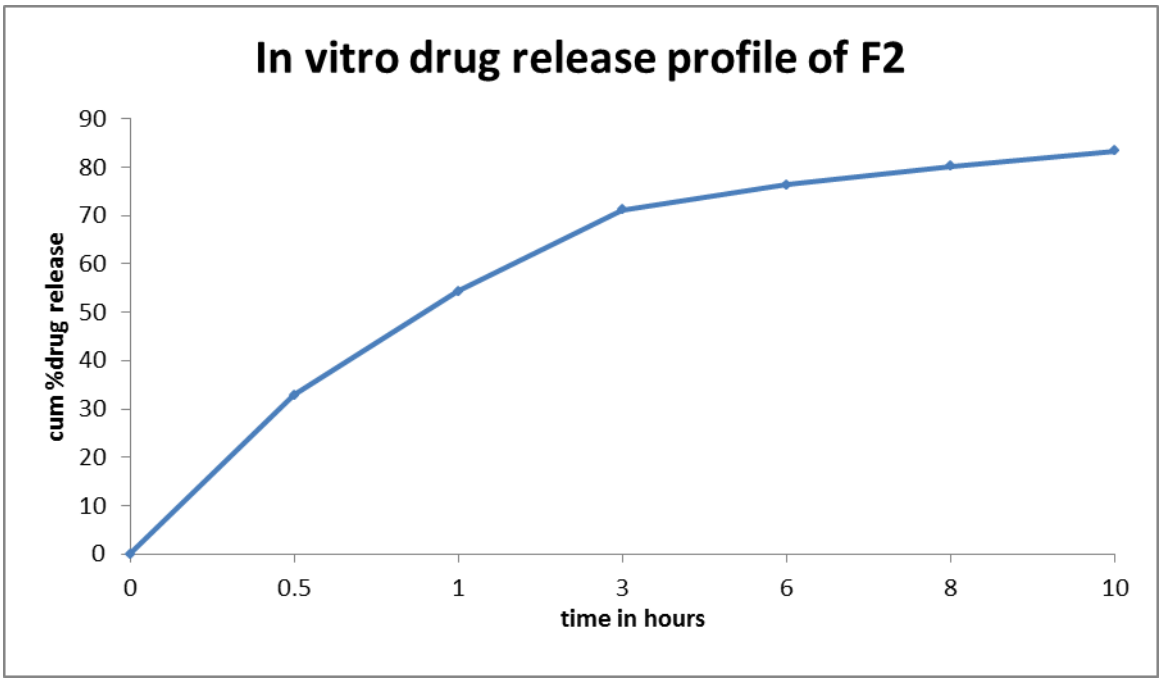

Figure :35 In Vitro drug release profile of F2.

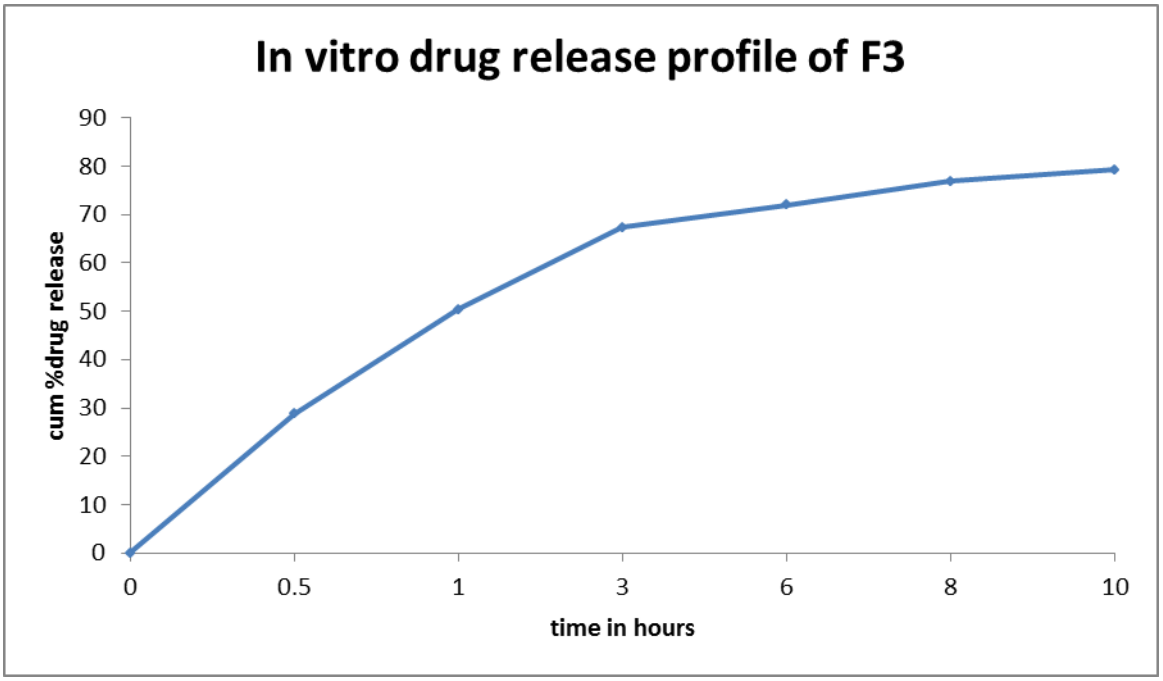

Figure :36 In Vitro drug release profile of F3.

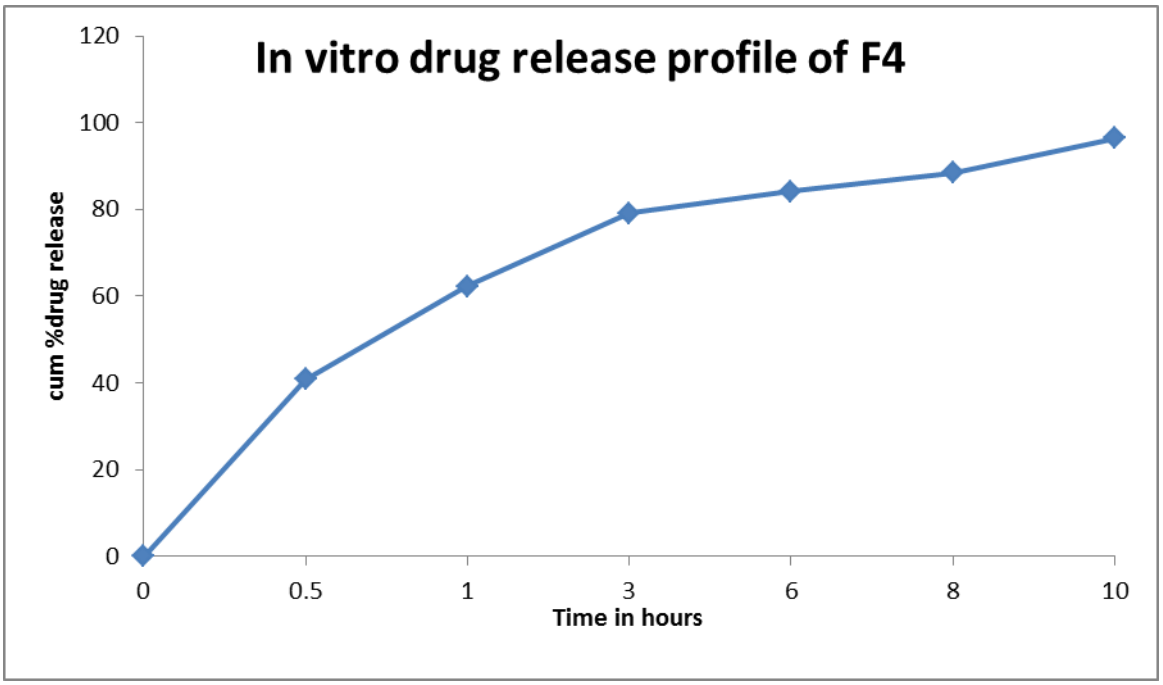

Figure :37 In Vitro drug release profile of F4.

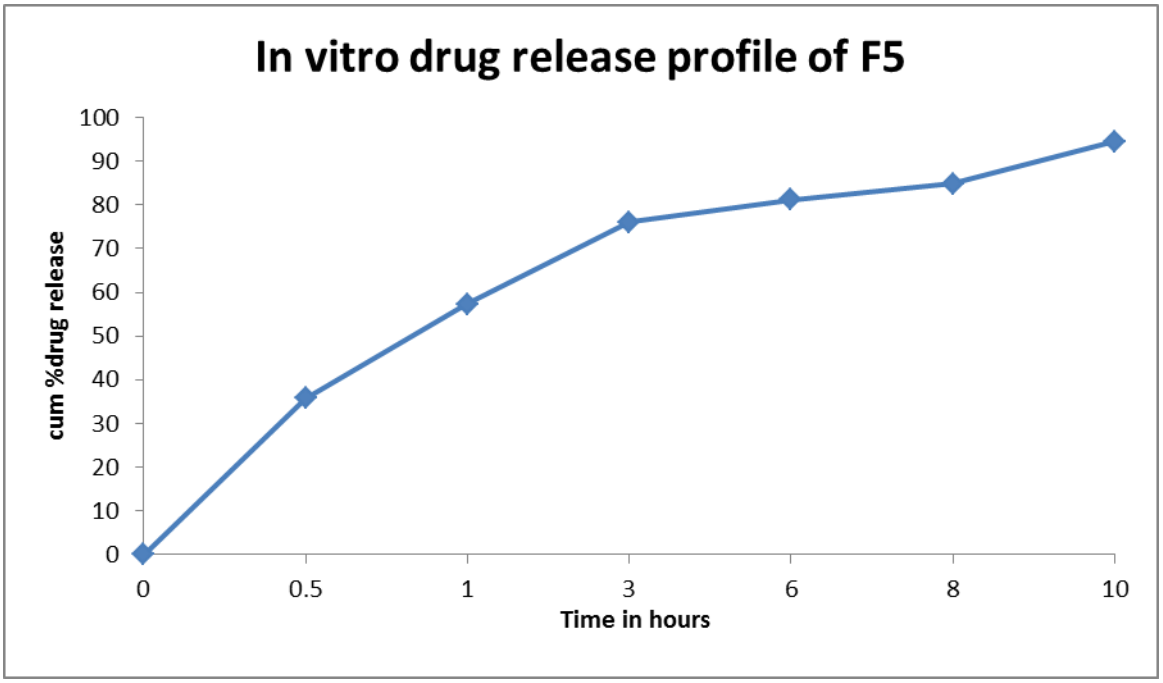

Figure :38 In Vitro drug release profile of F5.

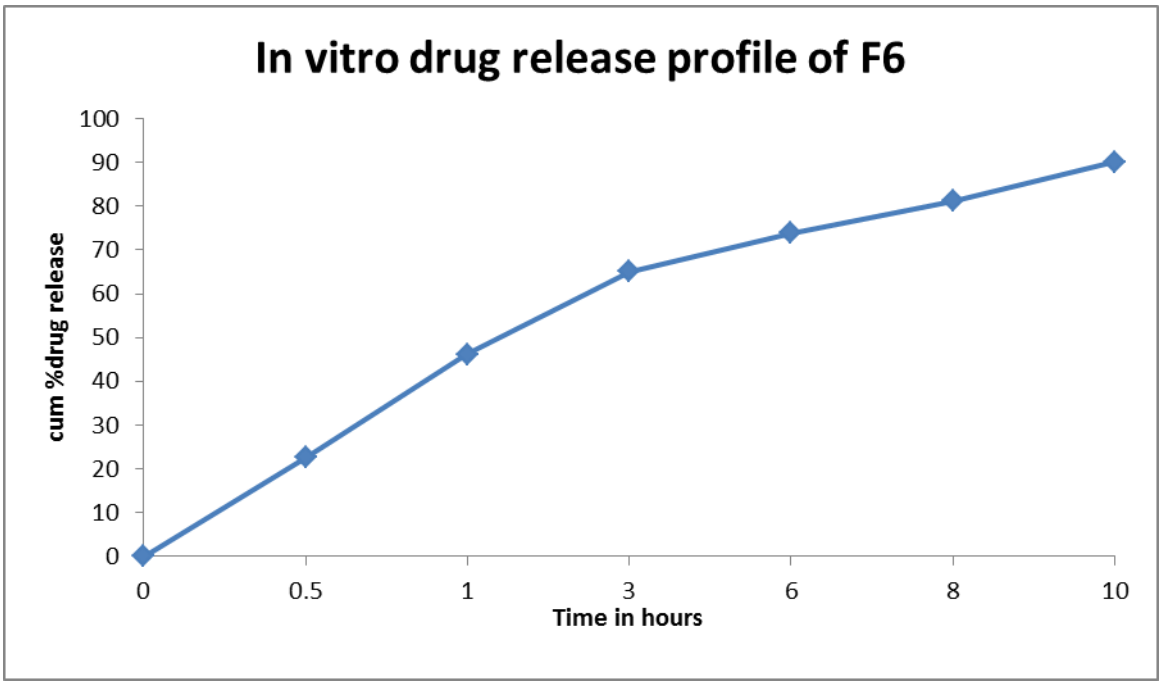

Figure :39 In Vitro drug release profile of F6.

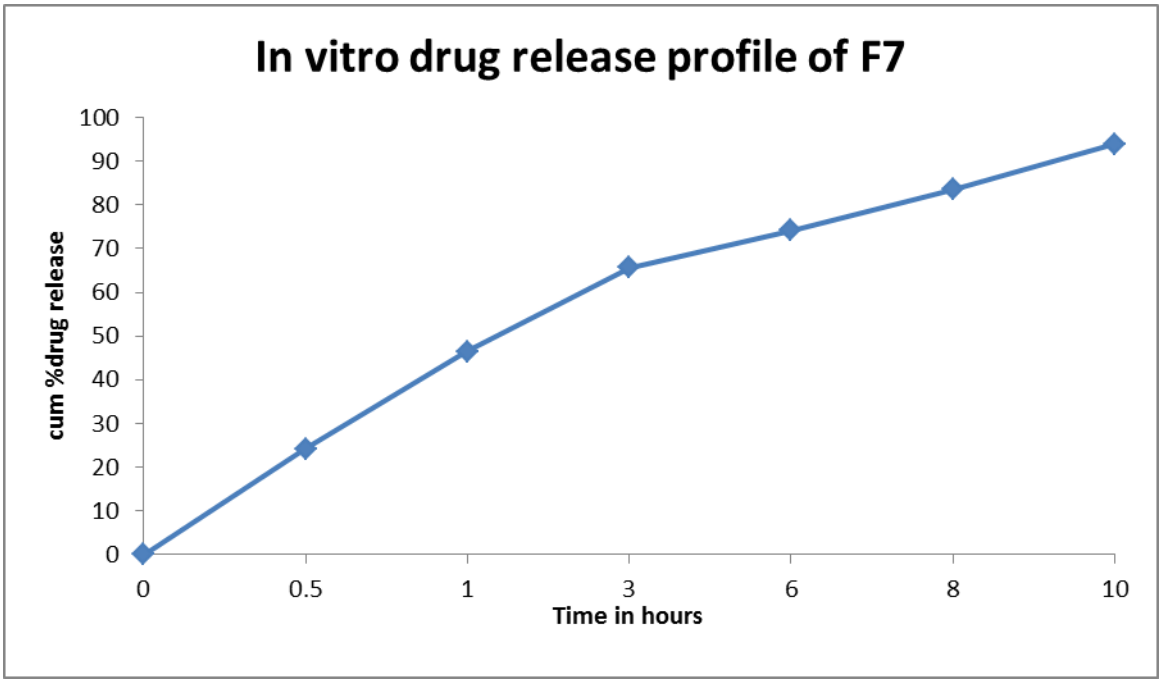

Figure :40 In Vitro drug release profile of F7.

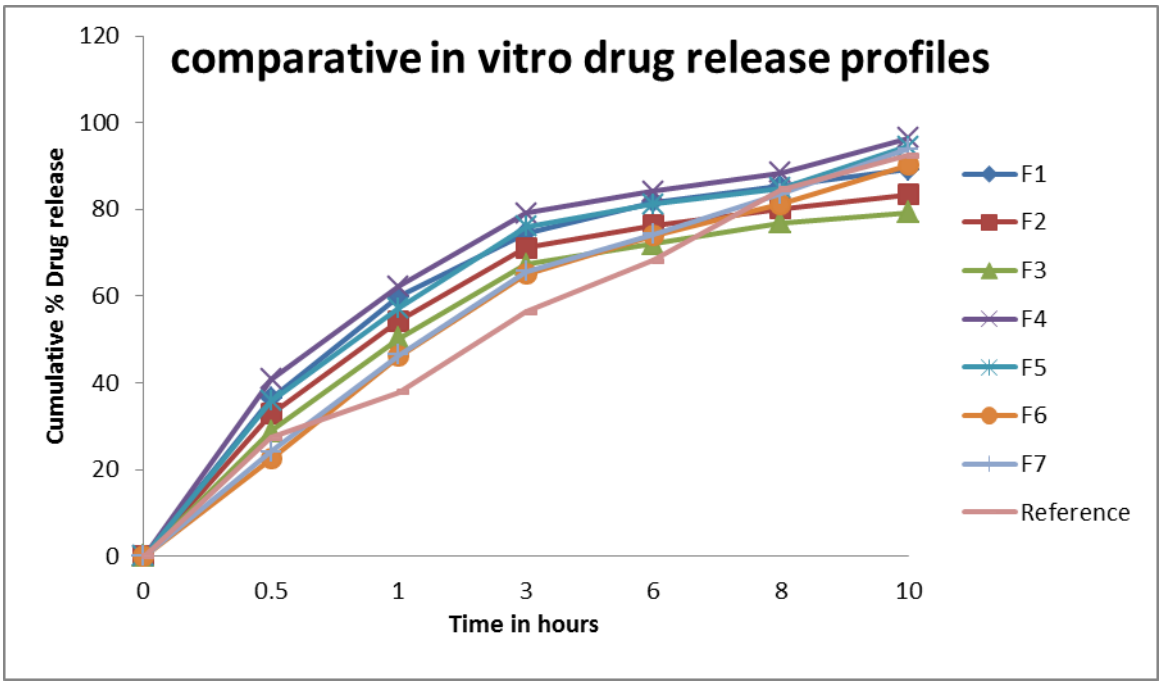

Figure :41 Comparitive in vitro drug release profiles.

Kinetic analysis of dissolution data:

The release rate kinetic data for the F7 is shown in Table16. As shown in Figures 39-42, drug release data was best explained by zero order equation, as the plots showed the linearity (r^2 = 0.821). As the drug release was best fitted in zero order kinetics, indicating that the rate of drug release is concentration independent.

Determination of release kinetics:

Release kinetics	**R^2**	**Intercept**	**Slope**
Zero order	0.821	23.91	7.734
First order	0.426	0.115	1.049
Higuchi	0.956	28.051	7.801
Korsmeyer peppas	0.818	-0.739	1.809

Table :19Drug Release Kinetics of Batch (F7) capsules

*** r^2 = Correlation coefficient**

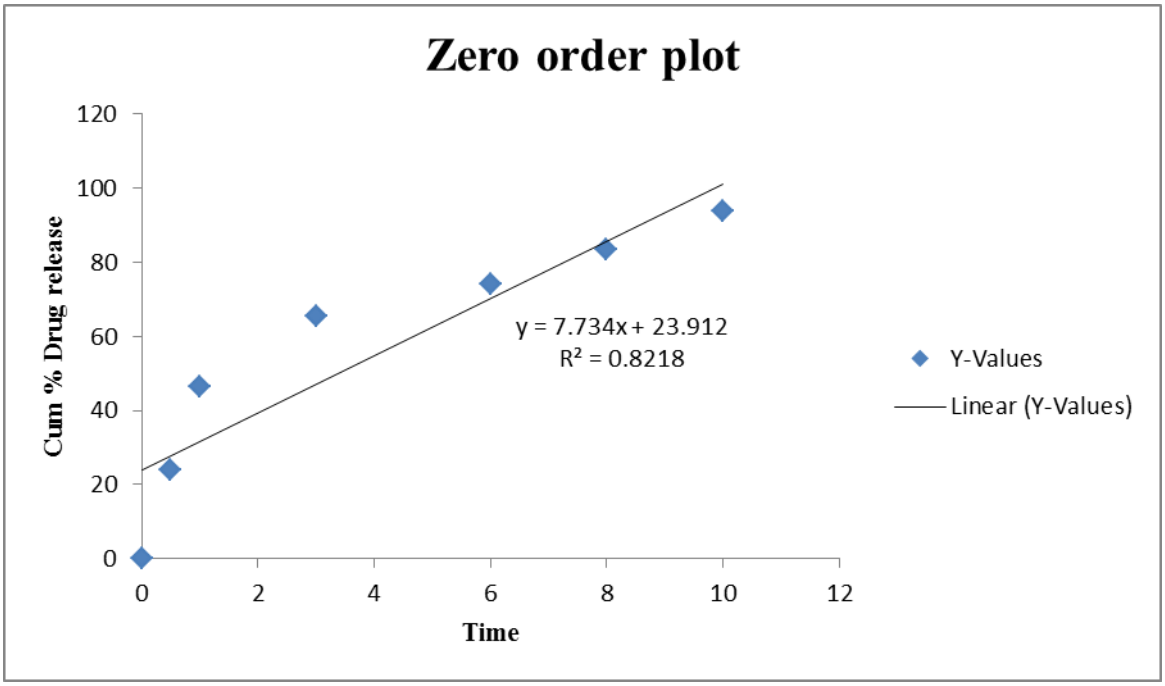

Figure :42 Zero Order Graph of Optimized Formulation(F7)

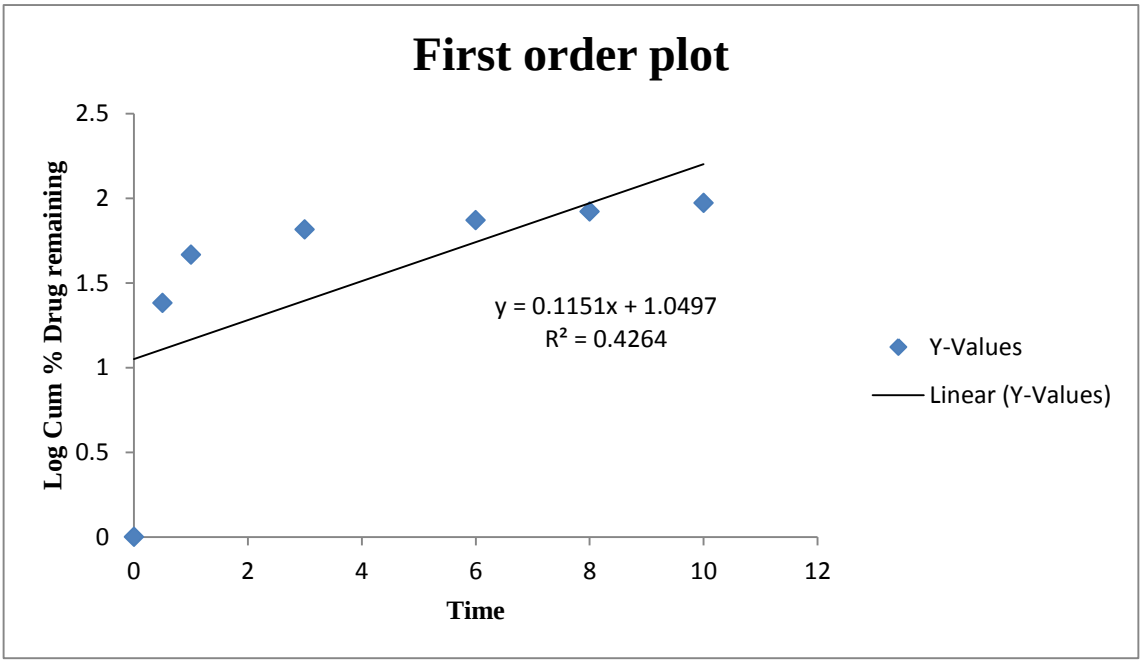

Figure :43 First Order Graph of Optimized Formulation(F7)

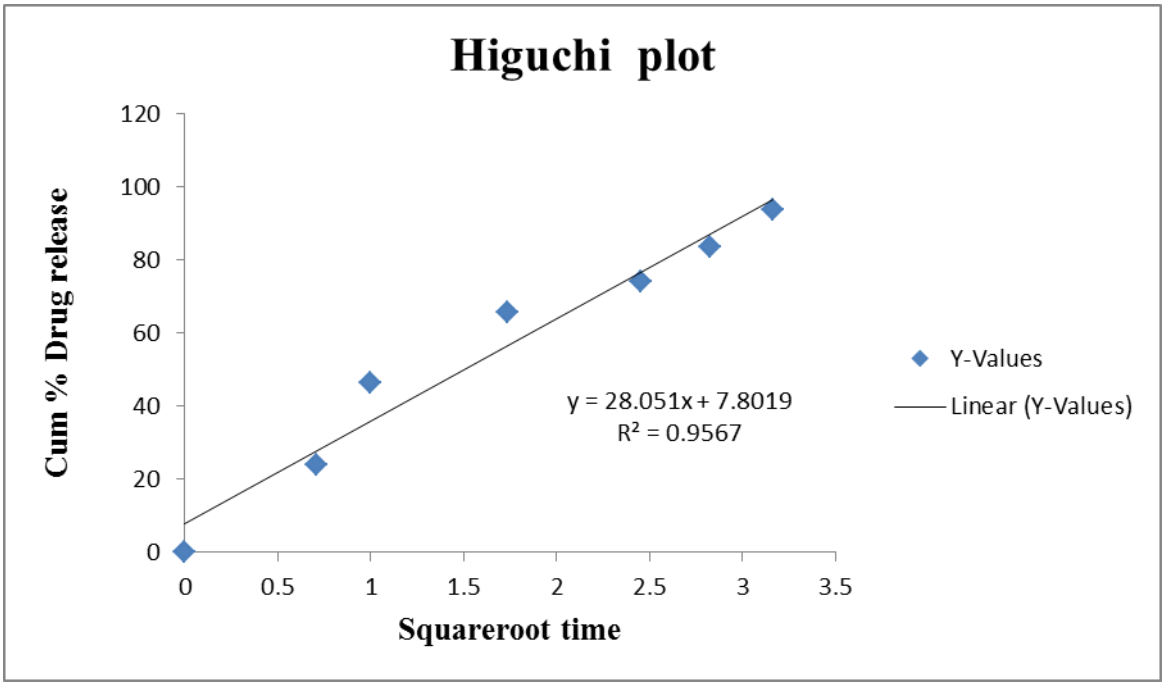

Figure :44 Higuchi Plot of Optimized Formulation (F7).

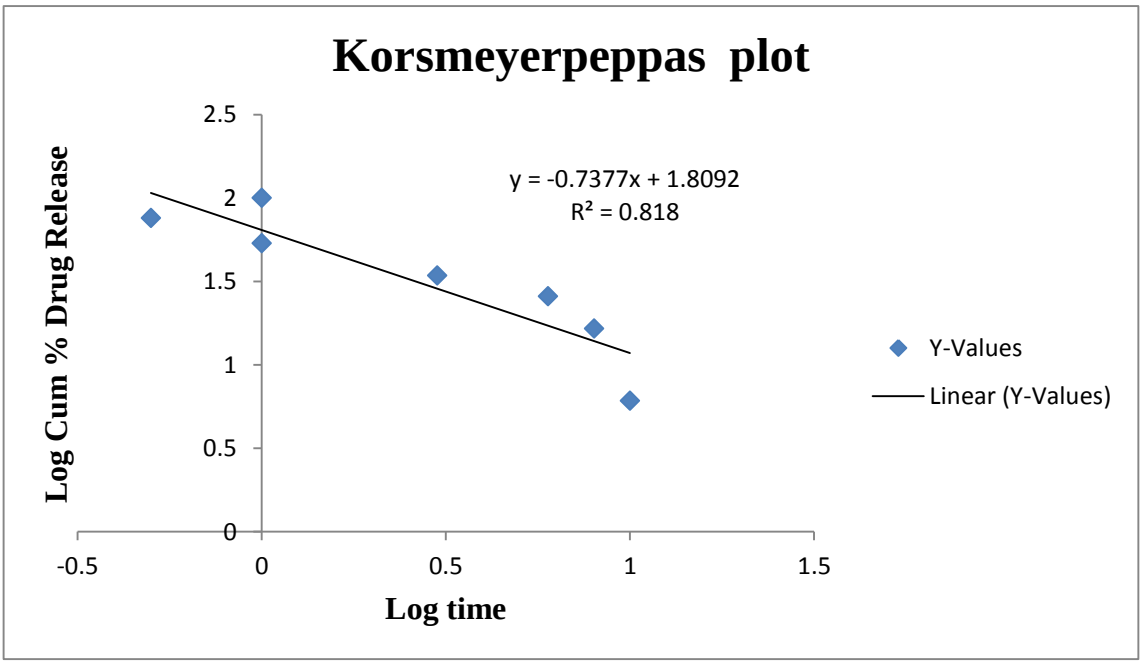

Figure :45 Korsmeyer-Peppas Graph of Optimized Formulation (F7).

Stability results:

S.No	Test	Storage Condition 40ºC ± 2ºC /75%RH ± 5%RH		Storage Condition 25ºc ± 2ºC /60%RH ± 5% RH	
		Initial	**90 days**	**Initial**	**90 days**
1	Physical Appearance	Off white	Off white	Off white	Off white
2	% Moisture Content	1.57	1.57	1.57	1.59
3	% Drug Content	100.1	99.9	100.1	100
4	**%** Drug Release	92.2	92.1	92.2	91.9

Table :20 Stability results for selected formulation

Discussion

Methylphenidate Hydrochloride controlled release capsules were prepared by using Fluidized Bed Process. Methylphenidate Hydrochloride was used to treat ADHD in children. Methylphenidate blocks dopamine uptake in central adrenergic neurons by blocking dopamine transport or carrier proteins.

In preformulation study**,** API characterization was done. Drug and excipient blends were subjected to compatibility studies. From the FT-IR reports, it was found that there was no incompatibility between Methylphenidate Hydrochloride and other excipients. Physical compatibility was also tested by subjecting the blend to various storage conditions and it was found that the blend was stable.

From DSC study ,it was concluded that for Methylphenidate Hydrochloride the onset of peak point was 218.5^0C and peak appeared at the point of 221.34^0C.So by these values, the melting point of Methylphenidate Hydrochloride was determined and the API used in the present study was stable.

Evaluation of drug Loaded pellets was carried out. All the Methylphenidate Hydrochloride formulations were tested for particle size by sieve analysis using mechanical sieve shaker. The size of pellets was found to be within the range of standard sieves. All the pellets were passed through sieve no.16 easily and retained on sieve No.20.

Bulk density of all formulations of Methylphenidate Hydrochloride pellets were found to be in the range of 0.64-0.67 gm/ml. Tap density of all formulations of Methylphenidate Hydrochloride pellets were found to be in the range of 0.68-0.71 gm/ml.

The percentage of moisture content of all formulations of Methylphenidate Hydrochloride pellets were found to be in the range of 1.42-1.98%.

Evaluation of drug loaded pellets also carried out. Weight variation of all formulations of Methylphenidate Hydrochloride capsules were found to be in the range of 453.5 to 455.9 mg. Lock length of the capsules containing pellets was found to be 7.8mm

Capsules containing Methylphenidate Hydrochloride formulations have shown the drug content uniformity in the range of 98.3%-100.1%.

In vitro dissolution studies were carried out for all formulations. Drug release profile of F1 was less when compared with the reference product.More percent of drug was released in initial hours.By gradually increasing the concentration of Ethyl Cellulose N-45 and PEG6000 release rate was decreased.So a pore former HPMC E5 in concentration of 10% of Ethyl cellulose N-45 was introduced in the formulation F4.In this case drug release rate was good but release profile does not match with the reference product.

From F5 formulation,HPMC E5 in concentration of 5% of Ethyl Cellulose N-45 was used .The percent drug release was better but it does not matches with the reference product drug release profile.

In F6 formulation,drug release profile was good but in last four hours drug release rate was less when compared with the innovator drug release profile .So in F7 Ethyl Cellulose N-45 concentration was reduced to 2.3% .In this formulation,a maximum of 93.9%drug release was obtained at the 10^{th} hour and also drug release profile was matches with the reference product release profile.So the formulation F7 batch was the optimized batch.

Stability studies were conducted for F7 at two different storage conditions 25ºC ± 2ºC /60%RH ± 5% , 40ºC ± 2ºC /75%RH ± 5% for a period of 90 days. The formulation was found to be stable with respect to physical appearance, percentage moisture content, percentage drug content and percentage drug release.

SUMMARY

Controlled release Methylphenidate Hydrochloride capsules were developed in order to meet the required bio-availability and its *in-vitro* release pattern was studied.

The present work involves Preformulation studies, Physical drug excipient compatibility studies, Analytical method development, Manufacturing of capsules filled with drug loaded pellets and Evaluation procedures for pellets and capsules.

In the preformulation studies, the API was studied for various parameters like physical description, Solubility and DSC studies.

Drug excipients compatibility study was done every week for any color change or lumps formation and flow, storing at 40^{o}C/ 75% RH, 2-8^{o}C. It was found that no change in the color for all combinations.From the FT-IR reports, it was found that there is no incompatibility.Standard graph for the drug Methylphenidate Hydrochloride was plotted and the results were found to be accurate and precise.

In this study Methylphenidate Hydrochloride extended release pellets (40 mg) were prepared by Fluidized Bed Processing. The pellets were evaluated for various parameters. Various formulations were developed by changing the strengtht of Ethyl cellulose N-45.

All the Methylphenidate Hydrochloride formulations were tested for particle size by sieve analysis. The size of pellets (841-1190µm) was found

to be within the range of standard sieves. Bulk density of all formulations of Methylphenidate Hydrochloride pellets were found to be in the range of 0.64-0.67 gm/ml. Tap density of all formulations of Methylphenidate pellets were found to be in the range of 0.68-0.71 gm/ml. The moisture content of all the formulations was found to be within the range of 1.20 – 1.98 %. The compressibility of all formulations was found to be within the range of 14.81-20.45.

Capsules filled with pellets were evaluated for various parameters. The weight variation was found to be within the limits. Lock length of the capsules containing pellets was found to be 7.8mm. Capsules containing Methylphenidate Hydrochloride formulations have shown the drug content uniformity in the range of 98.3%-100.5%.

Various formulations were developed by changing the strength of sugar spheres, Ethyl cellulose N-45 ,PEG6000 and HPMC E5. All the formulations showed better results with respect to physical appearance and particle size etc, but the drug release profiles were varying.

By increasing the concentration of Ethyl Cellulose N-45 the drug release profile was varying with other formulation. Formulations were done by increasing the concentration of Ethyl Cellulose N-45. At the strength of 2% w/w the drug release was below the reference drug release profile, at 2.5% w/w (F6) the profile was having good similarity but at optimum concentration of 2.3 % w/w (F7) the dissolution profile was found to be similar to the reference drug release profile.

It was found that while increasing the concentration of Ethyl cellulose, drug release was decreased from the formulations. So by incorporating the pore forming agent like HPMC E5,the drug release was increased. F7 formulation containing 2.3% Ethyl cellulose N45 polymer was

found to be best of all the formulations showing drug release of 93.9% and matching with the drug release profile of the reference product.

The best formulation was repeated again for reproducibility, and all the quality control tests were done for conformation. The results were found to be super imposable with each other.

Stability studies were conducted for optimized formulation (F7) at two different storage conditions 25ºc ± 2ºC /60%RH ± 5% , 40ºC ± 2ºC /75%RH ± 5%for a period of 90 days. The formulation was found to be stable with respect to physical appearance, percentage moisture content, percentage drug content and percentage drug release.

The optimized formula shall be utilized for the formulation development and also for other studies like bio-equivalence study, for successful launching of the product.

CONCLUSION

The formulation containing 40mg of Methylphenidate Hydrochloride was prepared as extended release capsules.These techniques are particularly useful for patients who should not administer the drug in repeated intervals.

The optimized formulation have consistent release profile to provide the drug release for longer duration of 10 hours. FTIR studies have shown that there was no considerable interactions between drug and excipients.The short term stability study also indicates no change in the physical characteristic of drug content.

The comparision of dissolution profiles between the Methylphenidate Hydrochloride extended release capsules 40mg and the reference drug, showed no major changes in the dissolution profiles. Hence, it can be concluded that the Methylphenidate Hydrochloride extended release capsules were successfully developed and evaluated.

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