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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF MACITENTAN

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Abstract:
The present study aimed to formulate and evaluate immediate-release tablets of Macitentan using super disintegrants to enhance rapid drug release. Tablets were prepared by incorporating cross povidone, croscarmellose sodium, and sodium starch glycolate in a 1:1 ratio using a suitable manufacturing method. The powder blends were evaluated for pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio, which indicated good flow properties. The compressed tablets were assessed for post-compression parameters including weight variation, hardness, thickness, friability, disintegration time, drug content, and in-vitro dissolution. All evaluated parameters were found to be within Indian Pharmacopoeia (IP) limits, confirming acceptable tablet quality. Among the developed formulations, F2 was identified as the optimized formulation, exhibiting rapid disintegration and a maximum drug release of 99.76%, which was superior compared to other formulations. The results suggest that the combination of cross povidone, croscarmellose sodium, and sodium starch glycolate in equal proportion is effective in developing immediate-release tablets of Macitentan with enhanced dissolution and potential for improved therapeutic performance.

Keywords: *Macitentan, cross povidone, croscarmellose sodium, and sodium starch glycolate*

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INTRODUCTION:

An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques [1,2]

Immediate release and fast dispersing drug delivery system may offer a solution to these problems. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities.

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. This term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.

Imipramine is a tricyclic antidepressant with general pharmacological properties similar to those of structurally related tricyclic antidepressant drugs such as amitriptyline and doxepin. A tertiary amine, imipramine inhibits the reuptake of serotonin more so than most secondary amine tricyclics, meaning that it blocks the reuptake of neurotransmitters serotonin and noradrenaline almost equally. It binds the Sodium-dependent serotonin transporter and Sodium-dependent noradrenaline transporter, preventing or reducing the reuptake of norepinephrine and serotonin by nerve cells. Peak plasma levels are reached in 2 to 8 hours, and plasma half-life ranges from 11 to 25 hours. It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; small amount is excreted in the faeces via the bile. Imipramine is one of the less sedating tricyclics and has moderate antimuscarinic activity. Imipramine is used for the treatment of nocturnal enuresis in children. Tricyclic anti- depressants are not recommended under 6 years of age.

Immediate release drug delivery is desirable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat unwanted defect or disease1.[3]

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour. To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important processes. Few Super-disintegrants are available commercially as Croscarmellose sodium, Crospovidone and SSG. [4]

Oral drug delivery system includes conventional dosage form and immediate release dosage form. For last so many decades' conventional dosage forms like tablets, capsules, pills, powders, solutions, emulsions, suspensions and aerosols are used in the treatment of acute or chronic diseases. Even today these formulations can be considered as primary pharmaceutical product commonly seen in market.

When such a conventional dosage form is administrated, the concentration of such drug in systemic circulation gradually rises to attend a therapeutic range and this concentration is maintained for some time and finally decreases to sub therapeutic value rendering the drug pharmacologically inactive. Each individual drug has a maximum safe concentration and a minimum effective concentration. Fluctuations in plasma concentration may mean that drug levels may leading to toxic/side effects; alternatively, drug may fall too low leading to a lack of efficacy. the plasma drug concentration in a patient at a particular time depends on the compliance with the prescribed dosage interval

Hence, the design of effective drug delivery systems has recently become an integral part of the development of new medicines. The goal is to provide a therapeutic quantity of medicine/s to the proper site in the body in order to achieve the desired effect and maintain such effect for the entire period of treatment. A new development namely, immediate release dosage forms, has evolved from the need for a prolonged drug effect, a better control of drug administration and the reduction of side-effects.

Novel drug delivery systems are developed for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance. In these solid formulations do not require sterile conditions and are therefore, less expensive to

manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipment's choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.

Oral route is very common and easy route of administration of drug is oral route because of its systemic effect, patient compliance and cheaper to manufacture. Tablets provide high precision dosing. Tablet form is the most widely used dosage form cause of self-administration and easy to produce.[5]
It is a solid dosage form each containing some unit dose- one & more medicament/s. Tablet dosage forms are solid, flat or biconvex discs prepared by compressing of drug or combination of drugs with the use of suitable excipients. Tablets may be swallowed whole or being chewed. Some tablets are used with dissolving or disperse in water before the administration. But some tablets are put in oral cavity, where the active ingredient is liberated at a predetermined rate. Implants may also be presented in form of tablet. Tablet may vary in shape and differ greatly in size, weight & others, depends on the amount of drug substance and the intended mode of administration.
Immediate-release tablets break into smaller particles through a process referred to as disintegration. Some limitations in developing direct techniques for evaluating disintegration profiles are linked to drawbacks in the disintegration testing apparatus and lack of theoretical models, difficulties in distinguishing the interplay between process and formulation parameters, and the complexity of tablet microstructure dynamics in liquids. Often, the disintegration kinetics is not the rate-limiting process for complete drug dissolution but rather the limiting factor for drug liberation.

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.[6]

METHODOLOGY:

Buffer Preparation:

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved 10 1000ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen Ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

Pre formulation Studies

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Drug-Excipients compatibility studies:

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly.

Analytical method development for Macitentan:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λmax was found to be 217nm. Hence all further investigation were carried out at the same wavelength.

b) preparation of Standard graph in pH 6.8 phosphate buffer

100 mg of Macitentan was dissolved in method 5ml , volumetric flask make up to 100ml of Phosphate buffer of pH 6.8., form primary stock 10ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 6.8, from this

secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 6.8, to produce 10,20,30,40 and 50µg/ml respectively. The absorbance was measured at 217nm by using a UV spectrophotometer.

Formulation Development:

- Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes.
- The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 minutes.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table: Formulation of Immediate Release tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Macitentan	10	10	10	10	10	10	10	10	10
Cross Povidone	10	20	30	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	20	30	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	10	20	30
Locust beam gum	5	5	5	5	5	5	5	5	5
Aspartame	3	3	3	3	3	3	3	3	3
Mg stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
MCC	63	53	43	63	53	43	63	53	43
Total weight	100	100	100	100	100	100	100	100	100

Total weight of tablets = 100mg

The tablets were prepared by using 6nm flat surfaced punch. The hardness of the tablets was maintained as 2.15 - 2.34 kg/cm^2.

Evaluation parameters:

Pre compression parameters:

Measurement of Micromeritic Properties of Powders

1. Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.[55]

$\tan \theta = h/r$ ……..(1)

where, h and r are the height and radius of the powder cone.

Table: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

2. Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_o is noted. The bulk density is calculated in g/cm^3 by the formula.[56]

Bulk density = M/V_0 …… (2)

M= Powder mass

V_0= apparent unstirred volume

3. Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml granulated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tapping's are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less than 2%, V_b is considered as a tapped volume V_f . the tapped density is calculated in g/cm^3 by the formula.[57]

Tapped density=M/V_f ……..(3)

M= weight of sample power taken

V_f= tapped volume

4. Compressibility Index

The Compressibility Index of the power blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is an below:

Carr's Index (%)=[(TD-BD)/TD]x100 ……..(4)

5. Hauser's ratio

The Hauser's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hauser's ratio. It is calculated by the following equation.[58]

H=ρT / ρB ……(5)

Where ρT= tapped density, ρB = bulk density

Table 4: Scale of Flowability

Compressibility Index (%)	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Post compression parameters:

a) Thickness

The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation

Twenty tablets randomly selected from each batch and individually. Weighed. The average weight and standard deviation three batches were calculated. It passes the test weight variation test if not more than two of the individual tablets weights deviate from the average weight by more than the allowed percentage deviation and more deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability

The friability values of the tablets were determined using a Roche-type Friabilator. Accurately weighed six tablets were placed in Roche Friabilator and rotated at 25rpm for 4 min.

Percentage friability was calculated using the following equation.

Friability = ([w_0-w] / w_0) x 100

d) Assay

The content of drug was carried out by five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder, this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 217nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Macitentan tablets

Drug release from Macitentan tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 phosphate buffer as the dissolution medium of quantity 500ml. the whole study is being carried out at a temperature of 37^0C and at speed of 50 rpm. 5 ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 15, 20, 25 and 30 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV Spectrophotometer. The concentration was calculated using standard calibration curve.

RESULTS AND DISCUSSION:

Determination of λ_{max} :

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 217 nm.

Calibration curve of Macitentan:

The standard curve of Macitentan was obtained and good correlation was obtained with R^2 value of 0.998, the medium selected was pH 6.8 phosphate buffer.

Table: Standard graph values of Macitentan at 217nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
10	0.118
20	0.237
30	0.365
40	0.479
50	0.595

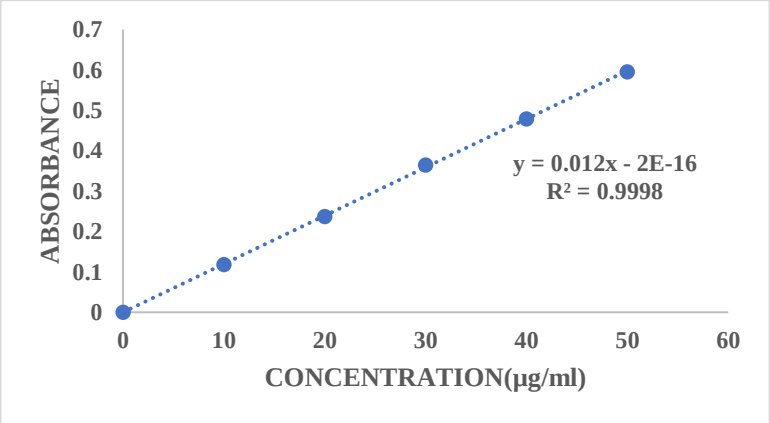

Fig: Standard curve of Macitentan

Drug-Excipient compatibility studies by FTIR studies:

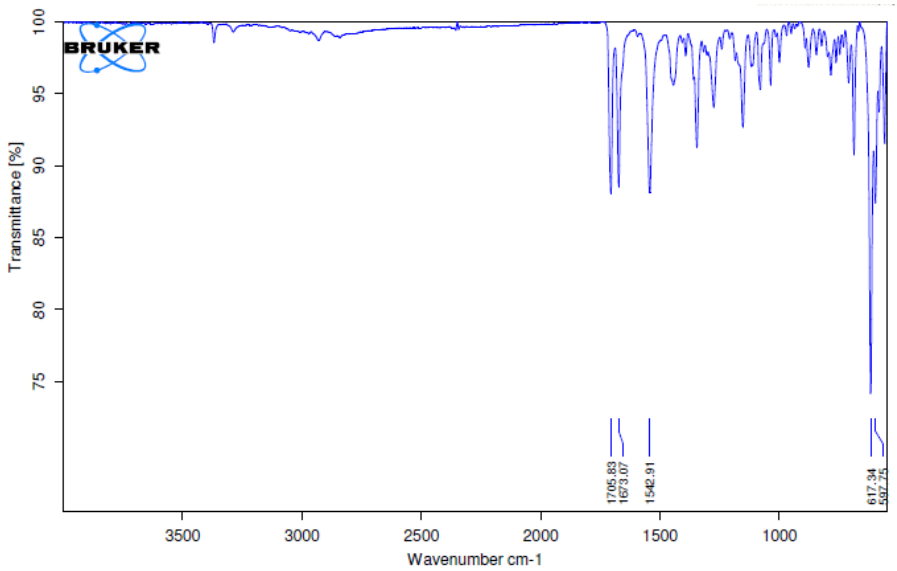

Fig : FTIR spectra of pure drug

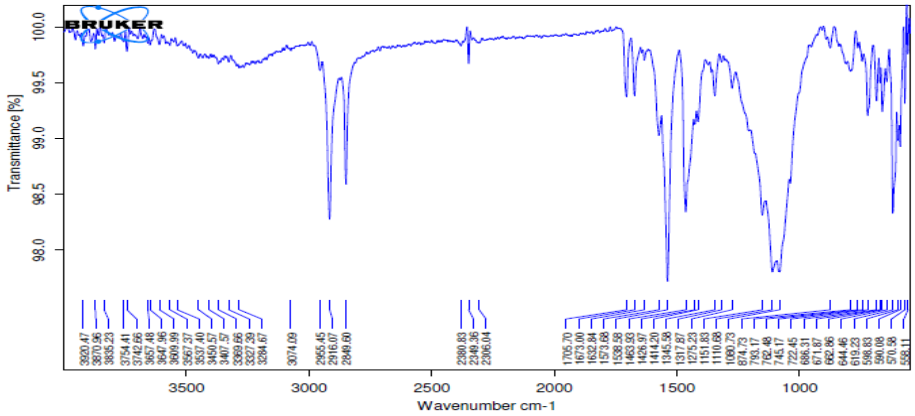

Fig: FTIR spectra of optimized formulation

Macitentan was mixed with various proportions of excipients showed no colour change at the end of two months, providing no drug –excipient interactions.

Evaluation:

Characterization of precompression blend:

The precompression blend of Macitentan were characterized with respect to angle of repose, bulk density , tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 28 ˚, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 foe all batches indicating good flow properties.

Table: Physical properties of precompression blend

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	27.38	0.43	0.51	15.47	1.18
F2	26.19	0.43	0.52	16.66	1.20
F3	28.18	0.43	0.51	15.29	1.18
F4	28.32	0.45	0.50	9.87	1.10
F5	31.10	0.44	0.50	13.41	1.15
F6	29.37	0.44	0.51	13.25	1.15
F7	27.17	0.41	0.50	18.60	1.22
F8	25.45	0.42	0.49	13.25	1.15
F9	25.78	0.41	0.47	14.28	1.16

All the values represent n=3

Evaluation of tablets:

Physical evaluation of Macitentan Immediate release tablets: The results of the weight variation, hardness, thickness, friability, and drug content of tablets are given in table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 2.15 - 2.34 kg/cm^2 and the friability values were < than 0.39±66 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 1.37 - 1.48. All the formulations satisfied the content of the drug as they contained 98-100% of Macitentan and good uniformity in drug content was observed. Thus, all physical attributes of the prepared tablets were found to be practically within control limits.

Table: Evaluation of Macitentan Immediate release tablets

Formulation code	Average Weight (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)	*In Vitro* Disintegration time (Minutes)
F1	99.58	1.38	2.24	0.63	99.89	2.43.
F2	100.31	1.45	2.28	0.45	98.64	2.23
F3	98.89	1.36	2.18	0.52	98.38	2.36
F4	99.73	1.41	2.25	0.33	97.77	2.38
F5	97.66	1.51	2.34	0.39	9.529	2.27
F6	96.22	1.48	2.27	0.46	97.28	2.35
F7	99.84	1.44	2.15	0.57	98.61	2.41
F8	101.92	1.39	2.22	0.44	99.83	2.25
F9	100.42	1.37	2.26	0.56	99.49	2.32

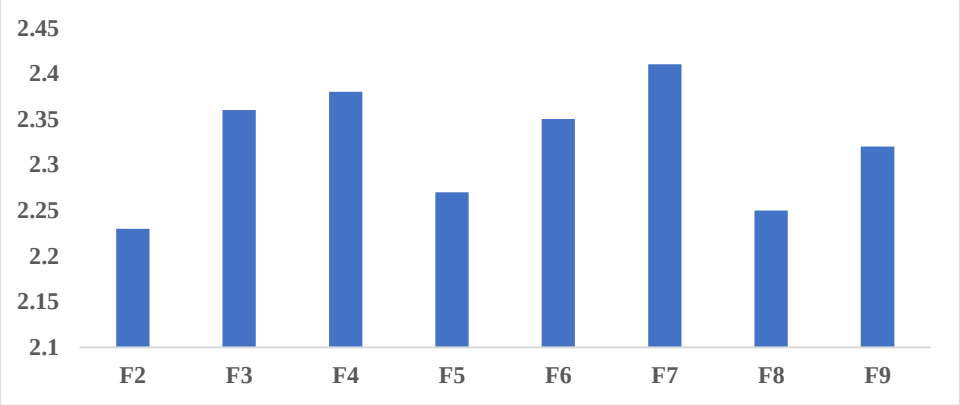

Figure: *In vitro* disintegration time Graph

***I*n vitro Dissolution:** The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 30 Minutes. and has analyzed after appropriate dilution by using UV spectrophotometer at 217nm

Table: *I*n vitro data for formulation F1- F9

Time (Minutes)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	19.21	19.52	22.83	26.85	25.18	28.74	18.83	24.64	37.12
10	29.39	36.38	39.59	29.37	36.44	39.94	45.26	37.85	49.08
15	41.73	49.97	55.28	47.83	49.75	46.76	55.48	48.73	58.22
20	53.59	64.63	69.89	64.48	65.47	52.92	68.59	58.29	66.31

25	67.86	78.88	76.48	82.22	76.66	88.11	85.46	78.59	82.46
30	79.35	99.76	92.37	91.88	89.73	96.48	93.83	89.15	96.85

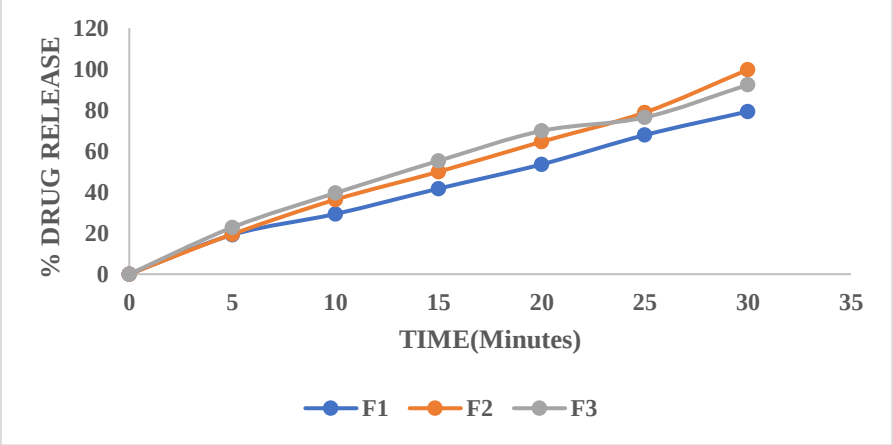

Fig: *I*n vitro dissolution data for formulation F1-F3

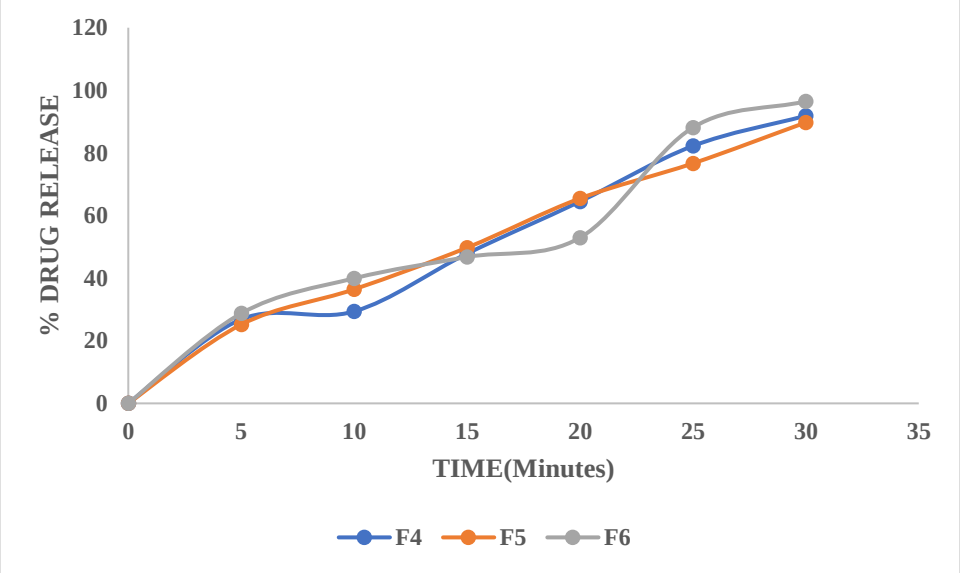

Fig: *In vitro* dissolution data for formulations F4 – F6

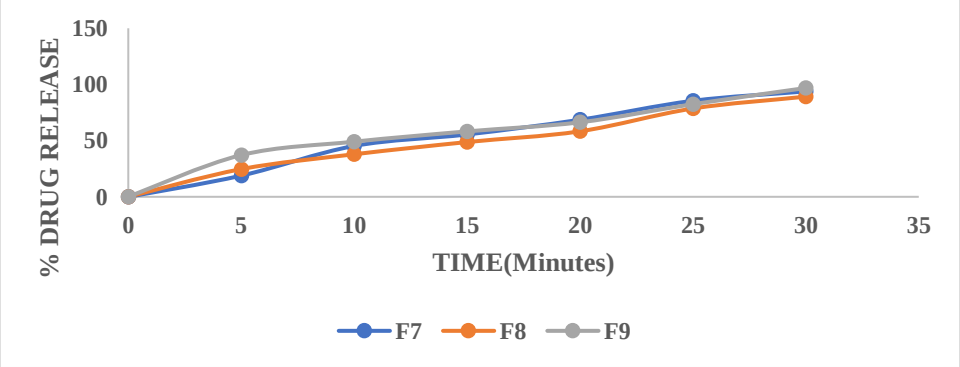

Fig: *In vitro* dissolution data for formulations F7 - F9

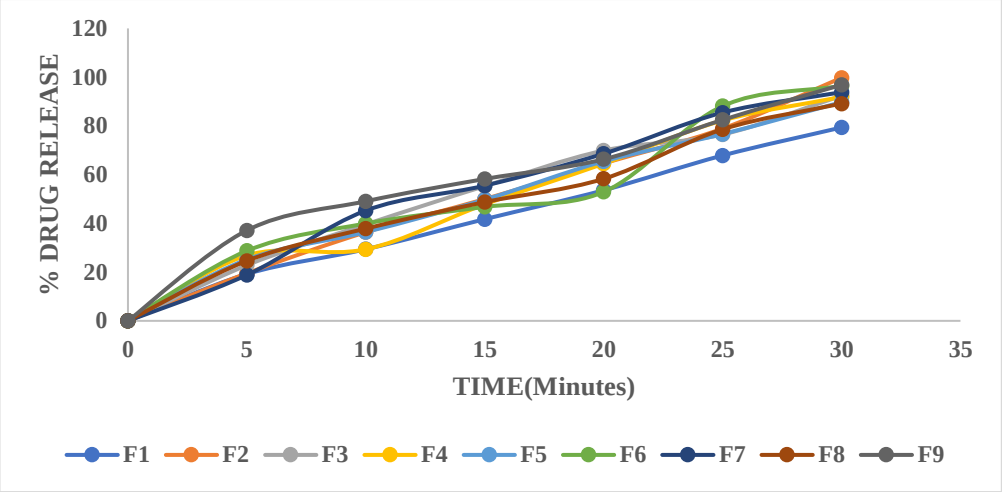

Fig: *In Vitro* dissolution data for formulations F1 – F9

Among all the formulations F2 formulation containing drug and explotab showed good result that is 99.76% in 30 minutes, at the concentration of 20 mg and F2 Formulation showed Less Disintegration time (2.23Minutes). Hence from all the formulations it is evident that F2 formulation is the better formulation.

CONCLUSION:

The present study successfully formulated and evaluated immediate-release tablets of Macitentan using super disintegrants, namely cross povidone, croscarmellose sodium, and sodium starch glycolate, incorporated in a 1:1 ratio. The prepared formulations demonstrated satisfactory pre-compression and post-compression parameters, indicating good flow properties, uniform weight variation, adequate hardness, and low friability. The inclusion of the selected polymers significantly enhanced tablet disintegration and promoted rapid drug release, confirming their effectiveness as super disintegrants in immediate-release systems. Among the evaluated formulations, the optimized batch exhibited rapid disintegration and satisfactory dissolution, ensuring prompt availability of Macitentan for therapeutic action. Overall, the study concludes that the combination of cross povidone, croscarmellose sodium, and sodium starch glycolate in equal proportion is a promising strategy for developing stable and effective immediate-release tablets of Macitentan.

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