FORMULATION AND *IN- VITRO* EVALUATION OF ATORVASTATIN CALCIUM IMMEDIATE RELEASE PELLETS

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Submitted by

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MELMARUVATHUR – 603 319

October 2012

CERTIFICATE

This is to certify that the research work entitled **" FORMULATION AND *IN-VITRO* EVALUATION OF ATORVASTATIN CALCIUM IMMEDIATE RELEASE PELLETS"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **PALUSURU SUSHMA (Register No.26106015)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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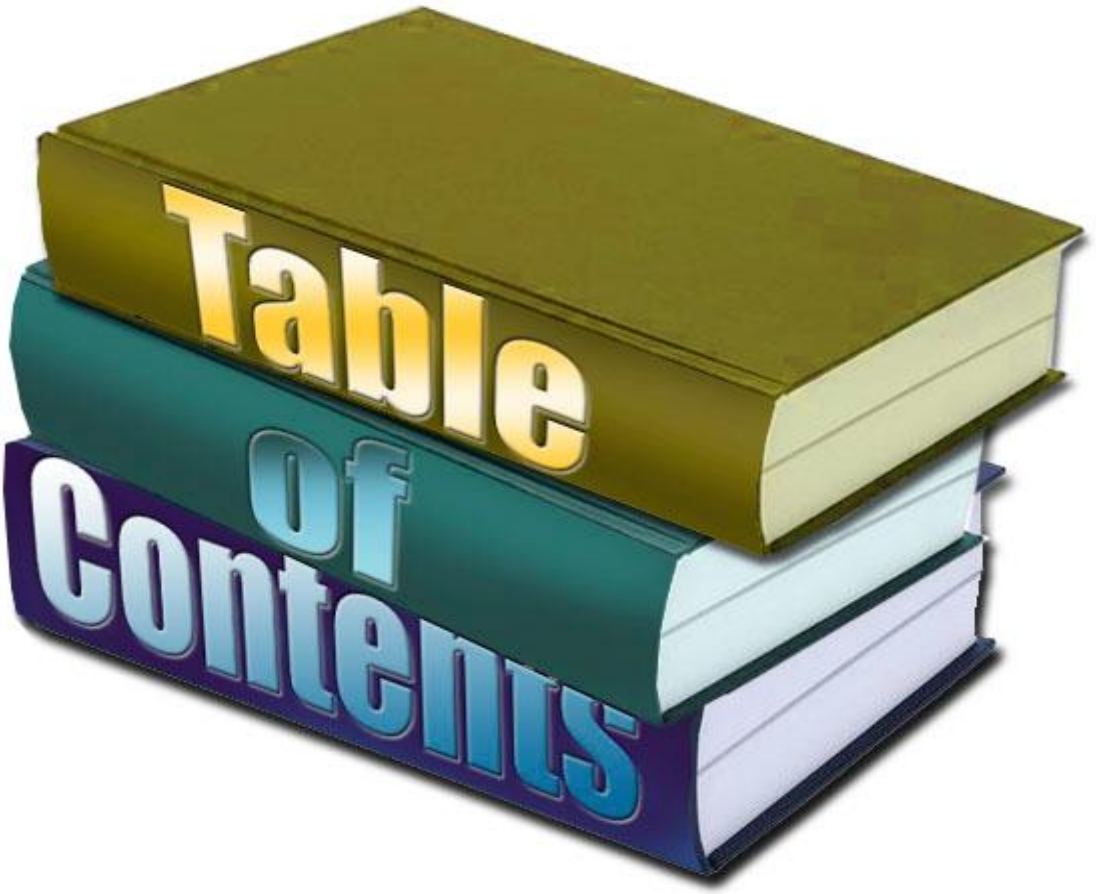
Dedicated To

My Beloved family

&

All My Friends... 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LIST OF ABBREVIATIONS

%	-	Percentage
µg	-	Microgram
API	-	Active Pharmaceutical Ingredient
ATC	-	Atorvastatin calcium
AUC	-	Area under curve
BP	-	British Pharmacopoeia
C	-	Slope
CH	-	cholesterol
CP	-	Crospovidone
CCS	-	Croscarmellose sodium
Cps	-	Centipoises
DDS	-	Drug Delivery System
F	-	Formulation
FT-IR	-	Fourier Transform Infra-Red spectrum
FDA	-	Food Drug Administration
Gm	-	Gram
GMP	-	Good manufacturing practice.
HMG-COA	-	Hydroxy methyl glutaryl coenzyme A
HCl	-	Hydrochloric acid
HDL	-	High density lipoproteins
Nm	-	Nanometer
N	-	Newton
ICH	-	International Conference on Harmonization

i.e	-	That is
IP	-	Indian Pharmacopoeia
-IRPs	-	Immediate release pellets
IV	-	Intravenous
KBr		Potassium Bromide
LOD	-	Loss On Drying
M	-	Slope, Units of response
MP	-	Macro phase
Ml	-	Milli litre
MUDFs	-	Multiple unit dosage forms
mg	-	Milligram
MCC	-	Micro crystalline cellulose
Mp	-	Melting point
MPDDS	-	Multi particulate drug delivery system
NDDS	-	Novel Drug Delivery System
pH	-	Negative Logarithm of hydrogen ion Concentration
RH	-	Relative Humidity
T	-	Time
$t_{1/2}$	-	Biological half-life
USP	-	United States Pharmacopoeia
UV-VIS	-	Ultraviolet-Visible Spectroscopy
VLDL	-	Very low density lipoprotein

INTRODUCTION

1. INTRODUCTION

1.1 ORAL DRUG DELIVERY SYSTEM

(Chein Y.W., 1995, Robinson J.R., et al., 2005)

The term drug delivery covers a very broad range of techniques used to get therapeutic agents into the human body. The limitation of the most obvious and trusted drug delivery techniques, those of the ingested tablet and of the intravenous (IV)/ subcutaneous (SC)/ intramuscular (IM) injections, have been recognized for some time now. The former delivers drug into the blood only through the hepatic system, and hence the amount in the blood stream may be much lower than the amount formulated into the tablet (ie; it has low bioavailability); furthermore, liver damage is an unfortunate side effect of many soluble tabletted drugs. The injection mode of delivery can be used to deliver any size of drug molecule and is versatile in this regard, but it suffers from the obvious.

Solid dosage forms are the most popular category of pharmaceutical formulations. They are in sense convenience dosage forms and in comparison to the liquid formulations, their stability is of a very high order.

Oral drug delivery has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Indeed oral administration improves patient's quality of life because it is practical and prevents intravenous drawbacks (catheter infection; thrombosis and extravasations) (Lagarce et al; 2011). However, limitations in the physical-chemical properties of the drug sometimes prevent a successful therapeutic outcome. Specifically problems of poor solubility and chemical stability in the gastrointestinal tract, poor permeability and sensitivity to metabolism are often causes that result in the rejection of potential drug candidates as commercial products.

Based on the desired therapeutic objectives, the Oral DDS may be assorted into different categories

- Immediate release DDS
- Delayed release DDS
- Controlled release DDS
- Sustained release DDS

- **Immediate release drug delivery system**

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as immediate release of drug without any special rate controlling features such as special coatings and other techniques.

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience drug administration to dysphasic patients, especially the elderly and bedridden and new business opportunities. Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants such as sodium starch glycolate, croscarmellose sodium and crospovidone.

Immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release dosage form has emerged as alternative dosage form. There are novel types of dosage forms that act very quickly after administration. The basic approach used in development of pellets is the use of superdisintegrants like croscarmellose sodium (CMC), sodium starch glycolate, crospovidone etc., which provide instantaneous disintegration after administration.

- **Delayed release drug delivery system**

The design of such system involves release of drugs only at a specific site in the gastrointestinal tract. The drugs contained in such a system are those that are

i. Destroyed in the stomach or by intestinal enzymes.
ii. Known to cause gastric distress.
iii. Absorbed from a specific intestinal site or
iv. Meant to exert local effect at a specific gastro intestinal site.

The two types of delayed release systems are:

I. **Intestinal release systems:** A drug may be enteric coated for intestinal release of several known reasons such as to prevent gastric irritation, prevent destabilization in gastric pH etc.

II. **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.

- **Controlled release drug delivery system**

Controlled drug delivery is delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time.

Advantages:

1. Improved patience compliance and convience due to less frequent drug administration.
2. Reduction in fluctuation in steady state and therefore better control of disease conditions and reduced intensity of local and systemic side effect.

3. Increased safety margin of high potency drugs due to better control of plasma levels.

4. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

Disadvantages:

1. Poor *in-vitro – in-vivo* correlations.

2. Possibility of dose dumping due to food, physiologic formulation variables or chewing or grinding of oral formulation by the patient and thus increased risk of toxicity.

3. Retrieval of drug is difficult in concentration of toxicity, poisoning or hypersensitivity reaction.

- **Sustained release drug delivery system**

The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration.

In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions.

Sustained release, sustained action, prolonged action, extended action are the terms used to identify drug delivery system that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Advantages:

1. Improvement of patient compliance because of decreased frequency of dosage.
2. Reduction in adverse effects, this is because of the nature of its release kinetics, a sustained release formulation should be able to use less total drug over the time course of therapy, than conventional preparation.
3. Avoidance of costly interventions such as laboratory services.
4. Optimization of duration of action of drug.
5. Controlling the site release.

Disadvantages:

1. Increased variability among dosage units.
2. Stability problems.
3. Increased cost per unit dose.
4. More rapid development of tolerance.
5. Need of additional patient education and counseling.

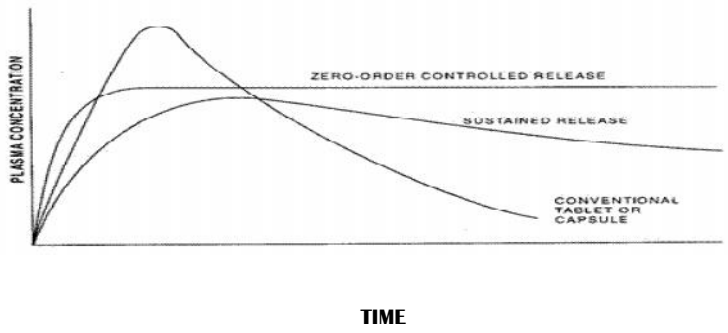


Figure: 1.1. Plasma drug concentration profiles for conventional, sustained, zero order controlled release formulations.

1.2. MULTI PARTICULATE DRUG DELIVERY SYSTEM

(*Kammali Lavanya., et al., 2011, Parag A. Kulkarni., et al., 2010)*

Oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally, oral dosage forms are classified as single unit and multiple unit dosage forms. Multi particulate dosage forms are receiving an immense attention as alternative drug delivery system for oral drug delivery even though single unit dosage forms have been widely used for decades. The most commonly used pharmaceutical solid dosage forms today include, granules, pellets, tablets and capsules, out of which tablets being the most popular dosage form, accounting for 70% of all ethical pharmaceutical preparations produced. But soon it was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphasia, etc) comes along with the single dose formulations. This lead to the dividing of monolithic dosage forms into multiples.

Multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits with diameter of 0.05-2.00 mm. To deliver the recommended total dose, these subunits are filled into a capsule or compressed into a tablet. They provide many advantages over single unit systems because of their small size. Multi particulates are less dependent on gastric emptying, resulting in less inter and intra–subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation.

Recently much emphasis is being laid on the development of multi particulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of local irritation and predictable gastric emptying.

MUDFs are formulated as granules, pellets or mini tablets. These MUDFs, can either be filled into hard capsules or compacted into bigger tablets or can be dispensed in a dose pouches or pack lets.

1.2.1. TYPES OF MPDDS (*www.ordonearresearchlibrary.org)*

- Drug crystals
- Irregular granules
- Spheronized granules (pellets)
- Drug – loaded non- pareils (pellets)
- Mini tablets
- Melt – spray – congeal microspheres

In order to get MPDDS, drug is distributed in small particles (0.05-0.2 mm) and then film coated to get desired drug release characteristics. Here is the account of different types of MPDDS.

❖ Drug crystals

Drug Crystals, of appropriate size and shape can be coated with a modified release film coating.

❖ Irregular granules

Granules used in the preparation of tablets, can be film coated. Irregular shape and variation in particle size make it difficult to achieve uniform coating thickness around each particle.

❖ Spheronized granules (pellets)

Sphere–shaped particles simplify the coating process. The production of spheroidal particles (pellets) is achieved by extruding the powdered mass, then cutting into small cylindrical particles and finally spheronizing these particles to spherical shape.

❖ Drug -loaded non –pareils (pellets)

Spherical particles about 1mm in diameter consisting primarily of sucrose and starch called 'non-pareils' which are available in the market. Following techniques can be used to get drug loaded non pareils.

- A powder- dosing technique involving alternate dosing of powder (containing drug substance) and binder liquid onto the surface of the non- pareils until the required dose of the drug has been loaded.
- Spray application of drug, either suspended or dissolved in a suitable solvent (usually water) containing a polymer (such as hydroxy propyl methyl cellulose or polyvinyl pyrrolidine) as a binder onto the surface of the non-pareils.

❖ Mini tablets

Many of the other types of multi particulates described suffer from two potential batch wise drawbacks, namely:

- Variation in particle size distribution.
- Variation in particle shape and surface roughness.

Such variability can result in variable coating thickness and thus product performance. This problem can be overcome by using mini compressed tablets (size range of 1-2 mm) produced using modification of traditional tabletting processes.

❖ Melt-spray-congeal microspheres

Spherical, smooth, 50-µm to 300-µm particles, typically with embedded API, can be produced by a continuous spinning disk process.

The current review focuses on the pelletized form of multiple units, they are prepared by process called Pelletization which is referred to as a size enlargement process and the final product obtained is called pellets.

1.3. PELLETIZATION *(Puniya Supriya., 2012)*

Definition

Pellets are described to be produced systematically, as geometrically defined agglomerate obtained from diverse starting materials using different processing conditions. They are free-flowing, spherical or semi-spherical solid units with a size range of about 0.5 - 1.5 mm and that are intended mostly for oral administration.

Ideal properties of the pellets

- Spherical shape and smooth surface.
- The particle size of pellets should be in range of 600-1000µm.
- The quantity of the active ingredient in pellets should be maximum in order to maintain size of pellet.

1.3.1. ADVANTAGES OF PELLETS **(***Patel H., 2010)*

In many cases the main reason for the use of pellets in the manufacture of products with controlled release properties. However there are reasons to believe that these multiple unit dosage forms in any case can offer a superior therapeutic effect even when modified release is not the primary objective.

1. Improved appearance of the product which is having fine pharmaceutical elegance.

2. Pelletization offers flexibility into the dosage form design and development.

3. Pellets improve the flow properties in formulation development.

4. They flow freely and are easy to pack without significant difficulties (resulting in uniform and reproducible fill weight of capsules).

5. Pellets are less susceptible to dose dumping.

6. It reduces accumulation of drugs especially proven advantageous in the case of irritating drugs.

7. It improves safety and efficacy of a drug.

8. Pelletization is a convenient way to manage the separation of incompatible drugs.

9. Pellets offer reduced variation in gastric emptying rate and intestinal transit time.

1.3.2. DISADVANTAGES OF PELLETS

1. Dosing by volume rather than number and splitting into single dose units as required.

2. Involves capsule filling which can increase the costs or tabletting which destroy film coatings on the pellets.

3. The size of pellets varies from formulation to formulation but usually lies between 1 to 2 mm.

1.3.3. THEORY OF PELLET FORMATION AND GROWTH

(Kammali Lavanya., et al., 2011)

Before selection and optimization of any Pelletization /granulation process, it is important to understand the fundamental mechanisms of pellet formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while others are derived by visual observations. Out of these hypothetical theories the most convincing classification is

of Pelletization process, involves three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.

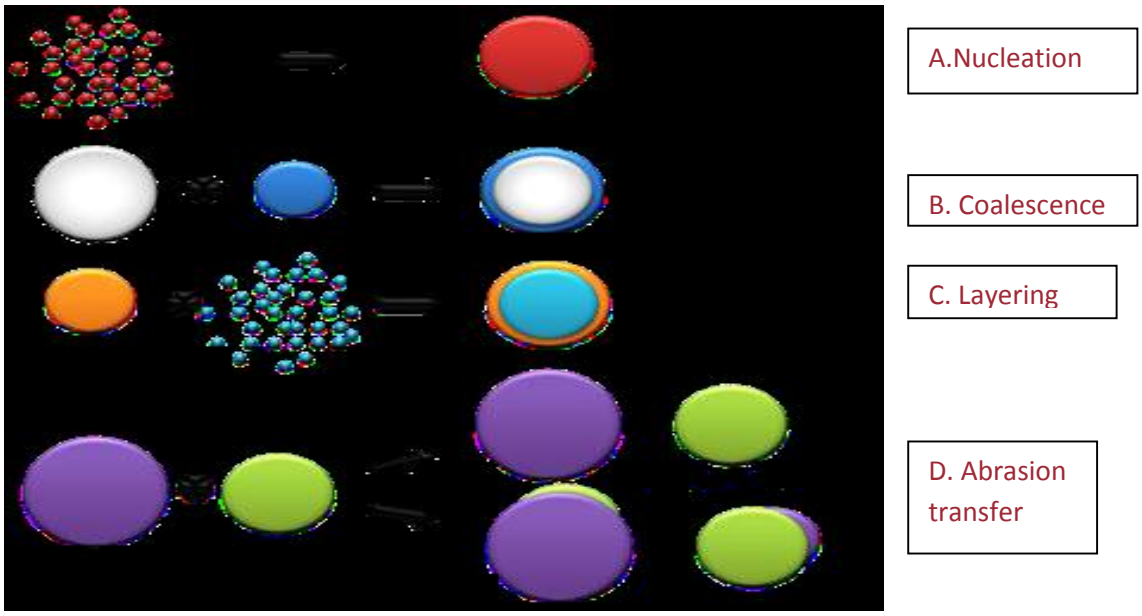


Figure: 1.2. Pellet Growth Mechanism.

The fines and the fragments produced through size reduction are taken up by larger pellets. Production of fines and subsequent coalescence and layering continues until the number of collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached. The main mechanism in the ball growth phase is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. This phase does not result in any change in the total number or mass of the particles. However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist.

1.3.4. METHODS OF PREPARING PELLETS

Compaction and drug layering are the most widely used pelletization techniques in Pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods such as globulation, balling and Compression are also used in development of pharmaceutical pellets although in a limited scale.

- **Drug layering**

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked off by the wet mass of pellets that is being layered.

Spraying → Wetting distribution → Layer formation → Pellet

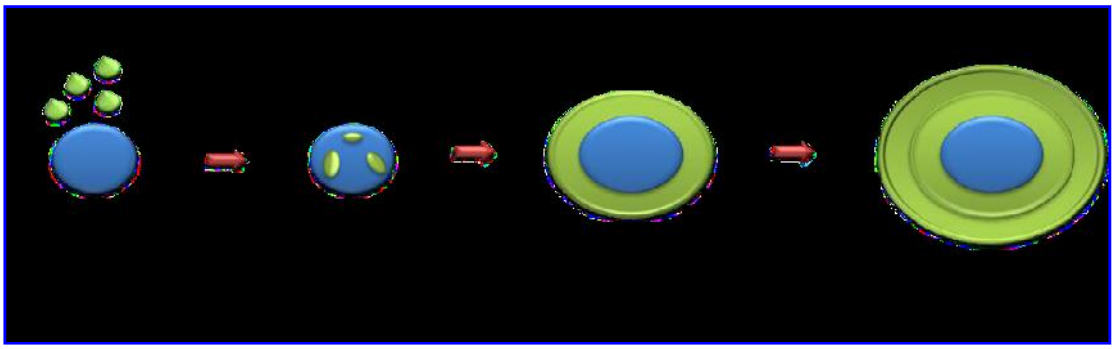


Figure: 1.3. Drug layering method by using solution.

- **Suspension layering**

Suspension layering involves the deposition of successive layers of suspensions of drug substances and binder over the starter/non-pareil seeds, which is an inert material or crystals/granules of the same drug. In fact the coating process involved in general is applicable to suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

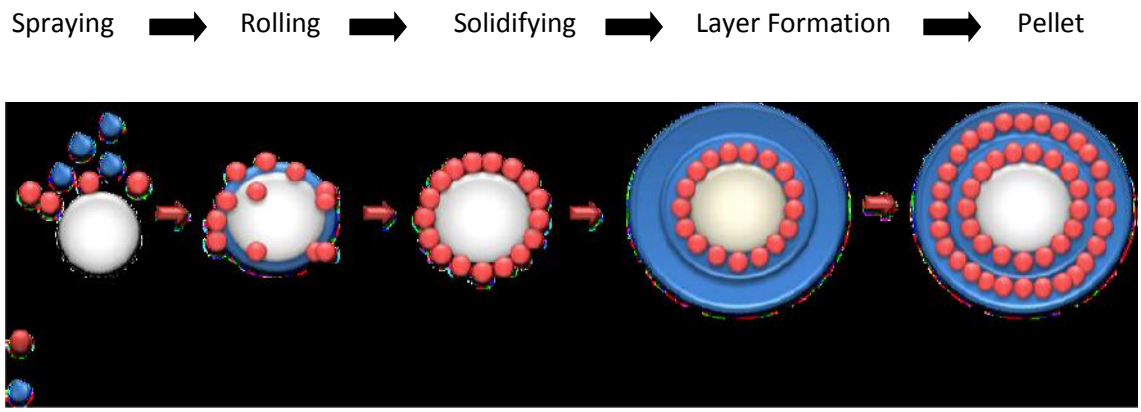


Figure: 1.4. Drug layering method by using suspension.

- **Pelletization by extrusion and spheronization**

The process involves first making the extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc). Beads are fine as 0.6mm can be made.

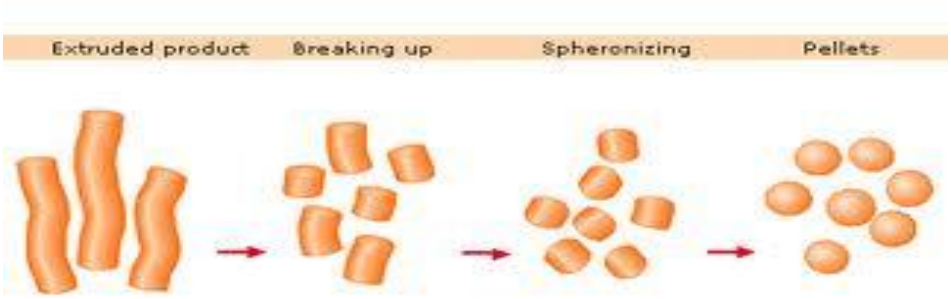


Figure: 1.5. Extrusion and spheronization process

- **Direct pelletization**

Sample material is blended and solvent or binder system is added to it. The material bed is then subjected to a centrifugal motion. The centrifugal forces act on the material in this process resulting in the formation agglomerates, which get rounded up into uniform sized dense pellets. The size, density and shape of the pellets formed are influenced by the speed of rotation. The moist pellets formed are then dried up in the fluid bed. Organic solvents can also be used if required.

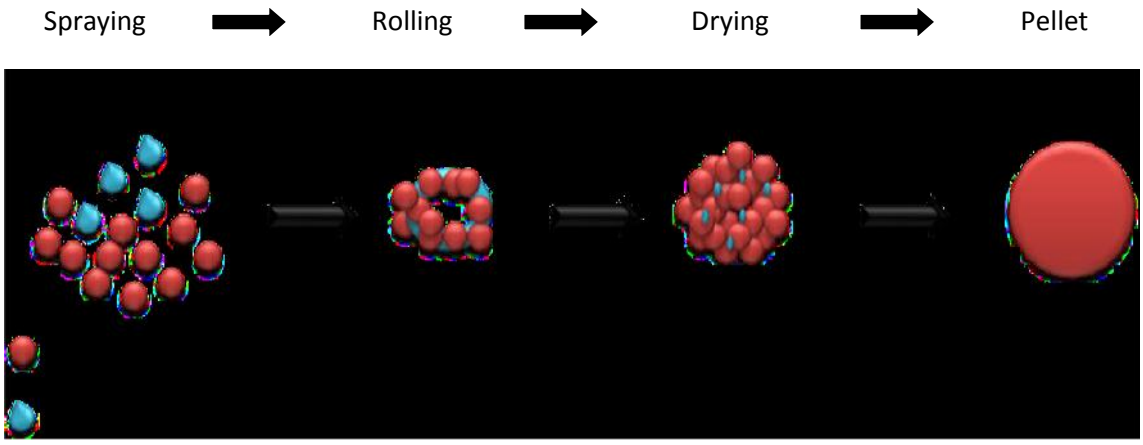


Figure: 1.6. Direct pelletization process for preparation of pellets.

- **OTHER PELLETIZATION METHODS**

Other pelletization methods such as globulation, cryopelletization, balling compression are also used, although a limited scale in the preparation of pharmaceutical pellets.

- **Globulation** or droplet formation consists of two related processes, spray drying and spray congealing.

❖ Spray drying

It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs.

❖ Spray congealing

It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate and controlled release pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables.

- **Cryopelletization**

It is a process in which the liquid formulation is converted in to solid spherical particles or pellets in the presence of liquid nitrogen as fixing medium. The shape depends up on the distance the droplet travel before contacting liquid nitrogen.

- **Compression**

It is one type of compaction technique for preparing pellets. Compacting mixtures or blends of active ingredients and excipients under pressure prepare pellets of definite sizes and shapes. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing.

- **Balling**

It is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles in to spherical particles upon the addition of appropriate amounts of liquid.

- **EXCIPIENTS FOR PELLETS**

Formulation aids or excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of the drug to the intended site, to impart favourable characteristics to the dosage form and to facilitate the manufacture of the product. Since pellets are intended to be administered orally, the excipients used in the pellet dosage forms are typically the same as those used in tablet or capsule formulations.

Excipients, Disintegrants, Surfactants, pH adjusters, Separating agents, Spheronization enhancers, Glidants and release modifiers etc. some examples of such excipients are given in

Table: 1.1. Examples of Excipients commonly used for pellets

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, SLS
Spheronization enhancer	MCC , sodium CMC
Glidant	Talc, starch, Mg stearate.
Release modifier	Ethyl cellulose, carnauba wax, shellac.

1.3.5. PELLET COATING PROCESS

The coating process for pellets is carried out primarily in order to modify the release of the drug from the pelletized drug delivery systems. Following are the some of the coating equipments used for this purpose Most of the coating processes use one of three general types of equipments.

- The standard Coating pan
- The Perforated Coating pan
- The Fluidized bed coater

❖ Standard coating pan

The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan .Coating solutions are applied by spraying the material on the bed surface.

❖ Perforated coating pan

Neocota is an automatic coating system for tablets and pellets.Neocota is a completely updated automatic coating system having a batch capacity of 500 g to 1 kg. This model efficiently carries out the following operations: Aqueous film coating of tablets/pellets; Non-aqueous organic solvent based film coating of tablets/pellets; and enteric film coating of tablets/pellets.

The basic units of the system are: Coating pan has perforations along its cylindrical portion. It is driven by a variable speed drive with a flame-proof motor. Supply of hot air and exhaust of drying air are arranged to facilitate the coating system through stainless steel platinums positioned on both sides of the perforated coating pan. The pan is enclosed in a

cylindrical air tight housing provided with a suitable door and front glass window. This housing of pan with drive is a stainless steel cabinet acommodating the gearbox, AC variable drive, power panel, hot air unit, ex-haust unit and an air fitter.

Liquid spray system is complete with stainless steel liquid storage vessel, variable flow-rate liquid dosing pump, automatic spray gun, and inter-connecting flexible hoses.

An important disadvantage of pan coater is limited process control. More recently modified pan coaters have been developed, which resolve many of the drawbacks related to the old system.

The problems of drug layering pelletization by conventional pan coaters had led to the development of two types of rotary granulators.

- Fluidized –bed granulators
- Centrifugal granulators.

These devices offer many advantages including lower manufacturing costs, flexibility of operation and ease of automation.

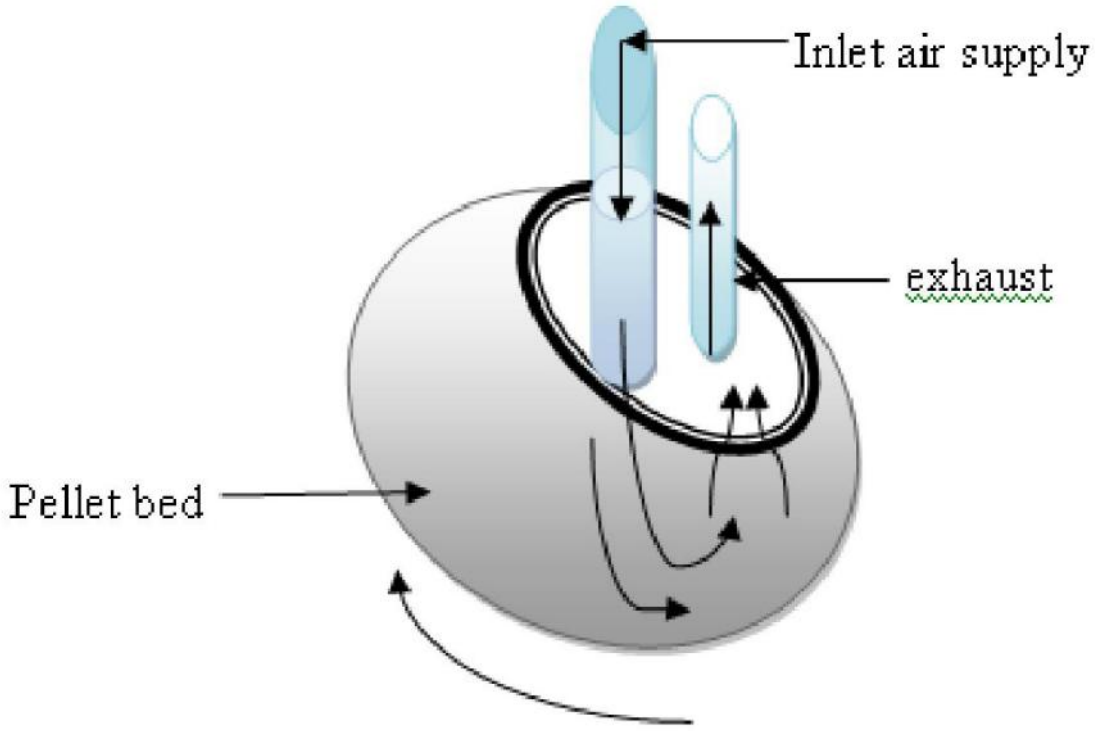


Figure: 1.7.Conventional pan coater

❖ THE FLUIDIZED BED COATER

The Fluid Bed Technology offers a very efficient coating technique. The major advantage of the Fluid Bed Systems is that it is as per GMP standards it is a closed system. The second advantage of the Fluid Bed Systems is that not only coating but granulation and pellet formation is also possible in the same machine. Fluidized bed coating is a process that takes place inside a fluidized bed whereby a coat is introduced to cover the intended object in order to protect it or modify its behaviour. Particulate coating is a form of fluidized bed coating involving the coating of solid particles inside the bed. In the process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution of the coating material. The fluidizing gas is also use to dry the deposited solution to form a coat on the surface of the particle. There is considerable diversity in methods of using fluidized bed

technology. For e.g. liquids can be applied to fluidized particles in a variety of ways, including top, bottom and tangential spraying. For a given product, each method can offer markedly different finished product characteristics. Fluidized beds are used for coating because of their high energy and mass transfer. Fluidized beds for film coating can be divided into three groups.

- Top -spray
- Bottom –spray equipments
- Tangential-spray

- **Top spray** (*Wurster.D., 1953*)

The expansion chamber is lengthened to allow powder to remain fluidized longer and to move with a higher velocity, so that agglomeration is minimized. The expansion chamber is conically shaped to allow uniform deceleration of air stream .The filter housing is larger and designed to shake the fines back into the bed interrupting fluidization this reduces agglomeration tendencies.

The nozzle is positioned low in the expansion chamber so that coating material impinge on the fluidized particle a short distance from the nozzle; this reduces droplet spray drying and provides for longer subsequent drying of the coated particles. The top spray coater has been used to apply aqueous and organic solvent based film coatings, controlled release coatings.

- **Bottom spray coating (wurster process, Make-GLATT)**

The wurster machine employs a cylindrical product container with a perforated plate. Inside the container is a second cylinder (coating partition) with is raised slightly above the perforated plate, centered in the plate below this partition is a spray nozzle used to dispense the coating solution. The perforated plate is designed with large holes in the area under the

coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter. The design allows the substrate particles to be pneumatically transported upward through the coating partition, and downward outside this partition. Material passing through coating partition receives a layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state. Material circulates rapidly in this fashion and receives layer of coating material, dries in the expansion chamber, and falls back in a semi fluidized state material circulates rapidly in this fashion and receives a layer of coating on each pass through the coating partition. The ring of large holes on the periphery of perforated plate prevents the accumulation of material at the container wall. It has been used for coating small particles, pellets and tablets.

Table: 1.2. Parameters Used in Bottom Spray Equipment

Inlet temperature	38-42ºC
Product temperature	32-36ºC
Exhaust temperature	32-38ºC
Spray rate	8-12mg/min
Peristaltic pump	12-18 rpm

- **Fluid bed coating**

Particles smaller than approximately 2mm should be coated in fluid bed equipments, because with decreasing particle diameter the specific surface area of a substrate increases dramatically. Thus, the required coating weight gain is much higher than tablet coating processes. In order to achieve acceptable process times, the high efficiency of fluid bed compared to pan coating equipment shows clear advantages in particles coating processes.

Shape - In order to achieve good flow properties, spherical particles with smooth surfaces are preferred, while needle shaped particles show poor flow properties and tend to form lumps. Another advantage of the latter is the increased risk of breakage during the coating process, creating uncoated spaces and leading to an increased coating weight gain .Besides crystals and pellets, granules can be used as substrates as a disadvantages. We may have uneven surfaces and often increased abrasion compared to the shapes mentioned first, which can also lead to increased surface areas which require higher amounts of coating.

Size- Usual particle sizes are in arrange of 0.2-1.2mm.smaller particles may have problematic flow properties in higher scale and may tend to break if the length /diameter-ratio is 2. Smaller particle size are required if particles are administered from sachets or incorporated into chewable tablets. In order to avoid damage by chewing, the coated particles should have a maximum size of 0.4mm smaller end products may given a better mouth felling but increasing specific surface areas requires higher coating amounts.

- **Tangential spray**

The tangential spray method is known and used for particle coating and granulation processes. Compared to other fluid bed coating technologies, the top spray method is susceptible for porous film structure, especially if organic coating formulations are processed. Bottom spraying (wurster process) is the usual method in particle coating due to a more uniform particle movement, better film structures can be achieved compared to the top spray method, and the required polymer weight gain for a certain function is usually lower to some extent. A disadvantage is that in case of nozzle blockage during the coating process, the product must be discharged before the nozzles can be cleaned. Tangential spraying system, which is commonly fitted with a rotating bottom plate, can achieve film quantities nearly as

good as bottom–spraying system. The rotation of the plate nicely supports product movement, so that the required air amount is mainly used for drying process and only to a smaller degree for the product movement.

Nozzles for the particle coating – Common spray gun are air-borne with a round spray pattern. Some equipment is fitted with a double air supply which is used for common atomizing air and extra microclimate air, which surrounds the spray pattern, preventing over wetting of the product and reducing spray drying effects.

Pump system – Peristaltic pumps fitted with silicon tubing are standard. Tubing can be selected in a wide range of internal diameters in order to keep the flow speed high and hence to prevent sedimentation. Therefore the use of tubing with small internal diameters recommended. Alternative pump systems include gear pumps and piston pumps.

Rotating disk granulation - Granulation techniques utilizing centrifugal fluidizing drive has been studied only recently. These techniques have been extended to coating operations and combined with an expansion chamber to form the rotating disk granulator and coater fluid bed device. The basic design employs a rotating disk in the product container. The disk can be moved up or down to create a variable slit opening between the outer perimeter of the disk and the sidewall of the container. Air is drawn into the product container through the slit under negative pressure. This fluidizes the material along the circumferential surface of the product container. At the same time the disk rotates at varying speeds and moves the product by the centrifugal force to the outer portions where it is lifted by the fluidizing air stream into the expansion chamber. As the material decelerates, it descends to the centre of the disk and repeats the same sequence. The fluidization pattern is often

described as a spiralling helix or rope-like pattern around the inside of the rotor chamber. Spray nozzles can be immersed in the bed of fluidized material and spray applied in tangential fashion with respect to the particle flow.

Table: 1.3. Different polymers used in the pelletization process

(*www.ijpsr.com)*

Polymer used in pelletization	Formulation	Applications
Carbopol 974P,NF, Resin.	Beads containing Weakly basic drugs.	Slower release of the salts of weakly basic drugs.
Crosscarmellose sodium or sodium starch glycolate.	Super-disintegrants in avicel pellets.	Increase dissolution rate, increase the pellet micropore volume.
Eudragit RS PO and RL PO.	Polymer (with combination) based pellets.	Better characterization like elastic modulus of the pellets, surface characteristics, sphericity.
Eudragit RL 30D, RS 30D, NE 30D.	A multiple- unit floating drug delivery system.	Prolong the gastric residence time and to increase the overall bioavailability of the dosage form.
Gelucire.	Lipidic –matrix pellets.	Controlled drug release.
Methocel-E5 (HPMC) or AMB, Eudragit L 30D-55.	Enteric coated pellets.	Improved film formation and polymer coalescence.
Microcrystalline cellulose, Ac-Di- Sol.	Floating pellets with bacterial antagonist.	Improving floating property.
Microcrystalline cellulose and hydroxy propyl methyl cellulose.	Pellets with water insoluble drugs in self-emulsified form.	Controlling the drug release from the oral dosage forms.
Pectins or alginates.	Polysaccharide gel coated pellets.	Oral administration of theophylline in the coated pellets.

1.4. CAPSULES

(*Lachman L., et al.,1991)*

Capsule is a solid oral dosage form consisting of a shell and a filling. The shell is composed of a single sealed enclosure, or two halves that fit together and which are sometimes sealed. Capsule shells may be made from gelatin, starch or cellulose, or suitable

material, may be soft or hard, and are filled with solid or liquid ingredients that can be poured are squeezed. Capsule is a shell or a container prepared from gelatin containing one or more medicinal and/or inert substances. The gelatin capsule shell may be soft or hard depending on their formulation. Capsules are intended to be swallowed whole by the patient. In instances where patients (especially children) are unable to swallow capsules, the contents of the capsule can be removed and added (e.g., sprinkled) on soft food immediately before ingestion. In this case, capsules are used as a vehicle to deliver premeasured medicinal powder. Capsule dosage forms occupy more than 10% of the total dosage forms on the market (Augsburger, 1990). An example is Contac 600 (GlaxoSmithKline) in which the active ingredients in the capsule are encapsulated in hundreds of micro beads in a sustained release form (based on the Spansule ® technology).

1.4.1. Advantages of capsules

a. Ease of swallowing.

b. Dosage accuracy/uniformity: Precise fill volume of liquid fill unit delivers a greater degree of accuracy and consistency from capsule to-capsule and lot-to-lot.

c. Consistent manufacturing requirements: More accurate compounding, blending, and dispensing of liquid fill facilitates manufacturing.

d. Liquid blends are more homogeneous.

e. Increase in bioavailability: Absorption and bioavailability can be enhanced by formulating compounds in solution including solubilizers and absorption enhancers, if necessary.

f. Water-insoluble drugs may be formulated in a soft gel. Clinical studies have shown enhanced absorption and bioavailability with soft gel forms. Examples are Temazepam and Ibuprofen.

g. Enhanced stability and security: The tight hermetical sealing protects fill from air and environmental contamination. Gelatin shell can be formulated to block out ultraviolet light. Streamlined, one-piece design is tamper-evident.

h. Pliable shell: Soft gel shell allows for custom shapes and sizes appropriate for oral, topical, chewable and suppository delivery.

i. Portability: Encapsulated liquid dosage formulations become highly portable for consumers/patients.

Applications

Soft gelatin capsules can be used to encapsulate a variety of liquids, such as oils, hydrocarbons, organic acids, polyethylene glycols, and nonionic surfactants. Some liquids can migrate through the capsule shell, and those liquids cannot be encapsulated into the soft gelatin capsules. These include water and low molecular weight water-soluble organic compounds. Soft gelatin capsules can also be used to encapsulate dry fills, such as powders, granules, and pelletized materials.

1.5. SUPER DISINTEGRANTS *(www.pharmainfo.net)*

A disintegrant helps the capsule to break up into small pieces upon contact with aqueous solution. Fast disintegration of a capsule in the oral cavity facilitates swallowing and increases the surface area of the capsule particles, which enhances the rate of absorption of the active ingredient to achieve the desired therapeutic effect. Every marketed pellets has a certain level of disintegrant and it is important to investigate which and how much disintegrant is necessary for a given pellet formulation. Disintegration starts when a small amount of water or saliva contacts the dosage form (wetting) and penetrates the capsule by capillary action. Therefore, the material properties of pharmaceutical excipients and also the pellet structure including pore size and distribution need to be considered for successful

formulation development. Since most disintegrants swell to some extent, swelling pressure is generally considered the main factor for pellet disintegration. Disintegrants or super disintegrants with efficient disintegrating properties at relatively low levels can be used in the formulation of immediate release pellets. They are generally added at a level of 1-10% (w/w %).

Disintegration efficiency is based on the force-equivalent concept (the combined measurement of swelling force development and amount of water absorption).Force equivalence expresses the capability of a disintegrant to transform absorbed water into swelling (or disintegrating) force. The optimization of pellet disintegration is commonly done by mean of the disintegration critical concentration. Below this concentration the pellet disintegration time is inversely proportional to the disintegrant concentration. Above the critical concentration, the disintegration time remains approximately constant or even increased. One of the most desirable properties of disintegrants is rapid swelling without an accompanying viscosity increase (no gel formation), because high viscosity on the surface of the capsule will hinder water penetration into the capsule matrix to slow disintegrants.

There are a lot of disintegrants and super disintegrants on the market and most of them can be considered for use in IRPs. Typical examples includes crospovidone (cross linked PVP) , Croscarmellose (cross linked cellulose), sodium starch glycolate (cross linked starch), and low- substituted hydroxypropylcellulose. Crospovidone is a synthetic and water insoluble cross-linked homo-polymer with the chemical structure of N-Vinyl-2-Pyrrolidone. A unique one-step polymerization process known as “pop corn” polymerization is used to synthesize crospovidone polymers. Cross linking chemically “entangles” the polymer chains and is a major determinant of the product properties. This process results in a porous structure with densely cross-linked polymers and a morphology that rapidly wicks liquid into a particle to

enhance swelling and disintegration. Crospovidone polymers are non-ionic. So their disintegration properties are independent of pH changes in the gastrointestinal tract. Moreover, they do not form gels.

Ac-Di-Sol (croscarmellose sodium) is internally cross-linked sodium carboxyl methyl cellulose. Primojel is a sodium starch glycolate produced by cross-linking and carboxyl methylation of potato starch. Both exhibit good water uptake with high capillary action and rapid swelling. The high swelling capacity together with high water penetration leads to fast tablet/capsule disintegration.

Disintegrants are usually water insoluble materials that swell on contact with moisture, therefore the addition of excess disintegrant can lead to grittiness after tablet disintegration. The appropriate disintegrant and disintegrant quantity should be carefully investigated for a given formulation.

The particle size distribution of Kollidon CL and Polyplasdone XL is similar. However, bulk and tapped densities of the both are significantly different due to the smoother surface of Kollidon CL or the porous structure of Polyplasdone XL, Kollidons CL-F and CL-SF have lower bulk densities than that of Polyplasdone XL because of their smaller particle sizes. Primojel has the highest bulk and tapped densities and Ac-Di-Sol is in between Kollidon CL and Primojel. Selection of right disintegrant depends on the formulation application and preparation procedure.

Crospovidone can work as an efficient disintegrant with fast swelling properties.

Need for fast disintegrating pellets *(Suresh Bandari., et al., 2010)*

The need for non-invasive delivery systems continues due to patients poor acceptance and compliance with existing delivery regimes , limited market size for drug companies and drug uses, coupled with cost of disease management.

The current needs of the industry are improved solubility / stability , biological half-life and bioavailability enhancement of poorly absorbed drugs. Key issues facing the biopharma industry are to improve safety (decreasing gastrointestinal side effects), improve efficacy for organ targeting, and improved compliance via sustained release or easy to swallow.

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical companies to survive. Pharmaceutical marketing is another reason for the increase in available fast-dissolving / disintegrating products. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast-dissolving / disintegrating pellet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusively , which can be provided by a fast- dissolving/ disintegrating dosage form, leads to increased revenue , while also targeting under served and under- treated patient populations. Although the cost to manufacture these specialized dosage forms exceeds that of traditional tablets, this additional cost is not being passed on to the consumer.

1.5.1. MECHANISM OF DISINTEGRANTS

The pellet breaks to primary particles by one or more of the mechanisms

- Capillary action (Wicking)
- Swelling
- Due to deformation
- Due to release of gases
- Due to disintegrating particle / particle repulsive forces
- By enzymatic action

- **Capillary action (wicking)**

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Capsule porosity provides way for the penetration of fluid into capsule. The disintegrant particles (with cohesiveness and compressibility) themselves act to enhance porosity and provide these capillaries into the tablet. Liquid is drawn up or leak into these ways by capillary action and rupture the inter-particulate bonds causing the capsule to break into small particles.

- **Swelling**

Not all disintegrants swell in contact with water swelling is believed to be a mechanism in which; certain disintegrating agents (like starch) impart their disintegrating effect. By swelling on contact with water the adhesiveness of other ingredients in a capsule is overcome causing the tablet to disintegrate.

Particles swell and break up the matrix from within swelling sets up localized stress spreads throughout the matrix.

Water is pulled into pores by disintegrants and reduces the physical bonding between Particles.

Figure: 1.8.Mechanism of capsule disintegration by wicking and swelling

- **Due to deformation**

Starch grains are generally thought to be "elastic" in nature that is the grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression force involved in tabletting, these grains are permanently deformed and are said to be "Energy Rich" with these energy being released upon exposure to water i.e., the ability for starch to swell is higher in "Energy Rich starch" grains than in starch grains that have not been deformed under pressure. It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms.

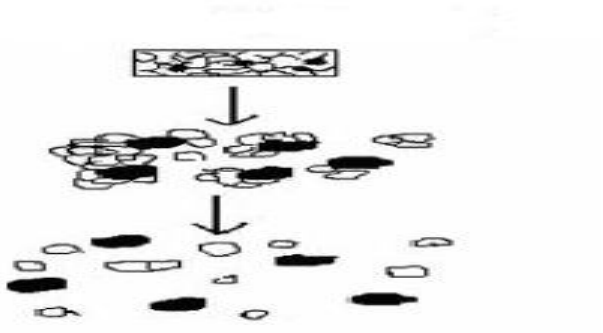


Figure: 1.9. Mechanism of capsule disintegration by deformation

Particles swell to pre compression size and break up the matrix.

- **Due to release of gases**

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when we needs to formulate very rapidly dissolving tablets or fast disintegrating tablet.

- **Due to disintegrating particle/ Particle repulsive forces**

Another mechanism of disintegration attempts to explain the swelling of capsule made with "non-swellable disintegrants". Guyot- Hermann has proposed a particle repulsion theory based on the observation of non swelling particles also cause disintegration of pellets.

- **By Enzymatic Reaction**

Table: 1.4. Enzymes presents in the body as disintegrants

ENZYMES	BINDER
Amylase	Starch
Protease	Gelatine
Cellulose	cellulose and its derivatives
Invertase	Sucrose

1.6. ANTI LIPIDEMIC DRUGS

Lipids

(*Anne Marie Helmenstine., 2005*)

The term 'lipid' was first used by the German biochemist Bloor in 1943 for a major class of tissue components and foodstuffs.

A lipid is a fat-soluble molecule. To put it another way, lipids are insoluble in water but soluble in at least one organic solvent. The other major classes of organic compounds (nucleic

acids, proteins, and carbohydrates) are much more soluble in water than in an organic solvent. Lipids do not share a common molecule structure.

Lipids are bio molecules which are soluble in organic non-polar solvents. Consequently, fats and lipids are insoluble in water. Glycerides and waxes form a sub-group of compounds which have an ester as the major functional group and including waxes, triglycerides, and phospholipids. Lipids without ester functional groups including steroids, fatty acids, soaps, sphingolipids and prostaglandins.

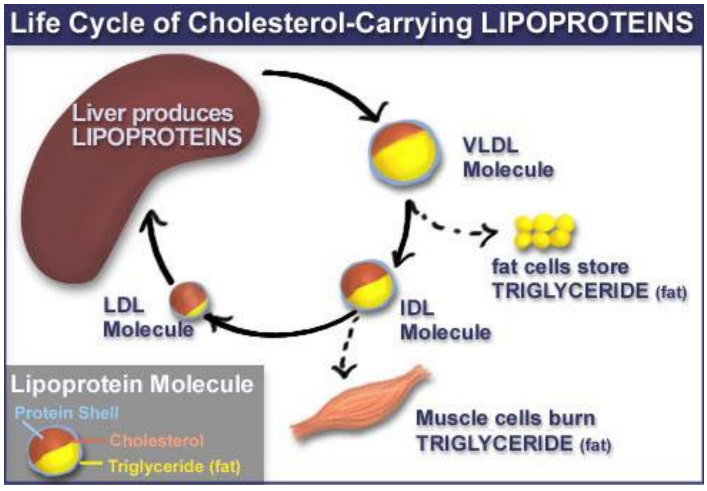


Figure: 1.10 Life Cycle of Cholesterol

Definition of lipids

(*James Richard Fromm., 1997*)

A lipid is defined as a water-insoluble bio molecule which has a high solubility in nonpolar organic solvents such as chloroform. The simplest lipids are the fats, which are tri esters made up of one glycerol and three fatty acids.

The term fats is also used as a general synonym for lipids, so the more precise terms triacylglycerols or triglycerides are preferable for the simplest lipids. Triacylglycerols are used primarily for energy storage in animals. More complex lipids, the phospholipids, glycolipids, and cholesterol, are the major constituents of biological cell membranes.

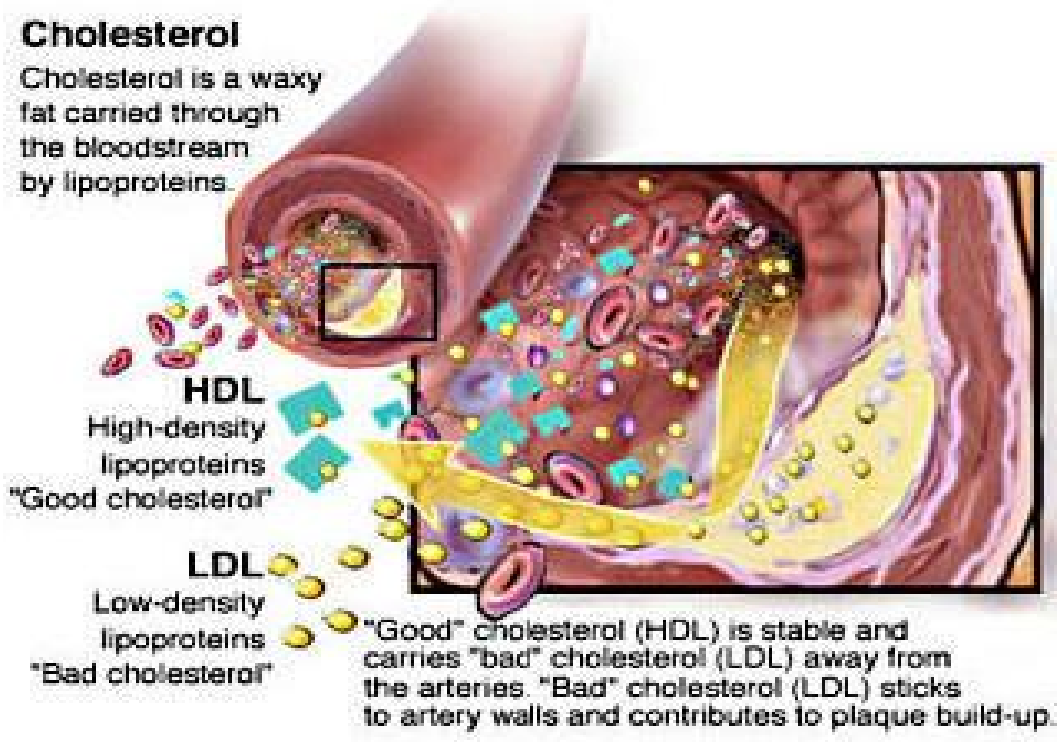


Figure: 1.11. Types of Lipids.

Examples of common lipids

(*Charles E and Ophardt ., 2003*)

Examples of common lipids include

- Butter
- Vegetable oil
- Cholesterol and other steroids
- Waxes
- Phospholipids
- Fat-soluble vitamins

Classification of lipids (*Charles E and Ophardt., 2003*)

Table: 1.5. Classification of lipids

LIPID CLASSIFICATION AND EXAMPLES	
Fatty Acids	**Glycerides**
Saturated Fatty Acids	Steroids
Unsaturated Fatty Acids	Lipoproteins
Soap (salt of fatty acid)	Triglycerides
Prostaglandins	Phosphoglycerides
Non glyceride Lipids	**-**
Waxes	**-**
Sphingolipids	**-**

1.6.1. Lipid structure

Although there is no single common structure for lipids, the most commonly occurring class of lipids are triglycerides, which are fats and oils. Triglycerides have a glycerol backbone bonded to three fatty acids. If the three fatty acids are identical then the triglyceride is termed a simple triglyceride. Otherwise, the triglyceride is called a mixed triglyceride.

The second most abundant class of lipids are the phospholipids, which are found in animal and plant cell membranes. Phospholipids also contain glycerol and fatty acids, plus the contain phosphoric acid and a low-molecular-weight alcohol. Common phospholipids include lecithins and cephalins.

The most important lipids present in blood plasma include fatty acids, triglycerides, cholesterol, phospholipids and steroid hormones.

- **Triglycerides, Cholesterol and Phospholipids**

Triglycerides are esters of fatty acids (e.g., stearic C-18 or palmitic C-16) and glycerols. Most of fatty acids are saturated, whereas nonsaturated fatty acids play an important role as prostaglandin precursors and in the process of cholesterol esterification.

Cholesterol also is a cellular membrane element and precursor of steroid hormones and biliary acids.

Phospholipids are structurally similar to triglycerides, except that one minor acid is substituted by a phosphorous group and nitrogen base.

➢ **Functions of lipids** (*Charles E and Ophardt., 2003*)

❖ Fats and lipids are important because they serve as energy source, as well as storage for energy in the form of fat cells.

❖ Lipids have a major cellular function as structural components in cell membranes. These membranes in association with carbohydrates and proteins regulate the flow of water, ions, and other molecules into and out of the cells.

❖ Hormone steroids and prostaglandins are chemical messengers between body tissues.

❖ Vitamins A, D, E, and K are lipid soluble and regulate critical biological processes. Other lipids add in vitamin absorption and transportation.

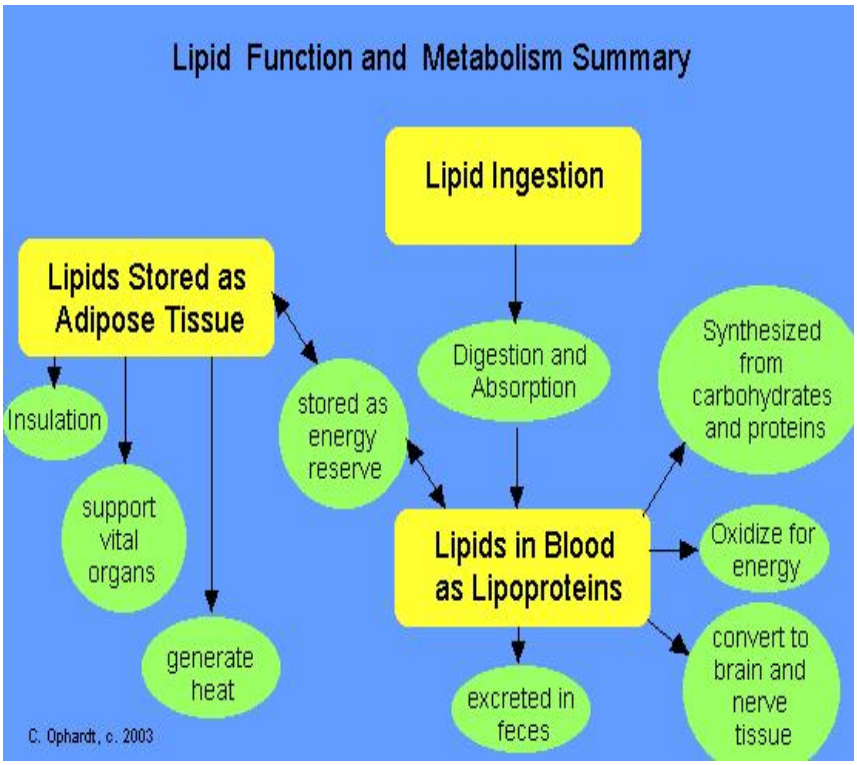


Figure: 1.12. Lipid function and metabolism

Lipids act as a shock absorber to protect vital organs and insulate the body from temperature.

- ❖ Energy storage, mobilization, and utilization
- ❖ Protection of organs
- ❖ Insulation
- ❖ Storage of vitamins-ADEK
- ❖ Hormone production.

Lipid metabolism impairments (*Charles E and Ophardt., 2003)*

Assessment of lipid metabolism impairments is based on plasma concentrations of cholesterol and triglycerides, and on data obtained by lipoprotein electrophoresis. Therefore, a

fasting period of 14-16 hours is required before blood sampling for analysis. Disorders due to lipid metabolism impairments are associated with a high risk of atherosclerosis.

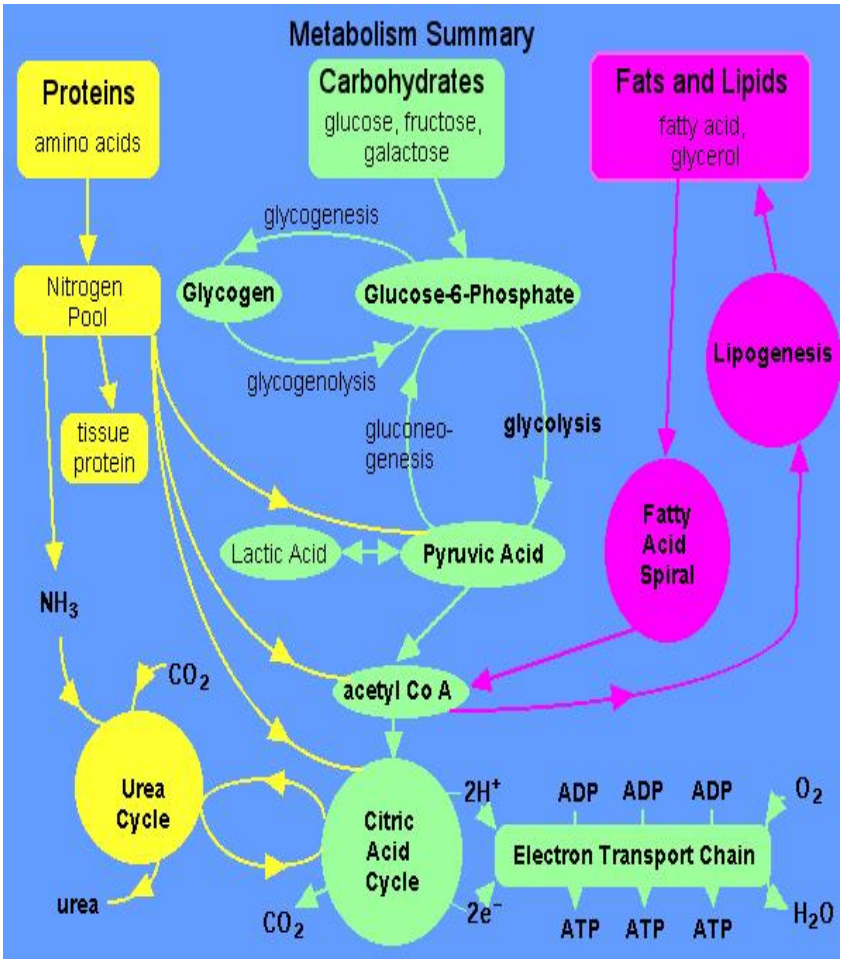


Figure: 1.13. Lipid metabolism impairments

Table: 1.6. Anti lipidemic drugs **(***Witiak D.T., et al., 1991*)

S.NO	CLASSIFICATION	NAME OF THE DRUGS
1.	HMG - CoA reductase inhibitors (Statins)	➢ Lovastatin
		➢ Simvastatin
		➢ Pravastatin
		➢ Atorvastatin
		➢ Rosuvastatin
		➢ Lovastatin
2.	Bile and sequestrants (Resins)	➢ Cholestyramine
		➢ Colestipol
3.	Active lipoprotein lipase (Fibric acid derivaties)	➢ Clofibrate
		➢ Gemfibrozil
		➢ Bezafibrate
		➢ Fenofibrate
4.	Inhibit lipolysis and triglyceride synthesis	➢ Nicotinic acid

1.7. HMG-CoA REDUCTASE INHIBITORS (STATINS)

In 1980s, this type was the most efficacious and best tolerated hypolipidaemic drugs. They competitively inhibit conversion of 3-Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate (rate limiting step in CH synthesis) by the enzyme HMG-CoA reductase. Therapeutic doses reduce CH synthesis by 2-50%. This results in compensatory increase in LDL receptor expression on liver cells—›increased receptor mediated uptake and catabolism of IDL and LDL. Over long term, feedback induction of HMG-CoA reductase tends to

increase CH synthesis, but a steady-state is finally attained with a dose-dependent lowering of LDL-CH levels

The daily dose for lowering LDL-CH by 30-35% is lovastatin 40mg, provastatin 40mg, simvastatin 20mg, Atorvastatin 10mg, Rosuvastatin 5mg. Moreover, maximum recommended doses simvastatin, Atorvastatin and Rosuvastatin can reduce LDL-CH by upto 45-55%, while the ceiling effect of lovastatin and Pravastatin is 35-40% LDL-CH reduction.

Table: 1.7. Mechanism of action and pattern of lipid lowering effect of important hypolipidaemic drug *(Michael E. Maragoudakis., 1970)*

S.NO	CLASSIFICATION	NAME OF THE DRUGS	DAILY DOSAGE	MECHANISM OF ACTION
1.	HMG-CoAreductaseinhibitors (Statins).	Lovastatin	(10-80mg)	▪ Decreased CH synthesis by inhibition of rate limiting HMG-CoA reductase
		Simvastatin	(5-40mg)	
		Pravastatin		
		Atorvastatin	(10-80mg)	
		Rosuvastatin	(5-20mg)	
		Lovastatin	(10-80mg)	
2.	Bile and sequestrants(Resins).	Cholestyramine	(4-16 mg)	▪ Decreased bile acid absorption, ▪ Increased hepatic conversion of CH to bile acids ▪ Increased LDL receptors on hepatocytes
		Colestipol	(5-30 mg)	
3.	Active lipoprotein lipase (Fibric acid derivatives).	Clofibrate		▪ Increased Activity of lipoprotein lipase ▪ Decreased release of fatty acids from adipose tissue
		Gemfibrozil	(1200 mg)	
		Bezafibrate	(600 mg)	
		Fenofibrate	(200 mg)	

HMG-CoA reductase pathway, which is blocked by statins via inhibiting the rate limiting enzyme HMG-CoA reductase

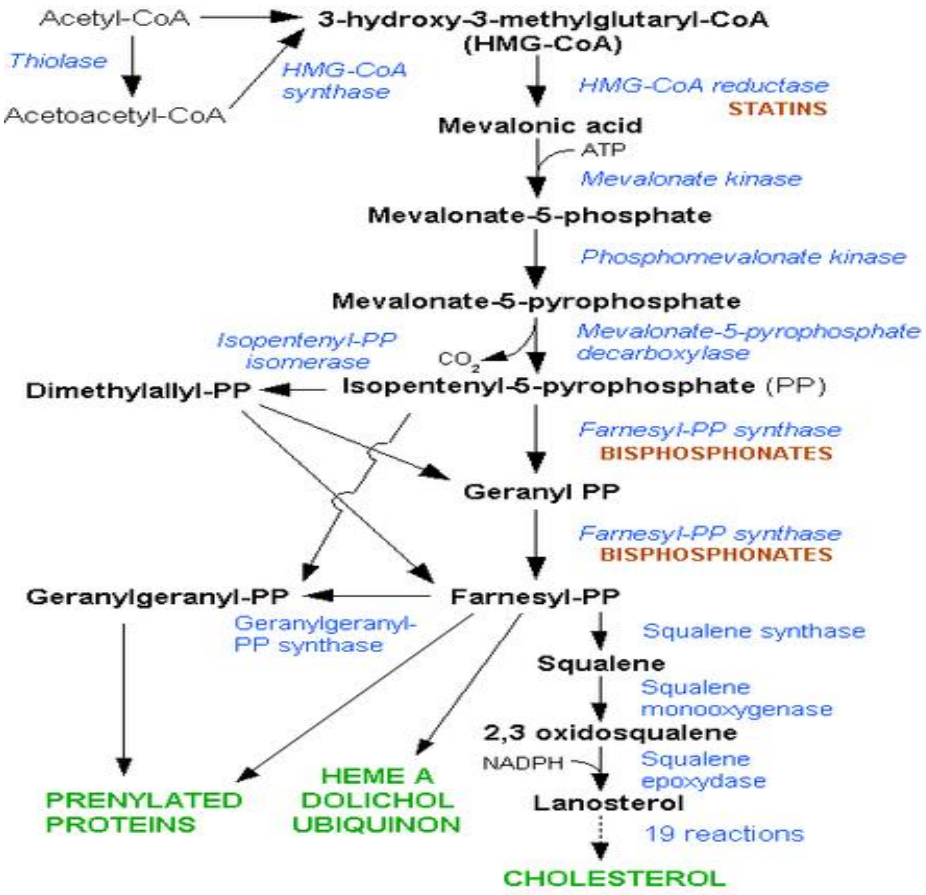


Figure: 1.14 HMG-CoA reductase pathways, which is blocked by statins via inhibiting the rate limiting enzyme.

The more effacious statins (simvastatin, atorvastatin, rosuvastatin) given at their high doses effectively reduce (by 25% to 35%). Because HMG-CoA reductase activity is maximum at midnight, all statins are administered at bed time to obtain maximum effectiveness. But, this is not necessary for atorvastatin and rosuvastatin, which have long plasma $t_{1/2.}$

1.7.1. Other statins drugs (*Richard N., Fogoros M.D., 2010)*

- **Lovastatin**

It is the first clinically used statin; is lipophilic and given orally in the precursor lactone form.

Lovastatin 40mg.

Systematic (IUPAC**) name**

1*S*,3*R*,7*S*,8*S*,8a*R*)-8-{2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate

Absorption – incomplete

Metabolism – bile

$t_{1/2}$ - short (1-4 hours)

Dose – 10 to 40 mg

- **Simvastatin**

It is a hypolipidemic drug used to control elevated cholesterol. Simvastatin is a member of the statin class of pharmaceuticals, is a synthetic derivate of a fermentation product of Aspergillusterreus.

Systematic (IUPAC**) name**

(1*S*, 3R, 7S, 8S, 8aR)-8-{2-[(2*R*, 4R)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl] ethyl}-3, 7-dimethyl-1, 2, 3, 7, 8, 8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate.

Absorption –Incomplete

Metabolism – bile

$t_{1/2}$- 2-3 hr

Dose – 5 to 20 mg

- **Pravastatin**

Pravastatin (marketed as **Pravachol** or **Selektine**) is a member of the drug class of statins, used for lowering cholesterol and preventing cardiovascular disease. Initially known as CS-514, it was originally identified in a bacterium called Non cardia autotrophica. It is also hydrophilic and given in the active form.

Pravastatin 10 mg

Systematic (IUPAC**) name**

(3*R*,5R)-3,5-dihydroxy-7-((1*R*,2*S*,6*S*,8*R*,8a*R*)-6-hydroxy-2-methyl-8-{[(2*S*)-2 methylbutanoyl]oxy}-1,2,6,7,8,8a-hexahydronaphthalen-1-yl)-heptanoic acid

Absorption – Incomplete

CH lowering effect - less

$t_{1/2}$- 1-3 hr

Dose – 40 to 80mg/day

- **Atorvastatin**

This newer statin is more potent and appears to have the highest LDL-CH lowering efficacy. All statins, including atorvastatin, prevent the production of cholesterol in the liver by blocking HMG-CoA reductase, an enzyme that makes cholesterol.

Atorvastatin 40 mg

$t_{1/2}$ - 18 - 24 hr

Dose – 10 to 40 mg

- **Rosuvastatin**

This is the latest and the most potent statin (10 mg rosuvastatin ≈ 20 mg atorvastatin), crestor 10 mg.

$t_{1/2}$ - 18 - 24 hr

LDL-CH reduction – Greater

TG levels – raised

Dose – 5 mg

❖ Equivalent dosages of statin groups

Table: 1.8. Equivalent dosages of statin groups.

% LDL Reduction (approx.)	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
10-20%	--	20 mg	10 mg	10 mg	--	5 mg
20-30%	--	40 mg	20 mg	20 mg	--	10 mg
30-40%	10 mg	80 mg*	40 mg	40 mg	5 mg	20 mg
40-45%	20 mg	--	80 mg*	80 mg*	5–10 mg	40 mg
46-50%	40 mg	--	--	--	10–20 mg	80 mg*
50-55%	80 mg	--	--	--	20 mg	--
56-60%	--	--	--	--	40 mg	--

- **Adverse effects of statins** **(***Tripathi K.D., 2004)*

  - Headache
  - Nausea
  - Bowel upset
  - Sleep disturbances
  - Rise in serum transaminase, but liver damage is rare
  - Muscle tenderness
  - Myopathy

- **Uses of statins** **(***Richard N., Fogoros MD.***,** *2010)*

  - Statins improve blood cholesterol levels primarily by inhibiting a liver enzyme called HMG Co-A reductase.
  - Reducing the size of plaques in the arteries.
  - Stabilizing plaques, so they are less likely to rupture (and therefore less likely to cause acute heart attacks).
  - Reducing inflammation (which is now thought to be an important component of plaque formation and rupture).
  - Reducing CRP levels
  - Decreasing blood clot formation (Blood clot formation at the site of plaque rupture is the cause of most heart attacks).

NEED AND OBJECTIVES

2. NEED AND OBJECTIVES

Atorvastatin calcium (INN) is the FDA-approved drug for clinical use for the treatment of lowering blood cholesterol, coronary heart diseases and angina conditions either alone or in combination with other antihypertensive. Atorvastatin calcium is 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor that is acts as rate limiting step in cholesterol biosynthesis. Atorvastatin calcium is absorbed rapidly following oral administration producing peak plasma concentration within 1 to 2 hours with 14 % bioavailability. Elimination half life is 14 hours and is usually administered in a starting dose of 10-20 mg daily in order to maintain effective concentration throughout the day. The main dose related adverse effect is myalgias, muscle cramps, neuropathy. In long term therapy fluctuations in the plasma concentrations, with high concentration peaks are common for drugs with rapid absorption and elimination. Such characteristic makes Atorvastatin calcium a suitable candidate for sustained release delivery.

Immediate release multi particulate drug delivery systems for oral dosing are effective in achieving immediate onset of action.IR Pellet preparation leads to an increased surface area as compared to traditional compressed tablet, which considerably decrease the disintegration time. These are more advantageous in emergency condition such as in case of sudden attack of strokes. One of the methods of fabricating immediate release formulations is incorporating of the drug in the pellet and coating with polymer and seal coated with superdisintegrants. The IRDDS is, thereby improving the oral bioavailability of the drug.

Increased cholesterol levels have been associated with cardiovascular diseases; so, atorvastatin calcium therefore used in the prevention of strokes and angina. It has a favourable effect including dementia, lung cancer, and nuclear cataracts.

The best selling statins is Atorvastatin calcium marketed as Lipitor and Torvast . So the present work involves use of immediate release drug delivery system (IRDDS) for atorvastatin calcium which is rapidly absorbed after administration. This will ensure minimum fluctuations in the plasma drug concentration and reduced dosing frequency which will result into improved patient compliance.

Objectives:

- Formulate and evaluate the immediate release pellets of atorvastatin calcium.
- To study the effect of different superdisintegrants and different concentration of individual superdisintegrants on the instantaneous disintegration after administration of capsule.
- To study the effect of different polymers and different concentration of individual superdisintegrants on the *in-vitro* dissolution studies and release of the drug from the formulation.
- To perform stability studies as per ICH guidelines.
- To reduce dosing frequency and improve patient compliance.

PLAN

OF

WORK

3. PLAN OF WORK

- **Literature review**
- **Selection of drug, superdisintegrants**
- **Procurement of drug and excipients**
- **Experimental work**

a) Pre formulation studies

- **Identification of drug**
  - By FT-IR spectroscopy
  - By melting point
- **Physicochemical parameters**
  - Organoleptic properties
  - Solubility profile
  - Loss on drying
- **Analytical methods**
  - Determination of λ max
  - Development of Caliberation curve of Atorvastatin calcium
  - Determination of percentage purity of drug
- **Determination of compatibility for drug with superdisintegrants**
  - By FT-IR spectroscopy
  - By DSC thermal analysis
- **Formulation of pellets**
  - By drug layering method

- **Kinetics of drug release**
- **Stability studies**

LITERATURE REVIEW

4. LITERATURE REVIEW

The basic outcome of this review will be the knowledge as to what data and other materials are available for operational purposes, which will enable the researcher to specify his own research problem in meaning full context.

Review on Formulation, Clinical and Analytical studies.

- **Balasubramaniam.J., et al., (2008)** worked on multi particulate pellets containing esomeprazole magnesium have been prepared using an extrusion spheronization process, employing povidone and croscarmellose as non-traditional processing aids. Attempts have been made to prepare pellets of various sizes and ultimately investigate the levels of enteric coating that need to be applied in order to achieve a suitable delayed-release dissolution profile. While acceptable pellets, displaying appropriate drug delayed-release characteristics have been achieved, it is evident from this initial study that further formulation and processing refinements, with respect to the formation of the initial pellets, need to be made in order to create pellets with optimal sphericity characteristics and narrower particle size distributions.
- **Damanjeet Ghai ., (2011)** had developed Pelletization: an alternate to granulation, here he concluded that Pelletization represents an efficient pathway for novel drug delivery system. The potential of this technology lies in the scope for different oral immediate or controlled delivery systems. Because of its simple design, high efficiency of producing spherical pellets and fast processing, pelletization has found a special position in pharmaceutical industry and especially in case of production of multi particulate oral controlled release dosage forms as compared to granulation. Pelletization technique produces more spherical pellets and offers more advantages than granulation process. In addition, hot –

melt extrusion method has provided a new, wider platform to produce spherical pellets of drugs which are not stable or have compatibility problems in presence of solvents.

- **Dr Fahan Jalees ahmed., et al., (2011)** had formulated and evaluated the Acyclovir Capsules. Hydrodynamic Balanced Systems (HBS) can remain in stomach for long periods and hence can release the drug over a prolonged period of time. The aim of the present study was to develop a hydro dynamically balanced system of acyclovir as single- unit floating capsules. Low- density polymers were used for formulation and development of these floating capsules. The capsules were prepared by physical blending of acyclovir and various polymers in different ratios. The formulation was optimized on the basis of *in- vitro* buoyancy and *in-vitro* release in 0.1 N HCl. HPMC K4M gave the best *in-vitro* percentage release and was found as the optimized formulation. By fitting the data into zero –order, first order and Higuchi models, we concluded that the release followed zero-order kinetics, as the correlation coefficient (R value) was higher for zero-order release.

- **Ganesh Shete., et al., (2010)** were developed solid state characterization of commercial crystalline and amorphous atorvastatin calcium samples. Atorvastatin calcium (ATC) , an anti-lipid BCS class II drug is marketed in crystalline and amorphous solid forms.The objective of this study was to perform solid state characterization of commercial crystalline and amorphous ATC drug samples available in the market. Six samples each of crystalline and amorphous ATC were characterized using X-ray powder diffractometry(XRPD) , differential scanning calorimetry and thermogravimetric analysis, Karl fisher titrimetry, microscopy, contact angle and intrinsic dissolution rate. All crystalline ATC samples were found to be stable form I, however, one sample possessed polymorphic impurity evidenced in XRPD and DSC analysis. Amongst, the amorphous ATC samples XRPD demonstrated five samples to be amorphous “form 27”, while, one matched amorphous “form 23”. Thermal behavior of amorphous ATC samples was compared to

amorphous ATC samples generated by melt quenching in DSC. ATC was found to be an excellent glass former with T_g/T_m of 0.95.Residual crystallinity was detected in two of the amorphous samples by complementary use of conventional and modulated use of DSC techniques. The wettability and IDR of all amorphous samples was found to be higher than crystalline samples. In conclusion, commercial ATC samples exhibited diverse solid state behavior that can impact the performance and stability of the dosage forms.

- **Golam Kibria ., et al., (2009)** the goal of the present study is to evaluate the influence of the formulation and operating conditions on pellet preparation by the pan technique. The effect of initial core weight on the physical parameters of pellets as well as to conduct stability study was also the goal of this study. For this domperidone maleate was selected as the model drug. Pellets were prepared by layering of powdered drug on sugar-based cores. Inert cores were intermittently treated with micronized drug powder and binding solution. This treatment led to the formation of multiple layers of drug particles around an inert core resulting in the production of pellets that can further be coated by different polymers to obtain modified release formulations. Scanning electron microscopy was employed to image the surface morphology of the prepared pellets. Drug loading efficiency, percentage yield, size, and shape uniformity of pellets were increased along with increasing the initial core weight. Drug content and dissolution study were performed by following HPLC and UV-Visible method. About 50% and 80% drug was released within 7.72 m and 13.66 m respectively in 0.1N HC l media (pH 1.2). Physical appearance of the prepared pellets, potency, moisture content, pellets size and shape, dissolution data, release rate constant, diffusion exponent (P<.05) over the stability period showed that the system is efficient for the production of highly stable formulations. This study also showed the good performance of the conventional coating pan system in obtaining instant release domperidone pellets prepared by the powder layering technique.

- **Jakob Kristensen., et al., (2005)** were developed the use of different grades of microcrystalline cellulose (MCC) and lactose in a direct pelletization process in a rotary processor. For this purpose, a mixed 2- and 3-level factorial study was performed to determine the influence of the particle size of microcrystalline cellulose (MCC) (60,80 and 100) and lactose (30, 40, and 60 &100), as well as MCC type (Avicel and Emcocel) on the pelletization process and the physical properties of the prepared pellets. A 1:4 mixture of MCC and lactose was applied, and granulation liquid was added until a 0.45 Nm increase in the torque of the friction plate was reached. All combinations of the 3 factors resulted in spherical pellets of a high physical strength. The particle size of MCC was found to have no marked effect on the amount of water required for agglomerate growth or on the size of the resulting pellets. An increasing particle size of lactose gave rise to more spherical pellets of a more narrow size distribution as well as higher yields. The MCC type was found to affect both the release of the model drug from the prepared pellets and the size distribution. Generally, the determined influence of the investigated factors was small, and direct pelletization in a rotary processor was found to be a robust process, insensitive to variations in the particle size and type of MCC and the particle size of lactose.

- **Kammali Lavanya., et al., (2011)** Pelletization Technology: a quick review. Pelletization process first came into existence way back during the 1950s, when the first product was introduced to the market. These pelletized dosage forms have gained popularity considerably from then because of their distinct advantages, such as ease of capsule filling because of better flow properties of the perfectly spherical pellets; enhancement of drug dissolution; ease of coating; sustained, controlled, or site-specific delivery of the drug from coated pellets; uniform packing; even distribution in the GI tract; and less GI irritation. Pelletized dosage forms can be prepared by a number of techniques, including drug layering on non pareil sugar or microcrystalline cellulose beads, spray drying, spray congealing, roto

granulation, hot- melt extrusion, and spheronization of low melting materials or extrusion – spheronization of wet mass. The present review outlines the recent findings on the manufacturing and evaluation of spherical pellets. The techniques namely extrusion-spheronization, hot melt extrusion, freeze pelletization, cryopelletization have been discussed along with formulation requirements for the process, parameters affecting pelletization. Evaluation of quality of the pellets is discussed with reference to the size distribution, shape, surface morphology, specific surface area, friability, tensile strength.

- **Lakshmi Narasaiah .V., et al., (2011)** were developed Enhancement of dissolution rate of atorvastatin calcium using solid dispersions by dropping method. It may be concluded that the prepared solid dispersions were extended to various characterizations. The solubility and dissolution studies showed there is a possibility of improved solubility of ATC through solid dispersion with Poly ethylene glycol 6000 than with Polyethylene glycol 4000. The dissolution rate of ATC from solid dispersions with PEG 6000 improved to more than 38.63% compared to the pure drug. Further, all the solid dispersions performed better than the corresponding physical mixtures. Also, the saturation solubility of the drug when formulated into solid dispersion with the polymer was higher than that of phase solubility achieved in the presence of the polymer. IR spectra indicated no well-defined interaction between the drug and polymer. A maximum increase in dissolution rate was obtained with ATC: PEG 6000 solid dispersion with a weight ratio of 1:3. PEG 6000 dispersion by dropping method showed faster dissolution rate when compared with that of PEG 4000 and pure drug.

- **Lori A. Dostal., et al., (1996)** department of Pathology and Experimental Toxicology, Parke – Davis Pharmaceutical Research, division of Wamer- Lambert Company Ann Arbor, Department of pharmacokinetics and drug metabolism, and these studies demonstrates no adverse effects of atorvastatin on fertility and reproduction in rats at doses up to 175 and 225 mg/kg no- effect dose.

- **Michael E. Maragoudakis ., et al., (1970)** On the mode of action of Lipid-lowering agents, kinetics of the inhibition *in vitro* of rat acetyl coenzyme A carboxylase, Rat liver acetyl coenzyme A carboxylase was purified about 200- fold and the inhibition of this enzyme by certain hypolipidemic drugs was studied. The inhibition was more pronounced if the drugs were added before rather than after the citrate activation of the enzyme. Kinetic analysis revealed non competitive inhibition of the drugs with respect to the substrates acetyl-CoA, ATP and HCO_3^- and competitive inhibition with respect to the activator, citrate. Sucrose density gradient centrifugations showed that the drugs reverse the aggregating effect of citrate to form the active polymeric forms of the enzyme from the inactive monomers. Arrhenius plots and heat- inactivation studies suggest gross conformational changes of the enzyme protein in the presence of the drugs.

- **Mustafa Sinan Kaynak., et al., (2007)** worked on Formulation of Controlled Release Glipizide Pellets Using Pan Coating Method by using Eudragit RL 100 PM and Eudragit RS 100 PM as coating polymers PIII 200 ml (RL1OO-17G) formulation was significantly lower than the previous formulations as a ratio of 70% of drug is released in 14 hrs. They concluded that method is suitable for preparation.

- **N. Arun kumar., et al., (2009)** were formulated preparation and solid state characterization of atorvastatin nanosuspensions for enhanced solubility and dissolution. In this study an attempt was made to improve the solubility and dissolution characteristics of a poorly soluble drug (atorvastatin calcium) using nanosuspension technology. Nanoparticles were characterized in terms of size and morphological characteristics. Saturation solubility and dissolution characteristics were investigated and compared to commercial drug. Crystalline of the drug was also evaluated by performing thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC) and powder X- ray diffraction (PXRD) to denote eventual transformation to amorphous state during the homogenization process. Through this

study, it has been shown that the crystalline state of drug is reduced following particle size reduction and dissolution rates of amorphous atorvastatin calcium nanoparticles were highly increased in comparision with commercial drug by the enhancement of intrinsic dissolution rate and reduction of particle size, resulting in an increased surface area.

- **Pandey Shivanand., et al., (2009)** worked on Design, Optimization and Physical and Chemical Evaluation of Domperidone Pellets optimization and *in-vitro* evaluation by using sodium lauryl sulphate at different concentration for increasing the release rate. Organoleptic and preformulation studies are conducted formulation of Domperidone pellets containing 0. 06% sodium lauryl sulphate, in formulation F-7 can be taken as an ideal or optimized formulation of drug layering pellets.

- **Parag A. Kulkarni., et al., (2010)** Pelletization techniques as a Pharmaceutical tool in the multi particulate drug delivery system: a review, Conventional medication systems that need frequent dosing are always with problems. So there is thrust in the area of pharmaceutical research to develop novel formulations, which will enhance the therapeutic efficacy of the existing drug. This is less costly as compared to discover new drug. Past few years multi particulate drug delivery system has emerged as a tool for the delivery of the drugs. These forms play major role in the design of solid dosage form because of their characteristic properties and flexibility found in their manufacturing .Use of pellets as a vehicle in multi particulate drug delivery system has received significant attention. This review focuses on the different pelletization techniques with their merits, demerits and its characterization, as a tool in the multi particulate drug delivery system.

- **R.Lankas., et al., (2004)** Merck research laboratories, West point, Pennsylvania has reported that “The role of maternal toxicity in atorvastatin- induced developmental toxicity”. The result of excessive maternal toxicity, which most likely involves a nutritional deficiency

associated with fore stomach lesions and reduced maternal food intake. *Birth Defects Res* B 71:111-123, ©2004 Wiley-Liss, Inc.

- **Rekkas., et al., (2008)** worked on 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 23 factorial design and an optimization technique. Pellets were prepared by wet granulation. Equal amounts of microcrystalline cellulose, a-lactose monohydrate, and distilled water were used as the granulation liquid. The size and the size distribution of the pellets were determined by sieve analysis. 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 not statistically significant. None of the 3 factors significantly affected the geometric standard deviation of the pellets. The rotor speed and the amount of water sprayed were further selected in order to construct a mathematical model that correlates these factors with the geometric mean diameter of the pellets. For this purpose, the optimization technique 32 was used. The derived equation described the relationship between the selected factors and the size of the pellets. As a result, the experimental design techniques applied were found to be suitable in optimizing the pelletization process carried out in a fluid-bed rotor granulator.

- **Sachin V. Wankhede., et al., (2010)** were developed formulation and stabilization of atorvastatin tablets. The present study is planned to develop atorvastatin calcium amorphous into immediate release tablets. Pre formulation studies and drug–excipient compatability studies was done initially and results obtained were directs the way and method of formulation. Pre formulation, drug- excipient compatibility, prototype formulation carried out for the highest dose of atorvastatin calcium (80 mg) and optimized to get the final formula. Atorvastatin calcium (amorphous) is highly susceptible to oxidation and hydrolysis. So wet

granulation method was avoided. All the mentioned batches were done by dry granulation method by roller compaction. Granules were evaluated for tests such as loss on drying (LOD), bulk density, tapped density, compressibility index, Hausner's ratio and sieve analysis before compression. Tablets were tested for weight variation, hardness, friability, thickness and dissolution. *In-vitro* dissolutions were performed and the formulations F1 and F2 values were calculated. Dissolution profile of F5 was matched perfectly with the innovator formulation and F2 value was found to be excellent. Also the impurity profile and stability result of F5 was found to be excellent. It can be concluded that the immediate release tablet was beneficial for delivering the drug which needs faster release to achieve the immediate action.

- **Salam W. Ahjel., et al., (2009)** were developed the enhancement of solubility and dissolution rate of different forms of atorvastatin calcium in direct compression tablet formulas. Atorvastatin , as a synthetic lipid- lowering agent, is an inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A(HMG-CoA) reductase which catalyzes the conversion of HMG-CoA to mevalonate , an early rate –limiting step in cholesterol synthesis. The bioavailability of atorvastatin is one of the key parameters for its therapeutic use and is dependent on the form of the atorvastatin calcium to be used in the pharmaceutical formulation. The patient should take a constant therapeutic daily dose, regardless to the pharmaceutical formulation of the ATC. The major finding of this study was that the addition of buffering agent will dramatically increase both, the solubility and dissolution rate of ATC regardless to the form used in the preparation of the direct compression formulas. The results were showed that it was possible to provide therapeutic equivalence of ATC in the pharmaceutical formulation regardless to the form used in the formulation.

- **Singh. SK., et al., (2009)** worked on Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, and are intended usually for oral

administration. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today. The study was undertaken with an aim to develop delayed release micropellet dosage form for Lansoprazole which is a benzimidazole antiulcer agent and is one of the most widely used drugs for treating mild and severe ulcers. The approach of the present study was to make a comparative evaluation among these polymers and excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The prototype formulation of micro pellets were prepared using the fluid bed coater (FBC) with the air pressure 2.0 bar and the spray rate 10-15ml/min. Temperature of bed is varied from 35°C to 50°C and inlet temperature is varied from 50°C to 70°C and the effect of various parameter were observed such as air pressure, inlet and outlet temperature of FBC, it is observed that at high pressure the pellets are breaking. For bed and inlet temperature it is observed that at low temperature lumps are curing in the formulation and at 2.0 bar air pressure, inlet temperature 60°C and bed temperature of 40°C is reliable for solution flow rate 10-15ml/min. Concerning results of prototype preparation of Lansoprazole the micro pellets were prepared using HPMC E5 polymer as release retardant in three different concentration i.e. 40%, 50%, 60% with three different concentration 8%, 10%, 12% of NaOH and Acrycoat L30D solution was used for enteric coating. Formulated micro pellets showed delayed *in-vitro* dissolution behavior, probably due to optimized concentration of polymer. The micro pellets drug was stable at room temperature, 25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines, after 3 months.

- **Subhadeep Chowdhury., et al., (2010)** had developed a statistical optimization of fixed dose combination of glimepiride and atorvastatin calcium in immediate release tablet formulation. Long term administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet with insulin. For this complication atorvastatin calcium can be used to reduce the

cardiovascular mortality. The objective of the present study was to evaluate the effects of two factors (amount of CMC sodium and SSG) on drug release of atorvastatin calcium and glimepiride from the tablet in order to optimize the formulation by 2 factor 3 level factorial design. Two independent variables taken were CMC sodium and SSG. The evaluated response were percentage release of atorvastatin calcium in 60 min(y_1) and percentage release of glimepiride in 60 min(y_2) was taken as a response variables. Drug release was measured in USP 2 apparatus using 900 ml 0.05 M phosphate buffer (pH 6.8) solution at a rotation speed of 75 rpm. The optimized formulation produced dissolution profiles that were closed to predicted values.

- **Tatsuya Ishikawa., et al., (2001)** Department Of Pharmaceutics and Biopharmaceutics, Showa Pharmaceutical University, Preparation of rapidly disintegrating tablet using new types of microcrystalline cellulose (PH-M Series) and low substituted-Hydroxypropylcellulose or spherical sugar granules by direct compression method, compared to this method in industry we have prepared the same formula for the direct compression method and result will be obtained, chemical and Pharmaceutical Bulletin, Vol. 49, No.2 134.

- **Thomayant prueksaritanont., et al., (2002)** Department of drug Metabolism, Merck research Laboratories, West point, Pennsylvania, Glucuronidation of statins in animals and Humans. A novel Mechanism of Statin Lactonization may play an important role, albeit previously unrecognized, role in the conversion of active HMG-CoA reductase inhibitors to their latent delta lactone forms. Vol. 30, issue 5, 505-512.

- **Venkatesh DP., et al., (2008)** formulated the orodispersible tablet of Ambroxol hydrochloride. Since the drug was very bitter to taste, is masked with the use of ion exchange resins like Indion- 204 and Indion – 234 which also act as super disintegrants. Tablets with both the resins had shown quick disintegrating features i.e., within 20 sec and also the

dispersion not showing any bitter taste, indicating the capability of ion exchange resins used, both as taste masking and super disintegrating agents.

DRUG AND EXCIPIENT'S PROFILE

5. DRUG AND EXCIPIENT'S PROFILE

5.1. DRUG PROFILE

(*Merck Index, 1997; CIMS, 2012; file:///H:/ATORVASTATIN CALCIUM.htm***)**

Atorvastatin calcium - (HMG- CoA reductase inhibitor).

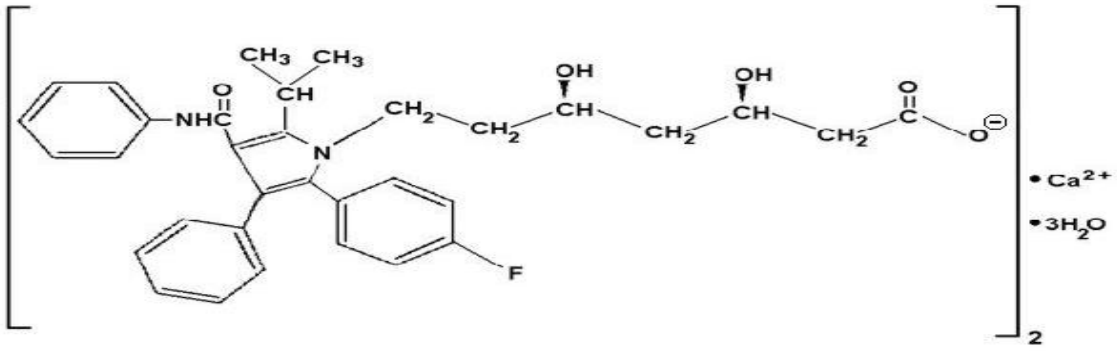
Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age >/= 55 years, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, Lipitor is indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk for revascularization procedures and angina.

❖ **Proprietary Name:** LIPITOR, CARDYL, SORTIS, TORVAST.

❖ **Structure:**



❖ **IUPAC NAME:** [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate.

❖ **CAS number:** 134523-00-5.

❖ **Molecular weight:** 1209.42

❖ **Molecular formula:** $(C_{33}H_{34}FN_2O_5)_2Ca.3H_2O$

❖ **Physical State:** Solid.

❖ **Melting Point:** 159.2-160.7^oC

❖ **Water Solubility:** Sodium salt soluble in water, 20.4 ug/mL (pH 2.1), 1.23 mg/Ml (pH 6.0)

Phase 1 Metabolising Enzyme (1-st Step of Metabolism): CYP3A4

Table: 5.1. Primary drug targeting

Name	HMG-CoA Reductase
Gene Name	HMGCR
Synonyms	3-hydroxy-3-methylglutaryl-coenzyme A reductase; EC 1.1.1.34; HMG-CoA reductase
General Function	Lipid transport and metabolism
Specific Function	This transmembrane glycoprotein is involved in the control of cholesterol biosynthesis. It is the rate-limiting enzyme of sterol biosynthesis
Pathway	map00100 Biosynthesis of steroids
Reaction	(R)-mevalonate + CoA + 2 NADP+ = (S)-3-hydroxy-3-methylglutaryl-CoA + 2 NADPH + 2 H+

❖ **Description:**

Atorvastatin calcium is a white to off white crystalline powder that is insoluble in aqueous solutions of pH4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer. And Acetonitrile, slightly soluble in ethanol and freely soluble in methanol.

CLINICAL PHARMACOLOGY:

❖ **Mechanism**

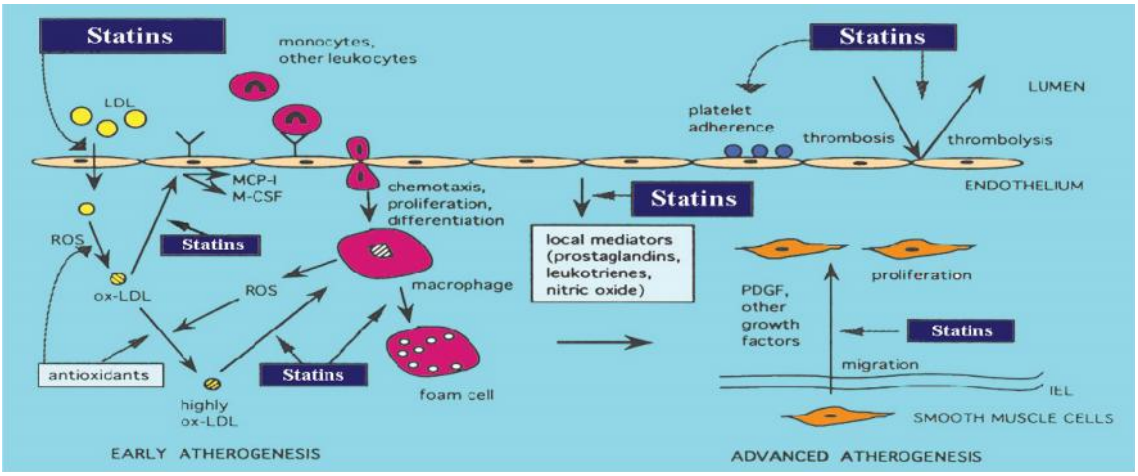


Figure: 5.1. Mechanism of statins.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzymeA to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily

through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and Apo-lipoprotein B (Apo- B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, Atorvastatin calcium lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL; Atorvastatin calcium also reduces LDL production and the number of LDL particles. Atorvastatin calcium reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin calcium reduces total-C, LDL-C, and Apo B in patients with homozygous and heterozygous FH, non-familial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and produces variable increases in HDL-C and Apo-lipoprotein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

❖ **Pharmacodynamics**

Atorvastatin as well as some of its metabolites are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage rather than systemic drug concentration correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response.

❖ **Pharmacokinetics and Drug Metabolism**

- **Absorption**

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to pre systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without

food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.

- **Distribution**

Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

- **Metabolism**

Atorvastatin is extensively metabolized to ortho and parahydroxylated derivatives and various beta-oxidation products. *In-vitro* inhibition of HMG-CoA reductase by ortho and para hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In-vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following coadministration with erythromycin, a known inhibitor of this Isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

- **Excretion**

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo Entero hepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

❖ **Special Populations**

- **Geriatric**

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults.

- **Gender**

Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for C_{max} and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with Atorvastatin calcium between men and women.

- **Renal Insufficiency**

Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary.

- **Hemodialysis**

While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

- **Hepatic Insufficiency**

In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease.

❖ **Dosage and administration**

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with atorvastatin.

❖ **Drug interactions**

The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals.

ANTACID

When atorvastatin and Maalox OTC suspension were co-administered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered.

ANTIPYRINE

Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

COLESTIPOL

Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

CIMETIDINE

Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

DIGOXIN

When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

ERYTHROMYCIN

In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with co-administration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4.

ORAL CONTRACEPTIVES

Co-administration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

WARFARIN

Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

❖ **Endocrine function**

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone and cimetidine.

❖ **CNS toxicity**

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by peri-vascular haemorrhages, edema, and mononuclear cell infiltration of peri-vascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

EXCIPIENT'S PROFILE

5.2. EXCIPIENT'S PROFILE

❖ Excipients

Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to provide support.

The excipients used must have following characteristics

- They must be stable both physically, chemically and must be biologically inactive.
- It must be free from microbial contamination
- Excipients used in pellet formulation must be accepted by regulatory agencies and should meet the entire current regulatory requirement.

Excipient's used are:

a) Hydroxy propyl methyl cellulose.

b) Croscarmellose sodium.

c) Crospovidone.

d) Sodium starch glycolate.

1. Hypromellose *(Raymond C Rowe., et al., 2003)*

❖ **Nonproprietary Names:**

BP: Hypromellose JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum USP: Hypromellose

❖ **Synonyms:**

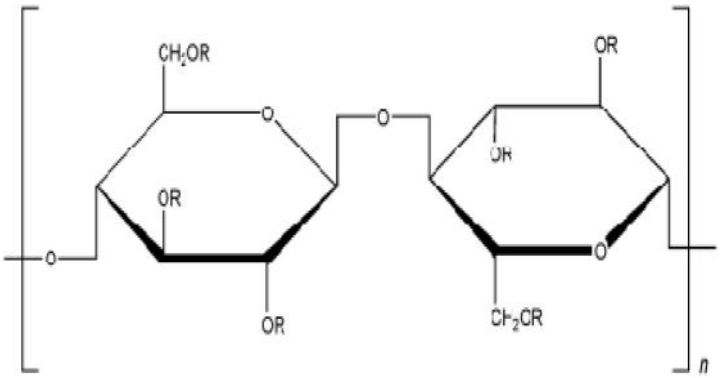
Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Tylopur*.

❖ **Chemical Name:** Cellulose hydroxyl propyl methyl ether.

❖ **CAS Registry Number:** [9004-65-3]

❖ **Molecular weight:** 10,000-15,00,000

❖ **Structural Formula:**



Where R is H, CH_3, or CH_3CH (OH) CH_2

❖ **Functional Category:**

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

❖ **Applications in Pharmaceutical Formulation or Technology:**

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as matrix for use in extended-release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

❖ **Description:**

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

❖ **Typical Properties:**

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.

Density (bulk) : 0.341 g/cm3.

Density (tapped) : 0.557 g/cm3.

Density (true) : 1.326 g/cm3.

Melting point : browns at 190–200°C; chars at 225–230°C.

Glass transition temperature is 170–180°C.

❖ **Moisture content:** Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

❖ **Solubility:** Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.

❖ **Viscosity (dynamic):** A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.

Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C.

***Methocel* product**	**USP 28 designation**	**Nominal viscosity (mPa s)**
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15 000
Methocel K100M Premium	2208	100 000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10 000
Methocel E3 Premium LV	2906	3
Methocel E5 Premium LV	2906	5
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Metolose 60SH	2910	50, 4000, 10 000
Metolose 65SH	2906	50, 400, 1500, 4000
Metolose *90SH*	2208	100, 400, 4000, 15, 000

❖ **Stability and Storage Conditions:**

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions.

Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively.

❖ **Incompatibilities:**

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts.

2. Crospovidone (*Raymond C Rowe., et al.,2003*)

- **Nonproprietary Name:** Crospovidone.
- **Synonyms :** BP : Crospovidonum;

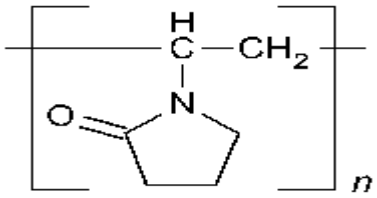
  PhEur: Polyplasdone XL;

  USPNF: Polyvinylpolypyrrolidone.
- **Chemical Name:**

  1-Ethenyl-2-pyrrolidinone homopolymer.
- **CAS number:** (9003-39-8).
- **Description:**

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

- **Empirical Formula and Molecular Weight**: $(C_6H_9NO)n$, 2,500 – 2,50,00,000 $g \cdot mol^{-1}$
- **Molecular structure:**



- **Functional Category:** Tablet disintegrant
- **Solubility:** Practically insoluble in water and most common organic solvents.
- **Stability and Storage Conditions:** Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

❖ **Incompatibilities:**

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

❖ **Applications:**

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5 % concentration in tablets prepared by direct compression or wet and dry-granulation methods. It can also be used as a solubility enhancer.

❖ **Related Substances:** Crospovidone, povidone.

3. Sodium Starch Glycolate (*Raymond C Rowe.,et al.,2003)*

❖ **Non proprietary names :** BP: sodium starch glycolate

PhEur: Carboxy methyl amylum natricum

USPNF: sodium starch glycolate

❖ **Synonyms:**

Explotab; Primogel; Vivastar. Carboxymethyl starch, sodium salt.

❖ **Chemical Name:**

Sodium carboxymethyl starch.

❖ **CAS number:** (9063-38-1)

❖ **Description:**

It is a white or almost white free-flowing very hygroscopic powder.

The Ph Eur states that when examined under a microscope it is seen to consist of: granules irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded,10–35 mm in size; compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric helium and clearly visible concentric striations. Between crossed Nicole prisms, the granules show a distinct black cross intersecting at the haulm; small crystals are visible at the surface of the granules. The granules how considerable swelling in contact with water.

❖ **Functional Category:**

Tablet and capsule disintegrant.

❖ **Solubility:**

Practically insoluble in water and insoluble in most organic solvents

❖ **Incompatibilities**

Sodium starch glycolate is incompatible with ascorbic acid

❖ **Stability and Storage Conditions**

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain changed for up to 3 years if it is stored at moderate temperatures and humidity

❖ **Applications in Pharmaceutical Formulation**

a. Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.

b. It is commonly used in tablet prepared by either direct compression or wet granulation processes.

4. Croscarmellose sodium *(Raymond C Rowe.,et al.,2003)*

❖ **Nonproprietary Name:** BP:Croscarmellose sodium

PhEur: Carmellosum natricum conexum

USPNF: Croscarmellose sodium.

❖ **Synonyms:** *Ac-di-sol*; carmellosum natricum conexum; Cross-linked carboxymethylcellulose sodium; *Explocel*:modified cellulose gum; *Nymcel* ZSX; *Pharmacel* XL; *Primellose*; *Solutab*; *Vivasol*.

❖ **Chemical Name:** Cellulose, carboxy methyl ether, sodium salt.

❖ **CAS number:** 74811-65-7

❖ **Functional Category:** Tablet and capsule disintegrant.

❖ **Description:**

Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

❖ **Solubility:**

Insoluble in water, although Croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

❖ **Stability and Storage Conditions:**

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with Croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 300^0C for 14 months. Croscarmellose sodium should be stored in a well closed container in a cool, dry place.

❖ **Incompatibilities:**

The efficacy of disintegrant such as Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose Sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

❖ **Applications:**

a. Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules.

b. In tablet formulations, Croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the Croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra- granularly) so that the wicking and swelling ability of the disintegrant is best utilized.

c. Croscarmellose sodium at concentrations up to 5% w/w may be used as tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3%w/w in tablet prepared by wet granulation process.

MATERIALS AND EQUIPMENTS

6. MATERIALS AND EQUIPMENTS

6.1. Raw materials

Table: 6.1. Raw materials with name of the supplier

S.NO	Name of raw material	Name of the supplier
1	Atorvastatin calcium	Vasavi Lab Pvt.ltd., Maharastra
2	Sodium starch glycolate	Richer Health Care, Hyderabad
3	Crospovidone	Richer Health Care, Hyderabad
4	Croscarmellose sodium	Richer Health Care, Hyderabad
5	Hydroxy propyl methyl cellulose E-15	Richer Health Care, Hyderabad
6	Non pareil seeds	Rainbow Health Care Products, Hyderabad
7	Polyvinylpyrolidone K-30	Richer Health Care, Hyderabad
8	Talc	Richer Health Care, Hyderabad
9	Potassium dihydrogen phosphate	Richer Health Care, Hyderabad
10	Methanol	Richer Health Care, Hyderabad
11	Ethanol (95%)	Richer Health Care, Hyderabad
12	Sodium hydroxide	Richer Health Care, Hyderabad
13	Isopropyl alcohol	Richer Health Care, Hyderabad
14	Acetonitrile	Richer Health Care, Hyderabad

6.2. Equipments

Table: 6.2. Equipments with company name

S.NO	Name of Equipment	Manufacturing Company
1	Electronic balance	Shimadzu Scientific instruments, Japan
2	Vernier Caliper	Shankar Scientific, Chennai
3	Friabilator	Roche Friabilator
4	pH meter	Model MP-1 Plus Susima Dharma
5	Hot air oven	Minicon Equipments Pvt Ltd.,
6	Dissolution Apparatus	LAB INDIA DISSO-2000
7	Double beam spectrophotometer	Shimadzu Scientific Instruments, Japan
8	FT-IR Spectrophotometer	Shimadzu Scientific Instruments, Japan
9	Coating pan	Rinak , kalweka HD410AC
10	Spray gun	Rinak , kalweka HD410AC
11	Hardness Tester	Dr.schleuniger, pharmatron,USA
12	Digital scanning calorimeter	Shimadzu DSC 60 , Japan
13	Bulk density apparatus	Indolab VTAP/MATIC-II
14	Standard sieve no(20 and 40#)	Jayant scientific IND

EXPERIMENTAL WORK

7. EXPERIMENTAL WORK

7.1.Pre formulation studies

Pre-formulation testing was an investigation of physical and chemical properties of a drug substance alone. It was the first step in rational development of dosage form.

7.1.1. Identification of drug

7.1.1.1. Identification by FT-IR spectroscopy *(Skoog D.A., et al., 1996; IP, 2007)*

Atorvastatin discs were prepared by pressing the Atorvastatin with potassium bromide and the spectra between 4000^{-1} to 500^{-1} cm was obtained under the operational conditions. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum in Table 8.1 and Figure 8.1.

7.1.1.2. Identification by melting point *(IP, 2007)*

Melting point of the drug was determined by capillary tube method.

7.1.2. Physicochemical parameters

7.1.2.1. Organoleptic properties

(Lachman L., et al., 1991; Bankar G.S. and Rhodes C.T., 1996)

The colour, odour and taste of the drug were recorded using descriptive terminology.

7.1.2.2. Solubility study *(Merck Index., 1997., IP, 2007)*

It was important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminologies specified in Indian pharmacopoeia, 2007.The solubility study was shown in Table 8.2.

7.1.2.3. Loss on drying: *(IP, 2007)*

Loss on drying was the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The accurately weighed 1gm of sample was transferred in stoppered-glass shallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and substance was dried at 105°C for 3 hours. The bottle was removed from oven and reweighed; loss on drying was calculated by following equation. It was shown in Table 8.3

$$LOD = \frac{Initialweightofsubstance - Finalweightofsubstance}{Initialweightofsubstance} \times 100$$

100

7.1.3. Analytical methods

7.1.3.1. Determination of λ max **(***Alka Gupta., et al., 2009)*

The absorption maximum of the standard solution was scanned between 200-400 nm regions on UV-VISIBLE spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum

7.1.3.2. Development of Caliberation curve of Atorvastatin in methanol

(*Alka Gupta., et al., 2009)*

25 mg of Atorvastatin Calcium was weighed accurately and transferred into 50 ml volumetric flask and dissolved in Methanol, after dissolution the volume was made up to the mark with Methanol (500µg/ ml). Further dilution was made by pipetting 1 ml of mother liquor into 50 ml to acquire 10 µg/ ml solution made up with methanol. The absorbance measurements of these solutions were carried out against methanol as blank at 246 nm. A calibration curve of Atorvastatin was plotted.

Preparation of methanol solution **(***IP, 2007)*

Methanol was prepared according to I.P. 2007.

Preparation of stock solution of Atorvastatin in methanol

Accurately weighed 100 mg of Atorvastatin and it was dissolved in little quantity of 100ml of methanol and 1ml of solution was taken & make up to 10ml (100µg/ml) volume was the same to prepared standard solution having concentration of 100 µg/ ml.

Procedure

From the stock solution, aliquots of 2, 4, 6, 8 and 10 ml were transferred to 10 ml volumetric flasks and final volume was made to 100ml with methanol. Absorbance values of these solutions were measured against blank (methanol) at 246 nm using UV-Visible spectrophotometer.

7.1.3.3 .Development of caliberation curve of Atorvastatin in 6.8 phosphate buffer

(IP, 2007)

Preparation of 6.8 phosphate buffer

Placed the 50 ml of 0.2M potassium dihydrogen phosphate in a 200 ml of volumetric flask, and added specified volume of 0.2 M sodium hydroxide then added water to volume to required.

Preparation of 0.2 M sodium hydroxide

Dissolved the sodium hydroxide in water to produce 40 to 60 %w/v solution and allow to stand and finally added 8 gm of sodium hydroxide in 1000 ml.

Preparation of 0.2 M potassium dihydrogen phosphate

Dissolved the 27.218 gm of potassium dihydrogen phosphate in water and diluted with water 1000ml.

Preparation of stock solution of Atorvastatin in 6.8 phosphate buffer

Accurately weighed 100 mg of Atorvastatin was dissolved in little quantity of 100ml of 6.8 phosphate buffer and 1ml of solution was taken & make up to 10ml (100µg/ml) volume was the same to prepared standard solution having concentration of 100 µg/ ml.

Procedure

From the stock solution, aliquots of 2, 4, 6, 8 and 10 ml were transferred to 10 ml volumetric flasks and final volume was made to 100ml with 6.8 phosphate buffer. Absorbance values of these solutions were measured against blank (6.8 phosphate buffer) at 246 nm using UV-Visible spectrophotometer

7.1.3.4. Determination of percentage purity of Drug

(IP, 2007)

Accurately weighed 25 mg of atorvastatin calcium was dissolved in little quantity of methanol and volume was adjusted to 100 ml with the same to prepare standard solution having concentration of 250 µg/ ml. From the above solution, aliquots of 3 ml were transferred to 50 ml volumetric flasks and final volume was made to 50 ml with methanol. Absorbance values of these solutions were measured against blank methanol at 246 nm using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. The percentage purity of drug was calculated by using calibration graph method (least square method).

7.1.4. Determination of drug-superdisintegrants compatibility

(Aulton M.E., 2002., Patil S.V., et al .,2009)

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. Each superdisintegrant used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form.

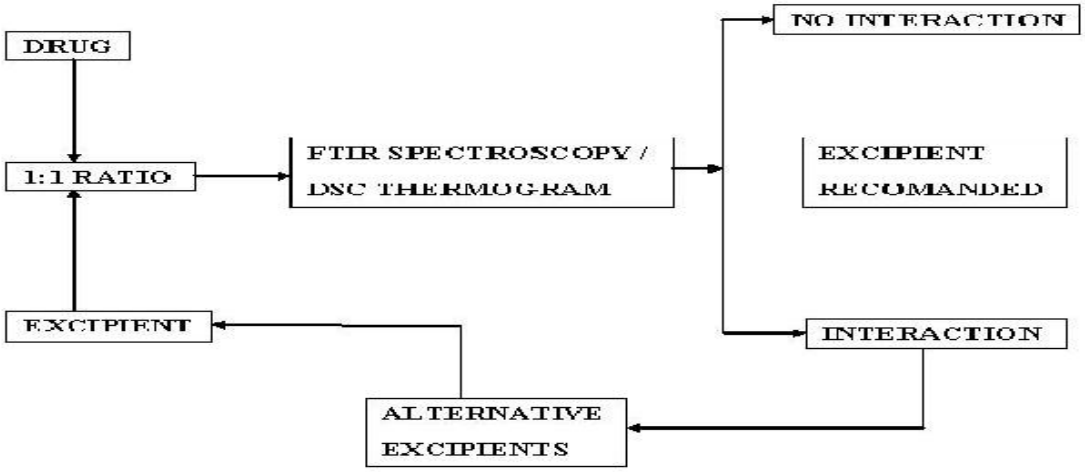


Figure: 7.1. Compatibility studies

7.1.4.1. Fourier transform infrared (FT-IR) spectroscopy

(Patil S.V., et al., 2009; IP, 2007)

FT-IR study was carried out to check compatibility of drug with superdisintegrants. Infrared spectrum of Atorvastatin calcium was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various superdisintegrants by using FT-IR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum represented in table 8.9 and also shown in figure 8.6.

7.1.4.2. Differential scanning calorimetry (DSC)

(Patil S.V., et al., 2009; Aulton M.E., 2002)

Any possible drug excipients interaction can be studied by thermal analysis. The DSC study was performed on pure drug, drug+ SSG, drug+ CP and drug+ CCS. The study was carried out using a DSC. The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºc at heating rate of 10ºc /min under nitrogen flow of 30ml/min. The results of DSC analysis were presented in figure 8.7 and table 8.10.

7.2. FORMULATION OF IMMEDIATE RELEASE PELLETS

(Kammali Lavanya., et al., 2011)

The pellets were prepared by Drug layering method, by using a different drug and superdisintegrants ratios. The formulations were designated as F_1, F_2, F_3, F_4, F_5 and F_6 respectively.

7.2.1 Drug layering method

Drug layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it required specialized equipments like spheronizer. The primary requirement in this process was that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder was picked off by the wet mass of pellets that was being layered.

- **STAGES:** Drug loading

↓

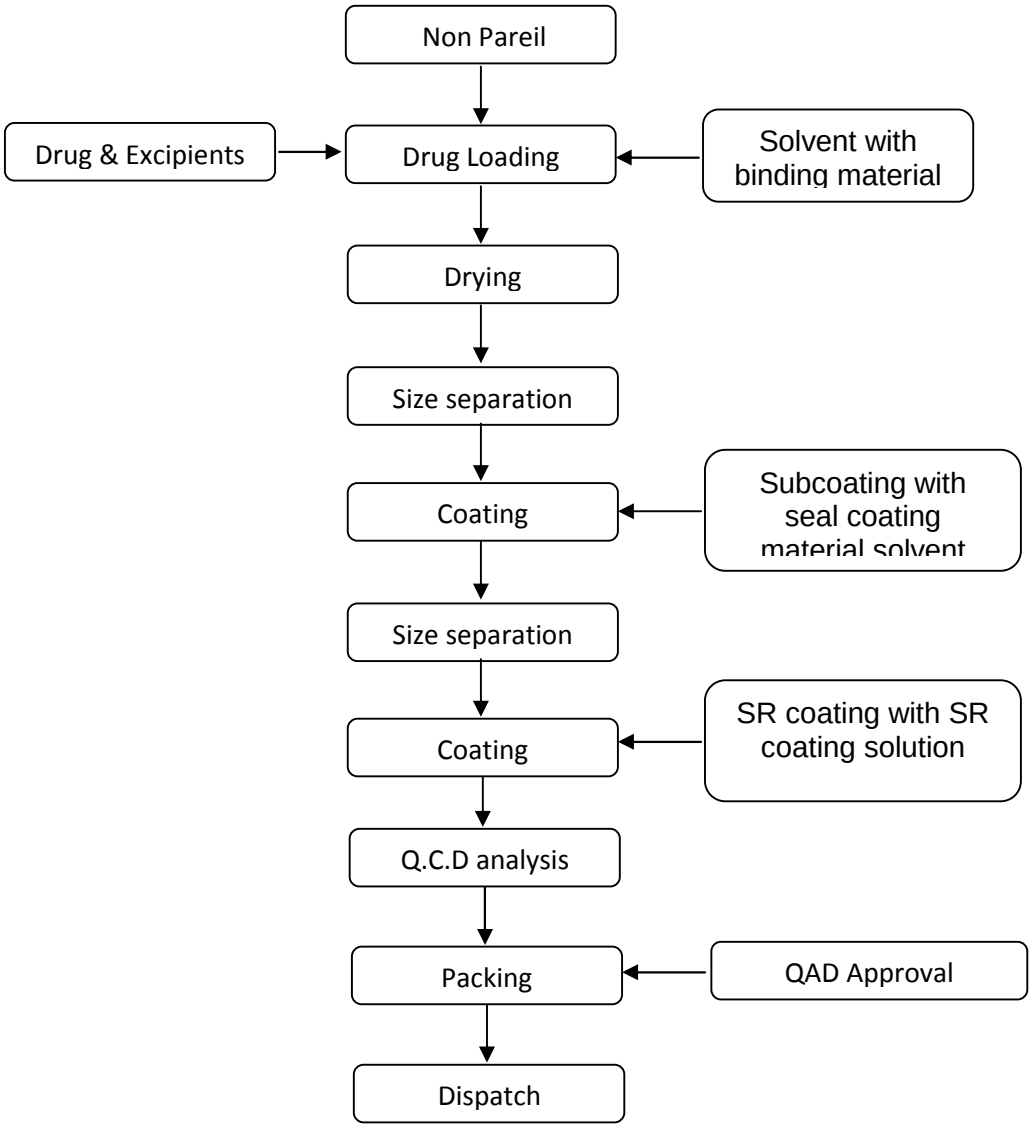
Drying

↓

Sub coating

↓

Coating



7.2.2. Figure: 7.2.Flowchart for method of preparation of pellets

Table: 7.1.Composition of formulations

INGREDIENTS (mg)*	**FORMULATION ***					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Atorvastatin calcium (ATC)	10	10	10	10	10	10
Non pareil seeds(pellets)	266	254	266	254	266	254
PVP K-30	9	9	9	9	9	9
Isopropyl alcohol	q. s	q. s	q. s	q. s	q. s	q. s
HPMC E15	3	3	3	3	3	3
Crospovidone	-	-	12	24	-	-
Sodium starch glycolate	12	24	-	-	-	-
Croscarmellose sodium	-	-	-	-	12	24
Total	**300**	**300**	**300**	**300**	**300**	**300**

*All the quantities are expressed as mg per capsule

7.2.3. Loose Bulk Density (LBD) *(Lachman L., et al., 1991)*

An accurately weighed powder from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density (LBD) of powder blends was determined using the following formula.

Loose bulk density = Total weight of powder / Total volume of powder

7.2.4. Tapped bulk density (TBD) *(Lachman L., et al., 1991)*

An accurately weighed powder from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder were determined using the following formula.

Tapped bulk density= Total weight of powder / Total volume of tapped powder

7.2.5. Hausner's Ratio *(Lachman L., et al., 1991)*

Hausner's ratio was determined by following equation,

Hausner's Ratio = Tapped bulk density/Loose bulk density

A hausner's ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

7.2.6. Carr's Compressibility Index *(Lachman L., et al., 1991)*

It is a simple index that can be determined on small quantities of powder. In theory, the less compressible a material the more flowable it is.

The compressibility indices of the powder blends was determined using following formula,

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flowability is shown in the table 7.2.

Table: 7.2. Standard values of Carr's index

S. NO.	Carr's index	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor*
5	33-38	Very poor*
6	>40	Extremely poor*

* May be improved by glidant

7.27. Angle of repose *(Lachman L., et al., 1991)*

The angle of repose was determined by the funnel method. The accurately weighed powder was taken into a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$$\tan(\theta) = \frac{h}{r}$$

Where '**h**' and '**r**' are the height and radius respectively of the powder cone

Table: 7.3. Standard values of Angle of repose

S. NO.	Flowability	Angle of repose **(θ)**
1	Excellent	<25
2	Good	25-30
3	Passable*	30-40
4	Poor	37-45
5	Very poor	>45

* Adding glidant for improving flow

7.3. EVALUATION OF IMMEDIATE RELEASE PELLETS

7.3.1. Appearance *(Lachman L., et al., 1991; Bankar G.S. and Rhodes C.T., 1996)*

The capsules were visually observed for morphological characters like color, shape and size etc.

7.3.2. Physicochemical characteristics

7.3.2.1. Dimension (Thickness and Diameter) *(Kammali Lavanya., et al., 2011)*

The thickness and diameter of pellets were important for uniformity of pellet size. The thickness and diameter of the pellet was determined using Vernier calipers (mitutoyo absolute vernier calipers). Three pellets from each type of formulation were used and average values were calculated.

7.3.2.2. Pellet Hardness *(Ranjana chopra; et al; 2001)*

For each formulation, the hardness of 6 pellets was determined using the Dr. Schieuniger hardness tester. The pellet was held in between the two jaws of the tester. At this point, reading should be zero Newtons. Then constant force was applied by rotating the knob until the pellet fractured. The value at this point was noted in Newtons.

7.3.2.3. Percent Friability *(Abbaspour MR; et al; 2008 ;)*

Friability is the measure of pellet strength. Friability of pellets are determined by using Erkewa type tablet friabilator for a fixed period of time combined with glass beads of certain diameter in order to generate abrasion and to generate friability index. The pellets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows,

$$\%F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

7.3.2.4. Weight Variation **(***IP, 2007; Lachman L., et al., 1991)*

To find out weight variation 20 capsules of each formulation were weighed individually using an electronic balance, average weight was calculated and individual capsule weight was then compared with average value to find the deviation in weight.

Table: 7.4. Specifications of Percentage weight variation allowed in capsules as per Indian Pharmacopoeia

S.NO	Average weight of capsules (mg)	Maximum percent deviation allowed (%)
1.	< 130	±10
2.	130 -324	±7.5
3.	>324	±5

7.3.2.5. Drug content **(***Lakshmi Narasaiah .V.,et al.,2011)*

The drug content in each capsule was determined by the UV –Spectroscopic method. An accurately weighed quantity of pellets equivalent to 10 mg of atorvastatin calcium was transferred to a 100 ml volumetric flask containing 10 ml of methanol and dissolved. The volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was filtered and the absorbance was measured after suitable dilutions by using UV – Spectrophotometer at 246 nm.

7.3.2.6. Disintegration test *(Salam W. Ahjet.,et al., 2009)*

Disintegration of pellets was one of the main characteristics for immediate release pellets. It was performed it in a tablet disintegration apparatus specially designed by inserting special transparent tubes of certain diameter and length with sieve of 710 mm mesh size at the bottom of tube. A superdisintegrant was incorporated in all pellet formulations in

order to fasten the rupture of capsule, which then will dissolve or release the drug faster than intact capsule.

7.3.3. *In-Vitro* drug release *(Lakshmi Narasaiah .V., et al., 2011)*

The release rate of atorvastatin calcium from capsules was determined using USP Dissolution Testing Apparatus type-II (paddle method; LAB INDIA DISSO 2000, Hyderabad). The dissolution test was performed using 900 ml of 6.8 phosphate buffer, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus for every 5 min and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 6.8 phosphate buffer. Absorbance of these solutions was measured at 246 nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were calculated by using PCP disso V3 software.

7.3.4. Release kinetics of *In-vitro* drug release

(*Benoy Brata Bhowmik.,* et al; 2006)

To study the released kinetics of *In-vitro* drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas.

- **Zero order**

$$C = K_0 t$$

Where K0 is the zero- order rate constant expressed in units of concentration / time.

t- is the time in min .

- **First order**

$$LogC = LogC_0 - Kt / 2.303$$

Where C_0 – is the initial concentration of drug,

K –is the first order constant

t – is the time in min.

- **Higuchi**

$$Qt = Kt^{1/2}$$

Where Qt - is the amount of the release drug in time t,

K – is the kinetic constant and

t - is the time in min.

- **Korsmeyer Peppas**

$$Mt/M\infty = Kt\ n$$

Where Mt – represents amount of the released drug at time t,

M∞ - is the overall amount of the drug (whole dose) released after 12 hrs,

K – is the diffusional characteristics of drug / polymer system constant,

n – is a diffusional exponent that characterizes the mechanism of release of drug.

Table: 7.5. Diffusion exponent and solute release mechanism

	Overall solute diffusion mechanism
< 0.5	Quasi-Fickian diffusion
0.5	Fickian diffusion
0.5 < n < 1.0	Anomalous (non – Fickian) diffusion
1.0	Case – II transport
> 1.0	Super case –II transport

7.4. Stability studies:

(Manavalan R. and Ramasamy S., 2004)

- **Introduction**

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

- **Objective of the study**

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 and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions

- **Long-Term Testing**: 25^{0} C $\pm 2^{0}$ C at 60% RH ±5% for 12 Months
- **Accelerated Testing:** 40^{0} C $\pm 2^{0}$ C at 75% RH ±5% for 6 Months

In present study the selected formulation F4 exposure up to 3 months stability studies at long term condition (25^{0} C $\pm 2^{0}$ C at 60% RH ±5%) and accelerated condition(40^{0} C $\pm 2^{0}$ C at

75% RH ±5%RH) to find out the effect of aging on hardness, friability, drug content and *In-Vitro* drug release.

- **Procedure**

Stability studies were carried out at long term condition (25^0 C ±2^0 C at 60% RH ±5%), accelerated condition (40^0 C ±2^0 C at 75% RH ±5%RH) for the optimized formulation F4. The capsules were stored at25^0 C ±2^0 C at 60% RH ±5% for long term stability and 40^0 C ±2^0 C at 75% RH ±5%RH for accelerated temperature in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1 month, 2 month and 3 month. The samples were analyzed for its Hardness, Percentage Friability, Drug content and *In-Vitro* drug release.

RESULTS

AND

DISCUSSION

8.RESULTS AND DISCUSSION

8.1. PRE FORMULATION PARAMETERS

8.1.1. Identification of drug

8.1.1.1. Identification by FT-IR spectroscopy

The FT-IR spectrum of atorvastatin calcium was shown in figure 8.1 and the interpretations of IR frequencies were showed in table 8.1.

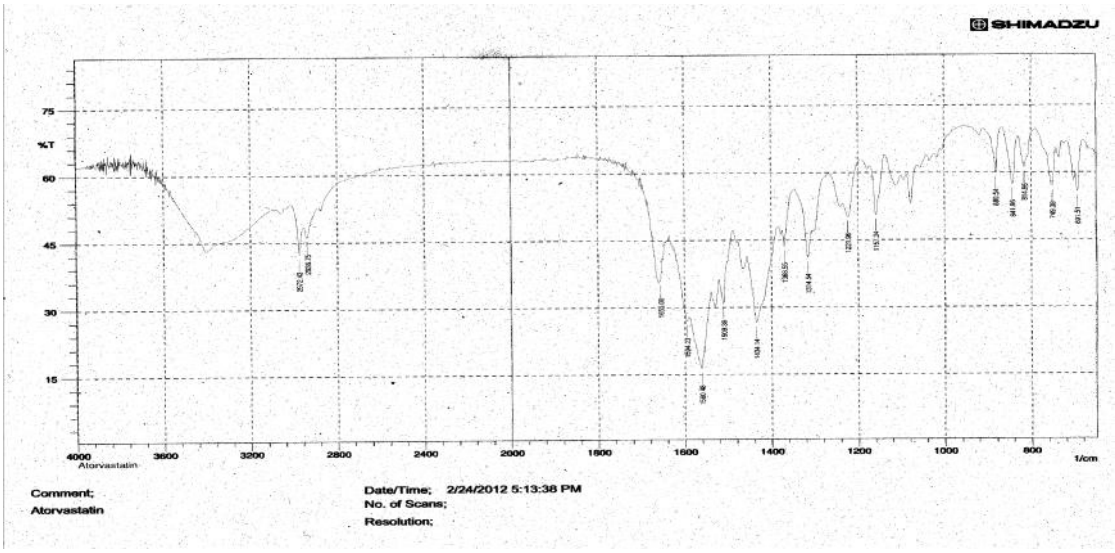


Figure: 8.1. FT-IR spectrum of Atorvastatin calcium

- **Interpretation of FT-IR Spectrum :**

Major functional groups present in atorvastatin calcium showed characteristic peaks in IR spectrum. Table 8.1 showed peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks were identical to functional group of atorvastatin calcium hence; the sample was confirmed as atorvastatin calcium.

Table: 8.1. Characteristic frequencies in FT-IR spectrum of Atorvastatin calcium.

Wave no.(cm^{-1})	Inference
2972.43	C-H Stretching
2936.75	C-H Stretching
1655.00	C=O Stetching
1594.23	C-H Stretching
1560.48	C=C Stretching
1157.34	C=S Stretching
841.96	C-H Bending
749.38	C-H Bending

8.1.1.2. Melting point

Melting point values of Atorvastatin calcium sample was found to be in range of 159.2^{0}C to 160.7^{0}C. The reported melting point for Atorvastatin calcium was 160^{0}C. Hence, experimental values were in good agreement with official values.

8.1.2. Physicochemical parameters of drug

8.1.2.1. Organoleptic properties

Odour: Pungent odour

Taste: Bitter taste

Colour: White to white off

Nature: Crystalline powder

8.1.2.2. Solubility study

Table: 8.2. Solubility profile of Atorvastatin calcium in various solvents.

Name of solvent	Parts of solvent required per solute	Solubility
Distilled water	210	Slightly soluble
Acetonitrile	140	Slightly soluble
Methanol	8	Freely soluble
Ethanol (95%)	1000	Very slightly soluble
Aqueous solution of pH 4 and below	10,000	Insoluble
pH 7.4 phosphate buffer	170	Slightly soluble

8.1.2.3. Loss on drying

Table: 8.3. Loss on drying of atorvastatin calcium

S. NO.	Percentage LOD	Avg. percentage LOD
1	0.3	0.33±0.152
2	0.2	
3	0.5	

*All values are expressed as mean ±S.D.,n=3

The sample passes test for loss on drying as per the limit specified in IP, 2007 (N.M.T. 0.5%).

8.1.3. Analytical methods

8.1.3.1. Determination of λ max

The absorption maximum for atorvastatin calcium in methanol was found to be 246 nm and absorption maximum was shown in figure 8.2.

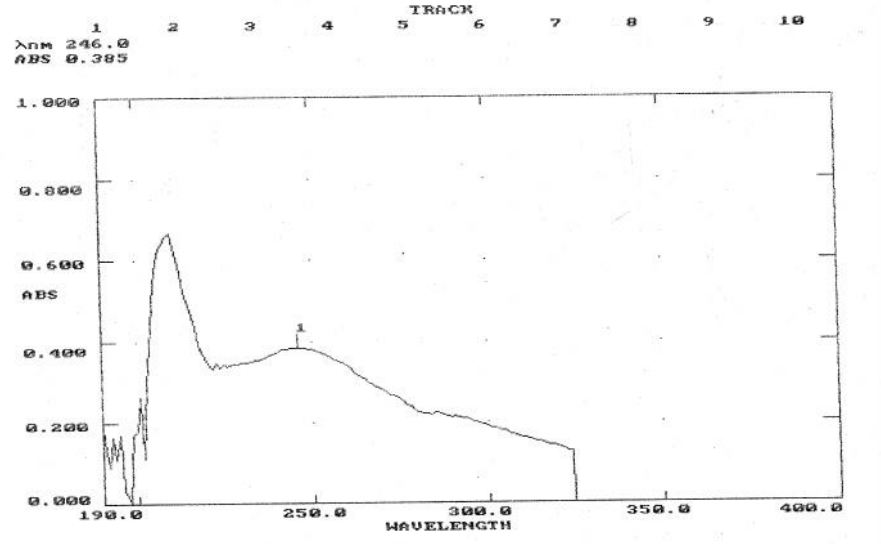


Figure: 8.2. λ max observed for Atorvastatin calcium in methanol

8.1.3.2. Preparation of caliberation curve of Atorvastatin calcium in methanol

UV absorption spectrum of Atorvastatin calcium in methanol showed λ max at 246 nm. Absorbance obtained for various concentrations of Atorvastatin calcium in methanol were given in table 8.4. The graph of absorbance vs concentration for Atorvastatin calcium was found to be linear in the concentration range of 2–10 µg /ml. The drug obeys Beer- Lambert's law in the range of 2–10 µg /ml.

Table: 8.4. Data of concentration and absorbance for Atorvastatin calcium in methanol

S. NO.	Concentration (µg/ml)	Absorbance
1	0	0.0000
2	2	0.08
3	4	0.156
4	6	0.24
5	8	0.312
6	10	0.4

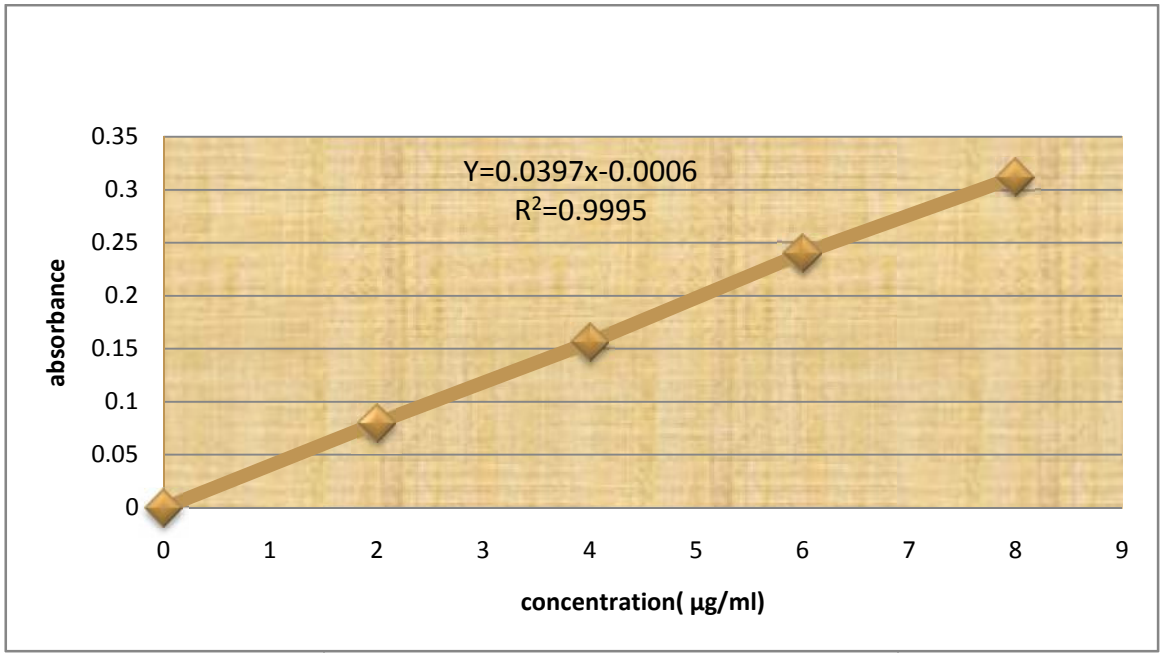


Figure: 8.3. Caliberation curve of atorvastatin calcium in methanol at 246 nm

Table: 8.5. Data for caliberation curve Parameters for Atorvastatin Calcium in methanol.

S. NO.	Parameters	Values
1	Correlation coefficient (r^2)	0.9995
2	Slope	0.0397
3	Intercept	0.0006

8.1.3.3.Determination of λ max in 6.8 phosphate buffer

The absorption maximum for Atorvastatin calcium in 6.8 phosphate buffer was found to be 245 nm and absorption maximum was shown in Figure 8.4

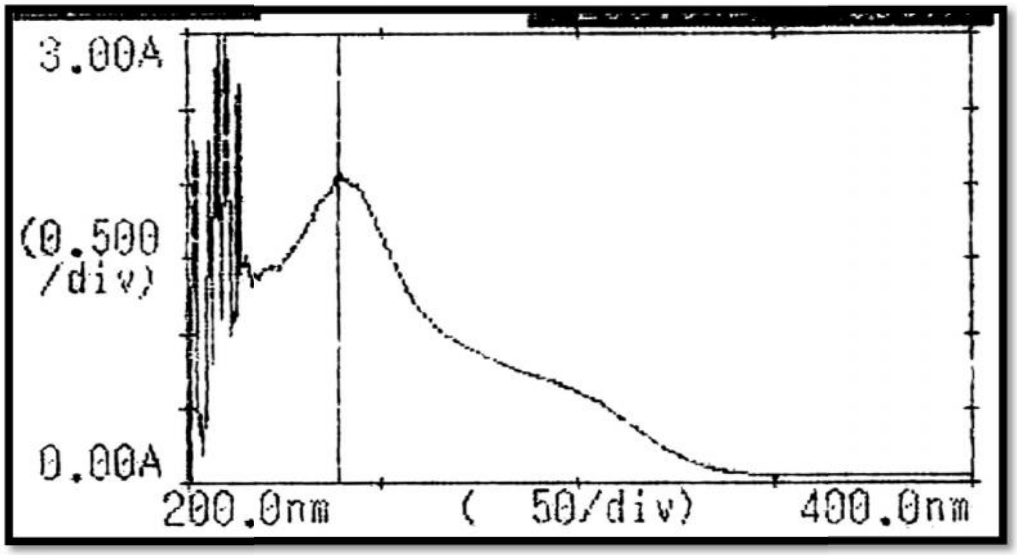


Figure: 8.4. λmax observed for Atorvastatin calcium in 6.8 phosphate buffer

8.1.3.4. Preparation of caliberation curve of atorvastatin calcium in 6.8 phosphate buffer

UV absorption spectrum of Atorvastatin calcium in 6.8 phosphate buffer showed λ max at 246 nm. Absorbance obtained for various concentrations of Atorvastatin calcium in 6.8 phosphate buffer were given in table 8.6. The graph of absorbance vs concentration for

Atorvastatin calcium was found to be linear in the concentration range of 2–10 µg /ml. The drug obeys Beer- Lambert's law in the range of 2–10 µg /ml.

Table 8.6: Data of concentration and absorbance for atorvastatin calcium in 6.8 phosphate buffer.

S.NO	Concentration(µg/ml)	Absorbance
1.	0	0.00
2.	2	0.071
3.	4	0.142
4.	6	0.211
5.	8	0.278
6.	10	0.349

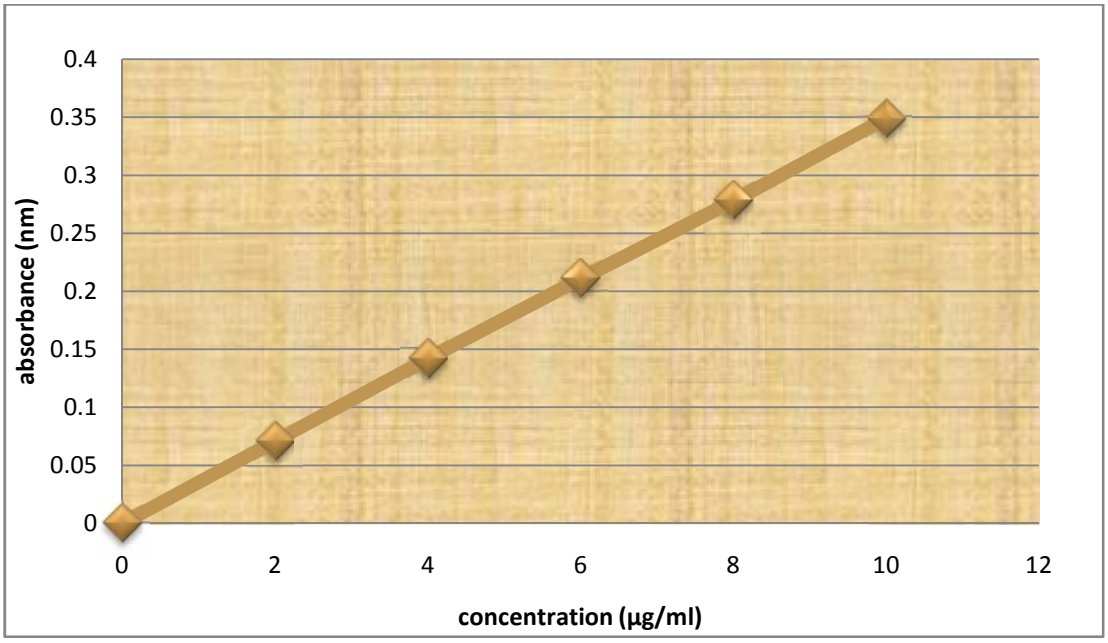


Figure: 8.5.Caliberation curve of Atorvastatin calcium in 6.8 phosphate bufferat 245nm

Table: 8.7. Data for caliberation curve parameters for Atorvastatin calcium in 6.8 phosphate buffer.

S.NO	Parameters	Values
1.	Correlation coefficient(r^2)	0.999936
2.	Slope	0.0070036
3.	Intercept	0.000464

8.1.3.5. Percentage purity of drug

The percentage purity of drug was calculated by using calibration graph method (least square method).

Table: 8.8. Percentage purity of Atorvastatin calcium

S. No.	Percentage purity (%)	Avg. percentage purity (%)
1	99.41	99.52±0.6322
2	98.95	
3	100.2	

*All the values are expressed as mean± S.D.,n=3

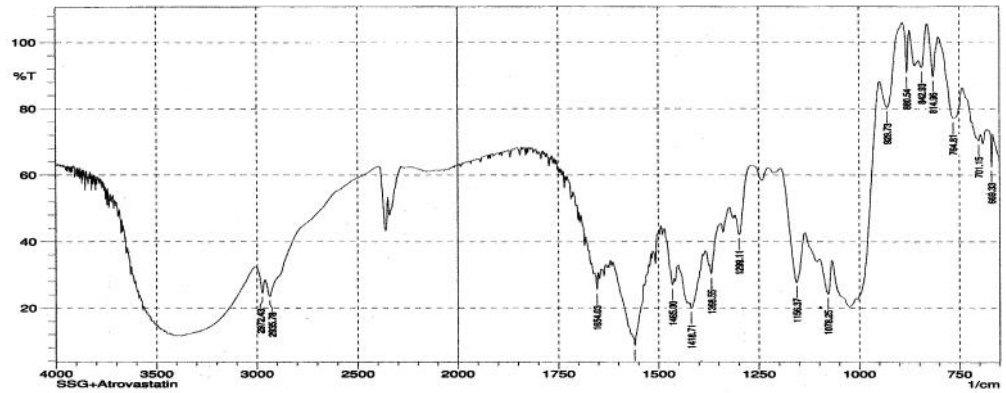
The reported percentage purity for atorvastatin calcium in IP 2007 is 98 to 102%.

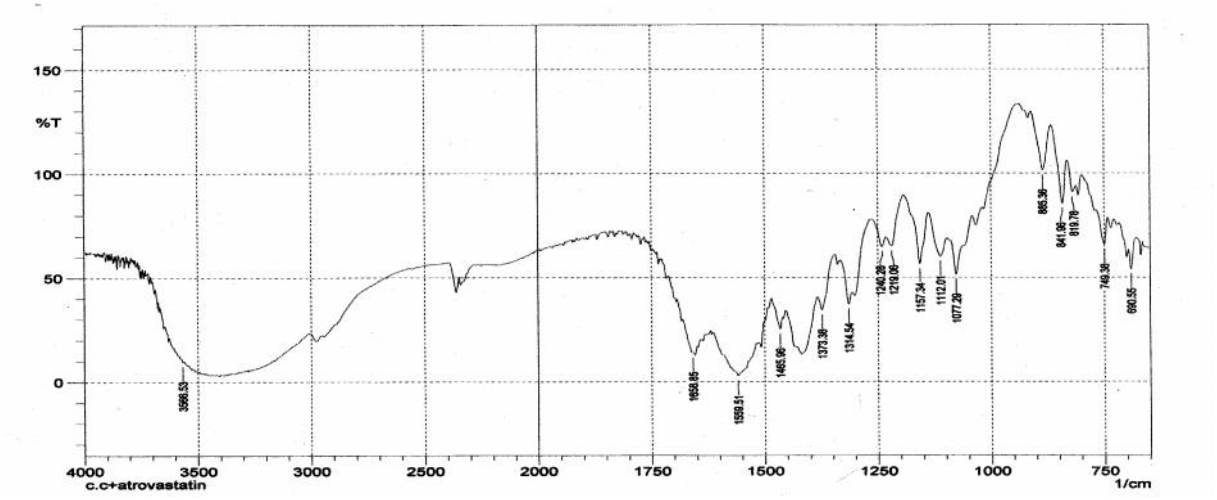
8.1.4. Determination of compatibility for drug with superdisintegrants

8.1.4.1. By FT-IR spectroscopy

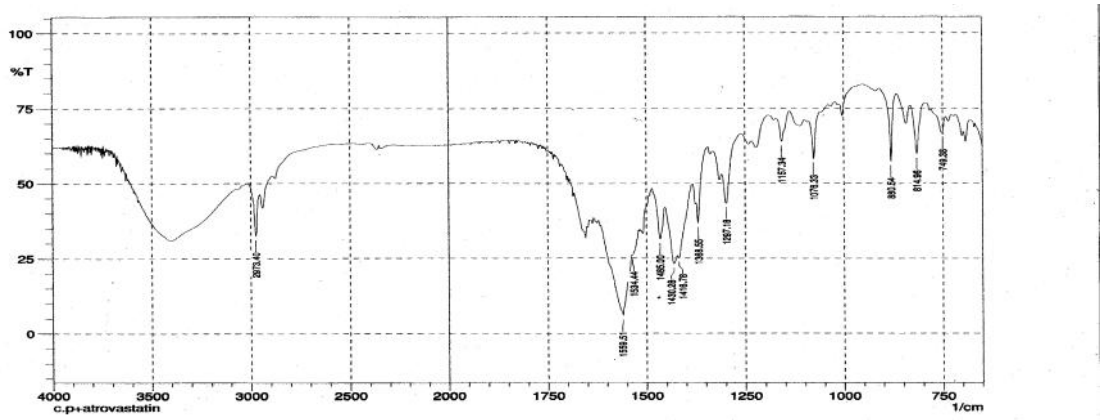
The FT-IR spectrums of atorvastatin calcium with different superdisintegrants used in formulation were shown in figure 8.6.

Atorvastatin calcium + SSG





Atorvastatin calcium + CP



Atorvastatin calcium + CCS

Figure: 8.6. FT-IR spectrum of atorvastatin calcium with SSG, ATC with CP and ATC with CCS

Table: 8.9. Major peaks observed in FT-IR spectrum of atorvastatin calcium and ATC with different superdisintegrants used in formulations.

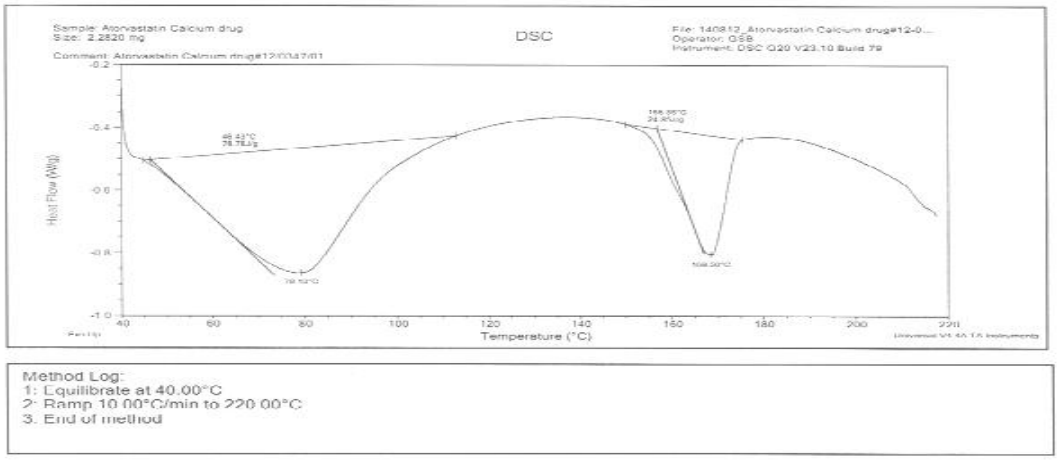
Wave No. (cm^{-1})	Functional group	Peak observed (Yes/No)			
		ATC	ATC+SSG	ATC+CP	ATC +CCS
2972.43	C-H Stretching	**Yes**	**Yes**	**Yes**	**Yes**
1560.48	C=C Stretching	**Yes**	**Yes**	**Yes**	**Yes**
1157.34	C=S Stretching	**Yes**	**Yes**	**Yes**	**Yes**
880.54	C-H Bending	**Yes**	**Yes**	**Yes**	**Yes**
841.96	C-H Bending	**Yes**	**Yes**	**Yes**	**Yes**
814.96	C-H Bending	**Yes**	**Yes**	**Yes**	**Yes**
749.38	C-H Bending	**Yes**	**Yes**	**Yes**	**Yes**

According to table 8.9 and figure 8.6 the major peaks observed in drug spectrum were also observed in spectrums of drug with superdisintegrants; therefore it could indicate that there was no incompatibility between drug and different superdisintegrants.

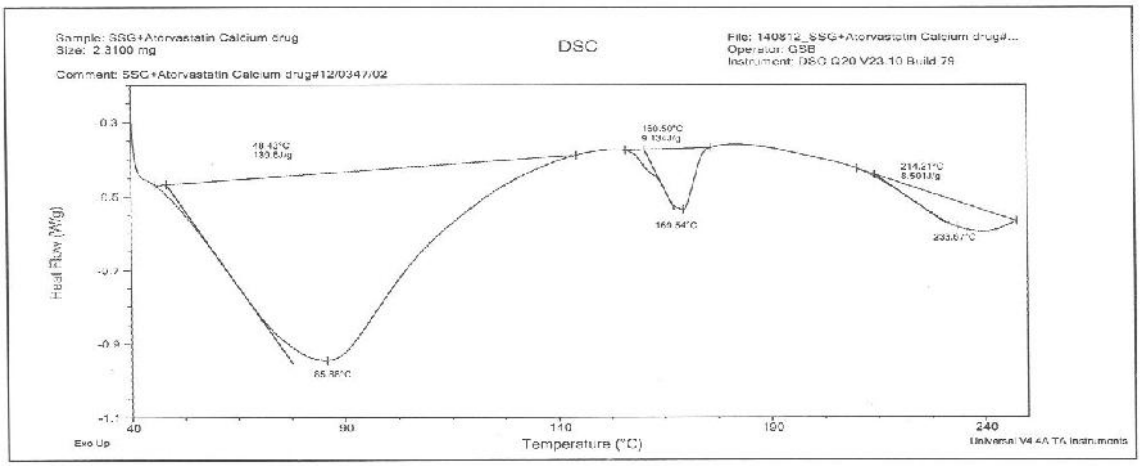
8.1.4.2. By DSC thermal analysis

The compatibility and interactions between drugs and superdisintegrants were checked using DSC thermogram and results obtained were represented in table 8.10 and figure 8.7

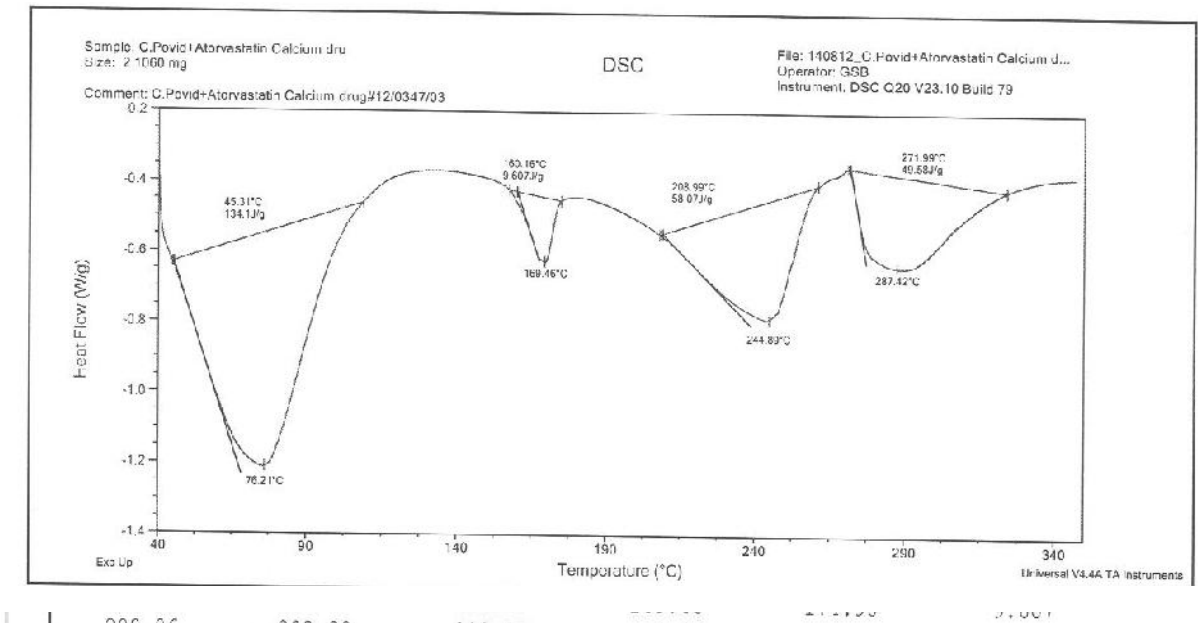
Atorvastatin calcium



Atorvastatin calcium + SSG



Atorvastatin calcium +CP



Atorvastatin calcium +CCS

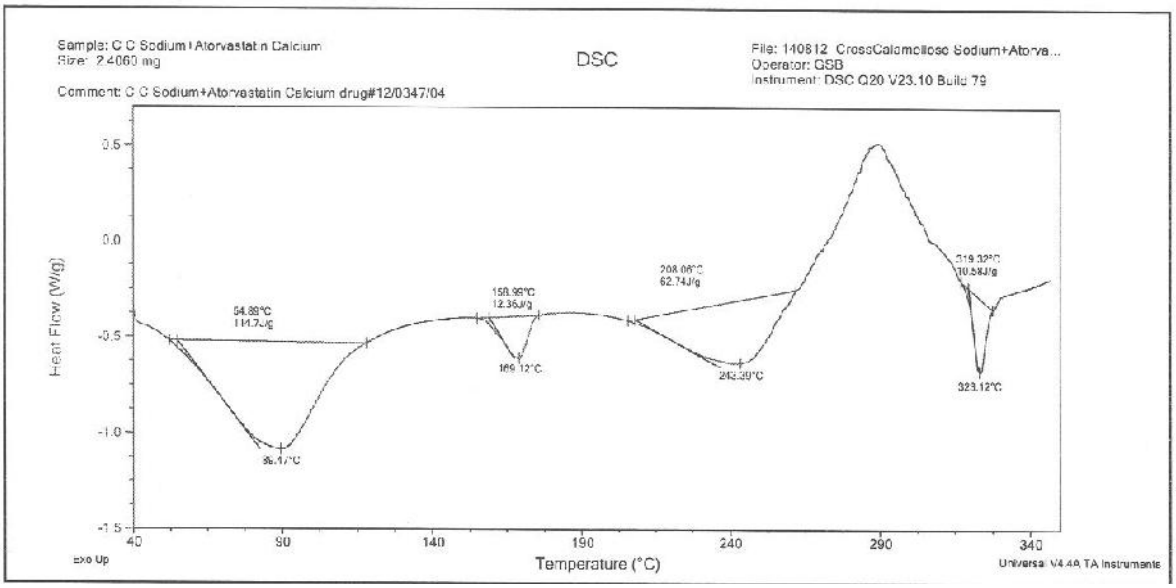


Figure: 8.7. DSC thermograms of Atorvastatin calcium, ATC with SSG, ATC with CP and ATC with CCS

Table 8.10: DSC thermogram parameters

S. No.	DSC Thermogram of ATC	Onset temperature (°C)	Peak temperature (°C)	Endset temperature (°C)
1	ATC (Drug)	158.2	159.7	160.5
2	ATC + SSG	157.8	159.3	160.8
3	ATC +CP	158.8	159.9	161.1
4	ATC +CCS	157.4	159.1	160.2

According to figure 8.7 and table 8.10, DSC thermogram showed that there was no major difference in onset temperature, endset temperature and peak temperature when compared with pure drug's thermogram. No interaction was found between drug and superdisintegrants. Therefore it could indicate that there was no incompatibility between drug and different superdisintegrants.

8.15. Pre formulation studies of powder

Table 8.11: Determination of Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose

S.No.	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility index (%)	Hausner's ratio	Angle of repose (θ)
1	0.517±0.005	0.653±0.005	20.92±1.509	1.246±0.0057	24˚.93″±0.251

*All the values are expressed as mean±S.D, n=3

8.1.6. Method of preparation and characterization of pellets

The pellets were prepared by layering of various ingredients mentioned in table 7.1 around the non pareil seeds and used for characterization of various flow properties of pellets.

8.1.6.1. Loose Bulk Density (LBD)

The powder blends of formulations have the bulk density ranged between 0.555±0.00 to 0588±0.01 gm/ml.

8.1.6.2. Tapped bulk density (TBD)

The powder blends of formulations have the tapped bulk density ranged between 0.588±0.01 to 0.666±0.01 gm/ml. These values indicate good packing characteristics and the powder was not bulky.

Table 8.12: Determination of Physical Characteristics of Atorvastatin calcium pellets before formulation

Formulation	Loose bulk density (gm/cm3)*	Tapped bulk density (gm/cm3)*	Hausner ratio (HR)*	Carr's index (CI)*
F1	0.588±0.01	0.625±0.01	1.062±0.002	5.882±0.003
F2	0.555±0.00	0.588±0.00	1.058±0.004	5.555±0.005
F3	0.588±0.01	0.625±0.02	1.062±0.001	5.882±0.001
F4	0555±0.02	0.588±0.01	1.058±0.003	5.555±0.002
F5	0.588±0.01	0.666±0.01	1.133±0.003	11.764±0.01
F6	0.555±0.01	0.625±0.01	1.125±0.002	11.111±0.008

*All the values are expressed as mean± S.D., n=3

8.1.6.3. Carr's Compressibility Index

The Carr's index for all the formulations was found to be below 12% indicating that the powders have a excellent compressibility.

8.1.6.4. Hausner's Ratio

The hausner's ratio for all the formulations was found to be <1.25, indicating good flow properties.

8.2. EVALUATION OF IMMEDIATE RELEASE PELLETS

8.2.1. Appearance

Colour: White colour.

Shape: Spherical shape.

8.2.2. Physico chemical characteristics

The physical characteristics of Atorvastatin calcium (F_1 to F_6) such as dimension, hardness, friability, drug content , disintegration time and weight variation were determined and results of the formulations (F_1 to F_6) found to be within the limits specified in official books.

Table 8.13: Physicochemical characterizations of atorvastatin calcium immediate release pellets before formulation.

Formulation	Dimension*	Hardness** (N)	Friability (%)*	Drug content (%w/w)*
F1	0.98±0.01	11±1.52	0.12±0.01	100.1±0.07
F2	0.97±0.01	15±2.00	0.16±0.02	98.85±0.06
F3	1.00±0.02	14±2.51	0.13±0.02	98.35±0.06
F4	1.05±0.02	16±2.00	0.17±0.02	100.05±0.16
F5	0.99±0.03	14±1.52	0.13±0.01	98.72±1.13
F6	1.02±0.02	12±2.03	0.14±0.02	99.89±1.28

All the values are expressed as mean± S.D., *n=3, **n=6.

8.2.2.1. Dimension (size)

Thickness and diameter specifications may be set on an individual product basis. There were no marked variations in the thickness and diameter of pellets within each formulation indicating uniform behaviour of pellets. The dimensions of pellets of all formulations were found to be in the range of 0.97±0.01mm to 1.05±0.02.

8.2.2.2. Pellet Hardness

A difference in pellet hardness reflects difference in pellet density and porosity which in turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the pellet and formation of gel barrier. The hardness of pellets was found to be in the range of 11±1.52 N to 16±2.00 N. This indicates good pellet strength.

8.2.2.3. Percentage Friability

Percentage friability of all the formulations of pellets was found between 0.12± 0.01 % to 0.17±0.02% .This indicated good handling property of the prepared pellet.

8.2.2.4. Drug content

The content of active ingredients in the formulation was found to be between 98.35± 0.06 % to 100.22±0.16% w/w, which was within the specified limit as per IP, 2007.

8.2.2.5. Disintegration time

The disintegration time of all the formulations was found between 6.3±0.23 min to 7.2±0.2 min, which was within the specified limit as per IP, 2007.

8.2.2.6. Weight Variation

A capsule was designed to contain a specific amount of drug. When the average mass of the capsule was 300 mg the pharmacopoeia limit for percentage deviation is ±7.5%. The percentage deviation from average capsule weight for all the capsules were found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopoeia specifications IP. 2007.

Table: 8.14 physicochemical characterizations of Atorvastatin calcium Immediate release pellets after formulation

Formulations	Disintegration time (min)*	Weight variation (%) ***
F_1	6.8±0.20	±0.02
F_2	6.5±0.15	±0.03
F_3	7.2±0.2	±0.05
F_4	6.3±0.23	±0.01
F_5	7.0±0.12	±0.09
F_6	6.9±0.2	±0.02

*All the values are expressed as mean ± S.D. *n=3, ***n=20

8.2.3. *In-Vitro* Drug released Studies

Table: 8.15. *In vitro* drug released data for formulation F_1

Time (min)	Dissolution medium	Absorbance	Concentration (µg/ml)	Amount (mg)	percentage drug released*
0	6.8 pH phosphate buffer	0.00	0.00	0.00	0.00
5		0.69	17.510	15.759	52.53±1.21
10		0.94	23.633	21.270	70.9±0.76
15		1.18	29.793	26.814	89.38±1.31
30		1.3	32.676	29.409	98.03±1.13

*All values are expressed as mean ±S.D. n=3.

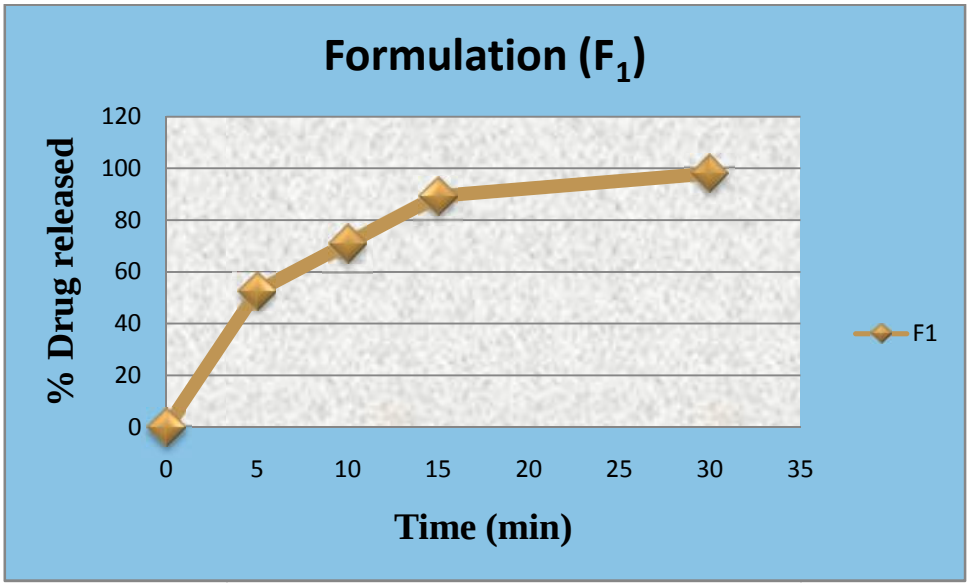


Figure: 8.8. Plot of *In-Vitro* drug released profile for formulation F_1

Table: 8.16. *In vitro* drug released data for formulation F_2

Time (min)	Dissolution medium	Absorbance	Concentration (µg/ml)	Amount (mg)	percentage drug released*
0	6.8 pH phosphate buffer	0	0	0	0
5		0.73	18.34	16.506	55.02±1.24
10		0.99	24.98	22.479	74.93±1.10
15		1.13	28.36	25.530	85.1±1.00
30		1.31	32.92	29.631	98.77±0.93

*All values are expressed as mean ±S.D. n=3.

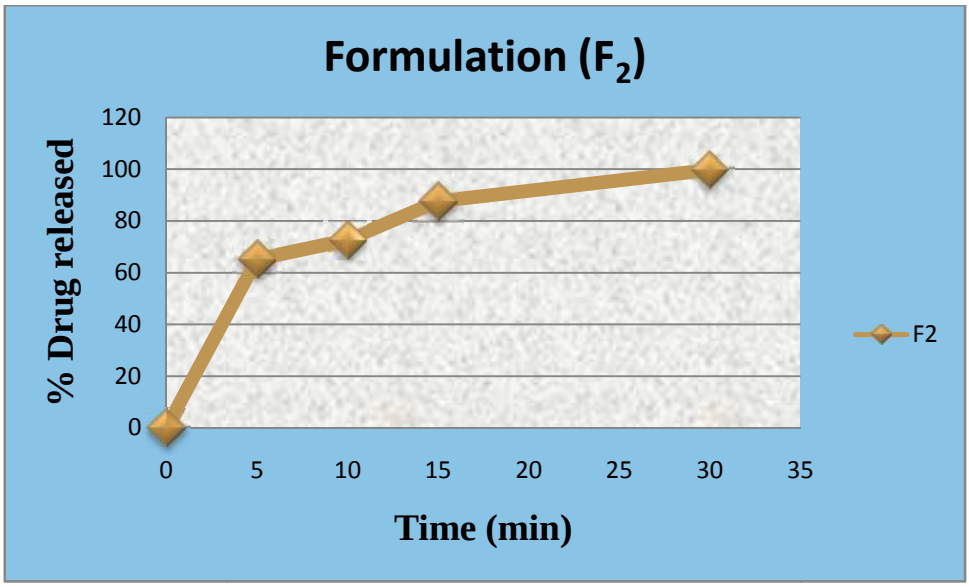


Figure: 8.9 Plot of In-*Vitro* drug released profile for formulation F_2

Table 8.17: *In vitro* drug released data for formulation F_3

Time (hours)	Dissolution medium	Absorbance	Concentration (µg/ml)	Amount (mg)	Percentage drug released*
0	6.8 pH phosphate buffer	0.00	0.00	0.00	0.00
5		0.89	22.55	20.295	67.65±0.44
10		1.05	26.45	23.811	79.37±0.52
15		1.18	29.67	26.703	89.01±0.45
30		1.31	33.1	29.760	99.2±0.41

***All values are expressed as mean ±S.D. n=3.

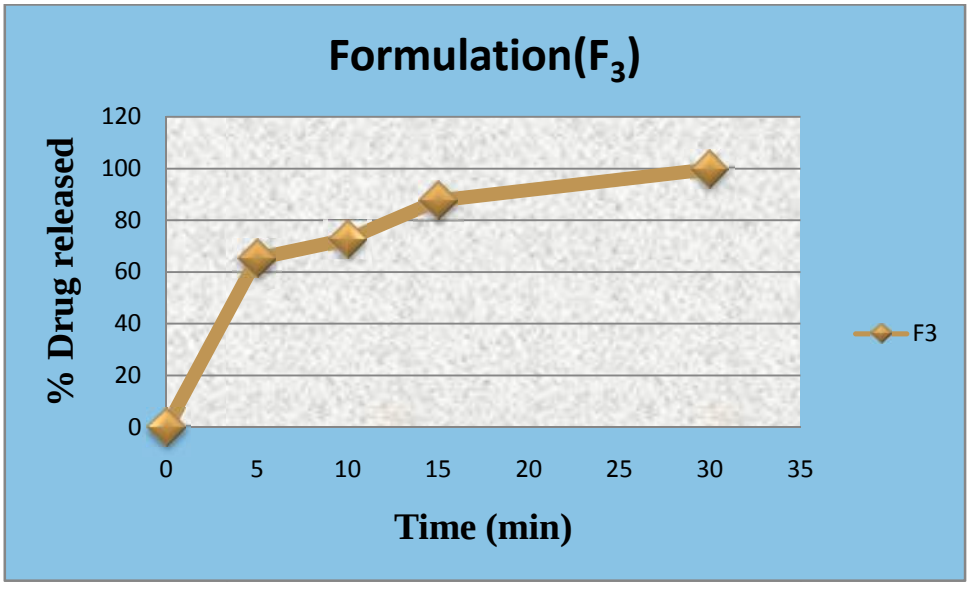


Figure: 8.10 Plot of In-*Vitro* drug released profile for formulation F_3

Table: 8.18. *In vitro* drug released data for formulation F_4

Time (min)	Dissolution medium	Absorbance	Concentration (µg/ml)	Amount(mg)	Percentage drug released*
0	6.8 pH phosphate buffer	0	0	0	0
5		0.94	24.08	21.669	72.23±0.21
10		1.12	28.17	25.353	84.51±0.40
15		1.21	30.53	27.480	91.6±0.38
30		1.33	33.4	30.060	100.2±0.30

***All values are expressed as mean ±S.D. n=3.

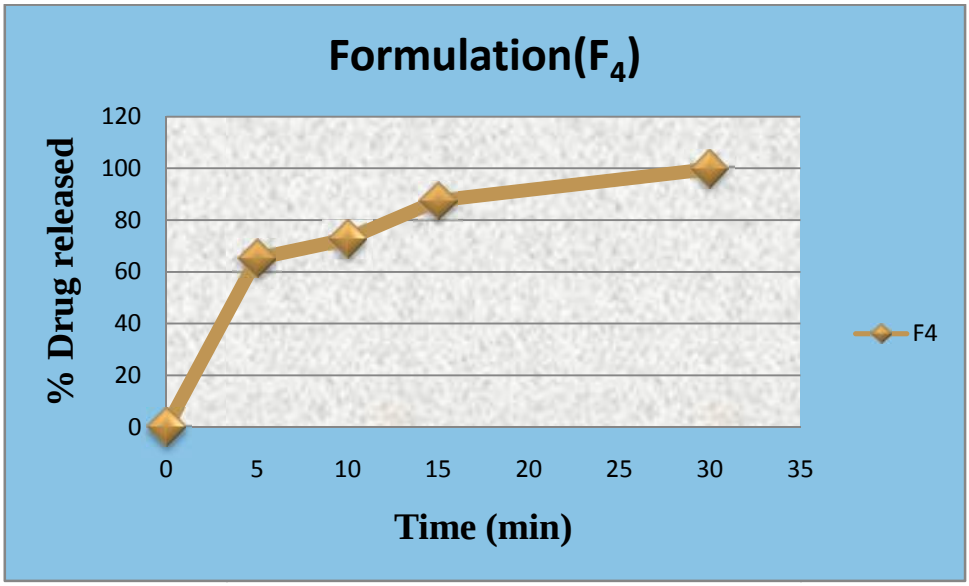


Figure: 8.11. Plot of *In-Vitro* drug released profile for formulation F_4

Table: 8.19. *In vitro* drug released data for formulation F_5

Time (min)	Dissolution medium	Absorbance	Concentration (µg/ml)	Amount (mg)	percentage drug released*
0	6.8 pH phosphate buffer	0	0	0.00	0.00
5		0.92	23.21	20.886	69.62±0.19
10		1.11	27.93	25.134	83.78±0.24
15		1.2	30.2	27.183	90.61±0.35
30		1.32	33.17	29.853	99.51±0.27

***All values are expressed as mean ±S.D. n=3.

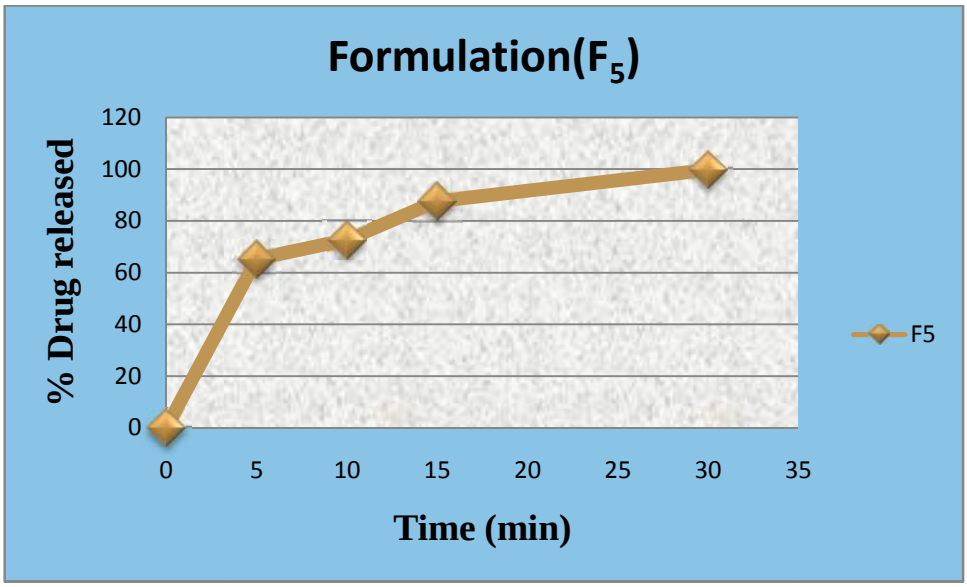


Figure: 8.12. Plot of In-*Vitro* drug released profile for formulation F_5

Table: 8.20. *In vitro* drug released data for formulation F_6

Time (min)	Dissolution medium	Absorbance	Concentration(µg/ml)	Amount (mg)	Percentage drug released*
0	6.8 pH phosphate buffer	0.00	0.00	0.00	0.00
5		0.86	21.73	19.554	65.18±0.20
10		0.96	24.22	21.801	72.67±0.34
15		1.16	29.19	26.271	87.57±0.28
30		1.32	33.25	29.925	99.75±0.17

***All values are expressed as mean ±S.D. n=3.

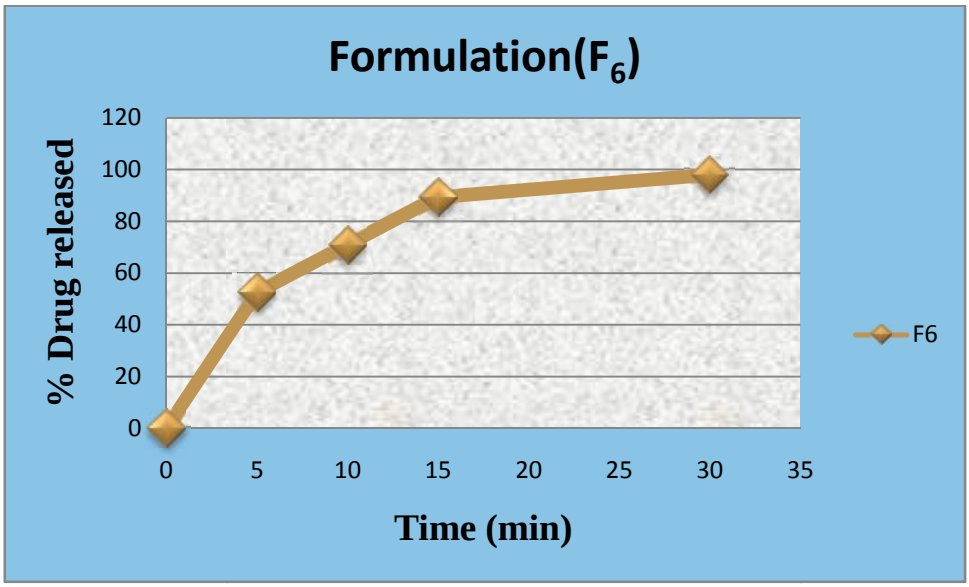


Figure 8.13: Plot of *In-Vitro* drug released profile for formulation F_6

The drug released data of dissolution studies of formulations F_1-F_2 containing SSG shown in table 8.15 & 8.16. The drug released from formulations F_1-F_2 containing SSG at two concentration levels of 4%, 8% were found to be 98.03±1.13% and 98.77±0.93% respectively.

The drug released from formulation F_3-F_4 containing Crospovidone at two concentration levels of 4% and 8% were found to be 99.2±0.41%and 100.2±0.30% respectively (Table 8.17 & 8.18). While the drug released from formulation F5-F6 containing croscarmellose sodium at two concentration levels of 4% and 8% were found to be 99.51±0.27%, 99.75±0.17 % respectively (Table 8.19& 8.20).

Table: 8.21. *In vitro* drug released data for Innovator drug

Time (min)	Dissolution medium	Absorbance	Concentration (µg/ml)	Amount (mg)	% Drug released*
0	6.8 phosphate buffer	0.00	0.00	0.00	0.00
5		0.17	23.58	21.228	70.76±0.17
10		0.20	27.96	25.167	83.89±0.02
15		0.22	30.81	27.726	92.42±0.25
30		0.234	33.43	30.093	100.31± 0.43

*All values are expressed as mean ± S.D. n=3.

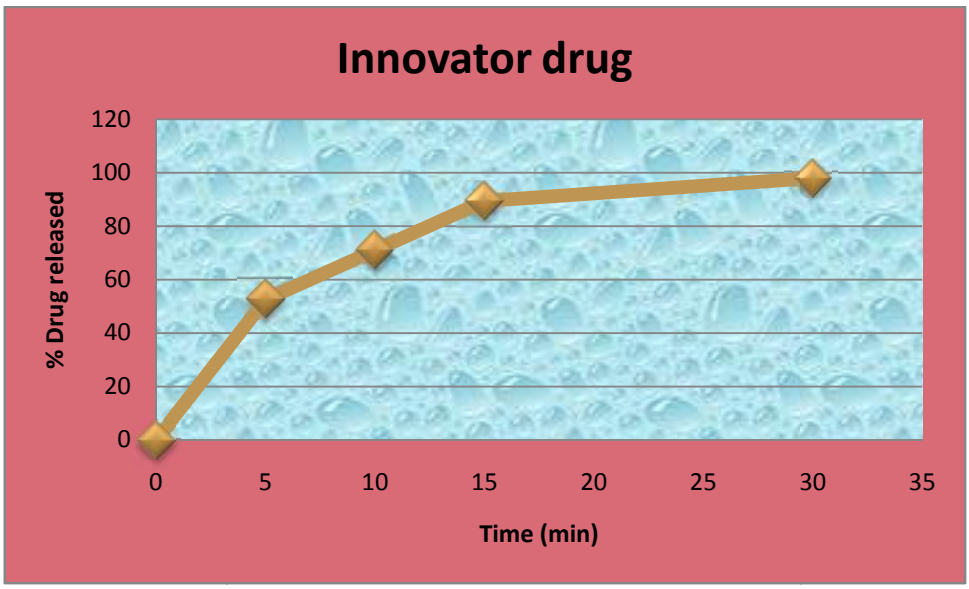


Figure: 8.14 Plot of *In vitro* drug released profile for Innovator drug.

Table: 8.22. Comprehensive *in vitro* drug released data for formulations F_1 – F_6 and Innovator drug.

Time (min)	Formulations*						Innovator drug*
	F_1	F_2	F_3	F_4	F_5	F_6	
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	52.53±1.21	55.02±1.24	67.65±0.44	72.23±0.21	69.62±0.19	65.18±0.2	70.76±0.17
10	70.9±0.76	74.93±1.10	79.37±0.52	84.51±0.40	83.78±0.24	72.67±0.34	83.89±0.02
15	89.38±1.31	85.1±1.00	89.01±0.45	91.6±0.38	90.61±0.35	87.57±0.28	92.42±0.25
30	98.03±1.13	98.77±0.93	99.2±0.41	100.2±0.30	99.51±0.27	99.75±0.17	100.31±0.4

*All values are expressed as mean ± S.D. n=3.

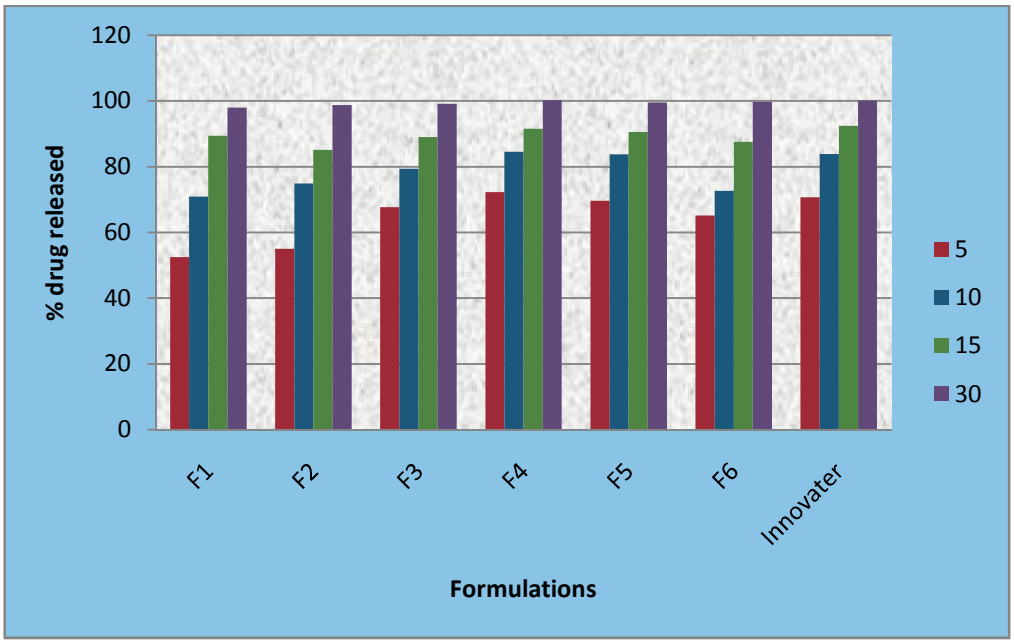


Figure: 8.15. Plot of *in vitro* drug released profile for formulations F_1 to F_6 and Innovator drug.

Table: 8.23. Time of drug released values of t_{25}, t_{50} and t_{90} for pellet formulations F_1 to F_6 and Innovator drug

Formulations	Time of % drug released (min)		
	25% (t_{25})	**50%(t_{50})**	**90%(t_{90})**
F1	2.4	4.8	16.6
F2	2.2	4.6	20
F3	1.8	3.85	17
F4	1.8	3.6	13.6
F5	1.8	3.6	14
F6	2.0	3.8	17.6
Innovator drug	1.85	3.6	13.6

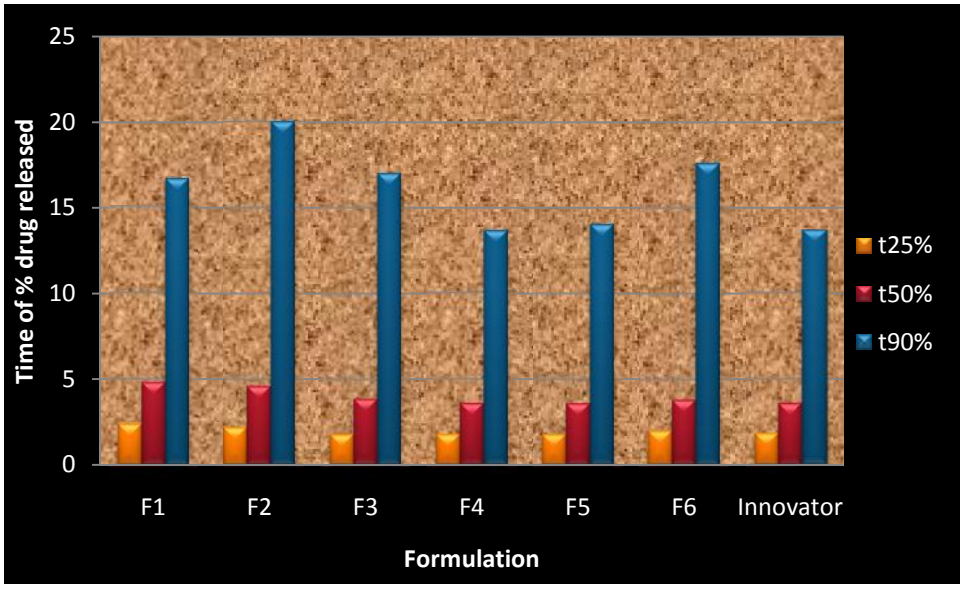


Figure: 8.16. Histogram for time of drug released values of t_{25}, t_{50} and t_{90} of formulations F_1 to F_6 and Innovator drug.

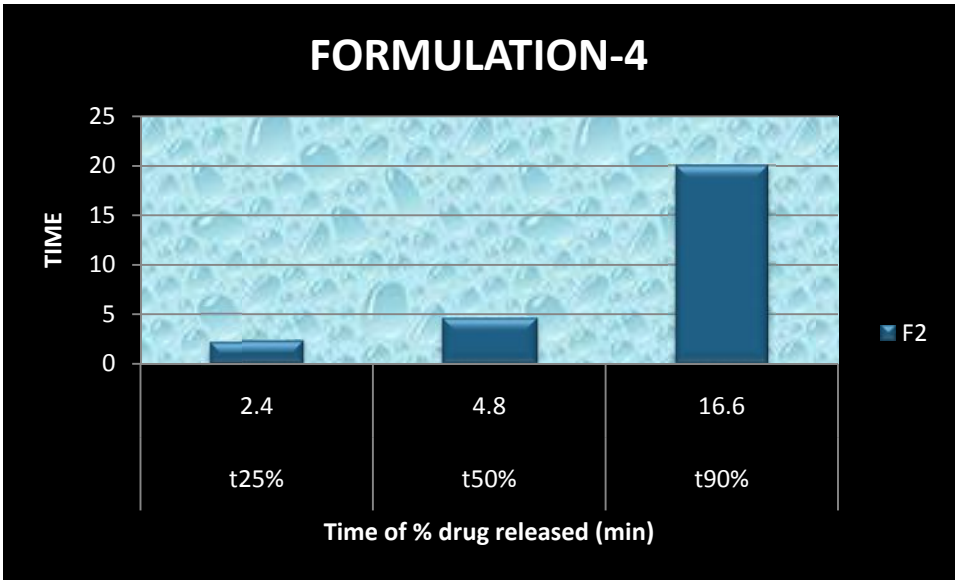


Figure: 8.17 Histogram for time of drug released values of t_{25}, t_{50} and t_{90} of optimized formulation (F_4)

The comparative effect of three different super disintegrants on the released profile of atorvastatin calcium from the immediate release formulations in terms of percentage drug release was found that crospovidone 8% release the drug quickly than those containing SSG and CCS. It was observed that formulations having low values of mean dissolution time (MDT) indicated the faster released of the drug than the other formulations.

The release profiles of all the batches were fitted to different models. But the superiority of other model was however statistically insignificant with Korsmeyer Peppas model as shown by the goodness of fit test (t-test). Thus it may be concluded that the drug release from Atorvastatin calcium immediate release pellets was best explained by Korsmeyer Peppas model.

By graphical method ,by taking time on x –axis and drug release on y -axis were used to find out time required to release 25% drug (t_{25}), time required to release 50% drug (t_{50}) and time required to release 90% drug (t_{90}) drug for each batch and Innovator drug.

The result of t_{25}, t_{50} and t_{90} are shown in table 8.23 and figure 8.16, according to the time of drug release values of t_{25}, t_{50} and t_{90} the formulation F_4 (8%)was selected as the best formulation of crospovidone respectively. The drug release profile of selected formulations was shown in figure 8.17; it shows that the formulation F_4 showed the immediate drug release profile for 30 min as compared to formulation F_3.

From the above study it was concluded that the formulation F_4 showed the immediate drug release profile with immediate onset of action, less disintegration time and less time of drug release as compared with the all batches for these reason the **formulation F_4** was considered as the best formulation among all the six formulations of this series. Hence the formulation F_4 was selected for further stability study.

8.2.4. Release Kinetics of *In-vitro* Drug Release

The kinetics of *in-vitro* drug released was determined by applying the drug release data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer – Peppas. The results were represented in table 8.24 and shown in figures 8.18 to 8.23.

Table: 8.24 Release kinetics of *in-vitro* drug release

Formulation	Zero order	First order	Higuchi	Peppas	Best fit model
	R^2	**R^2**	**R^2**	**R^2**	
F_1	0.6836	0.6742	0.9690	0.996	Peppas
F_2	0.6557	0.6671	0.9678	0.998	Peppas
F_3	0.4667	0.4629	0.9291	0.997	Peppas
F_4	0.3519	0.3742	0.9077	0.999	Peppas
F_5	0.3951	0.3609	0.9154	0.998	Peppas
F_6	0.5663	0.5581	0.9481	0.997	Peppas

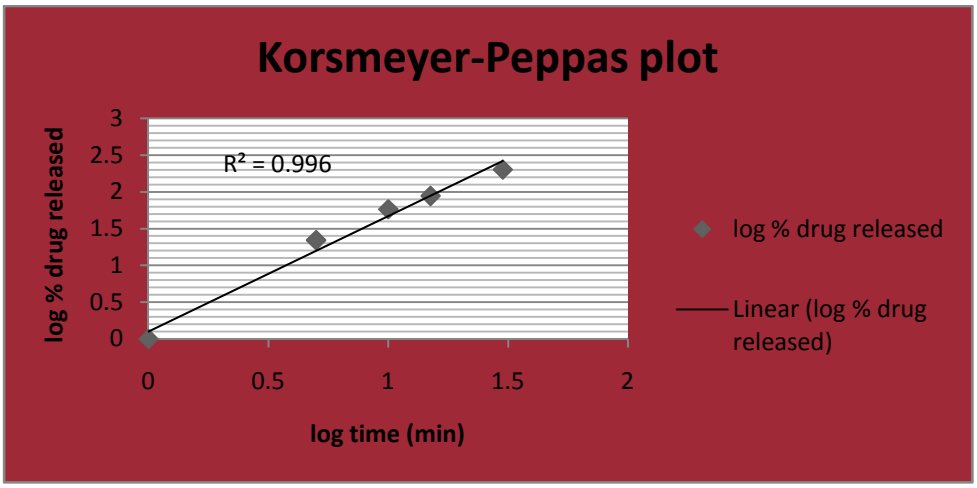


Figure: 8.18 Best fit model (Korsmeyer- Peppas) of formulation F_1

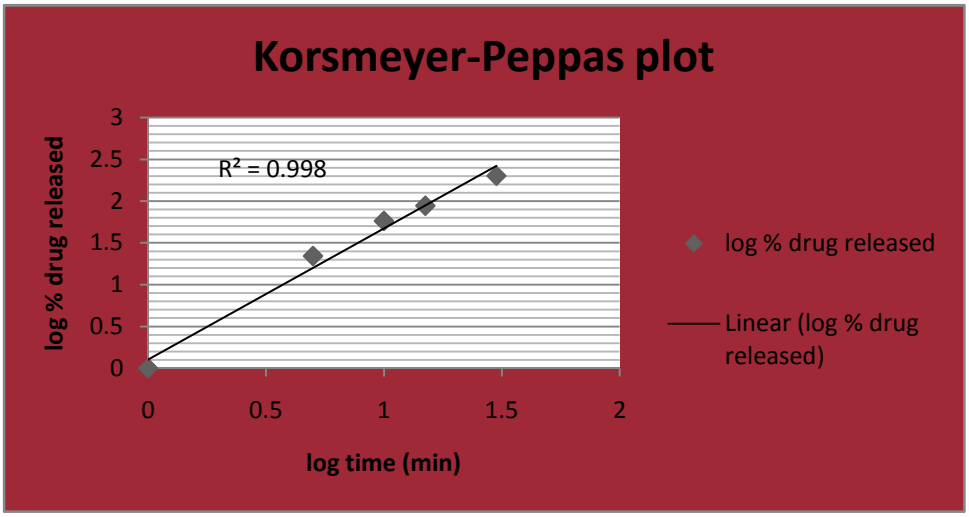


Figure: 8.19 Best fit model (Korsmeyer – Peppas) of formulation F_2

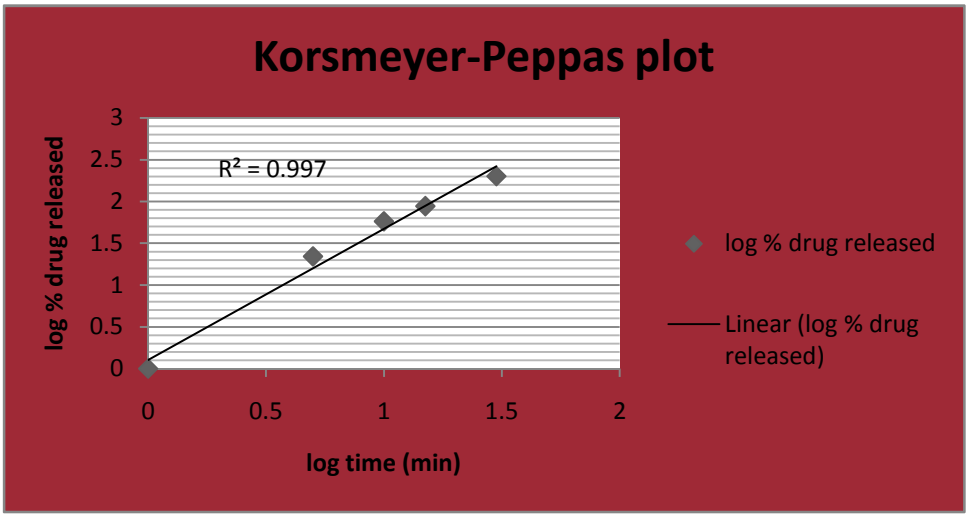


Figure: 8.20 Best fit model (Korsmeyer- Peppas) of formulation F_3

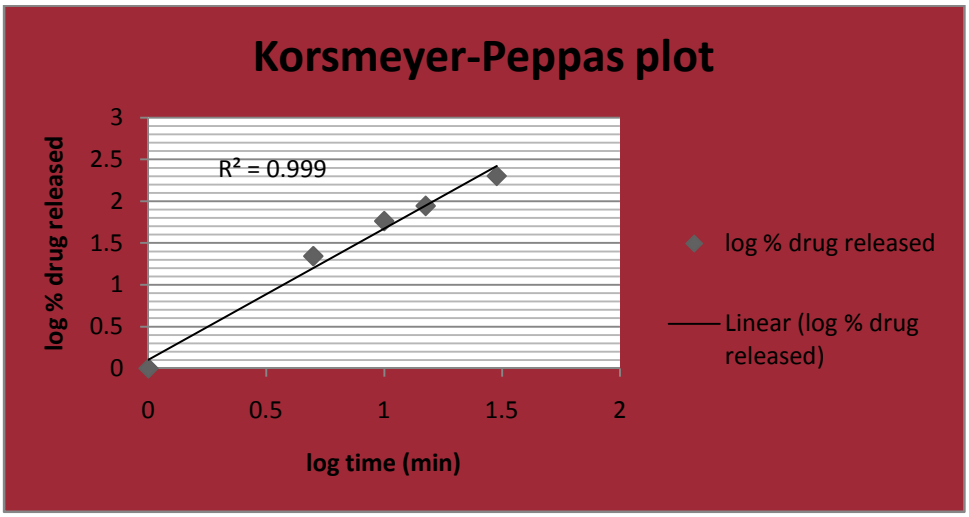


Figure: 8.21 Best fit model (Korsmeyer-Peppas) of formulation F_4

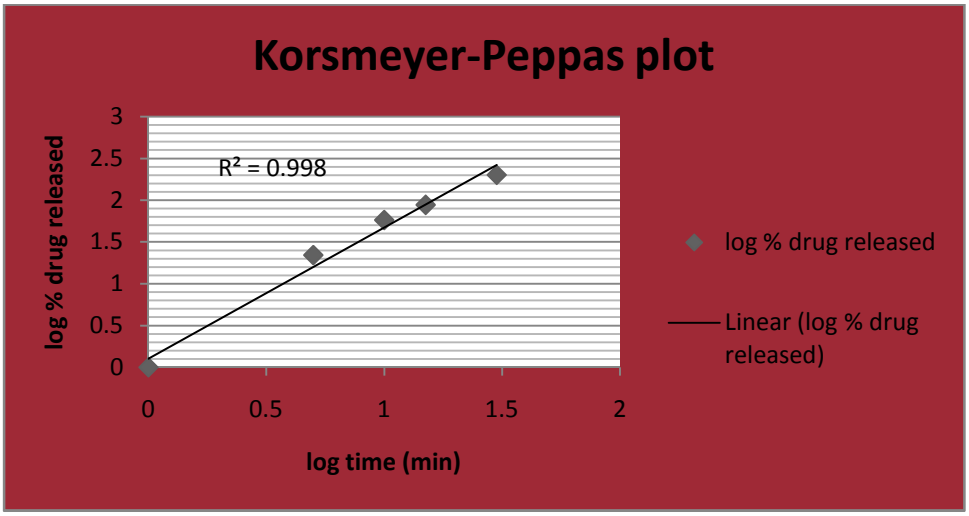


Figure: 8.22. Best fit model (Korsmeyer-Peppas) of formulation F_5

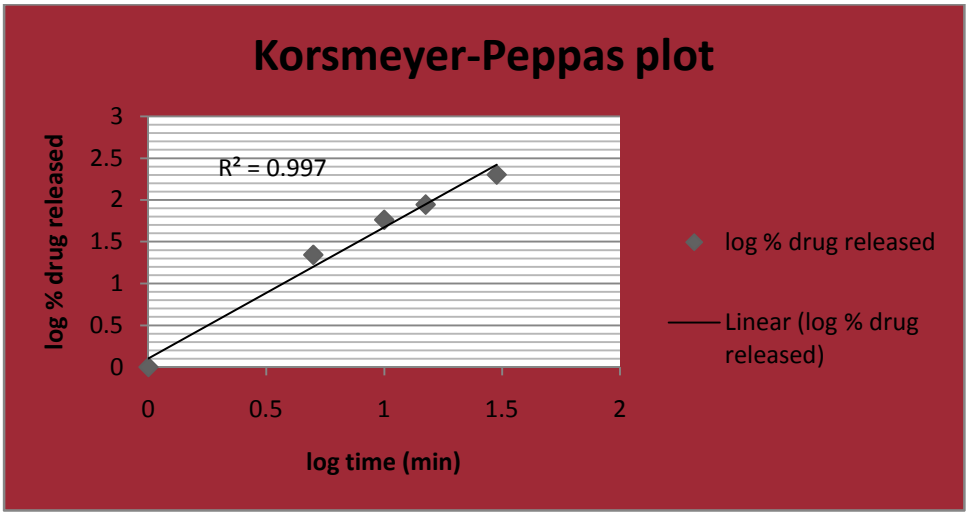


Figure: 8.23. Best fit model (Korsmeyer-Peppas) of formulation F_6

8.3. STABILITY STUDY OF SELECTED FORMULATION

8.3.1. Short term stability conditions for formulation F_4 at room temperature.

After exposing to short term stability conditions the formulation was analyzed for various evaluation parameters results were shown in table 8.25.

Table: 8.25. Stability studies of optimized formulation F_4 –Room temperature

S.NO	Parameters	Initial	At 25˚C±2˚C at 60%RH±5%		
			1st month	**2nd month**	**3rd month**
1	Description	complies	complies	Complies	Complies
2	Average weight(mg)	300	300	300	300
3	Average hardness(N)**	16±2.00	16±2.00	15.5±1.52	15.1±1.5
4	Friability (%)*	0.17±0.02	0.17±0.02	0.18±0.03	0.22±0.01
5	Drug content(%w/w)*	100.05±0.16	100.03±0.07	100±0.04	99.96±0.06
6.	*In-vitro* drug released (%)*	100.2±0.30	100±0.25	99.8±0.3	99.76±0.15

*All the values are expressed as mean± S.D., *n=3, **n=6

8.3.2. Short term stability conditions for formulation F_4 at Accelerated temperature

After exposing to accelerated stability conditions the formulation was analyzed for various evaluation parameters results were shown in table 8.26.

Table: 8.26 Stability studies of optimized formulation F_4 - Accelerated condition

SNO	Parameters	Initial	At At 40˚C±2˚C at 75%±5%RH		
			1st month	**2nd month**	**3rd month**
1	Description	complies	Complies	complies	Complies
2	Average weight(mg)	300	300	300	300
3	Average hardness(N)**	16±2.00	15.5±0.25	15±0.3	14.9±0.26
4	Friability (%)*	0.17±0.02	0.18±0.01	0.19±0.02	0.21±0.03
5	Drug content(%w/w)*	100.05±0.16	99.99±0.5	99.97±1.35	99.95±0.2
6.	*In- vitro* drug released (%)*	100.2±0.30	99.7±0.32	99.4±0.2	99.23±0.15

*All the values are expressed as mean± S.D., *n=3, ** n=6

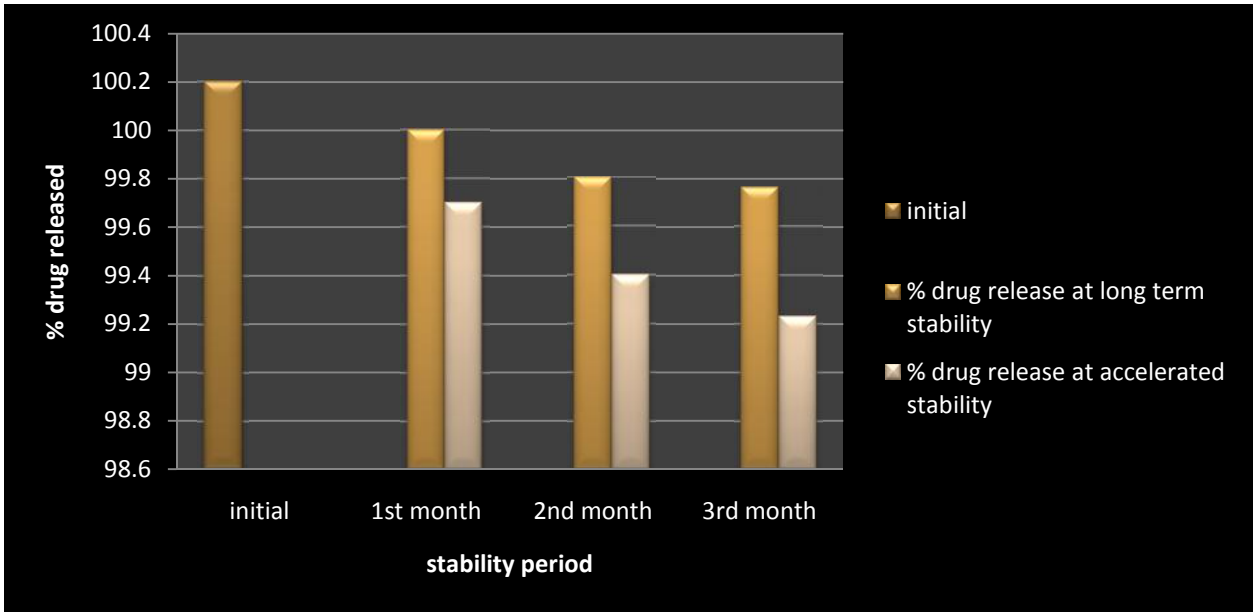


Figure: 8.24. Histogram for Percentage drug released of before and after stability studies for optimized formulation F_4.

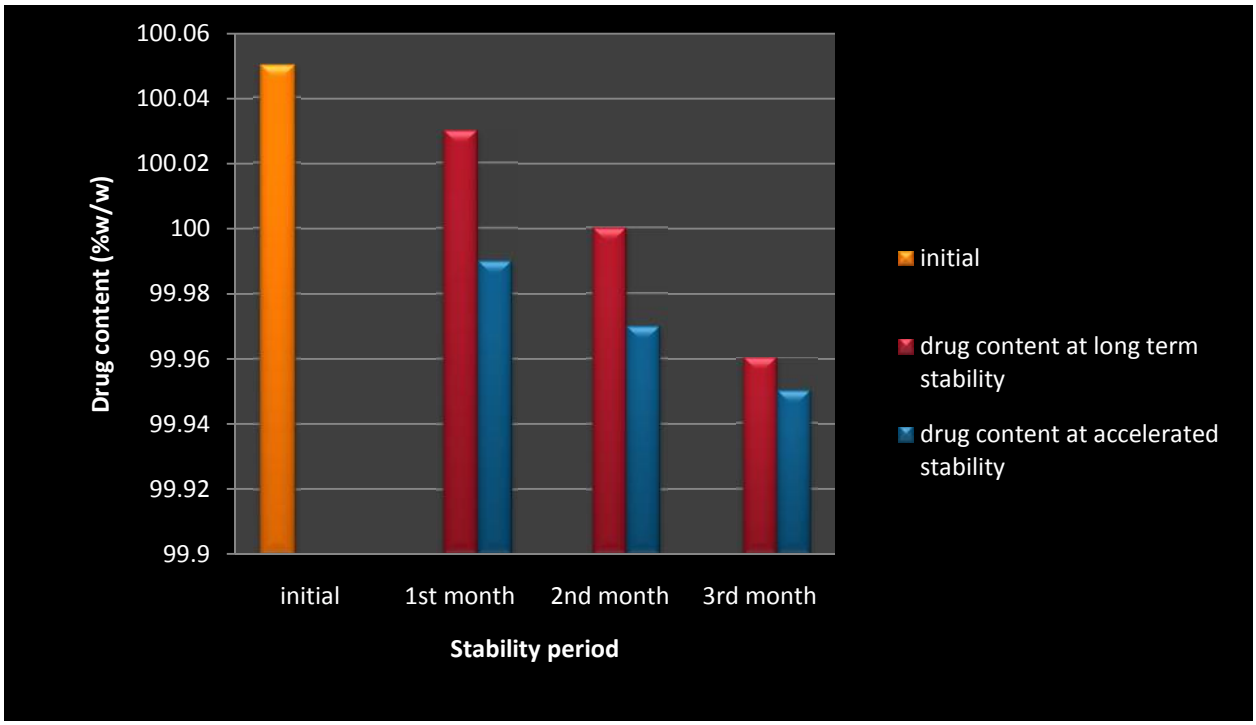


Figure: 8.25. Histogram for Percentage drug content of before and after stability studies for optimized formulation F_4.

No major difference was found between evaluated parameters before and after stability studies and all are in acceptable limits. The pellets showed satisfactory physical stability at 25º C at 60% RH and 40 º C at 75 % RH.

SUMMARY

AND

CONCLUSION

9. SUMMARY AND CONCLUSION

❖ The atorvastatin calcium was widely used in the anti lipedimic drug. It also stabilizes plaque and prevents inflammatory and other mechanisms. This research work mainly focused on therapeutic effect of the drug to increased bioavailability. The reported bioavailability of atorvastatin calcium was only 14% and it was highly soluble in acidic pH and absorbed in upper part of GIT. While forming the multi particulate drug delivery system in the form of immediate release pellets leads to an increased in the surface area to improved solubility and dissolution rate and significantly increased the bioavailability of drug.

❖ The drug fall under the class II (BCS classification; i.e. Low soluble: high permeability) from the ethical and pharmacokinetic view, dissolution test must be performed. Hence the prepared atorvastatin calcium pellets must comply with dissolution test as per innovator drug (LIPITOR).

❖ The identification of drug was carried out by FT-IR spectroscopy and melting point. The physicochemical parameters such as appearance, solubility study and loss on drying were performed by suitable methods. The analytical profile of drug was evaluated for determination of absorption maximum, development of standard curve and percentage purity of drug. Compatibility of drug and excipient mixture was done by performing FT-IR and DSC study. It was concluded that there was no interaction between the drug and superdisintegrants as the principle peaks of the drug were found unaltered in the FT-IR spectra and DSC thermogram of drug superdisintegrants physical mixture. The pellets was prepared by coating the drug and superdisintegrants in conventional pan coater until minimum weight was gained

and sieved through 40 #size to obtained uniform size and evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

❖ The present work was proposed to prepare pellets loaded with Atorvastatin calcium to achieve better bioavailability with low dose of the drug at the site, decreased the risk of adverse side effects based on *in- vitro* released study. Atorvastatin calcium pellets were prepared by drug layering method for all the formulations F_1 to F_6. Formulations were prepared composed of HPMC E15, polyvinyl pyrolidone as a binder, SSG (4% & 8%), CP (4% & 8%), and CCS (4% & 8%) as coating material, Isopropyl alcohol as a vehicle and talc as a glidant. The all formulations were evaluated for the appearance, dimension, hardness, percentage friability, disintegration time, drug content and *in- vitro* drug released. Also the all formulations were compared with one innovator product and results of products were compared. The formulation F_4 was best one compared to other formulations and Innovator product. On the performance with respected to disintegration time, and the *in- vitro* released characteristics, the **formulation F_4** was selected as the best formulation. This formulation showed an immediate released rate throughout its released period. Further the selected formulation F_4 was subjected to short term stability study at Room temperature (25±2˚C at RH 60% ± 5%) and Accelerated temperature (40±2˚C at RH 75% ±5%).

❖ According to stability study it was found that there was no significant change in hardness, drug content, percentage friability and *in-vitro* drug released of optimized formulation F4.

It may be concluded that the Immediate released pellets of Atorvastatin calcium was feasible and may be manufactured with reproducible characteristics with the aid of crosspovidone (8%) as a superdisintegrant. However it needs further in depth animal studies on suitable animal models with statistical clinical data for a dependable and successful pharmaceutical marketing formulation.

FUTURE PROSPECTUS

10.FUTURE PROSPECTUS

In the field of Multi particulate drug delivery system, there are many obstacles that need to be over come in order to able to claim true pellet formulation. Considering the advantages for improved delivery of drugs further clinical studies are needed to access the utility of this system for patients suffering from hypercholesterolemia.

This formulation holds promise for further systems. Animal studies, toxicological studies and *in- vitro-in- vivo* correlation (IV-IVC) will serve as a modelling the human organism and of gaining a better understanding of drug abortion and its dependence on *in -vitro* release process.

Once the technology is fully accepted, these systems will probably increase with new pipeline drugs that need enhancement to their bioavailability.

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