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ISSN: 0975-7538
Research Article

Formulation and characterization of pediatric paracetamol oral mouth dissolving film

Wadher Kamlesh J, Umekar MJ, Sheikh Ghousiya Bano*, Mohd Younus, Sapate Ruchika P, Ansari Namuna Fatima

Department of Pharmaceutical Technology, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur-441002, India

ABSTRACT

Oral mouth dissolving drug delivery system is considered to be an important alternative to the peroral route for the systemic administration of drugs, as it considered the most convenient, easy, safest route of administration. Mouth dissolving film may be preferred over the mouth dissolving tablets in terms of flexibility and comfort. The aim of this study is to formulate and characterize oral mouth dissolving film of paracetamol .Oral films were prepared by Solvent casting method using HPMC-E 15, PEG 400, glycerin, and other recipients. Films were evaluated for mechanical properties, disintegration time, and in- vitro drug release. The dissolution kinetics of optimized batch was applied to various dissolution models. The similarity factor (f_2) between the optimized batch and marketed Tablet (Dispirit) was determined using the data obtained from the drug release studies. Optimized batch showed maximum in- vitro drug release 97.48% following zero order kinetics. The release exponent 'n' was found to follow Non- Fiction diffusion and may indicate that the drug release was controlled by zero order release.

Keywords: HPMC-E15; Paracetamol; Mouth dissolving film; solvent casting method.

INTRODUCTION

Many conventional solid oral dosage forms, are available which releases the drug instantly to obtained fast and complete systemic drug absorption. Dysphasia is a common problem associated with the tablets and capsule which results in high degree of noncompliance. (Mahore JG et al., 2010). Fast dissolving drug delivery systems either dissolve or disintegrate within a minute and can be use without water or by chewing. They have emerged as a popular and easy way of administration, to persons with swallowing difficulties such as children and elders. Fast dissolving dosage forms include tablets, films/strips and microsphere (Aggarwal J et al., 2011)

Fast dissolving drug delivery systems such as Mouth Dissolving Films (MDF) or strips are advanced dosage forms that disintegrate or dissolve within the oral cavity. It is also called as oral wafers or strips. Mouth dissolving film may be preferred over the oral dissolving tablets in terms of flexibility and ease. The characteristic advantages which make MDF popular are administration without water, patient compliance, dose precision and quick onset of action. This type of system allow drug to avoid the first pass metabolism and ultimately improvement in bioavailability. (Kulkarni PK et al., Gavaskar B et al., 2010).

The methods adopted for the preparation of MDF are by solvent cast methods, solid dispersion extrusion and hot melt extrusion technology. The fast dissolving films reported in literature are generally made of a hydrocolloid and a plasticizer. Water-soluble polymers are used as film formers as they provide rapid disintegration, good mouth feel and mechanical strength to the films. Plasticizer improves the flexibility of the film and reduces the brittleness of the film. From many years Paracetamol is prescribing as an antipyretic and analgesic drug, in the form of tablets, dispersible tablets, suspensions, syrups and Fast disintegrating tablets. The objective of the present study is to formulate and evaluate Pediatric Mouth dissolving Films of paracetamol employing various polymers.

EXPERIMENTAL

MATERIALS

Paracetamol obtained as a gift sample from Vama Pharma, Nagpur. Hydroxy propyl methyl cellulose E15 (HPMC E15), Polyethylene glycol 400, Aspartame and glycerin were procured from S.D. Fine chemicals Ltd. All other chemicals used were of analytical grade.

* Corresponding Author
Email: kamleshwadher@gmail.com
Contact: +91-9960099619
Received on: 08-07-2017
Revised on: 10-07-2017
Accepted on: 14-07-2017

METHODS

Preparation of mouth dissolving film

The solvent casting method is used for the preparation of mouth dissolving film. The oral fast dissolving film were prepared by taking ingredient in different concentration of HPMC E15, glycerin, propylene glycol 400, tween 80 and distilled water as depicted in table 1. HPMC was dispersed in distilled water followed by continuous stirring up to 1hr on magnetic stirrer and kept for 30 min to eliminate entrapped air bubbles. To this tween 80 and plasticizer (glycerin/PEG 400) was added. Solution of aspartame was prepared in separate container. Both the solutions were mixed together followed by keeping the solution mixtures standing for 15-30 min to let the foams settle down. The resulting viscous solution was casted in specific amount (calculated according to the batch size) on a suitable inert platform (glass Petri dish of 35.23 cm^2) and then dried for about 24 hour at room temperature.

The film was properly checked for presence of defect and cut for the rectangular size (3 cm x 2 cm). The samples wrapped in aluminum foil were stored properly at appropriate temperature (Sutariya MR et al 2005; N. Patel et al., 2009)

Standard calibration curve of paracetamol

About 100 mg of Paracetamol was dissolved in 10 ml of methanol and volume was made up to 100 ml with the distilled water. By serial dilution, solutions with concentrations 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml were prepared as shown in table 2. Absorbance was taken at 257 nm to plot calibration curve.

Characterization of mouth dissolving film

Mouth dissolving film was evaluated for visual appearance, weight variation, thickness of the film, folding endurance, disintegration time

Visual Apperance (Kaur Mandeep et al)

The fast dissolving films were evaluated by visual observation such as clarity, transparency of Film.

Weight variation

Specific size of the film was cut from diverse locations of the film. The weight of individual film was taken and the weight variation was calculated accordingly.

Thickness

Vernier Callipers was used to measure average thickness of the film

Folding Endurance (Nishimura et al., 2009)

The folding endurance is the number of folds required for break or cracks the film. A small piece of film was folded repeatedly several times until breaking of film or crack observed.

Disintegration time

Film was placed in basket containing900 mL distilled water and time required for the film disintegrates was noted.

In-Vitro Dissolution Studies (Mishra, R et al., 2009)

The *in-vitro* dissolution studies were conducted in Basket type apparatus using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5 °C and at 50 rpm. Samples were withdrawn at 5, 10, 15, 20, 25 and 30 min. time intervals and after filtered through 0.45µm Whatman filter paper, analyzed spectrophotometrically at 257 nm.

Drug Release Kinetics (Wadher KJ et al., 2011)

The dissolution kinetics of optimized batch was applied to various dissolution models such as Zero order, First order, Higuchi, Korsemayer-Peppas and Hixson-Crowell. The best fitted model gives the highest R^2 value and least slope value. To describe the kinetics, the release data was analyzed according to Kosmeyer et al's equation as.

$$\frac{M_t}{M_\infty} = Kt^n$$

Where, Mt/M∞ = fraction solute release, t = release time, K = kinetic constant characteristic of the drug/ polymer system. n = exponent that characterizes the mechanism of release of traces. Based on various mathematical models, the magnitude of the release exponent "n" indicates the release.

Similarity Factor (Costa P et al., 2001)

The similarity factor (f_2) between the optimized film and marketed Tablet (Disprin) was determined using the equation:

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{N}\right) \sum (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\}$$

Where,

N = number of time points,

Ri and Ti = dissolution of reference and test product at time i

RESULTS AND DISCUSSION

Standard Calibration Curve of Paracetamol

The absorbance values were obtained as shown in Table 2. The calibration curve was plotted and are shown in Figure 1.The plot of Absorbance vs. Concentration (µg/mL) was found to be linear in the concentration range of 0 to 10µg/mL and found to obeys the beer-lambert's law in the same range.

Characterization of Mouth Dissolving Film

The results obtained of prepared films such as visual appearance, Weight variation, Thickness and folding endurance of the film are shown in table 3.

Table 1: Composition of Mouth dissolving film

F.Code	Ingredients						
	HPMC E15	PEG 400	Glycerine	Tween-80	Aspartame	Water	Drug
F1	300	0.2ml	-	0.2ml	30	9ml	100
F2	300	0.4ml	-	0.2ml	30	9ml	100
F3	300	-	0.2ml	0.2ml	30	9ml	100
F4	300	-	0.3ml	0.2ml	30	9ml	100
F5	300	-	0.4ml	0.2ml	30	9ml	100
F6	300	-	0.5ml	0.2ml	30	9ml	100

Table 2: Standard Calibration curve of Paracetamol

Concentration (µg/ml)	Absorbance
0	0.032
2	0.061
4	0.0148
6	0.231
8	0.286
10	0.364

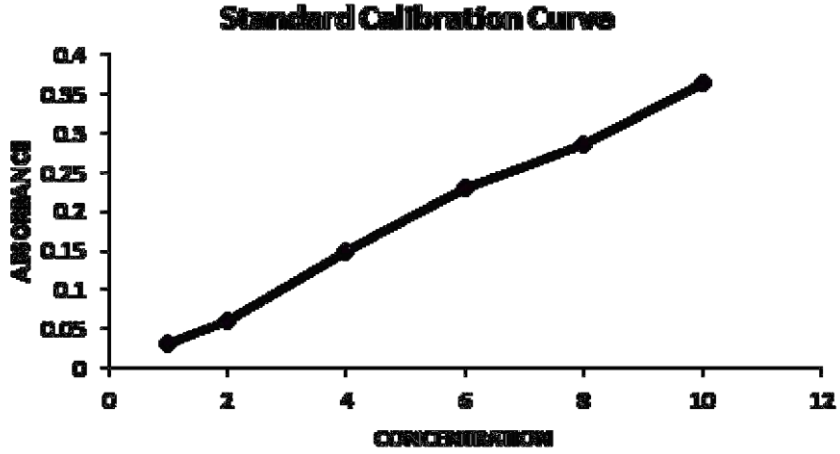

Figure 1: Standard Calibration curve of Paracetamol

Table 3: Evaluation of Mouth Dissolving Film

F Code	Visual Appear-ance	Weight Varioation (mg)	Thickness of films (mm)	Folding En-durance	Disintegration Time (sec)
F1	Transparent	0.0246±0.007	0.01	200	8
F2	Transparent	0.0248±0.006	0.01	209	6
F3	Semitransparent	0.0884±0.024	0.02	204	7
F4	Semitransparent	0.0843±0.043	0.02	175	4
F5	Semitransparent	0.01646±0.001	0.03	4	4
F6	Semitransparent	0.0333±0.0150	0.02	12	10

Visual Appearance

On visual appearance it was observed that all the film formed by using glycerin was semitransparent while film of PEG-400 was transparent in appearance which is given below

Weight variation of the film

2x3 cm film was cut from different locations in the caste film. The weight of each film was taken and the weight variation was calculated

Thickness of the film

The thickness of the film was measured by Vernier Callipers and the average thickness was calculated, F5 shown maximum thickness while minimum thickness in F1 and F2 film

Folding endurance

The film formed by using 0.4ml (F2) of PEG-400 have least value of folding endurance while film of 0.4ml (F5) of glycerine show height value of folding endurance

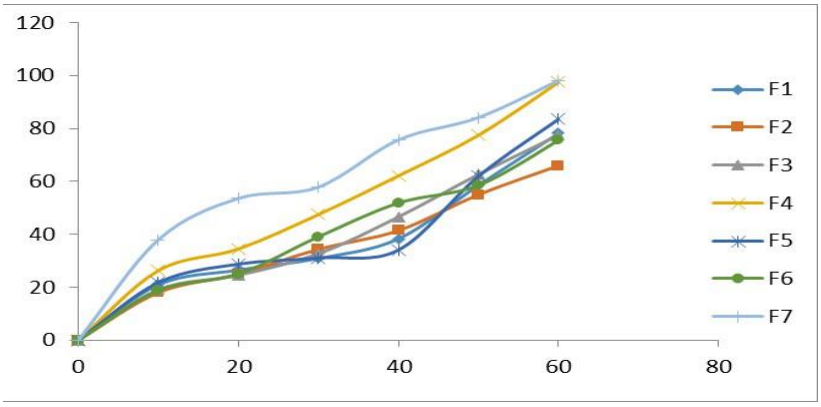

Figure 2: Cumulative percent Drug Release Profile F1-F7

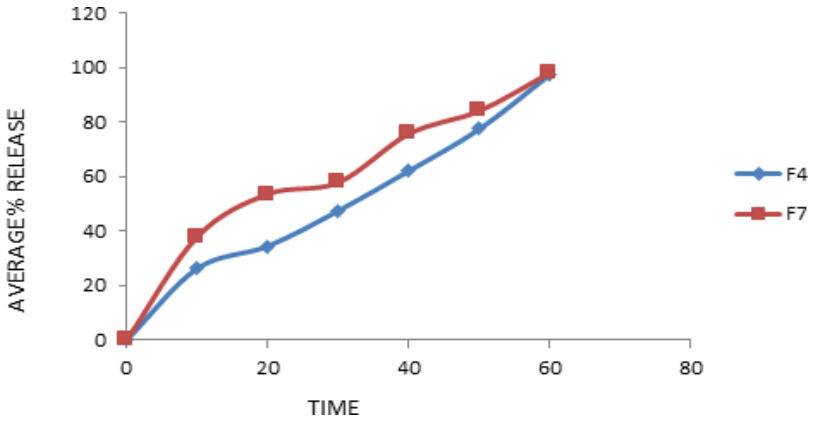

Figure 3: Drug release study of F4 and Marketed tablet

Table 4: Drug Release Kinetic study

F code	Zero order		1st order		Matrix		Hix.Crow		Korsmeyer-Peppas		
	R	K	R	k	R	K	R	K	R	n	K
F1	0.9923	1.2521	0.9678	-0.0198	0.9532	8.1540	0.9842	-0.005	0.9841	0.7882	2.7578
F2	0.9890	1.1069	0.9809	-0.0161	0.9598	7.2304	0.9889	-0.004	0.9851	0.7225	3.1220
F3	0.9470	1.2303	0.8662	-0.0213	0.8832	7.9428	0.9026	-0.005	0.8829	0.6784	3.8693
F4	0.9901	1.2428	0.9449	-0.0202	0.9290	8.0346	0.9676	-0.005	0.9654	0.7939	2.6176
F5	0.9867	1.1081	0.9573	-0.0165	0.9256	7.1633	0.9715	-0.004	0.9630	0.7960	2.3138
F6	0.9903	1.6026	0.8392	-0.0401	0.9530	10.443	0.9273	-0.009	0.9785	0.7319	4.3358
F7D	0.9983	1.7926	0.8894	-0.0477	0.9330	11.955	0.9647	-0.010	0.9853	0.515	11.230

Disintegration time

The film formed by using 0.3ml(F3) and 0.4ml (F4) of glycerine have taken least time for disintegration that is 4sec while maximum time have taken by 0.4ml glycerine film (F6)

***In-vitro* dissolution studies**

In vitro dissolution study of formulation from F1-F6 is shown in Figure 2 .Release of Optimized filom F4 was compared with the marketed tablet as F7 and the results are shown in figure 3

The drug release from different batches was observed to be depends on both concentration of plasticizer and type of plasticizer. It was found that as the plasticizer concentration increases, the release of drug increases in film formed by using glycerin, while in case of film formed by PEG-400 it decreases. F4 batch show maximum drug release up to 97.487% and F2 show lowest drug release of 65.928%.

The *in-vitro* dissolution studies was conducted and observed that the 0.3ml glycerine (F4) containing film showed maximum drug release and minimum drug

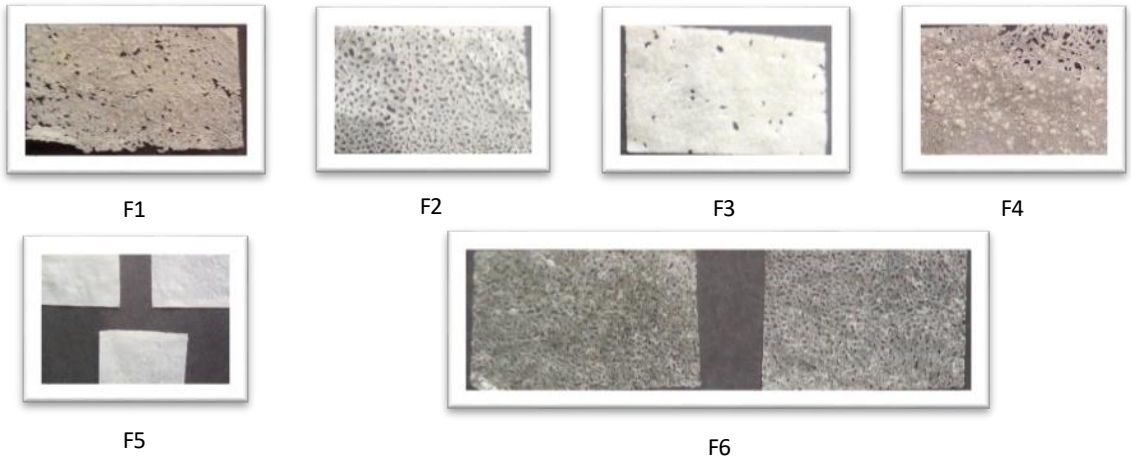

Figure 4: Visual Appearance

release showed by 0.4 ml PFG400 (F2) containing film. As the concentration of PEG400 in the film increases drug release decreases, where as it increases in case of glycerin .The *in-vitro* dissolution data and release drug profile of mouth dissolving film is given in table 4 and figure 5.

Dissolution kinetics

Various dissolution models such as Zero order, First order, Higuchi, Korsemayer-Peppas and Hixson-Crowell are as shown in table no 4.

The best fitting model for all formulation was calculated. All the batches F1 -F6 were found to follow zero order release. The Marketed Preparation also followed zero order release as shown in Table5. The values of *n* showed a non-Fickian release behavior which means a combination of both diffusion and chain relaxation mechanisms. All the batches shoed n value in the range of than 0.5-1, which indicate Non fickian release mechanism. Thus, the release of the drug from the prepared film is by swelling and erosion of the polymer.

Similarity Factor

A comparison of drug release formulations F4 and marketed preparation are shown in figure 6. f2 value was found to be 52.7, which showed that the F4 batch of formulation has comparable release profile as that of marketed preparation.

CONCLUSION

An attempt has been made to formulate paracetamol oral mouth dissolving film using polymer HPMC E15 and plasticizer Polyethylene glycol-400 and glycerin .The six preliminary batches were prepared to obtained final optimized batch .The mouth dissolving films were prepared with selected polymer and plasticizer by solvent casting method. The compositions of the formulation batches consisted of two different plasticizer with varing concentration of plasticizer. Formulated films were evaluated for physical characterization like thickness, uniformity of weight, surface pH and disintegration time.

In the present study, each mouth dissolving film cm in standard size and contained 100 mg Paracetamol. Thickness of the films was approximately 0.02mm. The films found to disintegrate completely within 1 minute.

In vitro dissolution studies of different formulation from F1-F6 and Marketed tablet (Disprin) were carried out at pH 6.8 Buffer. The drug release from formulation was observed to be depends on both concentration of plasticizer and type of plasticizer. F4 batch show maximum drug release up to 97.487% and F2 show lowest drug release of 65.928%. f2 value was found to be 52.7, which showed that the F4 batch of formulation has comparable release profile as that of marketed preparation. The batches F1-F6 were found to follow zero order release. The optimized film showed 97% drug release within 60 min. It was concluded that glycerin as a plasticizer found to have better visual appearance and release profile as compared with PEG 400. The prepared film seems to be an alternative to tablets and could be the choice of dosage for pediatric patient.

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