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DEVELOPEMENT, *IN-VITRO* EVALUATION AND OPTIMIZATION OF METOPROLOL SUCCINATE ORODISPERSIBLE TABLETS

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ABSTRACT:

The main objective of the present study is to design, evaluate and optimization of Metoprolol succinate orodispersible table (ODTs) with superdisintegrants. Orodispersible tablets disintegrate instantly on the patient tongue or buccal mucosa. It is suited for tablets undergoing high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to minimize side effect. Various formulations of Metoprolol succinate tablets were prepared by direct compression method using different concentration of Superdisintegrants (Kollidon CL and croscarmellose sodium) 2.5% to 5 %. The blend of ingredients was evaluated for Angle of Repose (θ), Bulk Density, Carr's Compressibility Index (CI) and Hausners Ratio. The Prepared tablets were evaluated for weight variation, thickness, hardness, friability, content uniformity, disintegration time and in vitro dissolution studies. All formulations were shows acceptable results for all the evaluation parameters and form the data formulation F4 was considered as an optimized formulation. Since it meets all standard requirements.

Keywords: *ODTs, Metoprolol succinate, Kollidon CL, croscarmellose sodium.*

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INTRODUCTION:

Now a day oral route of drug administration have wide acceptance of up to 70-80% of total dosage forms. Solid dosage forms are more stable than other dosage form and popular because of ease of administration, self-medication, pain avoidance and most importantly the patient compliance. The tablets and capsules are most popular solid dosage forms are. However one important drawback of these dosage forms is the difficulty to swallow. To avoid such problems and improve the patient's compliances the formulation of orodispersible tablet is one of the better way [1,2,3,4].

Hypertension is the most common cardiovascular disease; It is the principal cause of stroke, is a major risk factor for coronary artery disease and is a major contributor to cardiac failure, renal insufficiency. Hypertension is defined as a sustained increase in blood pressure ≥140/90 mm Hg. Metoprolol is a widely used beta blockers helps for the improvement in cardiac function after myocardial infarction. it reduces blood pressure (BP) by competitive antagonism of catecholamine peripherally and through suppression of rennin activity.

The basic approach in the development of the fast dissolving tablet is the use superdisintegrants. Kollidon CL, Sodium starch glycolate, Croscarmellose, polacrallin potassium are the best used superdisintegrants globally. Orodispersible tablets are also known as mouth dissolving tablets, fast dissolving tablets. Various Methods can be used to formulate orodispersible tablets [2,5]. Direct compression is one of the best techniques and requires the incorporation of a superdisintegrants into the formulation, the use or highly water soluble excipients to achieve fast tablet disintegration [6].

In this study all the above mentioned superdisintegrants are selected and best one is selected for further studies.

MATERIALS AND METHODS:

Metoprolol succinate was received as a gift sample from Glenmark Pharmaceuticals, India. All other ingredients were used are analytical grade.

Preparation of Metoprolol Succinate tablets.

Metoprolol Succinate ODTs were prepared using direct compression Method. Different formulations were designed to be prepared using two different super disintegrants, (Croscarmellose sodium and Kollidon CL). The composition of different batches of tablets is shown in table 1. All the ingredients weigh, sieved and blend to get uniform mixture. Tablets were compressed with the help of punch having diameter 8mm.

Evaluation Parameters

Compatibility study:

Compatibility study of drug and excipients were carried out by physical observation (color and odour) by placing the mixture of drug and each excipients separately and physical mixture of all ingredients' at a temperature 45^0C and 75% RH for period of one month.

Pre compression Parameters[6,7,9]:

Flow properties of powder

Angle of Repose (θ): It is defined as the maximum angle possible between the surface of a pile of the Powder and horizontal plane. For most pharmaceutical powders, the angle-of repose values range from 25 to 45°, with lower values indicating better flow characteristics. It can be calculated by following formula.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of repose
h = Height of pile
r = Radius of the base of pile

Bulk Density:

Bulk density is defined as the ratio of mass of a powder to the bulk volume. Bulk density of the various ingredients added to the granulation should be maintained as closely as possible, especially when formulating direct-compression products. 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.

$$\text{Bulk density} = \frac{\text{Weight of the powder (gm)}}{\text{Bulk volume (ml)}}$$

Carr's Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index (CI). Formula for calculating the CI is given by

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped density}} \times 100$$

Hausners Ratio:

It is determined by comparing tapped density to the bulk density by using following equation

$$\text{Hausners ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

Evaluation of Metoprolol succinate Tablets[6,8,10]:

The prepared tablets were evaluated for various parameters as follows.

Weight variation:
Twenty tablets were randomly selected, weighted and average weight was determined. Then individual tablets were1 weighed and percent deviation from the average weight was calculated.

Thickness:
The thicknesses of prepared tablets were measured by vernier caliper. Tablet thickness should be controlled within a ± 2% variation of a standard value. In addition, the average thickness and standard deviation were reported.

Hardness:
It was measured by using a Monsanto hardness tester (in Kg/cm^2). Five tablets from each batch were tested randomly and the average reading noted.

Friability:
Friability of the prepared tablets was determined by using Roche Friabilator. Pre weighed sample of tablets (20 tablets) were placed in the Friabilator and subjected to100 revolutions. That was set at 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches. After that tablets were de dusted using a soft muslin cloth and re weighed. The friability (f) is given by the formula.

$$F\ \% = \left(1- \frac{W0}{W}\right) \times 100$$

Where,

W0 = Weight of the tablets before the test and

W = Weight of the tablets after test

Content uniformity:
10 tablets were randomly selected, powdered and blend equivalent to 20mg of drug was weighed and dissolved in 100 ml of 6.8 pH phosphate buffer, filtered solution was suitably diluted and drug content analyzed using UV-Visible spectrophotomer at 223nm.

Disintegration time:

The disintegration time for all formulations was carried out in petridish. The sufficient amount of water was filled in a petridish and tablet was put at the center. The time required to complete disintegration was noted.

***In vitro* Dissolution studies:**
In vitro drug release of Metoprolol succinate ODTs was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 500 ml 6.8 pH phosphate buffer at temperature 37 ± 0.5 ^{0}C. The speed was maintained at 50 rpm. 5 ml of samples were withdrawn at time intervals of 5, 10, 15, 20, 30, 45 and 60min and same volume was replaced with fresh media. Absorbance of solution was measured at a wavelength of 223 nm and drug release was determined from standard curve.

RESULT AND DISCUSSION:
Metoprolol Succinate tablets was prepared and evaluated for the various parameters.

Compatibility study:
The Compatibility study of drug and excipients were carried out by physical observation (Table 2). There were no any physical change occur between mixture of drug-excipients and physical mixture of all ingredients it shows all the ingredients compatible with drug.

Evaluation of tablet blends
The physical properties such as bulk density, tapped density, %compressibility index, hausner ratio, angle of repose were determined (table 3) for the all tablet blends.

The angle of repose was found to be varies in between 24.01±1.10 ^{0} to 31.04±0.16^0 .The F4 shows lowest value i.e. 24.01±1.10^0 it indicate excellent flow property. Apart from that F1 to F7 except F4 were shows the angle of repose in between 25^0 to 30^0 which indicate good flow properties and F8 shows angle of repose 31.04±0.16$^{0.}$ It indicates blend had a passable flow.
The value for Carr's index was in between 13.00±0.24 to 22.92±0.11 indicating that most batches of powder blends were having good or fair compressibility. Hausner's ratio was found to be within limits (<1.25) except F1 and F6.

Evaluation of compressed tablets.

In the present work Metoprolol succinate orodispersible tablets were prepared by direct compression method using super disintegrants namely (croscarmellose sodium, Kollidon CL). All the formulations were evaluated for various parameters like hardness, friability, drug content, disintegration time given in table 3 and in vitro drug release studies given in table 4.

The hardness of the tablets was found to be in between 3.14 ± 0.57 to 5.35 ± 0.65 kg/cm2 and friability was found to be below 1% indicating good mechanical resistance.

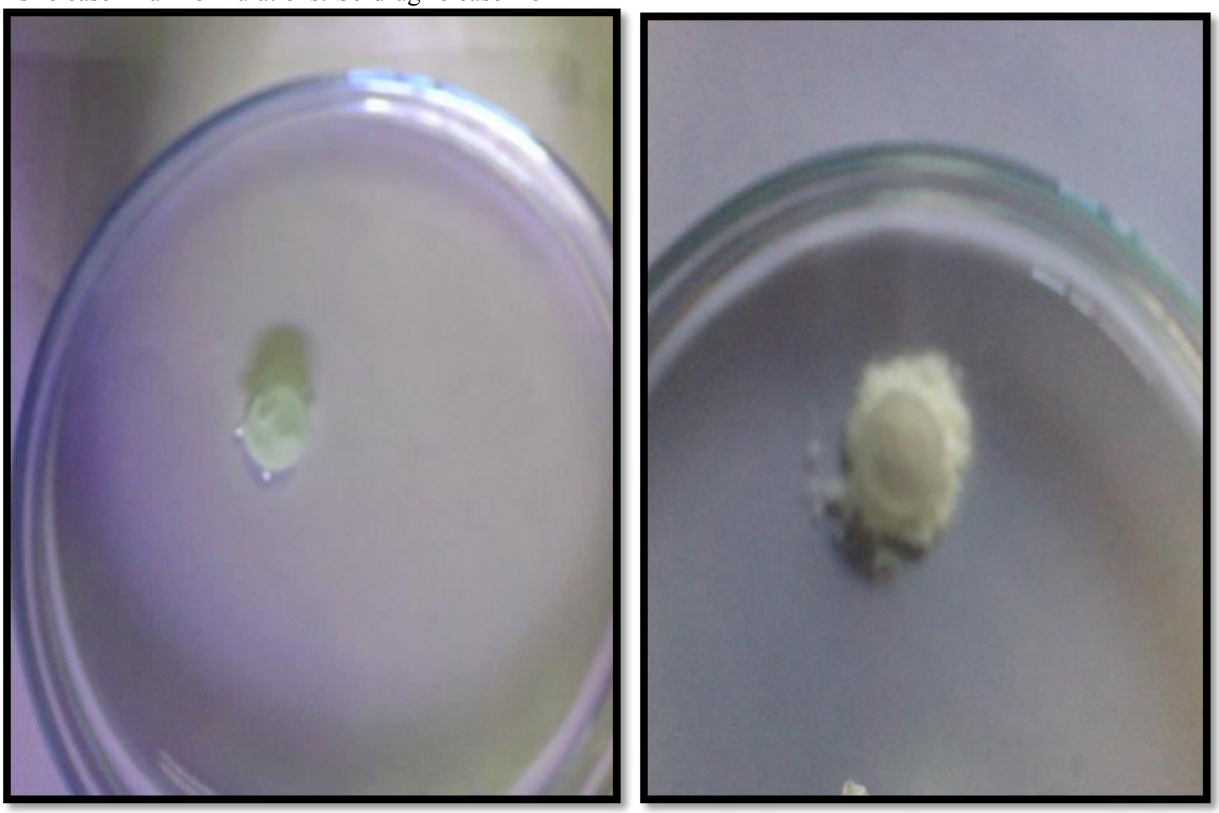
The thickness of the tablets was found to be in between 4.3 ± 0.3 mm to 4.6± 0.5 mm. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±1.5%.

The drug content was found to be in between 98.24 ± 0.10% to 101.2 ± 0.14 %, indicating uniform distribution of drug in the tablets.

Disintegration times of the tablets were found to be in between 18±0.10 sec to 23±1.50 sec given in Table 4. The formulation F4 (contains 5% Kollidon CL) shows lowest disintegration time it was found to be 18±0.10 sec.

In vitro drug release of all formulations was above 90% given in Table 4. The formulations F4 with 5% Kollidon CL has shown 97± 0.21 % drug release in 3.5 (h). So, it is considered as an optimized formulation with lower disintegration times and also improved the dissolution of the drug.
In-vitro drug release data of all formulations were subjected to linear regression analysis according to zero

order equation, first order equation, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. Data of the *in-vitro* release was fit into different equations and kinetic models to explain the release kinetics of tablets. As observed from the (Table 5), the regression correlation coefficient (r^2) values of Korsmeyer-Peppas models for drug release was more than (r^2) values of zero order equation, first order equation and Higuchi's release in all formulations. So drug release from tablets followed Korsmeyer-Peppas models for drug release kinetics.



a **b**

Fig.1. Metoprolol succinate orodispersible tablet
a-Before disintegration, b- during disintegration

Table 1 composition of Metoprolol Succinate tablets

Ingredients	Formulations code							
	F1	F2	F3	F4	F5	F6	F7	F8
Metoprolol succinate	25	25	25	25	25	25	25	25
Kollidone CL	1.25	1.50	2.0	2.5	-	-	-	-
Croscarmellose sodium(CCS)	-	-	-	-	1.25	1.50	2.0	2.5
Talc	15	15	15	15	15	15	15	15
Microcrystalline cellulose(MCC)	50	50	50	50	50	50	50	50
Sodium saccharin	1	1	1	1	1	1	1	1
Aerosil	4	4	4	4	4	4	4	4
Manitol	103.75	103.50	103.00	102.50	103.75	103.50	103.00	102.50
Total weight	200	200	200	200	200	200	200	200

***All above quantity in mg.**

Table 2: Compatibility study of drug and excipients by physical observation

Days	Drug+ CCS	Drug + Kollidone CL	Drug + Talc	Drug + MCC	Drug + Sodium saccharin	Drug + Aerosil	Drug + Manitol	Physical mixture
1	N	**N**	N	N	N	N	N	N
2	N	N	N	N	N	N	N	N
3	N	N	N	N	N	N	N	N
4	N	N	N	N	N	N	N	N
5	N	N	N	N	N	N	N	N
6	N	N	N	N	N	N	N	N
8	N	N	N	N	N	N	N	N
10	N	N	N	N	N	N	N	N
12	N	N	N	N	N	N	N	N
14	N	N	N	N	N	N	N	N
16	N	N	N	N	N	N	N	N
18	N	N	N	N	N	N	N	N
20	N	N	N	N	N	N	N	N
22	N	N	N	N	N	N	N	N
24	N	N	N	N	N	N	N	N
26	N	N	N	N	N	N	N	N
28	N	N	N	N	N	N	N	N
30	N	N	N	N	N	N	N	N

N – No physical change (colour, Odour)

Table 3: Evaluation of Pre compression Parameters

Formulation code	Angle of Repose(^{0}) (n=3)	Bulk Density (n=3)	Tapped Density (n=3)	% compressibility Index (n=3)	Hausner Ratio (n=3)
F1	29.02±0.15	0.37±0.06	0.48±0.02	22.92±0.11	1.30±0.05
F2	27.25±0.08	0.45±0.02	0.56±0.04	19.64±0.15	1.24±0.07
F3	25.05±0.10	0.39±0.05	0.45±0.08	15.33±0.06	1.15±0.02
F4	24.01±1.10	0.42±0.06	0.50±0.05	13.00±0.24	1.19±0.08
F5	30.44±0.05	0.35±0.08	0.41±0.03	14.63±0.18	1.17±0.04
F6	29.87±0.85	0.44±0.01	0.56±0.04	21.43±0.31	1.27±0.03
F7	28.35±0.20	0.40±0.03	0.47±0.07	14.89±0.24	1.18±0.07
F8	31.04±0.16	0.36±0.07	0.43±0.03	16.28±0.17	1.19±0.04

Mean ± SD (n)

Table 4: Evaluation of prepared tablet of Metoprolol Succinate

Formulation Code	Weight Uniformity (mg) (n=20)	Thickness (mm) (n=10)	Hardness (Kg/cm^2) (n=3)	% Friability (n=3)	Disintegration time (sec) (n=3)	% Drug Content (n=3)
F1	200 ± 0.3	4.3 ± 0.3	3.14 ± 0.57	0.45 ± 0.03	22±0.15	98.24 ± 0.10
F2	199 ± 1.0	4.4 ± 0.2	4.10 ± 0.35	0.41 ± 0.02	23±1.50	97.32 ± 0.71
F3	201 ± 0.8	4.5 ± 0.1	5.32 ± 0.38	0.48 ± 0.08	20±0.50	99.41 ± 0.24
F4	200 ± 0.2	4.3 ± 0.4	3.44 ± 0.25	0.38 ± 0.02	18±0.10	100.3 ± 0.91
F5	201 ± 1.7	4.6 ± 0.5	4.51 ± 0.34	0.49 ± 0.01	21±1.45	101.1 ± 0.43
F6	201 ± 0.6	4.2 ± 0.2	3.25 ± 0.47	0.54 ± 0.06	23±0.85	97.56 ± 0.17
F7	198 ± 1.5	4.3 ± 0.3	5.35 ± 0.65	0.51 ± 0.07	22±1.30	99.42 ± 0.32
F8	199 ± 1.3	4.5 ± 0.1	4.05 ± 0.46	0.47 ± 0.04	20±0.56	101.2 ± 0.14

Mean ± SD (n)

Table 5: *In vitro* drug release study of prepared tablet of Metoprolol Succinate

Time (h)	% Drug release(n=3)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	48± 0.35	51± 0.60	55± 0.24	52± 0.37	46± 0.52	51± 0.27	49± 0.30	45± 0.21
1.5	55± 0.65	60± 0.25	69± 1.13	66± 1.36	55± 1.20	59± 0.35	57± 1.35	51± 0.30
1.5	62± 1.15	69± 0.35	77± 1.65	74± 0.41	62± 0.64	63± 1.07	65± 0.98	60± 1.28
2.0	68± 1.02	76± 1.23	81± 0.71	84± 0.22	69± 1.30	71± 0.33	73± 0.11	69± 0.92
2.5	78± 0.47	82± 0.12	86± 0.87	91± 1.90	75± 0.21	76± 0.74	81± 0.42	77± 1.02
3.0	89± 0.87	88± 1.78	91± 0.28	94± 0.62	82± 1.66	83± 1.20	88± 1.08	83± 0.27
3.5	93± 1.25	95± 0.85	94± 1.35	97± 0.21	90± 1.05	92± 1.21	93± 0.34	92± 1.87

Mean ± SD (n)

Table 6: Release kinetics of prepared tablet of Metoprolol Succinate

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer Peppas
F1	0.642	0.904	0.989	0.990
F2	0.643	0.834	0.967	0.989
F3	0.542	0.752	0.898	0.991
F4	0.596	0.949	0.891	0.991
F5	0.680	0.868	0.914	0.996
F6	0.649	0.910	0.990	0.990
F7	0.584	0.901	0.984	0.985
F8	0.671	0.916	0.976	0.972

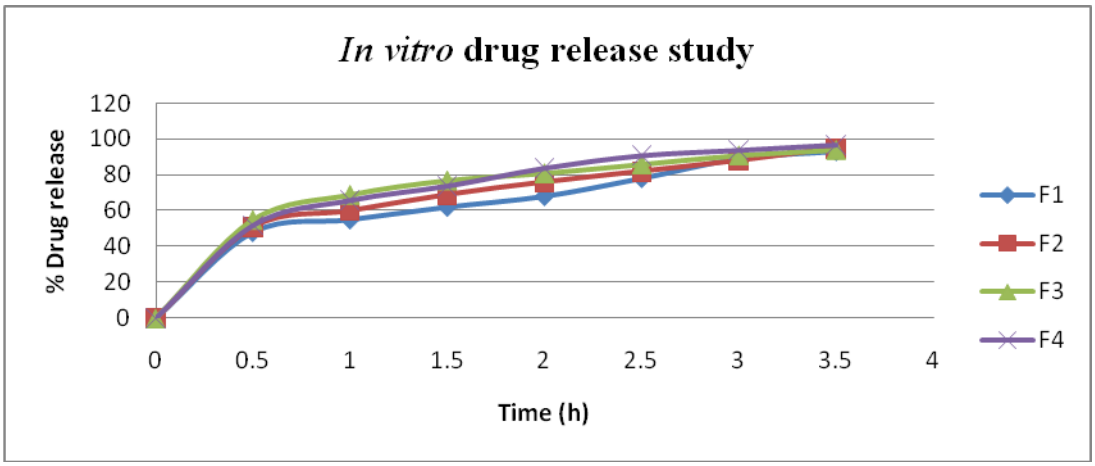


Fig. 4: *In vitro* drug release study of Metoprolol Succinate tablets (F1-F4).

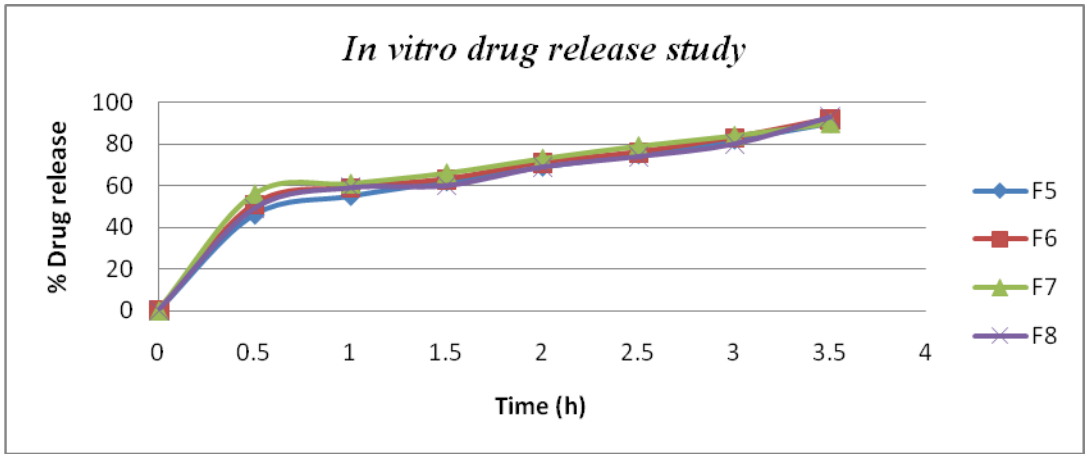


Fig. 4A: In vitro drug release study of Metoprolol Succinate tablets (F5-F8).

Fig. 5: Zero order release model of Metoprolol Succinate tablets (F1-F4).

Fig. 5A: Zero order release model of Metoprolol Succinate tablets (F5-F8).

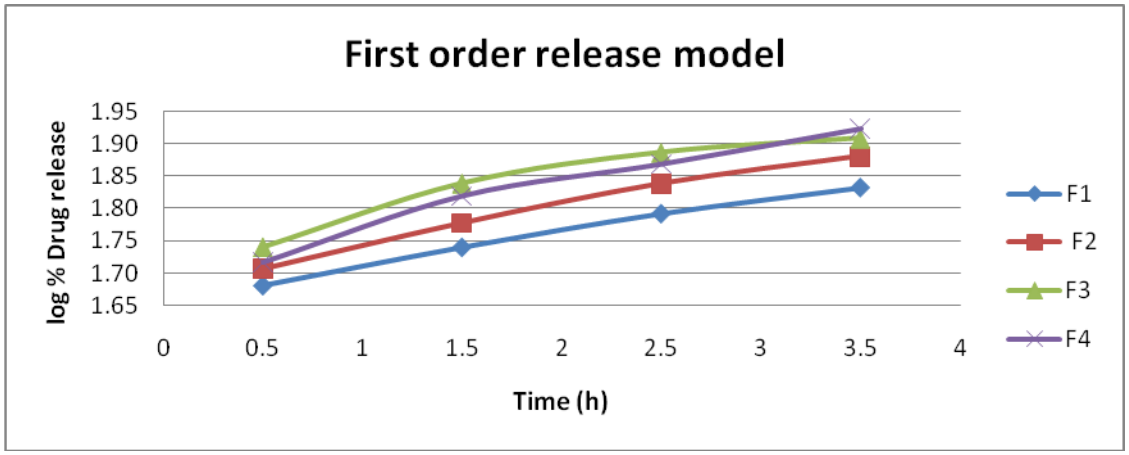


Fig. 6: First order release model of Metoprolol Succinate tablets (F1-F4).

Fig. 6A: First order release model of Metoprolol Succinate tablets (F5-F8).

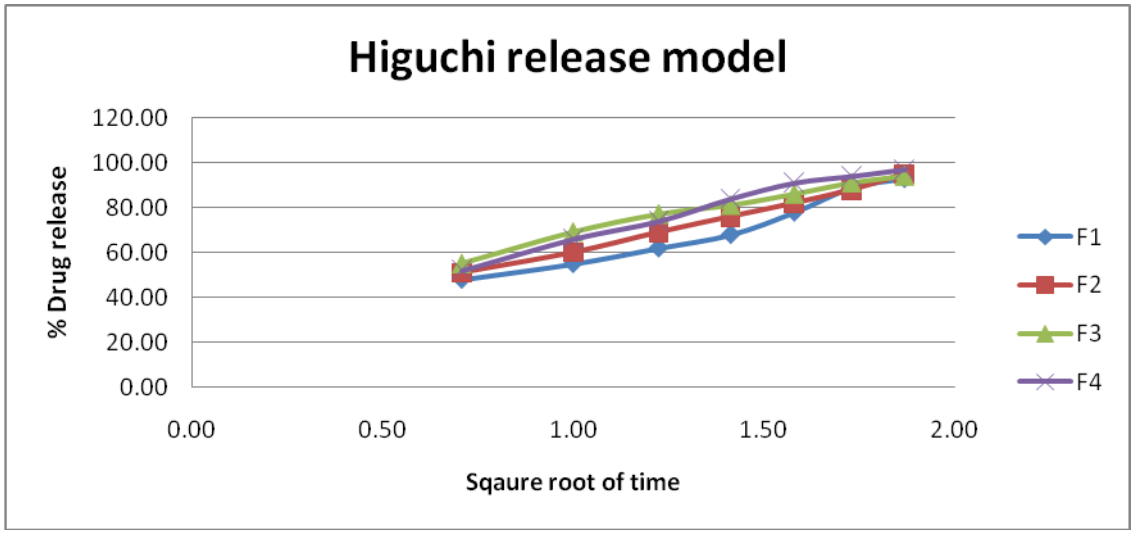


Fig. 7: Higuchi release model of Metoprolol Succinate tablets (F1-F4).

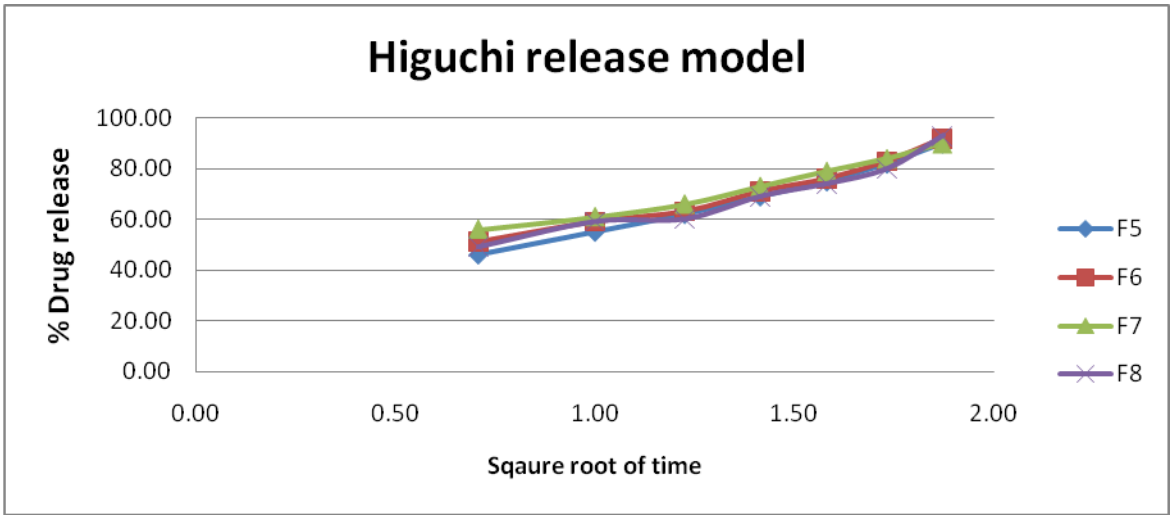


Fig. 7A: Higuchi release model of Metoprolol Succinate tablets (F5-F8).

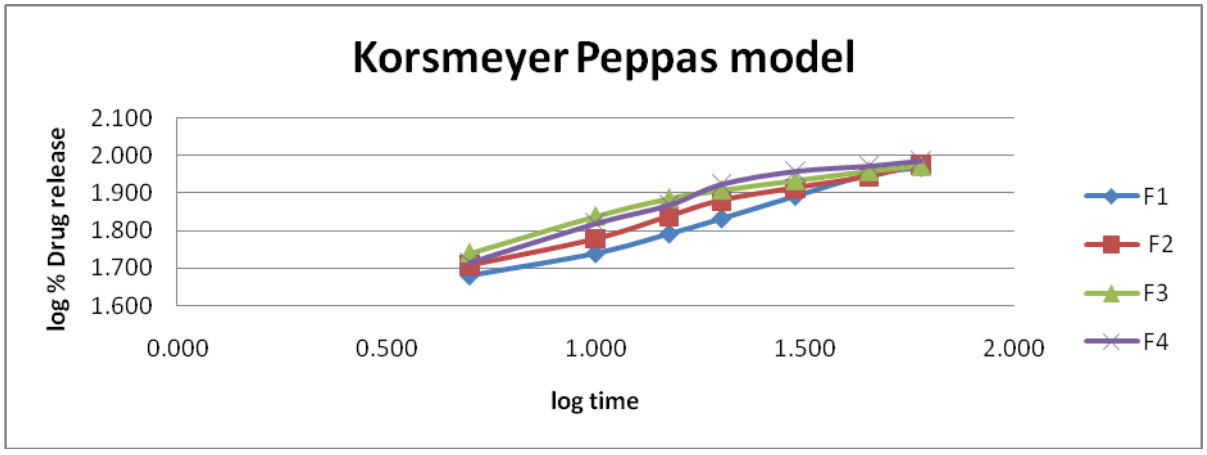


Fig. 8: Korsmeyer Peppas release model of Metoprolol Succinate tablets (F1-F4).

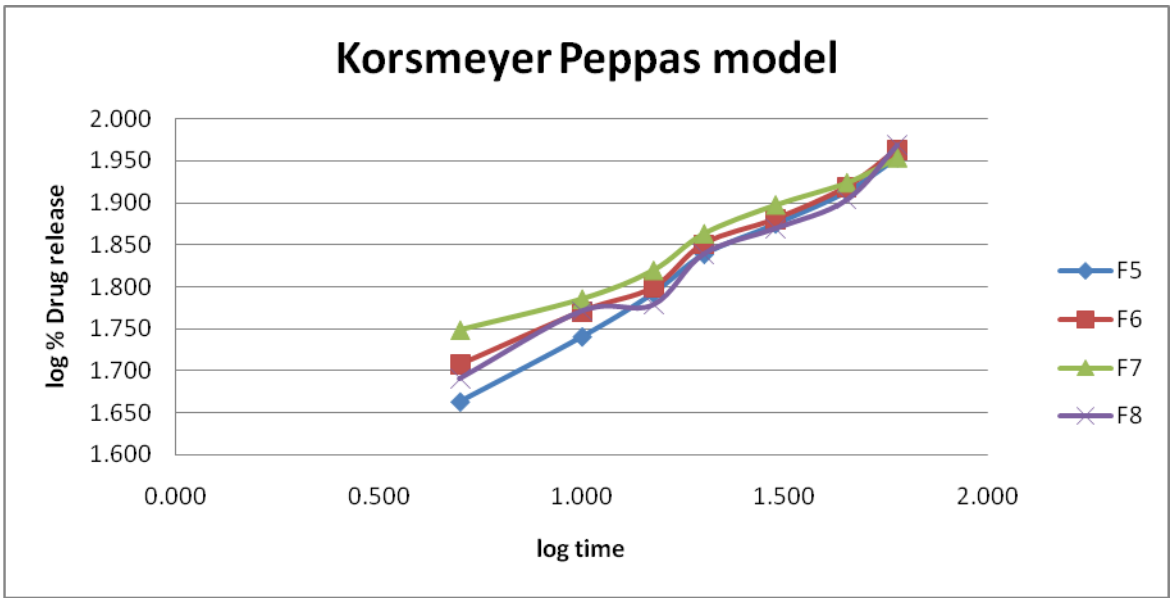


Fig. 8A: Korsmeyer Peppas release model of Metoprolol Succinate tablets (F5-F8).

CONCLUSION

The prepared ODTs of Metoprolol succinate can bypass extensive hepatic first-pass metabolism and improve bioavailability. The ODTs of Metoprolol succinate can show a disintegration time less than 25 secs. The formulation F4 with the 5% Kollidon CL shows disintegration time 18±0.10 and also 97± 0.21% *in vitro* drug release in 3.5 (h). Hence it can be concluded that formulation F4 could be the best formulation compare with other formulations.

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