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Research

Formulation And Invitro Characterization Of Macitentan Solid Dispersion By Hot Melt Extrusion Technique

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Abstract

Macitentan is indicated for the treatment of WHO group 1 pulmonary arterial hypertension (PAH) both alone and in combination with tadalafil. It is an BCS class-III drug having higher half-life. To improve the biological performance of Macitentan solid dispersion was formulated by using Soluplus, PEG 4000 and Mannitol. Solid dispersions of Macitentan were prepared with different carriers in differentratios of drug and carrier(1:1,1:2, 1:3 and 1:4). Results of prepared solid dispersions of Macitentan by hot melt extrusion method were discussed which includes solubility, melting point determination, drug content uniformity, and *invitro* dissolutionstudies. Characterization in solid state was done by various analytical techniques such as FT-IRstudies .Finally by comparing all the formulations, formulation (F12) containing Macitentan + Mannitol (1:4) shows better results by solvent evaporation method at the end of 60 min with maximum drug release of 98.35±1.49%, hence it was selected as the best formulation. The optimized formulation follows First order release kinetics.

Keywords: Macitentan, Mannitol, Solid Dispersion & FTIR.

INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bio availability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which

results in poor wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubalization by cosolvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles.

The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. solid dispersion technique was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea. Upon exposure to aqueous fluids the active drug released into fluids is fine, dispersed particles because of fine dispersion of the drug in the solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea. The possibility of using solid solution approach in which a drug is molecularly dispersed in soluble carrier was subsequently introduced.

A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980)[1].

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

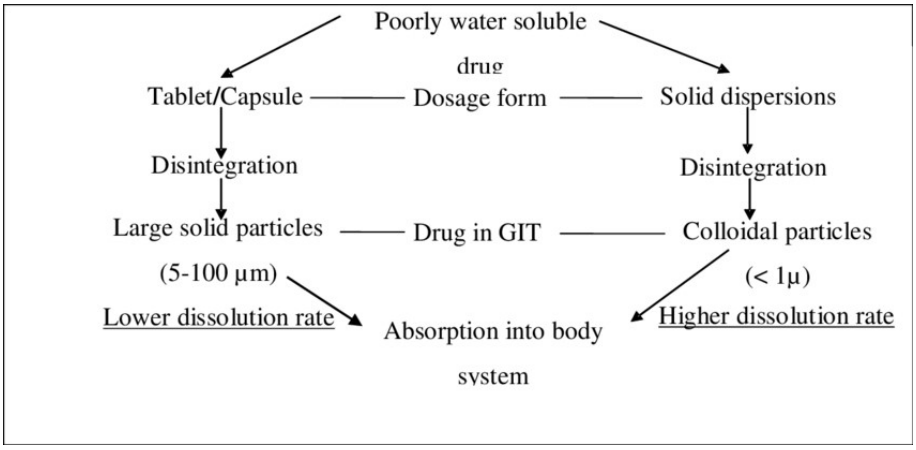


Fig 1: Schematic representation of bioavailability enhancement of poorly water soluble drug

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method4. The technique has been used for a wide variety of poorly aqueous soluble drug. Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyesh- Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oralAvailability[2].

The approaches that have commonly been used to overcome drawbacks associated with poorly water soluble drugs, in general includes micronization, salt formation, use of surfactant and use of pro- drug[5] however all these techniques have certain limitations. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions. Chiou and Riegelman outlined 6 types of drug carrier interactions in solid-state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates, and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition micronization is a high-energy process, which causes disruptions in the drug s crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. The amorphous regions are thermodynamically unstable and are therefore susceptible to re-crystallization upon storage, particularly in hot and humid conditions[6] . All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different form that of parent compound. However sodium and potassium salts of weak acids dissolve more rapidly than the free salts. Potential disadvantages of salt forms include high reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity.

Use of co-solvents or surfactants to improve dissolution rate pose problems, such as patient compliance and commercialization. Even though particle size reduction increases the dissolution rate, the formed fine powders showing poor wettability and flow properties. Solid dispersion technique has come into existence to eliminate all these problems. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches[7].

The dissolution of a drug from its solid oral dosage forms depends upon its release from the dosage form and its subsequent mixing into physiological fluids. It has been estimated that nearly 35-40% of the drugs suffer from poor aqueous solubility, thereby affecting their absorption from the gastrointestinal tract, which leads to poor oral bioavailability, high intra- and inter-subject variability, increase in dose, reduction in therapeutic efficiency and finally failure in formulation development. The development of solid dosage forms for water-insoluble drugs has been a major challenge for pharmaceutical scientists for decades. Various formulation strategies such as micronisation, micellarsolubilization, complexation, dendrimers for drug solubilization, formation of solid solutions or dispersions with hydrophilic carriers, self-microemulsifying drug delivery systems, spray drying, nano approaches, pro-drug approaches and salt synthesis have been developed to increase the dissolution rate of water-insoluble drugs. An attractive possibility is employing a simple solid dispersion technique making use of various hydrophilic carriers. Solid dispersions (SDs) are defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix in a solid state, and are prepared by the fusion, solvent or solvent-fusion method. This technique enables reducing particle size to a nearly molecular level, offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems of poor water-soluble drugs that are cost-effective and significantly reduced in dosage. It has been widely demonstrated that a hydrophilic carrier dissolves rapidly, exposing the drug particles to the dissolution medium as fine particles facilitating quick dissolution and absorption[8]. The mechanisms for increased dissolution rate may include reduction of crystallite size, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersability of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of the drug to an amorphous state. Schizophrenia is a severe non-curable illness of the brain with serious consequences if not properly treated and kept under control. It is the most common form of severe mental illness. Olanzapine (OLZ;2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno-[2,3-*b*],[1,5]benzodiazepine) is a relatively new benzodiazepine atypical antipsychotic medication, which belongs to the class of the thienobenzodiazepines and has proven efficacy against the positive and negative symptoms of schizophrenia, bipolar disorder and other forms of psychosis. It exhibits poor water solublility and belongs to Biopharmaceutic Classification System (BCS) class II of drugs (low solubility and high permeability), highly bound to plasma protein (about 93%). Following oral administration, *C*max is reached within 5–6 h of dosing. OLZ Ashish *et. al*., Am. J. PharmTech Res. 2014; 4(5) ISSN: 2249-3387 www.ajptr.com 594 undergoes extensive pre-systemic metabolism in the liver, resulting in relatively very low oral bioavailability. The objective of this work is to enhance the aqueous solubility of poorly water-soluble drug OLZ by adopting a solid dispersion approach using mannitol as the hydrophilic carrier and to physico-chemically characterize the *in vitro* dissolution behavior of the solid dispersions.

MATERIALS AND METHODS

Macitentan B.M.R. Chemicals, Hyderabad, Mannitol-S.D FINE CHEMICALS, Soluplus-S.D FINE CHEMICALS, PEG 4000-S.D FINE CHEMICALS, Methanol-B.M.R. Chemicals, Hyderabad.

METHODOLOGY

Pre formulation studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.

Definition: It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Objective: Overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms.

The following preformulation studies were carried out for Macitentan

a) Solubility studies

b) Drug–excipient compatibility studies

a) Solubility studies

Solubility of Macitentan was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Macitentan was determined spectrophotometrically at 280 nm

b) Drug–polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Macitentan, and the selected polymers. The pure drug and drug with excipient were scanned separately.

FT-IR studies

Sample/KBr ratio

The concentration of the sample in KBr should be in the range of 0.2% to 1%. The pellet is much thicker than a liquid film, hence a lower concentration in the sample is required (Beer's Law). Too high a concentration usually causes difficulties obtaining clear pellets. The IR beam is absorbed completely,or scattered from the sample which results in very noisy spectra.

Sample preparation

Completely dried potassium bromide was transferred into a mortar. About 2 % of drug sample was weighed in digital balance, mixed and grind to a fine powder. Two stainless steel disks were taken out of the desiccator. A piece of the precut cardboard (in the tin can next to the oven) on top of one disk was placed and cutout hole was filled with the finely ground mixture. The second stainless steel disk was kept on top and transfers the sandwich onto the pistil in the hydraulic press. With a pumping movement, hydraulic pump handle moved downward. The pistil will start to move upward until it reaches the top of the pump chamber. Then, the pump handle moved upwards and continued pumping until the pressure reaches 20,000 prf. Rest for a few seconds and with the small lever on the left side, the pressure was released. Removing of the disks and pulling apart. Obtained film was homogenous and transparent in appearance. Than inserted into the IR sample holder and attach with scotch tape and run the spectrum. The physical mixtures of drugs were prepared in 1:1 ratio and then passed through sieve # 30. Samples of drug and excipients were placed in vial, closed and labelled.

Analytical method development by U.V. Spectroscopy

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers. In qualitative analysis, organic compounds can be identified by use of spectrophotometer, if any recorded data is available, and quantitative spectrophotometric analysis is used to ascertain the quantity of molecular species absorbing the radiation. Spectrophotometric technique is simple, rapid, moderately specific and applicable to small quantities of compounds. The fundamental law that governs the quantitative spectrophotometric analysis is the Beer -Lambert law.

Scanning of λ_{max} of Macitentan

Preparation of Stock Solution

10 mg of Macitentan was taken in a 10ml volumetric flask. To that 2ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 6.8pH phosphate buffer to give 1000 µg /ml concentration. From the above solution 1ml is diluted to 10ml with 6.8pH phosphate buffer to give 100 µg /ml concentration. From the above solution, take 1ml, and diluted to 10ml with 6.8pH phosphate buffer, to give

10 µg /ml concentration. The prepared solutioni.e.,10µg/ml concentration was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

Calibration curve of Macitentan in 6.8pH phosphate buffer

10mg of Macitentan was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8pH phosphate buffer to give stock solution containing 1000µg/ml. The standard stock solution was then serially diluted with 6.8pH phosphate buffer to get 2 to 12 µg/ml of. The absorbance of the solution was measured against 0.1N HCL as blank at 280 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation of solid dispersions of macitentan by using hot melt extrusion:[70]

There are several carriers, which have been reported for the preparation of solid dispersions by using Soluplus, Mannitol and PEG 4000 various methods of preparation.

A single screw extruder system was employed for the hot melt extrusion process. To achieve homogenous extrudes, a die with a bore diameter of 2 mm was chosen after pre-screening many different dies. Macitentan, Soluplus®, PEG 4000, and Mannitol were combined in 1:1, 1:2, 1:3, and 1:4 ratios for a batch size of 20mg, 30mg, 40mg, 50mg using a mortar pestle for 4-5 minutes. Following that, the blend mixture was poured through the hopper on the revolving screw at a consistent feeding rate and a screw speed of 50 rpm. The extruder temperature was initially set to 84 °C (optimized early). The combination takes approximately 3 minutes to create a molten mass between the screw and extruder barrel walls. The residence duration for the Macitentan-Soluplus®, PEG 4000, and Mannitol combination mixes was around 15-20 minutes. A similar technique with varying batch sizes was used for additional drug-polymer combinations (e.g., 1:1, 1:2, 1:3, and 1:4) with varied temperature settings, as indicated in Table 1. The melt extrudates were ground and filtered using a 200 µm sieve. In this work, the SD with the maximum drug loading (i.e., 50%) are examined in terms of physicochemical and dissolving rate characterization.

Solid Dispersions

Table 1: Formulation table of Macitentan

Formulation Code	Ratio	Drug and Polymer	Dosage
F1	1:1	Macitentan: Soluplus	20mg
F2	1:2	Macitentan: Soluplus	30mg
F3	1:3	Macitentan: Soluplus	40mg
F4	1:4	Macitentan: Soluplus	50mg
F5	1:1	Macitentan: PEG 4000	20mg
F6	1:2	Macitentan: PEG 4000	30mg
F7	1:3	Macitentan: PEG 4000	40mg
F8	1:4	Macitentan: PEG 4000	50mg
F9	1:1	Macitentan: Mannitol	20mg
F10	1:2	Macitentan: Mannitol	30mg
F11	1:3	Macitentan: Mannitol	40mg
F12	1:4	Macitentan: Mannitol	50mg

RESULT AND DISCUSSIONS

Prcormulation studies

Solubility

Solubility of was carried out at 25^{0}C using 0.1 N HCL, 6.8 phosphate buffer, 7.4 pH buffer, methanol and ethanol.

Table 2: Solubility studies data of Macitentan

MEDIUM	SOLUBILITY (mg/ml)
0.1 N HCL	0.578±0.007
6.8 pH buffer	1.248±0.005
7.4 pH buffer	0.856±0.005
Methanol	0.985±0.007
Ethanol	1.178±0.004

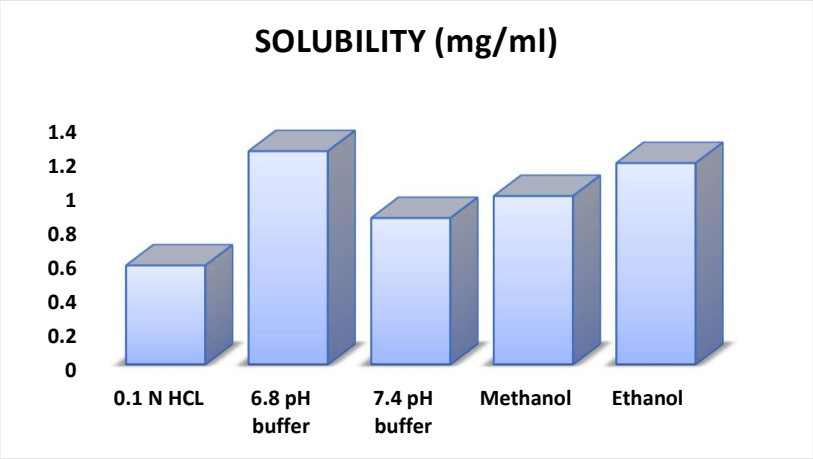
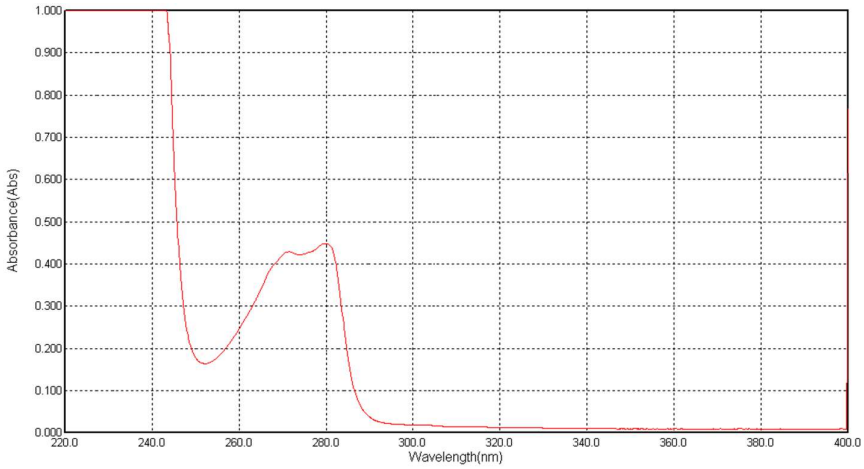


Fig 2: Graphical representation of Macitentan Solubility studies

From the above conducted solubility studies in various buffers we can say that 6.8pH buffer solution has more solubility when compared to other buffer solutions and in organic solvents it is more soluble in ethanol when compared to methanol

Analytical method development by U.V. Spectroscopy
Uv Scan Spectrum of Macitentan



Macitentan at 10µg/ml was found to be 280 nm.

Calibration curve data of Macitentan

Concentration (µg/ml)	Absorbance
0	0
2	0.129
4	0.240
6	0.341
8	0.458
10	0.573
12	0.685

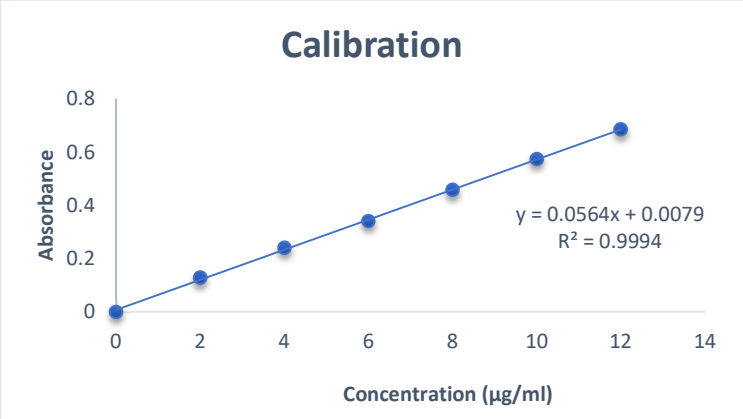


Fig 3: Calibration curve of Macitentan

Calibration curve of Macitentan was constructed in 6.8 pH phosphate buffer at maximum wavelength of 280 nm and analyzed for regression analysis. Regression analysis was selected because it minimizes the deviation and correct the variance heterogeneity. The regression line was defined by its slope (m) and its intercept (C) for normal regression analysis was found as 0.0564 and 0.0079, with regression coefficient of 0.9994 respectively

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

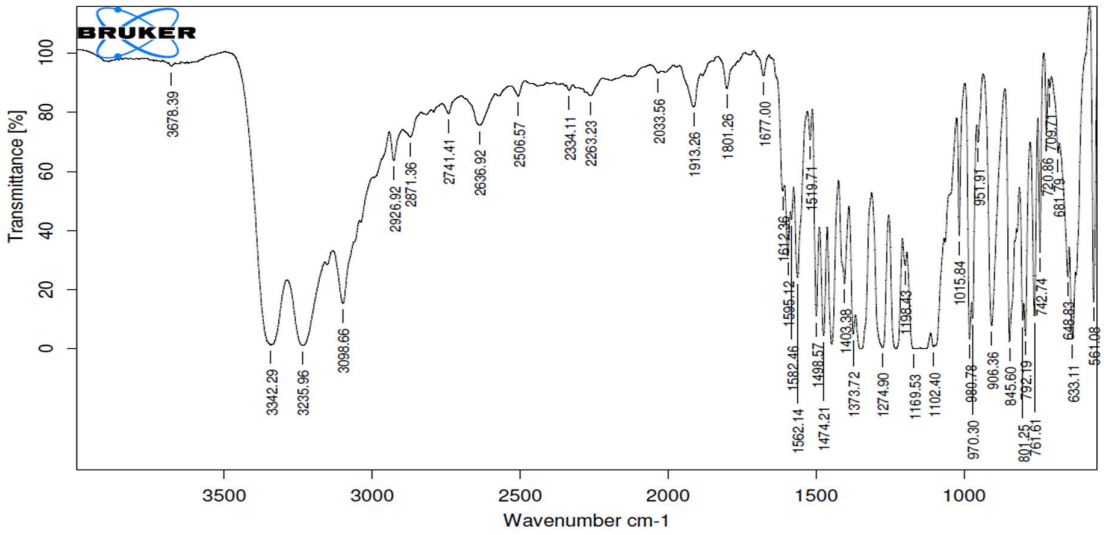


Fig 4: IR spectrum of pure Macitentan

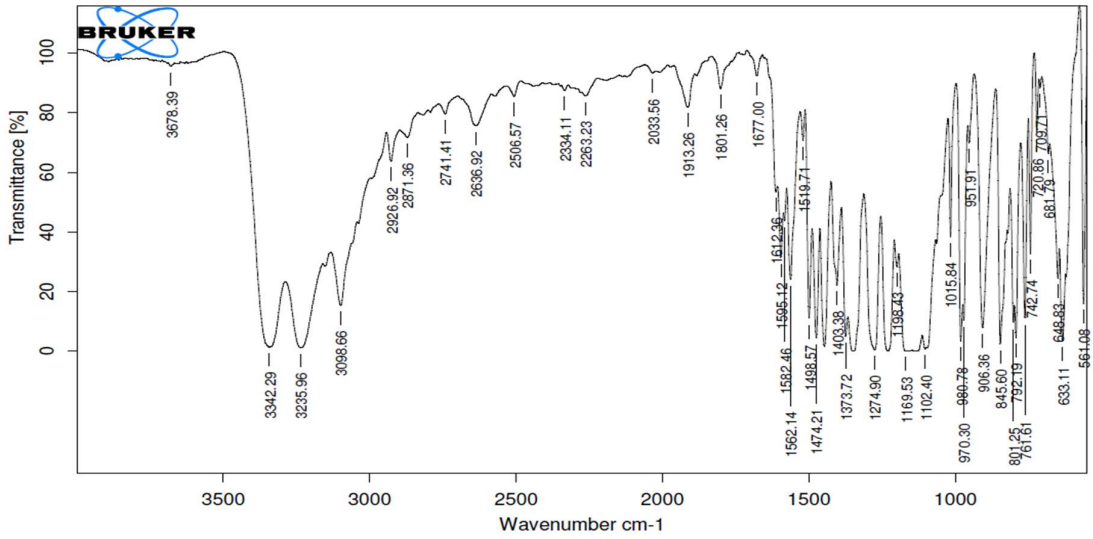


Fig 5: IR spectrum of Macitentan Optimised Formulation

From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Macitentan) and optimized formulation (Macitentan: excipients) which indicates there are no physical changes.

Drug Content of solid dispersions

Table 3: Drug Content of solid dispersions

Formulation code	Drug Content
F1	92.64±1.85
F2	94.43±1.20
F3	96.54±1.56
F4	97.12±1.84
F5	93.25±1.23
F6	95.36±1.47
F7	97.64±1.58
F8	98.67±1.26
F9	95.43±1.58
F10	96.78±1.26
F11	98.52±1.74
F12	99.37±1.58

The Drug Content of the formulated solid dispersions was found to be in the range of 92.64±1.85- 99.37±1.58% respectively.

Percentage yield of solid dispersions

Table 4: Percentage yield of solid dispersions

Formulation code	Percentage yield
F1	91.64±1.27
F2	93.43±1.45
F3	95.54±1.38
F4	96.12±1.52
F5	93.25±1.08
F6	95.36±1.64
F7	96.64±1.20
F8	97.67±1.74

F9	94.43±1.25
F10	96.25±1.86
F11	97.41±1.51
F12	98.56±1.78

The Percentage yield of the formulated solid dispersions was found to be in the range of 91.64±1.27- 98.56±1.78% respectively.

Invitro drug release studies of solid dispersions

Table 5: *Invitro* drug release studies for formulations (F1-F9)

Time (Min)	Percentage drug release							
	Macitentan : Soluplus				Macitentan : PEG 4000			
	1:1 (F1)	1:2(F2)	1:3 (F3)	1:4 (F4)	1:1 (F5)	1:2 (F6)	1:3(F7)	1:4 (F8)
0	0	0	0	0	0	0	0	0
5	34.42 ±1.84	43.26 ±1.10	47.62 ±1.72	50.21 ±1.27	37.53 ±1.78	46.44 ±1.28	50.21 ±1.25	54.34 ±1.27
10	42.16 ±1.27	48.63 ±1.28	51.35 ±1.26	57.25 ±1.49	45.92 ±1.27	52.02 ±1.45	55.12 ±1.48	61.54 ±1.45
15	55.85 ±1.45	57.98 ±1.21	63.03 ±1.48	66.16 ±1.20	59.36 ±1.45	61.48 ±1.36	67.51 ±1.37	68.28 ±1.29
30	60.32 ±1.27	62.09 ±1.45	70.32 ±1.78	74.34 ±1.46	65.62 ±1.18	64.23 ±1.74	79.02 ±1.45	77.65 ±1.75
45	69.19 ±1.45	74.32 ±1.26	76.56 ±1.45	79.48 ±1.28	72.43 ±1.37	77.04 ±1.52	80.36 ±1.27	86.48 ±1.46
60	81.26 ±1.20	84.42 ±1.84	88.12 ±1.26	90.45 ±1.45	84.56 ±1.45	86.45 ±1.52	90.02 ±1.45	92.37 ±1.26

Time (Min)	Percentage drug release			
	Macitentan: Mannitol			
	1:1(F9)	1:2(F10)	1:3(F11)	1:4 (F12)
0	0	0	0	0
5	40.53 ±1.42	48.21 ±1.47	53.35 ±1.20	59.24 ±1.48
10	48.92 ±1.47	56.36 ±1.25	58.12 ±1.45	68.18 ±1.41
15	56.36 ±1.51	65.48 ±1.41	69.51 ±1.20	75.38 ±1.26
30	68.62 ±1.26	71.21 ±1.34	84.02 ±1.46	84.15 ±1.74
45	75.43 ±1.48	79.16 ±1.57	88.36 ±1.28	92.29 ±1.20
60	87.56 ±1.29	89.39 ±1.45	94.02 ±1.75	98.35 ±1.49

In-vitro drug release of Macitentan solid dispersions with Soluplus in various ratios were observed which shows at the end of 60 mins, the formulation F1 releases 81.26±1.20%, formulation F2 releases 84.42±1.84%, F3 releases 88.12±1.26%, and F4 releases 90.45±1.45%, while PEG 4000 used as carrier shows formulation F5 releases 84.56±1.45%, formulation F6 releases 86.45±1.52%, and formulation F7 releases 90.02±1.45%, F8 releases 92.37±1.26% ,while Mannitol used as carrier shows formulation F9 releases 87.56±1.29%, formulation F10 releases 89.39±1.45%, and formulation F11 releases 94.02±1.75%,and F12 releases 98.35±1.49%. Among all formulation F12 formulation shows maximum drug release at the end of 60minutes so it was chosen as optimized formulation.

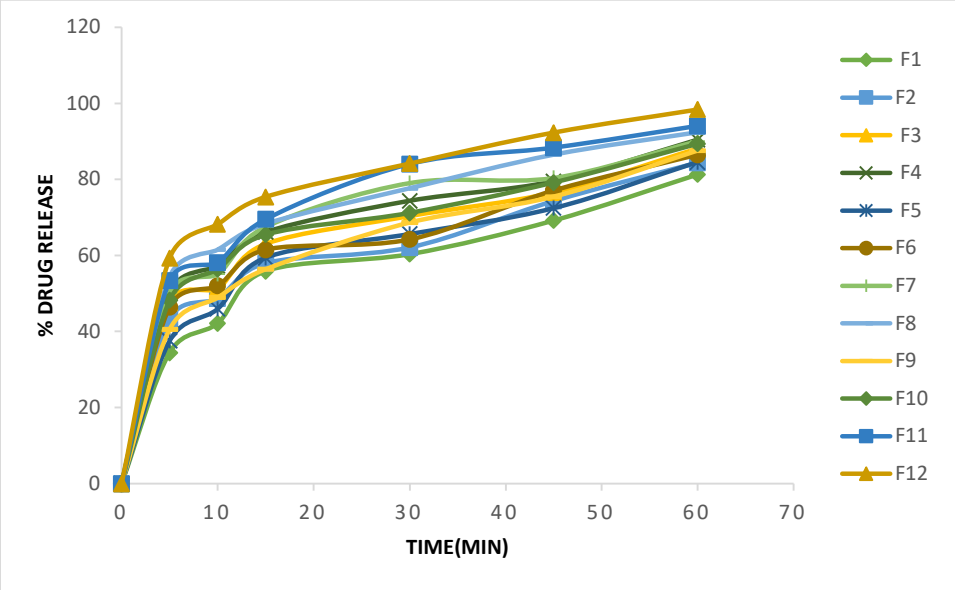


Fig 6: *Invitro* drug release profile for (F1-F12)

***In-vitro* drug release kinetics studies for best formulation F12**

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows first order release kinetics studies having R^2 value 0.906 were as zero order release kinetics studies having R^2 value 0.599, hence we can say that the best formulation follows first order release kinetics.

SUMMARY

The therapeutic efficacy of a drug product intended to be administered by the oral route depends on its absorption by the gastro–intestinal tract. It is well established that dissolution is frequently the rate-limiting step in the gastro intestinal absorption of a drug from a solid dosage form. Poorly soluble drugs have been shown to be unpredictable and are slowly absorbed as compared with drugs with higher solubility. Consequently, these drugs present great challenges to further development into bioavailable dosage forms. Hence it is important to enhance the aqueous solubility, dissolution rate and bioavailability ofthese drugs from its oral solid dosage forms. Solid dispersion technique by Soluplus, PEG 4000 and Mannitol have been used to improve the dissolution properties and bioavailability of poorly water- soluble drugs. This study has demonstrated the possibility of markedly improving the dissolution performance of Macitentan by solid dispersion technique. Macitentan is indicated for the treatment of WHO group 1 pulmonary arterial hypertension (PAH) both alone and in combination with tadalafil. Macitentan is an BCS class II drug having absolute bioavailability of Macitentan is low.

Therefore, a favourable formulation which can enhance solubility and dissolution rate of this model drug may help effectively. Thus, studies were carried out to improve the solubility and hence dissolution rate, efficiency and bioavailability of poorly soluble drug Macitentan through solid dispersion technique using Soluplus, PEG 4000 and Mannitol. The brief introduction about solid dispersions were explained in the introduction part. Further more, in this chapter introduction on dissolution rate and various approaches to improve the solubility; particularly on solid dispersion technology was elaborated. The aim and objective was also discussed. Drug profile and excipient profiles were included with complete drug description of Macitentan and outlined their usage, contraindication and side effects. Literature survey related to preparation and past research work on solid dispersions with various drugs and also by different methods.

Methodology as well as materials used and experimental methods employed in the present investigation were explained in detail. Later introduction regarding all the evaluation parameters and method of preparation of physical mixtures and solid dispersions of Macitentan by solvent evaporation was explained. Solid dispersions of Macitentan were prepared with different carriers in different ratios of drug and carrier (1:1, 1:2, 1:3 and 1:4). Results of prepared solid dispersions of Macitentan by hot melt extrusion method were discussed which includes solubility, melting point determination, drug content uniformity, entrapment efficiencyand*invitro* dissolutionstudies. Characterization in solid state was done by various analytical techniques such as FT-IR studies.

Finally by comparing all the formulations (F1-F12) formulation (F12) containing Macitentan+Mannitol (1:4) shows better results by solvent evaporation method at the end of 60 min with drug release of 98.35±1.49%, hence it was selected as the best formulation.

CONCLUSION

Mannitol was used in the preparation of solid dispersions by solvent evaporation method. By observing the dissolution studies the Macitentan with Mannitol (1:4). It Shows better drug release. And all the prepared solid dispersions were evaluated and results was explained in above mentioned data.
The following conclusions were drawn from the present investigations.

- From the Solubility studies in various buffers we can say that 6.8 pH buffer has more solubility when compared to other buffer solutions for Macitentan.
- Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes.
- All the formulations of Macitentan were prepared hot melt extrusion method
- All the prepared solid dispersions were evaluated for drug content
- The invitro dissolution studies of Macitentan was performed.
- From the optimized formulation of the solid dispersions(i.e.F12)

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