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Formulation and evaluation of fast dissolving oral film of mefenamic acid

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ABSTRACT

The present study was aimed to formulate and evaluate fast dissolving oral films (FDOF) of Mefenamic acid used in the management of Rheumatoid arthritis and Dysmenorrhea. Fast dissolving oral films are meant to be dissolved in saliva and remain in oral cavity until swallowed. The fast dissolving films were prepared by solvent casting method by using HPMC as film forming polymer, due to their hydrophilic nature and palatable taste. The films were characterized by UV, FT-IR Studies. The plasticizer concentration is used for to improve good mechanical properties of the films. All the film formulations (F1-F6) were evaluated for their weight variations, thickness, surface pH, folding endurance, tensile strength, percentage elongation, *in-vitro* disintegration, drug content and *in-vitro* drug release studies. The drug excipients interactions were investigated by FT-IR, results show that there is no interaction drug and excipients. The optimized formulation F3 also showed satisfactory surface pH, drug content (99.35%), effective *in vitro* drug release (99.8% in 12 min), disintegration time of 12 seconds and satisfactory stability.

Keywords: FDOF, Mefenamic acid, HPMC, Solvent casting method.

INTRODUCTION

Oral route drug administration is considered to be effective and acceptable form due to its better therapeutic efficacy and good patient compliance. The pharmaceutical dosage forms of pills, capsules, granules, powders and liquids. Generally, a pill is designed for swallowing intact or chewing to deliver a specific dose of medication to patients. The pills, which include tablets and capsules, are able to maintain their shapes under moderate pressure. However some patients are particularly pediatric and geriatric patients have difficult in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of throat chocking.

Later includes solutions/ suspension or emulsions offering more advantages over monolithic solid dosage forms. However they also possess certain disadvantages such as finding non toxic excipients and need preservatives, which might cause adverse effects in children, microbiological stability, and also shows problems with the taste masking and dose accuracy. To

overcome these problems are associated with the liquids dosage forms, Oral Dissolving Tablets (ODT's) were designed in early 19th century, which slowly led to their further development and thus came the existence of fast dissolving oral films.

The oral route of administration still continues to be widely used accepted route, contributing to 50-60% of total drug formulations because of ease of administration, self- medicament, and pain avoidance as compared to parenterals. Mainly elderly patients may experience problem, when patient is mentally ill, developmentally disabled and in nausea. In some cases motion sickness, sudden episode of allergic attack or coughing and unavailability of water, poses problem in swallowing. To fulfill these medical needs pharmaceutical technologies development several mouth dissolving drug delivery systems. Most of the existing fast dissolving drug delivery systems are in the form to tablets and are designed to dissolve or disintegrate in the patient's mouth within a few seconds or minutes without the need of water or chew. [4]

Normally these films are soluble in water at room temperature and will break up in 30 sec and disappear in one minute. The faster the drug goes into the solution quicker its absorption and onset of clinical effect. By altering the condition and formulation factors, it is possible to slow down or speed up dissolving rate in the mouth. The fast dissolving oral films contain active ingredients, flavors, sweeteners and other ingredients these materials are released as the film dissolves. The concept of fast dissolving oral films

These are rapid dissolving films offers several advantages like,

- Convenient dosing
- Fast disintegration or dissolution followed by quick effect which is desirable in some cases such as pain.
- The film alleviates fear of throat chocking
- The film is easy to handle and administer
- The film maintains a simple and convenient packaging
- The film alleviates unpleasant taste and is easy to manufacturer
- This system allows children, elderly and the general population to take their medication directly wherever and whenever needed.
- The fast dissolving action is primarily due to the large surface area of the film
- The film are tough, solid, soft, flexible and do not require special packaging
- The films are thin and can be carried in a patient pocket, wallet. [3]

MATERIALS

Mefenamic acid was obtained as a gift sample from Sun pharma Mumbai. Hydroxy propyl methyl cellulose from Himedia Laboratories Mumbai. All other chemicals used were analytical grade and were used without purification. Double distilled water was used in the study.

Preparation of films

Fast dissolving films of mefenamic acid were prepared by solvent casting technique using film forming polymer. Required amount of HPMC was weighed accurately and soaked aside for 1hour for swelling of polymer. Simultaneously mefenamic acid was weighed accurately and weighed sucrose as a sweetener, citric acid as a saliva stimulating agent dissolved in 5ml of distilled water in another beaker. Then drug solution was added to the polymer solution and propylene glycol was added as a plasticizer was mixed thoroughly with the help of magnetic stirrer. Entrapped air bubbles were removed by applying vacuum. Flat foil coated glass mould (Petridish) having diameter 9cm was placed over a flat surface and the resulting 10 ml solution with the help of measuring cylinder was transferred into Petridish slowly drop by drop and was spread uniformly. The Petridish containing polymeric solution of drug was kept for 24hours at 60^{o}c for drying. After drying the films were removed by peeling from the moulds then cut into a square dimension of 2× 2cm^2. [4, 6]

Table 1 Formulation Table of Mefenamic Acid Loaded Fast Dissolving Oral Films

S.No	Formulation	Drug (mg)	HPMC (mg)	Sucrose (mg)	Citric acid (mg)	Propylene Glycol(mg)	Flavor (mg)
1.	F1	25	900	980	70	150	25
2.	F2	25	950	980	70	200	25
3.	F3	25	1000	980	70	250	25
4.	F4	25	1050	980	70	300	25
5.	F5	25	1100	980	70	350	25
6.	F6	25	1150	980	70	400	25

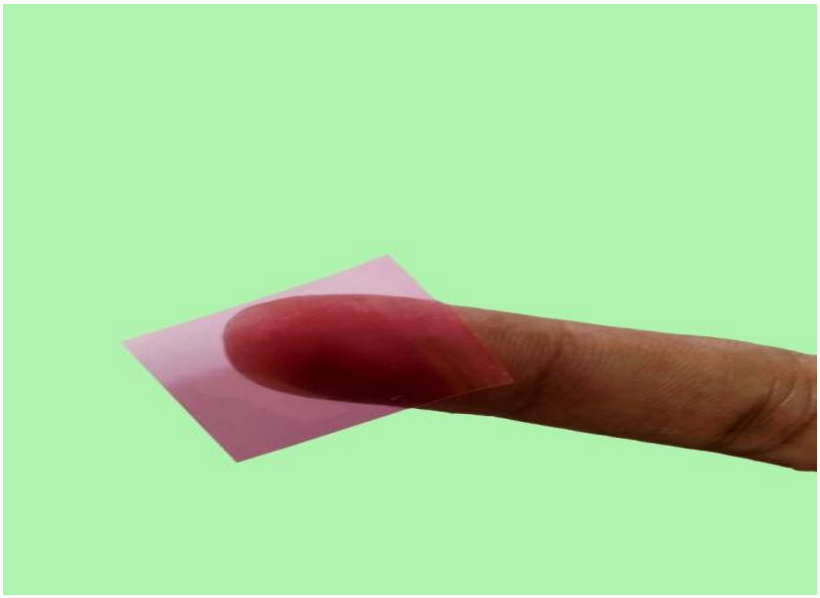

Fig 1 Optimized formulation (F3) Fast Dissolving Oral Film

EVALUATION OF FAST DISSOLVING ORAL FILMS

Film thickness

The thickness of each film was measured by using Digital venire caliber at different position of the film and the average thickness was calculated. This is as certain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip. [9, 10]

Weight variation

For weight variation three films of each formulation were randomly selected and weighed individually on digital balance then average weight was calculated. [7, 8]

Surface pH

The surface pH of fast dissolving film was determined in order to discover out the possible any *in-vivo* side effects. The film to be tested was located in a petridish and was moistened with 0.5 ml of distilled water and kept for 1 hour. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and kept for 1 min to allow equilibrium condition. The procedure was performed in triplicate and average with standard deviation was determined. [11, 12]

Moisture loss (moisture vapor transmission)

The percent moisture loss was determined by placing prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percent moisture loss was calculated using following formula [11, 12]

$$\text{Moisture loss} = \frac{W_0}{W_0 - W_t} \times 100$$

Where W_0= initial weight W_t = final weight.

Folding endurance

The folding endurance was determined by repeatedly folding one film at the same place till it broke. The numbers of times the film possibly will be folded at the same place without breaking gives the value of the folding endurance. [17, 18]

Tensile strength

Mechanical properties of the polymeric fast dissolving film were conveniently determined by measuring their tensile strength. The tensile strength of the fast dissolving film was determined using handmade tensile strength instrument. Average reading of three fast dissolving films was taken as a tensile strength. The fast dissolving film was fixed to the assembly, the weights required to break the film was noted. Tensile strength was calculated using following formula. [19, 20]

T.S =Break force/ L

Where, L-elongated length of the film

Percentage elongation

When stress is applied, a film or strip sample stretch and this is referred to as strain. Strain is essentially the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases. [21, 22]

% Elongation = (increase in length/ original length) × 100

Drug content

A film of 2x2cm^{2}diameter was cut and placed in 100 ml of phosphate buffer solution (pH 7.4). The contents were stirred by using magnetic stirrer to dissolve the film. The contents were transferred to a volumetric flask (100 ml). The absorbance of the solution was measured against the equivalent blank solution at 285 nm. As the absorbance noted above 1ml of the stock was additional diluted to 10 ml of phosphate buffer solution (pH 7.4) and absorbance was measured at 285 nm. The determination was carried out in triplicate for all the formulations. [29, 30, 31]

Disintegration time

This test was performed using disintegration test apparatus. 4cm^2 film was placed in the basket, raised and lowered it in such a behavior that the complete up and down movement at a rate to achieve equivalent to thirty times a minute. [23, 24]

In vitro dissolution studies

The phosphate buffer pH 7.4 was taken as the dissolution medium to determine the drug release. The dissolution profile of quick release films of mefenamic acid was carried out in USP I apparatus containing 900 ml of the phosphate buffer pH 7.4. The film was placed in the basket, maintained at37±5°C the agitation speed was 50 rpm. Aliquots (10 ml) of the dissolution medium were withdrawn at 2, 4, 6, 8, 10, 12 and 14 minutes time intervals and the same amount was replaced with the fresh medium. Samples were assayed spectrophotometrically at 285 nm. The cumulative percentage drug release was calculated. [25, 26, 27].

Stability studies

Stability studies on the optimized formulation of oral fast dissolving film were carried out to determine the effect of temperature and humidity on the stability of the drug. The film (optimized batch F3) was placed at 40°C/75%RH. The sample was withdrawn at after 30 days to determine disintegration time and cumulative % drug release [28].

RESULT AND DISCUSSION

Fourier transform infrared spectroscopy (FT-IR)

FT-IR studies conducted on pure drug, polymer and physical mixture of drug with polymer showed that there is no marked interaction between drug and selected polymers. The resultant graphs were showed in fig 2.

Film weight variation and thickness

A result showed that as the concentration of polymer increases weight of film also increases. The weight variation of the formulations was in the range of 0.19± 0.04 to 0.22 ±0.03 mm, which was acceptable. Thickness of oral dissolving film depends on the concentration of polymer. Thickness of all oral dissolving film was measured with Digital Vernier caliper. All the oral dissolving formulations of different polymers are show thickness value in the range of 0.05±0.03 to 0.22±0.08 mm (Table 2). The

optimized film has thickness of 0.05 ± 0.02. A result of thickness measurement showed that as the concentration of polymer increases, thickness of oral dissolving film also increases.

Surface pH

Surface pH of all oral dissolving films prepared by using different polymers was found to be in the range of 6.8 to 7.1 pH (Table 2), which was close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients.

% moisture loss

The %moisture loss of all the formulations were found in the range of 1.381 ± 0.003 to 2.882 ± 0.004 (Table 2) of mefenamic acid in this limit Moisture loss to produce the good mechanical properties of the film.

Swelling index study

The polymer concentration increases swelling index increases. It also affects the drug release from the strips, higher the swelling index minimum the drug release from the oral films. The results shown from Table 2

Folding endurance

Folding endurance gives an indication of brittleness of the film. It was shown that as the concentration of polymer and plasticizer increases, folding Endurance of oral dissolving film increases. The folding endurance value of the prepared films ranged from 21± 0.02 to 26± 0.03. (Table 3). The optimized film (F3) has folding endurance value of 24±0.03, which was desirable.

Tensile strength and % elongation

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and elongation at break. Tensile strength and percent elongation of all prepared formulation is shown in Table 3-. Results revealed that optimized formulation (F3) showed better tensile strength and moderate % elongation. From the result shown in table 3, it is clear that when the concentration plasticizer increases tensile strength and % elongation of oral dissolving film also increases. The optimized film (F3) has the tensile strength of 1.49 g/cm2 and percent elongation of 10.23.

Drug content

Drug content in the films was evaluated and the values were found to be between 97.68 to 99.06. % (Table 3) for three different cuts from each film.

In vitro disintegration

The disintegrating time of all the formulations was ranges from 13 to 18. The results were depicted in Table 3 the disintegrating time. The disintegration time of optimized formulation was found to be 12 sec, which was very less and desirable for quick onset of action.

In vitro dissolution time

Cumulative % drug release was calculated on the basis of drug content of mefenamic acid present in the respective film. The results obtained in the *in vitro* drug release for the formulations F1 to F6 is tabulated in table 4. The graphs are depicted in Figure 3. Formulation F1, F2, F3, F4, F5 and F6 shows drug release up to 95.8, 96.1, 99.8, 91.8 and 85.6 respectively at the end of 12 min.

Stability studies for (F3) optimized formulation

F3 formulation was selected for stability studies on the basis of high cumulative % drug release and also results of *in vitro* disintegration time. Stability studies were conducted under different conditions according to ICH guidelines. From these results it was concluded that, formulations F3 is stable and retained their original properties with minor differences. The results of disintegration time, drug content and transparency are shown in the Table 5, which indicates no alteration after storage.

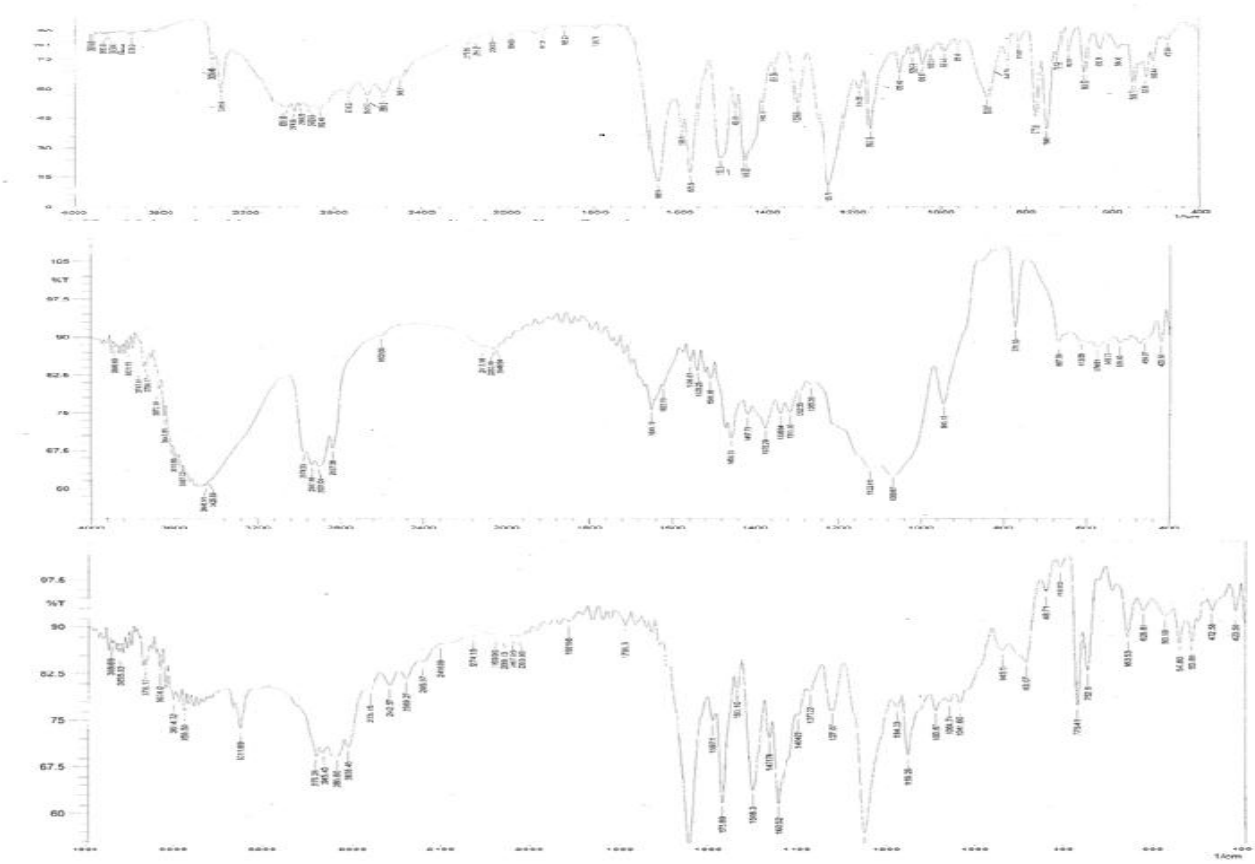

Fig 2 FT-IR Spectrum of Drug, polymer and physical mixture

Table 2 Physical Evaluation of Fast Dissolving oral films of Mefenamic Acid

S.NO	FORMULATION	WEIGHT VARIATION (MG)	FILM THICKNESS (MM)	SURFACE pH	% MOISTURE CONTENT	SWELLING INDEX
1.	F1	0.19 ±0.04	0.05 ± 0.03	6.92 ± 0.05	1.381 ± 0.003	1.51± 0.003
2.	F2	0.21±0.03	0.06 ± 0.08	6.92 ± 0.08	1.423 ± 0.005	1.83± 0.005
3.	F3	0.22±0.04	0.05 ± 0.02	7.05± 0.03	1.837± 0.004	1.73± 0.002
4.	F4	0.22±0.05	0.07 ± 0.06	7.1 ± 0.08	2.201± 0.003	1.93± 0.003
5.	F5	0.20 ±0.03	0.18 ± 0.05	6.95 ± 0.06	2.882± 0.004	2.31 ± 0.004
6.	F6	0.21±0.02	0.22 ± 0.08	6.82 ± 0.08	1.976± 0.006	2.03 ± 0.006

Table 3 Evaluation of Fast Dissolving oral films

S.No	Formulation code	Folding Endurance	Tensile strength	Percentage Elongation	Drug content (%)	Disintegration time(sec)
1.	F1	21±0.02	1.33	9.98	97.68	13±0.04
2.	F2	23±0.03	1.40	10.12	98.32	13±0.02
3.	F3	24±0.04	1.49	10.23	99.35	12±0.03
4.	F4	24±0.03	1.55	10.42	99.06	15±0.05
5.	F5	25±0.05	1.58	10.55	98.30	17±0.04
6.	F6	26±0.03	1.63	11.47	98.55	18±0.06

Table 4 *In-vitro* Drug Release Data of Mefenamic Acid fast dissolving films

Time	F1	F2	F3	F4	F5	F6
2min	25.2 ±1.02	25.9±1.03	26.3±1.07	17.6±1.09	14.3±1.12	12.1±1.25
4min	53.3±1.04	48.5±1.08	56.3±1.10	33.6±1.12	26.9±1.34	22.6±1.43
6min	71.3±1.03	76.2±1.22	70.8±1.24	47.1±1.25	42.8±1.43	38.4±1.54
8min	87.8±1.04	86.5±1.28	90.2±1.30	62.6±1.34	56.9±1.56	53.3±1.78
10min	94.6±1.07	90.2±1.32	94.3±1.36	78.9±1.37	74.9±1.76	69.9±1.65
12min	95.8±1.09	96.1±1.35	99.98±1.44	91.8±1.42	88.9±1.68	85.6±1.86

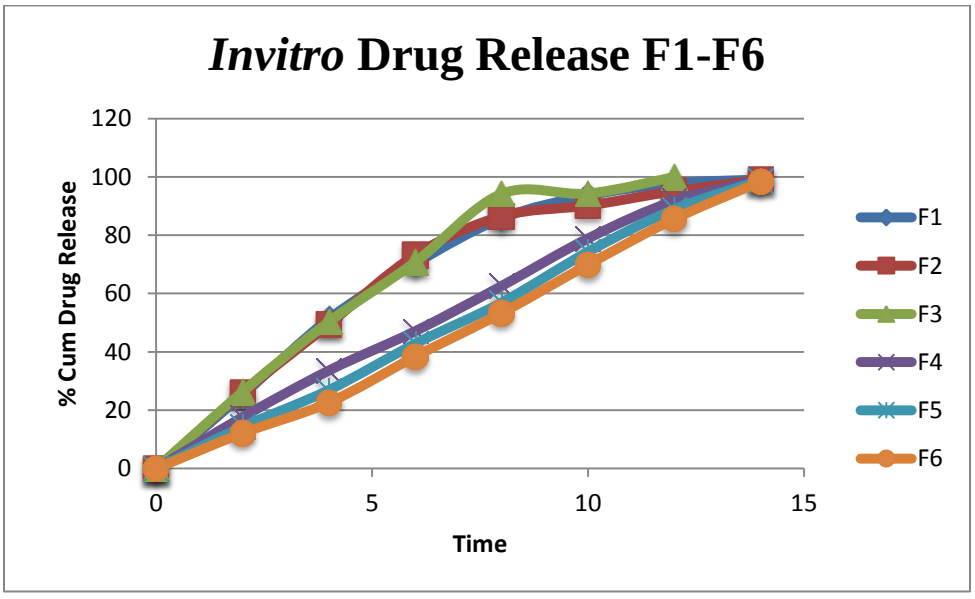

Fig 3 *In vitro* Drug Release F1-F6

Table: 5 Stability Study for Formulation F3

Parameters	Initial	After 30 days stability studies
Folding endurance	24±0.04	24±0.04
Drug content (%)	99.35	99.22
Surface pH	7.05 ± 0.03	6.9 ± 0.04
Disintegration time (sec)	15 ± 0.05	15 ± 0.05
Dissolution Time (12min)	99.98 ± 0.54	99.40 ± 0.87

CONCLUSION

Oral Fast dissolving films are ideal for many groups of patients including geriatrics, pediatrics, and psychiatrics as well as for those people who have difficulty in swallowing. Many drugs can be formulated in the form of Fast dissolving films to provide the advantages of fast dissolving drug delivery system.

A Preformulation study was carried out during the early stages of this work. The drug-polymer compatibility study was carried out to determine the interactions between the drug and the polymers used in the study. The FT-IR studies no interactions between drug and polymer. The Fast dissolving films were formulated by solvent casting technique. Different polymers concentrations were screened for the preparation of Fast dissolving films.

The prepared films were clear, homogenous, devoid of particulate matter, showed good folding endurance and all the prepared batches were showed good mechanical properties with *in-vitro* disintegration time. Later stability studies were of this formulation indicating that there was no degradation of formulation at high temperature and humidity conditions. It was indicating F3 formulation was stable. On the basis of data obtained from *in-vitro* dissolution studies that F3 formulation is suitable for the immediate release of mefenamic acid.

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