1.1 Oral drug delivery

The oral route of drug delivery is typically considered the most favorable and preferred route of drug administration in case of conscious and co-operating patients because of convenience, possibility of self administration and enhanced compliance. More than 60% of drugs are marketed in the form of oral products [1, 2].

Oral solid dosage forms can be classified as follows:

A) Conventional immediate release dosage forms

B) Modified release dosage forms:

Delayed release

Sustained (Prolonged/ Extended) release

Site specific release

Conventional immediate release dosage forms are associated with fluctuations in plasma drug concentration; hence multiple dosing is required for maintaining a steady plasma level [3].

Modified-release formulation technologies offer an effective means to optimize the bioavailability and resulting blood concentration-time profiles of drugs that otherwise suffer from such limitations. Modified release dosage forms can be classified into single unit and multiple unit dosage forms. Single unit modified release dosage forms include matrix or reservoir tablets, osmotic tablets etc. Multiple unit modified release dosage forms include pellets, microspheres etc.

1.2 Multiple unit particulate system (MUPS)

Multiple Unit Particulate system (MUPS) consists of dosage form in which the desired dose is distributed evenly onto multiple (hundreds) units which are typically in the size range of 5-2000µ [4]. As compared to the conventional non-disintegrating single-unit modified-release dosage forms, MUPS have gathered much more attention due to following advantages [5]:

- MUPS distribute more uniformly in the gastro intestinal tract, resulting in better drug absorption.

- The multiplicity ensures a good reproducibility of gastric transit kinetics of the drug throughout gastro intestinal tract, thereby improving control of the bioavailability and ultimately improving therapeutic efficacy.
- MUPs also reduce variation in gastric emptying rates and overall transit times, so that intra and inter subject variability of plasma level is minimized.
- The release profile of a drug can be tailored by using a mixture of microparticulates with different release pattern, thus ensuring a constant (or desired) plasma concentration level of the drug.
- Coated microparticulates of different drugs can also be effectively combined without intimate contact with each other, thus avoiding potential incompatibility, if any.
- Since each microparticle contains a reduced dose of the drug(s), the risk of damage to the tissue due to a high local concentration of the drug(s) is also reduced

MUPS with modified release properties are generally formulated into capsule or tablet. However, formulation of MUPS into tablet, the most preferred dosage form, is a challenging task as it encounters problems like segregation, fusion or rupture of the functional microparticles etc [6]. These microencapsulated products should neither be crushed nor chewed, since it destroys the modified-release property of such products, resulting in erratic blood levels, dose dumping and in some cases toxicity [7]. Moreover, these solid formulations are not always advantageous, especially in case of patients suffering from dysphagia. 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 [8]. Hence, there is an **acute need to develop a drug delivery system which can combine the advantages of MUPS as well as are easy to swallow like controlled release powder for reconstitution and controlled release orally disintegrating tablet**.

Formulating a convenient dosage form like controlled release powder for reconstitution (CRPFR) or controlled release orally disintegrating tablet (CRODT), can provide novel means of overcoming the potential barriers associated with the administration of MUPS to children, elderly and patients unwilling to swallow the solid oral medication.

MUPS formulated into powder for reconstitution will enable patients to easily prepare the suspension which is physically and chemically stable. ODT containing MUPS can be easily administered to patients having difficulty in swallowing, by simply placing the tablet in the oral cavity. Further, these dosage forms will retain the tablet attributes of **ease of handling, transportation and storage**. Despite palpable advantages of these alternate dosage forms, till date very few CRPFR or CRODT are available in the market. This is due to challenges associated with their formulation development, like minimizing the diffusion of drug into the suspending vehicle upon reconstitution or during storage in case of CRPFR [9] and avoiding rupture of functional coat in case of CRODT [7].

1.3 Chronic disorders

Chronic disorders are characterized by long duration and generally slow progression. Chronic disorders like diabetes, hypertension, cardio vascular and central nervous system disorders are the leading cause of mortality in the world, representing 63% of all deaths [10].

1.3.1 Drawbacks encountered in chronic therapy

1.3.1.1 Dysphagia

A condition in which a person experiences difficulty in swallowing is termed as **dysphagia**. Major drawback associated with chronic therapy is that the patient has to daily take the medicine often several times, which causes non-compliance with the therapy. Extended release formulations have arisen to solve this problem. However, daily administration of drug/s in case of chronic diseases decrease patient compliance especially in patient population which includes pediatrics, geriatrics and hospitalized patients. Factors associated with dysphagia are:

Age: Children and adolescents, as well as the elderly, are more likely to have difficulty swallowing tablets or capsules. There is no set age at which children are able to swallow solid medicines, but some can struggle until they reach their early teens and even beyond. Around 60% of people aging over 60 struggle to take solid medicines like tablets or capsules at some time[11].

Dry mouth: In older age less saliva is produced in the mouth which makes swallowing tablets more difficult. Also some medicines like tricyclic anti depressant can cause mouth dryness [12].

Medical conditions: Body position, fluid intake, and the presence of certain medical conditions like Parkinson's, Alzheimer's and motor neurone disease (e.g., multiple sclerosis, muscular dystrophy) can affect a person's ability to swallow solid medicines. For instance, around 50% of people with Parkinson's disease have difficulty with swallowing. People with long term diabetes may develop some degree of swallowing problems. After having a stroke, many people have swallowing difficulties for at least first few months. In the early stages of stroke, nearly 80% of patients have some sort of swallowing problem [13].

Throat or neck problems - Tumours or radiotherapy in this area can lead to swallowing difficulties.

Thus variety of factors affects the ability of a patient to swallow a tablet or capsule. Although not all patient factors can be addressed through pharmaceutical design and manufacture, the physical characteristics of a drug product can be addressed. Moreover, drugs used in chronic therapies belong to various classes of BCS. Hence development of a **common platform technology** for effective delivery of these medicaments becomes difficult.

1.3.2 Cardio vascular disorders

Heart disease or cardiovascular disorders is the class of disorders that involves heart or blood vessels. Cardiovascular disease (high blood pressure, coronary heart disease, heart attack, stroke, etc.) is the leading cause of death in developed countries. As per WHO report published in 2013, globally cardiovascular disease accounts for approximately 17 million deaths a year, nearly one third of the total. Of these, complications of hypertension account for 9.4 million deaths worldwide every year. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke [14].

Metoprolol succinate (MS) is an oral beta1-selective adrenoceptor blocking agent indicated for long term treatment of hypertension, angina pectoris and heart failure. The

main disadvantage of beta blockers in general is that it may cause hypotension, bradycardia and heart failure in patients suffering from asthma and peripheral vascular diseases. In such cases, maintenance of constant plasma concentration can avoid these adverse effects. **Plasma half life varies from 3-7 h**. It is absorbed throughout GIT and undergoes metabolism in liver to inactive metabolites. Plasma levels following oral administration of conventional MS tablets, however, fall to approximately 50% of levels following intravenous administration, thereby indicating about **50% first-pass metabolism** [15].

1.3.3 Diabetes

It is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin or because cells do not respond to the insulin that is produced. As per WHO, in 2014 the global prevalence of diabetes was estimated to be 9% among adults aging above 18 years. In 2012, an estimated 1.5 million deaths were directly caused by diabetes. The WHO estimates that diabetes will be the 7th leading cause of death in 2030 affecting 439 million people globally [16]. As per same estimation, the prevalence in India was expected to be 7.1%, affecting 50.76 million adults in 2010 which would increase to 8.6% and 87.03 million adults by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries. 36% of the anticipated absolute global increase of 154 million people with diabetes is projected to occur in India and China alone [17]. The cost of treating diabetes and its complications exceeds $100 billion annually. In India, there are going to be 80% of all diabetics from the entire world population, making it the diabetic capital of the world [18].

Metformin hydrochloride (MH) is a biguanide anti hyperglycemic medication that has been proven to be safe and effective in patients with Type 2 diabetes with minimal risk of hypoglycemia. Chemically it is N, N-dimethylimidodicarbonimidic diamide available as hydrochloride salt. Unlike the mechanism of action of other oral agents used to treat Type 2 diabetes, MH has been shown to reduce the rate of glucose production through a reduction in hepatic gluconeogenesis. Additionally, it improves peripheral sensitivity to insulin in the muscle and adipose tissue. Patients treated with MH generally do not gain weight and some may even lose weight. MH has an **oral bioavailability of 50–60%**

under fasting conditions. The average elimination half-life in plasma is 6.2 h. It does not undergo hepatic metabolism or biliary excretion [19].

1.4 Problems associated with Metoprolol succinate and Metformin hydrochloride

1.4.1 Dosing frequency/ plasma drug levels

The conventional immediate release dosage forms are associated with fluctuations in plasma drug concentration, hence multiple dosing are required to maintain a steady plasma level. Daily administration of medication in case of chronic diseases in solid dosage form would decrease patient compliance to the existing therapy [20]. Thus, there exists a strong need for development of controlled release dosage forms which are easy to swallow and promote patient compliance by reducing the dosing frequency and the fluctuations in the plasma drug concentration, thereby providing a more uniform therapeutic effect over time for MS and MH. The enhanced therapeutic efficacy for such drugs through the provision of constant rate input and maintenance of steady-state blood levels is well documented [21]. Moreover, dosage form containing MUPS would be advantageous over a single unit dosage form as it will distribute more uniformly in the gastro intestinal tract, resulting in better drug absorption. The multiplicity will ensure a good reproducibility of gastric transit kinetics of the drug throughout GIT, thereby improving control of bioavailability and ultimately improving therapeutic efficacy.

1.4.2 Life cycle management

As one of the most important strategies for **Life Cycle Management** (LCM), new drug delivery systems provide commercial opportunities through intellectual property, product differentiation and recognition. By **infusing the existing drug into an enhanced delivery system**, this strategy is valuable and cost-effective in the management of overall product lifecycle resource. **It improves the product's therapeutic benefits and patient's convenience as well as compliance to the therapy**. With extended product's profitable life, it also fends off generic competition and gives back financial advantages to pharmaceutical companies [22]. Formulation technologies for LCM are numerous and include modified-release for oral delivery, taste masking, ODT, depot formulations, emerging technologies for bioavailability enhancement, etc. Over the years, a variety of

platform technologies have also emerged, many of which led to the success of marketed products [23].

Developing oral sustained release dosage form for highly soluble drugs like MS and MH has always been a challenge for the pharmaceutical scientists [24, 25]. No new dosage form has been introduced for MS and MH since many years (Table 1.4.1). Hence current chronic therapies suffer from drawback of **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 marketed product's life cycles.

Table 1.4.1: Dosage form introduction in US market for MS and MH

Product	**BCS Class**	**Year of introduction**
a) Metoprolol succinate immediate release tablet 25, 50, 100 and 200 mg	Class I	1978
b) Metoprolol succinate extended release tablet 25, 50, 100 and 200 mg		1992
a) Metformin hydrochloride immediate release tablet 500, 850 and 1000 mg	Class III	1995
b) Metformin hydrochloride extended release tablet 500, 750 and 1000 mg		2000
c) Metformin hydrochloride immediate release solution 500, 1000 mg		2003

Even the European Medicines Agency (EMA) recommends the pharmaceutical industry through its guideline on Pharmaceutical Development of Medicines for Pediatric Use to investigate the feasibility of bringing different dosage forms to the market (e.g. oral liquid) [26].

Hence, formulation of alternate drug delivery systems for drugs used in such conditions can improve patient compliance for pediatric, geriatric and hospitalized patients. Also, the US FDA recommends the pharmaceutical industries to design and develop drug products to minimize swallowing difficulties, which can encourage and improve patient

compliance with medication regimens along with use of Quality by design approach [27].

1.5 Quality by design (QbD)

Quality by design (QbD), a science and risk based approach is one of the recent tools in pharmaceutical development. Product development by QbD approach ensures that the quality is build into the product and not just checked terminally. It requires an understanding of how product and process variables influence product quality. The target or goal which consists of elements that define the drug product is termed as Quality Target Product Profile (QTPP). A subset of these elements that are likely to change based upon formulation and process variations are called as Critical Quality Attributes (CQAs). Risk management strategy is applied to control these attributes and reduce the associated risk using tools like Failure Mode Effect Analysis (FMEA). Optimization of formulation development is carried out to determine a design space using design of experiment (DoE).Thus, all these techniques are helpful in formulation development as DoE helps to establish a design space (changes within which would yield similar results), study the presence of interactions of one or more variables on each other. FMEA helps to anticipate the potential chances of failure and risk involved during various stages of formulation development. Hence, they help to evaluate all the potential factors simultaneously, systematically and speedily [28].

1.6 Objective

The objective of the present study was to prepare controlled release multi unit particulate system, by QbD approach utilizing DoE technique, which can be easily formulated into controlled release powder for reconstitution and controlled release orally disintegrating tablet, suitable for administration in patients who are unable or unwilling to swallow oral medication; for example pediatric and geriatric patients or patients suffering from dysphagia.

These alternate dosage forms would be interesting for the pharmaceutical market in terms of therapeutic (increased patient convenience, enhanced compliance to the therapy, sustained release of drug, reduced dosing frequency) and commercial aspects (extend

product's profitable life, add on to the existing product portfolio, find new markets and continue growth phase of the product's life cycle).

1.7 Hypothesis

The present work would provide platform technology for manufacturing CRPR and CRODT dosage forms while overcoming the associated difficulties in formulation development of the same. It may serve as a platform technology particularly for drugs like **metoprolol succinate** and **metformin hydrochloride** which are required to be administered chronically or for a long period of time. In addition it may also be beneficial for high dose drugs which need to be administered for longer duration or for those drugs which need to be administered frequently or in conditions wherein the patient suffers from dysphagia or in case where the patient has difficulty/ inability of swallowing.

1.8 Plan of work

- Literature survey, procurement of APIs and excipients
- Analytical method selection/ development (UV/HPLC)
- Preformulation studies – Screening of excipients and characterization of API, Drug Excipient compatibility studies
- Formulation of MUPS for Metoprolol succinate and Metformin HCl
- Optimization of process and formulation variables by DoE
- Formulation of CRPFR and CRODT
- *In vitro* characterization and drug release studies of above formulations
- Stability studies – Short term stability studies as per ICH guidelines
- *In vivo* pharmacokinetic studies

REFERENCES

[1] M.N. Siddiqui, G. Garg, P.K. Sharma, A short review on "A novel approach in oral fast dissolving drug delivery system and their patents", Advances in Biological Research, 5 (2011) 291-303.
[2] A.K. Anal, Time-controlled pulsatile delivery systems for bioactive compounds, Recent patents on drug delivery & formulation, 1 (2007) 73-79.
[3] J. Robinson, V.H. Lee, Controlled drug delivery: fundamentals and applications, Informa Health Care, 1987.
[4] N. Dey, S. Majumdar, M. Rao, Multiparticulate drug delivery systems for controlled release, Tropical Journal of Pharmaceutical Research, 7 (2008) 1067-1075.
[5] S. Abdul, A.V. Chandewar, S.B. Jaiswal, A flexible technology for modified-release drugs: multiple-unit pellet system (MUPS), Journal of Controlled Release, 147 (2010) 2-16.
[6] A. Dashevsky, K. Kolter, R. Bodmeier, Compression of pellets coated with various aqueous polymer dispersions, International journal of pharmaceutics, 279 (2004) 19-26.
[7] S.H. Jeong, K. Park, Development of sustained release fast-disintegrating tablets using various polymer-coated ion-exchange resin complexes, International journal of pharmaceutics, 353 (2008) 195-204.
[8] J.J. Hirani, D.A. Rathod, K.R. Vadalia, Orally disintegrating tablets: a review, Tropical Journal of Pharmaceutical Research, 8 (2009).
[9] M. Cuna, J.V. Jato, D. Torres, Controlled-release liquid suspensions based on ion-exchange particles entrapped within acrylic microcapsules, International Journal of Pharmaceutics, 199 (2000) 151-158.
[10] W.H. Organization, WHO, Global status report on noncommu-nicable diseases 2010, WHO Library Cataloguing-in-Publication Data, in, ISBN 978-92-4-156422-9, 2011.
[11] I. Strachan, M. Greener, Medication-related swallowing difficulties may be more common than we realise, Pharm Pract, 15 (2005) 411-414.
[12] C. Nordqvist, Dysphagia: Symptoms, Diagnosis and Treatment, in: Medical News Today. MediLexicon, Intl.
[13] D. Wright, N. Chapman, M. Foundling-Miah, R. Greenwall, R. Griffith, A. Guyon, H. Merriman, Consensus guideline on the medication management of adults with swallowing difficulties, Berkhamsted: Medenium Group Publishing, (2006) 1-8.
[14] S. Mendis, Hypertension: a silent contributor to the global cardiovascular epidemic, in: Reg Health Forum, 2013, pp. 1-6.
[15] USFDA, Prescribing Information for Toprol-XL
[16] W.H. Organization, Diabetes Action Now Booklet, in.
[17] J.E. Shaw, R.A. Sicree, P.Z. Zimmet, Global estimates of the prevalence of diabetes for 2010 and 2030, Diabetes research and clinical practice, 87 (2010) 4-14.
[18] A. B, India: The Diabetic Capital of The World in, 2010.
[19] USFDA, Prescribing Information for Glucophage, in, USA.
[20] D. Yadav, S. Survase, N. Kumar, Dual coating of swellable and rupturable polymers on Glipizide loaded MCC pellets for pulsatile delivery: Formulation design and in vitro evaluation, International journal of pharmaceutics, 419 (2011) 121-130.

[21] V. Pillay, R. Fassihi, A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system, Journal of controlled release, 67 (2000) 67-78.
[22] C. Darwin, Product Life Cycle Management In Pharmaceuticals: A Review, Pharmatutor, 1-3.
[23] J. Stark, Product lifecycle management, in, Springer, 2016, pp. 35.
[24] S. Siddique, J. Khanam, P. Bigoniya, Development of sustained release capsules containing "coated matrix granules of metoprolol tartrate", AAPS PharmSciTech, 11 (2010) 1306-1314.
[25] D.-W. Kim, J.-B. Park, Development and pharmaceutical approach for sustained-released metformin succinate tablets, Journal of Drug Delivery Science and Technology, 30 (2015) 90-99.
[26] E.M. Agency, Guideline on pharmaceutical development of medicines for paediatric use in, pp. EMA/CHMP/QWP/805880/802012 Rev. 805882.
[27] F. U.S. Department of Health and Human Services, Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules, in, June 2015 pp. Pharmaceutical Quality/CMC.
[28] S. Kan, J. Lu, J. Liu, J. Wang, Y. Zhao, A quality by design (QbD) case study on enteric-coated pellets: Screening of critical variables and establishment of design space at laboratory scale, asian journal of pharmaceutical sciences, 9 (2014) 268-278.