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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF METOPROLOL TARTRATE

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ABSTRACT

Aim: Metoprolol tartrate, commonly used as antihypertensive agent, has poor bioavailability due to extensive first pass metabolism. The objective of present study is to develop fast dissolving oral films of Metoprolol tartrate with high porosity which dissolves rapidly in mouth, using HPMC E15, HPMC E5 and PVA as hydrophilic polymers. Methods: Fast dissolving oral films were prepared by solvent casting method. Different concentrations of all three polymers (HPMC E15, HPMC E5, and PVA) and their combinations were used to investigate the film forming capacity, thickness and drug content of films. Glycerin was used as plasticizer. The drug - polymer mixture was homogenized on magnetic stirrer for 45 min. The casted films were dried for 12 h. to allow complete dryness of films. The fast dissolving oral films were evaluated for average weight, thickness, pH. determination, percentage moisture absorption, percentage moisture loss, in-vitro disintegration time, drug content and in-vitro drug release. Drug-excipient interaction was investigated by FTIR and DSC study. Best formulation was evaluated for stability as per ICH guideline. Results: All films had in vitro disintegration time Less than 73 sec, drug content were within limits. FTIR study revealed no drug-excipient interaction. A stability study for optimized F2 formulation as per ICH guideline for 90 days showed no changes in drug content. Conclusion: Therefore, it may be concluded that developed fast dissolving oral films of metoprolol tartrate dissolve rapidly in mouth within 43 sec and showed 97% drug release.

KEY WORDS: Fast dissolving oral films, plasticizer, HPMC E15, HPMC E5, PVA.

INTRODUCTION

About 60% of the available dosage forms are the oral solid dosage forms such as tablets, capsules etc. due to ease of ingestion, pain avoidance, versatility and most importantly, the patient compliance. The lower bioavailability, long onset time and dysphagia patient may be the reason to attract manufacturer to fast dissolving formulations [1]. A new oral fast dissolving dosage form such as the fast dissolving film has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water. Oral fast dissolving film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers, which rapidly dissolves/disintegrate on tongue or buccal cavity [2] Oral Fast dissolving films (FDF) are also known as mouth dissolving films (MDF), oral strips, oro-dispersible films (ODF). 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. It then rapidly disintegrates and dissolves to release the medication for oro-mucosal and intragastric absorption via the oral mucosa therefore target plasma levels are reached quicker [3, 4].

Oral film includes various ingredients for its formulation which includes polymers, active pharmaceutical ingredient, and film stabilizing agents, sweeteners, flavors, colors, saliva stimulating agents, preservatives, and surfactants [5, 6]. It eliminates the fear of chocking as an alternative to fast dissolving tablets. The fast dissolving action is primarily due to the large surface area of the film, The films are tough, solid, soft, flexible and do not require special packaging, The films are thin and can be carried in a patients pocket, wallet [7]. Mouth dissolving films, a new drug delivery system for the oral route, was developed based on the technology of the transdermal patch [8].

FDFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, 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 [9, 10]. Mouth dissolving films have all the advantages of tablets (precise dosage, easy application) with those of liquid dosage forms (easy swallowing, rapid bioavailability). Oral film a type of film which is used in acute conditions such as pain, antiemetic, anti-migraine, anti-hypertension, congestive heart failure, and asthma etc. oral dissolving film has gained popularity due to its availability in various size and shape [11].

MATERIALS AND METHODS

Materials

Metoprolol tartrate, HPMC E15, HPMC E5 and PVA was obtained gift sample from Alkem laboratories Ltd., Navy Mumbai. All chemicals and buffers used were of analytical grade.

Formulation of Fast Dissolving Oral Films

Fast dissolving films of Metoprolol tartrate were prepared by using solvent casting method[12]. The formulation codes and their respective compositions are given in Table 1. The polymer was dissolved in half the quantity of water. Drug was dissolved in remaining quantity of water. Drug solution was added to polymeric solution. Aspartame was dissolved in alcohol. This alcoholic solution was added to above mixture and finally to this glycerin was added. The resulting solution was stirred for 45 min. The thick viscous solution was degassed to remove entrapped air by using ultrasonicator. Measured quantity of solution was casted on a 64 cm^2 petri dish and dried at room temperature for 12 h., then it was removed from the petri dish and cut to the required size to deliver the required dose- 25mg (2.5 × 2.5cm^2) per strip. The films were packed in a butter paper and stored in a desiccator.

Table 1: Formulation Table of Fast Dissolving Oral Films

Formulation code	Metoprolol tartrate (mg)	HPMC E15 (mg)	HPMC E5 (mg)	PVA (mg)	Glycerin (mg)	Aspartame (mg)
F1	250	200	-	-	80	20
F2	250	300	-	-	120	30
F3	250	400	-	-	160	40
F4	250	-	200	-	80	20
F5	250	-	300	-	120	30
F6	250	-	400	-	160	40
F7	250	-	-	200	80	20
F8	250	-	-	300	120	30
F9	250	-	-	400	160	40
F10	250	150	150	-	120	30
F11	250	200	100	-	120	30
F12	250	225	75	-	120	30
F13	250	200	200	-	160	40
F14	250	225	-	75	120	30

Evaluations of Fast Dissolving Oral Films

Visual Inspection [13]

Oral fast dissolving films were inspected manually for their transparency and presence of air bubble.

Determination of pH of FDOF

The pH was determined by dissolving three films of each formulation in 2 ml of distilled water and then the pH of the obtained solution was measured by pH paper. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible.

Determination of Average Weight and Weight Variation of FDOF

Three films of each formulation were taken and weighed individually on a digital balance (Shimadzu AX200). The average weight and weight variation was determined.

Thickness of the Film [15]

All the batches were evaluated for thickness by using calibrated digital vernier calipers (Mitutoyo). This test was done in triplicate for each batch.

Percentage Moisture Absorption (PMA) [15]

The PMA test was carried out to check the stability of the mouth dissolving film at high humid conditions. In this study the moisture absorption capacity of the film was determined by keeping the preweighed film in a desiccator containing saturated solution of potassium chloride (84% relative humidity) at room temperature for 72 hours. Then the film was weighed. Values for the percentage of moisture uptake, calculated as per the following formula-

$$\text{PML} = \frac{(\text{Final weight} - \text{Initial weight})}{(\text{Initial weight})} \times 100$$

Percentage Moisture Loss (PML) [15]

Percentage moisture loss was calculated to check the integrity of film on exposure to dry condition. The film was weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. This was done in triplicate. The percentage moisture loss was calculated by using:-

$$\text{PML} = \frac{(\text{Initial weight} - \text{Final weight})}{(\text{Initial weight})} \times 100$$

Folding Endurance [16]

The folding endurance is related to the flexibility of a film and it was measured manually by firmly folding a film repeatedly through the middle. The number of folds on the same crease, required to produce crack in the film was noted as the value of folding endurance.

In-Vitro Disintegration Time [17]

Disintegration test was performed in the USP disintegration test apparatus. Phosphate buffer, pH 6.8 was used as medium. The films were placed in the tubes of the container and the disk were placed over it .The average disintegration time of six films from each formulation batch was noted.

Drug Content [18]

A film placed in a beaker containing 10 ml of phosphate buffer, pH-6.8. The contents were stirred on magnetic stirrer to dissolve the film. After the filtration the contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured after suitable dilution against blank solution at 222.5 nm. A blank solution was prepared in a similar manner by using a blank polymer film. The experiment was carried out in triplicate and average value was calculated.

In-Vitro Drug Release [13]

The drug release rate of fast dissolving films of metoprolol tartrate was studied using USP Dissolution Test Apparatus (Electrolab TDT-06L) using basket method. The dissolution test was performed using 900 ml of Phosphate buffer solution (pH 6.8), at 37 ± 0.5°C with the basket speed of 50 rpm. 5 ml of Aliquot was drawn at time interval of 1, 3,5,7,10,15,20,25,30,35,40,50 min and was replaced with same amount of fresh dissolution medium. Absorbance of the filtrates was measured at 222.5 nm. Aliquots were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating basket not less than 1 cm apart from the vessel wall. Cumulative percentage (%) drug release was calculated using an equation obtained from a standard curve. Release studies were performed in triplicate.

Stability Studies [16]

A stability study on the optimized formulation of oral fast dissolving film packed in aluminum foil were carried out to determine the effect of temperature and humidity on the stability of the drug. Stability study of 3 months was carried Out at 40°C±2°C and 75%±5%

relative humidity. After 15, 30, 45, 60 and 90 days the films were evaluated for the physical appearance, folding endurance, disintegration time, and drug content.

RESULT AND DISCUSSION

The aim of present study was to optimize the fast dissolving film oral formulation with highest drug release and disintegration time below 60 sec. The increase in concentration of polymer also increases average weight, and thickness, folding endurance and disintegration time, as shown in Table 2 and 3. This study revealed that the disintegration time of formulations with polymer concentration 200 and 300 for all HPMC E15, HPMC E5 and PVA were found to be satisfactory as shown in Table 3. All the formulated films formulations were of uniform weight and thickness with acceptable variation. The moisture absorption test was carried out to check the physical stability of the mouth dissolving film at high humid conditions, it was found to be 1.75 ± .035 - 2.71 ± 0.021 % .To find out effect of dry weather moisture loss was calculated by exposing the film to dry condition to check the integrity of films. The moisture loss was found to be1.785 ± 0.05 - 0.835 ± 0.06%. Drug content was found to be between 81.79 ± 0.3 - 97.67 ± 0.90 as shown in table 3. All the batches of fast dissolving films for each formulation were found to disintegrate in less than 73.67 ± 1.5 sec. Formulation f7 and f4 showed minimum disintegration time of 33.67 ± 1.15 and 31.33 ± 1.15 sec. respectively as compared to other formulations.

Table 2: Average weight, thickness folding endurance and disintegration time of formulations F1-F14

Batch code	Average wt (mg)*	Thickness (mm)*	Folding endurance*	Disintegration time (sec)*
F1	66.53 ± 0.35	0.11 ± 0.005	68.33 ± 3.51	38.67 ± 1.15
F2	82.37 ± .75	0.14 ± 0.011	105 ± 3.6	49 ± 1
F3	97.33 ± .96	0.20 ± .005	130.33 ± 2.51	73.67 ± 1.5
F4	64.33 ± .51	0.10 ± 0.005	67.67 ± 1.52	31.33 ± 1.15
F5	81.03 ± .67	0.14 ± 0.01	85.67 ± 1.52	38.33 ± 1.5
F6	96.43 ± 1.2	0.15 ± 0.005	110.67 ± 3.05	64.67 ± 1.5
F7	66.1 ± 0.9	0.071 ± 0.05	80.33 ± 2.08	33.67 ± 1.53
F8	80.77 ± 0.57	0.143 ± 0.005	91.33 ± 2.51	40.33 ± 2.08
F9	96.9 ± 1.21	0.156 ± 0.006	110 ± 2.64	64.67 ± 1.53
F10	81.1 ± 0.46	0.12 ± 0.005	84.33 ± 3.5	43 ± 1
F11	81.9 ± 0.92	0.12 ± 0.01	82.33 ± 4.5	45.67 ± 0.5
F12	96.8 ± 0.95	0.16 ± 0.005	95 ± 2.6	43 ± 1
F13	97.03 ± 0.8	0.19 ± 0.005	114.33 ± 2.01	66.67 ± 1.15
F14	81.07 ± 0.61	0.146 ± 0.006	96.66 ± 2.51	45.33 ± 2.51

*All values are mean ± SD, (n=3)

Table 3: Percentage Moisture Absorption, Percentage Moisture Loss, %Drug Content And % Drug Release of Formulations

Batch code	% moisture absorption*	% moisture loss*	Drug content (%)*	% drug release in 40 min*
F1	2.43 ± 0.021	1.785 ± 0.05	95.2 ± 0.18	78.55 ± 0.27
F2	1.84 ± 0.014	0.9975 ± 0.031	97.67 ± 0.90	97.54 ± 0.1
F3	1.41 ± 0.021	0.805 ± 0.035	96.61 ± 0.88	94.99 ± 0.96
F4	2.71 ± 0.021	1.645 ±0.1	87.6 ± 0.65	75.03± 0.44
F5	2.29 ± 0.042	1.635 ± 0.13	96.13 ± 0.76	96.47 ± 0.29
F6	1.75 ± .035	0.835 ± 0.06	86.8 ± 0.77	83.28 ± 1.13
F7	2.74 ± 0.021	1.635 ± 0.063	84.07 ± 0.02	85.6 ± 0.38
F8	2.29 ± 0.014	1.065 ± 0.091	93.76 ± 0.24	94.62 ± 0.84
F9	1.51 ± 0.1	0.835 ± 0.077	89.48 ± 0.55	90.04 ± 1.02
F10	2.55 ± .042	1.31 ± 0.08	84.87 ± 0.27	78.6 ± 1.02
F11	2.33 ± .035	1.11 ± 0.14	82.66 ± 0.41	82.74 ± 1.03
F12	2.25 ± 0.028	1.105 ±0.035	95.02 ± 0.48	95.39 ± 0.51
F13	2.1 ± 0.04	1 ± 0.05	81.79 ± 0.3	66.25 ± 2.55
F14	2.24 ± 0.04	1.495 ± 0.021	93.84 ± 0.18	94.38 ± 0.7

Table 1: Formulation Table of Fast Dissolving Oral Films

Formulation code	Metoprolol tartrate (mg)	HPMC E15 (mg)	HPMC E5 (mg)	PVA (mg)	Glycerin (mg)	Aspartame (mg)
F1	250	200	-	-	80	20
F2	250	300	-	-	120	30
F3	250	400	-	-	160	40
F4	250	-	200	-	80	20
F5	250	-	300	-	120	30
F6	250	-	400	-	160	40
F7	250	-	-	200	80	20
F8	250	-	-	300	120	30
F9	250	-	-	400	160	40
F10	250	150	150	-	120	30
F11	250	200	100	-	120	30
F12	250	225	75	-	120	30
F13	250	200	200	-	160	40
F14	250	225	-	75	120	30

Table 2: Average Weight, Thickness Folding Endurance and Disintegration Time of Formulations F1-F14

Batch code	Average wt (mg)*	Thickness (mm)*	Folding endurance*	Disintegration time (sec)*
F1	66.53 ± 0.35	0.11 ± 0.005	68.33 ± 3.51	38.67 ± 1.15
F2	82.37 ± .75	0.14 ± 0.011	105 ± 3.6	49 ± 1
F3	97.33 ± .96	0.20 ± .005	130.33 ± 2.51	73.67 ± 1.5
F4	64.33 ± .51	0.10 ± 0.005	67.67 ± 1.52	31.33 ± 1.15
F5	81.03 ± .67	0.14 ± 0.01	85.67 ± 1.52	38.33 ± 1.5

F6	96.43 ± 1.2	0.15 ± 0.005	110.67 ± 3.05	64.67 ± 1.5
F7	66.1 ± 0.9	0.071 ± 0.05	80.33 ± 2.08	33.67 ± 1.53
F8	80.77 ± 0.57	0.143 ± 0.005	91.33 ± 2.51	40.33 ± 2.08
F9	96.9 ± 1.21	0.156 ± 0.006	110 ± 2.64	64.67 ± 1.53
F10	81.1 ± 0.46	0.12 ± 0.005	84.33 ± 3.5	43 ± 1
F11	81.9 ± 0.92	0.12 ± 0.01	82.33 ± 4.5	45.67 ± 0.5
F12	96.8 ± 0.95	0.16 ± 0.005	95 ± 2.6	43 ± 1
F13	97.03 ± 0.8	0.19 ± 0.005	114.33 ± 2.01	66.67 ± 1.15
F14	81.07 ± 0.61	0.146 ± 0.006	96.66 ± 2.51	45.33 ± 2.51

*All values are mean ± SD, (n=3)

Table 3: Percentage moisture absorption, percentage moisture loss, %drug content and % drug release of formulations

Batch code	% moisture absorption*	% moisture loss*	Drug content (%)*	% drug release in 40 min*
F1	2.43 ± 0.021	1.785 ± 0.05	95.2 ± 0.18	78.55 ± 0.27
F2	1.84 ± 0.014	0.9975 ± 0.031	97.67 ± 0.90	97.54 ± 0.1
F3	1.41 ± 0.021	0.805 ± 0.035	96.61 ± 0.88	94.99 ± 0.96
F4	2.71 ± 0.021	1.645 ±0.1	87.6 ± 0.65	75.03± 0.44
F5	2.29 ± 0.042	1.635 ± 0.13	96.13 ± 0.76	96.47 ± 0.29
F6	1.75 ± .035	0.835 ± 0.06	86.8 ± 0.77	83.28 ± 1.13
F7	2.74 ± 0.021	1.635 ± 0.063	84.07 ± 0.02	85.6 ± 0.38
F8	2.29 ± 0.014	1.065 ± 0.091	93.76 ± 0.24	94.62 ± 0.84
F9	1.51 ± 0.1	0.835 ± 0.077	89.48 ± 0.55	90.04 ± 1.02
F10	2.55 ± .042	1.31 ± 0.08	84.87 ± 0.27	78.6 ± 1.02
F11	2.33 ± .035	1.11 ± 0.14	82.66 ± 0.41	82.74 ± 1.03
F12	2.25 ± 0.028	1.105 ±0.035	95.02 ± 0.48	95.39 ± 0.51
F13	2.1 ± 0.04	1 ± 0.05	81.79 ± 0.3	66.25 ± 2.55
F14	2.24 ± 0.04	1.495 ± 0.021	93.84 ± 0.18	94.38 ± 0.7

*All values are mean ± SD, (n=3)

Table 5: Physical Evaluation Parameters of Formulation F2 during Stability Study

Time (In days)	Parameters						
	Weight variation*	Thickness* (mm)	Surface PH	Folding endurance	Disintegration time (sec)	Drug content (%)	% drug release
0	82.5 ±1.25	0.14 ± 0.57	6-7	103	51	97.58	97.43
15	82.4±1.15	0.13 ± 0.57	6-7	100.69	49	96.62	97.28
30	82.1 ±1.38	0.13 ± 0	6-7	99.16	48	96.56	96.89
45	81.94± 1.57	0.13 ± 0.42	6-7	98.53	48	96.28	96.84
60	81.92± 0.68	0.13 ± 0.26	6-7	97.28	47	96.84	96.58
90	81.92± 0.13	0.13 ± 0	6-7	95	47	96.21	96.68

*All values are mean ± SD, (n=3)

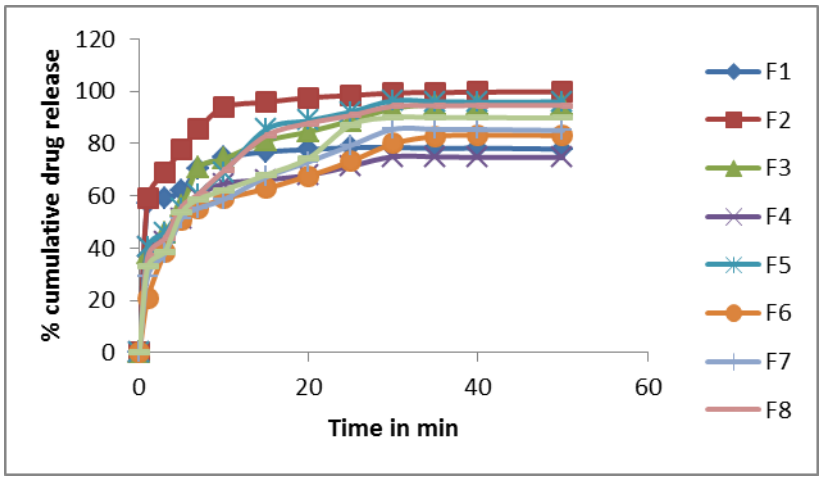

Fig. 1: % Cumulative Drug Release of Formulations F1-F9

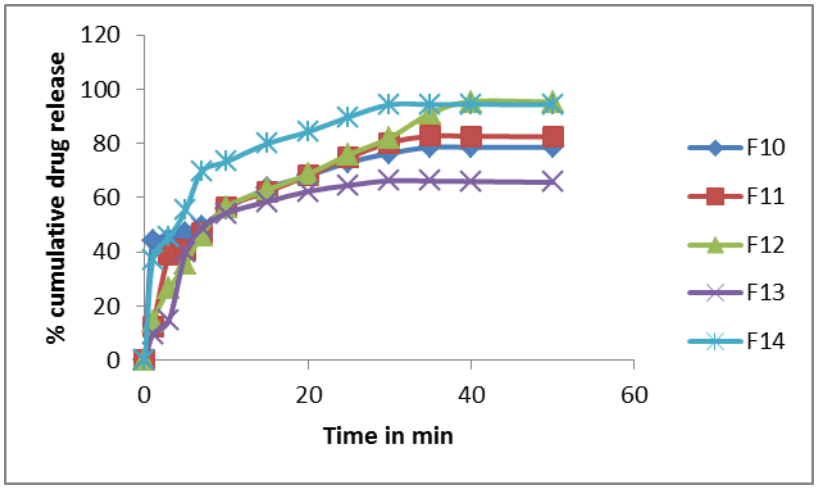

Fig. 2: Percentage Cumulative Drug Release of Formulations F10-F14

In-Vitro Drug Release

The drug release of film containing 200mg of polymer was less as compare to film containing 300mg of polymer. This observation may be due to increase in weight of polymer, as the weight of polymer increases the films was becoming more hydrophilic and thus increase in drug release. On further increase in the weight of polymer to 400mg the drug release was decreased. The probable justification can be as the weight of polymer increases, the viscosities of formulation also increases. Thus release rate decreases. This was the observation for all the three polymers. So it was decided to prepare films with polymer weight equal to 300mg and 400mg for further studies. In formulations F10, F13 HPMC E15 and HPMC E5 were used in 1:1 ratio such that the total weight of polymer was 300mg and 400mg respectively. HPMC E15 and HPMC E5 were also used in ratio 2:1 (F11) and 3:1 (F12) so that the final weight of these polymers was 300mg.Out of all formulations drug release was highest for formulation F2 i.e. 97.72 ± 0.22%, as shown in Table 3 and fig. 1 & 2.

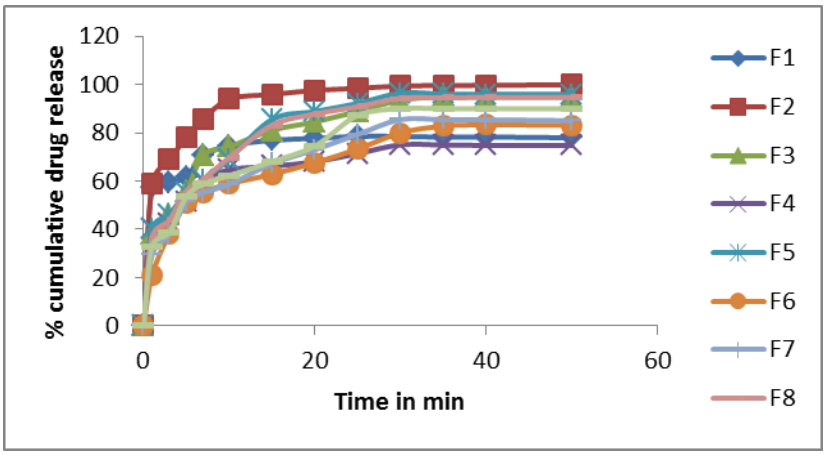

Fig. 1: % Cumulative Drug Release of Formulations F1-F9

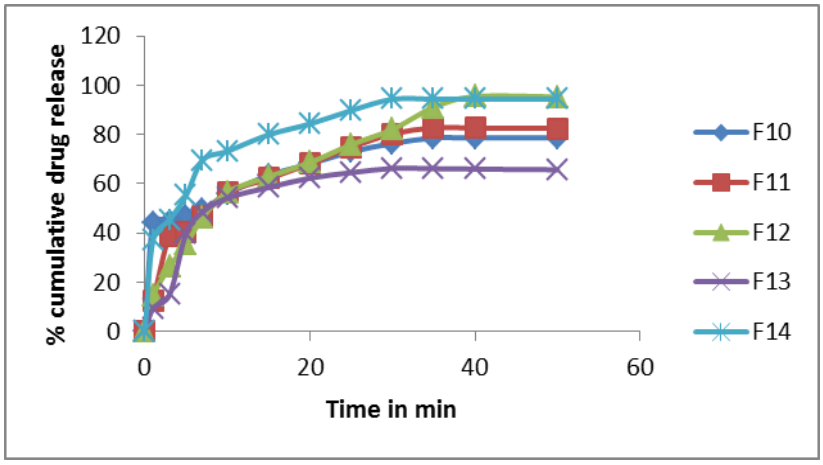

Fig. 2: Percentage Cumulative Drug Release of Formulations F10-F14

Stability Studies

A stability study on the optimized formulation F2 of oral fast dissolving film packed in aluminum foil were carried out to determine the effect of temperature and humidity on the stability of the drug. Physical evaluation parameters of formulation F2 during stability study are shown in Table 5. From the result it was concluded that there is no change in parameters of prepared films.

Table 5: Physical evaluation parameters of formulation F2 during stability study

Time (In days)	Parameters						
	Weight ariation* (mg)	Thickness* (mm)	Surface PH	Folding endurance	Disintegration time (sec)	Drug content (%)	% drug release
0	82.5 ±1.25	0.14 ± 0.57	6-7	103	51	97.58	97.43
15	82.4±1.15	0.13 ± 0.57	6-7	100.69	49	96.62	97.28
30	82.1 ±1.38	0.13 ± 0	6-7	99.16	48	96.56	96.89
45	81.94 ± 1.57	0.13 ± 0.42	6-7	98.53	48	96.28	96.84
60	81.92± 0.68	0.13 ± 0.26	6-7	97.28	47	96.84	96.58
90	81.92± 0.13	0.13 ± 0	6-7	95	47	96.21	96.68

CONCLUSION

Amongst all the formulations, formulation containing HPMC E15 as film forming polymer (300 mg polymer concentration) has shown excellent *in-vitro* disintegration time (49 seconds) and *in-vitro* cumulative percent dissolution (97.54 %), compared to other formulations and so considered as the best formulation. As the concentration of film forming polymers gets increased it also increases the film formingcapa city (up to certain limit) of the films. From above discussion, it can be concluded that Metoprolol tartrate can be successfully formulated as fast dissolving film using HMC E15. Hence metoprolol tartrate can be conveniently administered orally in the form of films.

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