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DESIGN, FORMULATION AND EVALUATION OF MONTELUKAST SODIUM MOUTH DISSOLVING FILM

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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 Monteleukast Sodium. Oral films were prepared by a Solvent casting method using HPMC-E 15, Propylene glycol, and other recipients. Films were evaluated for mechanical properties, disintegration time, and in- vitro drug release. From the dissolution study, optimized batch was showed maximum in- vitro drug release 98.22%.

KEYWORDS: Oral Dissolving Film, HPMC E15, Solvent casting technique.

INTRODUCTION

Many novel drug delivery utilized in formulation development to achieve goal of any drug delivery system for the successful delivery of the drug, in which almost 90% of the drugs are administered to the body for the treatment of various disorders and diseases by means of safest, most convenient and most economical method of drug delivery system having the highest patient compliance.[1]

For oral drug delivery system, fast dissolving oral film is the novel drug delivery system for the drugs is an ultra-thin film prepared using hydrophilic polymers that rapidly dissolves on the top or the floor of the tongue or buccal cavity. They vary from an ultrathin strip size (50-150 microns thick) of postage stamp size with the inclusion of an active agent and other excipients developed on the basis of transdermal patch technology.[2] More than 60% of all

dosage forms available in the form of solid oral solid dosage form. Due to lower bioavailability, long onset time and dysphagia results in patients non-compliance and hence the manufacturer formulate drugs into the parenterals and liquid orals. But the liquid orals have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance.[3]

Nowadays, most pharmaceutical companies have reformulated existing drugs into new dosage forms such as oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue, or buccal cavity, results in better bioavailabilty, convenient and hence patients adhere to patient compliance.[4-6] Fast dissolving oral films as a novel approach in oral drug delivery systems more suitable for patient compliance, especially in case of pediatrics and geriatrics patients. They possess many advantages over conventional dosage form and can also be used when quick action is required as well as cases of dysphagia, Parkinson's disease, mucositis or vomiting etc.

Montelukast sodium acts as antagonist of leukotriene receptor and inhibits the cysteinyl leukotriene receptor. It is a selectively used as an alternative to anti‑inflammatory medications in the prevention and chronic medication of asthma, exercise‑induced bronchospasm, and to relief symptoms of seasonal allergies. Montelukast sodium is a physically white to off‑white colored powder, and it is freely soluble in ethanol, methanol, water, and practically insoluble in acetonitrile. By the means of oral route bioavailability of montelukast is 64% and more than 99% bound to plasma proteins and extensively metabolized in the liver with cytochromes P450 3A4 and 2C9. Montelukast sodium is available in various dosage forms such as 10 mg film‑coated tablet, 4 and 5 mg chewable tablets, and 4 mg oral granules sachet. Montelukast in the solution forme reported unstable on exposer to sunlight and lead to the creation of its cis‑isomer as the main photolized product.[7-10]

The Literature survey reveals that the Montelukast drug in tablet formulation[11-15] and in film formulation were developed by using various novel approaches[16-20] to improve its bioavailabilty and there is no one method yet available to formulate montelukast sodium oral mouth dissolving film using polymer HPMC E15 and plasticizer propylene glycol. Hence our aim is to design, prepare and characterize oral mouth dissolving film using polymer HPMC

E15 and plasticizer propylene glycol. The objective is to study the effect of different varying concentration of film forming polymer and plasticizers on the development of film.

MATERIAL AND METHODS

Materials

Montelukast sodium procured as a gift sample from Snehal pharmaceuticals Pvt Ltd, India. Polymer HPMC E15 and plasticizer propylene glycol purchased from Loba chemicals and Rainbow Inc. Mumbai, whereas Aspartame purchased from SAMAR chemicals Pvt Ltd.

Method:-Factorial design

In statistics, a full factorial experiment is an experiment whose design consists of two or more factors, each with discrete possible values or "levels", and whose experimental units take on all possible combinations of these levels across all such factors. A full factorial may also be on called a fully crossed design. Such an experiment allows the investigator to study the effect of each factor on the response variable, as well as the effects of interactions between factors on the response variable. Factorial designs allow the effect of a factor to be estimated at several levels of the other factors, yielding conclusions that are valid over a range of experimental conditions. The amount of variables in 3^2factorial design batches and experimental design is given in Table 1 and 2 respectively.

Table 1: Amount of variables in 3^2factorial design batches.

Coded Values	Actual Values (mg)	
	X1	X2
-1	150	0.2
0	250	0.5
+1	350	0.7

Table 2: Experimental design.

Formulation code	Coded values	
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

Table 3: Formulation of factorial design batches containing hpmc e15 and propylene glycol.

Formulation code	Ingredients	
	HPMC E15 (mg)	Propylene glycol(ml)
F1	150	0.2
F2	150	0.5
F3	150	0.7
F4	250	0.2
F5	250	0.5
F6	250	0.7
F7	350	0.2
F8	350	0.5
F9	350	0.7

Preparation of film

The solvent casting method is used for the preparation of fast dissolving strip formulation. The oral fast dissolving strips were prepared by taking ingredients in different concentration of HPMC E15 and propylene glycol as depicted in table 1 and different composition in table 4. HPMC and drug Montelukast was mixed and dispersed in distilled water, followed by continuous stirring up to 1 hour on magnetic stirrer and kept for 30 min to remove all the air bubbles entrapped. To this plasticizer (propylene glycol) was added. Solution of aspartame was prepared in separate container.

Both the solutions were mixed together followed by keeping the solution mixture standing for 15-30 min to let the foams settle down. Then this solution was kept in the sonicator for at least 15 min. The resulting solution was casted in specific amount (calculated according to the batch size) on a suitable inert platform of film former and the temperature of the film former was set to 40°c. After drying the film was scraped from the film former. Then the film was checked for any imperfections and cut according to the size required for testing (1×1inches). The samples were in a glass container coated with aluminum foil maintained at an appropriate temperature. Both the fast dissolving film with drug and blank film without drug were prepared and evaluated.

Table 4: Composition of formulation of films.

Formula-tion code	Ingredients				
	HPMC E15 (mg)	Propylene glycol (ml)	Montelukast sodium (mg)	Aspartame (mg)	Distilled water in ml
F1	150	0.2	25	5	5
F2	150	0.5	25	5	5
F3	150	0.7	25	5	5
F4	250	0.2	25	5	5
F5	250	0.5	25	5	5
F6	250	0.7	25	5	5
F7	350	0.2	25	5	5
F8	350	0.5	25	5	5
F9	350	0.7	25	5	5

Evaluation of mouth dissolving film: Mouth dissolving film was evaluated for Visual appearance, weight variation, thickness of the film, folding endurance, disintegration time as given as follows:

Visual appearance: The fast dissolving films were evaluated by visual observation, such as transparent and semitransparent nature of film.

Weight variation of the film: 2.5×2.5 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: The thickness of the film was measured by the micrometer 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 the brittleness of the film. A small strip of 2.5×2.5cm 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 dimension (2.5×2.5cm) required for dose delivery was placed in a basket containing 900 mL distilled water. The time required for the film to break and disintegrate was noted as in-vitro disintegration time.

Surface pH: Film is slightly wet with the help of water. The pH is measured by bringing the electrode in contact with the surface of the oral film. This study is performed on three films of each formulation.

Drug content: A film of 1.5×1.5cm was cut and dissolved in 100ml of 0.5% SLS and filtered. From this solution 1mL of solution was pipette out and the volume was made up to 10mL. The drug is determined spectroscopically at 342nm.

In vitro dissolution studies

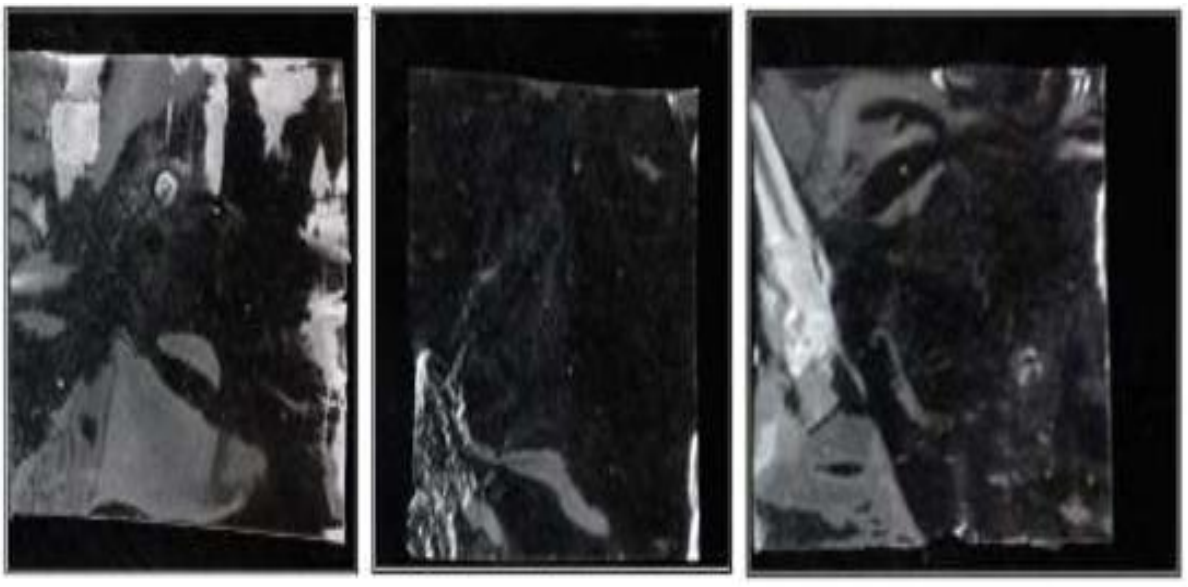
The in-vitro dissolution studies were conducted using pH 6.8 phosphate buffer (900ML). The dissolution studies were carried out using eight basket dissolution apparatus at 37±0.5°c and at 50 rpm. Each film with dimension (2.5×2.5 cm) was placed in a stainless-steel basket. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 5,10,15,20 min. time intervals and filtered through 0.45µm Whatman filter paper and were analyzed spectrophotometrically at 342nm.To maintain the volume, an equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment.

RESULTS ANDDISCUSSION

Evaluation of mouth dissolving film

The evaluation of mouth dissolving film was carried out by using following parameters given as follows and images of films are given in figure 1:-

Visual appearance: On visual appearance, it was observed that all the film formed by using propylene glycol was transparent in appearance as given below



(FA) **(FB)** **(FC)**

(FD) **(FE)** **(FF)**

(FG) **(FH)** **(FI)**

Figure 1: Visual appearance of formed films.

Weight variation of the film: 2.5×2.5 cm film was cut from different locations in the caste film. The weight of each film was taken and the weight variation was calculated as given in table 5 (a).

Thickness: Thickness of the film was measured by micrometer and the average thickness was calculated, F7 shown maximum thickness while minimum thickness in F3 shown in table 5 (a).

Folding endurance: The folding endurance is expressed as the number of folds required for breaking the specimen or developing visible cracks. From the observation the film formed by using 0.7ml (F9) of propylene glycol has least value of folding endurance while film of 0.2ml (F1) of propylene glycol shows highest value of folding endurance as mention in table 5 (b).

Disintegration time: The film formed by using 0.5ml (F5) of propylene glycol has taken least time for disintegration that is 38sec while maximum time have taken by 0.7ml of propylene glycol (F9) shown in table 5 (b).

Surface pH: The surface pH was found to be the least of formulation (F1 & F2) of 6.83 pH and the highest pH of F5 was 7.04 as shown in table 5 (b).

Drug content: The drug content of the films was found and the result was shown in table 5 (b).

Table 5 (a): Evaluation of mouth dissolving film.

F. Code	Visual Appearance	Weight of filmsin mg±SD	Thickness inμm ±SD
F1	Transparent	12±0.57	0.025±0.005
F2	Transparent	15.33±0.33	0.025±0.005
F3	Transparent	13.33±0.88	0.01±0.0
F4	Transparent	31.33±0.88	0.05±0.0
F5	Transparent	32.66±1.33	0.035±0.005
F6	Transparent	31.66±0.33	0.035±0.005
F7	Transparent	52±0.57	0.10±0.0
F8	Transparent	49.33±0.33	0.05±0.0
F9	Transparent	49.66±0.88	0.06±0.0

Table 5 (b): Evaluation of mouth dissolving film.

F.Code	Folding endurance	Surface pH	Disintegration time in sec±SD	Drug content in%
F1	80±2	6.83	45.5±0.5	96.27
F2	27.5±0.5	6.83	47.5±0.5	97.11
F3	20.5±0.5	7.01	41.5±0.5	96.85
F4	20±2	6.86	49.5±0.5	99.68
F5	20±0	7.04	38.25±0.25	98.46
F6	20±0	6.84	40.25±0.25	94.65
F7	78.5±0.5	6.95	51±1	94.35
F8	17.5±0.5	6.89	53.5±0.5	106.05
F9	15.5±0.5	6.40	58.75±0.25	95.20

In-vitro dissolution studies: In-vitro dissolution studies of different formulations from F1-F9 and Marketed tablet MT (Minolast-LC) was carried out and the release data are shown in figure 2.

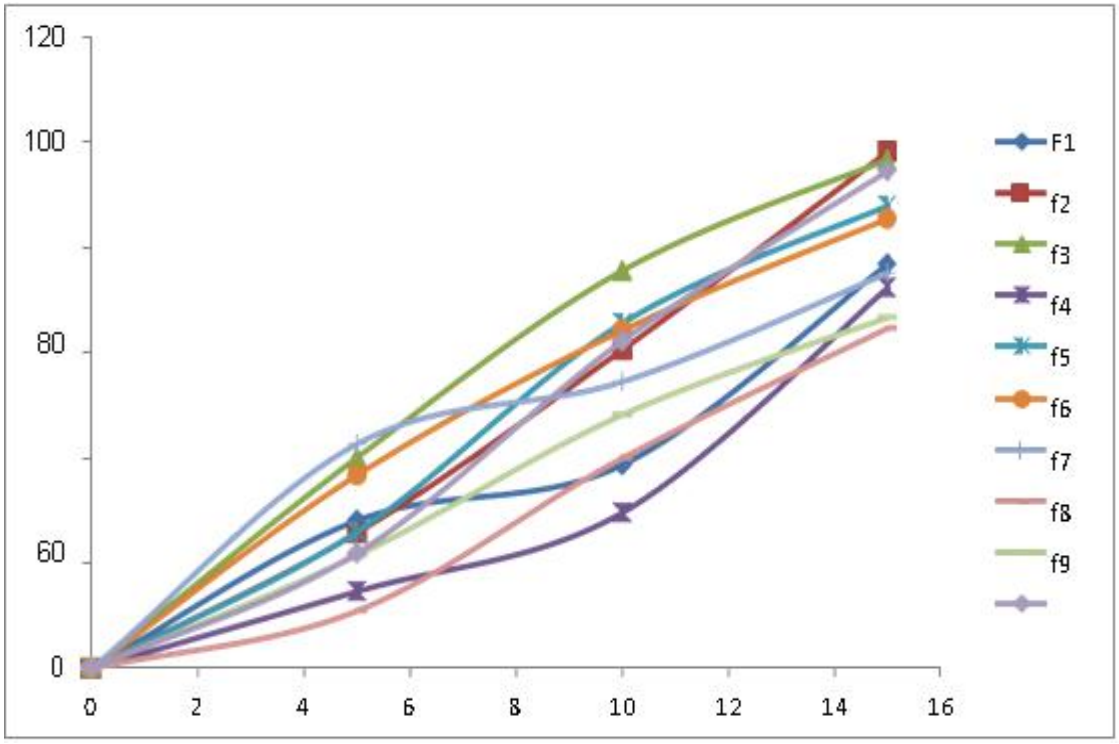


Figure 2: Cumulative percent Drug release of F1-F9 & MT.

The drug release from different batches was observed to be depends on the concentration of plasticizer. As the concentration of plasticizer (propylene glycol) increases, the drug release will decrease. F2 batch show maximum drug release up to 98.226% and F8 shows lowest drug release of 64.7%. From the drug release study of above formulations, it was observed that as the concentration of plasticizer (propylene glycol) in the film increases, the drug release will decreases. The In-vitro dissolution data and release drug profile of mouth dissolving film is given in table 6 and figure 3.

Table 6: Drug release study of batch F1-F9 & T.

Formulation Code	Time(min)			
	0	**5**	**10**	**15**
F1	0.00	28.125	38.7	76.925
F2	0.00	25.8	60.6	98.266
F3	0.00	40.1	75.66	96.76
F4	0.00	14.625	29.625	72.4
F5	0.00	26.03	65.66	88.00
F6	0.00	36.76	64.3	85.53
F7	0.00	42.675	54.525	75.175
F8	0.00	10.925	40.00	64.7
F9	0.00	21.475	48.225	66.75
MT	0.000	21.94	62.268	94.6

A comparision of drug release formulation F2 and marketed preparation are shown in figure 3.

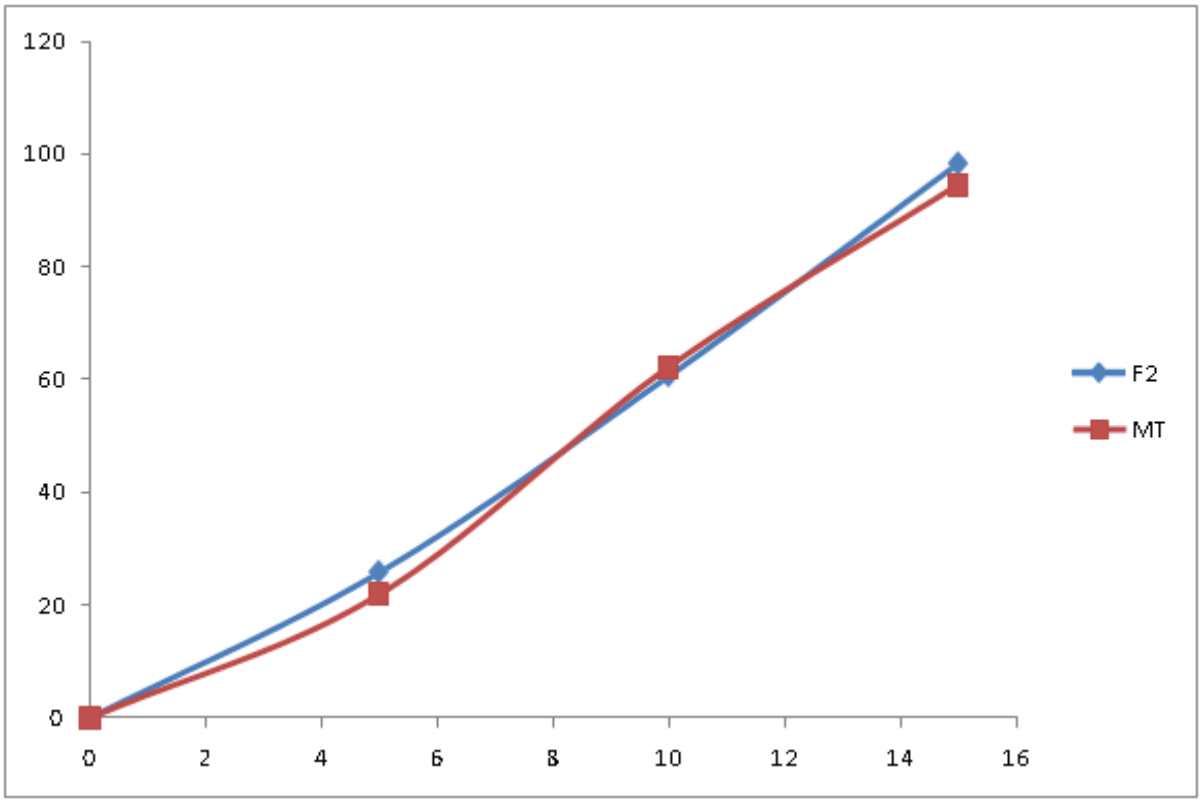


Figure 3: Drug release study of F2 and Marketed tablet.

CONCLUSION

An attempt has been made to formulate montelukast sodium oral mouth dissolving film using polymer HPMC E15 and plasticizer propylene glycol. The nine 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 various concentration of polymer and plasticizer. Formulated films were evaluated for physical characterization like thickness, uniformity of weight, surface pH, disintegration time, drug content.

In vitro dissolution studies of different formulation from F1-F9 and marketed tablet (Minolast LC) were carried out at pH 6.8 phosphate buffer. The drug release from formulation was observed to be depends on concentration of plasticizer. F2 batch show maximum drug release up to 98.226 and F8 show lowest drug release of 64.7. The F4 batch of formulation has comparable release profile as that of marketed preparation. The best fitting model for all

formulation was calculated. The batches F1, F2, F3, F4, F5, F6, F7, F8, F9 and MT were found to be zero order release.

In the present study, each mouth dissolving film was 2.5×2.5 cm in size and contained 5mg of montelukast sodium. The thickness of the films was approximately 0.02-0.04 mm. The film disintegrated completely within 1 minutes. In vitro dissolution studies were carried out in phosphate buffer of pH 6.8. The optimized formulation showed 98% drug release within 15 min. The prepared film seen to be an attractive alternative to conventional marketed formulations and could be the choice of dosage for pediatric patient.

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