"FORMULATION DEVELOPMENT AND CHARACTERIZATION OF TOLTERODINE TARTRATE EXTENDED RELEASE MULTIPLE UNIT PELLET SYSTEM"

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BIOPHARMACEUTICS

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CERTIFICATE

This is to certify that the dissertation work entitled "Formulation, Development and characterization of Tolterodine Tartrate Extended release Multiple Unit Pellet system" submitted by Ms. Ishani Harish Pandit with Regn. No. (14MPH109) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutical Technology and Biopharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics, Institute of Pharmacy, Nirma University and at Formulation & Development Department, Oral Solid Dosage Unit (OSD), Amneal Pharmaceuticals PVT LTD under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that the dissertation entitled "Formulation Development and characterization of Tolterodine tartrate Extended Release Multiple Unit Pellet System", is based on the original work carried out by me under the guidance of Prof. Tejal A. Mehta, Professor & Head, Department of Pharmaceutics, Nirma University and Mr. Tarun Patel, Assistant Manager, F&D, OSD, Amneal Pharmaceuticals PVT LTD. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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Date: 20th May, 2016 *Ishani Pandit*

List of Abbreviations

Sr. No.	Short Form	Abbreviation
1	MUPS	Multiple Unit Pellet System
2	MPDDS	Multiparticulate Drug Delivery System
3	MR	Modified Release
4	DR	Delayed Release
5	ER	Extended Release
6	API	Active Pharmaceutical Ingredient
7	TT	Tolterodine Tartrate
8	FBP	Fluidised Bed Processor
9	XRD	X-Ray Diffraction
10	SEM	Scanning Electron Microscopy
11	HPMC	Hydroxy Propyl Methyl Cellulose
12	EC	Ethyl Cellulose
13	RH	Relative Humidity
14	NLT	Not Less than
15	NMT	Not More than
16	HPLC	High Performance Liquid Chromatography

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Formulation, Development and Characterization of Tolterodine Tartrate Extended Release Multiple Unit Pellet System

Tolterodine Tartrate is Muscarinic receptor antagonist which is used in the treatment of Urinary frequency in patients with over active Bladder disease. The aim of the present work was to develop an extended release dosage form of Tolterodine tartrate using Multiparticulate drug delivery system that will reduce the dosing frequency and will make the drug available for the longer period of time. The purpose of selecting multiparticulate system is to develop a formulation having all the advantages of Conventional/monolithic system and yet do not have disadvantage of alteration in drug release due to unit to unit variation. Tolterodine Tartrate is a BCS Class-I drug and also a potent drug having a dose of 4 mg once a day. In the present investigation, Solution Layering Technique was adopted due to low dose of drug that allows us to spray the desired amount of drug on the starter cores. To design this dosage form, first of all inert cores of suitable size were selected and drug was coated onto the pellets along with binder. In the drug layering the ratio of drug to HPMC as well as Methanol: Water was optimized and the effect was analysed. The drug layering was followed by coating with water insoluble polymer that retard the drug release. The controlled release coated pellets were further coated with drug layering solution followed by extended release coating of ethyl cellulose in the form of aqueous dispersion along with pore forming agent. The ratio of water insoluble polymer and pore former was optimized to get the desired drug release profile. The curing time required at each stage of coating was optimized to achieve the complete film formation. These pellet were filled in the capsules of suitable size. The coated pellets were evaluated for assay, percentage yield, and in-vitro drug release study. The formula was optimized to generate the formulation which gives same release profile as that of marketed formulation. Hence the present study concludes that multiparticulate drug delivery system gives efficient drug release over an extended period of time.

Aim & Objective of present Investigation

The oral route of drug delivery is considered as the most preferred and most patient-convenient route of drug administration. The controlled release formulation technologies offer an effective means to modify the properties of a drug by making rate of drug release slower. The aim of this approach was to extend the absorption of the drug within the gastrointestinal (GI) tract, and thus prolonging the duration of the therapeutic action of the drug. Extended Release drug delivery system is one of the approaches which can be used for the drugs having shorter half-life and high dosing frequency. Extended release product will improve therapeutic safety and efficacy of a drug and also improve the patient convenience and compliance. Recent scenario indicates that multiparticulate drug delivery systems are most suitable for achieving extended release of oral formulations with less risk of dose dumping, flexibility in release profiles and reproducible and short gastric residence time.

Tolterodine Tartrate is popular muscarinic receptor antagonist which is used in the treatment of urinary incontinence or urinary frequency/urgency occur in patients suffering from overactive bladder syndrome. Tolterodine Tartrate is BCS Class-I drug having a short half-life of 1.9-3.7 hours. The dose of drug is 4 mg once a day and it is potent drug. Hence this drug is suitable for administering it in form of modified release formulation. Findings says that tolterodine tartrate immediate release 4 mg (2 mg bid) is equivalent to extended release 4 mg, therefore to reduce the dosing frequency it was decided to formulate once-a-day extended release formulation of tolterodine tartrate using multiparticulate drug delivery system. Urinary Incontinence is emerging problem worldwide, in which a person may feel sudden and extreme need to urinate. Therefore it requires prolonged and extended effect of drug throughout the treatment. Thus it requires such a dosage form, which gives effect over an extended period of time upon once-a-day administration. To achieve this aim, such a formulation was designed and developed using multiparticulate drug delivery system. Purpose of selecting Multiparticulate System is to reduce the dosing frequency and maintain the therapeutic concentration over an extended period of time. It reduces the side effect of drug as it leaves the stomach continuously and improve the patient compliance. The main advantage of pellets is its flexibility, it can be filled into

capsules or compressed as a tablet. Formulation of multiple unit system such as coated pellets offers flexibility to target the release profile. Also the safety and efficacy of such formulation is higher as compared to other formulations.

So, in the present investigation the aim was to deliver Tolterodine Tartrate over an extended period of time with once-a-day dosage regimen. To achieve this aim a multiple unit pellet systems was the preferred option as it gave effective and reliable product without any complications. The innovator was first authorised to market a new product as it has patent till 20 years on the basis of quality, safety and efficacy. This provides patent protection to the innovator and to make revenue and achieve good initial cost incurred by the organization in research, development and marketing expenses, to develop new drug. On other side generic product is therapeutic equivalent to the innovator product, and thus ensuring safety and efficacy profile. Innovator product plays an important role in medications, but generics products are cost effective. Indian market of generic drugs is increasing day by day. The present investigation work was planned with the aim of formulation, development and optimization of stable and equivalent dosage form of Tolterodine Tartrate in comparison with its US innovator formulation. The formulation to be developed as a multiple unit pellet system (Pellets) was filled into capsule of suitable size to provide extended release upon once-a-day administration.

So the aim of present work is

1. To formulate and develop extended release dosage form of Tolterodine Tartrate using Multiple Unit Pellet System.
2. Optimization of Process and Product variables that have direct or indirect impact on drug release.
3. Optimization of concentration and ratio of film forming polymers as the thickness of film have direct effect on drug release.
4. Optimization of dissolution profile of developed formulation in-line with US Innovator's formulation.
5. To carry out stability study of optimized batch under controlled conditions.

2.0 Introduction

2.1 Extended Release Drug Delivery System

Extended release drug delivery system is considered as a very useful tool in Pharmaceutical development, offering a wide range of benefits to the patients. Oral drug delivery is the most preferred route for number of drug molecules, because of ease of its advantages. So, oral extended release drug delivery system becomes a very promising approach for those medications that are given orally but having the shorter half-life and high dosing frequency. Extended release formulations conjointly decrease the aspect impact of drug by preventing the fluctuations in plasma concentration of the drug in the body. Recent scenario indicates that multi-particulate drug delivery systems are especially suitable for achieving extended release of oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from pellets depends on a variety of factors including the carrier used to form pellets and the amount of drug contained in them. Consequently, pellets provide tremendous opportunities for designing new controlled and extended release oral formulations, thus extending the frontier of future pharmaceutical development.[1]

The terms "Sustained release", "prolonged release", "modified release", "extended release" or "depot formulations" are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[1]

The reasons behind attractiveness of these dosage forms:[1]

- It provides increased bioavailability of drug product
- It reduces the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and
- Possibly improves the specific distribution of the drug.

There are certain considerations for the preparation of extended release formulations: If the active moiety has a long half-life, it will sustained on its own, If the pharmacological activity of the active moiety is not directly associated with its blood

levels. But, if the absorption of the drug involves an active transport and the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors could have direct issues on style of Extended unharness drug delivery system.

2.2 Introduction to Multi-particulate Drug Delivery System

MUPS is a short form of Multiple-Unit Pellet System. But generally it is considered as compacted tablets and thus, the resulting tablets are prepared by compaction of coated pellets are called as MUPS. The word "Pellet" describes a number of systematically produced, geometrically defined agglomerate shaped particles obtained from diverse starting of materials using different processing conditions.[2]Multiparticulate drug delivery systems are oral dosage forms consisting of multiple small descrete units, in which API is present as a number of independent subunits.[3] The common size range of pellet is between 0.5-2.0 mm, but different sizes can also be prepared. Pellets for medication purposes are made for oral controlled-release dosage forms. For such purposes, coated pellets are administered in the form of capsules or disintegrating tablets that release their contents of pellets in the stomach. As drug delivery systems become more sophisticated and advanced, the role of pellets in the design and development of dosage forms is consistently increasing. Formulating drugs in multiple-unit systems, such as coated pellets filled in capsules or compressed into tablets, offers great flexibility to target release properties. The safety of the formulation is more as compared to single unit dosage forms. Pellets can be divided into required dose strengths without any changes in process or product and can also be mixed to deliver bioactive ingredients which are biologically inactive. Additionally pellets have wide range of advantages over traditional single units dosage forms, such as tablets and powder-filled capsules. Pellets when taken orally, disperse freely in the GIT, and maximize the drug absorption, minimize local irritation of the mucosa, hence reduce inter and intra-patient variability. Due to the clarity of advantages of pellets over single unit dosage forms, pharmaceutical industries started to devote resources to conduct research in pellet technology and acquire advanced equipment suitable for the manufacturing of pellets. Pellets may be prepared by using different methods according to the requirement and the choice of

manufacturer. The most widely used processing techniques are extrusion-spheronization and solution/suspension layering as well as powder layering techniques.

2.2.1 Therapeutic advantages of pellets over single unit dose system: [3,4]

When taken orally

- They disperse freely in gastrointestinal tract.
- Enhance the drug absorption, decrease peak plasma fluctuation, reduce irritation of mucosa, minimize potential side effect by reducing drug bioavailability.
- Least risk of dose dumping with enhanced safety and efficacy of drug.
- Pellets are more suitable for fabrication of formulation with the acid sensitive drug.

2.2.2 Advantages of MPDDS (Pellets):[3,4]

- Pellets provide reproducible, predictable and short gastric residence time.
- Less inter and intra subject variability and enhanced bioavailability
- Reduced adverse effects and improved tolerability.
- Limited risk of local irritation &modified release causes less dose dumping than the reservoir.
- No risk of dose dumping and flexibility in design.
- Ease of combining pellets with different compositions or release patterns.
- Improve stability.
- Improve patient comfort and compliance.
- Achieve a unique release pattern.
- Extend patent protection, globalize product, and overcome competition.
- Better in-vitro in-vivo release of drug
- Homogeneous spreadability in GIT
- Useful in case of difficulty in swallowing and dysphagia like in the case of children and aged people.

2.2.3 Disadvantages of MPDDS: [3,4]

- Low drug loading.
- Higher need for excipients as compared to single unit dosage forms.
- Lack of manufacturing reproducibility and efficacy.
- A Largenumber of process variables.
- Multiple formulation steps.
- Higher cost of production.
- The need of advanced technology and equipment.
- Trained/skilled personnel needed for manufacturing.

2.2.4 Ideal Properties of MPDDS: [3,4]

For Coated Pellets

- Uniform spherical shape and smooth surface and optimum size
- Better flow characteristics.
- Enhanced physical strength and integrity.
- Good hardness and low friability.
- Low dust-producing capacity
- Greater bulk density.
- Ease and superior properties for coating.
- Reproducible packing of beds and columns.

For Uncoated Pellets

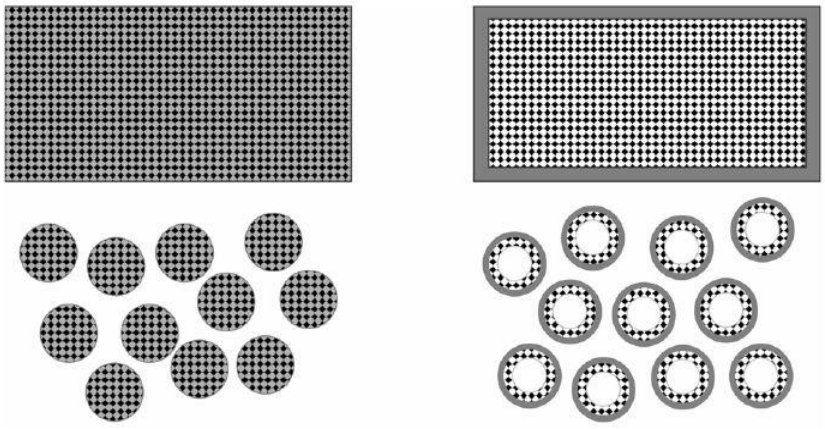
- Maintain all the properties of coated pellets.
- Contain as much as possible of the active ingredient to keep the size of the final dosage form within specified limits.
- Have optimum drug release characteristics.

2.2.5 Types of Multiparticulate System[3,5]

A. Matrix System

Matrix system contains solution or dispersion of polymer and drug, which is granulated with other excipients to obtain extended release. The drug uniformly distributed within the polymer is either dissolved or dissolved. Matrix system has some of the advantages such as easy manufacturing, low cost- single step process, reduced risk of dose dumping and the improvement of aqueous drug solubility. It may have chances of drug-polymer interaction, moreover fast initial release and then incomplete release in a specified time which can be reduced by coating sugar cores with different polymer: drug combinations which contains more concentrated layer of drug deeper inside the matrix system. Matrix system are suitable for controlled release of drug.

Figure: 2.1 Schematic representation of Matrix and reservoir System: (a) Matrix System (b) Reservoir system. (Black: Drug; Grey: Polymer; White: Other excipients)



(a) (b)

B. Reservoir Coated Systems

Reservoir system contains drug layered core surrounded by a polymer. The advantages of this system is that very high drug loadings can be applied and different release profiles can be achieved, by varying the type of polymer. The mechanism of reservoir systems is complex and those mechanisms include: 1) Diffusion through the

polymer film surrounding the drug containing core and then dissolution of drug outside the pellets. 2) Release can occur through pores containing water due to leaching of water-soluble components into the release medium or due to cracks formed by hydrostatic pressure inside these systems upon water uptake. 3) Drug release occurs as an osmotically active core which is coated by a semi-permeable membrane.

2.2.6 Drug Release Mechanism[2,3,5]

General Mechanism of drug release from multiparticulate system

Diffusion:

Upon contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion:

Some coatings can be designed to erode gradually overtime, thereby releasing the drug contained within the particle.

Osmosis:

In allowing water to enter under the right circumstances, an osmotic pressure can be built upwith-in the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

2.2.6.1 Drug Release Mechanism[2,3,5]

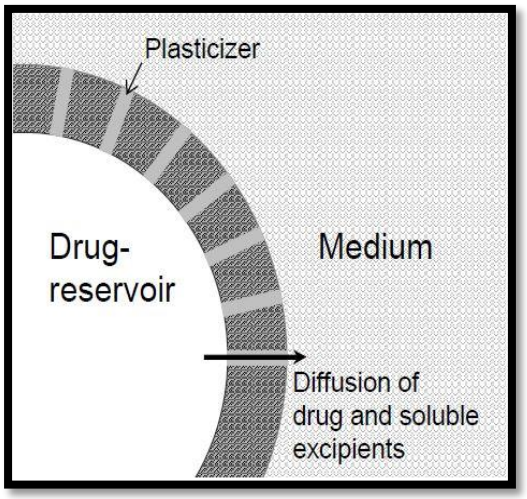
The drug release mechanism from reservoir coated pellets depends on coating type and thickness, drug type and core type. One of those mechanisms if found to be diffusion through polymeric membranes which is surrounding the core loaded drug.

In drug release, water penetrates through the polymer till it reaches the pellet core. Afterwards, drug is dissolved and released. The drug is released due to the concentration gradient generated inside the pellet (Ci) versus outside the pellet. In the appropriate sink conditions the amount of drug released (dM) within a certain time period (dt) can be calculated as per Fick's law of diffusion:

$$\frac{dM}{dt} = \mathbf{Dm * A * K *} \frac{Ci}{d}$$

- "Dm" is the apparent diffusion coefficient of the drug in the polymeric film,
- "A" the surface available for diffusion,
- "K" the partition coefficient of the drug (aqueous phase –polymeric phase) and
- "d" denotes the thickness of the film coating.

Figure: 2.2 Drug Release from Reservoir Coated Pellets



Drug release from ethyl cellulose coating membrane with pore forming agents has been studied by many investigators. It was found that at lower pore former content (HPMC) contents, drug was released through osmotic pumping, but above a specific value of pore former, drug was released via diffusion. It was found that adding of small concentration of polyvinyl alcohol-polyethylene glycol graft copolymer to ethyl cellulose coatings control the drug release from coated pellets independent of the solubility of drug and type of core. The mechanism of drug release was found to be diffusion through intact polymeric membranes.

2.3 Pelletization[3,6–8]

2.3.1 Introduction to Pelletization

Pelletization can be defined as a process which involves conversion of fine powdery material to small free flowing agglomerates. The size of pellets are generally 0.5 – 2 mm. The most important property of the pellets are the spherical shape and the narrow particle size distribution around the desired particle size.

Pellets are generally coated with polymer films to improve therapeutic and aesthetic property of the drug and to achieve modified release patterns. In paediatrics, the dose can be easily adjusted depending on the patient's body weight by measuring a specific volume of pellet. Due to broad range of advantages, pellets has built a special place in pharmaceutical formulation development. Different drug can be formulated in pellets using single unit dosage form. This facilitates the delivery of two or more drugs at the same site in the GIT. Pellets with different release rates of the same drug can be formulated in a single dosage form. The most important reason behind the broad acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release formulations. Controlled release dosage forms are useful for delivering drug at specific site or sustain the action of drug over an extended period of time. With the use of pelletized drug delivery system, above stated goals can be achieved through the application of coating materials, which provides the desired functions.

2.3.2 Advantages of Pelletization

- Pelletization produces pellets with high drug loading capacity without producing extensively large particles.
- Pellets exhibit better spheroidal shape and have excellent flow and packing properties by the pelletization technique.
- Particles having diameter less than 2 mm, can pass rapidly through the GIT and they are able to leave the stomach continuously.

- Drug safety can also be increased by using pelletization, particularly for modified release systems. Pellets reduce local irritation and chances of dose dumping can also be decreased.

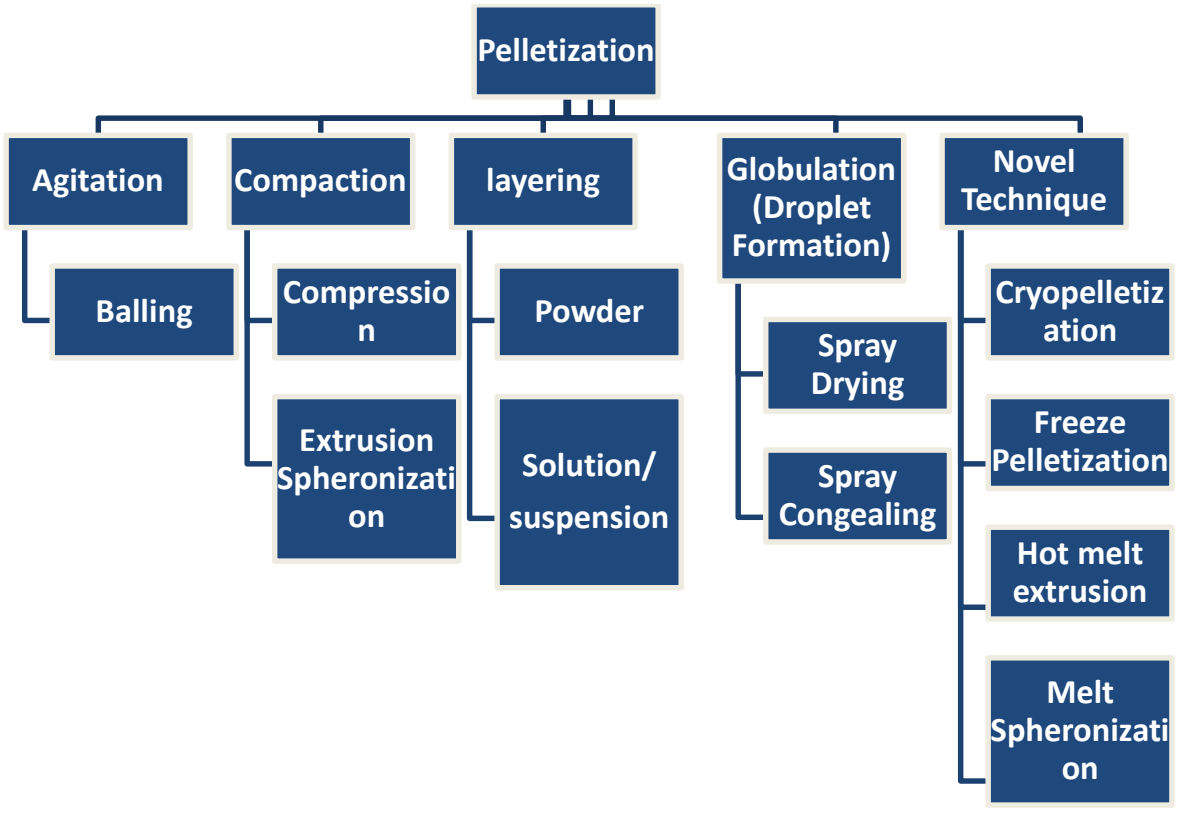
2.3.3 Disadvantages of Pelletization

- The manufacturing of pellet is complicated and costly process, the filling of multiple units in gelatin capsules is difficult to accomplish especially in the case where different subunits are involved.
- The preparation process of multiparticulates requires extra care and fine adjustments of various equipment.

2.3.4 Pelletization Techniques[2,3,7–11]

Pellets can be prepared by number techniques which can be subdivided into the basic types of systems shown below:

Figure: 2.3 Pelletization Techniques



2.3.5 Layering

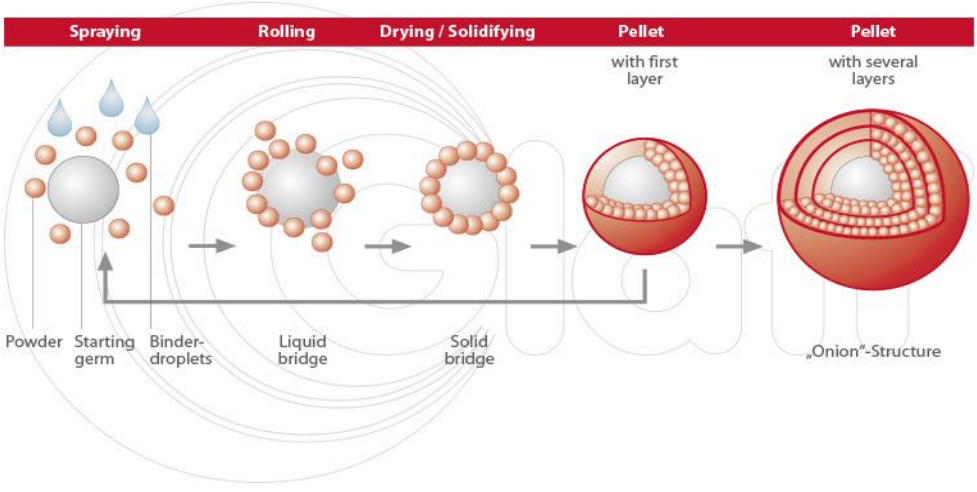
The layering process includes deposition of consequent layers of API from solution, suspension or dry powder on a core or inert starter seeds. They are classified into two categories: powder layering and solution/suspension layering.

2.3.6.1 Powder Layering:

Powder Layering is a technique which involves preparation of pellets directly from powder. It is a fast process and consumes less amount of auxiliary materials. Prepared pellets are compact, round shaped and uniform and have more density than granulates and agglomerates.

Process principles: Powder to be used is homogenously mixed and moistened, in which a solvent or binder is to be added. The powder bed is set into a centrifugal motion. The impact and acceleration forces used in this process results in the formation of agglomerate particles, which become rounded. The rotation speed has a direct effect on the size and density of the pellets. The moist pellets are then dried in the fluid bed.

Figure: 2.4 Powder Layering Technique



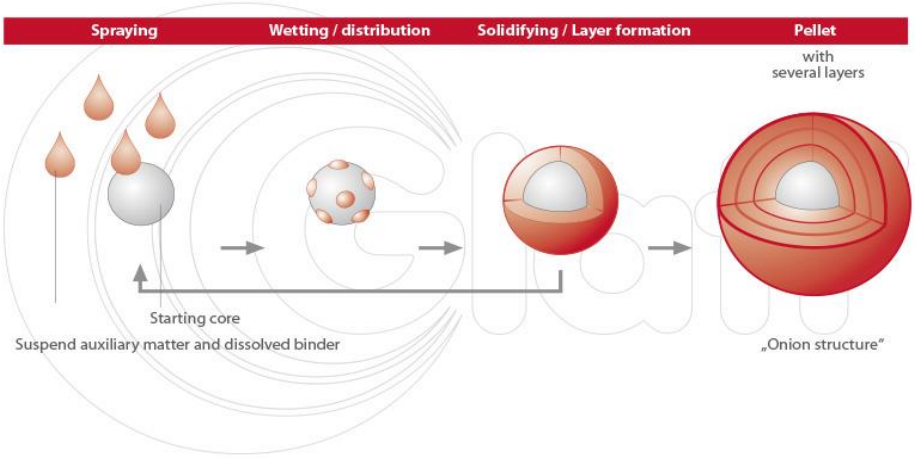
The problem associated with this technique is formation of fines due to inter-particulate friction and friction between wall and particles. Care is required to control moisture in pellets. It is necessary to deliver the powder at a predetermined rate throughout the process which maintains equilibrium. If the powder addition rate is

high, dust generation takes place, and if the liquid addition rate is high, over wetting of the pellets may occur and due to this quality and yield cannot be maximized.

2.3.6.2 Solution/Suspension Layering[2,3,10]

Solution/suspension layering technique includes formation of successive layers of solutions and/or suspensions of drug substances and binders on starter seeds. During processing, all the components of the formulation are dissolved or dispersed in a suitable medium to make an appropriate viscosity and sprayed onto pellets. These sprayed droplets tend to impinge on the surface of cores with appropriate drying conditions. The process continues till the desired quantity of drug substance and thus the desired potency of the pellets are achieved. In this technique, the amount of particle remains same but size and total mass increase along with time.To avoid the settling of particles, generally high viscosity binders are recommended. The particle size of the API should be less than 10 - 50 μm for suspension layering technique.

Figure: 2.5 Solution/Suspension Layering Technique



Wurster process (bottom spray technique): Wurster equipment generally have cylindrical insert in product chamber and orifice plate, which allows dry air to pass through. As the particles leaves partition they enter into expansion chamber. Here, velocity of the air generally decrease than the entrainment velocity. Particles tends to fall on the surrounding area and wall which is known as down bed from where particles are transported to the area between orifice and partition via suction. Partition

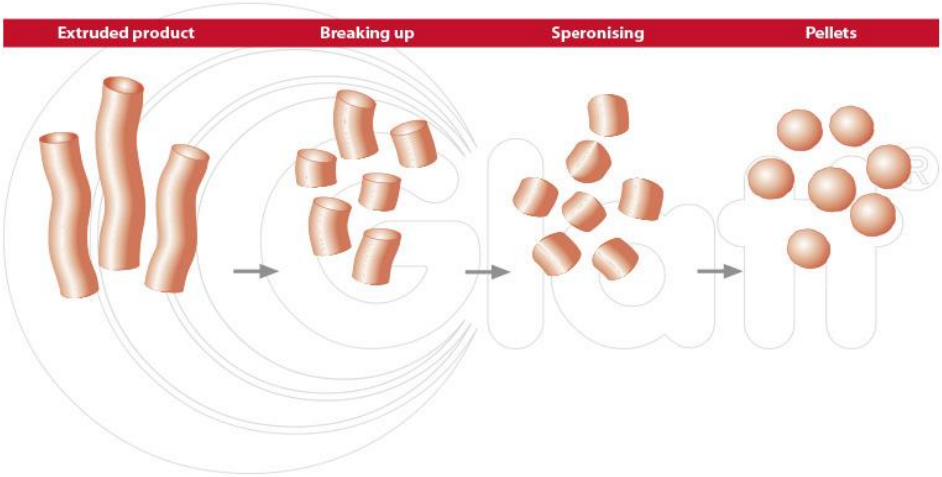
height can be optimized as per the requirement. Main advantage is nozzle clogging. Therefore cleaning is necessary requirement. Important parameters that affect the entire process are solubility, viscosity of solution/suspension, concentration of binder, particle size.This process is suitable for low drug loadings due to which higher potency pellets can be prepared.

2.3.6 Other Methods of Pelletization[2,3,8,10]

1. Extrusion and Spheronization

Extrusion spheronization technique is generally used to make dense granules with high drug loadings with the use of minimum amount of excipients. It is a multi-step process consists of dry mixing, wet-massing, extrusion and spheronization. The major advantage of this method is it can produce pellets with higher drug loading without producing excessively larger particles.

Figure: 2.6 Extrusion and spheronization Process



Stages of Extrusion-Spheronization Process:

Dry mixing: To get homogeneous powder dispersion, dry mixing is done using different types of mixers.

Wet Massing: To produce a sufficient plastic mass for Extrusion. The process is similar to the wet granulation method.

Extrusion: In this method, pressure is applied to wet mass to pass/flow through the opening/orifice of the extruder. Rod shaped particles are obtained due to bonding of wet mass gained by solvent system. Extrudes formed should have enough plasticity to deform but not to adhere in spheronization operation. The solvent used for granulation acts as binding agent and also acts as a lubricating agent.

2. **Balling:**

In this technique fine particles are transformed after the addition of appropriate amount of liquid to spherical particles by a uniform rolling or tumbling motion. The liquid may be added during the agitation stage or prior to agitation. Equipments used are pans, discs, drums, or mixers etc.

3. **Compression:**

In this process, mixtures or blends of drug and excipients are compacted under pressure to generate particles of defined shape and size. These pellets are filled into capsules. The factors that affect the formulation and processing of pellets are same as of tabletmanufacturing. In-fact, pellets produced by compression are nothing but small tablets that areapproximately spherical in shape.

4. **Globulation and Droplet Formation:**

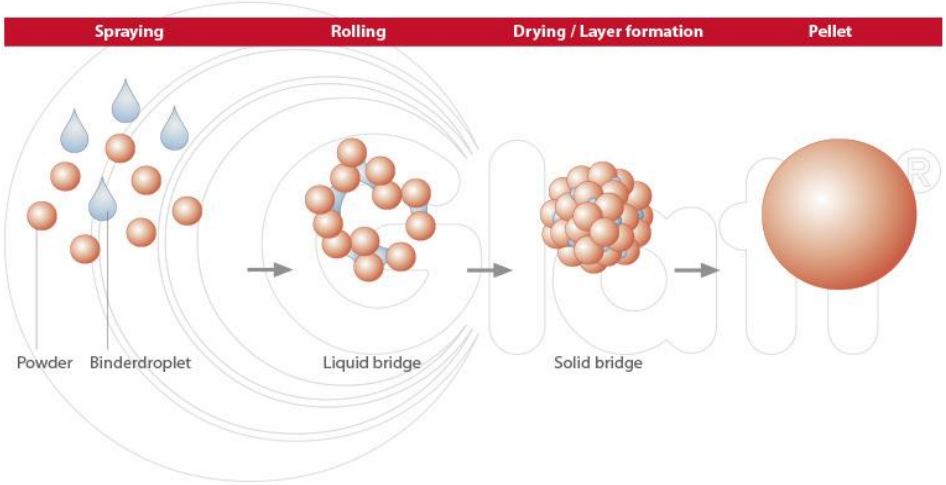
Spray Drying:

In Spray Drying, solution or suspension of drug are sprayed in a hot air stream to get dry and spherical particles. Use of this technique enhance dissolution rate and bioavailability of drug.

Spray Congealing:

In this process drug is allowed to melt, disperse or dissolved in hot melts of gums, waxes and fatty acids and then it is sprayed into an air chamber in which temperature is set below the melting point of formulation to be prepared. With this technique, immediate or controlled release pellets can be produced depending on the physicochemical properties of ingredients and other formulation variables.

Figure: 2.7 Spray Congealing



5. **Freeze pelletization:**

In freeze pelletization, a molten form of solid carrier with drug is introduces in form of droplet to an inert and immiscible column containing liquid. It is an easy, simple and inexpensive method.

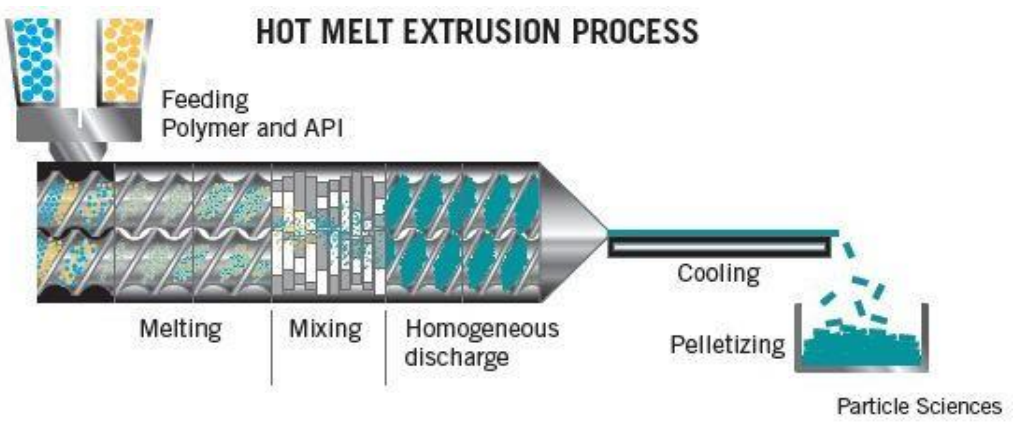
6. **Cryopelletization:**

Cryopelletization is carried out by allowing droplets of solution/suspension to come in contact with liquid Nitrogen at -160°C. These particles are then allowed to freeze-dried or lyophilized toremove water or organic solvents. The importent step in this technique droplet generation which is affected by viscosity, surface tension and solid content.

7. **Hot-Melt Extrusion:**

It is a novel method for preparation of controlled release pellets to overcome the limitations in wet mass extrusion and spheronzation in which thermal agent get melted/softens during the process.

Figure: 2.8 Hot Melt Extrusion process



8. Melt Spheronization:

In this technique, drug and excipients are converted to molten or semi-molten mass and then shaped using appropriate instrument to generate solid sphere or pellet. This method is done in jacketed or high shear mixer where components of formulation are melted together to generate spherical particle. Due to randomness of inter-particulatecollisions, the particle size distribution of pellet tends to be wide as is commonly observed with balling.

2.3.7 Challenges in Formulating MUPS[12]

There are so many challenges and problems observed during manufacturing of MUPS

- To ensure uniformity of content and weight.
- To compress the coated pellets to tablets with sufficient hardness and low friability without damaging the film coatings.

Factors influencing design of MUPS are as follows:

1. Formulation variables such as core pellets, coating and cushioning agents

2. Process variables

3. Equipment variables such as development of an electrostatic charge on pellet surfaces can interfere with their flow during tablet compression cycle, alteration of drug release characteristics after compaction into tablets.

2.3.8 To Overcome Challenges:[12]

Following factors are important while formulating pellets:

1. Pellet shape: Pellet shape should be uniform enough. Deviation in spherical shape results in flaws and cracks during compression.
2. Pellet size: The maximum size of the coated pellets can be up-to 2 mm to withstand pressure. Large sized pellets cause rupture to the coating and then undergo direct exposure of the transmitted force by the upper punch to lower punch. This influences content uniformity of the final tablet.

3. Pellet core and Core material: Pellet core and core material can have direct impact on drug release profile. Ideally Pellets should have low surface to volume ratio. Pellet core should have plasticity to deform during compression without any damage to the film. Core material should not be hard which obstructs the flow of pellets.
4. Polymer coating and Film flexibility: Polymers are widely used in attaining specific release profiles. Some of the polymers are cellulose derivatives and polyacryls. Cellulose and its derivatives like HPMC, HPMCP forms hard and brittle films, whereas polyacryls and copolymers of acrylics form flexible film deforms easily on compression. Plasticizers like triethyl citrate, triacetin and polyethylene glycol are widely used in the formation of films. Polymers like Eudragit along with plasticizers triethyl citrate provide greater flexibility to the film in required quantity.
5. Selection of Solvents: Both aqueous and non-aqueous coatings can be used as a vehicle. Aqueous coating is eco-friendly, but it has certain disadvantages like degradation of the drug due to entrapped moisture; when pellets are cured for more time to evaporate moisture, the higher temperature also results in degradation. Whereas, non-aqueous coatings shows intermediate sol-to-gel transmission helps to coat the polymeric solution and the solvent evaporate much earlier than aqueous solvents.
6. Mechanical resistance: Film flexibility provides mechanical stability and film integrity to prevent deformation of pellets.

7. Coating thickness: The thickness of coating layer is related to mechanical resistance of pellets during compaction. Higher thickness supports elastic properties, lower thickness films tend to break. Drug release profile also depends on coating type and thickness
8. Electrostatic charges: This problem is usually solved by adding talc, which acts as a glident.

2.4 Introduction to the role of Fluidized Bed Processor in Layering of Pellets[3,8,11,13,14]

Fluidized bed processor is an equipment that facilitates multiple functioning like coating, drying, granulation and pelletizing. It has highly efficient drying and coating system. It can protect product against moisture, light, air etc. This technique is ideal for control release film coating, pellet granulation and hot melt coating.

2.4.1 Principle of Fluidization: [14]

When a gas flow is sent to the particles through a nozzle with a velocity greater than the settling velocity, the particles get suspended in the air and continue in the upward gas stream. When the particles reach the top of the equipment, due to gravitational pull they fall down and suspending continues.

2.4.2 Fluidized Bed Coating for Layering of Pellets:[13]

- It is a novel, innovative processes for coating the products.
- Film coating, lipid hot melt coating, Coating of granules, pellets, tablets.
- Manipulation of the particle surface morphologies.
- Manipulation of the way in which the particle get dissolved or decompose or the release of active ingredients.
- Process advantages: Uniform product coating. Both aqueous and organic coatings can be used. Coating and drying take place in one machine. The coating process and filling-emptying of the machine can be carried out in total isolation and without product spreading into the environment.

2.4.3 Basic Principles of Operation of Fluid Bed Coating[3,8,11,13,14]

Three different spray patterns are used for pelletization:

A. Top Spray Coating:

This process is generally used for powder granulation, enteric coating and particle/pellet coatings. With the top spray method, particles are allowed to get

fluidized in hot air stream, which is introduced into the product container through base plate. The coating liquid is then sprayed into chamber from above through counter-current by means of a nozzle, after specific temperature is achieved. Drying takes place simultaneously as the particles continue to move upwards in the airflow.Small droplets and a lower viscosity of the spray medium ensure that the distribution is uniform. Coating in the fluid bed system is suitable for protective coatings/colour coatings. The product is continuously added through one side of the machine and is transported via the sieve bottom using air flow. Dried particles are continuously collected.

Advantages of top spray:

- Agglomeration or granulation processes:
  - Lowest generation of fines and enhanced flow
  - Reduced segregation
  - Uniform distribution of all components
  - Controlled bulk density and optimized solubility
- Coating process:
  - taste masking and lipid coating
  - coatings that protect moisture and oxidation
  - Enteric coatings

B. Bottom Spray Coating (Continuous Fluid Bed):[3,11,13,14]

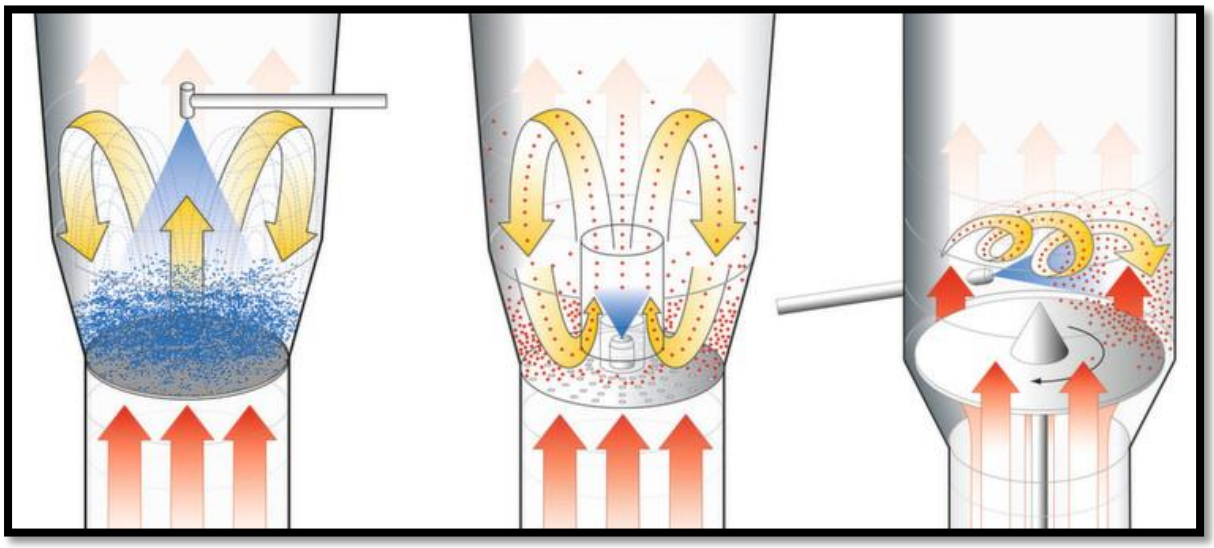
The process is suitable for suspension/solution coating or film/sugar coating, particularly useful for a control release of active ingredients. In this method a complete film formation can be achieved with low usage of coating material. This method uses pneumatic mass transport within the wurster insert, consists of base plate with perforations. Most of the process air is channelled by central tube that sucks product from outside the partition.

The equal and uniform residence time of particles results in very uniform coating. Due to the situation of nozzle directly in contact with particles, premature viscosity change can be avoided.

The Wurster bottom spray method can help to obtain high-class results in coating. The advantages of this methods are as follows:

- Aqueous or organic can be done from polymer solutions or dispersions
- Controlled release and Enteric coating can be achieved
- Coating of fine particles and Drug layering

Figure: 2.9 Top Spray, Bottom Spray, Tangential Spray



C. Tangential Spray Coating (Rotor Pellet Coating/Centrifugal Fluid Bed granulator):[3,11,13,14]

This process is used for powder coating, suspension coating or film/sugar coating. The principle involved in this technique is centrifugal force, fluidization air velocity and gravitational force which is similar to bottom- spray coating. The only difference is that the fashion of production is generated by a motor driven rotor disc.

Uses of tangential spray:

- Used in granulation process for improved dissolution, better compressibility, higher density, spherical morphology
- Spheronization of the product leads to higher density, production of pellets, Higher amount of drug.

- For powder layering and narrow particle size distribution
- Film coating, enteric coating, delayed release and hot- melt coating.

2.4.4 Parameters affecting Fluid Bed System:[14]

A. Equipment parameters:

- Position of base-plate that handles the air
- Size and shape of equipment
- Height of nozzle
- Pressure applied during the process
- Inlet and outlet temperature
- Spray rate

B. Processing parameters:

❖ Drying parameters:

1) Temperature: As the inlet air temperature increases, rate of drying also increases. Which should be carefully observed because exposure to the thermo-labile substances that causes degradation.
2) Humidity: If humidity is less, drying completes faster as compared to presence of higher humidity.

❖ Granulation parameters:

1) Position of nozzle: The position of nozzle should be adjusted for efficient drying.
2) Spray rate: Spray rate should be adjusted to prevent over granulation.
3) Spray pressure: Change in pressure causes improper drying.

❖ Coating parameters:

1) Distance of spray nozzle: more distance leads to evaporation of the coating solution and the less distance leads to over wetting of the particles or the dosage forms.

2) Droplet size: Droplet size is inversely proportional to the efficiency of coating. As the droplet size is less, the more is the uniformity of coating of the solution.
3) Spray rate: Optimum spray rate should be maintained for better coating.
4) Spray pressure: Atomization of coating solution depends on the spray pressure.
5) Moisture in the equipment degrade hygroscopic material so, coating solution is to be dried well so that uniform coating occurs.
6) Time of drying also plays a major role in coating process as the time of drying increases, the coating layer may get brittle and leads to processing problems and if coating layer is not well dried, the doublets and the triplets are formed due to the sticking of the tablets to one another. The coating solution is to be selected based on the parameters used.

2.4.5 Equipment Description:[13]

A GPCG (Glatt-Powder-Coater-Granulator) from Glatt are most widely used Fluidised Bed Processor. They are uniform, reproducible and gentle on the product using fluid bed techniques.

It offers advantages such as:

- ❖ All in one Technology: The technology supports powder coating, simple drying, granulation/ agglomeration, particle coating or pelletizing. Spraying from above (Top Spray), from below (Bottom Spray) or from the side (Tangential Spray) can be possible.
- ❖ Unique technology of GPCGs provide an optimum ratio of air volume flow to quantity of product used. The conical pressure relief zone and reduced flow speed allow very fine products to be processed. A single pipe nozzle is situated at the centre. This combines outstanding spray behaviour with optimum media delivery and easycleaning.
- ❖ Simple handling: Both horizontal and vertical product flow can be obtained easily.
- ❖ Innovative Anti-Bearding-Cap technology allows spraying without bearding. The important feature of ABC technology is unique nano-coating to the nozzle that prevents the deposit of coating material on the nozzle cap.
    - No process downtime due to cleaning of the nozzle

- No blocked liquid inserts
- No interference of spray pattern

Figure: 2.10 Industrial Scale Fluidised Bed Processor (GPCG, GLATT)

2.4.6 Characterization of Multiple Unit Pellet System[1,3,7,10,11]

1. Bulk density and tapped density

A specified quantity of formulation is transferred to measuring cylinder and the volume of cylinder is measured.Tapped density is calculated using following formula.

Bulk density =weight of sample in g /volume occupied by the sample in ml

A given quantity of the formulation is transferred to the measuring cylinder and it is tapped mechanically either manually or mechanical device till a constant volume is obtained.

Tapped density = Wt. of sample in g /Tapped volume in ml

It is determined simply by USP density apparatus. The bulk density of pellets can be measured by using an automated tapper.

2. Carr's compressibility index

Compressibility index (C.I.) or Carr's index value of micro particles was computed according to the following equation: Carr's index = [Tapped density – Bulk density/Tapped density] X 100 The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

3. Hausner's ratio

Hausner's ratio of micro particles was determined by comparing the tapped density to the bulk density using the equation:

Hausner ratio = Tapped density/Bulk density

4. Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. It can be calculated by following equation:

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

Where, θ is the angle of repose, h is the height and r is the radius.

5. Moisture content

Moisture content is determined by means of Karl Fisher titration.

6. Content uniformity

Content uniformity (assay) is performed for each batch as per the procedure given in the official pharmacopoeia.

7. Drug content

Drug containing core as well as final functional coated pellets were evaluated for drug content. Drug content was determined using calibration curve.

8. Surface morphology

Scanning electron microscopy is used to examine the surface morphology and cross section of pellets. The sampling pellets are mounted onto the aluminum stub, sputter-coated with a thin layer of Platinum using sputter coater (Polaron, UK) under Argon atmosphere, and then examined using SEM. The use of optical microscopy to examine the microstructure of pellet surface.

9. Sphericity & shape analysis

Sphericity can be calculated using Aspect ratio.

Aspect ratio = d_{max} / d_{min}

Where, d_{max} and d_{min} are maximum diameter and minimum diameter of pellets respectively.

10. Friability: Friability is a measure of strength to withstand attrition during processing, transport and storage. A friability of less than 0.08% is generally accepted for tablets, but for pellets this value could be higher due to the higher surface area/unit and subsequent involvement of frictional force.

11. Disintegration time: It is important in case of immediate release pellets. The reciprocating cylinder method (USP APP3) with certain diameter and length with sieve of 710mm mesh size at the top and bottom of tube is used.

12. Dissolution test: most commonly done by USP I (basket) and USP II (paddle) apparatus with some modifications to study the release pattern of the coated pellets.

2.4.7 Different Marketed Formulations of MUPS:[5,12]

Table: 2.1 Marketed Formulations of MUPS

Product	Company	Drug	Therapeutic Catagory	Formulation Type
losec MUPS	Astra Zeneka	Omeprazole Magnesium	Antiulcer	Delayed release
Esomeprazole	Astra Zeneka	Esomeprazole Magnesium	Antiulcer	Delayed Release
Toprol XL	Astra Zeneka	Metoprolol Tartrate	Antihypertensive	Extended release
Prevacid SoluTab	Takeda	Lansoprazole	Antiulcer	Delayed Release
Theodur	Key	Theophylline	Antiasthmatic	Extended Release

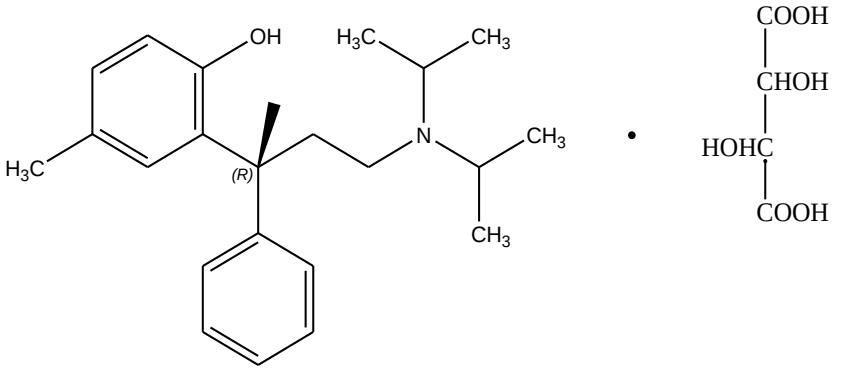
2.4.8 Application of Pellets[2,3,10]

These solid dosage forms are generally available in the form of tablets or capsules containing higher concentrations of drug substance. Product characteristics include dense and smooth coat-able pellets, narrow particle size distribution and higher %Yield and flowability.

Important pharmaceutical applications include:

- Controlled release pellets for encapsulations
- Sustained release / Delayed release pellets with enteric coating
- Multi-particulate systems
- Erosion matrix pellets
- Pellets for special tableting approaches
- Immediate release pellets for sachets
- Taste Masking capacity
- Dose variation without reformulation
- Chemically incompatible product can be prepared

2.5 Introduction to Tolterodine Tartrate[15–20]

Property	Description
Identification	
Name	Tolterodine Tartrate
Physical Form	Cryatalline White Powder
Structure	
Molecular weight	475.6
Chemical Formula	$C_{26}H_{37}NO_7$
IUPAC name	(R)-N,Ndiisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate
Category	Muscarinic Receptor Antagonist
BCS Class	Class-I
Solubility	12 mg/ml in water
Pharmacology	
Indication	It is used for the treatment of overactive bladder with symptoms of Urge urinary incontinence, urgency and frequency.
Pharmacodynamics	After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5- hydroxymethyl derivative, a pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic property same as

	that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and its metabolite exhibit a high affinity for muscarinic receptors and have a very weak affinity for α-adrenoreceptors, histamine receptors, neuromuscular junction, and calcium channels. Preclinical studies have shown that tolterodine is as active as oxybutynin in inhibiting contractions of the detrusor muscle from the guinea pig; it has a potency similar to that of oxybutynin in inhibiting electrically induced contractions of human detrusor muscle from stable and overactive bladders ex vivo.
Mechanism of Action	Tolterodine L-tartrate, is a competitive muscarinic receptor antagonist, which has been shown to inhibit carbachol-induced contraction of isolated bladder preparations from rats, guinea pigs, and man. Tolterodine L-tartrate (henceforth referred to as tolterodine) inhibits contractions of the detrusor muscle from the guinea pig, and electrically induced contractions of human detrusor muscle from stable and overactive bladders ex vivo. Tolterodine is significantly more active in inhibiting acetylcholine-induced urinary bladder contractions than electrically induced salivation in the anesthetized cat.
Absorption	Tolterodine is rapidly absorbed; bioavailability is at least 77%. T max is within 1 to 2 h (immediate release) and 2 to 6 h (ER). Food increases bioavailability (approximately 53%) of immediate-release tolterodine, but has no effect on ER tolterodine.
Distribution	Tolterodine is highly protein bound, primarily to alpha-1 acid glycoprotein. Vd is approximately 113 L.
Metabolism	Tolterodine is extensively metabolized by the liver. The primary metabolic route involves oxidation of the 5-methyl group and is mediated by the CYP2D6 iso-enzyme and leads to a

	pharmacologically active 5-hydroxymethyl tolterodine (5-HMT) metabolite.
Excretion	77% is recovered in urine and 17% is recovered in fecaes within 7 days. Half-life is approximately 2 h (immediate release) and 7 h (ER).
Half life	1.9 – 3.7 hours
Solubility	Soluble at 12 mg/mL in water at room temperature, soluble in methanol, slightly soluble in ethanol and practically insoluble in toluene.
pH	3.0-4.5 in water
pKa	9.9
Melting Point	206°C - 212°C
Volume of Distribution	113 ±26.7 L
Drug Interactions	• Anti-cholinergics: • Class IA (eg, procainamide, quinidine) or class III (eg, amiodarone, sotalol) antiarrhythmic agents: • Cyclosporine: Tolterodine plasma concentration may be increased. • CYP3A4 potent inhibitors (eg, clarithromycin, erythromycin, itraconazole, ketoconazole, miconazole, nefazodone, protease inhibitors [eg, ritonavir]) • Fluoxetine • Potassium chloride • Proton pump inhibitors • Vinblastine • Warfarin
Adverse Reactions	• Cardiovascular: Palpitations, tachycardia.

	• CNS: Headache (7%); vertigo/dizziness (5%); fatigue (4%); somnolence (3%); anxiety (1%); confusion, disorientation, hallucinations, memory impairment. • Dermatologic: Dry skin (1%). • EENT: Xerophthalmia (3%); abnormal accommodation (2%); abnormal vision (1%). • GI: Dry mouth (35%); constipation (7%); abdominal pain (5%); diarrhea, dyspepsia (4%). • Genitourinary: Dysuria (2%). • Metabolic: Weight gain (1%); peripheral edema (postmarketing). • Musculoskeletal: Arthralgia (2%). • Respiratory: Sinusitis (2%). Miscellaneous: Influenza-like symptoms (3%); chest pain (2%); infection (1%); anaphylaxis, angioedema.
Precautions	• Pregnancy • Lactation • Children • Renal Dysfunction • Hepatic Dysfunction • Special Risk Patients: Use with caution in patients with clinically significant bladder outflow obstruction, GI obstructive disorders (eg, pyloric stenosis), decreased GI motility (eg, intestinal atony), controlled narrow-angle glaucoma, or myasthenia gravis. • Anaphylaxis/Angioedema • QT prolongation: Consider this when prescribing to patients with a known history of QT prolongation or in patients taking class IA (eg, quinidine, procainamide) or class III antiarrhythmics (eg, amiodarone, sotalol).

2.6 Introduction to Disease

Urinary Incontinence/Urge incontinence

- Urinary incontinence is referred to as "overactive bladder" or "spastic bladder," which involves involuntary loss of urine that generally occurs when a person has a strong and sudden need to urinate. Urge incontinence is not a disease but an underlying problem.
- Urge incontinence is caused by abnormal bladder contractions. Normally, strong muscles called sphincters control the flow of urine from the bladder. With urge incontinence, the muscles of an "overactive" bladder contract with enough force to override the sphincter muscles of the urethra, which is the tube that takes urine out of the body.

The bladder may experience abnormal contractions for the following reasons:

- Damaged nerve due to various diseases such as diabetes, stroke, multiple sclerosis or Parkinson's disease.
- Damaged spinal cord
- Irritated Bladder
- Some unidentified reasons

Symptoms of Urge Incontinence

Sudden need to urinate or involuntary loss of urine at inappropriate times

How Is Urinary Incontinence is treated?

Urge incontinence can be treated by behavioural treatments, medications, electrical stimulation, or with surgery. Sometimes a combination of treatments is used.

- **Behavioural Treatments for Urge Incontinence**

One way of dealing with urge incontinence is to simply changing behaviour. For instance, if you can anticipate when your bladder is overactive and may be contracting abnormally, you can take action to avoid any mishaps or urine leakage.

❖ **Medical treatments for urge incontinence include:**

Medications: There are several medications that are used to treat urge incontinence. They include:

- Darifenacin (Enablex)
- Fesoterodine (Toviaz)
- Mirabegron (Myrbetriq)
- Oxybutynin (Ditropan, Ditropan XL, Gelnique, Oxytrol)
- Solifenacin (Vesicare)
- Tolterodine (Detrol, Detrol LA)
- Trospium (Sanctura)

2.7 Introduction to Excipients[21]

2.7.1 Sugar Spheres

1. Non-proprietary Names

BP: Sugar spheres

PhEur: Sacchari spheri

USPNF: Sugar spheres

2. Synonyms

Non-pareil; non-pareil seeds; NPTAB; Nu-Core; Nu-Pareil PG; sugar seeds; Suglets.

3. Functional Category

Tablet and capsule diluent.

4. Applications in Pharmaceutical Formulation or Technology

- Sugar spheres are generally used as inert cores in capsule and tablet formulations, particularly multiparticulate sustained release formulations.
- They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating.
- Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating.
- Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings. Sugar spheres are also used in confectionery products.

5. Description

The USPNF 23 describes sugar spheres as approximately spherical granules of a labelled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch. The PhEur 2005 states that sugar spheres contain not more than 92% of sucrose calculated on the dried basis. The remainder consists of corn (maize) starch and may also contain starch hydrolysates and colour additives. The

diameter of sugar spheres varies from 200 to 2000 mm and the upper and lower limits of the size of the sugar spheres are stated on the label.

6. Typical properties

Density: 1.57–1.59 g/cm^3 for Suglets less than 500 mm in size; 1.55–1.58 g/cm^3 for Suglets more than 500 mm in size.

Flowability: <10 seconds, free flowing.

Particle size distribution: Sugar spheres are of a uniform diameter.

Table: 2.2 The following sizes are commercially available from various suppliers (US standard sieves):

Mesh Aperture (Range)	Size (mm)
45-60	250-355
40-50	300-425
35-45	355-500
35-40	420-500
30-35	500-600
25-30	610-710
20-25	710-850
18-20	850-1000
16-20	850-1180
14-18	1000-1400

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

Specific surface area:

0.1–0.2 m^2/g for Suglets less than 500 mm in size;

>0.2 m^2/g for Suglets more than 500 mm in size.

8. Stability and Storage Conditions

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

2.7.2 Hypromellose

1. Non-proprietary Names

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

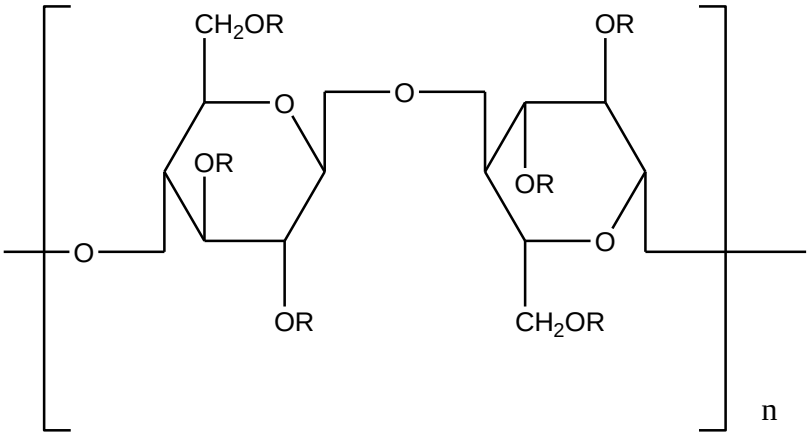
USP: Hypromellose

2. Synonyms: Benecel MHPC, hydroxypropyl methylcellulose, HPMC, Methocel; methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, Tylopur.

3. Chemical Name: Cellulose hydroxypropyl methyl ether

4. Molecular Weight : 10000-150000 g/mol.

5. Structural Formula:



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

7. 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 a matrix for use in extended-release formulations.
- Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes.
- 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.
- Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.
- Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, and Pharmacoat. Hypromellose is also used as a suspending and thickening agent in topical formulations.
- Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use.
- Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.
- Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.
- In addition, hypromellose is used in the manufacturing of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

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

9. Typical Properties

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

Ash: 1.5–3.0%, depending upon the grade and viscosity.

Autoignition temperature: 360°C

Density (bulk): 0.341 g/cm^3

Density (tapped): 0.557 g/cm^3

Density (true): 1.326 g/cm^3

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

Glass transition temperature is 170–180ºC.

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. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 1.26

Viscosity (dynamic):

Table: 2.3 Typical Viscosity Values of Methocel

Typical Viscosity values for 2% w/v aqueous solution of Methocel at 20°C		
Methocel Product	**USP 28 designation**	**Nominal Viscosity (mPas)**
Methocel K100 Premium LVEP	2208	100
Methocel K4M Premium	2208	4000
Methocel K15M Premium	2208	15000
Methocel K100M Premium	2208	100000
Methocel E4M Premium	2910	4000
Methocel F50 Premium	2906	50
Methocel E10M Premium CR	2906	10000
Methocel E3 Premium LV	2906	3
Methocel E5 Premium LV	2906	5
Methocel E6 Premium LV	2906	6
Methocel E15 Premium LV	2906	15
Methocel E50 Premium LV	2906	50
Methocel 60SH	2910	50, 4000, 10000
Methocel 65SH	2906	50, 400, 1500, 4000
Methocel 90SH	2208	100, 400, 4000, 15000

10. Stability and Storage Conditions:

Hypromellose powder is a stable material, although it is hygroscopic after drying.

11. Incompatibilities

Hypromellose is incompatible with some oxidizing agents.

2.7.3 Ethyl Cellulose

1. Non-proprietary Names

BP: Ethylcellulose

PhEur: Ethylcellulosum

USPNF: Ethylcellulose

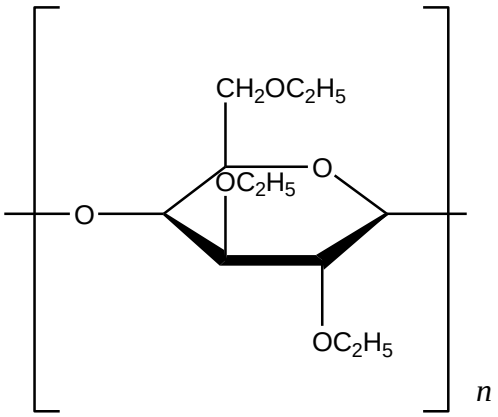
2. Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

3. Chemical Name and CAS Registry Number: Cellulose ethyl ether [9004-57-3]

4. Empirical Formula and Molecular Weight: Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_nC_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydro-glucose units joined together by acetal linkages.

5. Structural Formula



6. Functional Category: Coating agent; flavouring fixative; tablet binder; tablet filler; viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology

- Ethylcellulose is widely used in oral and topical pharmaceutical Formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation.
- Modified release tablet formulations may also be produced using ethylcellulose as a matrix former.
- Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films.
- Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer.
- An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents.
- Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating.
- High-viscosity grades of ethylcellulose are used in drug microencapsulation.
- Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral and topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels.
- EC has been studied as a stabilizer for emulsions. Ethylcellulose is additionally used in cosmetics and food products.

Table: 2.4 Use of EC

Use	Concentration (%)
Microencapsulation	10.00 – 20.00
Sustained release tablet coating	3.00 – 20.00
Tablet Coating	1.0 – 3.0
Tablet Granulation	1.0 – 3.0

8. Description

Ethylcellulose is a tasteless, free-flowing, white to light tan colored powder.

9. Pharmacopeial Specifications for Ethylcellulose Viscosity:

Table: 2.5 Viscosity of EC

Test	PhEur 2005	USPNF 23
Nominal Viscosity		
>6 mPa s	75 – 140% of that stated for its nominal viscosity	75 – 140% of that stated for its nominal viscosity
6 – 10 mPa s	80 – 120% of that stated for its nominal viscosity	80 – 120% of that stated for its nominal viscosity
≤10 mPa s	80 – 120% of that stated for its nominal viscosity	90 – 110% of that stated for its nominal viscosity

10. Typical Properties

Density (bulk): 0.4 g/cm^3

Glass transition temperature: 129–1338ºC

Moisture content: ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily

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

Specific gravity: 1.12–1.15 g/cm^3

Viscosity: the viscosity of ethylcellulose is measured typically at 258ºC using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene:20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available.

Table: 2.6 Typical Viscosity values of different grades of Ethyl cellulose

Grade	Supplier	Solution Viscosity (mPas)	Mean Particle Size (µm)
Ethocel Std 4 Premium	Dow Chemical	3.0-5.5	-
N-7	Aqualon	5.6-8.0	-
Et hocel Std 7FP Premium	Dow Chemical	6.0-8.0	5.0-15.0
Ethocel Std 7T-10 Premium	Dow Chemical	6.0-8.0	310.0
T-10	Aqualon	8.0-11.0	-
N-10	Aqualon	8.0-11.0	-
Ethocel Std 10FP Premium	Dow Chemical	9.0-11.0	3.0-15.0
Ethocel Std 10P Premium	Dow Chemical	9.0-11.0	375.0
N-14	Aqualon	12.0-16.0	-
Ethocel Std Premium	Dow Chemical	18.0-22.0	-
N-22	Aqualon	18.0-24.0	-
Ethocel Std Premium	Dow Chemical	41.0-49.0	-
N-50	Aqualon	40.0-52.0	-
N-100	Aqualon	80.0-105.0	-
Ethocel Std Premium	Dow Chemical	90.0-110.0	30.0-60.0
Ethocel Std Premium	Dow Chemical	90.0-110.0	465.0

11. Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340nm range. Ethylcellulose should be stored at a temperature not exceeding 328C (908F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

12. Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Literature Review of Drug

Sirisha et al[22] developed sustained release pellets of Tolterodine tartrate using MUPS. Pelletization technique was used for the formulation of pellets with coating material like HPMC E-5 in fluid bed coating. The pellets so formed were evaluated by percentage of moisture content, percentage yield, micromeritic properties, friability, in-vitro dissolution studies stability studies and IR analysis. No interaction between drug and excipients was found from the drug Excepient interaction studies. Sustained release of drug was found to be for 18 hours following zero order kinetics and non-fickian release mechanism. The release when compared with marketed formulation the release profile match.

Sundarsan Venkata et al[23] developed an extended-release formulation of Tolterodine Tartrate using MUPS. Sugar spheres were selected as an inert core on which the drug is to be coated to form pellets. Pellets were then mixed with suitable excipients and were filled in capsules. The drug and excipients were proved to be compatible by drug- excipient compatibility studies. The fix ratio of ethylcellulose and HPMC was used as a coating material in the formulation for subsequent coating. The release pattern obtained was satisfactory and similar to that of marketed product.

Rajabalaya Rajan et al[24] formulated a transdermal patch of TT using solvent casting method. The in-vivo study showed release up to 89.9% and the in-vivo animal study was successfully carried out. DSC and FTIR studies showed that there was no interaction between drug and excipients and hence transdermal patches were formulated that follows Higuchi drug release model.

Pradhan Roshan et al[25] prepared sustained release matrix tablet of tolterodine tartrate using direct compression technique. The tablet contains HPMC 2910 and HPMC 2208 as release retardants, coated with HPMC 606 and ethylcellulose for further modify the drug release. The optimized formulation was evaluated for in-vitro dissolution studies in different pH conditions and dissolution data was fitted in different kinetic models. The release profile was compared with marketed formulation. The similarity value was found to be 70.25. The formulation was analysed for different pharmacokinetic parameters in human volunteers. The

parameters observed were completely different from marketed formulation which suggests that the formulation was bioequivalent to that of marketed formulation.

Lakshmi et al[26] developed membrane controlled transdermal patches by fabricating drug reservoir in the rate controlling membrane by means of solvent casting method. The drug reservoir was developed using various polymers and rate controlling membranes like Eudragit RL100 and Eudragit RS 100. In-vitro, ex-vivo studies were conducted on rat abdominal skin and release was 52.98 ± 1.12 μg/cm^2 over the control (8.85 ± 0.74 μg/cm^2). The flux was 3.574 μg/cm^2/hr, lag time was 0.8 hours, permeability coefficient was 1.068 cm/hr and permeation was enhanced by 2.33 fold for optimized formulation. The optimized formulation (F3) exhibited controlled drug release profile with zero order drug release kinetics and Fickian diffusion mechanism.

Devireddy et al[27] formulated tolterodine tartrate matrix transdermal system using HPMC E15, Eudragit RS100 and Eudragit RL 100 by solvent evaporation method with dichloromethane and Methanol as solvents. The formulation was optimized for different ratios of polymers, plasticizer, and penetration enhancer. The physicochemical parameters such as thickness, weight variation, moisture content, drug content and moisture absorption and in vitro release, ex vivo permeation etc were checked for the optimized batch. Different kinetic models were applied to determine the release patterns and mechanism. Permeation profiles of all formulations of drug followed Higuchi square root model as it was evidenced by highest regression coefficient value. The drug release mechanism was said to be non fickian diffusion.

Prasanthi et al[28] studied the permeation enhancing effect of co-solvents on transdermal gel formulation of TT using experimental design technique. Two factors concentration of ethanol and propylene glycol were chosen for Taguchi robust design. The influence of co-solvents on the in-vitro penetration through a synthetic membrane and abdominal rat skin from carbopol gels were investigated using Keshary-chein type diffusion cells. Penetration through the synthetic membrane was well described by the Higuchi model whereas when using rat skin, the penetration rate was controlled by the membrane (skin) the penetration rate was controlled by the membrane (skin). The permeation rate of TT significantly increased in proportion to the ethanol and propylene glycol concentration showing co-solvent action. In conclusion, a

transdermal TT gel was formulated successfully using the technique of Taguchi robust design and these results were useful in finding the optimum formulation for transdermal drug release. The optimized ratios of co-solvents were ethanol (60%) and propylene glycol (10%).

Lakshmi et al[29] studied the comparative and combination enhancement of transdermal drug through physical and chemical penetration enhancement methods. Tolterodine tartrate loaded invasions were prepared using soya lecithin, ethanol, and three different terpenes viz. limonene, fenchone, and anethole. The FT-IR results showed the compatibility of these excipients with the drug. Ex- Vivo skin penetration data revealed that the intasome dispersion showed a significantly enhanced penetration of the drug through the skin compared to vesicles without terpenes, ethanolic drug solution, and drug solution. Invasome formulation containing limonene showed high penetration because of its lipophilicity and low boiling point. The results of iontophoretic drug transport showed that the permeability of tolterodine tartrate released from invasomes was higher compared with that of free drug proving the additive effect of invasomes and iontophoresis. Hence, successful transdermal penetration was obtained in combination with both physical and chemical penetration techniques.

Literature Review on MUPS Technology

Gotta Kranthikumar et al[30]developed extended release capsules of Indomethacin using pelletization technique. To develop such a dosage form, the appropriate size of inert sugar spheres was selected and the drug was coated on it along with povidone k-30. HPMC and ethylcellulose were used as coating polymer for extended release action. The capsules so prepared were evaluated for content uniformity, weight variation, in-vitro disintegration time, assay, and in-vitro drug release study. All the formulation exhibited assay, content uniformity within the range given in USP. The optimized formulation had 2.31 g of HPMC and 0312 g of EC showed 100% drug release in 12 hours. The release profile was matched with innovator and was observed to have a same release profile.

Mayalavarapu P. et al[31] developed duloxetine hydrochloride delayed release enteric coated pellets in capsules using fluidised bed processing technique. Different enteric coating polymers like PVAP, Kollicoat MAE 30 DP, Eudragit L30 D55 and HPMC etc. were used. The pellets were analysed for in-vitro drug release and analysed using HPLC technique. The release kinetics was analyzed using the zero-order model, first-order model, and Higuchi's square root equation. FTIR and DSC showed the compatibility of drug and excipients. SEM was performed to analyse the size and morphology of pellets. The optimized formulation has similarity with marketed product.

Wang Yuli et al[32] developed ethylcellulose coated pellets of metoprolol succinate with pore former. It was observed that presence of the drug in EC coating improve coating process and reduce the pellet stickiness. Optimization was carried out using Central composite design and response surface methodology. It was observed that pore former had a positive effect on drug release and coating level had a negative effect. In-vivo drug release confirmed the absence of initial lag phase which ensures successfully optimized formulation.

Ramu S. et al[33] formulated delayed release dosage form using different enteric coating polymers by employing Solution-suspension layering technique in FBP. The formulation was compared with marketed dosage form. The formulation was

developed by drug loading, sub coating, enteric coating, and lubrication steps. The prepared formulation was characterized by solubility, water content, loss on drying bulk density, tapped density, carr's index, Hauser's ratio, the angle of repose, melting point and particle size distribution. Evaluation of delayed release formulations was carried out by assay, acid resistance, dissolution (in acid stage followed by buffer stage), content uniformity, average net fill content, and friability etc. Coated pellets were found to be optimum and then filled into capsules and were evaluated and results were found to be similar with innovator product.

Sirichandana G. et al[34] developed sustained release pellets of domperidone with different grades of EC using drug layering technique. Pellets were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index, and angle of repose shows satisfactory results. The formulation was optimized on the basis of acceptable pellet properties such as friability, drug content moisture content and loss on drying and in-vitro drug release. The in-vitro release studies of pellets were carried out in 0.1N HCL for 2 hours and 6.8 pH phosphate buffer for 12 hours. The drug release can be modulated by varying the concentration of the polymer. The formulations were further characterized to identify any possible interactions by FTIR spectroscopy and DSC.

Baskara Haripriya et al[35] developed sustained release formulation of Tramadol hydrochloride by wurster for the process. FTIR showed the interaction of the drug with polymers. The prepared formulation was analysed for the angle of repose, tapped density, bulk density etc. The parameters were found to be within the limits and pellets prepared by wurster process were satisfactory for further studies.

Sirisha et al[36]developed extended-release pellets of Propranolol Hydrochloride by extrusion-spheronization. These drug pellets were coated with different viscosity grades of extended release polymers using a combination of hydrophobic and hydrophilic cellulose derivatives in different ratios and different coating levels. Prepared pellets were evaluated for flow properties, drug content (by HPLC) and in-vitro drug release (by UV Spectroscopy). The dissolution profile of pellets was evaluated in 0.1N HCL (pH 1.2) for first 1.5 hours followed by phosphate buffer (pH 6.8) for remaining hours. It was observed that the formulation with the combination of

polymers ethyl cellulose EC and HPMC in the ratio 75:25 at a coating level of 8% w/w to the drug pellets exhibited a dissolution pattern equivalent to the predicted release and able to extend the drug release for a prolonged period of time. The optimized formulation was analysed for surface morphology, release kinetics, and stability. The mechanism of drug release followed first order kinetics. An accelerated stability study of the finalized extended release pellets was found to be well within the acceptable range for 6 month.

Literature Review on Role of Fluidised Bed Processor in Pelletization

Namrata et al[37] Studied qualitative analysis of Fluidised Bed Technology for the formulation development of Tolterodine Tartrate pellets using layering process in Wurster based Fluidised bed processor. The release profile of developed multiparticulate system was then compared with marketed product in various media. The effects of some independent process variables were analysed. The effect of the various process parameters such as inlet air temperature, product temperature, exhaust temperature, atomization speed, spray pump speed, atomization air volume and air flow on the Wurster process was studied. The results showed that the process parameters vary with the physical properties of the drug, polymers and solvents used in process for layering of pellets.

K. Anusha et al[38] prepared sustained release pellets of Quetiapine fumarate in fluidised bed processor using sugar pellets as starter cores and then coated with EC and Cellulose Diacetate as SR polymers. Pellets were characterized by SEM, DSC and in-vitro dissolution studies. The optimized formulation was found to release the drug over an extended period of time i.e. up-to 16 hours. It was observed that as the concentration of the polymer increased the drug release from the pellet formulations was reduced. The formulation maintain the sustained release profile successfully.

Naik Nagarjuna et al[39] developed coated tablets for Esomeprazole magnesium dihydrate delayed release multiparticulate system to reduce the gastrointestinal tract side effects. The delayed release multiple units were prepared by using fluid-bed wurster technology. multiple unit pellets were formulated by seal coating, drug coating and enteric coating. Pellets were evaluated for assay, acid resistence, drug release, dissolution, Kinetic studies of Innovator and Optimized formulation, Stability studies of Optimized formulation. Thus Esomeprazole magnesium dehydrate pellets can be prepared by using combination of polymers studied and we can reduce the GI tract side effects.

3.4 Patent Review [40–47]

Patent N0. : US 8,871,275 B2

Date of Patent: Oct. 28, 2014

Jaiswal Sunil et al invented alternate extended release pharmaceutical compositions of tolterodine or its salts to avoid the use of a combination of drug and polymer in the drug layer or drug core as taught in prior art. The aim of the invention was to provide extended release pharmaceutical compositions wherein the compositions comprise of an inert core; drug layer comprising of tolterodine or its salts, monosaccharide and/or disaccharide on the inert core; and polymer layer comprising extended release polymer on the drug layer.

Patent No.: US 8,110,226 B2

Date of Patent: Feb. 7, 2012

Boyong Li et al invented composition containing a coated bead is used in the manufacture of immediate release and/or controlled release drug compositions includes an inert core of a water soluble or water swellable material which has been coated with a seal layer formed from a non-polymeric hydrophobic material. Beads may be used to formulate tablet or capsule and the method of making beads by sequential deposition of multiple layers on the inert cores is also described.

Patent N0.: US 8,486,452 B2

Date of Patent: Jul. 16, 2013

Rossi et al invented that a seal coat deposited on an inert core made up of a non-polymeric hydrophobic material; and a layer containing the acid-stabilized tolterodine-L-tartrate is then deposited on the seal layer which can be used to make beads compressed into tablets or filled into capsules. The method include a step of combining tolterodine-L-tartrate with a stabilizing amount of a pharmaceutically acceptable pH-modifying acid to obtain an acid stabilized tolterodine-L-tartrate. The acid-stabilized tolterodine-L-tartrate is combined with excipients and compressed into a tablet or filled into a capsule.

Patent N0.: US 8,642,078 B2

Date of Patent: Feb. 4, 2014

Legan et al invented that sustained release pharmaceutical composition is made by applying various layers containing active ingredient over inert core, and the penetration of gastric or intestinal fluid through those layers dictates the kinetics of release or alternatively by incorporating the active into a core. for example into a tablet Whereas the kinetics of release is dictated by slow disintegration/ dissolution of said tablet. An Immediate release pharmaceutical composition (e.g. tablets) can be administered more than once a day, but also a preparation of a sustained release composition, by applying to immediate release composition preferably only one coating layer which provides for sustained release.

Pub. No.: US 2011/0123610 A1

Pub. Date: May 26, 2011

Krishsagar et al invented extended release solid composition containing Tolterodine which can be prepared in dosage forms of different strength by adjusting the quantities of the excipients and the drug, thereby providing a pharmaceutical linearity, Without affecting the dissolution profile and bioavailability of the active ingredient. The method of preparation enhance the release rate of the active ingredient and being stable over a long period of time and improving the pharmaceutical characteristics of the composition.

4.0 Experimental Work

4.1 Instruments and Material

Table 4.1 Instruments used in present investigation

Name of Instrument	Manufacturer
GPCG 1.1	GLATT CORPORATION, binzen, Germany
Tap Density Apparatus	Electrolab ETD-1020, Mumbai, India
Dissolution test apparatus	Electrolab -TDT-08T, Mumbai, India
Vernier Callipers	Electrolab VDT-08L, Mumbai, India
Electronic Weighing Balance	Shimadzu PhilipinesMfg.Inc. Rosario, Philippines
Electronic Weighing Balance	Mettler Toledo
Electronic Weighing Balance	Sartorius
SEM	Jeol JSM-5610LV, Tokyo, Japan
HPLC System	Waters Corporations, Milford, Massachusetts, US
HPLC System	Shimadzu Corporation, Japan
UV- Spectrophotometer	Shimadzu UV-1800, Kyoto, Japan
Overhead stirrer	Remi motor, Mumbai, India
FTIR	Jasco FTIR 6100 Type A, Tokyo, Japan

Table 4.2Material used in Present investigation

Ingredients	Supplier	Category
Sugar Spheres (20-25#)	Colorcon, West Point, PA, USA	Inert starter Cores
Tolterodine Tartrate	Hetero Drugs LTD, Andhra Pradesh, India	API
Surelease Clear E-7-19040	Colorcon, West Point, PA, USA	Film Forming Polymer
HPMC 6 cps (Pharmacoat 606)	ShinETSU, Japan	Binder, Pore Former
Methanol	Finar Chemicals pvt LTD, Mumbai, India	Organic Solvent
Purified Water	-	-

4.2 Pre-formulation Studies[48–50]

Pre-formulation study is the first step in the rational development of dosage form. Activities done prior to formulation development are called as pre-formulation studies. It can also be defined as "an investigation of physical and chemical property of a drug alone and when combined with excipients". Physicochemical properties are those that can be determined from in-vitro experiments.

The main objective is to generate information useful to the formulation in developing most stable and bioavailable dosage form. Pre-formulation investigations are designed to identify the physicochemical properties of drug and excipients that may influence the formulation design, method of manufacture and pharmacokinetic – biopharmaceutical properties of the resulting product. It describes the process of optimizing the delivery of drug through determination of physical and chemical properties of new drug molecule that affect drug performance and development of an efficacious, stable and safe dosage form. Pre-formulation studies on a new drug molecule provides useful information for subsequent formulation of a physic-chemically stable and biopharmaceutically suitable dosage form.

Parameters included in the pre-formulation study are as follows:

4.2.1 Organoleptic properties

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

4.2.2 Solubility

Tolterodine Tartrate is BCS Class-I drug. Solubility of API was checked in Dimethylformamide and methanol.

4.2.3 Physicochemical Properties

Density Measurement

Density measurement were performed to characterize the API and its flow property. Generally two types of density measurements are performed i.e. Bulk density and tapped density.

Bulk Density

An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP], was carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. The volume was measured directly from the graduation marks on the cylinder as ml. The volume measured is described as the bulk volume and the bulk density was calculated by following formula.

Bulk Density = $\frac{m}{Vo}$ ...

m = bulk mass (gm),

Vo = apparent volume (ml)

Tapped Density

After measuring the bulk density the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 500 taps drop per minute and operated for 500 taps from a distance of 14 ± 2 mm. The tapped volume (V_0) was measured to the nearest graduated unit. The tapping was repeated additional 750 times and volume was noted as (V_f). If the difference between V_0 and V_f is not greater than 2% then V_f is considered as the final tapped volume. The tapped density is calculated by the following formula.

Tapped Density = $\frac{m}{vf}$

Where,

m = Bulk mass (gm),

V_f = Final volume (ml) after tapping.

4.2.4 Flow Properties

Angle of Repose

Flow property is characterized in terms of angle of repose. For the determination of angle of repose, funnel method was used. The sample was poured gently through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above a hard surface. The drug was poured till the time when the upper tip of the pile surface was touched to the lower tip of the funnel.

Angle of Repose was calculated using following formula:

$$\theta = \tan^{-1}\frac{h}{r}$$

Where,

$\boldsymbol{\theta}$= Angle of repose.

$\boldsymbol{h}$ = Height of pile.

$\boldsymbol{r}$ = Radius of the base of the pile.

Table 4.3 Interpretation of Angle of Repose for Powder flow

Angle of Repose	Flow Property
< 25	Excellent
25-30	Good
30-40	Average
> 40	Very Poor

Carr's Index [Compressibility Index]:

It is one of the most important parameter to characterize flow properties of powders and granules.

Following formula was used to calculated Carr's Index (CI)

$$\textbf{Carr's Index} = \frac{\boldsymbol{Tapped}\ Density - Bulk\ Density}{\boldsymbol{Tapped}\ Density} \times 100$$

Table 4.4 Interpretation of Carr's Index for Powder Flow

% Compressibility	Flowability
5-15	Excellent

12-16	Good
18-21	Fair-passable
23-35	Poor
33-38	Very poor
> 40	Extremely poor

Hausner's Ratio

Hausner's Ratio can be calculated by following formula:

Hausner's Ratio = $\frac{Tapped\ Density}{Bulk\ Density}$

Table 4.5 Interpretation of Hausner's Ratio for Powder Flow

Hausner's Ratio	Flowability
< 1.25	Good Flow
1.25-1.5	Passable
>15	Poor Flow

Result & Discussion

(Result and Discussion of Pre-formulation study is based on Vendor's CoA)

Table 4.6 Results of Pre-formulation Study

Test	Specification	Result	Reference
Description	White to Off-White Crystalline Powder	A white Crystalline Powder	Visual Inspection
Solubility	Soluble in Methanol and Dimethylformamide	Complies	Visual Inspection
Loss on Drying	Should not be more than 1.0% w/w	0.35% w/w	USP <731>
Tartric Acid Content	Should be between 30.0 % and 33.0 % w/w	31.8% w/w	USP <541>
Assay by HPLC (on dried basis)	Not less than 98.0 % and Not more than 102.0 % w/w	99.5% w/w	USP <621>

Table 4.7 Related Compound by HPLC <USP 621>

Test	Specification		Result	Reference
Chromatographic Purity by HPLC	2-Methoxy-5-methyl-N,N-bis(1-methylethyl)-gamma-phenylbenzenepropanamine **(Related Compound-A)**	Not more than 0.15%	0.03% (LOQ = 0.004%)	USP <621>
	Maximum single unknown impurity	Not more than 0.10%	0.01%	
	Total impurities	Not more than 1.0%	0.04%	
Enantiomeric purity by HPLC	2-[(1S)-3-[bis(1-methylethyl)amino]-11phenylpropyl]-4-methylphenol tartric acid **(Related Compound-B)**	Not more than 1.0%	088% (LOQ = 0.17%)	USP <621>

Table 4.8 Physicochemical Characterization

Parameter	Result
Angle of Repose	42.27°
Bulk Density	0.3125 g/ml
Tapped Density	0.6578 g/ml
Compressibility Index	52.493%
Hausner's Ratio	2.1049

- From the results of Pre-formulation studies of API, it was concluded that API has Poor flow property and poor compressibility index.

4.3 Estimation of API

4.3.1 Standard Calibration Curve of API in pH 6.8 Phosphate Buffer

Procedure:

Accurately weighed 4 mg quantity of TT was transferred to a 900 ml volumetric flask and dissolved in pH 6.8 Phosphate buffer to prepare a stock solution (4.44 ppm). This stock solution was considered as 100% level of concentration. From the stock solution different concentration were prepared as 10%, 20%, 50%, 100% and 120%. To prepare these concentrations levels, 0.444 µg/ml, 0.888µg/ml, 4.44 µg/ml, 2.22 µg/ml and 5.328 µg/ml solutions were prepared subsequently by diluting stock solution with water. After preparing solutions, immediately area response were measured in HPLC system using UV detector at 210 nm. Calibration curve was prepared by plotting concentration Vs. Area Response. The results of standard calibration curve are shown in table.

Table 4.9 Standard calibration curve of API in Phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Area Response			Average Area Response	Std. Deviation
		1	2	3		
1	0	0	0	0	0	0
2	0.45	24485	24489	24495	24489	5.033223
3	0.89	47345	47360	47371	47366	13.05118
4	2.23	110360	110345	110379	110356	17.03917
5	4.45	219064	219068	219060	219064	4
6	5.34	275395	275400	275425	275406	16.07275

Figure 4.1 Standard Calibration Curve of API in pH 6.8 Phosphate Buffer

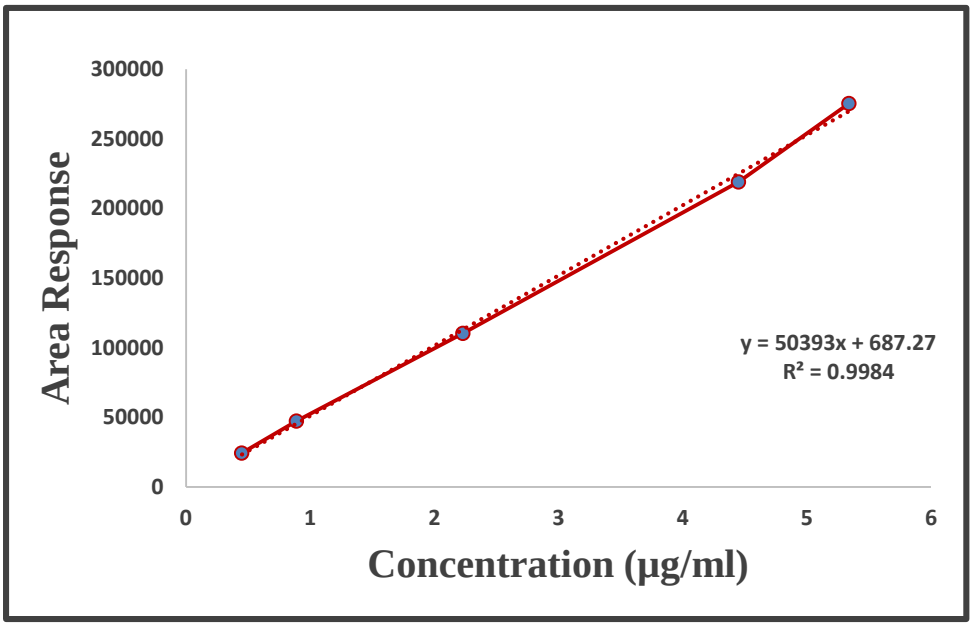


Table 4.10 Regression Parameters of calibration curve of API in pH 6.8 Phosphate Buffer

Regression Parameter	Value
Correlation coefficient (R^2)	0.9984
Slope (m)	50393
Intercept (c)	687.27

Equation of the Line:

Area = (50393 × Concentration) + 687.27

4.3.2 Chromatographic Estimation of API

Chromatographic estimation of API was done using HPLC system in order to obtain a specific peak that indicate the presence of pure active substance.

Mobile Phase

A mixture of Buffer solution, Acetonitrile and methanol (HPLC grade) in the ratio of 55:30:15 (%v/v) was prepared respectively. Mixed well and degased by sonication.

Sample Solvent Preparation

The chromatography was carried out in Cosmosil C18 (150 mm × 4.6 mm) analytical column at 1 ml/minute flow rate. The injection volume was 20.0µL, Column oven temperature was at 30ºC. Detection at 210 nm, and chromatographic run time of 8.0 min was used. Before injection of the drug solution, the column was equilibrated for at least 10 minutes with the initial time gradient mobile phase conditions flowing through the system.

Standard stock solution and sample solution of tolterodine tartrate was prepared and following chromatographic conditions were maintained:

Table 4.11 Chromatographic Conditions

Parameter	Condition
Column	Cosmosil C18 (150 mm × 4.6 mm)
Flow Rate	1 ml/minute
Detector	UV at 210 nm
Column Oven Temperature	30° C
Injection Volume	20 µL
Run Time	8 minutes

Figure: 4.2 Chromatogram of Standard Tolterodine Tartrate

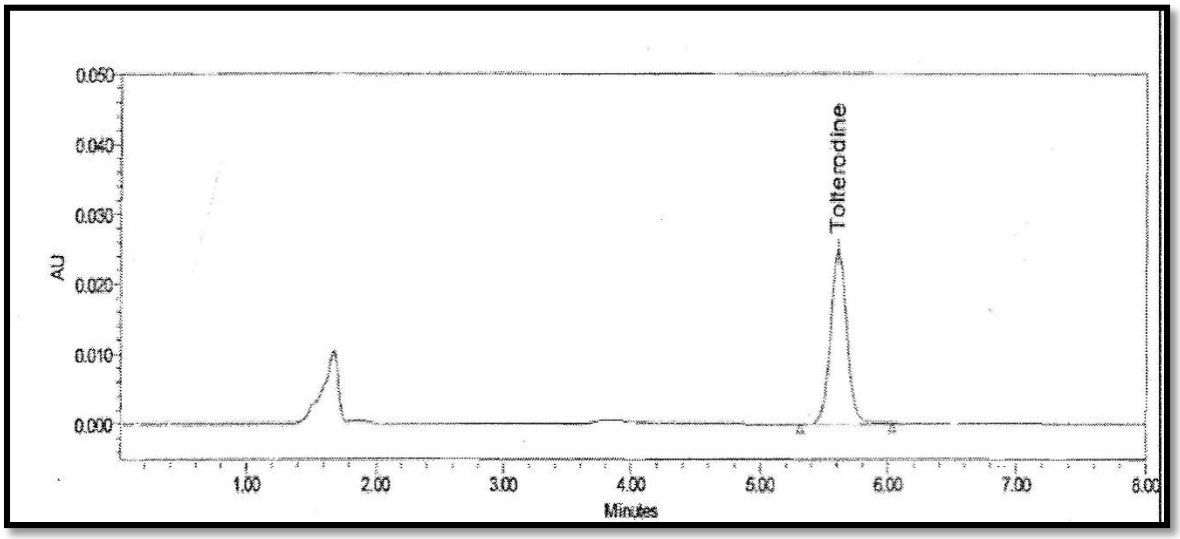
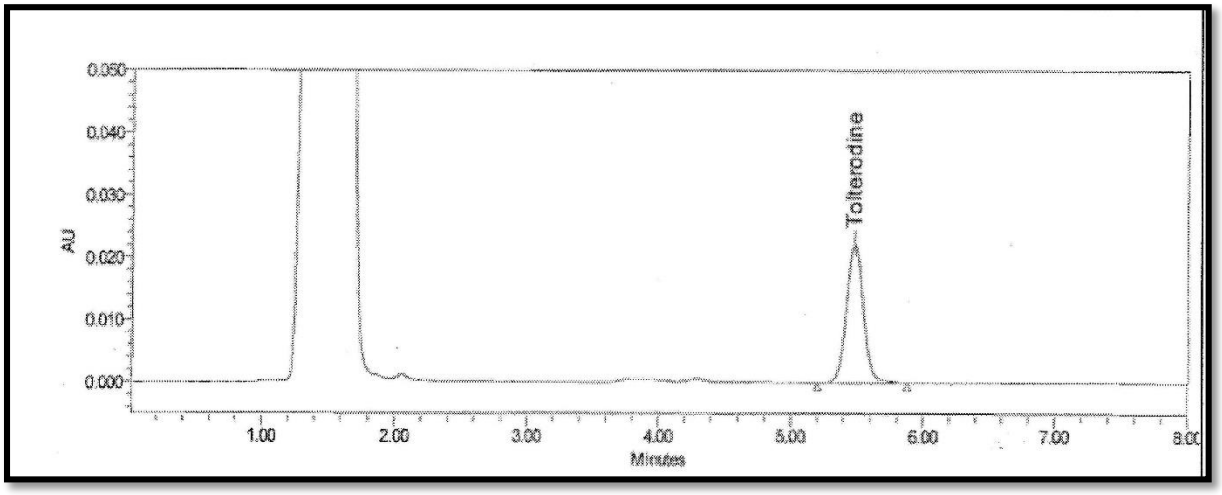


Figure: 4.3 Chromatogram of sample solution of Tolterodine Tartrate



Result:

Table 4.12 Results of Chromatographic Analysis

	Parameter	Result
Standard	Retention Time (RT)	5.61 min
	Area (Response)	219064
Sample	Retention Time (RT)	5.48
	Area (Response)	193943

In both the Chromatogram, the retention time obtained has not much difference, while area response obtained is almost similar. Therefore it was concluded that the API is pure can be used for further investigation.

4.4 Drug-Excipient Compatibility Study

Drug excipients compatibility study was performed to check the compatibility of API with the other excipients in different conditions.

4.4.1 Physical Observation

a. Drug –Excipient Compatibility study at Initial

Table 4.13 Drug-Excipient compatibility study (Initial)

Sr. No.	Material	Ratio	Observation
1.	API alone	-	White crystalline powder
2.	API + All excipients	1:5.5	White blend
3.	API + Sugar spheres	1:5.0	White blend
4.	API + HPMC 6 cps	1:0.1	White blend
5.	API + Opadry OY-29020	1:0.1	White blend
6.	API + Surelease clear E-7-19040	1:1.5	White blend

b. **Packing Details:** Amber coloured glass vials with rubber stopper and aluminium seal
c. **Stoarge Condition:** 40°C/75% RH
d. **Testing Frequency:** Samples charges in stability chamber for 1 month at 40°C/75% RH
e. **Test to be performed:** Physical Observation and related compound (Impurities)

Procedure:

API and excipients were properly homogenized in predetermined ratio and passed through the sieve # 40 and then the blend was filled in amber coloured glass vials which were then closed with gray rubber stoppers and sealed with aluminum seal and kept in to different conditions i.e. initial, open and close. Similarly API was also kept in all conditions as the sample. Samples should be withdrawn for analysis as per the compatibility study plan.

Result & Discussion

Table 4.14 Result of Physical Characterization

Sr. No.	Material	Ratio	Initial Observation	1 month (40°C/75% RH)
1.	API alone	-	White crystalline powder	No Change
2.	API + All excipients	1:5.5	White blend	No Change
3.	API + Sugar spheres	1:5.0	White blend	No Change
4.	API + HPMC 6 cps	1:0.1	White blend	No Change
5.	API + Opadry OY-29020	1:0.1	White blend	No Change
6.	API + Surelease clear E-7-19040	1:1.5	White blend	No Change

Result and Discussion for Physical Characterization:

- Initially, all the samples showed same appearance i.e., white powdery form. Physical observation was done after 1 month for any colour change or lumps formation or any other physical change.
- There was no colour change observed in the API alone in the conditions 40ºC / 75% RH. There was no colour change or lumps formation observed in the samples of API with excipients in the conditions 40ºC / 75% RH.

4.4.2 Detection of Related Impurity (After 1 month)

UI = Unknown Impurity; IMP = Impurity

Table 4.15 Related Impurities for drug-excipient compatibility study

Impurity	API	API + All Excipients	API + Sugar spheres	API + HPMC 6 cps	API + Opadry OY-29020	API + Surelease clear E-7-19040
IMP-1	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
IMP-2	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
IMP-3	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
IMP-4	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
UI-1	0.026	0.028	0.032	0.052	0.017	0.015
UI-2	0.015	0.028	0.015	0.021	0.016	0.019
UI-3	0.021	0028	0.012	0.019	0.013	0.012
UI-4	0.046	-	0.015	0.022	0.041	0.012
UI-5	-	-	0.049	0.043	0.049	0.018
UI-6	-	-	-	-	-	0.022
UI-7	-	-	-	-	-	0.041
Total Unknown impurity	0.108	0.084	0.123	0.157	0.136	0.139
Total known impurity	0	0	0	0	0	0
Total IMP (known + unknown)	0.108	0.084	0.123	0.157	0.136	0.139

Conclusion:

Based on observation in drug-excipient compatibility study, there was no impurity or incompatibility observed with commonly used excipients. Hence, Excipients were proposed to be used in trial.

4.5 Innovator Product Characterization

Innovator: Pfizer (Pharmacia &Upjohns Co., Division of Pfizer Inc, NY, NY 10017)

Strength: 4 mg

Formulation: Capsule (Extended Release Pellets)

Table 4.16 Innovator Characterization

Parameter	Description
Appearance	 
Dosage form	Capsule (Extended Release Pellets)
Capsule Size	3
Lock Length	15.53 ± 2 mm
Weigh of Capsule (Empty)	48 mg
Fill Weight	181 mg
Total Weight	119 mg

4.5.1 Dissolution Profile of Innovator Product in Phosphate Buffer pH 6.8

Dissolution was performed in USP apparatus-I (Basket) at 100 RPM, 900 ml pH 6.8 Phosphate Buffer.

Table 4.17 Dissolution Profile of Innovator Product

Time (Hours)	Cumulative % Drug Release
0	0
1	10
2	27
3	46
4	62
5	74
6	82
7	85
9	88
12	90

Figure 4.4 Dissolution Profile of Innovator Product

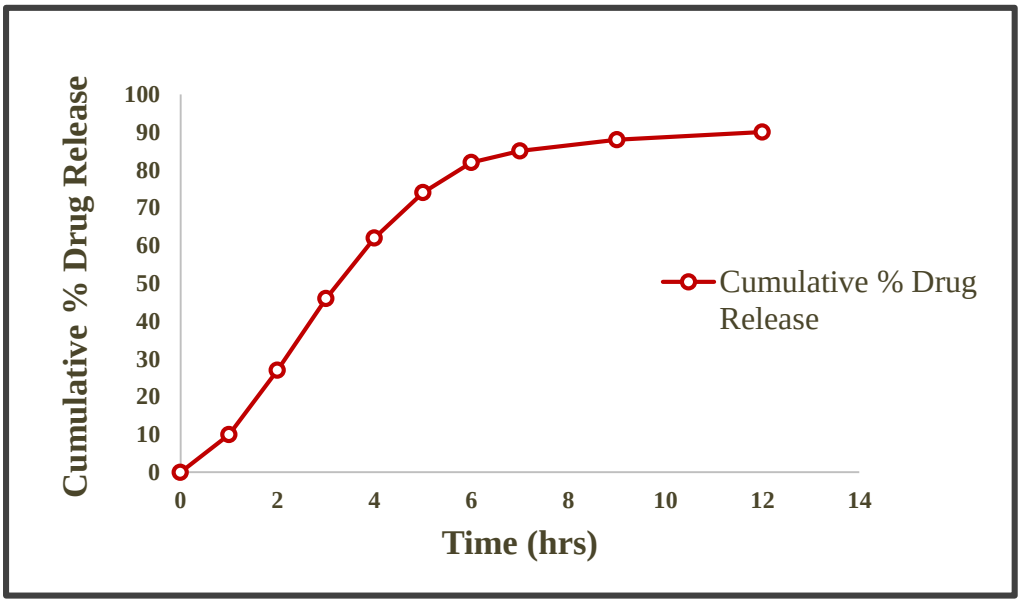
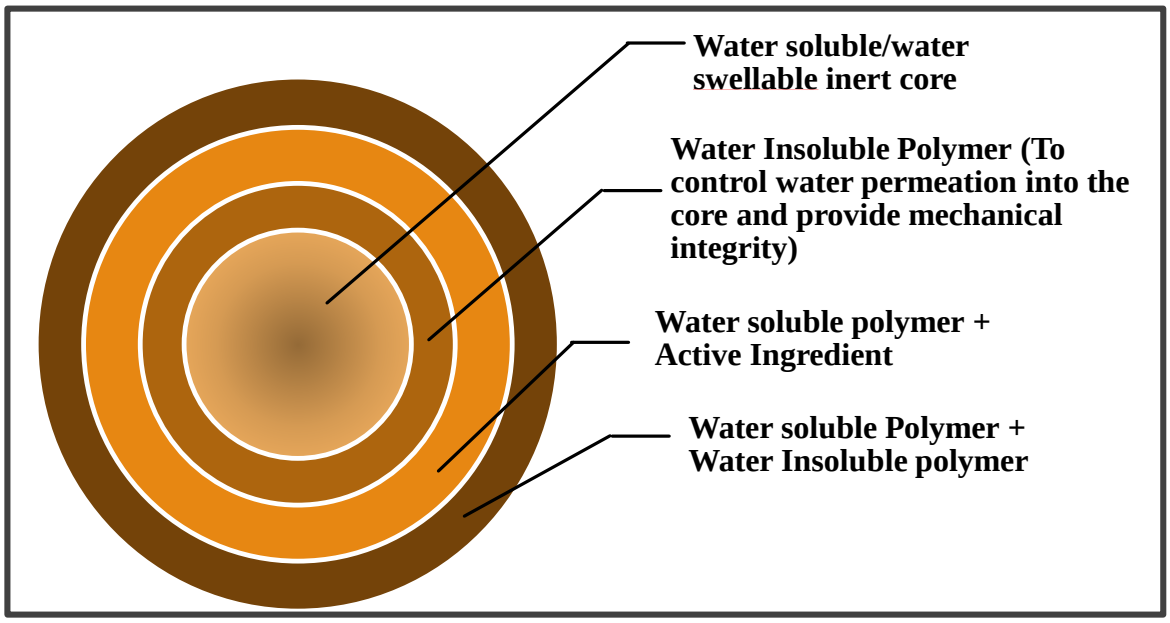


Figure 4.5 Innovator Formulation (According to patents specified in orange-book)



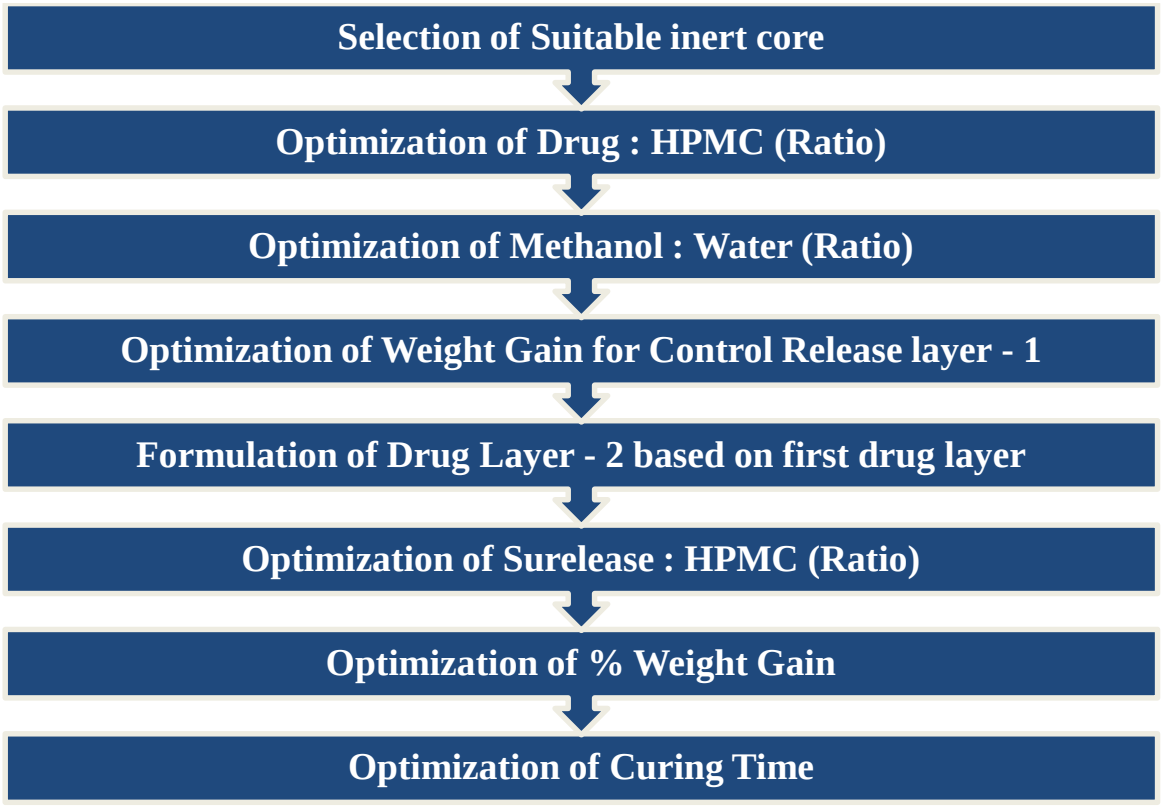
4.6 Bifurcation of Dose in Two drug layers and its Optimisation:

Why Bifurcation?

- Innovator Product shows 90% drug release in 12 hours therefore we cannot show 100% drug release in 12 hours.
- Innovator Product has 100% drug deposited in single drug release layer, therefore we cannot show 100% drug dose in single drug release layer. So the total dose is bifurcated in two release portions i.e., two drug release layers to by-pass the patent (due to patent infringement).
- Here, Drug Layer-1 does not have any in-vivo significance or does not have significant impact on drug release profile (if it is considered for 12 hours).
- Therefore, total dose of drug is bifurcated in two portions, i.e., 5% and 95%.

4.7 Formulation Development Strategy of Tolterodine Tartrate Extended Release Pellets:

Figure 4.6 Formulation Development Strategy



4.8 Selection of Solution Layering Technique over Extrusion Spheronization Technique

- High dose drugs are generally incorporated in matrix pellets via extrusion and spheronization process along with MCC, Lactose or blends of two. This technique allows sufficient high drug loading levels.
- These matrix pellets tend to disintegrate quickly when it comes in contact with medium and thus require an outer polymer film coating in order to obtain control release.
- In case of matrix coated pellets, release controlling polymer can be co-applied with the drug from the same solution or dispersion.
- This approach has disadvantages like higher risk of drug-polymer interaction, fast initial release and incomplete release. Therefore a separate polymer coating subsequent to the drug layering is commonly used, called as "Reservoir Pellets".
- Therefore, potent low dose drugs can be formulated easily by spraying them onto inert starter core in FBP.

4.9 Selection of Suitable Inert Core

Sugar Spheres were selected over any other type of inert cores i.e., MCC starter cores because:

- MCC Spheres are water insoluble.
- It was reported that drugs tends to adsorb on MCC which may slow down the release of drug.
- Sugar dissolves the major constituent (Approx. 75%). Sucrose can be released, thus increasing the volume inside the pellet which can be filled by medium. This could be beneficial to the dissolution of drugs with poor solubility.
- Strong osmotic activity of sucrose starter cores has been reported to cause faster and higher water uptakes, which results in increased tensile stress on membrane. It causes dilution of the drug concentration inside the pellet and potentially the formation of counter current to the outward diffusion of drugs.

- After the sugar is released, the fluid filled spheres could show a high sensitivity to mechanical stress.
- Slower release has also been reported for ethyl cellulose coated sugar pellets, when comparing pellets based on sugar cores with MCC starter cores. This was again explained by faster water uptake in sugar pellets which could act as a counter current to drug diffusion.

4.10 Optimization of Drug Layer – I

- Drug Layering was performed on sugar spheres along with binder. The Rationale of addition of Binder (HPMC) in Drug Solution:
- Here binder is used because drug particles can stick to the starter cores and make a uniform drug coating so that appropriate amount of drug can be loaded on the selected quantity of pellets.
- Binder is not only for sticking the drug onto starter cores but forms spray dried layer through solid drug solution.
- HPMC has been shown to improve wettability, dissolution rate and solubility. It prevents recrystallization and prolongs super-saturation in a wide variety of formulations.
- Using Bottom Spray coater, increased Binder concentration led to slightly improved efficiency but had no effect on drug release.
- Higher aqueous solubility (Here in case of Tolterodine tartrate) usually results in enhanced diffusion through hydrated coating or aqueous channels which is reflected in Fick's law where release rate is directly proportional to drug solubility.
- Two Process Parameters (1) Drug : HPMC (Ratio) and (2) Ratio of Solvent (Methanol : Water) can have direct impact on drug layering of pellets, hence, these two parameters are optimised for getting appropriate drug loading on pellets.

4.10.1 Procedure for Preparation of Drug Layering Solution

- Purified Water was taken in Solution preparation tank and methyl alcohol was added in it and stirred for minimum 2 minutes.
- Then Tolterodine Tartrate was added in prepared solution under stirring condition. Stirred for minimum 15 minutes.
- After that, Hypromellose (Pharmacoat 606) was added in solution under stirring condition, stirred for minimum 45 minutes.
- The solution was filtered through 60# ASTM sieve.
- Sugar Spheres were loaded in the Fluidised Bed Processor (GPCG 1.1) and the process was started. Heater was turned on and after 3 minutes, prepared solution of drug was sprayed on sugar spheres using bottom spray method.
- After Completion of Spray, Curing was performed for 15 minutes at 50°C Inlet Air Temperature.
- Process parameters were maintained and noted throughout the process. The pellets were unloaded from FBP and passed from 30# sieve to remove the agglomerates. Good quality of pellets were collected and % yield was calculated.

Table 4.18 Process Parameters for Drug Layering-I

Coating Parameter	Condition Maintained
Inlet Temperature	40-45ºC
Product Temperature	33-37ºC
Atomization	1-1.5 bar
Blower Drive Speed	65-70 CFM
Pump rpm	7-9 rpm

4.10.2 Optimization of Drug: HPMC (Ratio)

To analyse the effect of Drug: HPMC ratio following batches were prepared.

Table 4.19 Optimization of Drug: HPMC Ratio

Batch No.	**B1**		**B2**		**B3**	
Drug: HPMC (Ratio)	**1:1**		**1:0.5**		**1:1.5**	
Ingredients	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**
Sugar Spheres	140	420	140	420	140	420
Tolterodine tartrate	0.2	0.6	0.2	0.6	0.2	0.6
HPMC 6 cps	0.2	0.6	0.1	0.3	0.3	0.9
Methanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**140.4**	**421.2**	**140.3**	**420.9**	**140.5**	**421.5**

Result & Discussion

Assay and % yield of Batch B1, B2 and B3

Table 4.20 Results of Batch B1, B2 and B3

Batch	**% Yield**	**Assay**
B1	96.293	94.4 ± 2.15
B2	99.311	99.8 ± 1.50
B3	94.678	95.3 ± 2.50

- To determine the effect of Drug to HPMC Ratio, Batches B1, B2 and B3 were prepared and effect was analysed. In case of Batch B1, it has same concentration of Binder as that of drug. Generation of Fines and to some extent doublets were observed which decrease % yield and assay also.

- In case of Batch B3 has higher concentration of binder, tremendous amount of doublets and triplets were generated which showed drastic decrease in %Yield and assay.
- Whereas in Batch B2, having Binder concentration 0.5% that is half of the drug concentration, least amount of agglomerates formed and even spray drying was observed which leads to high and sufficient % yield and assay.
- As Drug: HPMC:: 1: 0.5 was found sufficient for the binding of drug to pellets, Batch B2 was used as optimized batch for further studies.

4.10.3 Optimization of Methanol: Water (Ratio)

- Combination of Methanol and Water is used for preparation Drug Solution as Tolterodine Tartrate is highly soluble in water and methanol.
- Combination of Methanol and water yields a hydro-alcoholic system which enhance the % yields and decrease the loss during processing.
- Methanol: Water (Ratio) was optimised by using different ratio.

Batch Size: 3000 capsules

Solution contains 2.6% solid

Table 4.21 Optimization of Methanol: Water (Ratio)

Batch No.	**B4**		**B5**		**B6**	
Methanol: Water (ratio)	**30:70**		**20:80**		**10:90**	
Ingredients	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**
Sugar Spheres	140	420	140	420	140	420
Tolterodine Tartrate	0.2	0.6	0.2	0.6	0.2	0.6
HPMC 6 cps	0.1	0.3	0.1	0.3	0.1	0.3
Methanol	3.3715	10.1145	2.2476	6.7430	1.1238	3.3715
Water	7.8668	23.6006	8.9907	26.9721	10.1145	30.3436
Total	**140.3**	**420.9**	**140.3**	**420.9**	**140.3**	**420.9**

% Yield of Batch B4, B5 and B6:

Table 4.22 Results of Batch B4, B5 and B6

Batch	% Yield
B4	95.886
B5	99.548
B6	91.803

- To determine the effect of solvent ratio, different batches were prepared and effect was analysed. In case of Batch B6, having higher concentration of organic solvent, sticking of pellets was observed during processing which leads to decrease in % yield. Whereas in case of Batch B4 % B5 less sticking was observed. Comparing the results of Batch B4 & B5, Higher % yield is observed in B5. Therefore, it was concluded to select batch B5 for further studies.

4.11 Optimization of Control Release Layer – I

- After Drug layering-I, It was decided to coat pellets with Control Coat using Ethyl Cellulose as the Ethyl cellulose is water insoluble polymer. For that purpose ready mix pre-plasticized Ethyl Cellulose Dispersion i.e., Surelease was used to get reproducible results.
- To prepare the Dispersion, based on preliminary trials, it was decided to prepare 15% w/w solid dispersion from surelease which is supplied as 25% w/w pre-plasticized ready mix. To make 15% w/w solid dispersion, a quantity of Purified Water was added based on calculation.
- To analyse the effect of coating level (% weight gain) of surelease, different batches were prepared and analysed.

4.11.1 Procedure for preparation of Control Release Coating-I Dispersion

- Ethyl cellulose dispersion type-B (Surelease Clear E-7-19040) was taken in solution preparation tank and Purified water was added under continuous stirring condition using stirrer and stirred for minimum 45 minutes.
- The above prepared solution was filtered through 40# ASTM sieve.
- Pellets were loaded in FBP and spray was started after 3-5 minutes. After
- Completion of spray curing was performed for 60 minutes at 55°C inlet Temperature.

Table 4.23 Process parameters of Control Coating-I

Coating Parameter	Condition maintained
Inlet Temperature	55ºC-60ºC
Product Temperature	40ºC-45ºC
Atomization	1.5-1.8 bar
Blower Drive Speed	60-65 CFM
Pump rpm	7-10 rpm

4.11.2 Optimization of Control Release Layer-I

Batch Size: 3000 Capsules

Coating Solution is 15% w/w

Table 4.24 Optimization of Control Release Layer-I

Batch No.	**B10**		**B11**		**B12**	
% Weight Gain	**12%**		**13%**		**14%**	
Ingredients	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**
Drug Layer-coated Pellets	140.3	420.9	140.3	420.9	140.3	420.9
Surelease Clear	16.836	50.508	18.239	54.717	19.642	58.926
Surelease dispersion	67.344	202.032	72.956	218.868	78.568	235.704
Purified Water	44.896	134.688	48.637	145.911	52.378	157.134
Total	**157.136**	**471.408**	**158.539**	**475.617**	**159.942**	**479.826**

Table 4.24 Optimization of Control Release Layer-I (continue)

Batch No.	**B13**		**B14**	
% Weight Gain	**15%**		**16%**	
Ingredients	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**
Drug Layer- coated Pellets	140.3	420.9	140.3	420.9
Surelease Clear	21.045	63.135	222.448	67.344
Surelease dispersion	84.18	252.54	89.792	269.376
Purified Water	56.12	168.36	59.861	179.583
Total	**161.345**	**484.035**	**162.748**	**488.244**

4.11.3 In-Vitro dissolution studies of Batch B10 to B14

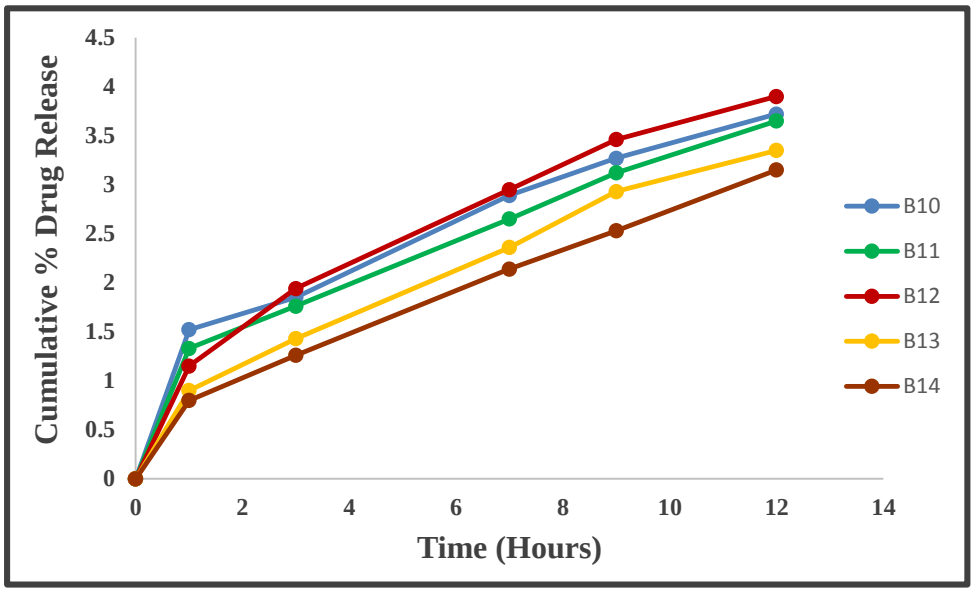
Dissolution Specifications:

- USP Apparatus: I (Basket)
- Speed: 100 RPM
- Medium: Phosphate Buffer pH 6.8

Table 4.25 Cumulative % drug release of D.L.-I & C.R. Layer-I coated Pellets

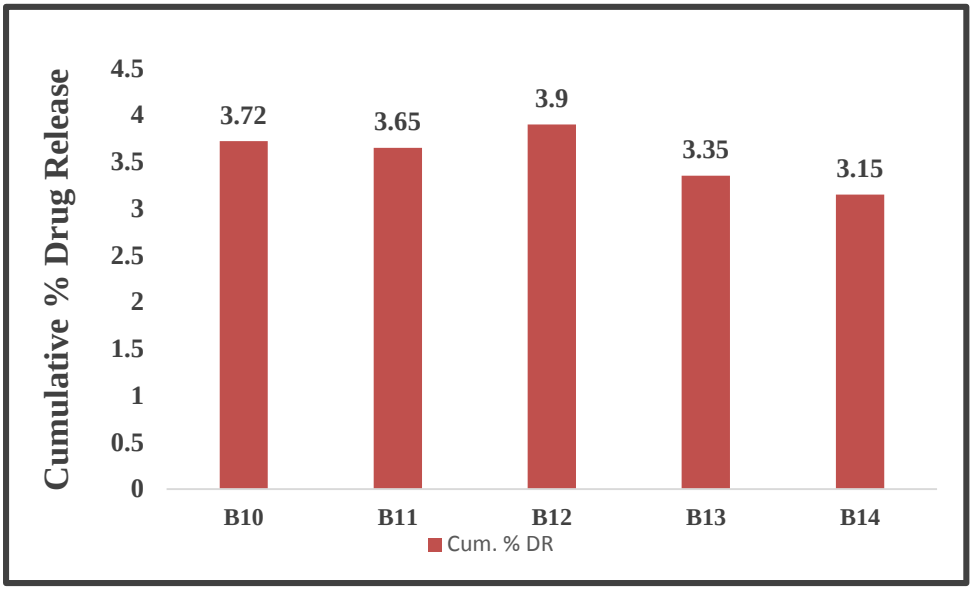
Time (Hours)	Cumulative % Drug Release				
	B10	B11	B12	B13	B14
0	0	0	0	0	0
1	1.52	1.33	1.15	0.9	0.8
3	1.85	1.76	1.94	1.43	1.26
7	2.89	2.65	2.95	2.36	2.14
9	3.27	3.12	3.46	2.93	2.53
12	3.72	3.65	3.9	3.35	3.15

Figure 4.7 Comparative in vitro drug release profile of batches B10 to B14



4.11.4 Result and Discussion:

Figure 4.8 Total % of Drug Release of Batches B10 to B14



- From the In-Vitro Drug release study it was observed that as the % Weight Gain or coating concentration increases, the thickness of control release layer increases, which reduce the % drug release.
- Batch B10 and B11 showed faster drug release profiles as compared to batches B12, B13 and B14. B10 and B11 releases drug upto 3.75% and 3.65 respectively which in turn showed more % drug released in 12 hours than B13 and B14.
- Batch B13 and B14 showed slower release profiles i.e., less than 2.5% in 12 hours. Moreover Cum. % Drug release is much less as compared to B10, B11 and B12.
- Batch B12 showed maximum drug release upto 3.9% which is optimum (slower than B10 & B11 and faster than B12 & B13) amongst all the batches. Comparing the results of all the batches, higher % drug release was observed in B12 so it was concluded to select B12 for the further studies.

4.12 Formulation of Drug Layer – II (95%) based on Drug Layer-I

- Drug Layering-II was performed on C.R.-I coated pellets. After control release-I coat, the optimized batch was used for the further investigation and subjected to drug layering-II.
- Drug: HPMC (Ratio) was kept same i.e., 1:0.5 and Methanol: Water was also kept same as optimized in D.L.-I i.e., 20:80.

4.12.1 Procedure for the preparation of Drug Layering solution

- Purified Water was taken in Solution preparation tank and methyl alcohol was added in it and stirred for minimum 2 minutes. Then Tolterodine Tartrate was added in prepared solution under stirring condition. Stirred for minimum 15 minutes.
- Then, Hypromellose (Pharmacoat 606) was added in solution under stirring condition, stirred for minimum 45 minutes.
- The solution was filtered through 60# ASTM sieve and sprayed on C.R.-I coated pellets.
- After completion of spray, curing was performed for 15 minutes at 50°C Inlet Temperature.

Table 4.26 Process Parameter for formulation of Drug Layer-II

Coating Parameters	Conditions maintained
Inlet Temperature	40ºC-50ºC
Product Temperature	30ºC-35ºC
Atomization	1-1.5 bar
Blower Drive Speed	60-65 CFM
Pump RPM	10-15 rpm

Batch Size: 3000 Capsules

Solution contains 2.6% Solid

Table 4.27 Formulation of D.L-II Coated pellets

Ingredients	95% of Total Dose	
	mg/capsule	gm/batch
C.R.-I coated pellets	159.942	479.826
Tolterodine tartrate	3.8	11.4
HPMC 6 cps	1.9	5.7
Methanol (20%)	42.706	128.118
Water (80%)	170.824	512.472
Total	**165.642**	**496.926**

% Yield and Assay results of the Drug layered-II pellets are as follows:

Table 4.28 Results of D.L.-II coated pellets

Parameter	Result
% Yield	98.686
Assay	99.5 ± 1.3

The results were found satisfactory and the batch was used for further investigation.

4.13 Optimization of Control Release Layer – II

- Control Release Coating-II was performed on Drug Layered-II pellets. As the Surelease was selected as coating agent and HPMC was added as a pore forming agent.
- Ethylcellulose (EC) is a commonly used barrier membrane for achieving extended release with multiparticulate formulations. Desired Drug Release profile can be achieved using hydrophilic polymers along with pore forming agent. Hypromellose (HPMC) is commonly used as a pore former in EC barrier films.
- Two Process Parameters (1) Surelease : HPMC (Ratio) and (2) % weight Gain can have direct impact on functional coating of pellets, hence, these two parameters were optimised for getting appropriate drug release profile.
- From the literature, it was found that at low coating level, drug release occurs through pores in the coating while at higher coating levels, drug release rate was controlled by diffusion through the coating. Also, higher aqueous solubility of drug results in enhanced diffusion through hydrated coatings or aqueous channels.

4.13.1 What is Surelease?

- Surelease is a composition of film forming Polymer, Plasticizer and Stabilizer; available in 25% w/w solid content. From the literature, it was found that for best results, it is diluted to 15% w/w solid.
- Surelease is formulated with oleic acid (OA) or in combination with medium chain triglycerides (OA-MCT) or dibutylsebacate (OA-DBS) as plasticizer.
- It is used primarily as a barrier membrane **for developing extended release dosage forms.**
- Drug Release is primarily by diffusion through surelease semipermeable membrane. And the rate of drug release can be modified by increasing or decreasing the amount of surelease applied.
- Release profiles are controlled by surelease film thickness and are found to follow “Fick’s law of diffusion”.

- The shelf life of surelease is 18 months and due to high pH, addition of lake colours should be avoided.

4.13.1.1 Key characteristics of Surelease:

- Aqueous Dispersion, Independent of pH
- Easy to use and environment friendly
- Consistent and reproducible drug release profile
- FBD is preferred technique
- Regulatory acceptance in the United States, Europe and certain other regions

Table 4.29 Surelease Composition:

Ingredients	% w/w
Purified Water	70.600
Ethyl Cellulose 20 cps	18.800
Ammonium Hydroxide 28%	4.400
Medium Chain Triglycerides	4.000
Oleic Acid	2.200

4.13.2 Procedure for the preparation of Coating Dispersion for Control Release Coating-II

- Purified Water was taken in to solution preparation tank and HPMC was added in it under continuous slow stirring condition using stirrer, stirred for minimum 45-50 minutes.
- After preparation of HPMC solution, it was transferred to the solution preparation tank containing Ethyl Cellulose Dispersion (Surelease Clear) under continuous slow stirring condition using stirrer, and stirred for 45-50 minutes.
- After Stirring, the prepared solution was filtered through 40# ASTM Sieve.

Table 4.30 Parameters for C.R. Coating-II

Coating Parameters	Conditions maintained
Inlet Temperature	55ºC-60ºC
Product Temperature	40ºC-45ºC
Atomization	1.5-1.8 bar
Blower Drive Speed	60-65 CFM
Pump RPM	7-10 rpm

4.13.3 Optimization of Surelease: HPMC (Ratio) in Control Release Layer –II

- To determine the effect of Surelease: HPMC, batch B15 was performed with surelease: HPMC :: 90:10 at 15% weight gain.

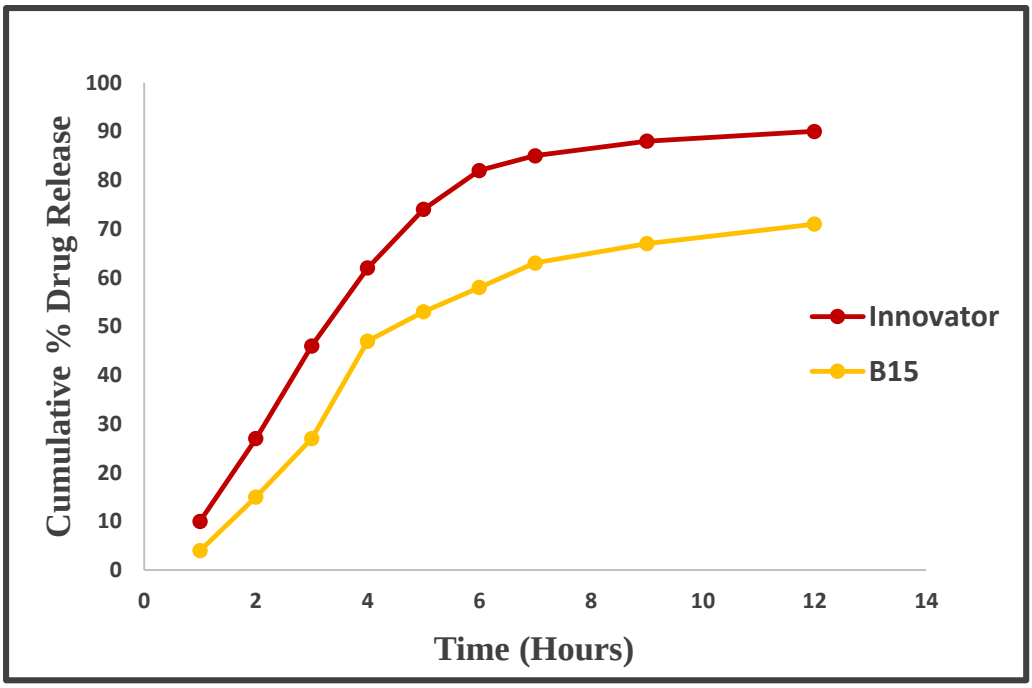
Table 4.31 Formula of Batch B15 (Optimization)

Batch: B15	Surelease: HPMC :: 90:10	
	15% weight gain	
Ingredients	**mg/cap**	**gm/batch**
D.L. – 2 coated pellets	165.642	496.926
Surelease Clear	22.3616	67.0848
Surelease Dispersion	89.4466	268.3398
HPMC 6 cps	2.4846	7.4538
P.Water	73.7107	221.1321
Total	**190.4883**	**571.4646**

Table 4.32 In-Vitro Drug Release Study of Batch B15

Time (Hours)	Cumulative % Drug Release
0	0
1	4
2	15
3	27
4	47
5	53
6	58
7	63
9	67
12	71

Figure 4.9 Cumulative % Drug Release of Batch B15



- From the In-vitro drug release study of Batch B15, It was observed that only 71% drug was released in 12 hours which was much slower as compared to innovator.

- From the results it was concluded that higher concentration of coating agent i.e., surelease: HPMC :: 90:10 at 15% weight gain retard the drug release and slow down the dissolution.
- As the B15 doesn't match the release profile of innovator, It was decided to decrease the ratio of Surelease: HPMC as well as % weight build-up to match the innovator profile.
- Therefore, another batch was performed with relatively lesser concentration of coating agent and % weight gain.

4.13.4 Optimization of Surelease: HPMC Ratio by keeping % Weight Build-up Constant

Batch B16, B17 & B18 at Constant (13%) Weight Gain

- To analyse the effect of Surelease: HPMC, different batches were prepared using different ratio keeping 13% weight gain constant.
- As the Surelease : HPMC Ratio was decided to decrease, Batches B16,B17 and B18 were prepared consisting Surelease : HPMC 87:13, 86:14 and 84:16 respectively.

Table 4.33 Formula of Batch B16 and B17 (Optimization)

Batch No.	**B16**		**B17**	
Surelease: HPMC	**87:13**		**86:14**	
Ingredients	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**
D.L.-II Coated Pellets	165.642	496.926	165.642	496.926
Surelease Clear	18.7341	56.2023	18.5187	55.5561
Surelease Dispersion	74.9364	224.8092	74.0748	222.2244
HPMC 6 cps	4.5220	13.566	3.01467	9.0441
Purified Water	65.8203	197.4609	66.4665	199.3989
Total	**187.1754**	**566.6943**	**187.1754**	**561.5262**

Table 4.33 Formula of Batch B16 and B17 (Optimization)

Batch No.	**B16**	
Surelease: HPMC	**87:13**	
Ingredients	**mg/cap**	**gm/batch**
D.L.-II Coated Pellets	165.642	496.926
Surelease Clear	18.0881	54.2643
Surelease Dispersion	72.3524	217.0572
HPMC 6 cps	3.4453	10.3359
Purified Water	67.7583	203.2749
Total	**187.1754**	**561.5262**

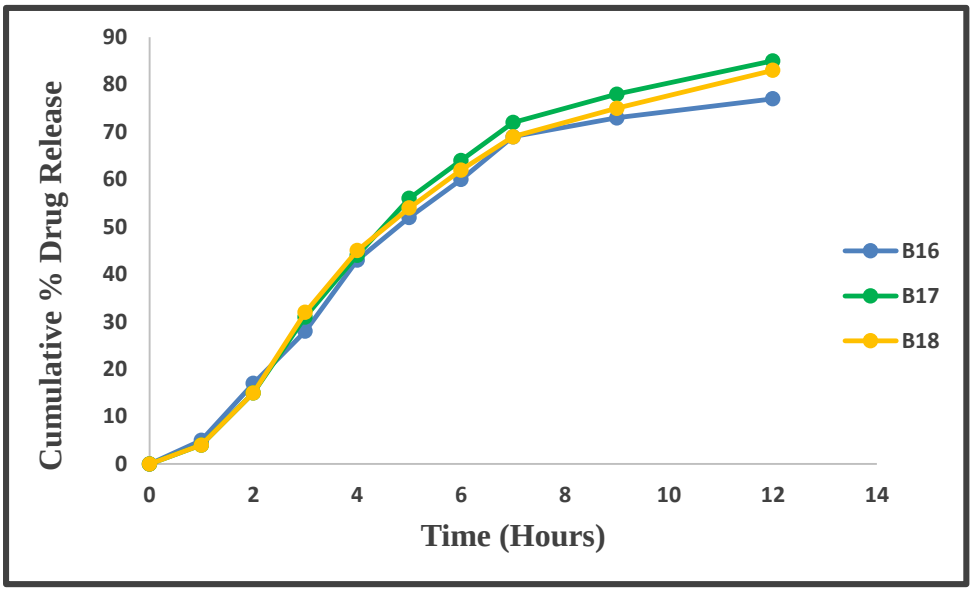
All the three batches were subjected to in-vitro drug release study in order to determine the amount of drug released in desired period of time.

4.13.4.1 In-Vitro Drug Release Study of Batch B16, B17 & B18

Table 4.34 In-Vitro Drug Release Study of Batch B16, B17 & B18

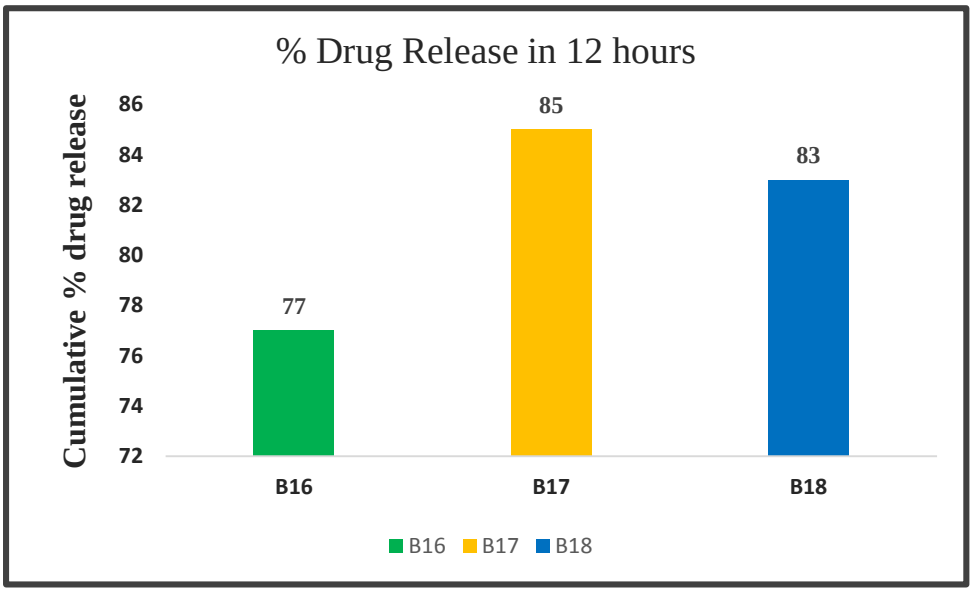
Time (Hours)	**Cumulative % Drug Release**		
	B16	**B17**	**B18**
0	0	0	0
1	5	4	4
2	17	15	15
3	28	31	32
4	43	44	45
5	52	54	56
6	60	64	62
7	69	72	69
9	73	78	75
12	77	85	83

Figure 4.10 Cumulative % Drug Release of Batch B16, B17 and B18



4.13.4.2 Result & Discussion

Figure 4.11 Total % of Drug Release of Batches B16, B17 and B18



- From the in-vitro drug release study of batch B16, B17 and B18 it was observed that B16 releases only 77% of drug in 12 hours which is much less as compared to the innovator product. While B18 releases 83% of drug in 12

hours upto satisfactory level but still less as compared to the innovator product.

- Batch B17 showed optimum drug release as compared to B16 and B18 i.e., 85%. But all the three batches showed comparatively slower drug release. Here, at 6 hours' time point all the batches releases approximately 60% drug. While innovator product releases 80% drug at 6 hours' time point.
- Therefore, in order to match the dissolution profile it was decided to decrease the % weight build-up and analyse the effect of it on % Drug Release. For the further studies, it was decided to select the batch B17 (having surelease: HPMC:: 86:14) as it showed 85% drug release which is comparatively optimum.

4.13.5 Optimization of % Weight Gain by keeping Surelease : HPMC (Ratio) 86:14 constant

- To analyse the effect of % Weight Gain on drug release, different batches were prepared having 12%, 11%,10% and 9% Weight Gain respectively.
  The following table contains the formula of all the batches.

Table 4.35 Formula of Batch B19 and B20 (Optimization)

Batch No.	**B19**		**B20**	
Surelease: HPMC	**86:14**		**86:14**	
% Weight Gain	**12%**		**11%**	
Ingredients	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**
D.L.-II Coated Pellets	165.642	496.926	165.642	496.926
Surelease Clear	17.0942	51.2826	15.6697	47.009
Surelease Dispersion	68.3774	205.131	66.6789	200.036
HPMC 6 cps	2.7827	8.3481	2.5508	7.6524
Purified Water	61.3563	184.0689	56.241	168.723
Total	**185.5190**	**556.5567**	**183.8626**	**551.5874**

Table 4.36 Formula of Batch B21 and B22 (Optimization)

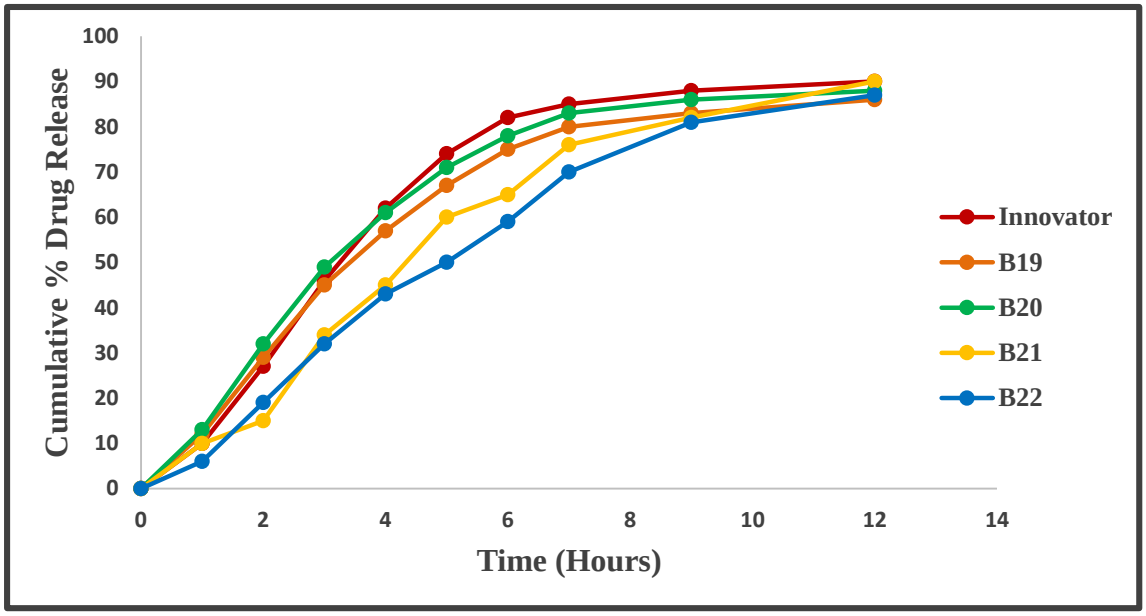
Batch No.	B21		B22	
Surelease: HPMC	86:14		86:14	
% Weight Gain	10%		9%	
Ingredients	**mg/cap**	**gm/batch**	**mg/cap**	**gm/batch**
D.L.-II Coated Pellets	165.642	496.926	165.642	496.926
Surelease Clear	14.2452	42.7356	12.8206	38.4618
Surelease Dispersion	56.9808	170.9424	51.2827	153.8481
HPMC 6 cps	2.3189	6.9569	2.0870	6.261
Purified Water	51.1282	153.3846	46.0154	138.0462
Total	**182.2062**	**546.6185**	**18.5497**	**541.6488**

4.13.5.1 In-Vitro Drug Release Study of Batch B19, B20, B21 & B22

Table 4.37 In-Vitro drug release study of Batches B19, B20, B21 and B22

Time (Hours)	B19	B20	B21	B22
0	0	0	0	0
1	12	13	10	6
2	29	32	15	19
3	45	49	34	32
4	57	61	45	43
5	67	71	60	50
6	75	78	65	59
7	80	83	76	70
9	83	86	82	81
12	86	88	90	87

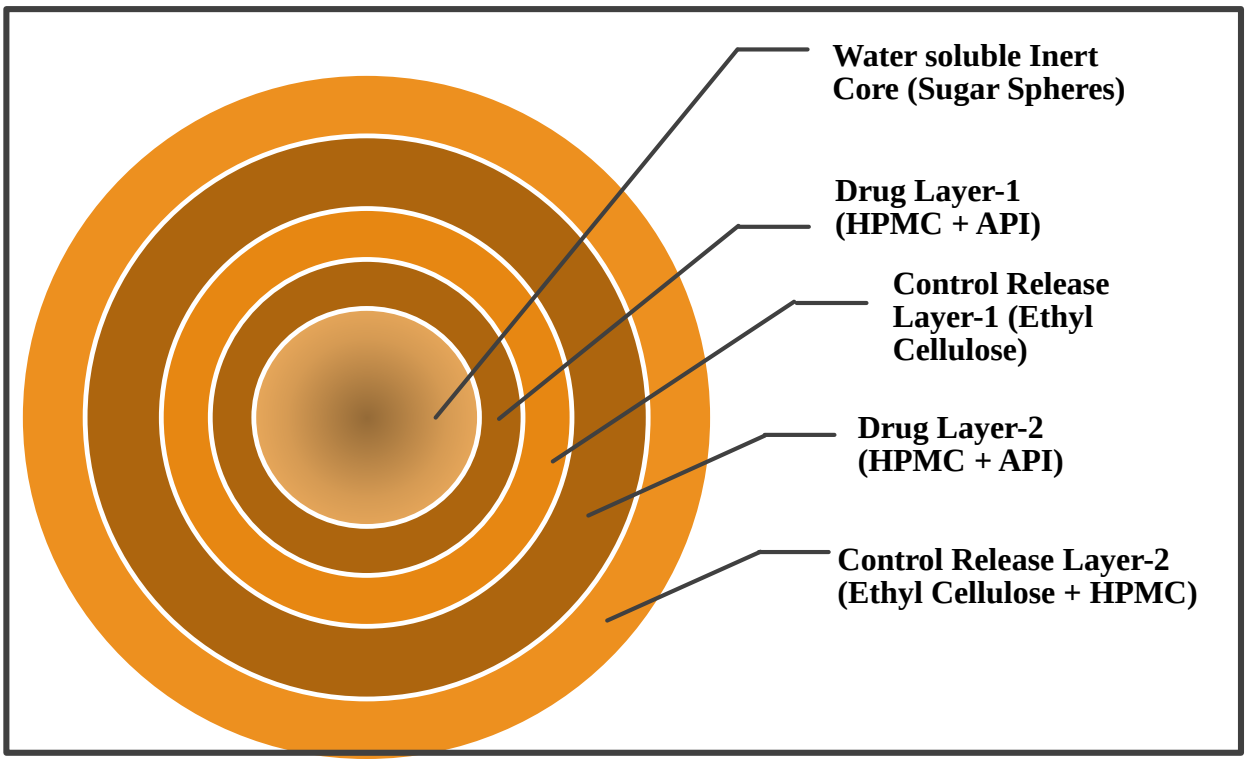
Figure 4.12 Comparative In-vitro drug release profile of Batches B19, B20, B21 and B22 with Innovator Product



4.13.5.2 Result and Discussion

- From the in-vitro drug release study of all the batches, it was observed that % weight build-up has direct impact on drug release. As the % weight gain decreases, drug release becomes faster.
- Here, all the batches showed more than 85% Drug Release. From the chart, it was observed that batch B21 and B22 released 90% and 87% of drug respectively but comparatively slower release profiles. whereas Batch B19 and B20 released 86% and 88% of drug respectively.
- It was clear from the chart that batch B20 has maximum similarity with that of innovator profile. Therefore, it was decided to select batch B20 as final optimized formula having surelease: HPMC ::86:14 at 13% weight gain.

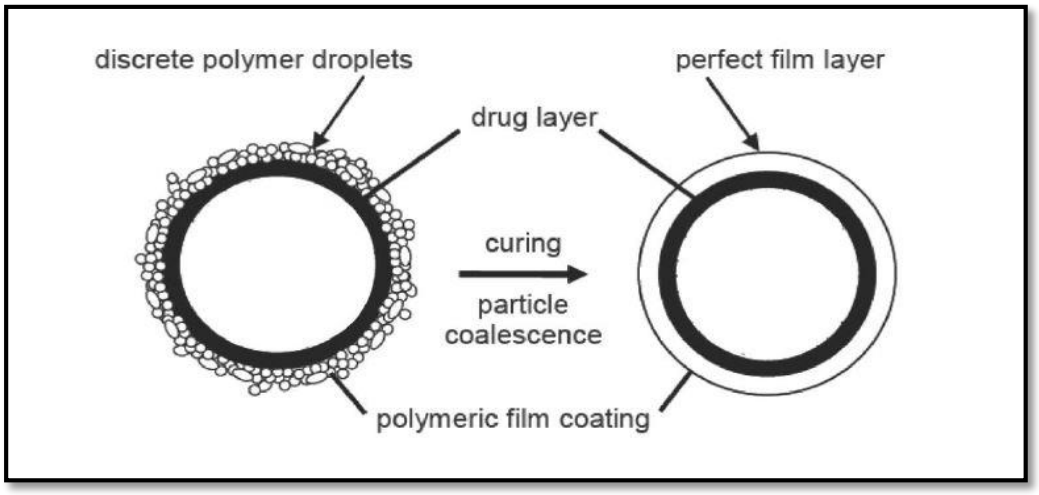
Figure 4.13 Proposed Formulation



4.14 Optimization of Curing Time – Effect of Curing

- After coating process a short thermal treatment is given to the product so that complete film formation can be achieved.
- The temperature of curing higher than glass transition temperature mobility of polymer increases in chain form and then latex coalescence enhances.

Figure 4.14 Effect of Curing and Curing Time



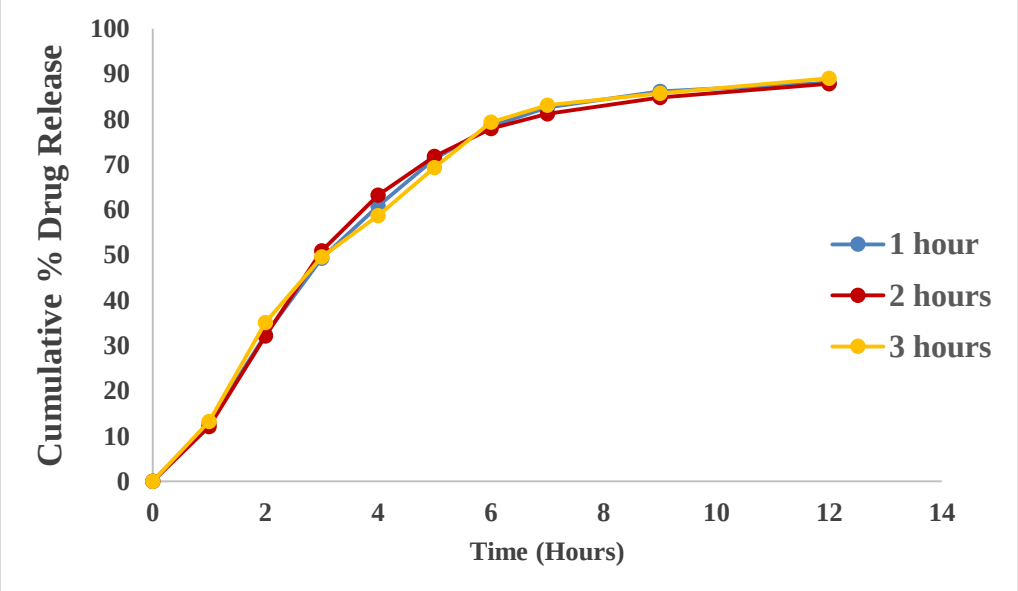
- The curing step may be performed in an oven or in the fluidized bed coater immediately after the coating process.
- Lower curing temperatures leads incomplete film formation, whereas too high temperatures can lead to tackiness and agglomeration.
- The curing step can be performed at several temperatures or different times and in the presence of controlled humidity. All these factors can potentially affect drug release rate.
- Therefore to analyse the effect of curing time on Drug Release, Final Optimized formulation was subjected to curing for different time i.e., 1 hour, 2 hours and 3 hours. The effect of curing time on drug release was analysed.
- In order to evaluate the effect of duration of curing on drug release characteristics, Extended Release pellets were exposed to the temperature 55°C for 1 hour, 2 hours and 3 hours.

Table 4.38 In-Vitro drug release study for the optimization of Curing Time

Time (Hours)	Cumulative % Drug Release		
	1 hour	2 hours	3 hours
0	0	0	0
1	13	12	13
2	32	32	35
3	49	51	48
4	61	63	59
5	71	72	69
6	78	78	79
7	83	81	83
9	86	85	86
12	88	88	89

4.14.1 Result and Discussion

Figure: 4.15 comparative in vitro drug release profile for all the three batches



From the in-vitro drug release study it was observed that there is no significant difference in dissolution of all the three batches upto 3 hours. Therefore minimum curing Time i.e. 1 hour was finalized.

4.15 Drug Release Mechanism

- Drug release mechanism from EthylCellulose coatings with pore formers was investigated by many researchers.
- At lower pore former content (HPMC) contents, drug release occurred through osmotic pumping, but above a certain value diffusion also contributed to overall drug release.
- Addition of small amounts of polyvinyl alcohol-polyethylene glycol graft copolymer to ethylcellulose coatings was found to control drug release from coated pellets irrespective of the drug solubility and type of core formulation.
- The mechanism controlling drug release was shown to be diffusion through intact polymeric membranes.

4.15.1 How the Drug Release from Reservoir Pellets takes place?

- Media is taken up by pellets. Soluble components like drug, binder and sucrose starter cores are dissolved and then released from the pellet across the barrier of polymer coating.
- For pellets coated with insoluble film (here surelease), different “Passage Ways” are generated Following concentration gradient. Drug diffuses through Channels made by Plasticizers or Pore formers.
- Diffusion through intact polymer is often described quantitatively by applying Fick’s Law to Coated System.

4.16 Formulation of extended Release Pellets

- Based on preliminary trials, the optimised coating level (% Weight build-up) of control Release coat-I and Control Release Coat-II are 14% and 11% respectively. In Drug Layer, optimized Drug: HPMC is 1:0.5 and Methanol: Water is 20:80.
- In Functional Coat (C.R.-II), the optimized Surelease: HPMC is 86:14 and % Weight gain (coating level) is 11%.
- Following is the final optimized formula of Extended Release Pellets.

Table 4.39 Final Formulation of Optimized Batch

Ingredients	mg/capsule	gm/batch
Sugar Spheres	140	420
Drug Layer-I (5%)		
Tolterodine tartrate	0.2	0.6
HPMC 6 cps	0.1	0.3
Methanol (20%)	2.2476	6.7430
Water (80%)	8.9907	26.9721
Control Coat-I (14%)		
Surelease Clear	19.642	58.926
Surelease Dispersion	78.568	235.704
Purified Water	52.378	157134
Drug Layer-II (95%)		
Tolterodine tartrate	3.8	11.4
HPMC 6 cps	1.9	5.7
Methanol (20%)	42.706	128.118
Water (80%)	170.824	512.472
Control Coat-II (11%) – Functional Coat		
Surelease Clear	15.6697	47.009
Surelease Dispersion	66.6789	200036
HPMC 6 cps	2.5508	7.6524
Purified Water	56.241	168.723
Total	183.8626	551.5874

4.17 Evaluation of Optimized Extended Release Multi Unit Pellet System

- ❖ Physical Description: Prepared Extended Release pellets were evaluated for their shape, colour, physical description etc.
- ➢ Shape: Spherical
- ➢ Colour: pale yellow to off-white
- ❖ Density : The density of pellets was measured by USP-I auto tapped density apparatus.
- ➢ Bulk Density: 0.8 g/ml
- ➢ Tapped Density: 0.8695 (500 tappings); 0.9523 (750 tappings)

Figure: 4.16 (a) & (b) Photographs of ER pellets of optimized Batch

- ❖ Scanning Electron Microscopy Study: Scanning Electron Microscopy was performed to obtain a visual assessment of pellets before filling it into a capsule. Photographs of pellets of final optimized batch i.e., B20 were obtained using scanning electron microscope.

SEM analysis of Whole Pellet

Figure: 4.17 SEM Photograph of Whole Pellets

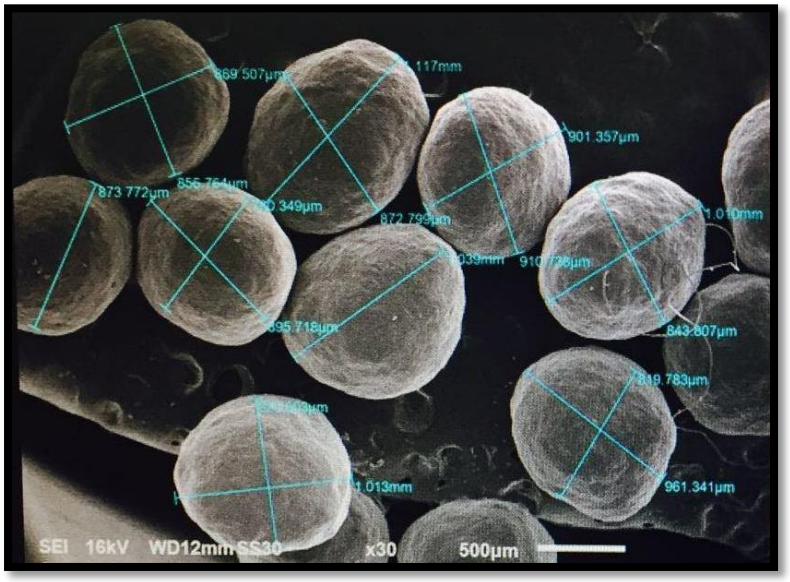
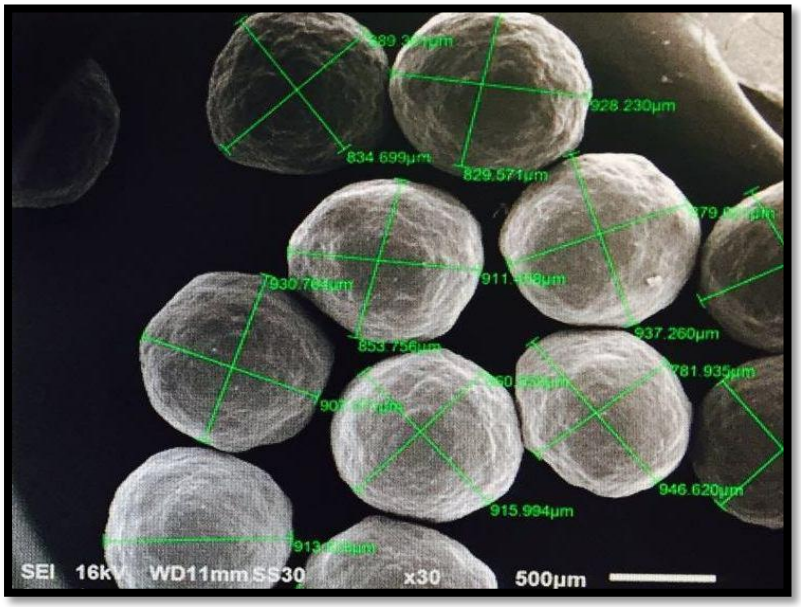


Figure: 4.18 SEM Photograph of Whole Pellets



SEM analysis of cross section of pellet

Figure: 4.19 SEM Photograph of cross section of pellet

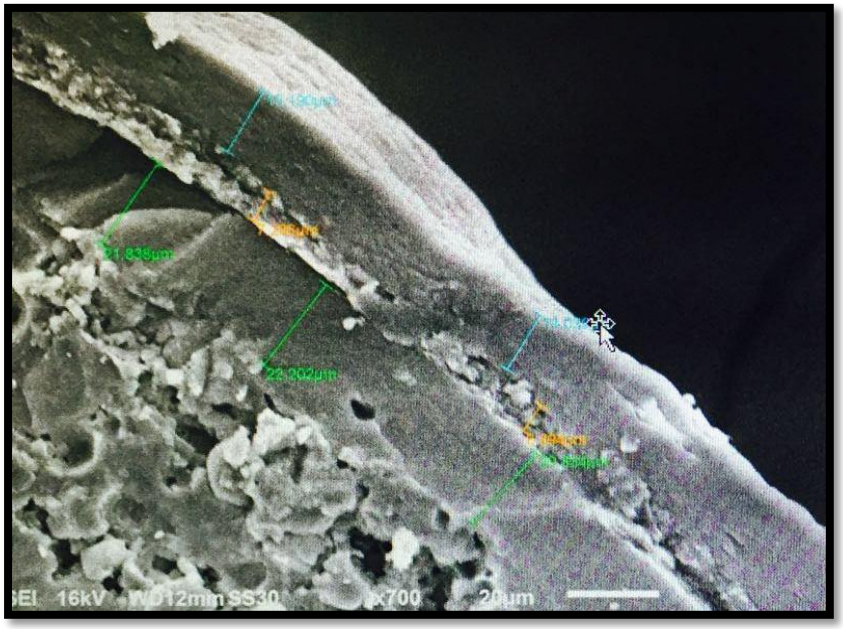


Figure: 4.20 SEM Photograph of cross section of pellet

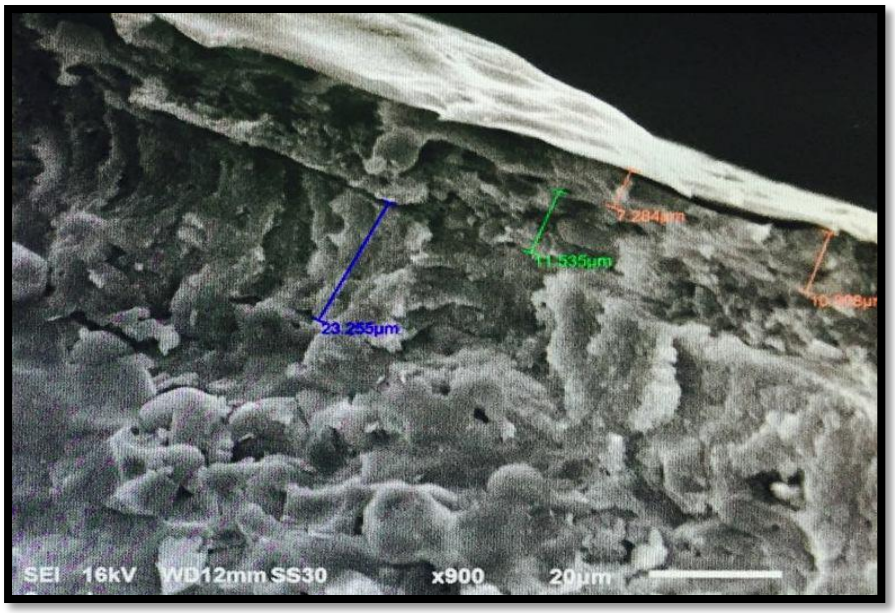
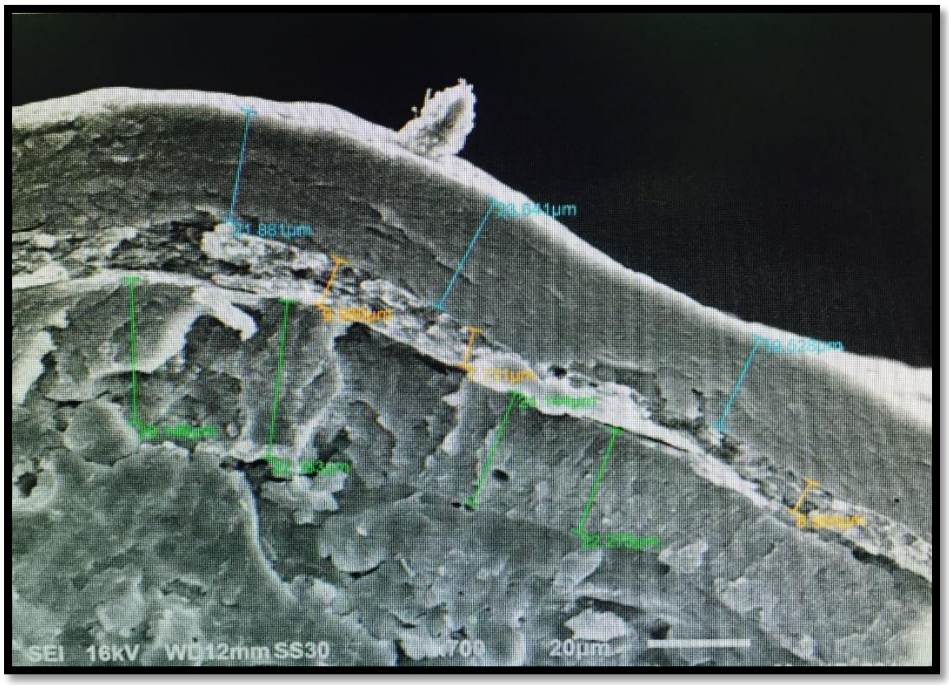


Figure: 4.21 SEM Photograph of cross section of pellet



SEM photographs of coated pellets reads all the four different layers coated on the sugar sphere clearly, which were observed with their individual thickness in the cross section of functional coated pellets.

- **Sphericity of Pellets :**

Aspect Ratio represents the sphericity of pellet and also its flow property. Aspect ratio should be near to one or less than one for the best results. Aspect Ratio can be calculated from the following formula:

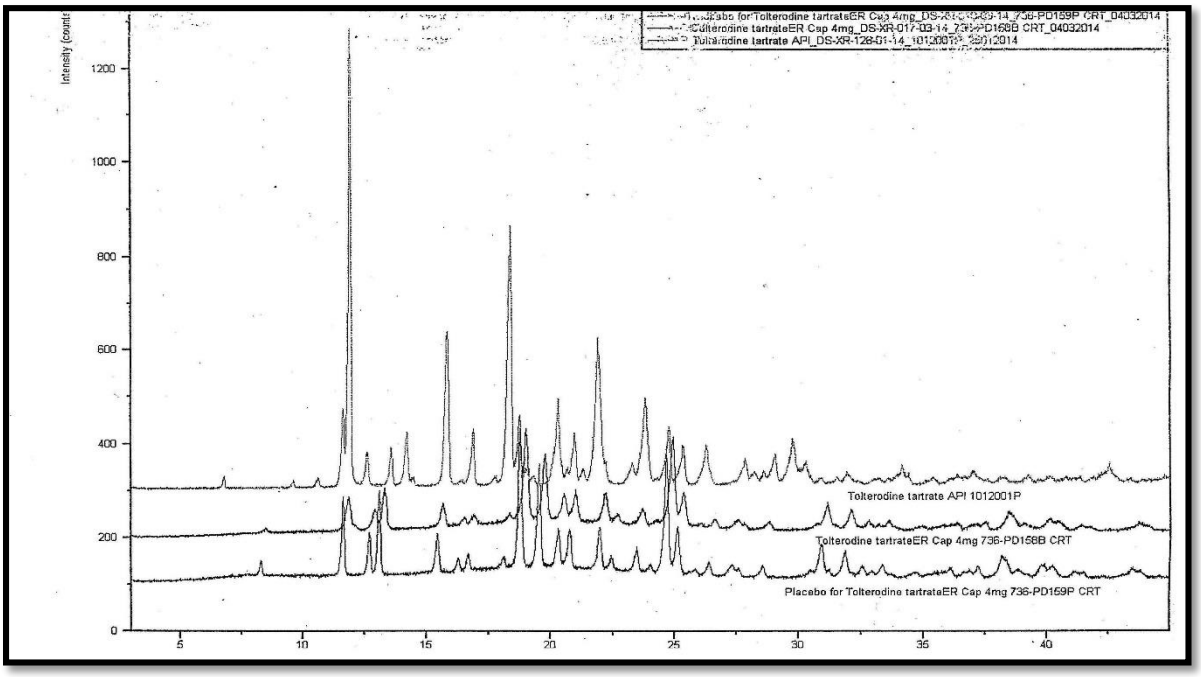
Aspect ratio = Length of the pellet / Width of the pellet

Result: As the aspect ratio was found to be 1.05, it can be concluded that the developed multiparticulate system possess spherical shape.

4.18 X-Ray Diffraction Analysis

XRD/XRPD analysis is powerful tool to identify the phase of crystalline material and can provide information based on unit cell dimension. For X-Ray Diffraction, the material to be analysed is finely ground, homogenized and bulk composition is determined. Results are commonly obtained as peak positions at 2θ and X-ray counts (intensity) in the form of a table or an x-y plot. Intensity (I) is either reported as peak height intensity, that intensity above background, or as integrated intensity, the area under the peak. The relative intensity is recorded as the ratio of the peak intensity to that of the most intense peak.

Figure 4.22 XRD Analysis of Pure API, Optimized Formulation and Placebo



Conclusion:

From the XRD analysis it was observed that the intensity of peaks obtained in API were changed in case of XRD-graph of formulation. Hence it was concluded that crystalline form of Drug was changed and assumed to be transformed into any other form and also the solubility was assumed to be enhanced.

4.19 Evaluation of Capsules filled with optimized Extended Release Pellets

Capsules filled with pellets were evaluated for the following parameters.

Physical Characterization

Appearance: Each capsule was evaluated for denting problem.

Lock Length: The Lock Length of capsules was determined using digital Vernier calipers.

Content Uniformity of capsules: The content uniformity test was done to check the uniform distribution of the API in the batch. The test was done by determining the content for 10 capsules. Each capsule was weighed individually and then content was removed; emptied shells were also weighed accurately. The net weight was estimated by subtracting the weight of empty shell from respective original total weight of capsule. The drug content was determined by result of assay of individual capsule.

Table 4.40 Content Uniformity of the optimized formulation

Unit	% Content
1	101.9
2	102.4
3	100.9
4	100.7
5	100.2
6	100.7
7	101.2
8	101.6
9	100.5
10	101.4
Mean	**101.2**
Min	100.2
Max	102.4
SD	0.6819
RSD	0.7

Table 4.41Result of Physical Characterization of Capsules

Test	Result
Capsule Size	3
Weight of Capsule (Empty)	48 mg
Fill Weight	183.86 mg
Average Weight	231.86 mg
Average Lock Length	15.53 ± 2 mm
Content Uniformity	99 ± 2.05

Conclusion: Capsules filled with ER pellets of tolterodine tartrate were evaluated successfully.

4.20 Release Kinetics of the Optimized Batch[51–55]

To determine the release mechanism of optimized formulation, different kinetic models were tested such as zero order, first order, Higuchi model, Hixson-Crowell model, Korsmeyer - Peppas model and Weibull model.

Release Kinetics was determined by using following equations of different models. The data was processed for regression analysis and interpretation of data was based on the value of resulting correlation coefficients.

Zero Order **$Q_t = Q_0 + K_0 t$** Q_t = Amount of drug released at time t K_0 = Apparent diffusion rate constant or zero order release constant Q_0 = Initial concentration of drug in the solution resulting from burst effect
First Order **$\ln Q_t = \ln Q_0 + K_1 t$** Q_t= Amount of drug released at time t Q_0= Initial concentration of drug in the dosage form K_1 = First order release constant
Higuchi Model **$Q_t = K_H \times t^{1/2}$** Q_t= Amount of drug released at time t K_H = Higuchi release rate constant
Hixon – Crowell Model **$Q_0^{1/3} - Q_t^{1/3} = K_s t$** Q_0 = Initial concentration of drug in the dosage form. Q_t = Amount of drug remaining in the dosage form at time t K_s = Constant incorporating the surface or volume relationship
Weibull Model **$\text{Log}\,[-\ln(1-(Q_t/Q_\infty)] = \beta \times \log(t - Ti) - \log a$** a = Scale parameter that defines the time dependence

Ti = lag time of onset of the diffusion or release process which in most cases will be zero β = Shape of the dissolution curve progression
Korsmeyer – Peppas Model **$Q_t / Q_\infty = Kt^n$** K = Constant incorporating structural and geometric characteristic of the drug dosage form n = Release exponent indicative of the drug release mechanism

Result

Table 4.42 Results of determination of Release Kinetics

Model	SSR	R2	MSE	MSC
Zero order	2921.592	0.9753	324.6213	0.4943
First order	140.7524	0.9844	15.701	3.5271
Higuchi Model	618.3089	0.9313	68.701	2.0472
Hixson-Crowell Model	197.7287	0.978	21.9699	3.1872
Weibull Model	**54.0397**	**0.994**	**7.72**	**4.0844**
Korsmeyer-Peppas Model	608.9944	0.9323	76.1243	1.8623

From the Result table, it was clear that higher value of correlation coefficient was obtained in case of Weibullmodel. Therefore, it can be concluded that Anomalous diffusion was the predominant mechanism of drug release.

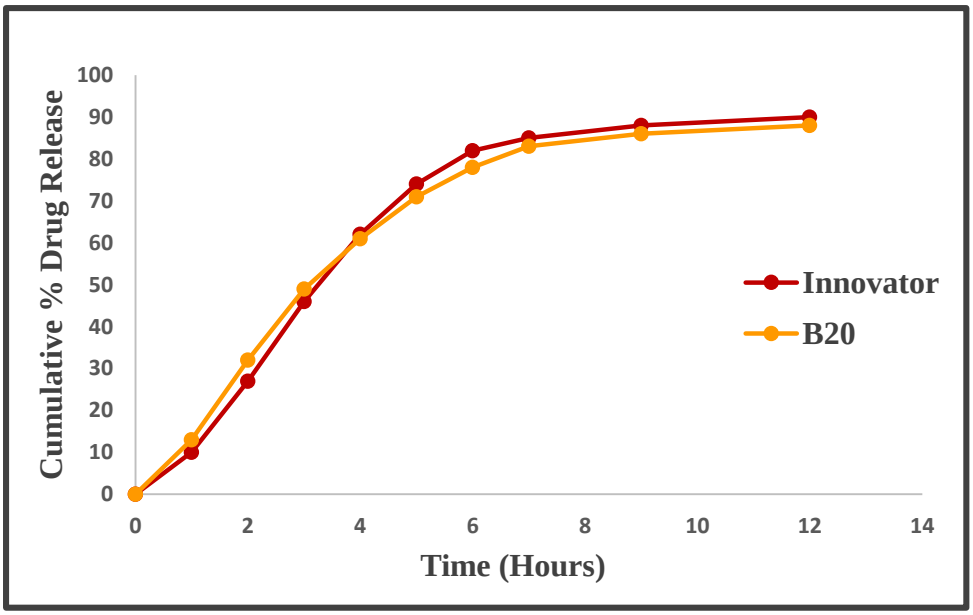
4.21 Comparison of Optimized Batch with Innovator Product

The dissolution profile of the optimized batch was compared with the marketed products and f_2 value was calculated.

Table 4.43 Comparative In-Vitro drug release profile of optimized formulation with innovator Product

Time (Hours)	Cumulative % Drug Release	
	Innovator Product	B20
0	0	0
1	10	13
2	27	32
3	46	49
4	62	61
5	74	71
6	82	78
7	85	83
9	88	86
12	90	88

Figure: 4.23 Comparative In-Vitro Drug release profile of Batch B20 with the innovator Product



The similarity factor, (f2value) was obtained by comparing the dissolution profile of Batch B20 with the innovator product. The f2 was calculated using following equation:

$$f_2 = 50 \text{ Log } \{[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)\ 2\ ]^{-1/2} * 100\}$$

- f_2 value was found 75, which is greater than 50, so it was concluded that there is no significant difference between the dissolution profiles of innovator and batch B20. Thus it can be concluded that developed extended release multiparticulate drug delivery system can give similar site specific release as that of the marketed product.

4.22 Stability Study

The Optimized Formulation was subjected to stability study in order to determine the stability of the formulation in different conditions. The Optimized formulation was stored in different conditions such as:

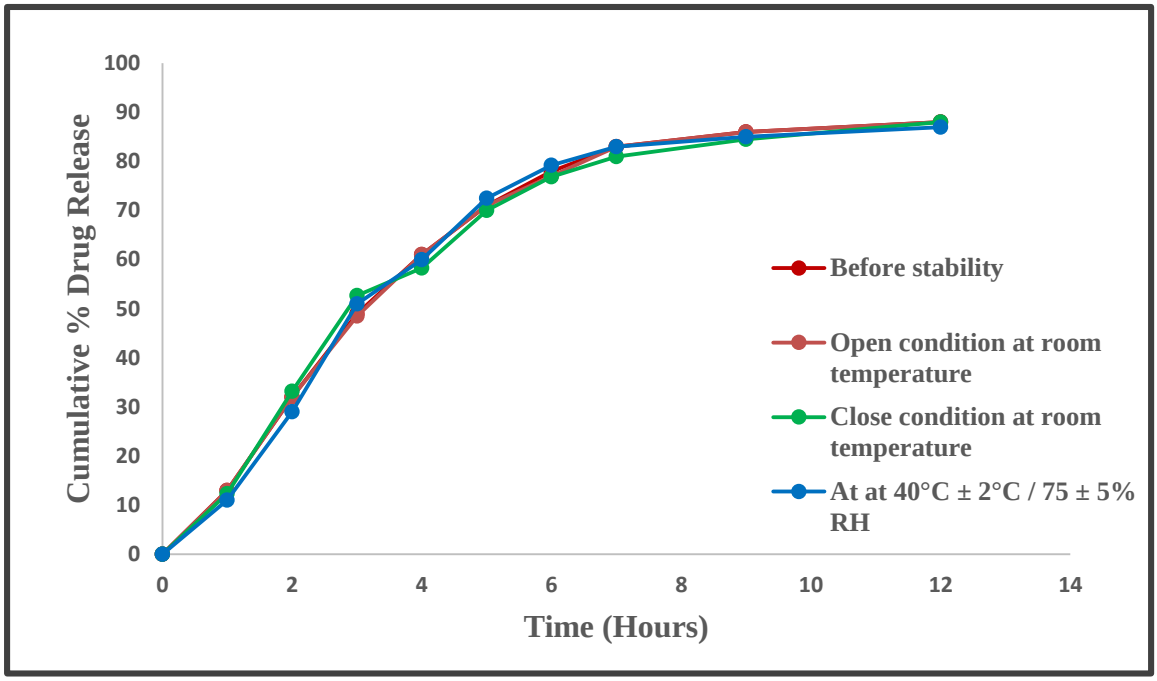
1. Open condition at room temperature
2. Closed condition at room temperature
3. In stability chamber for 1 month at 40°C ± 2°C / 75 ± 5% RH

The formulation was then evaluated for drug release profile.

Table 4.44 In-Vitro drug release study of optimized batch before and after stability study

Time (Hours)	Before Stability	Open condition at room temperature	Close condition at room temperature	at 40°C ± 2°C / 75 ± 5% RH
0	0	0	0	0
1	13	13	12.3	11
2	32	32	33.2	29
3	49	48.5	52.7	51
4	61	61	58.3	60
5	71	71	70	72.5
6	78	77	76.9	79.2
7	83	83	81	83
9	86	86	84.5	85
12	88	88	88	87

Figure: 4.24 Comparison of dissolution profile of optimized formulation before and after stability study.



Result:

The Figure showed that there is no much difference between release profile of the formulation before and after stability study of 1 month. The $f_2$value (Similarity Factor) was found to be 86.81 which showed that there was similarity between the in-vitro release of the optimized formulation before stability study and after stability study.

Paired t-Test for two sample of means:

T_{stat}: 0.656208

$T_{critical}$ One-tail: 1.859548

$T_{critical}$ two tail: 2.306004

After applying paired t-test for two sample of means, $t_{stat}$was found to be smaller than t_{tail}. Hence it was concluded that difference between dissolution profile of optimized formulation before and after stability study was insignificant. Therefore, The formulation was found to be stable after 1 month.

Conclusion:

From the results of stability study it was concluded that the formulation of optimized batch passed the stability study.

5.0 Summary

This investigation was carried out to develop extended release pellets of tolterodine tartrate using multiparticulate drug delivery system. The formulation development was carried out using variable concentration of polymer coatings by employing Solution/Suspension Layering Technique. Pellets of Optimized Batch was then filled into capsule of suitable size.

Tolterodine Tartrate is popular muscarinic receptor antagonist used in the treatment of urinary incontinence or urinary frequency/urgency occur in patients suffering from overactive bladder syndrome. Tolterodine Tartrate is BCS Class-I drug having a short half-life of 1.9-3.7 hours. The dose of drug is 4 mg once a day and it is potent drug. Hence this drug is suitable for administering it in form of modified release formulation. Findings says that tolterodine tartrate immediate release 4 mg (2 mg bid) is equivalent to extended release 4 mg, therefore to reduce the dosing frequency it was decided to formulate once-a-day extended release formulation of tolterodine tartrate using multiparticulate drug delivery system.

Pre-formulation study was done for physical characterization of tolterodine tartrate which showed that the drug was having crystalline nature with poor flow property and poor compressibility. Hence it was decided to prepare extended release pellets which could reduce the dosing frequency and enhance the therapeutic effect of drug. Due to poor flow property and compressibility the prepared pellets were filled in capsules of suitable size. Chromatographic analysis of the drug was carried out using HPLC, and from the chromatogram, it was concluded that there was complete similarity between standard API and sample API. Hence it was concluded that the API was pure. Drug-Excipient compatibility study revealed that there was no incompatibility between drug and excipient. Detection of related impurity showed that no impurity was observed after 1 month of storage at 40°C/75% RH. Hence all the excipient were found to be compatible with drug.

Trials were carried out for the optimization of different ratios of solvent as well as polymers. As the process was lengthy and complex, different process parameters were optimized which could affect the desired outcome of the final formulation.

Optimization of Drug: HPMC (Ratio) was carried out by using different ratios as it affect the viscosity of the layering solution and the final ratio optimized was 1: 0.5 which gave the satisfactory results. Further Methanol: Water (Ratio) was optimized as proper combination of organic and aqueous solvents required for the desired results. Excessive concentration of methanol may lead to stickiness and higher amount of aqueous solvent may lead to tackiness. Hence proper ratio was selected as 20: 80 as it gave higher % Yield. % Weight Build up after the innermost layer (Drug Layer-I) was most important as it affect the dissolution profile of the formulation. Concentration of Polymer coating was optimized by performing different % weigh gain on the starter cores and 14% weight build-up was optimized as it gave maximum drug release within 12 hours i.e. 3.9% out of 5%. As the dose was bifurcated in two drug layers, after optimization of control coat-I, Drug layer-II was applied using same optimized ratio of Drug: HPMC and Methanol: Water i.e., 1:0.5 and 20:80 respectively. After drug layering, final optimization of functional coat was carried out employing different concentration of surelease: HPMC and % weight build-up. Surelease: HPMC (Ratio) was optimized by keeping % weight gain constant as 13%, and the final optimized ratio was 86:14. Further % weight build-up was optimized by keeping optimized ratio as surelease: HPMC as 86:14. % weight gain was finalized as 11% as it gave the desired drug release profile similar to the innovator. After formulation-optimization, the curing time was optimized to achieve the complete film formation and finalized as 1 hour as there was no much difference observed.

The optimized formulation showed good sphericity and aspect ratio. SEM photographs clearly showed all the four different layers of the polymer. XRD was performed to check the transformation of crystalline nature of API into some other polymorphic form. XRD clarified that the API was in the pure form and does not transform into any other polymorphic form.

Release kinetics of the optimized batch concludes that the formulation follows Weibull model and Anomalous diffusion. The optimized batch was compared with the innovator product and the f_2 value was found to be 75 based on the drug release profile, hence it was concluded that the optimized formulation was similar to the innovator formulation. From the stability data, it was found that there was no

incompatibility in drug release before and after stability study. Therefore it was concluded that the optimized formulation was stable and showed the drug release profile same as that of innovator product.

References:

(1) Shah Samir, Shah Paresh. A Review on Extended Release Drug Delivery System and Multiparticulate System. *World J. Pharm. Pharm. Resesarch* **2016**, *4* (8), 724–747.

(2) Katedeshmukh, R. G. Multiple Unit Pellet System - A New Path for zDrug Delivery. *Int. J. Univers. Pharm. Bio Sci.* **2013**, *2* (August), 401–415.

(3) Bhairy Srinivas. Pellets and Pelletization as Multiparticulate Drug Delivery Systems (Mpdds): A Conventional and Novel Approach. *Int. J. institutional Pharm. life Sci.* **2015**, *5* (August).

(4) Gandhi, B.; Baheti, J. Multiparticulates Drug Delivery Systems : A Review. *Int. J. Pharm. Chem. Sci.* **2013**, *2* (3), 1620–1626.

(5) Sachdeva, V.; Alam, S.; Kumar, R.; Kataria, M. K. Oral Multiunit Pellet Extended Release Dosage Form : A Review. *Int. Curr. Pharm. J.* **2013**, *2* (September), 177–184.

(6) MC, V.; SK, S. K.; S, P. Pelletization Technique in Drug Delivery System. *Int. J. Pharm. Dev. Technol.* **2012**, *3* (1), 13–22.

(7) Gavali Harshal. MULTIPARTICULATE DRUG DELIVERY SYSTEM AND THEIR. *World J. Pharm. Pharm. Resesarch* **2015**, *4* (6), 1949–1960.

(8) Vikash, K.; Article, R.; Vikash, K.; Kumar, M. S.; Amit, L.; Ranjit, S. Multiple Unit Dosage Form - Pellet and Pelletization Techniques : An Overview. *Int. J. Res. Ayurveda Pharm.* **2011**, *2* (1), 121–125.

(9) Rajesh, A.; Reetika, D.; Sangeeta, A.; Ashok, B. Wurster Coating- Process and Product Variables. *Int. J. Pharm. Inoovations* **2012**, *C* (2), 61–66.

(10) V., Nair, G. S. B. An Overview on Multi Unit Pellet Drug Delivery System. *Int. J. institutional Pharm. life Sci.* **2015**, *5* (June), 356–370.

(11) Kandukuri, J. M.; Allenki, V.; Eaga, C. M.; Keshetty, V.; Jannu, K. Pelletization Techniques for Oral Drug Delivery. *Int. J. Pharm. Sci. Drug Res.* **2009**, *1* (2), 63–70.

(12) Panda, S. K.; Parida, K. R.; Roy, H.; Talwar, P. A Current Technology for Modified Release Drug Delivery System : Multiple-Unit Pellet System (MUPS). *Int. J. Pharm. Sci. Heal. Care* **2013**, *6* (3), 51–63.

(13) Jawahar, N.; Anilbhai, P. H. Multi Unit Particulates Systems (MUPS): A

Novel Pellets for Oral Dosage Forms. *J. Pharm. Sci. Res.* **2012**, *4* (9), 1915–1923.

(14) Pusapati, R.; Rao, T. Fluidized Bed Processing: A Review. *Indian J. Res. Pharm. Biotechnol.* **2014**, *5674* (August), 1360–1365.

(15) https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2cad3579-d197-4019-ae94-460525b6a8d9.

(16) http://www.drugbank.ca/drugs/DB01036.

(17) http://www.drugs.com/cdi/tolterodine.html.

(18) http://www.webmd.com/drugs/2/drug-7372-8152/tolterodine-oral/tolterodine-oral/details.

(19) http://www.rxlist.com/detrol-la-drug.htm.

(20) http://www.drugs.com/ppa/tolterodine-tartrate.html.

(21) Leary, M. R. [Ed]; Hoyle, R. H. [Ed]. Handbook of Pharmaceutical Excipients. In *(2009)*; 2009.

(22) Sirisha, M.; Rajasree, C.; Haripriya, H.; Boyanapalli, N.; Pradesh, A.; Sirisha, M.; Nagar, A.; Pradesh, A. Formulation and In-Vitro Evaluation of Tolterodine Tartrate Sustained Release Pellets. *Int. J. Univers. Pharm. Bio Sci.* **2013**, *2* (October), 327–345.

(23) G. Venkata Sudarsan; Veerareddy, P. reddy. FORMULATION AND EVALUATION OF TOLTERODINE TARTRATE EXTENDED. *J. Glob. Trends Pharm. Sci.* **2014**, *5* (2), 1692–1698.

(24) Rajabalaya, R.; Mun, C. Y.; Chellian, J.; David, S.; Chakravarthi, S. Development and Evaluation of Matrix Type Transdermal Delivery of Tolterodine Tartrate for Overactive Bladder Treatment. **2013**, No. 126, 57000.

(25) Pradhan, R.; Kim, Y.; Woo, S.; Oh, J. Preparation and Evaluation of Once-Daily Sustained-Release Coated Tablets of Tolterodine- L -Tartrate. *Int. J. Pharm.* **2014**, *460* (1-2), 205–211.

(26) Lakshmi, P. K.; Pawana, S.; Rajpur, A.; Prasanthi, D. Formulation and Evaluation of Membrane-Controlled Transdermal Drug Delivery of Tolterodine Tartarate. *Asian J. Pharm. Clin. Res.* **2014**, *7* (SUPPL. 2), 111–115.

(27) Devireddy, S. R. The Transdermal Delivery of Tolterodine Tartrate: In-Vitro

and Ex-Vivo Characterization. *Int. J. Pharm. Technol.* **2012**, *4* (1), 4060–4066.

(28) Prasanthi, D.; Lakshmi, P. K. OPTIMISATION OF TRANSDERMAL GEL FORMULATIONS OF TOLTERODINE TARTRATE BY EXPERIMENTAL DESIGN. **2013**, *10* (2), 273–285.

(29) Kalpana, B.; Lakshmi, P. K. Transdermal Permeation Enhancement of Tolterodine Tartrate through Invasomes and Iontophoresis. *Der Pharm. Lett.* **2013**, *5* (6), 119–126.

(30) Kumar, K. K.; Babu, N. D.; Pasupathi, A. Design and Evaluation of Multi Particulate System of Extended Release Indomethacin Capsules USP. *Res. J. Pharm. Biol. Chem. Sci.* **2010**, *1* (4), 74–82.

(31) Mylavarapu Preethi, S. P. Formulation and Evaluation of Doxycycline Hydrochloride Delayed Release Enteric Coated Tablets. *Int. J. Pharma Bio Sci. Res.* **2012**, *4* (1), 249–255.

(32) Wang, Y.; Yang, J.; Qian, Y.; Yang, M.; Qiu, Y.; Huang, W.; Shan, L.; Gao, C. Novel Ethylcellulose-Coated Pellets for Controlled Release of Metoprolol Succinate without Lag Phase: Characterization, Optimization and *in Vivo* Evaluation. *Drug Dev. Ind. Pharm.* **2015**, *41* (7), 1120–1129.

(33) Ramu, S.; Reddy, P. C. G.; Rao, D. S.; Ramakrishna, G. Formulation and Evaluation of Lansoprazole Delayed Release Pellets. *Int. J. Pharm. Chem. Biol. Sci.* **2015**, *5* (4), 860–878.

(34) Kulkarni, S. V. Formulation and Evaluation of Sustained Release Pellets of Domperidone. *Int. J. Drug Deliv. Res.* **2015**, *7* (1), 162–172.

(35) Haripriya Baskara, D. reddy S. Formulation and Evaluation of Sustained Release Pellets of Tramadol Hydrochloride. *Int. Res. J. Pharm.* **2013**, *4* (2), 127–130.

(36) Sri, K. V. I. J.; Devanna, N.; Suresh, K. Multiple Unit Extended Release Pellets of Propranolol Hydrochloride : Preparation and Characterization. *Int. J. Pharm. Pharm. Sci.* **2013**, *5* (3).

(37) Gautam Namrata, T. P. Formulation & Development of Pellets of Tolterodine Tartrate : A Qualitative Study on Wurster Based Fluidized Bed Coating Technology. *J. Drug Deliv. Ther.* **2012**, *2* (4), 90–96.

(38) Anusha, K.; Babu, M.; Babu, P. Formulation of Sustained Release Pellets of

Quetiapine Fumarate by Fluidized Bed Coating Process. *Int. J. Pharm. Sci. Invent.* **2013**, *2* (12), 20–33.

(39) R, N. N.; Potti, L. R.; Mogali, R. K.; M, P. R.; Sivasankar, R.; Group, S.; Reserved, A. R. Formulation and Evaluation of Esomeprazole Magnesium Dihydrate Multiple Unit Particulate System as a Delayedcrelease Dosage Form. *Int. J. Res. Dev. Pharm. Life Sci.* **2014**, *3* (2), 935–942.

(40) Jaiswal Sunil Beharilal, S. A. J. EXTENDED RELEASE COMPOSITIONS COMPRISING TOLTERODINE. US 8,871,275 B2, 2014.

(41) Kshirsagar Rajesh. Extended Release Compositions Containing Tolterodine and Process for Preparing the Same. US 2011/0123610 A1, 2011.

(42) Rossi David T., L. B. Stabilized Tolterodine Tartrate Formulations. US 2013/0296439 A1, 2013.

(43) Li, B. Drug Formulations Having Inert Sealed Cores. US 8,110,226 B2, 2003.

(44) Jaiswal Sunil Beharilal, S. A. J. Extended Release Formulations Comprising Tolterodine. US/2011/0150937 A1, 2011.

(45) Legen, I. I.; Si, G. Coated Formulations for Tolterodine. US 8,642,078 B2, 2014.

(46) Park, C.; Us, N. Y.; Us, N. Y.; Walter, D. J. Extended Release Compositions for High Solubility, High Permeability Active Pharmaceutical Ingredients. US2011/0159094 A1, 2007.

(47) Rossi David T., L. B. Stabilized Tolterodine Tartrate Formulations. US 8778397 B2, 2014.

(48) Kulkarni, S.; Sharma, S. B.; Agrawal, A. Preformulation - A Foundation for Formulation Development. *Int. J. Pharm. , Chem. Biol. Sci.* **2015**, *5* (2), 403–406.

(49) Gopinath, R.; Naidu, R. A. S. Pharmaceutical Preformulation Studies – Current Review. *Int. J. Pharm. Biol. Arch.* **2011**, *2* (5), 1391–1400.

(50) Sahitya, G. Importance of Preformulation Studies in Designing Formulations for Sustained Release Dosage Forms. *Int. J. Pharm. Technol.* **2012**, *4* (4), 2311–2331.

(51) Kumar, M. S.; Das, B.; Raju, S. V. S. R. Formulation and Evaluation of Multiunit Pellet System of Venlafaxine Hydrochloride. *J. Pharm. Biomed. Sci.*

2012, *18* (18).

(52) Dash Suvakantha, P. N. M. Kinetic Modeling on Drug Release from Controlled Drug Delivery Systems. *Polish Pharm. Soc.* **2010**, *67* (3), 217–223.

(53) Shaikh, H. K.; Kshirsagar, R. V; Patil, S. G. Mathematical Models for Drug Release Characterization : A Review. *World J. Pharm. Pharm. Sci.* **2015**, *4* (4), 324–338.

(54) Singhvi, G.; Singh, M. Review: In Vitro Drug Release Characterization Models. *Int. J. Pharm. Stud. Res.* **2011**, *II* (I), 77–84.

(55) Zhang, Y.; Huo, M.; Zhou, J.; Zou, A.; Li, W.; Yao, C.; Xie, S. DDSolver: An Add-in Program for Modeling and Comparison of Drug Dissolution Profiles. *AAPS J.* **2010**, *12* (3), 263–271.