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FORMULATION AND CHARACTERIZATION OF FAST DISSOLVING ORAL FILMS OF DIACEREIN

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ABSTRACT

The objective of this research was to prepare fast dissolving oral films (FDOF) containing Diacerein, an anti-inflammatory, analgesic and osteoarthritis drug. Fast dissolving oral films deliver drug directly in the vascular system and bypass hepatic metabolism so dose of the drug was also reduced significantly. Films were prepared using solvent casting method, hydrophilic polymers (HPMC E 5 and HPMC E15) were selected as film forming agents and propylene glycol was used as plasticizer to give flexibility to the films. Initially blank films were prepared and evaluated on physical parameters to optimize the type and concentration of the polymer. Formulation containing 200mg of HPMC E5 & 400mg, 500mg of HPMC E15 showed the optimum results for incorporation of drug. *In-Vitro* release studies revealed that formulation F6 containing 300 mg of HPMC E15 shows best results as it disintegration and dissolution time was short it released drug to a greater extent compared to other formulations. As dose of the drug gets reduced, therefore adverse effects of the drug also get reduced. Therefore fast dissolving oral films can play an important role in oral drug delivery.

INTRODUCTION

Oral route is the most commonly used and acceptable drug delivery route among all other delivery routes. Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing. The first developed fast-dissolving dosage form consisted in tablet form, and the rapid disintegrating properties were obtained through a special process or formulation modifications[2,3]. More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients fear of chocking and overcome patent impediments. Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hot-melt extrusion. Initially FDOF were introduced in the market as personal care and breathe freshener products, later their importance for therapeutic benefits was observed. First therapeutic FDOF was Chloraseptic®, containing 7-benzocaine for the treatment of sore throat was launched in the market. This fast dissolving action is mainly because of the large surface area of the film which wets quickly when exposed to moist environment of the oral cavity[4,5].

FDOF is prepared using hydrophilic polymer that rapidly dissolves, delivering the drug to the systemic circulation via buccal mucosa and as the drug released by FDOF is directly delivered to the systemic circulation so it leads to faster onset of therapeutic action. FDOF dosage form is primarily formulated for drugs having low oral bioavailability due to extensive first pass metabolism[6]. FDOF is useful in pediatric and geriatric patients as they have difficulty in swallowing conventional oral dosage forms resulting in poor patient compliance. FDOF are getting good response and acceptance from patients as they can be self-administered even without water uptake. The present investigation was done with the objective of formulating FDOF and to enhance the convenience and compliance by the elderly and pediatric patients and enhance oral bioavailability and rapid onset of action. In the present study Diacerein drug was used it is an anti-inflammatory, analgesic and osteoartheritis drug. Oral bioavailability of Diacerein is low i.e. 40%, it is because of high first pass metabolism degradation of the drug. Incorporating Diacerein in fast dissolving oral films will help in bypassing the first pass metabolism and therefore its oral bioavailability will increase significantly[7]. Reduction in dose

of the drug will also help in lowering the risk of side effects of drug. During research work all these objectives were achieved.

Advantages of oral films

- Improved oral bioavailability of drug as hepatic first pass effect is reduced.
- Fast onset of action as drug enters directly in the systemic circulation.
- No fear of obstruction or chocking.
- No need of water during film administration.
- Reduction in dose of the drug.
- Taste masking.
- Improved patient compliance.
- Large surface area film lead to quick disintegration and dissolution within oral cavity.
- Available in various sizes and shapes

MATERIALS AND METHODS

Diacerein was obtained as gift sample from Torrent Pharmaceutical Ltd. HPMC E5 & HPMC E15 were purchased from S D Fine-Chem Limited, Mumbai. Propylene glycol was purchased from Merck specialists Pvt. Ltd., Mumbai. All other chemicals were of analytical grade.

FOMULATION OF BLANK FILMS

Blank oral films were prepared using solvent casting method. HPMC 5cps and HPMC 15cps were used as the film forming agent/polymer and propylene glycol was used as plasticizer. First of all polymeric solution (Solution A) was prepared by dissolving desired amount of polymer in sufficient quantity of distilled water (70%). Specific quantity of propylene glycol and other excipients were dissolved in small amount of water (30%) with continuous stirring (Solution B). Later solution B was slowly added in solution A with continuous stirring. Final solution obtained was kept aside for 30 minutes for defoaming. After defoaming final solution was poured in petri plate and dried at 450C in hot air oven for 24 hours. Film casted in petri plate was then peeled off and cut into pieces of desired shape and size. Composition of different blank oral films prepared is shown in Table 1.

Table 1: Formulation chart of blank oral films using different polymer and concentration

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
HPMC E5 (mg)	200	300	400	500	-	-	-	-
HPMC E15 (mg)	-	-	-	-	200	300	400	500
Propylene Glycol (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid (mg)	10	10	10	10	10	10	10	10
Sodium starch glycolate (mg)	2	2	2	2	2	2	2	2
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

EVALUATION OF BLANK FILMS: Films were then evaluated on the basis of certain physical parameters so as to optimize the type and concentration of the polymer to be used in the formulation of fast dissolving films.

Weight variation: Three films of same size were selected from each formulation and films were weighed individually and then mean weight of film of every batch was calculated.

Visual appearance: All blank oral films were evaluated by visual observation to check whether they are transparent or semi-transparent in appearance.

Thickness: The thickness of films were determined by using screw guage at five different places of the film. Average thickness and standard deviation of each blank oral film formulation was determined.

Folding endurance: Folding endurance is determined by folding the film of uniform cross sectional area and thickness until it breaks[9]. The number of times film folded without breaking is noted as its folding endurance.

Disintegration time: Disintegration time is the time at which the film starts disintegrating or it breaks into pieces. Ideal disintegration time of oral film is less than 60 seconds. The disintegration time of fast dissolving films prepared using different polymers and was determined visually in a beaker 30 ml distilled water was taken and film was immersed, water was swirled at every 10 seconds. The time at which film starts breaking is noted as its disintegration time[11]. It was performed in triplicate for every blank formulation and average disintegration time was calculated.

PREPARATION OF DRUG LOADED FILMS

On the basis of evaluation parameters mentioned in Table 2, three formulations were selected for incorporation of drug. Drug loaded oral films were prepared by using solvent casting method. HPMC E5 and HPMC E15 were used as the film forming agent/polymer and DMSO was used as drug solubilising agent. First of all, polymeric solution (Solution A) was prepared by dissolving desired amount of polymer in sufficient quantity of distilled water (70%). Specific quantity of propylene glycol and other excipients were dissolved in remaining water (30%) with continuous stirring (Solution B). Later solution B was added slowly in solution A with continuous stirring and finally the drug was added in solution A. Final solution obtained was kept aside for 30 minutes for defoaming. After defoaming final solution was poured in petri plate and dried at 45 °C in hot air oven for 24 hours. Film casted in petri plate was peeled off and cut into pieces of desired shape and size. Formulation composition of drug loaded oral films is shown in Table 3.

CHARACTERIZATION OF FAST DISSOLVING ORAL FILMS OF DIACEREIN

Characterization of all drug loaded formulations was done on the basis of various physio-chemical parameters so as to select the best drug loaded fast dissolving oral film formulation.

Weight variation: Three films of same size were selected from each formulation and films were weighed individually and then mean weight of film of every batch was calculated.

Folding endurance: Folding endurance is determined by folding the film of uniform cross sectional area and thickness until it breaks. The number of times film folded without breaking is noted as its folding endurance.

Moisture loss studies: To determine the integrity and physical stability of the film, percent moisture loss test was done. A film patch of same size was cut and weighed preciously. After that the film patch was placed in a desiccator containing fused anhydrous calcium chloride for three days. After three days film patch was taken out and weighed again, and the percentage moisture loss of the film was calculated using the following formula[12,14].

Percent moisture loss = Initial weight – Final weight × 100/initial weight

Drug content: Method to determine drug content was developed in-house to find out amount of drug present in 1 strip. Strip was dissolved in 100ml of volumetric flask containing phosphate buffer pH 6.8. Medium was stirred for proper dissolution on magnetic stirrer for 6 hours . Later the content was filtered using Whattman filter paper and the filtrate sample was analysed by UV

spectrophotometer at 341nm wavelength. Drug content was determined from standard calibration curve of drug in phosphate buffer pH - 6.8[14].

***In Vitro* Dissolution/ Drug release:** The dissolution studies were conducted using phosphate buffer pH 6.8. All drug loaded formulations were subjected to in-vitro drug release study to choose the best polymer out of two film forming polymers used, which can release the drug rapidly. In a beaker 30ml phosphate buffer pH 6.8 was taken as the dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5˚C and revolution speed was set to 50rpm[13]. Film was immersed in the dissolution media and sample of 5ml was withdrawn at every 20sec interval, filtered and 5ml fresh dissolution medium was added in the beaker. Samples were taken and analysed spectrophotometrically at 341nm using UV-VIS 1700 (Shimadzu) double beam spectrophotometer. Dissolution experiments were performed in triplicate[15].

Table 2: Evaluation parameters of blank films

PARAMETER	F1	F2	F3	F4	F5	F6	F7	F8
Visual Appearance	T	S	S	S	T	T	T	T
Weight (mg)	15±2	21±4	30±5	38±1	21±2	27±3	35±3	46±2
Thickness (mm)	0.22±0.04	0.37±0.03	0.48±0.01	0.62±0.04	0.21±0.03	0.33±0.01	0.45±0.02	0.56±0.03
Disintegration time (sec)	28±0.04	42±0.02	64±0.05	78±0.01	13±0.04	20±0.02	31±0.03	48±0.05
Folding endurance	78±1	93±3	70±5	56±2	67±2	86±2	73±3	53±4

T=Transparent, S=Srmitransparent

Table 3: Formulation of the drug loaded films

INGREDIENTS	F1	F6	F7
Drug (mg)	220	220	220
HPMC E5 (mg)	200	-	-
HPMC E15 (mg)	-	300	400
Propylene Glycol (ml)	0.2	0.2	0.2
Citric acid (mg)	10	10	10
Sodium starch glycolate (mg)	2	2	2
DMSO (ml)	3	3	3
Water	q.s	q.s	q.s

Table 4: Evaluation parameter of Loaded drug

PARAMETER	F1	F6	F7
Weight (mg)	19±3	29±1	36±4
Thickness (mm)	0.26±0.03	0.37±0.02	0.52±0.02
Disintegration time (sec)	35±0.05	30±0.02	36±0.01
Folding Endurance	86±1	102±3	113±2
Drug content (%)	82.45	90.57	88.32
Moisture loss	0.24	0.31	0.33

Table 5: Percentage cumulative drug release of selected formulations

Time (sec)	F1	F6	F7
0 sec	0	0	0
15 sec	12.54±0.02	15.4±0.05	10.12±0.08
30 sec	22.45±0.11	24.69±0.09	23.31±0.21
45 sec	29.32±0.34	39.45±0.21	36.02±0.03
60 sec	42.2±0.03	51.2±0.11	49.16±0.32
75 sec	57.5±0.06	63.32±0.04	61.32±0.10
90 sec	73.7±0.12	76.65±0.04	75.64±0.04
105 sec	76.45±0.03	84.07±0.21	81.34±0.11
120 sec	76.21±0.11	88.43±0.06	86.16±0.5
135 sec	76.03±0.03	90.75±0.21	86.4±0.02
150 sec	76.01±0.01	90.45±0.11	86.2±0.02

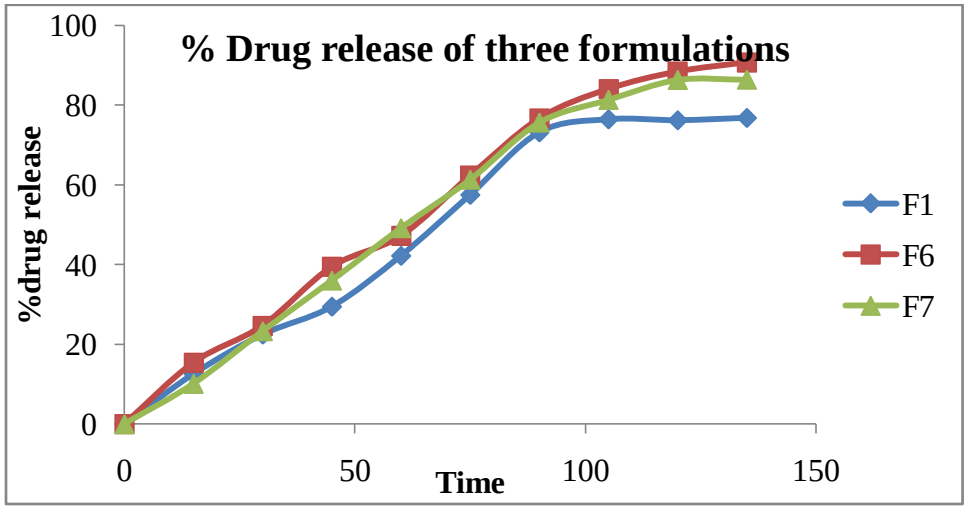

Figure 1: Comparative In Vitro Drug release of three formulations

RESULT AND DISCUSSION

Evaluation of blank films

Evaluation of blank fast dissolving oral films was done to optimize the polymer and its concentration. Evaluation of blank films was done on the basis of various parameters i.e. weight, thickness, disintegration time, folding endurance and visual appearance. During evaluation study it was observed that as the concentration of polymer increased; weight, thickness and disintegration time also increased but opposite effect was seen on folding endurance i.e. folding endurance decreased with increase in polymer concentration as higher polymer concentration leads to brittleness in film. Results of various evaluation parameters are shown in Table 2.

Characterization of fast dissolving oral films of Diacerein

Drug loaded fast dissolving oral films of F1, F6 and F7 of Diacerein were prepared and characterized on the basis of various parameters i.e. weight, thickness, disintegration time, folding endurance and physical appearance as shown in Table 4.

Average weight of the films was found to be in range of 19 - 36 mg. Thickness was found in the range of 0.26 - 0.52 mm and no major difference was observed. Disintegration time of the films was in the range 30-36 seconds, it showed that films disintegrated rapidly which is necessary for rapid onset of action. All selected film formulations showed folding endurance in the range of 86-113 folds, so all films have good flexibility.

Drug content in oral films was found in the range of 82.45 - 90.57%. No significant difference in the drug content was seen in different film pieces of same batch, which proves the drug content uniformity in the prepared fast dissolving oral films. Moisture loss of the film formulations was found to be 0.24 - 0.34% which is within the British Pharmacopoeia limits.

In Vitro dissolution studies

The release pattern as shown in Figure 1 and values tabulated in Table 5 revealed that the drug release from F6 is faster than the F1 and F7. Moreover, formulation F6 released about 91% drug while release rate was slow in case of formulation F1 and F7 i.e 76% and 86% respectively.

Thus it was concluded that formulation F6 containing 300 mg of HPMC E15 has an excellent film forming property among the two polymers used. It gives smooth, shiny, homogeneous films with lowest disintegration and dissolution time which leads to maximum drug release. Therefore formulation F6 was selected as best formulation.

STABILITY STUDIES

A stability study of the prepared films was carried out by storing films in an aluminium package for 60 days at 40° C/ 75% RH. The films were observed for physical change (form and color), disintegration time and drug content. Fast dissolving films of Diacerein were found to be physically and chemically stable as they showed no significant change in terms of physical characteristics (no discoloration & no change in shape), disintegration time and drug content under all storage conditions as shown in Table 6.

Table 6: Stability study result of formulation F6 at Accelerated conditions

Time (days)	Refrigerated condition (40° C / 75% RH)		
	Physical Appearance	Disintegration Time (sec)	Drug Content (%)
0	No change	30	90.57
7	No change	31	89.45
15	No change	33	89.12
21	No change	37	88.05
30	No change	35	87.45
45	No change	40	87.02
54	No change	39	86.35
60	No change	39	86.13

CONCLUSION

The present study revealed that fast dissolving oral films of Diacerein can be prepared by using HPMC E15 and by solvent casting technique. The main objective of this study were to increase the oral bioavilability by reducing the hepatic first pass metabolism and to improve the patient compliance. Formulation F6 showed good mechanical properties and good drug release. Stability studies indicating that there was no degradation of the formulation at high temperature and humidity. The formulation was stable.

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