THESIS ISSN: 2349-2678

Contents lists available at www.ijpba.in
International Journal of Pharmaceutical and Biological Science Archive
PubMed (National Library of Medicine ID: 101738825)
Index Copernicus Value 2017: 71.80
Volume 7 Issue 2; March-April; 2019; Page No. 57-79

"FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF MIRABEGRON

Ms. Kajal A Prajapati

PG Research Scholar, Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat

Dr. Dhara B Patel

Associate Professor, Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat

Mr. Anil G Raval

Assistant Professor, Department of Pharmaceutics, Sharda School of Pharmacy, Pethapur, Gandhinagar, Gujarat

ABSTRACT

Mirabegron Orally Disintegrating Tablets were prepared using a direct compression approach with a novel approach of combining effervescence agents and super disintegrants to achieve a rapid disintegration. A screening study was performed using Crospovidone XL 10, Croscarmellose Sodium and Sodium Starch Glycolate at two levels to least Disintegration Time, which was achieved by Croscarmellose Sodium. The prepared tablets were evaluated for Weight variation, Thickness, Hardness, Disintegration time, Dissolution, and Water uptake study. A full factorial statistical optimization was carried out on the best optimized formulation to establish the design space for selected factors i.e., Level of Effervescence agents and Croscarmellose Sodium against Response Disintegration Time and Dissolution. A significant effect of both factors was found on DT as well as Dissolution rate, which justifies the use and rationale of the excipients.

Key words: Mirabegron, ODT, Direct Compression, Effervescence agents, Super disintegrants

1. INTRODUCTION

1.1 Introduction of Drug Delivery System

1.1.1 Introduction of Orodispersible tablets [1-5]

Regardless of colossal advancements in the field of medication conveyance, the oral course remains the most favored course of organization of helpful operators due to the reasons like exact portion, minimal effort, plausibility of self drug, simplicity of organization and non obtrusive technique, the general impact being the abnormal state of patient consistence. Among the oral measurement frames tablets and cases have more extensive acknowledgment.

One noteworthy disadvantage of such measurement shapes is 'dysphagia' or trouble in gulping. In cases like movement affliction, sudden assaults of unfavorably susceptible hack and inaccessibility of water, gulping customary strong measurements structures might be troublesome. This trouble is basically met by pediatric and geriatric patients.

In 1998 a CDER Nomenclature Standards Committee confined the accompanying definition for an ODT as another measurement shape: "A strong dose frame containing therapeutic substances which break down quickly, for the most part inside only seconds, when put upon the tongue". "These are recognized as a different measurement frame in view of the particular, planned execution qualities of such an item, which are quick oral breaking down in salivation with no requirement for biting or drinking fluids to ingest these items. These qualities, which are a guide to quiet utilize and consistence, are the essential attributes that establish the reason for characterizing an item as an ODT".

**Corresponding author: Ms. Kajal A Prajapati |*

As of late, the European Pharmacopeia received the term orodispersible tablet for a tablet that scatters or breaks down in less than 3 minutes in the mouth before gulping. Since the tablets break down inside the mouth, medications might be caught up in the buccal, pharyngeal and gastric locales. Therefore, quick medication treatment mediation and expanded bioavailability of medications are conceivable. Since the pre-gastric medication ingestion evades the primary pass digestion, the medication portion can be lessened if a lot of the medication is lost through the hepatic digestion.

1.1.1 Methods for manufacturing of ODTs :- [5, 6]

A. Freeze drying or Lyophilization

This is a process of preparing an orally disintegrating tablet containing pharmaceutically active substance by removing solvent from a solution or suspension of drug. Suspension can be a ceaseless period of coarse particles of pharmaceutically dynamic substance in a bearer material, diminishing the temperature of the suspension to build the thickness of suspension and limit sedimentation of particles. This structures discrete units of the cooled suspension. Ceaseless stage can be expelled to create quickly breaking down structures.

B. Molding

Molded tablets have quick dissolution, accepted stability and taste. This dosage form is suitable for the administration of drugs with unpleasant taste. The tablet triturate form includes a cementary network constituted by a water soluble but ethanol insoluble carbohydrate.

C. Cotton candy process

This involves the formation of a particulate support matrix which dissolves or disintegrates in few seconds, when placed in aqueous environment. First step consists of formation of a porous particulate powder matrix. In the second step, drug and additives are added to the mixture. Third step consists of converting this mixture into tablet.

D. Spray drying

Process involve the formulation of a particulate support matrix for making tablet which dissolve or disintegrate in a matter of few seconds once placed in the oral cavity. The support matrix can be comprised of two polymeric components, one may be non hydrolyzed gelatin and the second may be a hydrolyzed gelatin and a bulking agent. The porous particulate powder can serve as the tablet support matrix, to which the drug can be added.

E. Melt granulation

In this method a hydrophilic waxy binder, super polystate is made use of. This material not only acts as a binder but also helps in the disintegration of tablets as it melts in mouth and solubilises very rapidly without leaving residues.

F. Direct compression method

This is the most popular method for the manufacture of ODTs. This may be due to the reasons like, it is the simplest and cost effective tablet manufacturing technique. We require only the conventional tablet manufacturing and packaging machine. Excipients with improved flow, compressibility and disintegration properties such as disintegrants are easily available.

1.1.2 Superdisintegrants [7, 8]

The disintegration and dissolution of directly compressed tablets depends on the disintegrants used. Superdisintegrants are the agents which are effective at lower concentrations with greater disintegrating efficiency and mechanical strength. The swelling of disintegrant particles is perhaps the most widely accepted mechanism for tablet disintegration.

This is because almost all disintegrants swell to some extent. Disintegration time of the tablet can be optimized by focussing on the concentration of the disintegrants used. If the concentration is lower than the critical level, disintegration may be in the opposite direction. Above the optimum level the

disintegration time may remain almost constant. Table 3 enlists some commonly used superdisintegrant in the preparation of orodispersible tablets.

Table 1: Commonly used super disintegrants in the preparation of ODTs

Superdisintegrant	Mechanism of action
Croscarmellose	In less than 10 sec, swells 4-8 folds. It has both swelling and wicking property
Crospovidone	Swells very little
Sodium starch glycolate	Water uptake followed by rapid and enormous swelling
Acrylic acid	Wicking action
Sodium alginate	Swelling
Carnboxy methyl cellulose	Wicking action

1.1.3 Mechanism of action of superdisintegrant [8]

a. Swelling is considered as a mechanism by which the disintegrant exert its effect. When comes in contact with water tablet swells and burst apart.
b. Porosity and capillary action (wicking) Aqueous media penetrate into a tablet. This causes replacement of air adsorbed and causes weakening of intermolecular bond and breaking of tablets into fine particles.
c. Due to particle - particle repulsive force The repulsive force between particles is sometimes responsible for disintegration
d. Due to deformation during the compression of tablets the particles may get deformed. It may return to its original structure when come in contact with aqueous media.

1.1.4 Advantages of ODTs [9]

- ✓ Ease of administration to patients who cannot swallow the solid oral dosage forms.
- ✓ Enhancement of bioavailability.
- ✓ Rapid drug therapy intervention.
- ✓ Beneficial for travelling people and those who do not have easy access to water
- ✓ Rapid dissolution of drug and absorption which may produce rapid onset of action
- ✓ Obstruction free dosage form, since it dissolves in the mouth.

1.1.5 Challenges to develop ODT [10]

- ✓ Minimum or no residue in the mouth
- ✓ Rapid disintegration and sufficient mechanical strength
- ✓ Good mouth feel
- ✓ Taste masking for bitter drugs

Allow the manufacture using conventional processing and packaging equipments.

1.1.6 Solubility Enhancement [11, 12]

Solvency is plot in quantitative terms in light of the fact that the centralization of the issue amid an immersed reply at a correct temperature and in subjective terms, it ought to be laid out on the grounds that the unconstrained communication of 2 or a ton of substances to make an unvaried atomic scattering. A soaked answer is one amid which the issue is in harmony with the dissolvable.

The dissolvability of a medication could likewise be communicated as components, rate, molarity, molality, volume portion, and mole part. Medication dissolvability is that the most centralization of the medication substance broke down inside the dissolvable underneath particular state of temperature, pH scale and weight. The medication solvency in immersed answer could be a static property wherever in light of the fact that the medication disintegration rate could be a dynamic property that relates extra intently to the bioavailability rate. The dissolvability of a medication is depicted in shifted enlightening terms that depends on the quantity of medication broke up in dissolvable and said in Table-4.

Table 2: Definitions of solubility

Descriptive terms	Approximate volume of solvent in ml per gram of solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very Slightly Soluble	From 1000 to 10000
insoluble	More than 10000

1.1.7 Need of Solubility [13]

Medication retention from the stomach related tract is frequently confined by a scope of things most fundamental supporter being poor fluid dissolvability and poor film porousness of the medication atom. Once regulated a brimming with life operator orally it should first break up in stomachal as well as viscus liquids before it will pervade the layers of the obnoxious individual to accomplish dissemination. Thus, 2 zones of pharmaceutical examination that work in up the oral bioavailability of dynamic specialists incorporate; improving of solvency and disintegration rate of inadequately water dissolvable drug.

The BCS could be a logical system for grouping a medication substance bolstered its paired compound solvency and interior organ permeability. With respect to BCS class II and IV solution rate restricting advance is tranquilize release from the dosage write and solvency in inward organ liquid and not the assimilation, in this manner expanding the dissolvability progressively increment the bioavailability for BCS classification II and IV drug. BCS framework is said in Table-5.

Table 3: Biopharmaceutical Classification system

BCS Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

The change of medication dissolvability in this way its oral bioavailability stays one among the preeminent troublesome parts of medication improvement technique especially for oral-sedate conveyance framework. There ar shifted approaches available and supposed in writing to strengthen the solvency of inadequately dissolvable drug. The methods ar picked on the possibility of beyond any doubt viewpoints like properties of medication into account, nature of Excipients to be hand-picked, and nature of gathered measurements kind. The poor solvency and low disintegration rate of ineffectively water solvent solution inside the twofold compound channel liquids ordinarily cause light bioavailability. Especially for advancement II (low solvency and high penetrability) substances with regards to the BCS, the bioavailability could likewise be expanded by expanding the dissolvability and disintegration rate of the medication inside the channel liquids. Concerning BCS classification II medicine rate restricting advance is sedate release from the measurements kind and dissolvability inside the inward organ liquid and not the ingestion, thusly expanding the solvency progressively will build the bioavailability for BCS classification II pharmaceutical.

1.1.8 Methods for Solubility Enhancement [14]

The change of oral bioavailability of inadequately solvent prescription stays one among the first troublesome parts of medication improvement however salt arrangement, solubilization, and molecule estimate lessening have normally been acclimated increment the disintegration rate and along these lines oral retention and bioavailability of such medicine.

A. Particle Size Reduction

- Conventional methods
- Micronization
- Nanosuspension

B. Hydrotropy
C. Cosolvency
D. Solubilization by Surfactants

E. Solid Dispersion

- The fusion (melt) method
- The solvent method
- Dropping method

A. pH adjustment
F. High Pressure Homogenization
G. Supercritical fluid recrystallization(SCF)
H. Sonocrystallisation
I. Complexation

- Physical Mixture
- Kneading method
- Co-precipitate method

J. Spray Drying
K. Inclusion Complex Formation-Based Techniques

- Kneading Method
- Lyophilization/Freeze-Drying Technique
- Microwave Irradiation Method

L. Liquisolid technique
M. Micro-emulsion
N. Self-Emulsifying Drug Delivery Systems
O. Neutralization
P. Cryogenic Method
Q. Polymeric Alteration
R. Salt formation

Solid Dispersion [15]

A pharmaceutical strong scattering is relate insinuate blend of a medication substance (solute) with diluents, named a transporter (dissolvable or consistent stage). Strong scattering frameworks amid which the medication is dispersed in strong water dissolvable grids either molecularly or as fine particles have furthermore demonstrated promising lead to expanding bioavailability of inadequately solvent drug.

Among the systems to broaden twofold compound solvency/disintegration rate the plan of strong scatterings is one in all the chief far reaching ones. when dissolving the strong scatterings, it's trusted that the medication substance in free as meager separate units in view of a snappy disintegration of the basically solvent bearer. On the off chance that the medication dissolvability inside the transporter is sufficiently high, a claimed arrangement will be gotten. Such an arrangement would then be able to gives a framework simply like a sub-atomic determination once the transporter has been broken down. For such frameworks it's been asserted that the disintegration of the transporter is that the rate – constraining advance. The development of arrangement is in this manner unremarkably limited to similarly low grouping of medicine.

The term strong scattering alludes to the scattering of 1 or a considerable measure of dynamic fixings in relate degree latent bearer or grid at strong state prepared by the liquefying (combination), "dissolvable or the softening dissolvable philosophy." The scattering of a medication or medicine amid a strong diluents or diluents by antiquated mechanical commixture isn't encased amid this class. The strong scattering may moreover be alluded to as strong state scattering.

1.1.9 Classification [16]

Solid dispersions have been classified mainly into five major categories

a. *Simple eutectic mixtures,*
b. *Solid solutions,*
c. *Glass solutions of suspension,*
d. *Compound or complex formations between the drug and the carrier,*
e. *Amorphous precipitations of a drug in a crystalline carrier.*

Preparation of Methods of Solid Dispersion [16]

Generally, there are two methods employed to prepare the solid dispersion: fusion or solvent process.

1. Fusion Process

In the combination procedure of readiness, the bearer is warmed to a temperature essentially higher than its temperature and accordingly the medication is consolidated into the framework. The blend is cooled with steady mixing to homogeneously scatter the medication all through the lattice. an essential impediment of the combination strategy of planning is that the introduction of prescription to raised temperatures, fundamentally if the bearer might be a high-liquefying strong and in this way the medication is warm touchy.

Advantages:

This technique is to a great degree suitable for prescription and transporter that square measure miscible inside the liquefied state, making softening of the fixings horribly easy to achieve. making prepared strong scattering by the relax procedure isn't time extraordinary. in this manner a few clumps of the stock might be prepared {in a|during a|in an exceedingly|in a terribly} brief time. the strategy is also profitable for aggravates, that don't bear essential warm corruption.

Disadvantages:

The primary inconveniences of the mollify procedure grasp warm debasement, sublimation, and compound change, which may affect the concoction science properties of the medication together with its rate of disintegration. The disintegration or warm debasement is regularly piece reliant and covered with liquefying time and along these lines the rate of cooling.In request to downsize decay to satisfactory levels, dissolving is likewise distributed at a temperature basically higher than the absolute best softening component of the scattering, that completely liquefies each medication and thusly the bearer.

2. Solvent Method:

In the dissolvable technique of readiness, the transporter and thusly the dynamic fixing square measure broke down amid a fitting natural dissolvable. This dissolvable is vaporous at Associate in Nursing hoisted temperature or underneath vacuum. since the dissolvable is being evacuated, super immersion happens took after by cooccurring precipitation of the constituents prompting a strong buildup. The coprecipitate is then dried underneath vacuum to drive out any dissolvable openly sticking to the molecule surface.

Advantages:

The technique is proper for prescription that zone unit thermolabile; diminished weight and lower temperatures will be wont to dissipate dissolvable. For fluid frameworks, solidified temperatures will be wont to vanish the dissolvable, which may improve the trustworthiness of the medication.

Disadvantages:

Finding an appropriate solvent that may dissolve each the drug and therefore the carrier is extremely troublesome and generally not possible. this can be as a result of most of the carriers square measure deliquescent whereas most of the medication square measure hydrophobic organic substances. this might be additional difficult by the actual fact that completely different|completely different} polymorphic styles of a similar drug is also obtained if different solvents square measure used. antihypertensive dispersions in polyvinylpyrollidone were gaseous from solutions of fermentation alcohol, acetonitrile, and chloroform, severally.

1.1.10 Characterization of Solid Dispersions [16]

A number of methods have been used to characterize solid dispersions including.

1. Differential Scanning Calorimetry:

DSC may be a offline used thermo analytical technique that generates knowledge on melting endotherms and glass transitions. Thermal analysis of samples is often administrated on a differential scanning measurement (DSC).

2. Powder X-ray Diffraction:

Powder diffraction is accustomed qualitatively find material with long vary order. cheater optical phenomenon peaks indicate a lot of crystalline material. Recently developed X-ray instrumentation is semiquantitative.

3. Microscopial Studies:

Polarized microscope has been accustomed examine the nucleation and crystal growth dynamics .Polarized microscope is a lot of sensitive than DSC or XRD in police work the onset of conversion from the amorphous to crystalline drug in solid solutions. Typically, samples are often examined beneath the polarized microscope and pictures are often taken victimisation photographic camera and analyzed by the Motic pictures and 2.0 software.

4. Spectroscopic Methods:

Especially I.R: FTIR spectra are often accustomed sight polymer-drug interactions by following the shift in undulation or stretching bands of key practical teams. This methodology has been utilized to spot polymer-drug interactions in solid molecular dispersions.

5. Dissolution Rate Determination:

Dissolution measurement measures the energy of dissolution that relies on the crystallinity of the sample. Usually, dissolution of crystalline material is energy-absorbing, whereas dissolution of amorphous material is energy-releasing.

1.2 Introduction of Disease

- **Over Reactive Bladder [17, 18]**

Overactive bladder (OAB) is a typical condition that influences a huge number of individuals. Overactive bladder isn't an illness. It's the name of a gathering of urinary side effects. The most widely recognized side effect of OAB is a sudden inclination to urinate that you can't control. A few people will spill pee when they feel the desire. Spilling pee is classified "incontinence." Having to go to the washroom commonly amid the day and night is another side effect of OAB.

OAB can hinder your work, public activity, exercise and rest. Without treatment, OAB side effects may make it difficult to get past your day without loads of excursions to the restroom. You may understand anxious about running with companions or doing ordinary exercises since you're apprehensive you may not discover a restroom when you require one.

A few people start to modest far from get-togethers. This can make them feel forlorn and separated. OAB may influence your associations with your mate and your family. It can likewise deny you of a decent night's rest. Too little rest will abandon you worn out and discouraged. What's more, on the off chance that you spill pee, you may create skin issues or contaminations. You don't need to give OAB indications a chance to transform you. There are medications accessible to help. In the event that you think you have OAB, see your medicinal services supplier.

2. AIM & OBJECTIVES

2.1 Aim of Work

"Formulation and Evaluation of Orally Disintegrating

Tablets of Mirabegron"

2.2 Rationale

- ✓ Mirabegron is used for treating ***overactive bladder diseases***.
- ✓ Mirabegron is in a class of medications called ***beta-3 adrenergic agonists***.
- ✓ It works by relaxing the bladder muscles to prevent urgent, frequent, or uncontrolled urination.
- ✓ Mirabegron is a ***BCS class III*** drug and its oral ***bioavailability is 29%.***
- ✓ Water solubility of mirabegron is ***0.082 mg/ml.***
- ✓ Oral recommended dose is ***25/50 mg***.
- ✓ Over active bladders are generally common in geriatrics. Moreover, frequent dosing requires frequent water intake, which further aggregates the condition of over active bladder.
- ✓ Hence a need arises to develop an ODT which does not require the need to consume water with every dosage. Moreover, most of geriatric populations are dysphagic patients and an orally disintegrating tablet would appeal far more than a conventional tablet.

2.3 Objectives of Work

- ✓ To carry out the Preformulation study to check the drug- excipients compatibility.
- ✓ To develop and formulate ODT tablets.
- ✓ To optimize the disintegrant concentration.
- ✓ To achieve drug release more than 90% of drug within 10 min.
- ✓ To achieve disintegration time within 30 sec.
- ✓ To evaluate the optimized formulated dosage form for various physico-chemical parameters like weight variation, Hardness, thickness, drug content disintegration time and Dissolution.

To carry out accelerated stability studies on the most satisfactory formulation as per ICH guideline.

5. EXPERIMENTAL WORK

5.1 Preformulation Study

5.1.1 MELTING POINT DETERMINATION:

Melting point was determined by capillary method.

5.1.2 IDENTIFICATION OF PURE DRUG:

Identification of drugs was carried out by Differential Scanning Calorimetry.

5.1.3 EVALUATION OF PREPARED MIRABEGRON MOUTH DISSOLVING TABLETS

- ✓ **Pre-compression Parameters:**

- **Micromeritic Properties:**

Angle of Repose (θ): Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

Method: Angle of repose was determined by funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated. It is the angle produced between the heap of the pile and base.

Angle of repose, $\tan(\theta) = h / r$

Where θ = Angle of repose,

h = Height of heap,

r = Radius of pile.

Table 4: Angle of Repose

<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density:

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Method: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 seconds interval. The taping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula;

$$LBD = \frac{\text{Weight of the powder}}{\text{Volume of the packing}} \quad \text{-------- (a)}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}} \quad \text{--------- (b)}$$

Compressibility index:

The simplest way of measurement of free flow of powder is compressibility. The indication of the ease with which a material can be induced to flow is given by compressibility index.

$$I = [(Vb - Vt) / Vb] \times 100 \quad \text{----- (c)}$$

Where Vb = Bulk volume

Vt = Tapped volume.

Table 5: Carr's Consolidation Index

Consolidation Index (Carr %)	Flow
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to passable
23 – 35	Poor
33 – 38	Very poor
>40	Very very poor

5.1.4 Solubility studies:

Solubility studies were performed by adding excess amount of drug in a conical flask containing 10 ml media and shaken continuously for 24 hours at 37°C. After 24 hours samples were filtered and diluted and estimated using UV spectroscopy.

5.1.5 Analytical Method for Estimation of the Drug:

5.1.5.1 UV Absorption:

Mirabegron was dissolved in 0.1 N HCl and suitable dilutions were made to obtain a concentration of 100 µg/ml. This stock solution was scanned by UV spectrophotometer to between 200 – 400nm to check for absorption maximum of the drug.

5.1.5.2 Standard Calibration Curve:

Accurately weighed 200 mg Mirabegron was dissolved in 100 ml of 0.1N HCl. Take 10 ml of this solution in a 100 ml of volumetric flask and make up the volume with 0.1N HCl to get working stock-solution having concentration 100 µg/ml. From this stock-solution aliquots of 1ml, 2ml, 3ml, 4ml, 5ml and 6ml were pipetted out into a series of 50 ml volumetric flasks and make up to mark with 0.1N HCl in order to get a concentration within the Beer's range from 2- 12 µg/ml. The absorbance of the resulting solution was then measured at 251 nm using UV Spectrophotometer against respective parent solvent as a blank (i.e. 0.1N HCl). The standard curve was obtained by plotting absorbance V/s concentration in µg/ml.

5.1.6 COMPATIBILITY STUDIES OF DRUG WITH EXCIPIENTS

Prior to the development of the dosage forms the preformulation study was carried out. Hence infrared spectra of the physical mixture of the Mirbegron and the excipients were taken. Also the infrared spectra of the Mirbegron were run individually.

5.2 Preparation of Formulation

Direct Compression:

Direct Compression is the easiest and cheapest tableting approach. When it comes to ODTs Direct Compression is frequently adopted as method of choice due to fast production rates and lower cost of production.

Table 6: Formulation Optimization Table

Ingredients		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
		mg/tab													
1	Mirabegron	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
2	Mannitol SD 250	261.50	241.50	231.50	221.50	201.50	181.50	194.00	171.50	194.00	171.50	194.00	171.50	186.50	179.00
3	Sodium Bicarbonate	-	10.00	20.00	30.00	45.00	60.00	45.00	45.00	45.00	45.00	45.00	45.00	45.00	45.00
4	Citric acid Monohydrate	-	10.00	10.00	10.00	15.00	20.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
5	Crospovidone	-	-	-	-	-	-	7.50	30.00	-	-	-	-	-	-
6	Croscarmellose Sodium	-	-	-	-	-	-	-	-	7.50	30.00	-	-	15.00	22.50
7	Sodium Starch Glycolate	-	-	-	-	-	-	-	-	-	-	7.50	30.00	-	-
8	Sucralose	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
9	Colloidal Silicon dioxide	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
10	Talc	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
11	Magnesium Stearate	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00	6.00
	Total	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**

Procedure:

Post Compression Parameters:

1) Weight variation test:

The 20 tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following (Table No.12) percentage deviation in weight variation is allowed. The mean SD values were calculated.

Table 7: Weight variation Table

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

In all the formulations the tablet weight is 300 mg, 7.5 10% maximum difference allowed.

2) Thickness:

The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding calliper scale. The tablet thickness was measured using vernier calliper (Mitutoyo, Japan).

3) Hardness:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

4) Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability

of tablets was determined by using Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The percentage friability was then calculated by,

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \quad \text{----- (d)}$$

% Friability of tablets less than 1% is considered acceptable.

***5) In-vitro* disintegration time:**

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using purified water maintained at 37±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the purified water maintained at 37±2°C.

6) Wetting Time and Water Absorption Ratio: [38, 39]

A piece of tissue paper folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of buffer solution simulating saliva, pH 6.8. A tablet was placed on the paper and the time taken for complete

wetting was noted. Three tablets from each formulation were randomly selected and the average wetting was recorded.Also along with that the weight of individual tablets was also recorded to assess the weight gain in order to determine the absorption ratio.

Absorption ratio was determined using following equation:

Absorption Ratio = 100 X (Wa – Wb)/Wb

where Wa and Wb are the tablet weights after and before wetting

7) *In-vitro* dissolution studies:

In vitro release studies were carried out using tablet USP type II dissolution test apparatus. Paddle speed was maintained at 50 rpm and 900 of pH 1.2 HCl buffer was

used as the dissolution medium. Samples (5 ml) were collected at predetermined time intervals and replaced with equal volume of fresh medium, filtered through a What man filter paper, and analyzed with a UV-Visible spectrophotometer at λ = 251 nm.

8) Stability Studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods and shelf lives to be established .

ICH specifies the length of study and storage conditions:

Accelerated testing 40°C ±2 °C / 75 % RH ± 5 % for 1 month

6. RESULTS AND DISCUSSION

6.1 Preformulation Study

The results and conclusion of the Preformulation studies carried out on Active Ingredient are documented below

6.1.1 MELTING POINT DETERMINATION:

The melting point of Mirabegron determined by capillary method was found to be 140°C which is consistent with the reference standard of Mirabegron.

6.1.2 IDENTIFICATION OF PURE DRUG:

The identification of the pure drug was done by Differential Scanning Calorimetry. Pure Mirabegron shows melting range of between 137°C to 143.8°C. The melting endotherm of Mirabegron was found at 140.89°C which matches with reference Mirabegron.

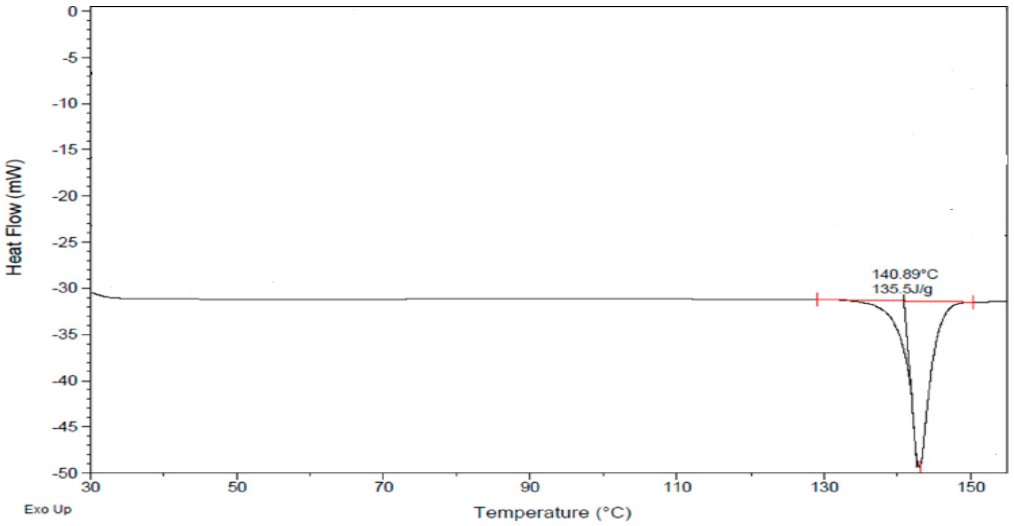

Figure 1: DSC Curve of Pure Mirabegron

6.1.3 Physical Characterization of drug:

Observations from the test results of physical characterization of the drug are as follows:

Table 8: Results of Physical Characterization of Mirabegron

Sr. No.	Test	Results
1	% Loss on Drying (at 105°C)	0.23%
2	Angle of Repose	46.8
3	Bulk Density (g/cc)	0.237
4	Tapped Density (g/cc)	0.413
5	Hausner's Ratio	0.743
6	Carr's Consolidation Index	42.61

6.1.4 ANALYTICAL METHOD FOR ESTIMATION

6.1.4.1 UV ABSORPTION

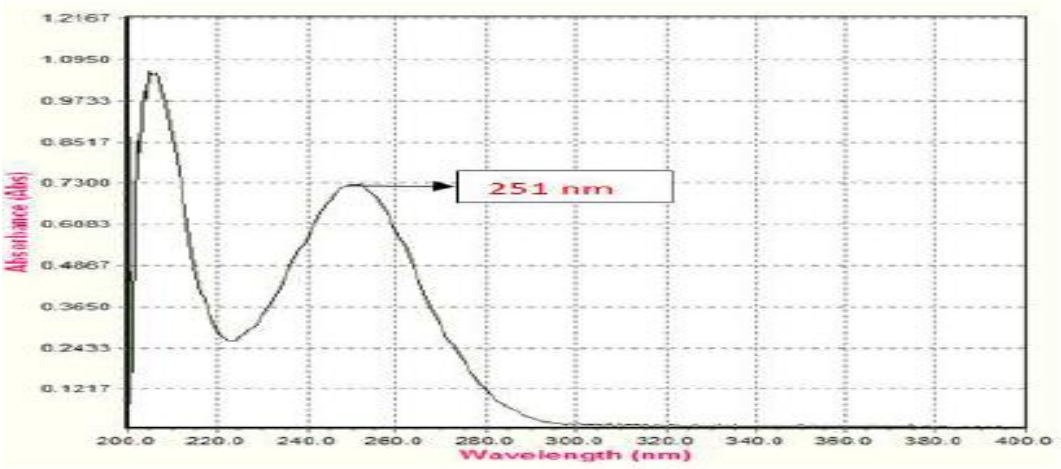

Figure 2: λmax of Pure Mirabegron

Stock solution of Mirabegron in 0.1 N HCl showed λmax at 251 nm. Further evaluation to be done at this particular wavelength.

6.1.5.2 STANDARD CALIBRATION CURVE

Standard calibration curve was performed in 0.1 N HCl and the results are tabulated below

Table 9: Details of linearity Range

Sr. No.	Parameters	Results
1	Concentration Range	2-12 µg/ml
2	λmax	251 nm
3	Correlation coefficient	0.998
4	Slope	0.071

Table 10: Linearity Table

Concentration (µg/ml)	Absorbance (Zero Order Curve)
2	0.152 ± 0.02
4	0.311 ± 0.04
6	0.461 ± 0.09
8	0.587 ± 0.05
10	0.727 ± 0.07
12	0.882 ± 0.03

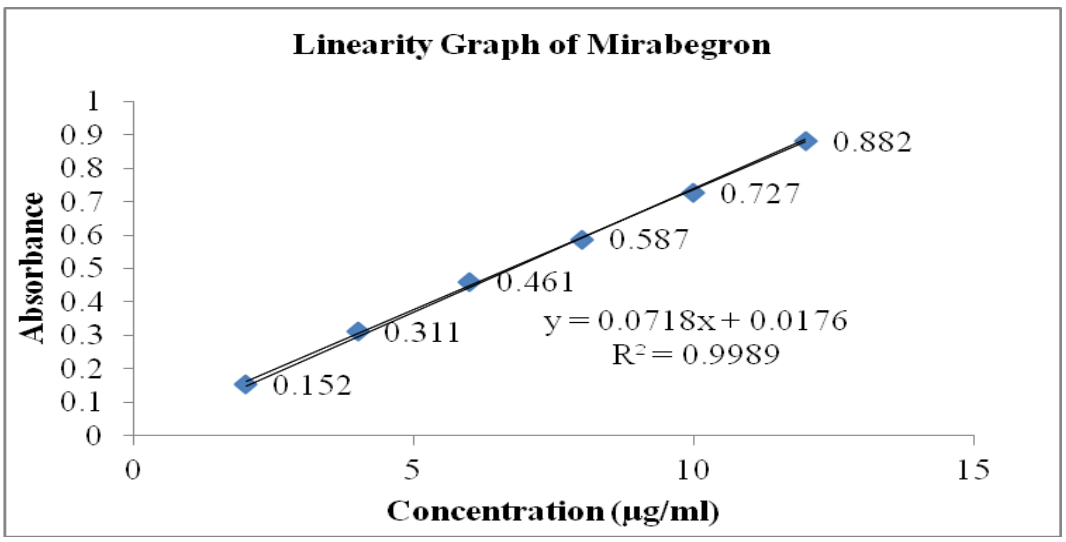

Figure 3: Linearity Graph of Mirabegron

6.1.4 Solubility Studies: [47]

Solubility of pure Mirabegron was evaluated in different media and the results were recorded in the table below.

Table 11: Solubility Studies Data

Sr. No.	Media	Solubility (mg/ml)
1	pH 1.2 HCl buffer	11.32
2	pH 4.5 acetate buffer	0.46
3	pH 6.8 phosphate buffer	0.12
4	Purified Water	0.08

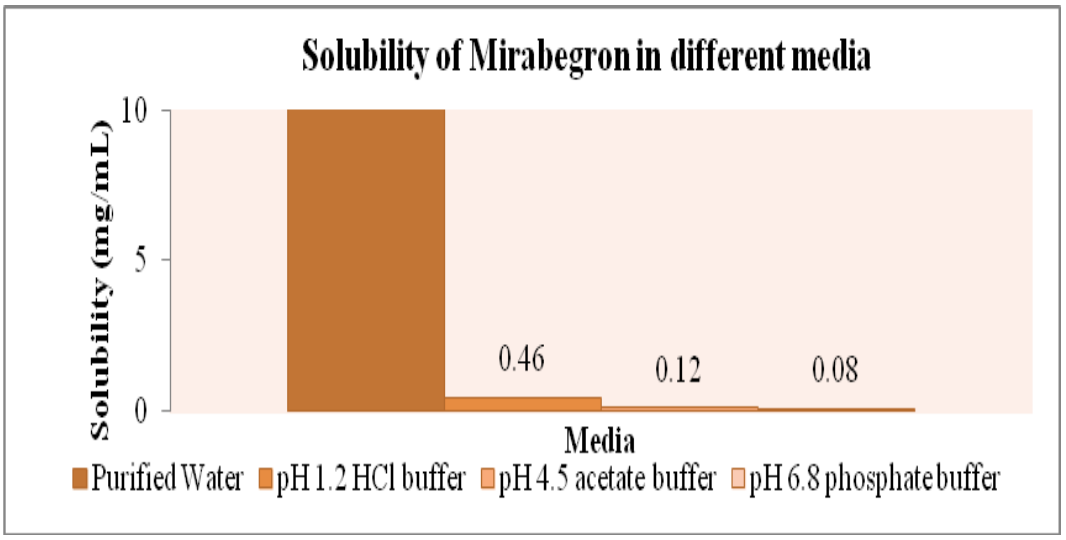

Figure 4:

6.1.6 DRUG-EXCIPIENT COMPATIBILITY

6.1.6.1 DSC Studies

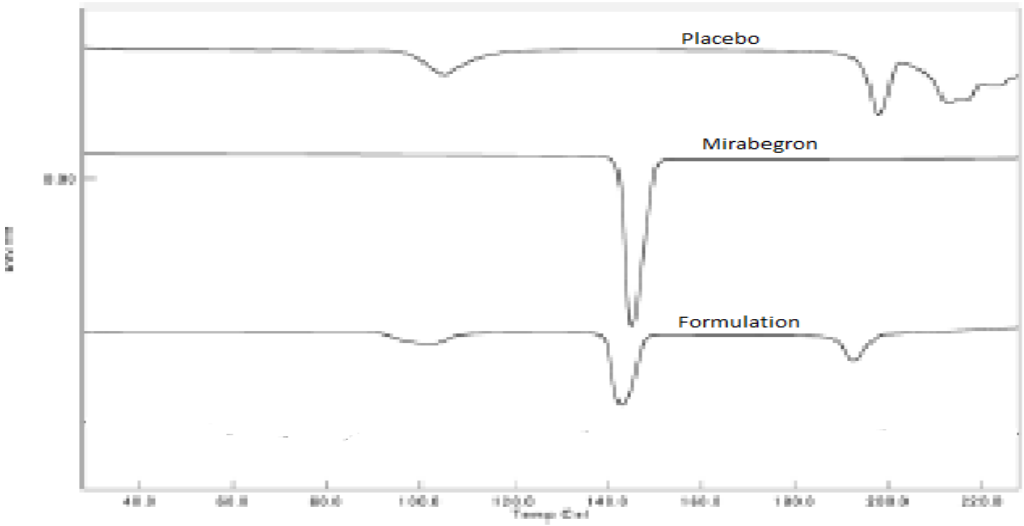

Figure 1: DSC of Mirabegron + Excipients

DSC Study was carried out on Placebo, Pure Drug and formulation to evaluate the compatibility of excipients with the drug.

Conclusion from Preformulation Studies:

1. The purity of the drug was confirmed by Melting point and DSC Studies.
2. Physical characterization shows that the drug has very poor flow and proper selection of formulation variables is must.
3. UV Absorption shows λmax at 251 and the current method is linear from 2-16µg/ml following a Correlation coefficient of 0.998
4. Solubility data reveals that the drug has pH dependent solubility with maximum solubility at pH 1.2. As the pH increases solubility decreases exponentially.

Excipient compatibility was proven by DSC studies where the melting endotherm of Mirabegron (140°C) was maintained and only the intensity of the endotherm decreased due to lower concentration of drug in formulation compared to pure drug.

6.2 Evaluation of Formulation

All the formulations were evaluated for pre-compression and post-compression parameters discussed beforehand.

6.2.1 PRE-COMPRESSION PARAMETERS

Table 12: Results of Pre-Compression Parameters of blend

Formulations	Angle of Repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner's Ratio	Carr's Consolidation Index (%)
F1	25.4 ± 0.15	0.316 ± 0.05	0.412 ± 0.05	1.305 ± 0.02	24.292 ± 0.12
F2	26.7 ± 0.19	0.321 ± 0.04	0.424 ± 0.04	1.321 ± 0.03	23.488 ± 0.23
F3	27.2 ± 0.20	0.329 ± 0.06	0.430 ± 0.06	1.307 ± 0.05	25.123 ± 0.24
F4	27.9 ± 0.25	0.304 ± 0.05	0.406 ± 0.05	1.336 ± 0.06	23.060 ± 0.19
F5	28.3 ± 0.17	0.347 ± 0.06	0.451 ± 0.07	1.300 ± 0.07	24.540 ± 0.18
F6	29.7 ± 0.19	0.369 ± 0.07	0.489 ± 0.06	1.325 ± 0.05	24.490 ± 0.28
F7	27.0 ± 0.13	0.333 ± 0.04	0.441 ± 0.07	1.324 ± 0.06	25.935 ± 0.31
F8	26.4 ± 0.09	0.297 ± 0.03	0.401 ± 0.05	1.350 ± 0.08	25.383 ± 0.18
F9	25.3 ± 0.16	0.341 ± 0.05	0.457 ± 0.06	1.340 ± 0.09	24.645 ± 0.19
F10	25.7 ± 0.18	0.318 ± 0.06	0.422 ± 0.08	1.327 ± 0.08	23.944 ± 0.24
F11	26.1 ± 0.23	0.324 ± 0.08	0.426 ± 0.09	1.315 ± 0.07	26.243 ± 0.26
F12	27.4 ± 0.24	0.371 ± 0.09	0.503 ± 0.10	1.356 ± 0.05	26.106 ± 0.27
F13	24.3 ± 0.19	0.334 ± 0.08	0.452 ± 0.09	1.353 ± 0.03	26.846 ± 0.17
F14	25.8 ± 0.18	0.327 ± 0.07	0.447 ± 0.08	1.367 ± 0.04	24.292 ± 0.13

6.2.2 POST COMPRESSION PARAMETERS:

1) Weight Variation:

Weight Variation of all the Formulations was found well within the prescribed pharmacopoeial limits of NMT 7.5%.

2) Thickness:

Thickness of all the formulations was found to be similar which could be because of the fact that drug loading was less and major portion of the formulation was diluent.

3) Hardness:

Target Hardness was selected to 3-4 kg/cm^2, keeping in mind the friability and disintegration of the formulation. All formulation blends were successful in achieving target hardness which shows good compatibility of the blend.

4) Friability:

Friability for all the formulation was well below the Pharmacopoeial limit of NMT 1.0%.

5) Disintegration Time:

For a tablet to be claimed as Orally Disintegrating Tablet, as per USP, the limit is not more than 30 sec. Formulations with high level of disintegrants achieved this limit, i.e. F8, F10, F13 and F14. Apart from these the Disintegration time of all tablets was above 30 sec

6) Wetting Time and Water Absorption Ratio:

Wetting Time and Water Absorption Ratio showed good correlation with level of disintegrants used. Formulation F10 will maximum concentration of Croscarmellose Sodium showed highest water absorption ratio and lowest wetting time which could be because of swelling and wicking mechanism of CCS.

7) Drug Content:

Drug Content in all the formulations was found to be similar i.e., near to 100 which shows that the process is robust and there is no drug loss during batch manufacturing.

8) Dissolution:

Dissolution was rapid for all the formulations except formulation with all the formulation achieving almost complete release in 30 mins.

Table 18 shows effect of changes in effervescence agents:

A proper ratio of Sodium Bicarbonate and Citric acid can generate CO_2 at a faster rate and achieve faster disintegration. Based on Trials F1 to F6, formulation F5 was selected for further optimization with Sodium Bicarbonate 45 mg/tab and Citric Acid 15 mg/tab.

Table 19 shows screening study of Super disintegrants:

Superdisintegrants such as Crospovidone, Croscarmellose Sodium and Sodium Starch Glycolate were used at two levels, i.e. minimum and maximum. Based on these screening trials it was concluded that for present formulation Croscarmellose Sodium, which is an ionic super disintegrant was most effective and was able to achieve least Disintegration Time at similar concentration when compared to other disintegrants. Thus, Croscarmellose Sodium was further evaluated.

Table 20 shows optimization of Croscarmellose Sodium:

Croscarmellose Sodium was optimized at 4 different levels. Formulation F13 with 15mg/tab Croscarmellose Sodium was able to pass all criteria's of an ODT and was able to achieve more than 90% drug release in under 10 minutes. So formulation F13 was finalized.

Table 13: Results of Post-Compression Parameters

Formulations	Weight Variation (%) (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F1	300.2 ± 2.9	4.33 ± 0.03	3.4 ± 0.2	0.21
F2	300.6 ± 3.4	4.31 ± 0.04	3.6 ± 0.3	0.23
F3	299.6 ± 2.8	4.29 ± 0.03	4.1 ± 0.3	0.24
F4	298.9 ± 2.6	4.24 ± 0.03	2.6 ± 0.5	0.26
F5	301.5 ± 3.5	4.23 ± 0.02	4.2 ± 0.4	0.25
F6	300.6 ± 4.1	4.23 ± 0.05	3.7 ± 0.5	0.27
F7	300.8 ± 4.5	4.46 ± 0.04	3.9 ± 0.6	0.21
F8	301.4 ± 3.6	4.51 ± 0.05	2.3 ± 0.5	0.20
F9	301.9 ± 3.5	4.45 ± 0.04	2.6 ± 0.4	0.22
F10	300.5 ± 2.9	4.49 ± 0.05	4.0 ± 0.3	0.23
F11	299.7 ± 2.8	4.41 ± 0.05	4.2 ± 0.2	0.17
F12	300.5 ± 3.0	4.42 ± 0.06	3.6 ± 0.3	0.20
F13	301.7 ± 4.2	4.47 ± 0.06	3.4 ± 0.4	0.18
F14	299.9 ± 4.0	4.49 ± 0.04	4.4 ± 0.6	0.21

Table 14: Results of Post-Compression Parameters

Formulations	Disintegration Time (sec)	Water Absorption Ratio (%)	Wetting Time (sec)	Assay (%)
F1	89 ± 2	37.2 ± 1.7	112 ± 2	99.8 ± 0.2
F2	65 ± 3	36.8 ± 2.1	103 ± 3	99.6 ± 0.4
F3	57 ± 4	36.4 ± 1.9	97 ± 5	100.3 ± 0.6
F4	52 ± 2	37.3 ± 2.3	90 ± 4	101.2 ± 0.5
F5	47 ± 3	34.4 ± 1.5	85 ± 6	98.9 ± 0.6
F6	46 ± 5	35.9 ± 2.5	81 ± 2	99.6 ± 0.4
F7	42 ± 6	51.0 ± 2.9	75 ± 3	99.0 ± 0.3
F8	29 ± 2	76.4 ± 1.4	60 ± 4	100.3 ± 0.4
F9	35 ± 4	55.3 ± 1.8	72 ± 1	101.7 ± 0.5
F10	22 ± 6	84.2 ± 2.4	46 ± 3	100.8 ± 0.7
F11	44 ± 2	48.7 ± 2.6	77 ± 4	99.6 ± 0.5
F12	32 ± 4	71.3 ± 2.3	63 ± 6	99.9 ± 0.6
F13	28 ± 6	63.5 ± 2.4	60 ± 5	100.0 ± 0.4
F14	26 ± 5	71.4 ± 2.8	53 ± 2	101.2 ± 0.3

Table 15: Results of Dissolution Studies: Optimization of Effervescence Agents

Formulations	% Cumulative Drug Release in 900 ml, 0.1N HCl, at 50 RPM Paddle					
		5 min	10 min	15 min	20 min	30 min
F1	%CDR	33.2	56.4	62.1	69.5	78.9
	%RSD	12.3	9.4	7.6	5.4	4.2
F2	%CDR	49.7	65.4	73.3	78.6	84.6
	%RSD	11.4	8.2	6.4	4.1	3.7
F3	%CDR	54.3	69.9	78.4	82.7	92.4
	%RSD	10.2	7.2	6.1	4.8	3.7
F4	%CDR	59.4	75.2	82.9	88.8	98.6
	%RSD	9.1	7.6	6.1	4.2	2.1
F5	%CDR	65.1	81.4	89.6	93.9	99.7
	%RSD	8.4	6.2	5.0	3.2	1.7
F6	%CDR	67.5	84.3	92.7	95.4	99.9
	%RSD	7.1	4.2	3.1	2.7	1.9

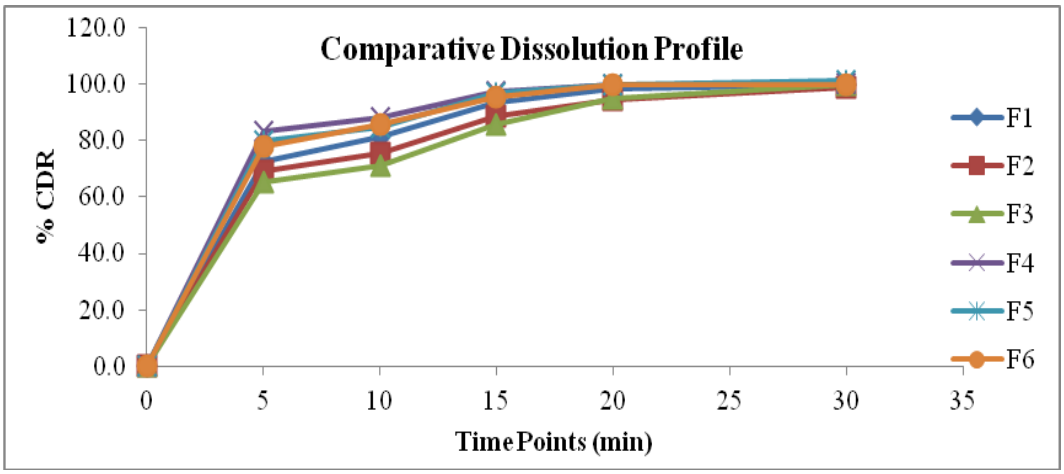

Figure 2: Comparative Dissolution Profile of Formulation Optimization

Table 16: Results of Dissolution Studies: Screening of Super Disintegrants

Formulations	% Cumulative Drug Release in 900 ml, 0.1N HCl, at 50 RPM Paddle					
		5 min	10 min	15 min	20 min	30 min
F7	%CDR	72.3	85.9	93.7	99.7	100.0
	%RSD	6.2	5.1	3.0	2.7	2.2
F8	%CDR	89.9	95.8	99.9	100.1	99.9
	%RSD	4.9	3.2	2.1	1.7	1.6
F9	%CDR	76.4	88.7	96.4	99.7	100.1
	%RSD	5.4	4.7	3.1	1.6	1.5
F10	%CDR	92.4	99.8	99.9	99.9	100.3
	%RSD	3.3	1.6	1.5	1.5	1.4
F11	%CDR	69.9	86.4	95.3	99.7	100.1
	%RSD	5.6	4.7	3.2	1.9	1.5
F12	%CDR	87.8	94.3	99.4	100.0	100.3
	%RSD	6.1	3.9	3.1	1.7	1.6

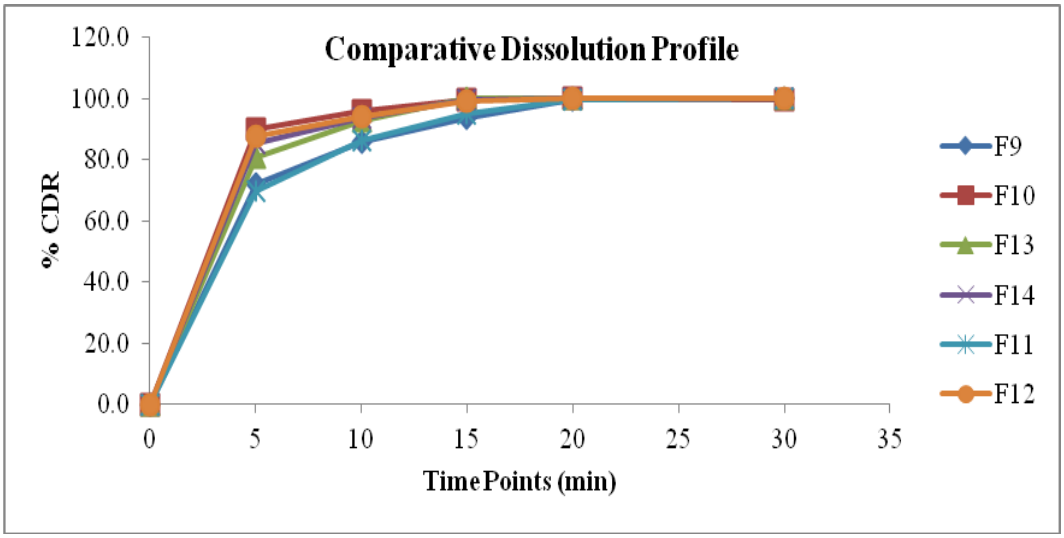

Figure 3: Comparative Dissolution Profile of Formulation Optimization

Table17 : Results of Dissolution Studies: Optimization of level of Super Disintegrant

Formulations	% Cumulative Drug Release in 900 ml, 0.1N HCl, at 50 RPM Paddle					
		5 min	10 min	15 min	20 min	30 min
F9	%CDR	76.4	88.7	96.4	99.7	100.1
	%RSD	5.4	4.7	3.1	1.6	1.5
F10	%CDR	92.4	99.8	99.9	99.9	100.3
	%RSD	3.3	1.6	1.5	1.5	1.4
F13	%CDR	80.7	92.6	100.3	100.1	100.0
	%RSD	4.5	3.2	1.4	1.5	1.5
F14	%CDR	85.2	93.6	99.8	100.0	100.1
	%RSD	3.9	2.4	1.5	1.6	1.6

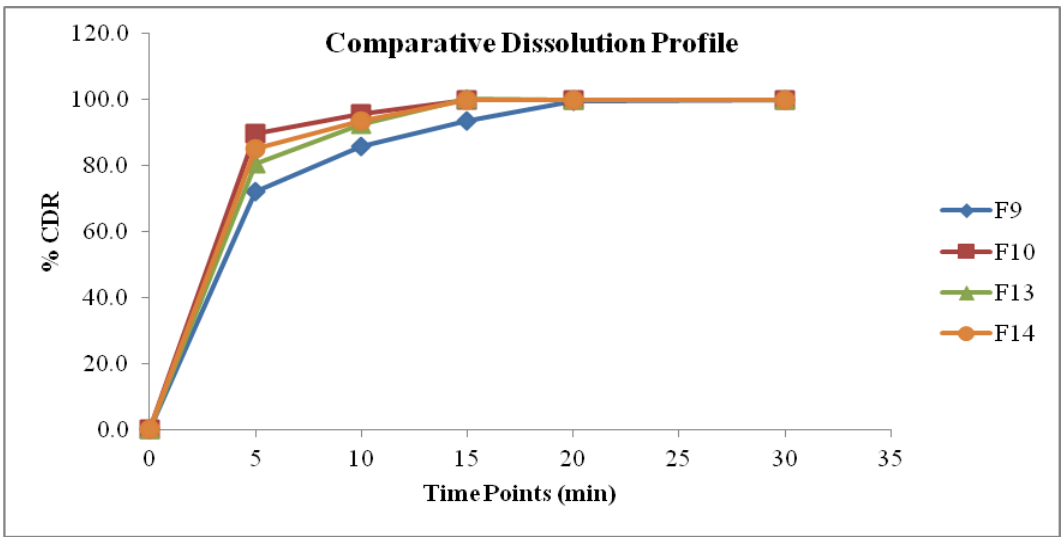

Figure 4: Comparative Dissolution Profile of Formulation Optimization

6.3CONCLUSION

Mirabegron Orally Disintegrating Tablets were successfully formulated by Direct Compression method.

- Preformulation studies of drug were performed; the infrared spectral analysis and DSC studies revealed that there is no chemical interaction with excipients used was compatible with drugs.
- ation were satisfactory as per Pharmacopoeial Standards.
- In the preliminary screening batches, Formulation F13 was considered the best formulation keeping in mind all the CQAs of an ODT which was achieved by careful optimization of Effervescence agents (both ratio and quantity) and selection of superdisintegrant along with its quantity.
- A Statistical DoE Optimization was performed on batch F13, to obtain a design space for critical attribute such as CCS quantity and quantity of effervescence agents. It was observed that both CCS quantity and quantity of effervescence agents level had a drastic impact on the response i.e., DT and dissolution.

The final optimized formulation O1 was tested for Accelerated Stability Studies as per ICH guidelines and was found stable.

REFERENCES

1. Arya A, Chandra A. "Fast drug delivery systems: a review." *Der Pharmacia Lettre,* **2010,** 2 (2), 350-361.
2. Ankit M, Sanjay J, Sandeep J, Gopal G, Rahul K. "Formulation and characterization of fast disintegrating tablets containing Cefdinir solid dipersion." *International Journal of Pharmacy and Life Sciences*. **2012**, 3 (12), 2190-2199.
3. Edward Rudnic. "In Remington's The Science and Practice of Pharmacy" 21st edition. **2005**, 893.
4. Farhan Ahmed, Gaurav. Jain. "In Lachman Lieberman's The Theory and Practice of Industrial Pharmacy" 4th edition. **2013**, 483.
5. Lalit Jejurkar. "Formulation and evaluation of fast disintegrating tablet of Etoricoxib using natural superdisintegrants." *Asian Journal of Pharmaceutical and Clinical Research*. **2011,** 4 (4), 85-89.
6. Erande, K,Joshi, B., "Mouth Dissolving Tablet: A comprehensive Review," *Int. J. of Pharma Research and Review*, **2013**, 2 (7), 26-28.
7. Habib W, Khankari RK, Hontz J. "Fast-dissolve drug delivery systems." *Crit Rev Ther Drug Carrier Sys*, **2000,** 17, 61-72.
8. Garg A, Gupta M, "Mouth dissolving tablets: a review." *Journal of Drug Delivery and Therapeutics*, **2013**, 3 (2), 207-214.
9. Kundu S, Sahoo P. K. "Recent Trends in the Developments of Orally Disintegrating Tablet Technology." *Pharma Times*. **2008**, 40 (4), 11-15.
10. Manivannan R. "Oral disintegrating tablets: a future compaction." *Inter. J. Pharma Res. Development*. **2009**, 1(10), 1- 10.
11. Sandeep Kumar, Pritam Singh, "Various techniques for solubility enhancement: An overview", *The Pharma Innovation Journal*, **2016**, 5(1), 23-28.
12. Ketan T, Anuradha K, Jignasa K, "Drug Solubility: Importance and Enhancement Techniques", *International Scholarly Research Network*, **2012**, 01-10.
13. Kadam S, Shinkar S, Saudagar R, "Review on Solubility Enhancement Techniques", *International Journal of Pharmacy and Biological Sciences*, **2013**, 3 (3), 462-475.
14. Sharma N, Bharkatiya M, "Solubility Enhancement Techniques: A Review", *International Journal of Pharmaceutical Erudition*, **2011**, 1 (3), 40-53.
15. Mohini S., Sheetal Z, Saudagar B, "Solubility Enhancement by Various Techniques: An Overview", *World Journal of Pharmacy and Pharmaceutical Sciences*, **2013**, 2 (6), 4558-4572.
16. Praveen K, Chhater S, "A Study on Solubility Enhancement Methods for Poorly Water Soluble Drugs", *American Journal of Pharmacological Sciences*, **2013**, 1 (4), 67-73.
17. Disease Information, October 2018: - https:// www. Urology health. Org / urologic-conditions /overactive-bladder-(OAB).

18. Disease Information, October 2018: - https:// www. Mayo clinic. Org /diseases-conditions /overactive-bladder.

19. Drug Information, October 2018: - https://www.drugbank.ca/drugs/DB08893.

20. Drug Information, October 2018: - http://www.Chemspider.com/Chemical-Structure. 8041219.html.

21. Drug Information, October 2018: - https://pubchem.ncbi.nlm.nih.gov/compound/Mirabegron.

22. Drug Information, October 2018: - https://en.wikipedia.org/wiki/Mirabegron.

23. Drug Information, October 2018: - https://www.drugs.com/cdi/mirabegron.html.

24. Naveen K, Swathi K, and Thirumal M. "Formulation and evaluation of fast dissolving Piroxicam tablets using different super disintegrants." *International Journal of Pharmacy and Pharmaceutical Sciences.* **2012**, 4 (2), 334-337.

25. Biraju P, Dhaval Pa, Ramesh P, Chirag P, Tejas S. "Development and in vitro evaluation of fast dissolving tablets of Glipizide." *International journal of pharmacy and pharmaceutical sciences*. **2009**, 1 (1), 145-150.

26. Devendra R, Hemant N, Vikas V, Vinod M, Vijay R. "Formulation and evaluation of 136 fast dissolving tablet of Albendazole" *International Current Pharmaceutical Journal.* **2012**, 1(10), 311-316.

27. Chowdary K and Aishwarya K "Preparation and evaluation of fast dissolving tablets of Paracetamol employing superdisintegrants." *Journal of Global Trends in Pharmaceutical Sciences.* **2013**, 4 (4), 1329-1334.

28. Vishal D, Gaurav J, Vaibhav J, Sheorey. "Formulation and in vitro evaluation of fast dissolving tablets of Telmisartan." *International Journal of Pharmacy & Life Sciences.* **2012**, 3 (11), 2159-2164.

29. Vinay P, Roopa SP, Kusum D and Sarasija S. "In vitro-in vivo evaluation of fast-dissolving tablets containing solid dispersion of Pioglitazone hydrochloride." *Journal of Advanced Pharmaceutical Technology and Research*. **2012**, 3 (3), 160-170.

30. Tong W, Guanhua W, Caihong S, Jinghan L, Na Z, Zihao D, Weisan P, Xiangrong Z, "Development and evaluation of orally disintegrating tablets containing the mosapride resin complex", *Acta Pharm*., **2018**, 68, 159–170.

31. Shahabaz S, Soujanya C and Kishore K, "Formulation and Evaluation of Oral Disintegrating Tablets of Nimodipine," *World Journal of Pharmacy and Pharmaceutical Sciences*, **2018**, 7 (1), 926-946.

32. Jalali, M. B., Valizadeh, H., Shadbad, M. S., Adibkia, K., Mohammadi, G., Farahani, A., Arash, Z., Nokhodchi, A. "Cogrinding as an approach to enhance dissolution rate of a poorly water-soluble drug (gliclazide)." *Powder Tech.* **2010**, 197 (3), 150–158.

33. Shinde, V. R., Shelake, M. R., Shetty, S. S., Chavan-Patil, A. B., Pore, Y. V., Late, S. G. "Enhanced solubility and dissolution rate of lamotrigine by inclusion complexation and solid dispersion technique." *J. Pharm. Pharmaco l*, **2008**, 60 (9), 1121-9.

34. Bhoghra, R. J., Kothawade, P. C., Belgamwar, V. S., Nerkar, P. P., Tekade, A. R., Surana, S. J. "Solubility, dissolution rate and bioavailability enhancement of irbesartan by solid dispersion technique." *Chem. Pharm. Bull.* **2011**, 59 (4), 438- 441.

35. Papadimitriou S. A., Dimitririous, B., Konstantinous, A. "Microwave-induced enhancement of the dissolution rate of poorly water soluble tibolone from poly (ethylene glycol) solid dispersions." *J. Appl. Polym. Sci.* **2008**, 108 (2), 1249-1258.

36. Pandya, P. R., Gattani, S. G., Jain, P., Khirwal, L., Surana, S. J. "Co-solvent evaporation method for enhancement of solubility and dissolution rate of poorly aqueous soluble drug Simvastatin: In vitro-In vivo evaluation." *AAPS Phar.Sci Tech.* **2008**, 9 (4), 1247-1252.

37. Patel, M. B., Tekade, A. R., Gattani, S. G., Surana, S. J. "Solubility enhancement of lovastatin by modified locust bean gum using solid dispersion techniques." *AAPS Pharm.Sci.Tech*. **2008**, 9 (4), 1262-1269.

38. Panchumarthy R, V. Sree Vidya, P. Durga Nithya and P. Srinivasa Babu, "Validated UV spectrophotometric method for quantitative determination of Mirabegron in bulk and Pharmaceutical dosage form", *Der Pharmacia Lettre*, **2016**, 8 (14), 96-103.

39. Yuuki K, Keiichi Y, Takehiko Y, Kazuhiro S, Shinya U, and Noriyuki N, "Oral Sustained Release of a Hydrophilic Drug Using the Lauryl Sulfate Salt/Complex", *Chem. Pharm. Bull*. **2016**, 64, 1304–1309.

40. Emilio S and Riccardo B, "Mirabegron: a review of recent data and its prospects in the management of overactive bladder", *Therapeutic Advances in Urology*, **2012**, 4 (6), 315–324.

41. "ICH Harmonised Tripartite Guideline," Cover Note for Revision of Q1A(R) Stability Testing of New Drug Substances and Products, Q1A (R2).
42. Khan S, Kataria P, Nakhat P, Yeole P, "Taste masking of Ondansetron hydrochloride by polymer carrier system and formulation of rapid- disintegrating tablets", *AAPS pharmscitech*, **2007,** 8 (2) :1-7.
43. Bhati S, Sethi V, "Formulation and evaluation of fast dissolving tablets of metoclopramide hydrochloride using natural sweetening agent of stevia leaf powder", *Int. J. Res. Dev. Pharm. L. Sci*, **2013**, 3 (1): 833-838.
44. Ashok T, Veeravalli S, Pavan M, Roshitha B, "Effect of Effervescence in Combination with SuperDisintegrants in the formulation of Propranolol HCl Oral Disintegrating Tablets", *Asian Journal of Pharmaceutical and Clinical Research*, **2017**, 10 (3): 227-234.
45. Neha T, Mohit, T, Neha G, Upendra N, "Formulation and Evaluation of Fast Disintegrating Tablets of Caffeine by Using Effervescent Formulation Approach", *Der Pharmacia Lettre*, **2012** 4 (5): 1490-1494.
46. Priyanka N, Kusum S, Iti C, Madhu V, Mohd Y, Azad K, Rajat S, Nandini G, "Orally disintegrating tablets: Formulation, Preparation techniques and evaluation", *Journal of Applied Pharmaceutical science*, **2011**, 01 (04): 35-45.
47. Yuuki K, Keiichi Y, Takehiko Y, Kazuhiro S, Shinya U, Noriyuki N, "Oral Sustained Release of a Hydrophilic Drug Using the Lauryl Sulfate Salt/Complex, *Chem Pharm. Bull,* **2016,** 64, 1304-1309.