Modified release oral drug-delivery systems are the most acceptable form of controlled-release system in patients. There are two broad classes for oral modified drug-delivery systems namely single unit dosage forms (SUDFs) and multiple unit dosage forms (MUDFs) [1]. Recent trends indicate that multiple unit dosage forms are especially suitable for achieving controlled release. Scientists have shown growing interest in multiparticulate drug-delivery systems (MDDS), in recent years, not only because of their ability to control drug release, but also for the modified drug-release profiles they facilitate [2].

2.1 Multiparticulate drug delivery systems (MDDS)

MDDS consist of multiplicity of small discrete units that exhibit different characteristics and is based on subunits such as granules, beads, microspheres, pellets, spheroids and Minitab. These subunits show various advantages over monolithic devices (non-divided forms). In MDDS, dosage form of the drug molecules are divided into number of subunits, typically consisting of thousands of spherical particles having diameter of about 0.05-2.00 mm. These subunits are compressed into tablets or filled into sachets or encapsulated to deliver the recommended dose [3]. These systems release the drug with constant or variable release rates, thus maintaining drug concentration within the therapeutic window for a prolonged period of time. The desired release profile facilitates controlled absorption through the target site in the body, ensures good therapeutic activity, and reduces side effects [4]. They can be prepared by different methods like extrusion–spheronization, pelletization, granulation, spray drying, spray congealing, etc.

2.1.1 Salient aspects of pellets

Traditionally the word 'Pellet' has been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. These products may be fertilizers, animal feeds, iron ores or pharmaceutical dosage forms [5]. Pellets meant different things for different industries.. It was only in the early 1950’s, in response to a desire to sustain the release of drugs over an extended period of time, that the pharmaceutical industry developed a keen interest in developing pellets. The role of pellets, especially of spheroids, in oral dosage form design and development has increased substantially during recent decades. Currently, pellets containing the active ingredients are administered in the form of

suspensions, capsules or tablets, a great number of this kinds of pharmaceutical products being available on the market [6]. In pharmaceutical industry, pelletization can be defined as an agglomeration process that converts fine powder of bulk drugs and excipients into small, free flowing, spherical or semi-spherical units, called as pellets [7].

Multiunit particulate system (MUPS) is one of the MDDS technique for controlled and modified drug delivery. Each discrete particle in a MUPS product incorporates its own release characteristics and further contributes to the product's therapeutic activity.

MUPS offer various advantages over other systems, including reduced risk of local irritation and toxicity, predictable bioavailability, reduced likelihood of dose dumping, minimized fluctuations in plasma concentration of drug and high dose-strength administration. Multiparticulate systems show more reproducible pharmacokinetic behavior and lower intra and inter subject variability than conventional single unit formulations [8]. The process is a high throughput, cost effective as the product losses are minimal due to the recirculation of the material into the ongoing process.

The applications for which MUPS formulations are developed include taste masking (e.g., of bitter drugs), enteric-release (e.g., of acid-labile drugs), and modified- or controlled-release orodispersible drugs for geriatric or pediatric patients. MUPS can be further filled in capsules, compacted into tablets, filled into sachets to be used as reconstituted powder for suspensions.

Table 2.1.1: Review of work done on MUPS

Author (Reference no.)	**Formulation**	**Drug**	**Polymer/Excipient used**	**Conclusion**
H. Ichikawa et al. 1997 [9]	Microcapsules	Diclofenac sodium	hydroxypropyl cellulose, polyethylene glycol 6000, Eudragit® L30D, Eudragit® RS30D	Prolonged drug release upto 10 h
P. Kuhl,	Tablet	Theophylline	Eudragit® RS/RL,	Coated drug

J.B. Mielck 2002 [10]			PH200 and PEG 4000	layered pellets were successfully compressed
A. Kramar et al.2003 [11]	Sustained release pellets	Diclofenac	Triethyl citrate, Eudragit RS, Eudragit RL	Prolonged drug release upto 6 h
Tae-Wan KIM et al. 2007 [12]	Pellet	Cisapride	Sugar spheres, polysorbate 80, Eudragit® RS 30D and L 30D	Dual layered pellets have potential as a sustained release dosage form for poorly water-soluble drugs.
Thommes M, et al. 2009 [13]	Pellet	Darunavir	Kappa-carrageenan or microcrystalline cellulose (MCC)	when compared with MCC pellets, the bioavailability of darunavir was substantially improved in kappa-carrageenan pellets, likely due to their better disintegration behavior.
E.L. McConnell et al. 2009 [14]	Pellets	Tramadol hydrochloride	Ethylcellulose, Ethanol, Sugar Spheres	Poor retardation of drug release was seen with alone ethanol whereas changing the solvent to an ethanol water mixture (90:10) which

				reduced the evaporation rate in the solution layering process.
Patel, H.P. et al. 2011 [15]	MUPS	Ramipril and hydrochlorothiazide	HPMC, Talc	MUPS prepared by incorporating ramipril pellets and hydrochlorothiazide with other excipients showed good stability along with degradation of ramipril and immediate action of tablet with highest bioavailability of both drugs..
K. Nikowitz et al. 2011 [16]	MUPS	Diltiazem hydrochloride	Acryl-EZE, Kollidon 25	Acryl-EZE is suitable for the making of delayed-release multilayer pellets without the use of additional excipients.
M Srujan Kumar et al. 2012 [17]	MUPS	Venlafaxine Hydrochloride	Microcrystalline cellulose, Hydroxypropyl Cellulose, Ethylcellulose	Extended release pellets in tablets of formulation have more drug release rate rather than innovator and it has better bioavailability.

Girish S. Sonar et al, 2015 [18]	MUPS tablet	Pantoprazole	Povidone, HPMC VLV, Eudragit L30D-55, PEG 6000	QbD can be applied for pharmaceutical development of Pantoprazole MUPS tablets, containing enteric coating polymer, ready mix plasticizer and cushioning extragranular excipients, which were reported to be reduce the cleavage of pellets during tabletting.

PATENTS

Inventor	**Title**	**Description**
Pratik,K. et al. 2011 [19]	Multi-unit compositions	A compressed tablet composition comprising (a) coated multiple units, containing at least one active pharmaceutical ingredient, (b) at least one compressibility enhancing agent comprising neutral spheres, (c) at least one cohesiveness imparting agent comprising binder(s). Such a composition provides solution to chipping, cracking and leaking problems associated with compression of coated multiple units (pellets or beads).
Tiziano Alighieri et al.2012 [20]	Oral pharmaceutical formulations of	The present invention describes pharmaceutical formulations suitable for oral administration of esomeprazole and methods of preparation to obtain tablets of the MUPS type of adequate hardness with minimum applied compression force.

	esomeprazole in the form of MUPS (multi unit pellets system) tablets	
Babu, G.A, et al, 2012 [21]	Pharmaceutical formulations	A particulate pharmaceutical composition for oral use comprising a) cores comprising an effective amount of a substituted benzimidazole drug and a stabilizing agent, present in an amount effective to stabilize the drug, b) an intermediate/barrier layer, and c) an outer enteric coating layer. Coated particleses may be further overcoated and co-granulated with one or more excipients.

2.1.1.1 Pelletization techniques

Pelletization is a technique that enables the formation of spherical beads or pellets with a mean diameter usually ranging from 0.05 to 2.0 mm. The pharmaceutical industry has developed a great interest in pelletization due to a variety of reasons [22] : prevention of segregation of co agglomerated components, resulting in an improvement of the uniformity of the content; prevention of dust formation, resulting in an improvement of the process safety, as fine powders can cause dust explosions and the respiration of fines can cause health problems; increasing bulk density and decreasing bulk volume; the defined shape and weight improves the appearance of the product; improvement of the handling properties, due to the free-flowing properties; improvement of the hardness and friability of pellets; controlled release application of pellets due to the ideal low surface area-to-volume ratio that provides an ideal shape for the application of film coatings. All these aspects can be considered as technological advantages of pelletization.

The most widely used pelletization techniques in pharmaceutical industry are extrusion/ spheronization, fluid bed granulation, spherical agglomeration, solution and suspension layering, dry powder layering and cryopelletization [6].

- **Extrusion / spheronization:** It is a multistage process for obtaining pellets with uniform size from wet granulates (extrudates). Extrusion involves application of pressure to wet mass until it passes through the calibrated openings of a screen or die

plate of the extruder and eventually break under their own weight to form small rod-shaped extrudates. Later spheronization is done which involves breaking of these small rods of extrudates to form spherical particles by a rotating friction plate in spheronization chamber.

- **Fluid-bed granulation:** In this method a granulation solution is sprayed onto the fluidized particles, which then are dried rapidly in the hot air stream.
- **Spherical agglomeration:** It is a particle engineering technique which involves the transformation of fine crystals into spherical shape particles by a variety of ways like salting out, quasi emulsion-solvent diffusion, solvent change etc.
- **Layering techniques:** The drug is sprayed on a seed material (usually, a coarse crystal or nonpareil) in solution, suspension or dry powder form to produce pellets of uniform size distribution. For dry powder layering, the starter seeds are wetted by spraying an adhesive solution and then the powder is sprayed that adheres to the seed material.
- **Cryopelletization:** It is a process in which the drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes, fatty acids or other melting solids. The dispersion is then sprayed into a stream of air and other gases with a temperature below the melting point of the formulation components to result spherical congealed pellets.

2.1.1.2 Pellet coating

Coating is one of the oldest pharmaceutical processes still in existence. This skilled art, which was originally carried out for decorative purpose, has evolved into much more sophisticated and controlled process. The design of new equipment, development of new coating materials, advances in technology have all contributed to improved products. As coating is an additional step in manufacturing process, it increases the cost of product; therefore, decision to coat the dosage form is usually based on one of the following objectives [23]:

i. To improve drug stability by protecting from gastric and atmospheric environment (air, light, moisture).
ii. To reduce risk of interaction between incompatible ingredients.
iii. To improve patient compliance by increasing ease of ingestion, masking unpleasant taste and odor.

iv. To improve product appearance.
v. To modify drug release, as in enteric coated, controlled or sustained release dosage form.

Significant improvements have been made over the past few years in the equipments, the coating process, and coating compositions, and the quality of film coatings. The materials used for coating consists of Film formers, Plasticizer, Detackifier etc [24, 25].

a. Film formers: The film former is the major ingredient in the coating formulation. As no polymer has all of the necessary physical and chemical properties such as chemical stability, chemical inertness, strong tablet adherence, flexibility and imprinting, to meet the various application needs, the coating composition must be plasticized polymers or mixtures of polymers to achieve the desired coating.

For aqueous based system, polymers can be divided into two classes:

- Water soluble polymers
- Water insoluble or pH dependent soluble polymers

Most commonly used aqueous soluble polymers are Carboxymethylcellulose sodium, Hydroxypropyl cellulose, Methyl cellulose, Polyethylene glycols, Povidone etc. Some of the most common insoluble polymers are Ethyl cellulose, Eudragit® RS, Eudragit® RS, Cellulose acetate phthalate, Hydroxypropyl cellulose phthalate, Polyvinyl acetate phthalate, etc.

b. Plasticizer: Films prepared from pure polymers frequently are brittle and crack on drying. To correct this deficiency, the polymer can be chemically modified or other excipients can be added to make the film more flexible. Plasticizer can be classified into two general categories:

- Internal plasticizer
- External plasticizer

Internal plasticizing involves chemical modification of basic polymer. It causes changes in degree of substitution and changes in polymer chain length. For example in case of acetate cellulose films, hemicellulose content (5%) present in bagasse was used as an internal plasticizer [26]

External plasticizer can be another polymer (Polyethylene glycol, Tri ethyl citrate, Triacetin etc), a non volatile liquid, or even the aqueous solvents. The plasticizer alters the polymer- polymer interactions to improve the flexibility of the film by relieving molecular rigidity.

c. Detackifier: These are used to avoid the tacking (sticking) problem encountered during the coating process. Mostly widely used detackifiers are Talc, Glyceryl Mono Stearate and Magnesium Stearate.

d. Supplemental coating ingredients: These are sometimes added to stabilize or improve the product. ex: antioxidants like Butylated Hydroxy Anisole, Butylated Hydroxy Toluene etc.

2.1.2 Fluidized bed (air suspension) systems

One of the promising equipment for pellet coating is fluid bed processor. This utilizes air suspension coating process where pellets get coated when suspended in air. Three types of fluid bed processes are mainly used for pellet coatings [27].

a. Top-spray fluidized bed coating is generally used for granulation.

b. Bottom spray coating (Wurster Coating) is used for sustained release and enteric release coating.

c. Tangential spray coating (Rotor Pellet Coating) is used for higher drug layering.

a. Top spray coating

This process is generally used for granulation. The particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The granulating liquid is sprayed onto the fluidized bed from the top against the airflow (countercurrent) by means of a nozzle [28] (Figure 2.1.1). Drying takes place as the particles continue to move upwards in the airflow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform. Depending on the application, the system is sub-divided into pre-heating zones, spray zones and drying zones. Dried, porous granules particles are produced after the completion of operation [29, 30]

Figure 2.1.1: Top spray assembly

b. Bottom spray coating (Wurster coating)

This process is particularly suitable for a controlled release of active ingredients. In this process, a complete sealing of the surface can be achieved with a low usage of coating substance. The spray nozzle is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed. By using a Wurster chamber (column), a cylindrical partition mounted in the center and a base plate with different perforations, the particles to be coated are accelerated inside the column and fed through the spray cone concurrently. As the particles continue traveling upwards, they dry and fall outside the column back towards the base plate [28]. They are guided from the outside back to the inside of the column where they are once again accelerated by the spray (Figure 2.1.2). This produces an uniform film and process is known as Wurster process [30, 31]

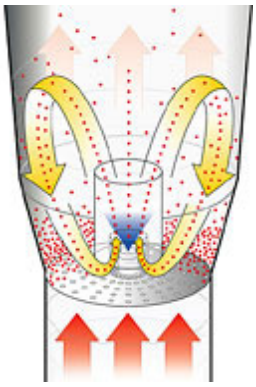

Figure 2.1.2: Bottom spray (Wurster) assembly

c. Tangential spray coating (rotor pellet coating)

This coating is best suited for cases in which higher amount of loading is required. The product is set into a spiral motion by means of a rotating base plate, which has air fed

into the powder bed at its edge. The spray nozzle is positioned tangentially to the rotor disc and sprays concurrently into the powder bed (Figure 2.1.3). Very thick film layers can be applied by means of rotor method. The challenge in achieving a successful coating process is to ensure that the sprayed coating material reaches the particles to be coated without excessive wetting [28, 32].

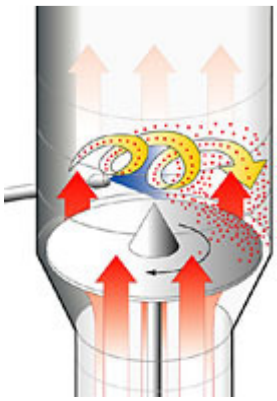

Figure 2.1.3: Tangential spray (Rotor pellet coating)

2.1.3 Parameters affecting fluidized bed coating

2.1.3.1 Equipment parameters

a. Spray gun

Atomization of the coating solution provides an ideal solution to the problem of introducing the solution to the bed. It solves the problem of local wet quenching which may be a result of excessive wetting of particles by large coating droplets. The position of the spray nozzle in a fluidized bed depends on the construction of the equipment, on the material to be processed and on the desired product. The nozzle may be positioned above the product bed (top spray assembly), at the bottom next to the distributor plate (bottom spray assembly) or placed tangentially to the product bed (rotor assembly). If the bottom spraying is employed in a fluidized bed, there is an increasing danger of defluidization by wet quenching. Therefore, the bottom spraying design is normally modified to move particles through the spraying zone as quickly as possible. Nozzle diameter also influence coating process. For more viscous solutions, bigger nozzle diameter is required. Spray rate should not be too fast or too slow, but should be of optimized rate for efficient coating and atomization of coating solution depends on the spray pressure, thus for proper atomization droplet size should be optimum [24].

b. Particle circulation

The first design of commercial fluidized-bed coating equipment by Wurster had an inner cylinder (also known as draft tube) to enhance the particle movement within the bed. The spray nozzle is placed at the bottom center of the distributor plate, so that the movement of the coated particles is in the same direction as the fluidizing gas. The assembly resulted in a draft movement of particles, which improved particle circulation but reduced the overall mixing. Other designs like Glatt used a cone at the center of the distributor plate to improve particle circulation. There is also a rotary tangential spray coater, which employs a variable speed disc and a slit instead of a conventional distributor plate to induce particle circulation [24, 33].

c. Temperature and humidity distributions

In fluidized bed coating, both heat and mass transfer must take place for the particles to be coated. The temperature and humidity readings are indicators of these transfers. The type, quality and thickness of any coating is determined by, among other factors, the temperature and humidity in the spraying region and in the rest of the bed there was an inverse proportionality between the size of the agglomerates and difference between the inlet dry bulb temperature and the outlet wet bulb temperature, that of similar particle size can be obtained by keeping the heat transfer driving force constant. Once the temperature and humidity profiles are established for a particular bed system, it is possible to optimize the size of the bed without running the danger of losing the bed to wet quenching [28, 33].

d. Air flow rate

Air flow rate should be controlled properly in order to get efficient use of drying air. As the air flow rate increases, the rate of drying increases but the cost of drying also increases. If drying air is allowed for sufficient time to remain in contact with the drying material, proper heat transfer and mass transfer takes place and thus drying cost decreases. Air flow rate should not be too fast or too slow but optimized to have efficient drying [29, 30].

2.1.3.2 Formulation parameters

a. Feed particle size

Particle size of pellets should be ideal for fluidization and coating. If the size is too large, it will be problematic to fluidize. If too small, twinning and agglomeration occurs [33].

b. Coating solution

Efficiency of coating depends on the quality of the coating solution. The coating solution should not get dried before reaching the fluidized substances viz. tablet, particles, and granule surface. In the early days of fluidized bed and pans coating processes, organic solvents were used in the preparation of coating solutions. They allowed fast coating at relatively low fluidization rates and temperatures, but their use has declined because of the stringent regulations on industrial hygiene, the working environments and safety measures required during their use. There has been an increasing use of aqueous solutions to replace the organic solvents, and these require higher fluidizing air capacities and heating systems. The concentration of the coating solution is limited to the range, where the solution remains sprayable [34].

c. Coating thickness and uniformity

For coated particles to be suitable in a sustained release application, the quality of the coating must be strictly controlled. Quality of the coat depends on the droplet size. So it should neither be too big nor be too small. This has done by establishing the optimum operating conditions for a particular coating material and seed particle. An ability to monitor the thickness and uniformity of the coating between particles and within an individual particle is essential in assessing the suitability of any set of process conditions. Although there are a number of ways to measure the Particle Size Distribution (PSD), many of these procedures may not be useful for determining uniformity of the coating deposited on the original particles [29].

2.2 Dysphagia

Dysphagia represents a condition in which a person experiences difficulty in swallowing. This difficulty might be due to an underlying pharmacological condition (cardio vascular stroke, diseases like Parkinson's, Alzheimer's, motor neuron disease etc.) or incapability (due to radiotherapy for head or neck region, medicines like tricyclic anti depressant

which causes dryness of mouth etc.) or simply unwillingness to swallow the medication [35].

The US FDA acknowledges the severity of dysphagia problem through its Guidance for Industry- Size, Shape and Other Physical Attributes of Generic Tablets and Capsules in June,2015 [36].

Children, old persons and incapacitated patients often experience discomfort when swallowing drugs in tablet or capsule form. This problem is exacerbated when the administered drug has a short plasma half life and must be taken frequently often leading to patient inconvenience and non compliance to therapy. A significant proportion of population like children, old patients and patients suffering from diseases like cancer are unable or unwilling to swallow the solid formulations for chronic use [35].

Difficulty in swallowing tablets and capsules can be a problem for many individuals and can lead to a variety of adverse events and patient noncompliance with treatment regimens. It is estimated that over 16 million people in the United States suffer from dysphagia [37]. For these individuals, swallowing a tablet or a capsule can be particularly challenging. A survey of adults on difficulties in swallowing tablets and capsules suggests that this problem goes well beyond the patient population with clinically recognized dysphagia and may affect as many as 40% of the population [38]. Of those who experience difficulty swallowing medication, less than 25% discuss the problem with a health care professional, 8% admit to skipping a dose of prescribed medication, and 4% have discontinued therapy because the tablets and/or capsules were difficult to swallow. Individuals who find it difficult to swallow tablets and capsules frequently blame the product size [38].

Size and shape of tablets and capsules affect the transit of the product through the pharynx and esophagus and may directly affect a patient's ability to swallow a particular drug product [39]. Larger tablets and capsules have been shown to prolong esophageal transit time which may lead to disintegration of the product in the esophagus and/or cause injury to the esophagus, resulting in pain and localized esophagitis, ulceration, stricture and perforation [40]. Other adverse events such as gagging, choking and aspiration are related to swallowing difficulties in the oropharyngeal phase of swallowing and increasingly occur at larger tablet and capsule sizes [41]. Studies in adults evaluating the effect of tablet and capsule size on ease of swallowing suggest that

increases in size are associated with increases in patient complaints related to swallowing [42].

2.2.1 Statistics for dysphagia

As per an estimate by American Speech Language Hearing Association (ASHA) 15 million people in US experienced difficulty in swallowing [43]. Out of these, 22% aged more than 50. Dysphagia affected more than 61% patients admitted to an acute trauma center, 50 to 75 % stroke patients, 60 to 70% patients undergoing radiation therapy for head and neck cancer, 24% suffering from multiple sclerosis and 81% from Parkinson's disease [44].

Harris Interactive had conducted an online study among 679 adults (513 aging 18-64 years, 166 aging 65 and more) to determine the extent and coping strategies of patients having swallowing difficulties. Demographic/propensity weights were applied to the data to ensure that the sample represents the general adult population. The researchers found that: A large percentage (40%) of population had experienced difficulty in swallowing tablets, although most had no problem in swallowing food or liquid. Of these patients, 14% have delayed taking their medication, 8% have skipped a dose while 4% have discontinued the therapy. As compared to men (27%) twice the number of women (51%) had tablet-swallowing problems. About 20% of patients, who take oral medications, hesitate to take tablets due to fear of swallowing them. Out of these patients, 84% attributed their hesitation to the size, while 29% to its shape. About 10% of patients have chosen pills, based on the anticipation of how difficult they might be to swallow. To facilitate swallowing, 55% drink lots of liquids, 48% drink water in big gulps, 43% tilt their heads back while 31% place the pill on the back of their tongue [45]. Other coping strategies were: 30% tried more than once to swallow the pill, 17% splitted the pill while 13% took a deep breath before taking the pill to minimize reflex. A majority (80%) of patients described the sensation as having a pill stuck in their throat, 48% had a bad after taste while 32% reported choking.

Above findings suggest that most patients do not benefit completely from the prescribed medications. As per an estimate by a consulting firm Capgemini, pharmaceutical companies lose more than $188 billion per year in the U.S. because patients fail to take their prescribed medications. The global loss would be enormous. Thus a massive

amount of money is lost by the pharmaceutical industry which is already experiencing patent expirations/challenges and scarcity of new chemical entities [46]. This clearly demonstrates the need for alternate, more patient friendly dosage forms of existing medications.

2.3 Product life cycle

It is the concept that products, like human beings, have a birth, a life and a death, and that they should be formulated and marketed with this in mind. Even as a new product is being launched, its manufacturer who should be preparing for the day when it has to be killed off. Its sales and profits start at a low level, rise to a high level and then decline again to a low level. This cycle is sometimes referred to simply as Product Life Cycle (PLC). Different phases of PLC are shown in Figure 2.3.1.

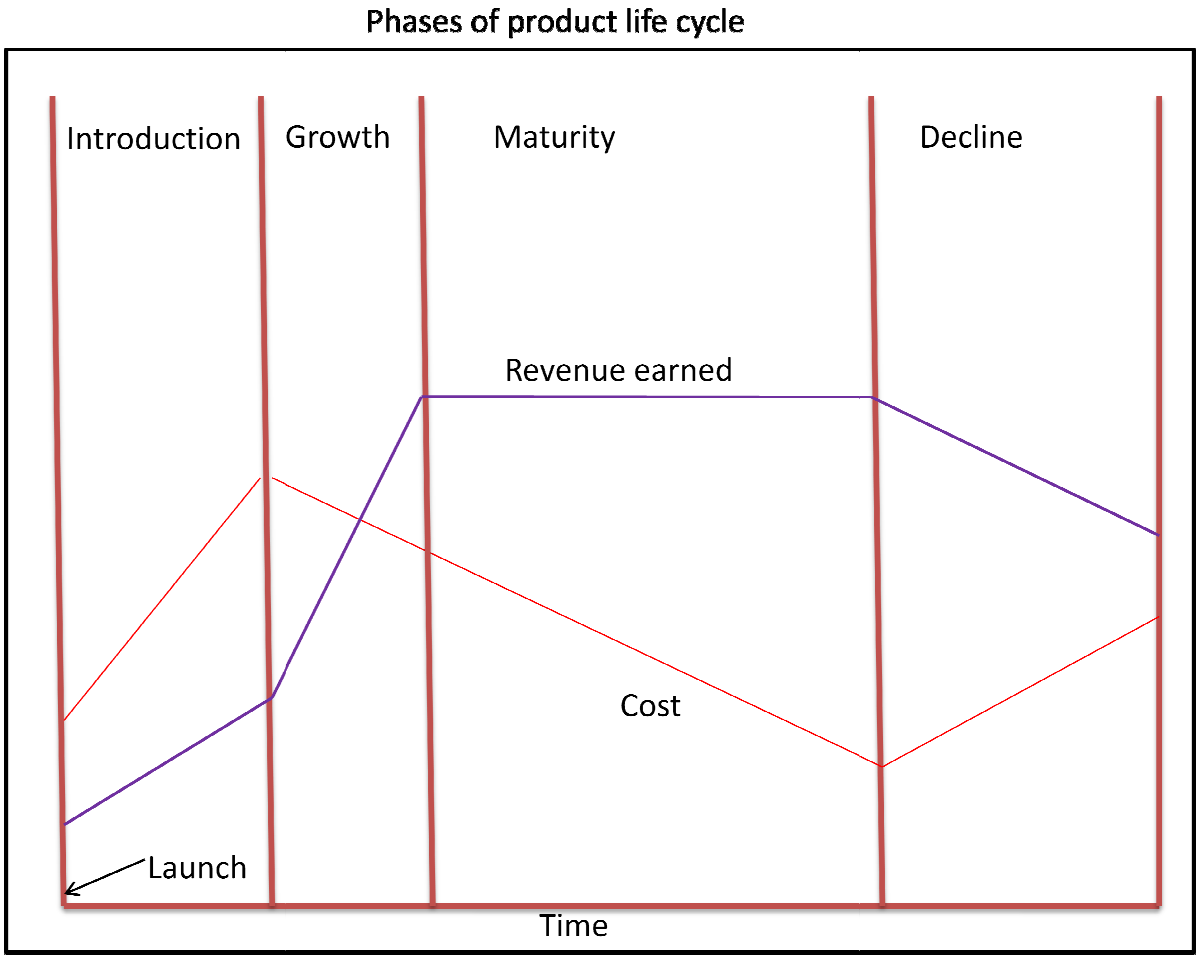

Figure 2.3.1: Different phases of Product Life Cycle

Famous marketing 'guru' Philip Kotler has divided the PLC into five different stages[47]:

2.3.1 Product development

This is the stage when a company looks for a new product. New products do not have to be "out-of-the-blue" new (like the video-cassette recorder or the compact disc). They might be merely additions to existing product lines (Ex. the first cigarette with a filter tip) or improvements to existing products (a new whiter-than-white washing powder).

2.3.2 Introduction

The product is launched into the market. The revenue earned is lesser than its costs due to high expenditure on advertising and marketing.

2.3.3 Growth

As the product is established, it begins to be accepted by the market and the company starts to recover the initial costs of the first two phases.

2.3.4 Maturity

By now the product is well established into the market and widely accepted. In this stage growth slows down due to pressure from competitors. The company has to spend again in order to defend the product's market position and survive in the tough competition.

2.3.5 Decline

In this stage the company is unable to fend off the competition or a change in consumer tastes or lifestyle will render the product redundant. At this point the company has to decide how to bring the product's life to an end-what is the best end-game that it can play?

2.4 Life Cycle Management

Above mentioned stages are applicable to all the commercial products including **pharmaceuticals**. However, it can't be exactly predicted when each phase will start and for how long it will last. Managing the product's life cycle effectively so as to get the maximum benefit is known as **Life Cycle Management (LCM)**.

2.4.1 History of LCM

Use of LCM can be traced back to 1898, when just 2 years after the foundation of Hoffmann-La Roche the third launched product was a LCM product. Thiocol cough syrup was reformulated with an orange flavour to improve patient compliance which proved to be successful.

2.4.2 LCM –importance to pharmaceutical industry

Mainstream development focuses on bringing therapeutic benefits to patients as rapidly as possible. Classic example can be quoted that of Imatinib (Glivec®) an anticancer drug which was developed in less than 1000 days. LCM focuses on tailoring drug product to patient's needs and preferences and on optimizing the therapeutic value of drug products. Ideally LCM leads to a higher market share for the brand i.e. it helps to increase the sales.

LCM can be achieved through:

- Alternative drug delivery systems
- Alternative packaging and devices
- New indications
- Alternative drug substance properties
- Improved manufacturing processes

As one of the most important strategies for LCM, **alternate drug delivery systems** provide commercial opportunities through intellectual property, product differentiation and recognition. By infusing the drug into an enhanced delivery system, this strategy is valuable and cost-effective in the management of overall product lifecycle resource.

"Alternative" drug delivery is not so much about fundamentally different "roads into the unknown" that have not been taken before, but it is about new dimensions of the known routes. In other words, alternative drug delivery systems consist of clever technical advancements along what ultimately are the known routes. It can be considered as marriage of drugs and devices to revive old established technologies. It improves the product's therapeutic benefits and patient's convenience, as well as compliance. With extended product's profitable life, it also fends off generic

competition, and gives back financial advantages to pharmaceutical companies [48]. Alternative drug delivery systems are of particular interest due to following reasons:

- Improvement of convenience for patient: Improvement of swallow-ability, Combination products, Reduced dosing frequency, Preferred administration route.
- Improvement of patient compliance: Administration without water, Optimal dosage forms for patient populations (children / elderly), Optimized dosage form for disease condition (acute/ chronic treatment)
- Improvement of therapeutic index (efficacy/ safety), Reduced side effects, Increased bioavailability and reduced variability, Optimized bioavailability based on PK-PD correlation

2.4.3 Example of LCM in pharmaceutical industry

Formulation technologies for LCM are numerous. They include modified-release for oral delivery; orally disintegrating tablets, taste masking, depot formulations, for bioavailability enhancement, etc. Over the years, a variety of technology platforms have also emerged, many of which led to the success of marketed products. The role of alternative delivery systems in drug LCM can be seen from some of the case studies, which demonstrate how smartly applied technologies can revive drugs that have lost patent protection or have not fully exploited their potential or completed their profitable phase of life cycle.

2.4.3.1 Case study 1: Powder for reconstitution replacing tablet and capsule dosage form

a. TAP Pharmaceuticals have developed Prevacid® (lansoprazole) sachets for delayed release oral suspension for patients who have difficulty in swallowing the approved capsule formulation. It was approved by the USFDA on 3rd May 2001. The sachet formulation differs from the capsules, in that it contains inactive granules in addition to lansoprazole pellets. Apart from this, the size of pellets used in sachets is smaller as compared to pellets filled into capsule. The unit dose packets are reconstituted with water to form a suspension which can be easily consumed orally [49].
b. Nexium (Esomeprazole magnesium) for delayed-release oral suspension, developed by Astra Zeneca, was approved on 15th Dec 2011. It is a unit dose packet containing

a fine yellow powder, consisting of white to pale brownish esomeprazole granules and pale yellow inactive granules [50].

Both TAP Pharmaceuticals and Astra Zeneca have used pelletization technique for development of their respective products. The delayed release pellets release the drugs in the duodenum which the site of absorption for all proton pump inhibitors.

c. Cipla too developed- Azipro® a sustained release microsphere formulation for azithromycin as powder for reconstitution. These formulations delivered an entire therapeutic course of azithromycin in a single dose with an improved tolerability profile [51]

2.4.3.2 Case study 2: Convenience and compliance improvement

Zolmitriptan (anti migraine drug) Fast melt tablets were developed which could be taken without water anytime and anywhere, even when patient feels nauseous. This improved patient compliance as compared to the conventional therapy.

2.4.3.3 Case study 3: Reduced dosing frequency

a. Procardia (Nifedipine) required to be taken three times a day, was going to loose patent protection in 1990. Anticipating the entry of other competitors, Procardia XL (once a day therapy) was developed and launched into the market in 1989 itself. This increased the sales annual sales from $400 mn in 1989 to around $1200 mn in 1994. Thus the profitable phase was prolonged for 10 years [52].
b. Cardizem® (Diltiazem HCl a cardiovascular drug), prescribed three-times-daily, achieved revenues of $260 million in 1988. Elan extended the product's life cycle by introducing Cardizem SR (twice-daily). Revenues peaked in 1989 at $400 million, remaining steady until 1991, when Cardizem CD was introduced for once-daily dosage. By 1996, revenues for Cardizem CD soared to almost $900 million [52].
c. Due to the short half-life of ropinirole immediate release formulations must be taken three times a day, and this can be a burden for Parkinson's patients that are typically on multiple medications. Skyepharma developed Requip® Ropinirole once-a-day dosage form. Further, the product is approved in more than 40 countries including the US where it was the first once-a-day oral ergot dopamine agonist indicated for

Parkinson's disease. It was approved in Japan in 2012 as one of the first once-a-day treatments for Parkinson's disease. It is marketed by GlaxoSmithKline [15].

d. Azithromycin belongs to macrolide class of antibiotics. It was observed from a clinical study that greater systemic exposure was achieved with a single dose of 2g sustained release azithromycin versus 1.5 g of immediate release azithromycin tablets administered over 3 days (500 mg/day) or 5 days (500 mg on day 1, 250 mg/day on days 2-5). As an oral single 2g dose it provides a full course of antibacterial therapy and a tablet formulation of such a high dose won't be palatable to the patient, with this view Pfizer developed Zithromax® for oral suspension as a single dose packet containing 1.2 g azithromycin dehydrate [53].

Table 2.4.1: Review of work done on Oral Powder for Reconstitution

Author (Reference no.)	**Drug**	**Technique**	**Polymer/Excipient used**	**Conclusion**
Shah and Mashru 2008 [54]	Primaquine Phosphate	Inclusion complexation	Beta-cyclodextrin.	Complete masking of bitter taste of Primaquine with beta-cyclodextrin.
Julian B. Lo et al. 2009 [55]	Azithromycin	Melt-spray-congeal	Glyceryl behenate, poloxamer 407, hydroxypropyl cellulose, xanthan gum	The combined suspension formulation for a 2-g dose of azithromycin provided taste-masking and good tolerability
E. Van Gyseghem et al. 2008 [56]	NNRTI-TMC278	Spray-dry technology	HPMC 2910 5 mPa, PEG 6000, PVP-VA 64, PVP K25 and Kollicoat IR, Cremophor EL	Provide potential dry formulations offering flexible dosage regimens

				combined with small dosage size, convenient for patients who are looking for a different approach for antiretroviral (ARV) therapy
Burcu Devrim et. al. 2011 [57]	Ibuprofen	Quasi-emulsion Solvent diffusion	Eudragit® RS-PMTM	Stable suspensions of ibuprofen-loaded microspheres could be formulated with 0.6% w/v xanthan gum by the addition of 20% w/v D-sorbitol.

PATENTS

Inventor	**Title**	**Description**
Sparks et. al.1994 [58]	Controlled release Powder and process for its preparation	Controlled release powder of discrete micro-particles which can be readily formulated in liquid form but which can also be formulated in other sustained release forms such as tablets which have improved properties
Rajesh Jain 2008 [59]	Controlled release formulation of coated microparticles	Controlled release compositions comprising microparticles which comprise a core and at least one coat, wherein the said compositions are formulated as oral reconstitutable pharmaceutical controlled release suspensions, which can be reconstituted using a suitable

		reconstituting medium such as water.
Gandhi, Mohan. P. 2011 [60]	Sustained release oral liquid suspension dosage form	A ready to use stable, sustained release oral liquid suspension dosage form of pharmaceutical active ingredients, which is easy to administer and particularly beneficial for the paediatric and geriatric patients.

Table 2.4.2: Review of work done on Orally Disintegrating Tablet

Author (Reference no.)	**Drug**	**Technique**	**Polymer/Excipient used**	**Conclusion**
K.G. Wagner et al. 2000 [61]	Bisacodyl	Pellets compressed into disintegrating tablet	Avicel PH 101, Eudragit® FS 30 D, Eudragit® L 30 D-55, Polysorbate 80 and triethyl citrate	Homogeneous distribution of the pellets within each tablet and little damage to the pellet coatings, almost independently of machine speed, was achieved by use of Avicel PH 101
A. Debunne et. al. 2004 [62]	Piroxicam	Enteric-coated pellets compressed into Tablet	Kollidon® CL, Avicel® PH 101 and Avicel® CL 611	Tablets containing piroxicam in combination with cushioning waxy pellets and 10% Kollidon® CL delayed the

				onset of the piroxicam plasma concentrations without affecting the extent of absoption.
Yoshihito Yaginuma, Naoya Yoshida 2007 [63]	Not disclosed	Wurster fluidized bed coating followed by compression	Celphere SCP-100, microcrystalline cellulose, ethylcellulose aqueous dispersion, Celioscoat EC-30A, D-Mannitol	Rapidly disintegrating tablets containing a large quantity of an intensely bitter drug were successfully developed with a suitable level of masking, tablet hardness, disintegration property, dissolution profile and mouth feel.
S.H. Jeong, K. Park 2008 [64]	Dextromethor-phan	Ion-exchange resin complexation followed by FBP coating	Ethyl cellulose (EC) and poly(vinyl acetate) (Kollicoat® SR30D)	Kollicoat® SR30D was a suitable polymer for the coating of ion-exchange resin

				complexes, which were granulated and compressed into fast-disintegrating tablets.
A. Fini et al. 2008 [65]	Ibuprofen	Granules by Wet Granulation followed compression	Phospholipon 80H (Saturated lecithin) Kollicoat SR 30, Kollidon 90F, Eudragit RD 100, Aspartame, Pearlitol SD 200, Kollidon CL	Fast dispersible/ slow releasing tablets that offer an alternative to traditional tablets for orally dispersible ibuprofen tablets and taste masking.

2.5 Quality by Design (QbD)

Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management [66]. It means designing and developing formulations and manufacturing processes to ensure a predefined quality. Thus, QbD requires an understanding how formulation and process variables influence product quality. Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8 Pharmaceutical Development [66], along with ICH Q9, Quality Risk Management [67], and ICH Q10, Pharmaceutical Quality Systems [68], indicate on an abstract level how quality by design acts to ensure drug product quality. ICH Q8, Pharmaceutical Development outlines type of information that may be provided in marketing application to demonstrate understanding of factors that influence product quality. It introduced the concepts of **Design Space** (DS), **Quality by Design (QbD)** and flexible regulatory approaches. ICH Q9, Quality Risk

Management (QRM) describes systematic processes for the **assessment, control** and **review** of quality risks. It includes principles, methodologies and examples of tools for QRM. Utilisation of QRM activities lead to a greater assurance of quality through risk control. ICH Q10, Pharmaceutical Quality Systems describes key systems that facilitate establishment and maintenance of a state of control into the organization, facilitates continual evaluation and upgradation. It applies to drug substance and drug product throughout product lifecycle. Comprehensive implementation of the three guidelines together is essential to achieve ICH Quality Vision. ICH Q8, Q9 and Q10 are linked together to provide a **modern, systematic, risk and science based approach** to pharmaceutical manufacturing and development. The first aspects of QbD are an articulation of the design goals for the product. Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. In order to design quality into a product, the requirements for the product design and performance must be well understood in the early design phase. In pharmaceuticals, these product requirements can be found in a Quality Target Product Profile (QTPP). QTPP has been defined as a 'prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product' [66]. QTPP should be established as soon as a product has been identified as a viable candidate for commercialization and should be revisited at key stages of product development, with any changes approved by the appropriate governance [69]. Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA has been defined as 'a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality'. CQA identification is best accomplished by using risk-based analysis, in accordance with the ICH Q9 guidance. Risk assessment can be done for either product design or process design. The ultimate goal is to identify high risk steps that affect the CQAs of Drug Product. Risk assessment includes several steps like all the components/ processes should be listed, process flow chart is to be prepared, all potential failure modes are to be identified, risk analysis, risk evaluation and control strategy should be designed. Many tools can be used for risk assessment viz. Ishikawa (fishbone) diagram, Capability Analysis, Failure Mode Effects Analysis (FMEA), Pareto diagram, etc. Amongst all, the most widely used tool is FMEA. FMEA or use of a prioritization matrix is helpful in identifying the process inputs that impact on quality attributes. It is

used to assess the potential degree of risk for every operating parameter in a systematic manner and to prioritize the activities, such as experiments, necessary to understand the impact of these parameters on overall process performance. To prioritize risks for corrective action Risk Priority Numbers (RPN) is to be identified [70]. It is defined as **RPN = Severity x Occurrence x Detection** where, the **severity** of each failure effect, the likelihood of **occurrence** for each cause of failure, and the likelihood of prior **detection** for each cause of failure and the RPN scores are then ranked to identify the parameters with a high enough risk to merit process characterization. A team consisting of representatives from process development, manufacturing and other relevant disciplines performs an assessment to determine severity, occurrence and detection. The severity score measures the seriousness of a particular failure and is based on an estimate of the severity of the potential failure effect at a local or process level and the potential failure effect at end product use or patient level. Occurrence and detection scores are based on an excursion (manufacturing deviation) outside the operating range that results in the identified failure. Although the occurrence score measures how frequently the failure might occur, the detection score indicates the probability of timely detection and correction of the excursion or the probability of detection before end product use [71].

Control strategy is defined as, a planned set of controls, derived from current product and process understanding that assures process performance and product quality [66]. The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements: procedural controls, in process controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach [72].

2.6 Design of Experiments

The traditional approach of optimizing a formulation or process essentially involves studying the influence of one variable at a time (OVAT), while keeping all others as constant. Using this OVAT approach, the solution of a specific challenging property can be achieved somehow, but attainment of the true optimal composition or process can never be guaranteed [73]. Design of experiments (DoE), on the other hand, is an optimization technique meant for products and/or processes, developed to evaluate all

the potential factors simultaneously, systematically and speedily [74]. Its implementation invariably encompasses the use of statistical experimental designs, generation of mathematical equations and graphic outcomes, portraying a complete picture of variation of the response(s) as a function of the factor(s), which can never be obtained using the traditional OVAT approach [75].

DoE optimization methodology encompass planning the study objectives, screening of influential variables, experimental designs, postulation of mathematical models for various chosen response characteristics, fitting experimental data into these model(s), mapping and generating graphic outcomes, and design validation using model-based response surface methodology [73]. DoE is an efficient procedure for planning experiments in such as way that the data obtained can be analyzed to yield valid and unbiased conclusions [76]. An experimental design is a strategy for laying out a detailed experimental plan in advance to the conduct of the experimental studies [77]. Before the selection of experimental design, it is essential to isolate the experimental domain within the factor space. There are numerous types of experimental designs. Various commonly employed experimental designs for RSM, screening, and factor influence studies in pharmaceutical product development are: factorial design, fractional factorial design, Plackett–Burman design, star design, central composite design, Box–Behnken design, center of gravity design, equiradial design, mixture design, Taguchi design, optimal design, Rechtschaffner design, Cotter design.

In the present study, a two factor, three level, face centred, central composite design (CCF) has been employed. Central Composite Design (CCD) has three different design points: edge points as in two - level designs (±1), star points at $\pm \alpha$; $| \alpha 1 \leq |$ that take care of quadratic effects and centre points (Figure 2.6.1). Three variants exist: circumscribed (CCC), inscribed (CCI) and face centred (CCF). In CCF, the star points are at the center of each face of the factorial space, i.e., $\alpha = \pm 1$. It requires 3 levels of each factor. CCF designs provide relatively high quality predictions over the entire design range. They do not require using points outside the original factor range [78].

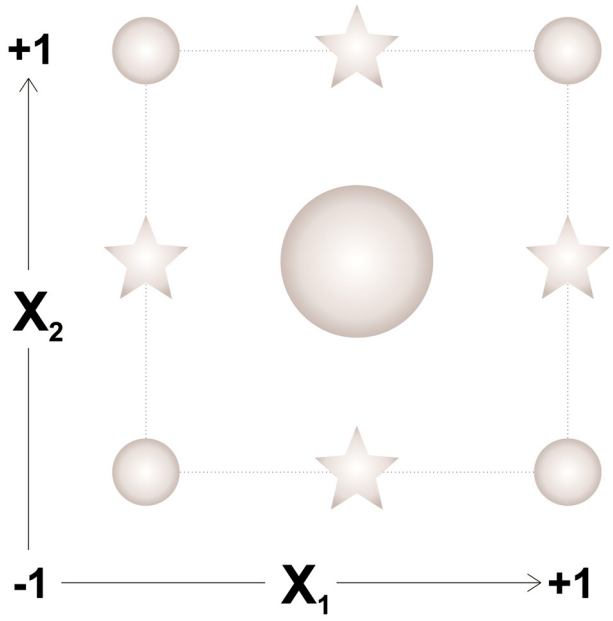

Figure 2.6.1: Star and centre points in face centred central composite design

2.7 Drug Profiles

2.7.1 Metoprolol succinate

Metoprolol succinate (MS), is a beta1-selective (cardio selective) adrenoceptor blocking agent, for oral administration. MS is chemically described as (±) 1(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt) [79]. Its empirical formula is $C_{34}H_{56}N_2O_{10}$ [80] and structural formula [79] is shown in Figure 2.7.1.

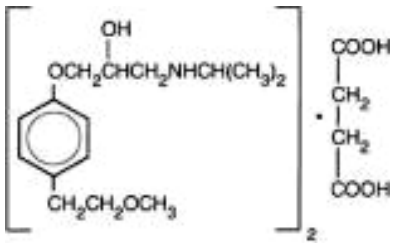

Figure 2.7.1: Structural formula of Metoprolol Succinate

MS is a white crystalline powder with a molecular weight of 652.8 g/mol. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptanes [81]. Some of the physical and biopharmaceutical properties of MS are given in Table 2.7.1.

Table 2.7.1: Physicochemical and biopharmaceutical properties of MS

Parameter	Value/Remarks
pH	Between 7.0 and 7.6
Melting point	136-138^{0}C
Volume of Distribution	5.6 L/kg
$t_{½}$	3 to 7 hours
pKa	9.5
Log P	1.6
Albumin Binding in plasma	About 12%
First pass metabolism	About 50%
Systemic Bioavailability	Approximately 50%

2.7.1.1 Mechanism of action

Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure.

2.7.1.2 Pharmacokinetics [82]

a. Absorption

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin.

b. Metabolism

Metoprolol is a racemic mixture of R- and S-enantiomers, and is primarily metabolized by CYP2D6. When administered orally, it exhibits stereoselective metabolism that is dependent on oxidation phenotype. Metoprolol is metabolized predominantly by CYP2D6, an enzyme that is absent in about 8% of Caucasians (poor metabolizers) and about 2% of most other populations. CYP2D6 can be inhibited by a number of drugs.

Concomitant use of inhibiting drugs in poor metabolizers will increase blood levels of metoprolol several-fold, decreasing metoprolol's cardio-selectivity.

c. Elimination

Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no beta-blocking activity. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

2.7.1.3 Adverse effects

The adverse reactions of metoprolol succinate extended release are a mixture of dose-dependent phenomena (primarily bradycardia and fatigue) and those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose independent phenomena (e.g., pancreatitis), the former much more common than the latter [83].

2.7.1.4 Analytical methods

The reported analytical methods for estimation of MS are as follows:

a. UV-spectrophotometric method

A simple accurate and sensitive UV-spectrophotometric method for estimation of MS in pH 6.8 Phosphate buffer was developed by Marucci, M., et al.,2013 [84].

b. HPLC method

A simple HPLC method was reported for MS analysis in plasma by Siddique et al 2010[85] The separation was performed on reverse phase OSD-AM column (4.6 X 250 mm). The mobile phase consist of mixture of phosphate buffer (pH 3, containing 0.5% triethylamine): methanol: acetonitrile (90:1:9). Flow rate was maintained 1.4 ml/min and compound eluted were recorded by UV detector at 274nm.

c. USP method

USP method is for determination of bulk drug is liquid chromatography. The liquid chromatograph is equipped with a 223 nm detector and a 4 mm X 12.5 cm column that contain 4µm packing L7. The column temperature is maintained at 30°C. The flow rate is about 0.9 ml/min [86].

2.7.1.5 Dosage and administration

Adult dose of MS for Hypertension (dose=25-100mg), Angina Pectoris (dose=100mg-gradually increased), and Heart Failure (dose=12.5-200mg).

Metoprolol succinate extended-release tablets are scored and can be divided; however, the whole or half tablet should be swallowed whole and not chewed or crushed.

Table 2.7.2: Review of work done on Metoprolol Succinate

Author (Reference no.)	Formulation	Technique	Polymer/Excipient used	Conclusion
R. Kumara velrajan et al. 2010 [87]	Osmotic tablet	Sandwiched osmotic tablet system	Polyethylene oxide 600,000 and 8,000,000 g/mole (PEO) and KCl	The sandwiched osmotic tablet system that could deliver Nifedipine and Metoprolol tartarate simultaneously for extended period of time was developed in order to reduce the problems associated with multidrug therapy of

				hypertension.
Gharge et al., 2014 [88]	Modified release tablet	FBP	HPMC, Ethylcellulose, Xanthan gum, Polyvinylpyrrolidone, Talc	Desired drug release pattern can be obtained by using a proper combination of HPMC and ethyl cellulose.
Vilas N. Malode et al. 2015 [89]	Floating multiparticulates	Hot melt extrusion (HME)	Eudragit® RS PO, polyethylene oxide (PEO) and hydroxypropyl methylcellulose (HPMC)	Controlled drug release upto12 h.
Ying Huang et al. 2015 [90]	Microspheres	Ultra-fine particle process system	Ethyl cellulose, Eudragit® RS 100	Sustained drug release upto 24 h.
Aleksandar Aleksovski et al. 2016 [91]	Matrix Tablet	Hot melt extrusion, compression of melt granulates and prilling	Mixed glycerides	Controlled drug release upto 24 h.
Nikhil Biswas et al. 2016 [92]	Mucoadhesive-floating beads	Ionotropic gelation method	Calcium chloride, calcium carbonate	Optimized formulation showed a higher percent inhibition of isoprenaline induced heart

				rate in rabbits for almost 12 h.
PATENTS				
Inventor	**Title**	**Description**		
Tomer Gold and Nava Shterman, 2007 [93]	Metoprolol succinate extended release tablets and methods for their preparation	The present invention provides extended release pharmaceutical compositions of a beta blocker such as, but not limited to, metoprolol succinate as the active ingredient and methods of preparing such extended release pharmaceutical compositions.		
Girish Jain, Mohan Kondapaturu, Utathya Bhadra 2007 [94]	Extended release compositions of metoprolol succinate	The present invention is a composition comprising Metoprolol succinate or its pharmaceutically acceptable derivatives thereof and the composition releases the drug over 24 hours. The composition further comprises hydrophilic polymer matrix based tablets. The present invention describes a sustained release tablet comprising sustained release matrix comprising of gelling agents comprising at least one hydrophilic polymer with one or more gum and gum derivatives.		
Joshi. P. S et al.2012 [95]	Multiple unit particulate system comprising metoprolol succinate	The extended release pellets of the invention comprise of water soluble or water swellable inert core, the drug layer and extended release polymer layer comprising at least one water insoluble polymer. These extended release pellets are compressed into tablets such that dissolution profile of the extended release pellets remains substantially unaffected.		
Mandaogade et al, 2014 [96]	Extended release dosage forms of metoprolol	Extended release dosage forms comprising a water insoluble and non-swellable inert core and one or more pharmaceutically acceptable excipients. The invention also relates to processes for the preparation of an inert core and extended release dosage forms.		

2.7.1.6 Formulations available

A glimpse at market scenario reveals that it is dominated by solid dosage form as 25mg, 50mg, 100mg, 200mg immediate release as well as extended release tablet and capsule.

Table 2.7.3: Metoprolol Succinate formulations with their introduction year

Product	**Year of introduction**
a) Metoprolol succinate immediate release tablet 25, 50, 100 and 200 mg	1978
b) Metoprolol succinate extended release tablet 25, 50, 100 and 200 mg	1992

2.7.2 Metformin hydrochloride

Metformin hydrochloride (MH) is a member of the biguanide class of oral antihyperglycemics. MH is chemically described as (N, N dimethylimidodicarbonimidic diamide hydrochloride). Its empirical formula is C4H11N5•HCl and structural formula is as shown in Figure 2.7.2.

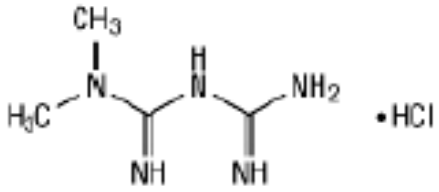

Figure 2.7.2: Structural formula of Metformin Hydrochloride

MH is a white to off-white crystalline powder with molecular weight 165.63 g/mol. It is freely soluble in water and is practically insoluble in acetone, ether, and chloroform [97]. Some of the physical and biopharmaceutical properties of MH are given in Table 2.7.4.

Table 2.7.4: Physicochemical and biopharmaceutical properties of MH

Parameter	**Value/Remarks**
pH (1% aqueous solution)	6.68±0.02
Melting point	232-236 °C
Volume of Distribution	654 ± 358 L
$t_{½}$	6.2 h

pKa	12.4
Log P	-0.5
Albumin Binding in plasma	Negligible
First pass metabolism	No
Systemic Bioavailability	50-60%

2.7.2.1 Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyper insulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

2.7.2.2 Pharmacokinetics [98]

a. Absorption

The absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin hydrochloride 500 mg to 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower mean peak plasma concentration (Cmax), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (Tmax) following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

b. Distribution

The apparent volume of distribution (V/F) of metformin following single oral doses of metformin hydrochloride 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 µg/mL. During controlled clinical trials of metformin, maximum metformin plasma levels did not exceed 5 µg/mL even at maximum doses.

c. Metabolism and elimination

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

2.7.2.3 Adverse effects

The most frequent adverse events thought to be related to Metformin HCl are diarrhoea, nausea, dyspepsia, flatulence, and abdominal pain [99].

2.7.2.4 Analytical methods

The reported analytical methods for estimation of MH are as follows:

a. UV-spectrophotometric method

A simple accurate and sensitive UV-spectrophotometric method for estimation of MH in pH 6.8 Phosphate buffer was reported in USP30 NF25 [100].

b. HPLC method

A simple HPLC method was reported for MH analysis in plasma by L. D. Hu et al., 2006 [101]. The separation was performed on Diamonsil^{TM}C18 column. The mobile phase

consist of mixture of methanol and 0.05mol L^{-1} $NH_4H_2PO_4$. The flow rate was maintained 1.0 ml/min and UV detector was set at 233nm.

c. USP method

USP method for determination of bulk drug is Potentiometric titration. 60 mg of MH is to be dissolved in 4mL anhydrous formic acid followed by addition of 50mL acetic anhydride. Titrate with 0.1N Perchloric acid and determine end point potentiometrically. Each mL of 0.1N Perchloric acid is equivalent to 8.28 mg of $C_4H_{11}N_5$.HCl [86].

2.7.2.5 Dosage and administration

According to the *Physician's Desk Reference*, the starting dose should be 500 mg of metformin twice a day. (An alternative option is 850 mg of metformin once a day). After one week, increase the dose of metformin to 1000 mg as the first dose of the day and 500 mg as the second dose. After another week, increase to 1000 mg of metformin two times a day. The maximum safe dose described in the *Physician's Desk Reference* is 2550 mg a day (which should be taken as 850 mg three times a day) [102].

Table 2.7.5: Review of work done on Metformin Hydrochloride

Author (Reference no.)	Formulation	Technique	Polymer/Excipient used	Conclusion
G.Di.Colo et al. 2002 [103]	Compressed matrix tablets	Co evaporation process	Poly(ethylene oxide) (PEO)–Eudragit® L100 (EUD L)	Gradual and complete release of MF·HCl from stomach to jejunum, unaffected by gastric pH fluctuations.
L.-D. Hu et al. 2006 [101]	MUPS	Centrifugal Granulation	Eudragit® L30D-55, Eudragit® NE30D	Metformin hydrochloride (MH) sustained-release pellets were successfully

				prepared by centrifugal granulation.
T.O. Oh et al. 2013 [104]	Porous matrix tablets	Sublimation method	Polyethylene oxide, Camphor, Hydroxypropyl cellulose	Floating for 24h observed. Oral administration of GR tablets in mini pigs showed an enhanced bioavailability as compared to commercial tablet formulation.
A.K. Nayak et al. 2014 [105]	Mucoadhesive beads	Ca2+ ion cross-linked ionic gelation	Tamarind seed polysaccharide, gellan gum (GG)	In vitro drug release showed controlled-release (zero-order) pattern over a period of 10 h.
Min. Xu et al. 2015 [106]	Sustained release pellets	Extrusion–spheronization	Ethyl cellulose, microcrystalline cellulose	Application of 400-DS dissolution apparatus 7 for individual pellet dissolution methodology by a design of experiment approach.
R. Priyadarshini	Extended release	Wet granulation	Polymethacrylamide-g-gellan (Pmaa-g-	Drug control up to 10h

et al.2016 [107]	matrix tablet	method (Composite matrix)	GG)-tamarind seed gum (TSG)	

PATENTS		
Inventor	**Title**	**Description**
Chandran et al.2005 [108]	Liquid formulation of Metformin	The liquid pharmaceutical composition comprises immediate release metformin in a liquid carrier, which also include sweetner that does not increase the blood glucose level of a subject after ingestion.
Chih-Ming Chen et al.,2011 [109]	Controlled release metformin formulations	The formulations provide therapeutic plasma levels of the antihyperglycemic drug to a human patient over a 24 hour period after administration.
Manish Chawala et al.,2004 [110]	Extended-release tablets of metformin	An extended-release metformin tablet, comprising about 500 mg to about 1000 mg metformin, 5-25% w/w rate-controlling polymer(s). The extended-release tablet wherein the cellulose derivative is selected from ethyl cellulose, methyl cellulose, hydroxymethyl cellulose or mixtures thereof.

2.7.2.6 Formulations available

A glimpse at market scenario revels that it is dominated by solid dosage form (immediate release as well as extended release). Solution / sachet available are for immediate release form only. IR Tablet: 500mg, 850mg, 1000mg; ER Tablet**:** 500mg, 750mg, 1000mg.

Table 2.7.6: Metformin Hydrochloride formulations and their introduction year

Product	Year of introduction
a) Metformin hydrochloride immediate release tablet 500, 850 and 1000 mg	1995
b) Metformin hydrochloride extended release tablet 500, 750 and 1000 mg	2000
c) Metformin hydrochloride immediate release solution 500, 1000 mg	2003

2.8 Excipients Profile

Detailed profiles of excipients are given in Appendix I.

2.9 Conclusions

Literature review of dosage forms currently available in the market for Metoprolol Succinate and Metformin hydrochloride revealed that no new dosage form has been introduced for these drugs since many years. Hence, current chronic therapies suffer from drawback of **poor patient compliance** and **market competition** due to **prevalence of same dosage form since long years**. Thus there exists a strong need to revive the stagnant growth phase of these product's respective life cycles.

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