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Original Article

FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILMS OF PARACETAMOL

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ABSTRACT

Objective: Fast dissolving drug delivery systems such as mouth dissolving films (MDF) are novel dosage forms that disintegrate or dissolve within the oral cavity. These offer a convenient way of dosing medications, not only to special population groups with swallowing difficulties such as children and the elderly, but also to the general population.

Methods: In the present study, mouth dissolving films of paracetamol were prepared by solvent casting method, which involved the deaeration of the solution, transfer of appropriate volume of solution into a mould, drying the casting solution, cutting the final dosage form into strips (size 2x3 cm) to contain the desired amount of drug (125 mg), packaging and storage. The films were specifically designed for people with swallowing difficulties such as pediatric and geriatric populations. Several formulations were developed by varying polymer (hydroxypropyl methyl cellulose) and plasticizer (glycerol) concentrations. Sweetening and flavoring agents were also added to make the formulation palatable. The films were evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution time and drug content.

Results: In the present study, each mouth dissolving film was 2x3 cm in size and contained 125 mg Paracetamol (PCM). Thickness of the films was approximately 2 mm. The strips disintegrated completely within 4 minutes. In-vitro dissolution studies were carried out in distilled water as well as in simulated salivary fluid (pH 6.8).

Conclusion The optimized formulation showed 92% drug release within 30 min. The prepared strips seem to be an attractive alternative to conventional marketed formulations.

Keywords: Mouth dissolving films, Buccal, Sublingual, First pass metabolism, Pediatric, Geriatric.

INTRODUCTION

Fast-dissolving drug delivery is rapidly gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within a minute, without needing water or chewing. An important benefit is the accurate dosing as compared to liquid dosage forms, mostly used with paediatric patients or in case of dysphasia. Moreover, these systems may offer superior clinical profiles with potential oromucosal absorption, thus increasing the drug bioavailability with respect to oral administration. Fast-dissolving drug delivery systems are mainly tablets, and their rapid disintegrating properties are obtained through special process (freeze-drying or tablet moulding, overall) or formulation modifications (super-disintegrants and sugar-based ingredients) [1].

Recently thin films have been proposed as an alternative fast dissolving dosage form. Films can be produced by solvent cast methods or hot-melt extrusion technology. It is well known that the solvent cast method suffers from several disadvantages over the hot-melt extrusion method due to the solvent residues within the film and the environmental risks in the case of organic solvents. In addition, extrusion facilities are economic as compared to solvent cast ones. The fast dissolving films reported in literature are generally made of a hydrocolloid (e.g. pullulan or cellulose derivatives) and a plasticizer [2].

Fast dissolving drug delivery systems such as MDF are novel dosage forms that disintegrate or dissolve within the oral cavity. They have emerged as a convenient way of dosing medications, not only to special population groups with swallowing difficulties such as children and the elderly, but also to normal people. MDF are prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution on contact with saliva. MDF are typically designed for oral administration, with the user placing the strip on or under the tongue (sublingual) or along the inside of the cheek (buccal). These drug delivery options allow the medication to bypass the first pass metabolism, thereby increasing its bioavailability. As the strip dissolves, the drug can enter the blood stream primarily buccally and sublingually [3].

Advantages of Mouth Dissolving Films

Larger surface area promotes rapid disintegration and dissolution in the oral cavity.

Enhanced oral bioavailability of molecules that undergo first pass effect.

Precision in the administered dose.

With the help of Mouth dissolving film drug delivery system those drugs can be given to the patients that are not crushed and not injected to patients.

Better patient compliance.

Ease of swallowing and no need of water has led to better acceptability amongst the dysphagic patients.

Oral films are flexible and thus less fragile as compared to orally disintegrating technologies (ODT). Hence, there is ease of transportation and during consumer handling and storage.

Dosage form can be consumed at any place and anytime as per convenience of the individual.

Table 1: Composition of different films

Formulation	HPMC	SLS	Mannitol	Glycerol	Paracetamol
MDF 1	225 mg	25 mg	50 mg	0.4 ml	125 mg
MDF 2	200 mg	50 mg	50 mg	-	125 mg
MDF 3	230 mg	20 mg	50 mg	-	125 mg

Mouth Dissolving Films are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs.

By passing the first pass effect leads to reduction of dose which can lead to reduction in side effects associated with the molecules [2,3,4].

MATERIALS AND METHODS

Paracetamol (PCM) as active ingredient, Hydroxy propyl methyl cellulose (HPMC) as a water soluble polymer, Sodium lauryl sulphate (SLS), Mannitol used as sweetening agent and Glycerol as humectant. HPMC, SLS, Mannitol and Glycerol were procured from S.D. Fine chemicals Ltd. All other chemicals used were of analytical grade.

General method of formulation of mouth dissolving films

Following processes are generally used to prepare mouth dissolving film: hot melt extrusion, solid dispersion, rolling, semisolid casting and solvent casting. In the present study, mouth dissolving films of paracetamol were prepared by solvent casting method, which involved the following steps: preparation of casting solution (containing drug, polymer, plasticizer, sweetener and flavor), deaeration of the solution, transfer of appropriate volume of solution into a mould, drying the casting solution, cutting the final dosage form into strips (size 2x3 cm) to contain the desired amount of drug (125 mg), packaging and storage. Different formulations were developed by varying polymer (hydroxypropyl methyl cellulose) and plasticizer (glycerol) concentrations. Sweetening and flavoring agents were added to make the formulation palatable. The films were evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution time and drug content.

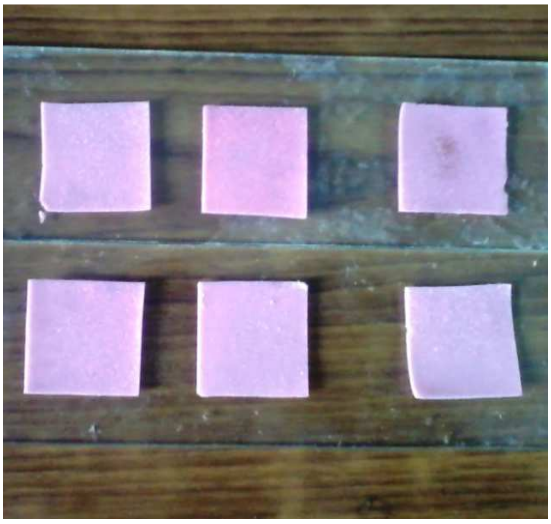

Fig. 1: Mouth dissolving films of paracetamol

Evaluation of Films

Standard curve of Paracetamol

Procedure- 100 mg of Paracetamol (PCM) was dissolved in 10 ml methanol and volume was made up to 100 ml with the distilled water. 10 ml of the above solution was diluted up to 100 ml with distilled water. From this solution, 1 ml was taken and volume was made up the 100 ml. (1µg/ml). Then by serial dilution, solutions with concentrations 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml were prepared. Absorbance was measured on a Shimadzu Double Beam Spectrophotometer (UV1601) at 257 nm.

Weight variation of the film

2x3 cm film was cut from different locations in the caste film. The weight of each film strip 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.

Folding endurance

The folding endurance is expressed as the number of folds required for breaking the specimen or developing visible cracks. This gives an indication of brittleness of the film. A small strip of 2x3 cm was subjected to this test by folding the film at the same point repeatedly several times until a visible crack was observed.

Disintegration time

Disintegration time study was slightly modified to mimic the *in-vitro and in-vivo* conditions. For the study, film as per the dimensions (2 x 3 cm) required for dose delivery was placed in a basket containing 900 mL distilled water. Time required for the film to break and disintegrate was noted as *in-vitro* disintegration time.

In-vitro dissolution studies

The *in-vitro* dissolution studies were conducted using pH 6.8 phosphate buffer (900 mL). The dissolution studies were carried out using six basket dissolution dissolution apparatus at 37 ± 0.5 °C and at 50 rpm. Each film with dimension (2 x 3 cm) was placed on a stainless steel basket. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 5, 10, 15, 20, 25 and 30 min. time intervals and filtered through 0.45µm Whatman filter paper and were analyzed spectrophotometrically at 257 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment.

Stability Study

Six months accelerated stability study was conducted successfully according to ICH stability conditions:

S. No.	Study	Storage conditions
1.	General case	30°C + 2°C
2.	Refrigerator	08°C + 2°C

Table 2: Characterization parameters of different batches

S. No.	Formulation Code	Weight (gm)	Disintegration time (min)
1.	MDF 1	0.758	4.0
2.	MDF 2	0.720	3.5
3.	MDF 3	0.738	4.0

RESULTS

Standard curve of PCM at different concentrations

a concentration dependent increase in absorbance was observed in agreement with Beer Lambert Law (Table 1). The obtained standard curve is shown in Fig 2.

Table 3: In-vitro dissolution profile of film of paracetamol for MDF 1

S. No.	Time (min)	Cumulative Percent Drug Released
1	5	60.23
2	10	68.12
3	15	74.05
4	20	81.31
5	25	86.45
6	30	91.52

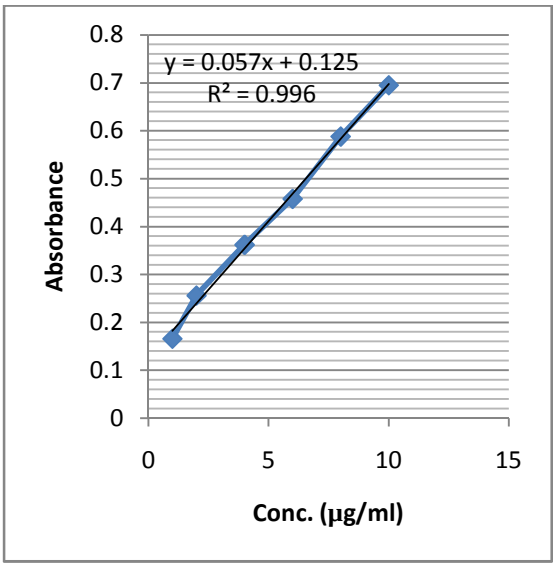

Fig. 2: Standard Curve of Paracetamol

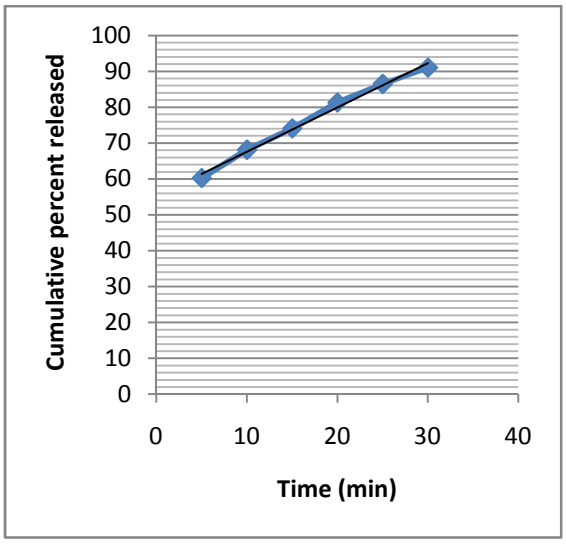

Fig. 3: Cumulative percent drug release of mouth dissolving film of PCM

CONCLUSION

In the present study, each mouth dissolving film was 2x3 cm in size and contained 125 mg Paracetamol (PCM). Thickness of the films was approximately 2 mm. The strips disintegrated completely within 4 minutes. In-vitro dissolution studies were carried out in distilled water as well as in simulated salivary fluid (pH 6.8). The optimized formulation showed 92% drug release within 30 min. The prepared strips seem to be an attractive alternative to conventional marketed formulations.

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