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Research Article

FORMULATION AND INVITRO CHARACTERIZATION OF MACITENTAN SOLID DISPERSION TO FAST DISINTEGRATING TABLETS

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ABSTRACT:

Macitentan is an endothelin receptor antagonist utilized for the management of pulmonary arterial hypertension to impede disease development.It is a BCS Class II medication. To enhance the biological efficacy of Macitentan, a solid dispersion was formed into an oral disintegrating tablet utilizing PEG 6000, Xylitol, and PVP K30. Solid dispersions of Macitentan were created using several carriers in distinct ratios of drug to carrier (1:1, 1:2, 1:3, and 1:4). The outcomes of the generated solid dispersions of Macitentan using the solvent evaporation method were examined, including solubility, melting point determination, drug content uniformity, and in vitro dissolution investigations.Characterization in the solid state was conducted using several analytical methods, including FT-IR investigations.Ultimately, while evaluating all formulations, formulation (F12) including Macitentan and PVP K30 in a 1:4 ratio demonstrated superior outcomes using the solvent evaporation technique after 60 minutes, achieving maximal drug release; hence, it was designated as the optimal formulation.Fast dissolving tablets were produced from the optimal formulation utilizing several disintegrants at varied concentrations.The pre-compression and post-compression parameters were analyzed, and the findings were presented. All findings fall within permissible limits.The in vitro drug release of the prepared tablets was conducted using a 6.8 pH phosphate buffer. The F12T12 formulation with 50mg of Cropovidone exhibits a drug release of 99.74±1.48% within 20 minutes. The improved formulation adheres to first-order release kinetics.

Keywords: Macitentan, Crospovidone, PVP K30, ODT & FTIR

INTRODUCTION

Pulmonary hypertension is a form of elevated blood pressure that impacts the pulmonary arteries and the right atrium of the heart.

In a specific kind of pulmonary hypertension known as pulmonary arterial hypertension (PAH), the blood arteries in the lungs are constricted, obstructed, or obliterated. The injury impedes blood circulation within the lungs. Pulmonary arterial pressure increases. The heart must exert greater effort to circulate blood via the lungs. The additional exertion ultimately leads to the weakening and failure of the cardiac muscle.

In certain individuals, pulmonary hypertension progressively deteriorates and may become life-threatening. There is no remedy for pulmonary hypertension. Treatments are accessible to enhance your well-being, extend your lifespan, and elevate your quality of life.[1]

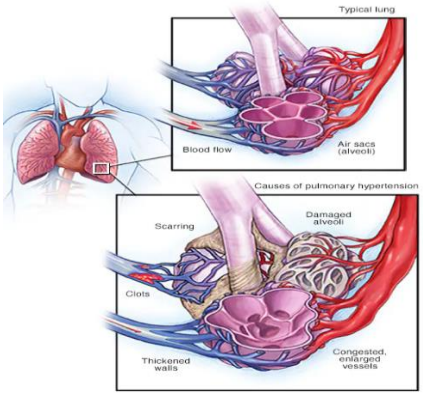

Figure No.1 Pulmonary hypertension

The oral route is the most often utilized method of medication delivery, being both easy and cost-effective.[2] The tablet is among the most prevalent oral dosage forms now available due to its ease of self administration, compactness, and straight forward production process.

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Rapidly dissolving dose forms can be decomposed, dissolved, or suspended by saliva in the oral cavity.[3] However, oral formulations utilizing low solubility dispersions (SDs) have conventionally served as an effective approach to enhance the dissolving characteristics and bioavailability of poorly water-soluble pharmaceuticals. For medicines with low water solubility, dissolution constitutes the rate-limiting factor in drug absorption. Diverse methodologies, including self-emulsifying drug delivery systems[4], solid dispersions[5] , crystal engineering[6] , complexation[7] , freeze drying[8] , fast dissolving tablet[9] , reduction of particle size, supercritical fluid methods[10] , solid dispersion granules using hot melt granulation technique were reported previously. [11]Fast-dissolving tablets are beneficial for people who experience difficulty swallowing traditional pills, such as pediatric patients and those undergoing chemotherapy.[12] To facilitate rapid dissolution of dose forms in the oral cavity, these delivery methods consist of either highly porous and soft-molded matrices or tablets compressed with little force.

Macitentan is an orphan medication used for the management of pulmonary arterial hypertension (PAH). Endothelin-1 (ET-1) is pivotal in the pathogenesis of pulmonary arterial hypertension (PAH). Macitentan, a novel dual endothelin receptor antagonist, has been shown to enhance the prognosis of patients with pulmonary arterial hypertension (PAH) by postponing disease development. It inhibits the binding of ET-1 to both endothelin A (ETA) and endothelin B (ETB) receptors. [13] Macitentan is an antagonist of endothelin receptors (ERA). Macitentan, marketed as Opsumit. This medication is produced by Actelion and sanctioned for the management of pulmonary arterial hypertension (PAH).[14] As of 2014, the other two marketed endothelin receptor antagonists (ERAs) are bosentan and ambrisentan. Macitentan is a dual endothelin receptor antagonist, targeting both ETA and ETB receptor subtypes. Macitentan has a 50-fold greater selectivity for the ETA subtype in comparison to the ETB subtype. [15] The pharmaceutical agent obtained authorization from the U.S. Food and Drug Administration (FDA) on October 13, 2013.

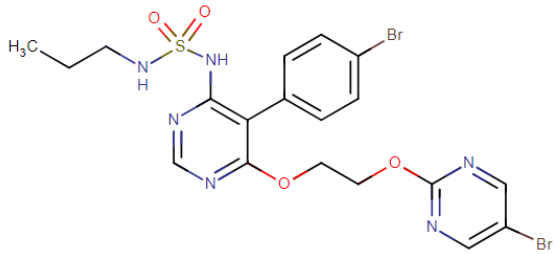

Figure No.2 Structure of macitentan

MATERIALS & METHODS USED: Macitentan API was procured from Anant Pharmaceuticals Pvt. Ltd, Hyderabad and Xylitol, PVP K30 were procured from S.D Fine Chemicals, PEG 6000, Lycoat, ludiflash, Crospovidone, MCC, Aspartame, Magnesium stearate and Talc were procured from B.M.R. Chemicals, Hyderabad.

PREPARATION OF SOLID DISPERSIONS OF MACITENTAN:

There are several carriers, which have been reported for the preparation of solid dispersions by using Soluplus, PVP K30 and SSG various methods of preparation.

Table No.1 Formulation of Solid dispersion

Formulation Code	Drug and Polymers Ratio	Drug and Polymers Ratio
F1	Macitentan: PEG 6000	1:1
F2	Macitentan: PEG 6000	1:2
F3	Macitentan: PEG 6000	1:3
F4	Macitentan: PEG 6000	1:4
F5	Macitentan: Xylitol	1:1
F6	Macitentan: Xylitol	1:2
F7	Macitentan: Xylitol	1:3
F8	Macitentan: Xylitol	1:4
F9	Macitentan: PVP K30	1:1
F10	Macitentan: PVP K30	1:2
F11	Macitentan: PVP K30	1:3
F12	Macitentan: PVP K30	1:4

Solvent evaporation method: Solvent evaporation involves emulsification of polymer in aqueous phase and dispersion in a volatile solvents. Then the solvent is evaporated using high temperature, vacuum, or by continuous stirring or the solvent was then rapidly evaporated with the aid of mild heat (up to about 50° C) and surface airflow with constant vigorous stirring to form a uniform solid mass.

In solvent evaporation method, the drug and carriers were mixed in 1:1,1:2 ,1:3 & 1:4 ratios in methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverized and passed through sieve# 60. And now the obtained product was collected.

FORMULATION OF MACITENTAN TABLETS:

Equivalent weight of Macitentan was added with suitable excipients and the tablets were formulated by direct compression according to the formulae given in the table. All the ingredients were passed through #40 mesh sieve separately. The drug and MCC were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside.

Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#40 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 5-6 kg/cm^2 for all batches. The weight of the tablets was kept constant for all formulations F12T1 to F12T12.

Table No.2 Formulation of Macitentan Tablets

Ingredients (mg)	F12 T1	F12 T2	F12 T3	F12 T4	F12 T5	F12 T6	F12 T7	F12 T8	F12 T9	F12 T10	F12 T11	F12 T12
Macitentan (weight equivalent to 10 mg)	50	50	50	50	50	50	50	50	50	50	50	50
Lycoat	20	30	40	50	--	--	--	--	--	--	--	--
Ludiflash	--	--	--	--	20	30	40	50	--	--	--	--
Cropovidone	--	--	--	--	--	--	--	--	20	30	40	50
MCC	116	106	96	86	116	106	96	86	116	106	96	86
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
Mg.stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSIONS

Solubility:

Solubility of was carried out at 250C using 0.1 N HCL, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer.

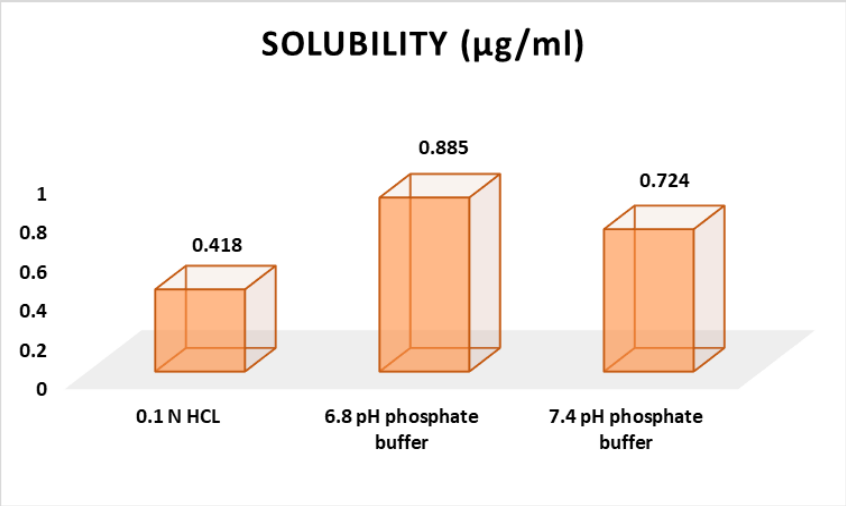

Figure No.3 Graphical representation of Macitentan Solubility studies

Discussion:

From the above conducted solubility studies in various buffers we can say that 6.8 pH phosphate buffer solution has more solubility when compared to other buffer solutions.

Analytical method development by UV Spectroscopy:

UV Scan Spectrum of Macitentan:

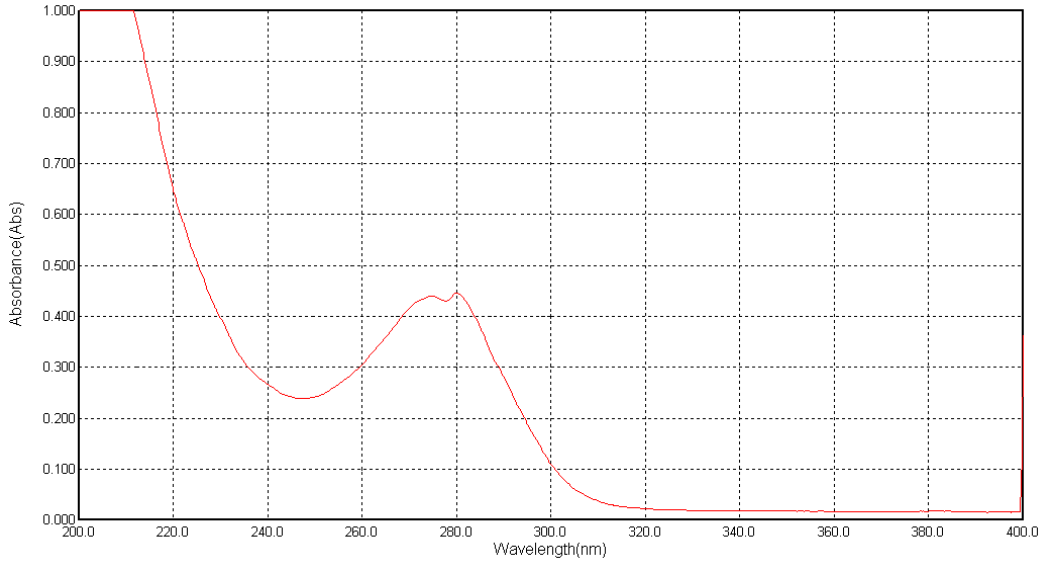

Figure No.4 UV Scan Spectrum of Macitentan

Discussion: The maximum absorbance of the Macitentan in 6.8 pH phosphate buffer was found to be 280 nm for 100% concentration solution as shown in Fig. Hence, the wavelength of 280 nm was selected for analysis of drug in dissolution media.

Calibration curve of Macitentan in 6.8 pH phosphate buffer:

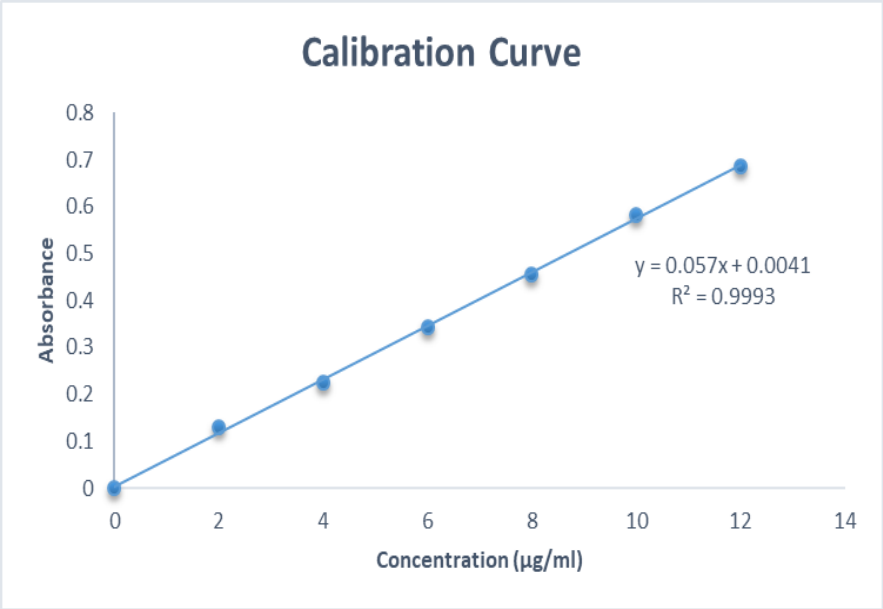

Figure No.5 Calibration curve

Discussion:

The linearity was found to be in the range of 2-12µg/ml in 6.8 pH phosphate buffer. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

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.

Pure Drug

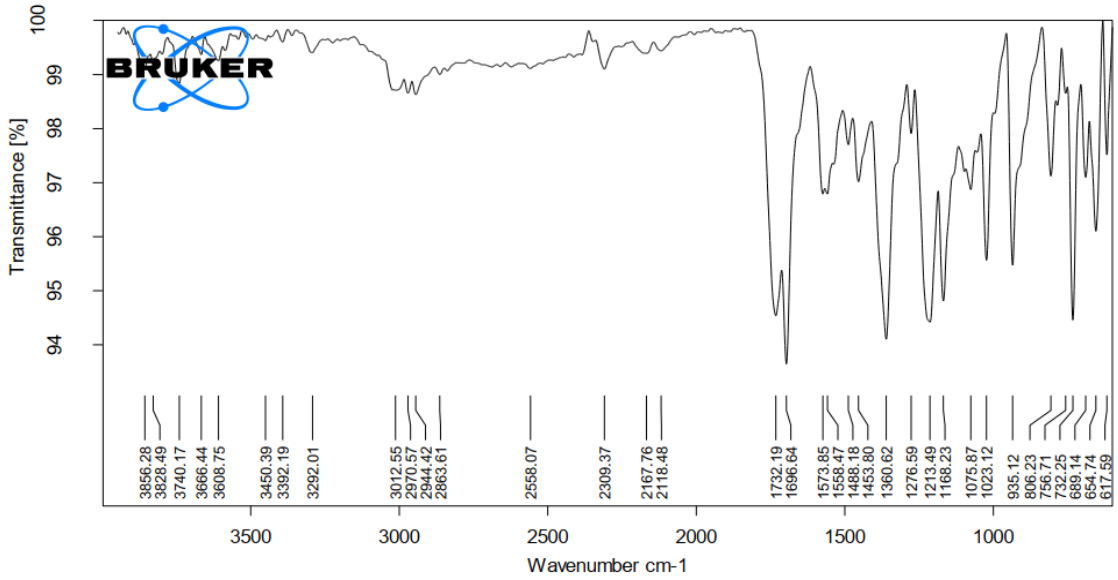

Figure No.6 IR spectrum of pure Macitentan

Optimized Formulation

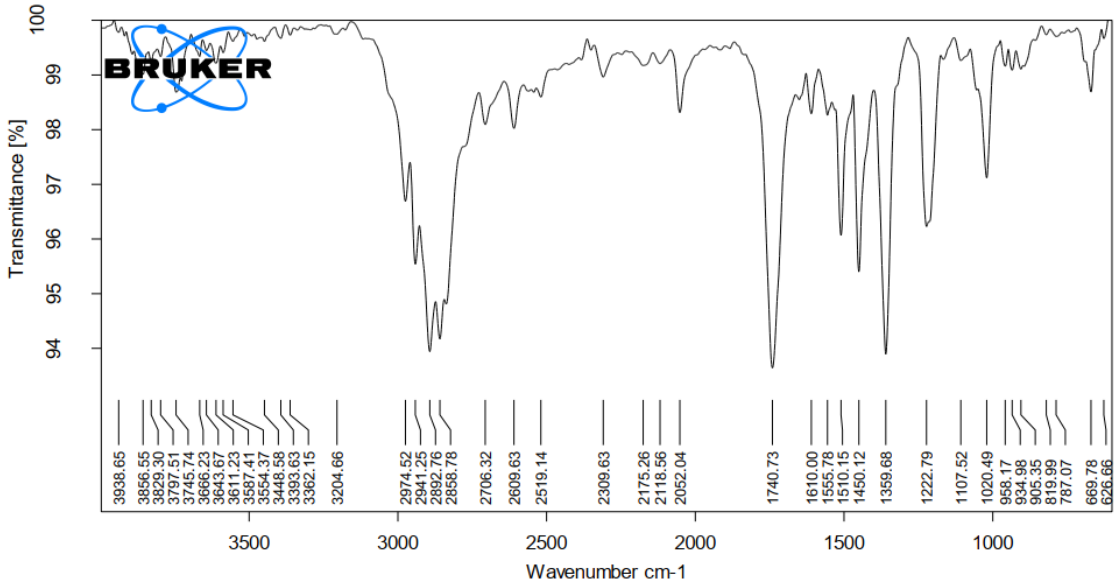

Figure No.7 IR spectrum of Macitentan Optimized Formulation

Discussion: 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.No.3 Drug content of solid dispersions

Formulation code	%Drug content
F1	93.47±1.47%
F2	95.27±1.65%
F3	96.75±1.58%
F4	98.11±1.75%
F5	94.57±1.45%
F6	96.78±1.20%
F7	97.61±1.68%
F8	98.19±1.45%
F9	94.45±1.78%
F10	95.67±1.20%
F11	97.38±1.24%
F12	98.24±1.20%

Discussion: The Drug content of the formulated solid dispersions was found to be in the range of 93.47±1.47%- 98.24±1.20% respectively.

Percentage Yield of Solid Dispersions:

Table.No.4 Percentage yield of solid dispersions

Formulation code	Percentage yield
F1	92.43±1.47%
F2	94.61±1.45%
F3	95.31±1.62%
F4	96.41±1.21%
F5	90.25±1.67%
F6	93.65±1.54%
F7	94.48±1.62%
F8	97.52±1.87%
F9	92.48±1.52%
F10	95.57±1.20%
F11	97.46±1.65%
F12	99.31±1.47%

Discussion: The Percentage yield of the formulated solid dispersions was found to be in the range of 92.43±1.47%- 99.31±1.47% respectively.

In Vitro Drug Release Studies of Solid Dispersions:

Table No.5 In vitro drug release studies for formulations (F1-F12)

Time (Min)	Percentage drug release											
	Macitentan : PEG 6000				Macitentan : Xylitol				Macitentan : PVP K30			
	1:1 (F1)	1:2 (F2)	1:3 (F3)	1:4 (F4)	1:1 (F5)	1:2 (F6)	1:3 (F7)	1:4 (F8)	1:1 (F9)	1:2 (F10)	1:3 (F11)	1:4 (F12)
0	0	0	0	0	0	0	0	0	0	0	0	0
5	44.16 ±1.27	47.58 ±1.07	53.15 ±1.24	57.24 ±1.23	40.16 ±1.20	43.67 ±1.25	50.64 ±1.25	58.24 ±1.27	46.16 ±1.24	57.26 ±1.37	60.64 ±1.37	67.24 ±1.74
10	56.24 ±1.45	50.17 ±1.54	67.48 ±1.48	69.24 ±1.57	55.24 ±1.45	57.41 ±1.67	55.35 ±1.67	67.24 ±1.54	58.24 ±1.67	62.63 ±1.57	67.35 ±1.74	79.24 ±1.28
15	63.43 ±1.65	58.46 ±1.25	73.34 ±1.36	77.45 ±1.65	60.43 ±1.26	65.26 ±1.54	62.03 ±1.45	75.45 ±1.68	66.43 ±1.54	79.98 ±1.54	76.03 ±1.25	85.45 ±1.21
30	75.29 ±1.74	65.48 ±1.68	83.58 ±1.74	86.25 ±1.52	69.29 ±1.74	70.63 ±1.21	78.32 ±1.20	87.25 ±1.25	79.29 ±1.20	85.09 ±1.59	88.32 ±1.20	90.25 ±1.24
45	87.49 ±1.20	74.85 ±1.74	91.27 ±1.45	94.29 ±1.28	75.49 ±1.54	76.98 ±1.65	86.56 ±1.57	93.29 ±1.27	90.49 ±1.57	91.32 ±1.74	93.56 ±1.67	95.29 ±1.68
60	92.37 ±1.57	85.19 ±1.26	98.14 ±1.25	98.48 ±1.74	86.37 ±1.59	88.09 ±1.58	92.11 ±1.20	97.24 ±1.68	95.37 ±1.68	96.42 ±1.20	98.11 ±1.26	99.84 ±1.25
75	95.76 ±1.47	98.47 ±1.50			92.27 ±1.57	93.32 ±1.75	98.42 ±1.42		98.24 ±1.20	99.48 ±1.29		
90	98.52 ±1.53				97.54 ±1.28	98.42 ±1.21						

Discussion: In vitro drug release of Macitentan solid dispersions with PEG 6000 in various ratios, the formulation F1 releases 98.52±1.53%, were observed which shows at the end of 90 mins, formulation F2 releases 98.47±1.50% were observed which shows at the end of 75 mins, F3 releases 98.14±1.25% were observed which shows at the end of 60 mins, and F4 releases 98.48±1.74% were observed which shows at the end of 60 mins. While Xylitol used as carrier shows formulation F5 releases 97.54±1.28% were observed which shows at the end of 90 mins, formulation F6 releases 98.42±1.21% were observed which shows at the end of 90 mins, and formulation F7 releases 98.42±1.42% were observed which shows at the end of 75 mins and F8 release 97.24±1.68% were observed which shows at the end of 60 mins. While PVP K30 used as carrier shows formulation F9 releases 98.24±1.20% were observed which shows at the end of 75 mins, formulation F10 releases 99.48±1.29% were observed which shows at the end of 75 mins, formulation F11 releases 98.11±1.26% were observed which shows at the end of 60 mins and formulation F12 releases 99.84±1.25% at the end 60 minutes. Among all formulation F12 formulation shows maximum drug release at the end of 60 minutes so it was chosen as optimized formulation.

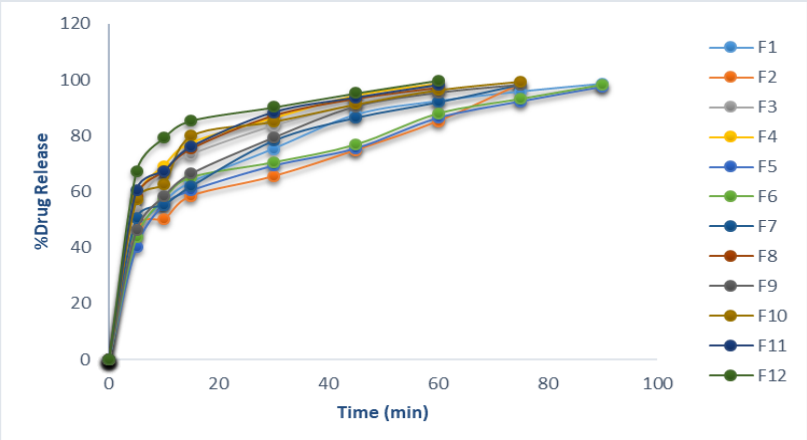

Figure No.8 In vitro drug release profile for (F1-F12)

In-vitro drug release kinetics studies for best formulation F12:
Zero order release kinetics studies:

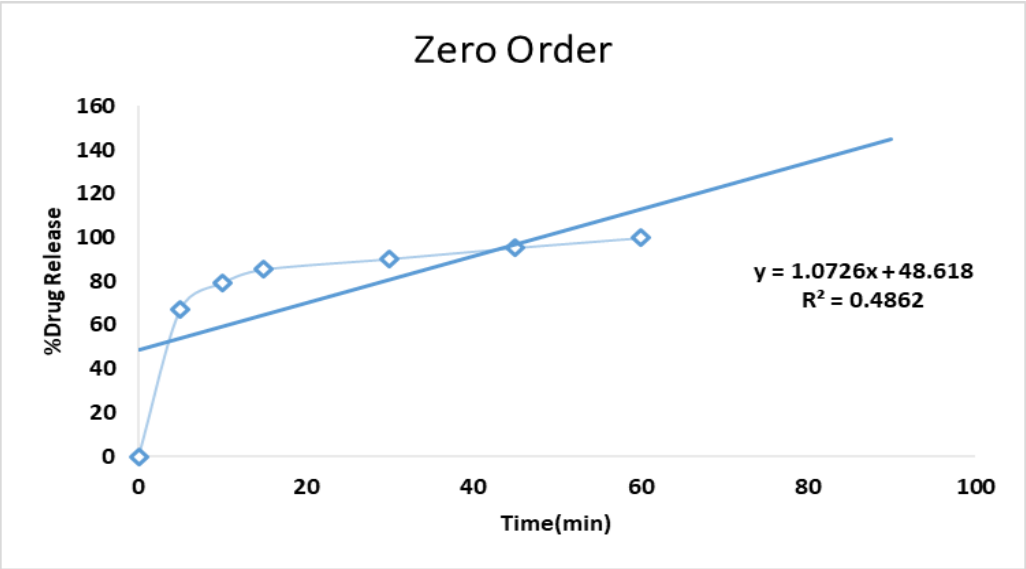

Figure No.9 Zero order release profile for best formulation (F12)

First order release kinetics studies:

Figure No.10. First order release profile for best formulation (F12)

Discussion: 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 0.985 were as zero order release kinetics studies having R^2 value 0.486, hence we can say that the best formulation follows first order release kinetics

Evaluation of Macitentan Fast disintegrating Tablets:

Table.No.6 Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD) g/cm3	Tapped Density (mean±SD)	Angle of Repose (mean±SD)	Carr's index (mean±SD) %	Hausner's ratio (mean±SD)
F12T1	0.321±0.007	0.437±0.004	24.45±1.27	18.24±1.20	1.18±0.03
F12T2	0.338±0.005	0.448±0.003	26.38±1.45	17.26±1.37	1.17±0.05
F12T3	0.345±0.002	0.456±0.005	25.74±1.68	15.48±1.45	1.15±0.06
F12T4	0.351±0.006	0.468±0.006	27.25±1.25	14.25±1.87	1.14±0.04
F12T5	0.310±0.003	0.451±0.009	22.45±1.67	17.46±1.57	1.19±0.02
F12T6	0.324±0.005	0.464±0.005	23.16±1.25	15.18±1.46	1.17±0.04
F12T7	0.337±0.004	0.474±0.007	24.38±1.28	14.34±1.28	1.16±0.03
F12T8	0.348±0.006	0.485±0.006	25.18±1.37	13.25±1.54	1.15±0.02
F12T9	0.349±0.003	0.455±0.003	24.45±1.57	14.46±1.21	1.16±0.05
F12T10	0.356±0.004	0.468±0.007	26.75±1.69	15.19±1.58	1.14±0.02
F12T11	0.367±0.005	0.474±0.005	27.69±1.25	13.37±1.37	1.13±0.04
F12T12	0.378±0.007	0.481±0.007	28.45±1.74	12.78±1.48	1.11±0.02

Discussion:

The angle of repose of different formulations was ≤ 28.45±1.74, which indicates that material had good flow property. So, it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.321±0.007g/cm3 to 0.378±0.007g/cm3. Tapped density was found between 0.437±0.004g/cm3 to 0.481±0.007g/cm3. These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 12.78±1.48%-18.24±1.20% and Hausner's ratio from 1.18±0.03-1.11±0.02, which reveals that the blends have good flow character.

Characterization of tablets

Post Compression parameters

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table

Table No.7 Characterization Macitentan Fast disintegrating tablets

Formulation	Weight variation	Thickness (mm)	Diameter (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)
F12T1	202.18±1.75	2.48±0.54	4.67±0.21	5.5±1.24	0.47±0.12	20±1.24
F12T2	199.47±1.85	2.75±0.38	4.48±0.38	5.8±1.47	0.58±0.37	18±1.45
F12T3	200.16±2.15	2.61±0.24	4.68±0.47	5.4±1.65	0.65±0.48	16±1.37
F12T4	198.38±1.86	2.52±0.15	4.48±0.47	6.1±1.25	0.41±0.67	15±1.49
F12T5	201.59±2.06	2.74±0.65	4.84±0.15	5.9±1.74	0.58±0.45	21±1.52
F12T6	202.48±1.75	2.69±0.45	4.52±0.37	5.8±1.52	0.64±0.54	19±1.45
F12T7	198.78±1.65	2.45±0.20	4.69±0.28	5.5±1.68	0.53±0.37	17±1.21
F12T8	200.48±1.54	2.38±0.74	4.45±0.47	6.0±1.20	0.49±0.26	16±1.37
F12T9	203.39±1.37	2.52±0.16	4.37±0.65	5.7±1.32	0.68±0.48	15±1.42
F12T10	201.21±1.56	2.28±1.57	4.48±0.57	6.0±1.27	0.54±0.41	14±1.43
F12T11	199.45±1.48	2.64±0.25	4.67±0.45	6.2±1.48	0.49±0.25	13±1.51
F12T12	200.47±1.67	2.78±0.74	4.85±0.28	6.5±1.51	0.46±0.41	11±1.42

Discussion: Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 5.4±1.65 – 6.5±1.51 kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F12T1 – F12T12 and considered to be satisfactory ensuring that all the formulations are mechanically stable.

Drug Content of tablets:

Table No.8 %Drug content of Tablets

Formulation code	Drug Content (%)
F12T1	92.37±1.47**%**
F12T2	94.21±1.65**%**
F12T3	95.43±1.37**%**
F12T4	97.45±1.45**%**
F12T5	94.37±1.25**%**
F12T6	96.45±1.20**%**
F12T7	97.17±1.67**%**
F12T8	98.51±1.08**%**
F12T9	95.48±1.34**%**
F12T10	96.58±1.28**%**
F12T11	97.65±1.16**%**
F12T12	98.74±1.37**%**

Discussion: The drug content values for all the formulations (F12T1 – F12T12) was found to be in the range of 92.37±1.47%-98.74±1.37**%.**

Dissolution studies of the tablets: The prepared tablets were subjected to dissolution studies in order to know the amount drug release.

Table. No.9 % Cumulative drug release of formulations F12T1 – F12T6

Time(min)	F12T1	F12T2	F12T3	F12T4	F12T5	F12T6
0	0	0	0	0	0	0
5	55.48±1.24	61.68±1.45	67.47±1.45	78.31±1.24	58.74±1.45	64.47±1.26
10	62.48±1.45	75.47±1.67	78.34±1.20	87.47±1.58	65.16±2.15	78.35±1.47
15	77.45±1.48	79.28±1.46	83.75±1.74	94.65±1.21	70.18±1.15	82.46±1.85
20	82.19±1.16	84.65±1.76	92.58±1.68	97.29±1.67	79.18±1.36	86.18±1.20
25	88.45±1.27	90.47±1.20	98.45±1.24		88.45±1.74	93.37±1.46
30	97.45±1.27	97.15±1.75			98.37±1.20	98.20±1.75

Table. No.10 % Cumulative drug release of formulations F12T7 – F12T12

Time(min)	F12T7	F12T8	F12T9	F12T10	F12T11	F1T12
0	0	0	0	0	0	0
5	66.24±1.27	75.47±1.48	62.78±1.72	68.10±1.20	79.74±1.37	87.67±1.37
10	74.38±1.46	88.38±1.54	70.65±1.65	77.34±1.46	85.48±1.45	91.75±1.56
15	87.28±1.37	94.48±1.20	79.17±1.84	85.20±1.37	90.68±1.23	96.58±1.25
20	93.45±1.48	98.78±1.62	86.34±1.24	92.18±1.45	94.45±1.49	99.74±1.48
25	98.26±1.20		93.45±1.46	95.59±1.20	98.18±1.21	
30			97.78±1.57	98.25±1.67		

Discussion: The formulations containing Crospovidone as a super disintegrant in different concentrations like 20mg, 30mg, 40mg and 50mg reveals that the increased in the super disintegrant concentration decreases the drug

release time and the F12T12 formulation containing Crospovidone 50mg shows maximum amount of drug release (99.74±1.48%) at the end of 20mins.

In Vitro Drug Release of F12T1-F12T12:

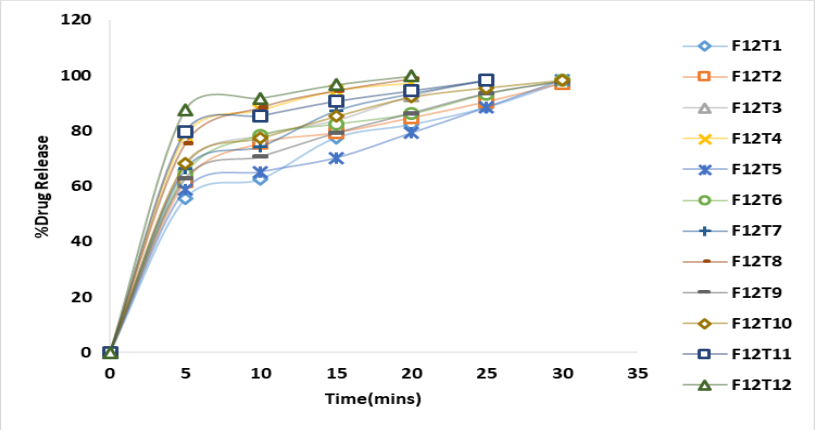

Figure No.11: in vitro drug release of formulations F12T1-F12T12

Drug release kinetics:

Zero order plot of F12T12:

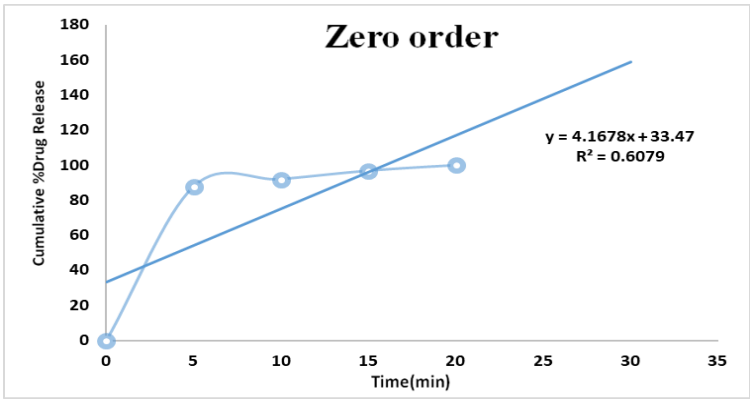

Figure No.12.: Zero Order Plot of F12T12

First order plot of F12T12:

Figure No.13 First Order Plot of F12T12

Table.No.11 order of kinetic values of Formulation F12T12

Order of kinetics	Zero Order	First Order
Regression values	0.607	0.984

Discussion: The drug release from the tablets was explained by using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation **F12T12** follows First order 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 of these drugs from its oral solid dosage forms. Solid dispersion technique by PEG 6000, Xylitol and PVP K30. 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 an endothelin receptor antagonist and it is an BCS class II drug having absolute bioavailability of is 74%. 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 PEG 6000, Xylitol and PVP K30. 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 method was explained. Solid dispersions of Macitentan were prepared with different carriers in different ratios of drug and carrier (1:1, 1:2, 1:3&1:4). Results of prepared solid dispersions of Macitentan by solvent evaporation method were discussed which includes solubility, melting point determination, drug content uniformity, entrapment efficiency and in vitro dissolution studies. 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+PVP K30 (1:4) shows better results by solvent evaporation method at the end of 60 min with drug release of 99.84±1.25%, hence it was selected as the best formulation. From the optimized formulation the FDT tablets were formulated using different disintegrants in different concentrations. The pre compression and post compression parameters were studied and the results were given. all the results are in the acceptable limit. The in vitro drug release of the formulated tablets were performed using 6.8pH Phosphate buffer. F12T12 formulation containing 50mg Cropovidone shows 99.74±1.48 % drug release in 20mins. The optimized formulation follows first order release kinetics.

CONCLUSION

PEG 6000, Xylitol and PVP K30 was used in the preparation of solid dispersions by solvent evaporation method. By observing the dissolution studies the Macitentan+PVP K30 (1:4) 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 6.8pH Phosphate 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 solvent evaporation method. All the prepared solid dispersions were evaluated for drug content .The in vitro dissolution studies of Macitentan was performed From the optimized formulation of the solid dispersions(i.e.,F12) weight equivalent of Macitentan was used along with the super disintegrants like Cropovidone. Pre compession and Post compression evaluation studies were performed. The

better drug release with 50mg of Cropovidone shows 99.74±1.48% of drug release at the end of 20mins. Drug release kinetics of the optimized formulation shows First order drug release.

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