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Formulation and Evaluation of Fast Dissolving Oral Films of Metoprolol Succinate



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ABSTRACT

Fast dissolving oral films are useful in patients such as paediatric, geriatric, bedridden or developmentally disabled who face difficulty in swallowing conventional tablets or capsules and liquid orals or syrups leading to ineffective therapy. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application.

The present study was aimed to formulate fast dissolving oral films to enhance bioavailability and avoid pre-systemic metabolism. The key is to develop successful oral film by solvent casting method and selected the right compatible excipients using FTIR studies. Oral film was fabricated using HPMC E5 and HEC polymer. The prepared films were evaluated for organoleptic evaluations, film weight, thickness, folding endurance, tensile strength, drug content uniformity of films, surface pH, disintegration time and *in-vitro* dissolution studies. The formulation F5 has disintegration time of 7 seconds and is more promising and showed drug release of 98 % after 5 minutes; hence formulation F5 was selected as best formulation.

INTRODUCTION

Fast dissolving drug delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets or capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral fast dissolving films (OFDFs). Amongst the plethora of avenues explored for the rapid drug releasing products, oral strip technology is gaining much attention ^[1].

Fast dissolving films (FDF), a type of oral drug delivery system for the oral delivery of the drug, was developed based on the technology of the transdermal patch. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption ^[2].

FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets/capsules. The oral thin film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the OTF technology ^[3].

Metoprolol succinate is β_1 selective (cardioselective) adrenoreceptor blocking agent. It is used as anti-hypertensive, anti-anginal and in acute myocardial infarction. The bioavailability of the Metoprolol succinate is about 40-50%, with 3-4 hr half life. In hypertension, it is given in 50 mg daily and according to response the dose may increases to 400 mg ^[4].

MATERIALS AND METHODS

Metoprolol Succinate was obtained as gift sample from Dr. Reddys Laboratories, Hyderabad. HPMC E-5 and HEC were obtained as a gift sample from Colorcon Asia Pvt. Limited, Verna. PEG-400 and Citric Acid were obtained from Merck Chemicals Ltd., Mumbai.

1. Preparation of Fast Dissolving Oral Films:^[5]

1.1. Calculation of drug loaded in the film:

Diameter of the Petridish:

Radius of the Petridish = Diameter/2 = 6/2 = 3 cm.

$$\pi r^2 = 3.14 \times 3 \times 3 = 28.26 \text{ cm}^2$$

Now, Dose is 5 mg and cut the pieces in 2 cm X 2 cm = 4 cm²

4 cm² contain 5 mg drug

So, 28.26 cm² contain (?) Drug = 35.32 mg Drug

2 mL contain 35.32 Drug

Then, 10 mL contain = (?) Drug = 176.60 mg Drug.

1.2. Procedure

Weigh accurate amount of polymer and soaked in 10 mL water for overnight. Required quantity of Metoprolol Succinate is dissolved in 10 mL of water. Added Citric Acid and orange flavour and stirred for 45 minutes. Mixed the solution and added polymer solution to it with continuous stirring. At last added PEG 400 as a plasticizer by stirring. Again stir it for 45 minutes and sonicate the solution for 15 minutes to remove the air bubbles. Then kept it aside for 1 hour to settle down the foam. Placed the solution in measuring cylinder. Lubricate the petridish with the help of Glycerol and kept the bangle in petridish then casted the prepared 2 mL of solution within the bangle.

The resulting bubble free viscous solution was casted on to Petri dish (area of 28.26cm²) then the films were cut in to size of 2×2 cm² containing 5 mg of Metoprolol Succinate. Then the prepared films were stored at room temperature.

Table No.1: Formulations of Metoprolol Succinate Oral Films

Formulation No.	Active Ingredient (mg)	HPMC E5 (gm)	HEC (gm)	PEG 400 (mL)	Citric Acid (mg)	Orange Flavour (mg)	Water (mL)
F1	176	0.9	–	1	200	10	q.s.*
F2	176	1.2	–	1	200	10	q.s.*
F3	176	1.5	–	1	200	10	q.s.*
F4	176	1.8	–	1	200	10	q.s.*
F5	176	2.1	–	1	200	10	q.s.*
F6	176	–	0.9	1	200	10	q.s.*
F7	176	–	1.2	1	200	10	q.s.*
F8	176	–	1.5	1	200	10	q.s.*
F9	176	–	1.8	1	200	10	q.s.*
F10	176	–	2.1	1	200	10	q.s.*

* Quantity sufficient

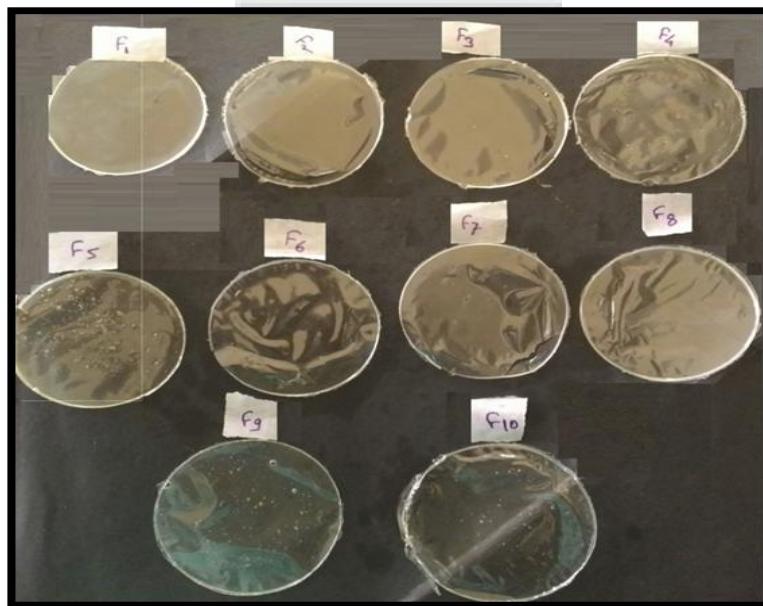


Figure 1: Prepared Fast Dissolving Oral Films

2. Evaluation of Fast Dissolving oral Films:

2.1. Organoleptic Evaluations:

Formulated films were evaluated for organoleptic evaluations like color, odor and taste.

2.2. Physical Appearance and Surface Texture:

Physical appearance was checked by visual inspection and surface texture was evaluated by touch or feel of the film.

2.3. Weight Uniformity: ^[6]

The cast film was cut at different places and the weight of each film was checked with the help of an electronic balance and the average weight was calculated.

2.4. Folding Endurance: ^[6]

Folding endurance was determined by repeatedly folding the film at the same position until it breaks. The number of times the films can be folded without breaking is termed as the folding endurance value.

2.5. Tensile Strength: ^[7]

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. The film size $5 \times 2 \text{ cm}^2$ and free of physical imperfection was placed between two clamps held 10mm apart. The film was pulled by clamp at a rate of 5mm/min.

It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\text{Tensile strength} = \frac{\text{Load at Failure} \times 100}{\text{Strip thickness} \times \text{Strip Width}}$$

This test was done on randomly selected three films from each batch and average values were reported.

2.6. Percentage Elongation: ^[7]

When stress is applied, a film sample stretches, and this is referred to as a strain. Strain is basically the deformation of film divided by the original dimension of the sample.

$$\text{Percentage elongation} = \frac{\text{Increase in length} \times 100}{\text{original length}}$$

2.7. Thickness of Films: ^[7]

The thickness of three randomly selected films from every batch was determined using a standard Vernier Caliper and average values were reported.

2.8. Disintegration Time: ^[8]

It can be performed by two methods for oral films:

- I. Slide frame method: one drop of distilled water was dropped by a pipette onto the oral films. Therefore the films were clamped into slide frames and were placed planar on a petridish. The time until the film dissolved and caused a hole within the film was measured.
- II. Petridish method: 2 mL of distilled water was placed in a petridish and one film was added on the surface of the water and the time measured until the oral film was dissolved completely.

This test was done on randomly selected three films from each batch and average values were reported.

2.9. Surface pH: ^[9]

The surface pH of the films was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The 2 cm X 2 cm film was dissolved in 2 mL of distilled water. The pH was measured by bringing the electrode in contact with the surface of the film and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate and average values were reported.

2.10. Drug Content of Films (% Assay): ^[10]

Standard preparation:

Weighed accurately 5 mg of Metoprolol Succinate was dissolved in 100 mL pH 6.8 phosphate buffer. Diluted 1 mL of this solution to 10 mL with pH 6.8 phosphate buffer.

Test Preparation:

A sample film of size 2×2cm² which were placed in a beaker containing 100 mL of methanol. Diluted 10 mL of this solution to 10 mL with methanol.

Procedure:

Absorbance of standard preparation and test preparation was taken using UV double beam spectrophotometer at 222 nm and % assay was calculated.

2.11. *In-vitro* Drug Release: [11]

The *in-vitro* dissolution study is carried out in stimulated saliva solution pH 6.8 phosphate buffer using USP paddle (Type II) apparatus at $37 \pm 0.5^\circ\text{C}$. Samples are withdrawn at regular time interval and analyzed by UV-Visible spectrophotometer. By this method cumulative drug release and cumulative percentage of drug retained were calculated. *In-vitro* drug dissolution was performed using USP paddle apparatus. The studies were carried out at 37°C with stirring speed of 75 rpm in 900 mL of pH 6.8 phosphate buffer dissolution medium. 5 mL of samples were withdrawn at predetermined time intervals of 2, 4, 6, 8, 10 minutes and replaced with the same volume of buffer. The samples were collected and the absorbance was determined at 222 nm UV visible spectrophotometer.

The results of *in-vitro* release data obtained for all formulations were fitted in two popular models of data treatments as follows:

- I. Zero-order kinetic model (cumulative percent drug released versus time)
- II. First-order kinetic model (log cumulative percent drug remaining versus time).

RESULTS AND DISCUSSION

Table 2: Physical Characterization of Fast Dissolving Oral Films

Parameters	FORMULATION CODE									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Weight Variation	18.37 ± 0.32	21.07 ± 0.232	19.64 ± 0.227	20.51 ± 0.470	22.69 ± 0.501	16.71 ± 0.445	17.72 ± 0.523	22.75 ± 0.420	18.81 ± 0.317	20.68 ± 0.476
Folding Endurance	207	218	229	237	259	218	231	245	256	268
Tensile Strength	0.93 ± 2.60	1.39 ± 3.08	2.69 ± 4.40	3.83 ± 6.20	4.29 ± 8.01	0.81 ± 3.12	1.22 ± 3.45	2.23 ± 5.03	3.35 ± 6.50	3.89 ± 8.55
Percentage Elongation	4	6	9	13	19	5	7	9	11	13
Thickness	0.040 ± 0.010	0.040 ± 0.020	0.037 ± 0.021	0.043 ± 0.015	0.047 ± 0.023	0.043 ± 0.015	0.050 ± 0.017	0.047 ± 0.021	0.047 ± 0.006	0.053 ± 0.015
Disintegration Time	28 ± 0.58	23 ± 1.15	16 ± 1.53	13 ± 1.53	7 ± 1.00	40 ± 0.58	37 ± 0.58	30 ± 1.00	13 ± 1.00	18 ± 0.58
Surface pH	6.65 ± 0.06	6.89 ± 0.10	6.90 ± 0.10	6.90 ± 0.13	6.90 ± 0.31	6.98 ± 0.12	6.90 ± 0.18	6.87 ± 0.28	6.95 ± 0.23	6.94 ± 0.24
Drug Content	98.0 ± 0.23	99.0 ± 0.28	97.1 ± 0.21	99.0 ± 0.31	99.80 ± 0.34	97.1 ± 0.40	98.0 ± 0.37	99.0 ± 0.25	96.1 ± 0.29	98.47 ± 0.20

1.1. Physical characterization of fast dissolving oral films:

The physical characterization of the formulated oral films was done by solvent casting method. The results were tabulated in Table 5. The weight variation and thickness of the films ranges from 16.71 ± 0.445 to 22.75 ± 0.420 mg and 0.037 ± 0.021 to 0.053 ± 0.015 respectively. Tensile strength and folding endurance of the films ranges from ± 2.60 to 4.29 ± 8.01 and 207 to 268 respectively.

Disintegration time and Drug content uniformity of films ranges from 7sec to 40 sec and 96.1 ± 0.29 to 99.80 ± 0.34 respectively. As the polymer concentration increases the thickness, folding endurance and disintegration time of the film also increases.

The formulation F5 shown maximum tensile strength of 429 and F10 shown maximum folding endurance upto 268. This might be due to the formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture.

The percent drug release of all the formulations was found to be in the range of 9.14 ± 0.35 to 98.980 ± 0.70 .

Among all the formulations, the formulation F5 emerged as the overall best formulation ($t_{25\%}$, $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ 1.00, 2.00, 3.12, 5.00 min respectively) based on drug release characteristics (in pH 6.8 phosphate buffer) and shown disintegration time of 7 ± 1.00 Sec. Whereas formulation F10 containing 21% of HEC shown disintegration time of 18 seconds and released 98.98% drug release in 9 mins.

5.2. Drug polymer compatibility studies:

FTIR studies conducted on pure drug and mixture of drug with excipients given in Figures 2, 3 and 4, which showed that, there is no marked interaction between drug and excipients used.

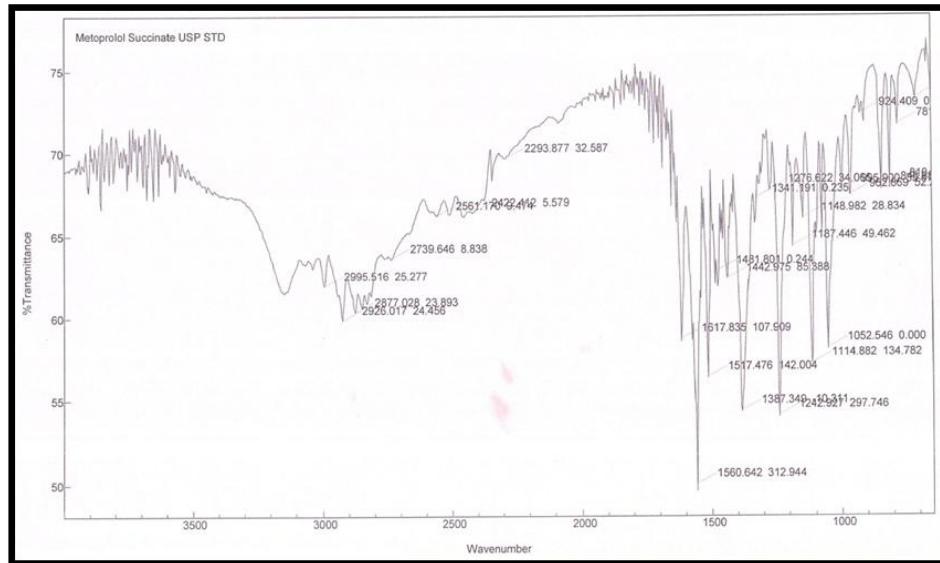


Figure 2: FTIR Spectra of Metoprolol Succinate Pure Drug

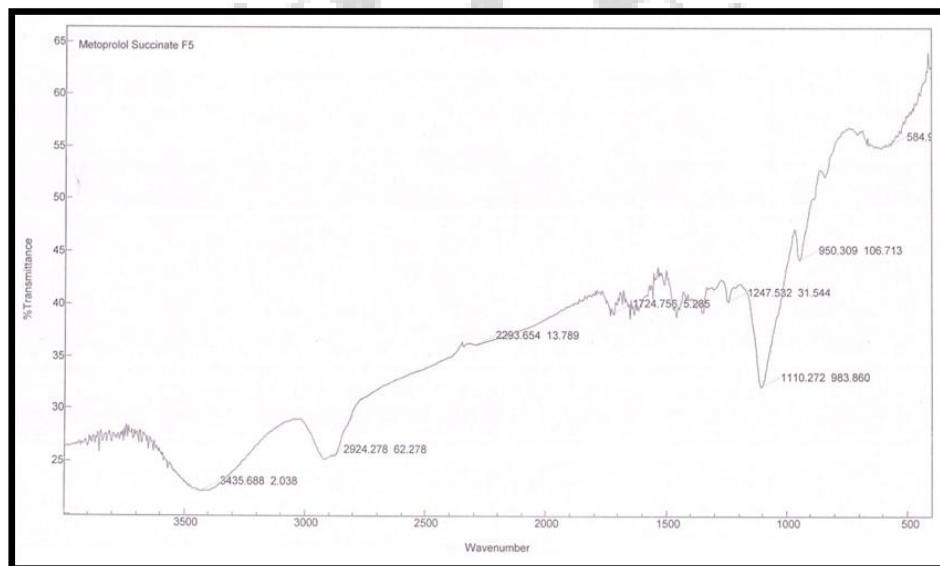


Figure 3: FTIR Spectra of Metoprolol Succinate Formulation F5

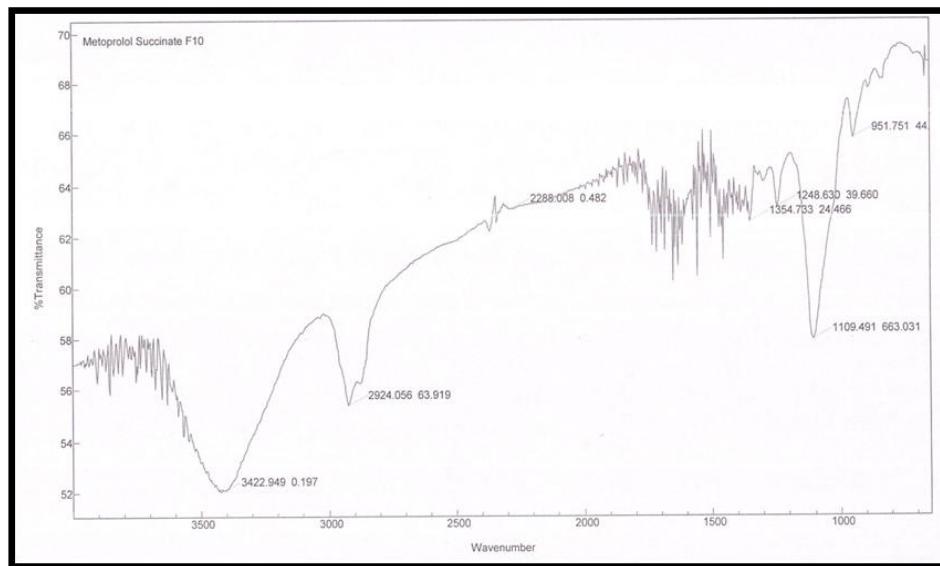


Figure 4: FTIR Spectra of Metoprolol Succinate Formulation F10

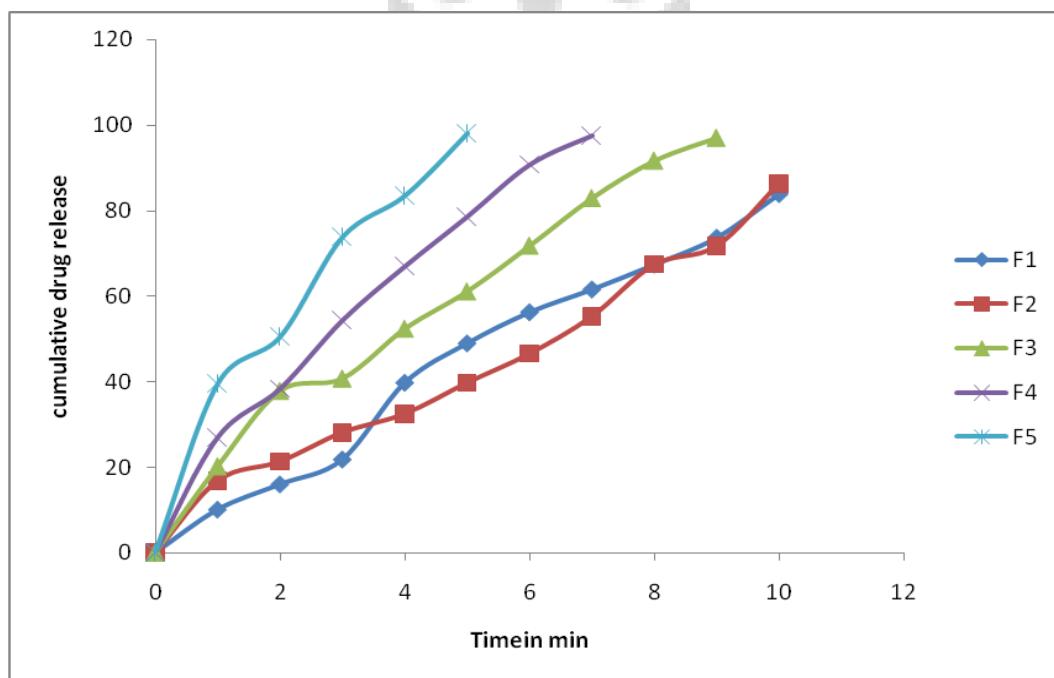


Figure 5: Cumulative Percent Drug Released v/s Time Plots (Zero Order) of formulations F1, F2, F3, F4 and F5 in pH 6.8 Phosphate Buffer

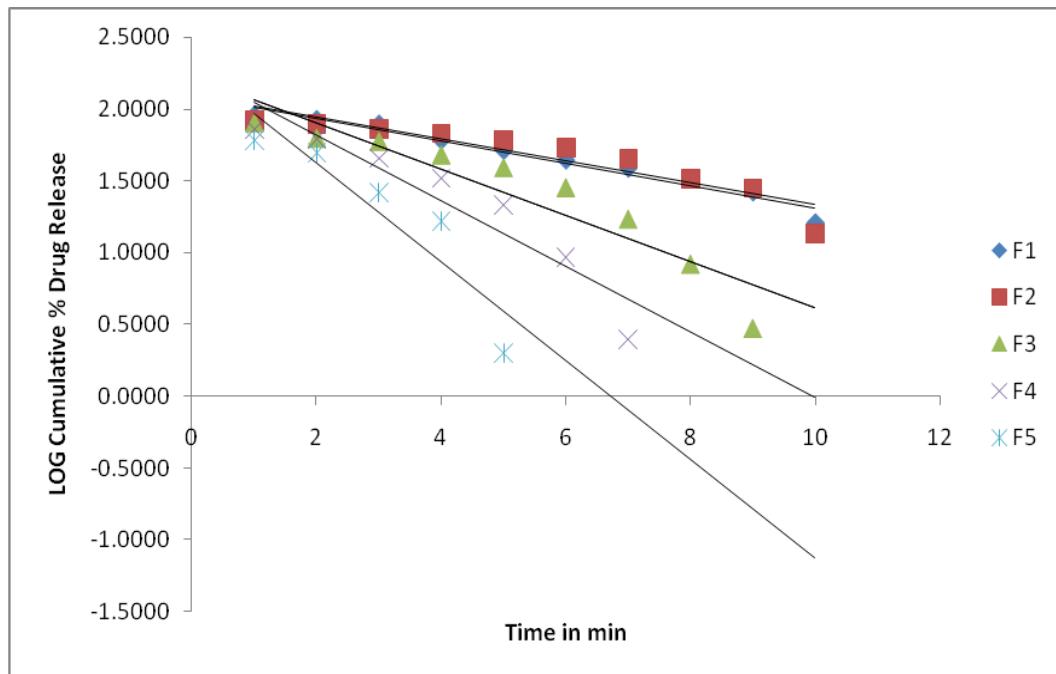


Figure 6: Log Cumulative Percent Drug Remaining v/s Time Plots (First Order) of formulations F1, F2, F3, F4 and F5 in pH 6.8 Phosphate Buffer

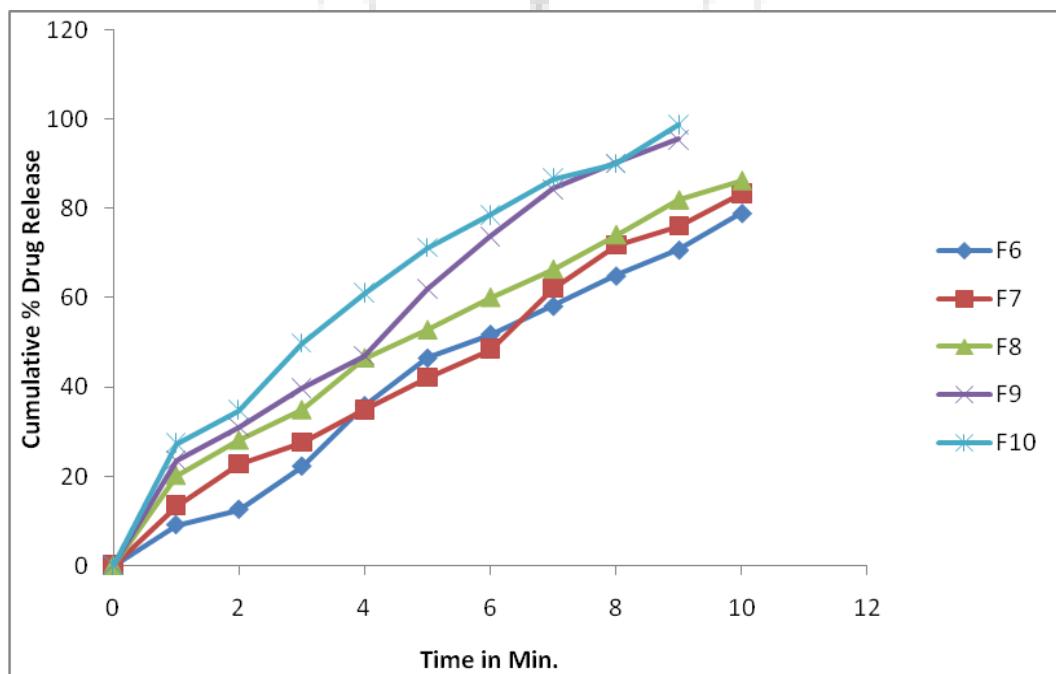


Figure 7: Cumulative Percent Drug Released v/s Time Plots (Zero Order) of formulations F6, F7, F8, F9 and F10 in pH 6.8 Phosphate Buffer

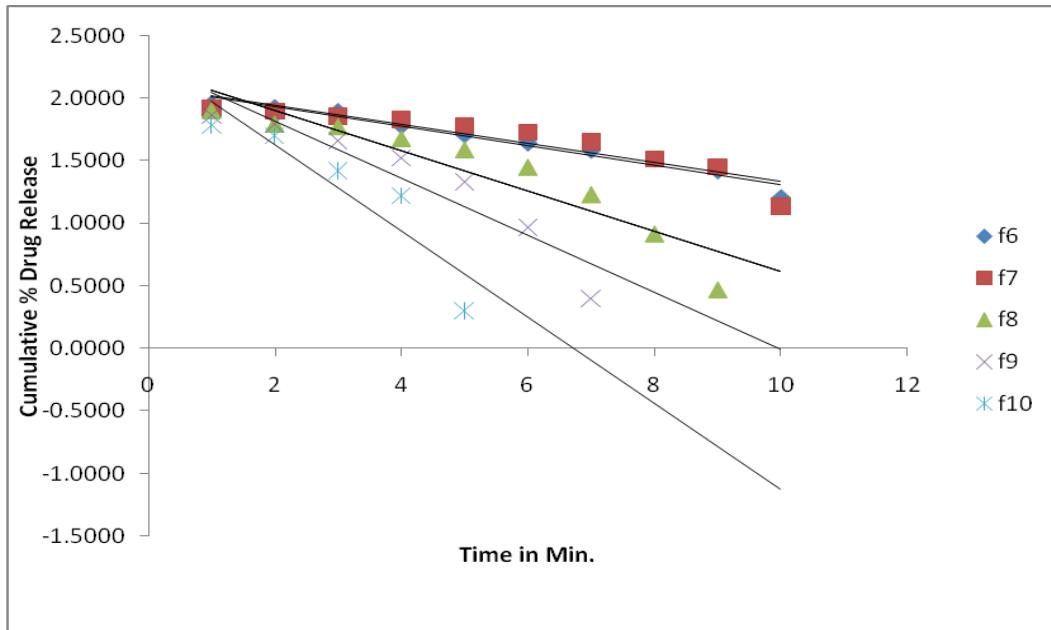


Figure 8: Log Cumulative Percent Drug Remaining v/s Time Plots (First Order) of formulations F6, F7, F8, F9 and F10 in pH 6.8 Phosphate Buffer

Table 3: Dissolution Parameters for the Formulations

Sr. No.	Formulation code	t _{25%} (min)	t _{50%} (min)	t _{70%} (min)	t _{90%} (min)	Cumulative % drug release in 10 minutes
1.	F1	2.48	5.48	8.12	>10	83.94
2.	F2	2.48	6.12	8.48	>10	86.36
3.	F3	2.00	4.00	6.00	>9	97.04
4.	F4	1.36	3.00	4.24	>8	97.52
5.	F5	1.00	2.00	3.12	>6	98.01
6.	F6	3.00	6.00	8.24	>10	79.08
7.	F7	2.48	5.48	8.12	>10	83.45
8.	F8	2.00	4.48	7.12	>10	86.36
9.	F9	2.12	4.00	6.00	>10	95.58
10.	F10	1.48	2.48	4.48	>10	98.98

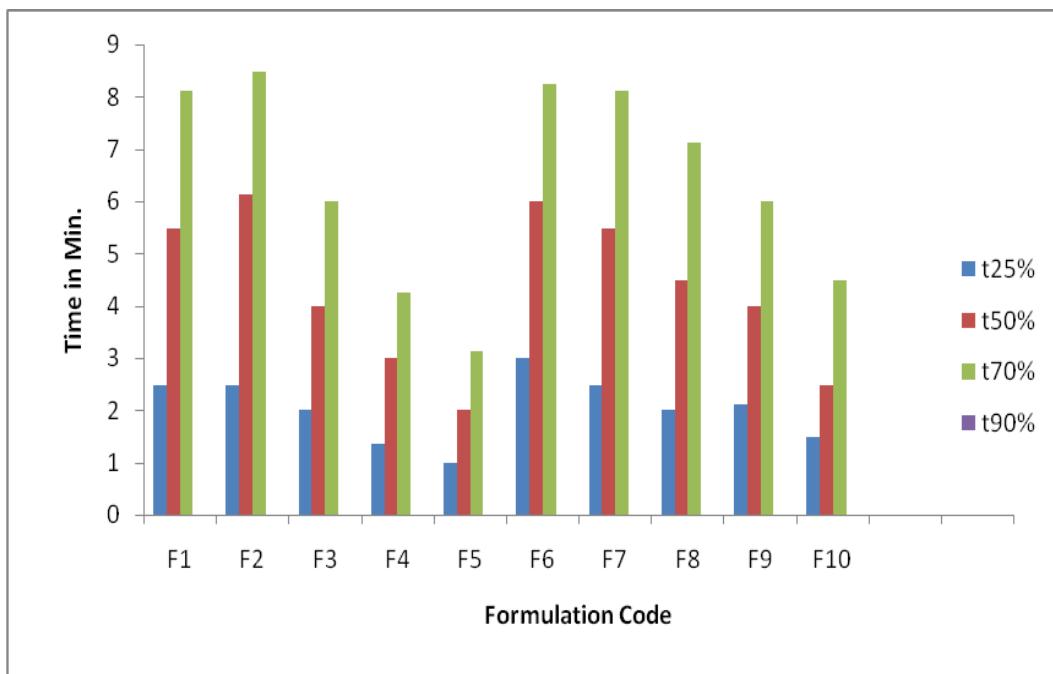


Figure 9: Comparison of Dissolution Parameters ($t_{25\%}$, $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$) of Fast Dissolving Films of Metoprolol Succinate

CONCLUSION

Preformulation study involving FTIR study showed no interaction between drug and polymer. Fast dissolving films prepared in the study exhibited good film characteristic features as indicated by thickness measured, folding endurance, disintegration time, tensile strength and drug content. The prepared films were found to be uniform, flexible and 98.98% of drug was released by formulation F10 in 9 minutes which was desirable for fast absorption. It can be concluded that oral thin film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population. Hence fast dissolving films of Metoprolol Succinate were found to be suitable for eliciting better therapeutic effect in the treatment of Antihypertension.

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