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Research Article

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Development and evaluation of mouth dissolving films of salbutamol sulfate

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ABSTRACT

The present investigation was undertaken with the objective of formulating mouth dissolving films (MDFs) of the anti-asthmatic drug, Salbutamol Sulfate (SAL) to enhance convenience and compliance to the elderly and pediatric patients for better therapeutic efficacy. Film former, Hydroxypropyl Methylcellulose (HPMC) of different viscosity grades along with film modifier/solubilizing agents, polyvinyl pyrrolidone K30 (PVP K30) and sodium lauryl sulphate (SLS) were used to formulate MDFs. The MDFs were prepared by wet film applicator technique and were evaluated for in vitro dissolution characteristics, in vitro disintegration time, and their physico-mechanical properties. MDFs with 13% (w/w) of HPMC E5 gave better dissolution properties when compared to HPMC E15. MDFs with 0.04% (w/w) of SLS gave superior dissolution properties when compared to MDFs without SLS. MDFs with 0.04% (w/w) PVP did not peel off from glass plate and hence were excluded from study. Overall, MDFs showed good mechanical properties like tensile strength, folding endurance and % elongation and HPMC is an excellent film former for the preparation of MDFs.

Key words: Salbutamol Sulfate; Mouth Dissolving Films; HPMC; Sodium Lauryl Sulphate

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INTRODUCTION

The oral cavity is the most prominent site of drug delivery for a long period of time. In 1847 Sobrero found that nitroglycerine was absorbed from the oral cavity[1]. Since then various active substances have been investigated for local or systemic use. Recent developments in the formulation technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or non-compliant patients. Novel bio-adhesive mucosal dosage forms including adhesive tablets, gels, patches and more recently the use of polymeric films for oral cavity delivery, also known as mouth dissolving films (MDFs) gained attention in formulation research. MDFs, a new and novel drug delivery system for per-oral delivery of the drugs, were developed based on the technology of the transdermal patch[2] . The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro-mucosal absorption or with formula modifications, will maintain the quick dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Various film formers like Polyvinyl alcohol, Polyvinyl pyrrolidone (PVP), Maltodextrin, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC), Methyl Cellulose (MC), Sodium Carboxy Methyl Cellulose (Na CMC), Chitosan and some natural gums have been used in the production of films[3].

SAL, an anti-asthmatic drug is short acting, selective beta2-adrenergic receptor agonist. It is 29 times more selective for beta 2 receptors than beta 1 receptors giving it higher specificity for pulmonary beta-receptors versus beta1-adrenergic located in the heart [4]. Its oral bioavailability is 50%. SAL undergoes rapid and complete first-pass metabolism following oral administration, resulting in reduced systemic bioavailability. It does not cross the blood-brain barrier, but does cross the placenta. The drug is extensively metabolized in the liver, principally to the inactive metabolite, SAL 4'-O-sulfate. After oral administration, the serum half-life in humans has been reported as 2.7-5 hours [5]. Very few reports were published on the orally disintegrating tablets of SAL[6] and one paper on the oral films containing polyvinyl alcohol as a polymer, glycerol as a plasticizer, and mannitol as filler was reported so far [7]. Hence, the main aim of this work is to develop a novel, fast dissolving drug product on the technology platform of a small and thin drug loaded film i.e. MDF for SAL in order to overcome first pass effect and to have quick onset of action for better therapeutic efficacy.

EXPERIMENTAL SECTION

Salbutamol Sulfate (Gift sample from Darwin Laboratories, Vijayawada), HydroxyPropyl MethylCellulose (E5, E15) (Loba Chemie, Mumbai), Methanol (Loba Chemie, Mumbai), Sodium Lauryl sulphate (Merck, India), PVP K30 (Dr. Reddy's Laboratories, Hyderabad), Pine apple flavor (Darwin Laboratories, Vijayawada), Aspartame (Darwin Laboratories, Vijayawada) were used. All other reagents are of analytical grade were used.

Preparation of Artificial Saliva:
Artificial saliva was prepared as per the method reported by [8]: Sodium chloride-0.844g; Potassium chloride-1.2g; Calcium chloride dihydrate-0.193g; magnesium chloride hexahydrate-0.111g; potassium phosphate dibasic-0.342g. These ingredients were added one by one to 500ml of distilled water and then the volume was made up to 1000ml using the same. The pH was adjusted with 0.1N hydrochloric acid to 5.7.

Preparation of SAL MDFs:
Films were prepared as per formula given in Table 1 to a batch size of 5g. Drug was dissolved in a mixture of solvents (water and methanol) in a beaker and other ingredients were added one by one and finally polymer HPMC was added and mixed thoroughly and the mixture was sonicated for 5 minutes to remove entrapped air bubbles and casted on a glass plate with a wet film applicator set at 10mil thickness (250µm) and it was dried at 40°C for 60min in hot air oven. Then the dried films were peeled off from the glass plate, cut into appropriate sizes, and stored in desiccator until use.

Table 1. Composition of different MDFs containing SAL

Ingredients	Formulae (Amounts in mg)			
	F1	F2	F3	F4
SAL	30	30	30	30
HPMC E5	650	650	-	-
HPMC E15	-	-	650	650
PEG 400	50	50	50	50
SLS	-	2	-	2
PVP	-	-	-	-
Water	1699.5	1697.5	1697.5	1697.5
Methanol	2600	2600	2600	2600
Pineapple flavor	10	10	10	10
Aspartame	10	10	10	10

Morphological Properties:
Properties such as homogeneity, color, transparency and surface of SAL MDFs are tested visually. All the formulations were stored at room temperature (25 ± 3°C) with relative humidity of approximately 65 ± 5% and were tested periodically every month for a period 6 months. The results were given in Table 2.

Drug Content:
1cm^2 film was taken in a 10mL volumetric flask and dissolved in 5mL of methanol and the volume was made up with methanol. Samples were suitably diluted with artificial saliva and the absorbance was measured at 223nm. The estimations were carried out in triplicate. The data was given in Table 2.

Variation of Mass:
Mass of 4×4cm^2 film from different batches of the formulations was noted on electronic balance. The results were given in Table 3.

Thickness:
The thickness of film was evaluated using screw gauge with range 0-10mm and revolution 0.001mm. Anvil of the thickness gauge was turned and the film was inserted after making sure that pointer was set to zero. The film was held on the anvil and the reading on the dial was noted down. The average of 3 readings was taken and the data was given in Table 2.

Disintegration studies:
Disintegration time gives an indication about the disintegration characteristics and dissolution characteristics of the film. Incase of MDFs the disintegration and dissolution procedures are hardly distinguishable. If the MDF disintegrates it concurrently dissolves in a small amount of saliva which makes it difficult to mimic these natural conditions and measures with an adequate method. However, in the present investigation two methods of disintegration were adopted.

Drop method:
In the first method one drop of distilled water was dropped by a pipette onto the oral films. Therefore the films were placed on a glass slide and placed planar on a petridish. The time until the film dissolved and caused a hole within film was measured. The results were given in Table 2.

Petridish method:
In this method 2ml of distilled water was placed in a petridish and one film was added on the surface of the water and the time required until the oral film was dissolved completely was measured. Drug-loaded films were investigated under both methods. The results were given in Table 2.

Tensile Strength:
Tensile strength is the maximum stress applied to a point at which the film specimen breaks [9]. It is calculated by the load at rupture divided by the cross-sectional area of the film as given below:

$$\text{Tensile strength} = \frac{Loadatfailure \times 100}{FilmThickness \times filmwidth}$$

It was measured using Shimadzu AG-100kNG (Winsoft tensile and compression testing). The film of size 3×2 cm2 and free of physical imperfections was placed between two clamps held 10 mm apart. The film was pulled by clamp at a rate of 5mm/min. Whole experiment was carried out in triplicate. The average of 3 readings was taken and the data was given in Table 3.

Percent Elongation (%E):
When stress is applied the film sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally elongation of the film increases as the plasticizer concentration increases [10].

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.

$$\text{Percentage Elongation} = [L\text{-}L0] \text{ X } 100 / L0$$

Where, L = Final length, L0 = initial length
The average of 3 readings was taken and the data was given in Table III.

Young's Modulus:
Young's modulus or elastic modulus is the measure of stiffness of film. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\text{Young's Modulus} = \frac{Slope \times 100}{FilmThickness \times CrossHeadSpeed}$$

The average of 3 readings was taken and the data was given in Table 3.

Hard and brittle film demonstrates a high tensile strength and Young's modulus with small elongation.

Folding Endurance:
Folding endurance is determined by repeated folding of the film at the same place till the film breaks. This gives an indication of brittleness of the film. The number of times the film is folded without breaking is computed as the folding endurance value [11]. The results were given in Table 3.

Dissolution studies:
As the MDFs are not official in any pharmacopoeia the following dissolution methods were used for testing the *in vitro* drug release profiles from MDFs.

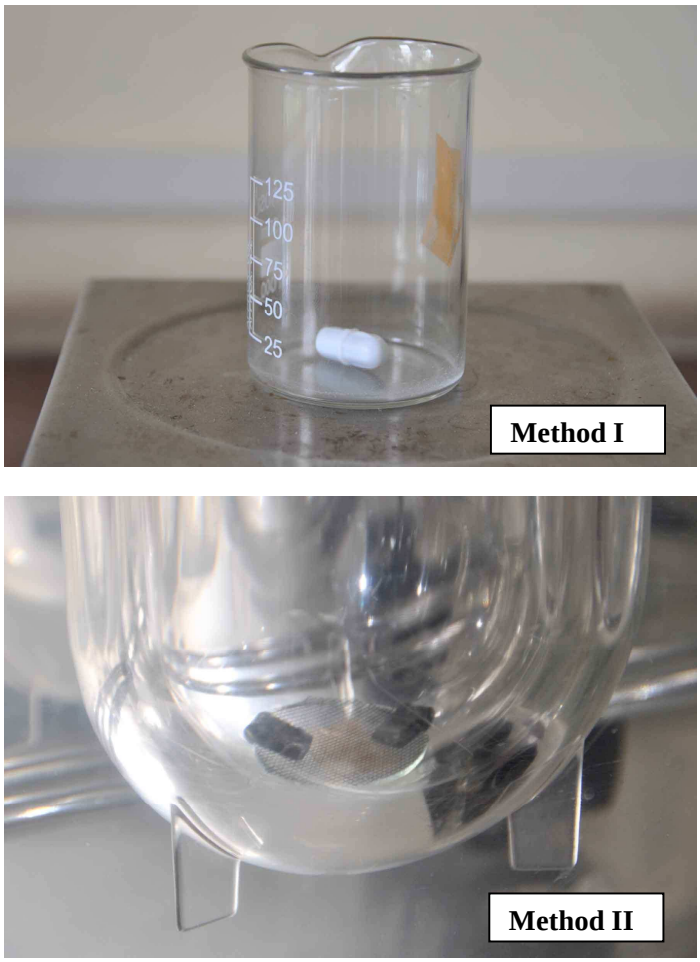

Fig 1. Dissolution setup for Method I (Beaker Stirring method) and Method II (Apparatus 5 method)

Beaker Stirring Method (Method I):
The *in vitro* dissolution studies were conducted using 150mL glass beaker with 125mL of artificial saliva as dissolution medium. Film (4×4 cm^2) was placed on one side of the beaker using double-sided tape (Figure 1). Medium was stirred at a speed of 200rpm using magnetic stirrer bar. 5mL samples were withdrawn at 10, 20, 30,

40, 50, 60, 80, 100, 120sec time intervals and every time replaced with 5mL of fresh dissolution medium. The samples were analyzed by measuring UV absorbance at 223nm. The dissolution experiments were conducted in triplicate.

Dissolution Apparatus 5 (Method II):
The *in vitro* dissolution studies were conducted using 600mL of artificial saliva as dissolution medium with modified type 5 dissolution apparatus. A temperature of 37º C and 50 rpm were used. Each film with dimension (4×4 cm^2) was placed on a watch glass covered with nylon wire mesh (Figure 1). The watch glass was then dropped into dissolution flask. 5mL samples were withdrawn at 10, 20, 30, 40, 50, 60, 80, 100, 120 sec time intervals and every time replaced with 5mL of fresh dissolution medium. The samples were analyzed by measuring absorbance at 223nm. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Preparation and Physical characterization of SAL MDFs:
Initially placebo MDFs were prepared with different polymers like HPMC (E5, E15, and K4M), HPC, MC, Na CMC, PVP, Gelatin, and sodium alginate. Finally, from these trials made and results obtained, HPMC E5 and HPMC E15 were selected for further development. In the initial trials 50mg of drug was added to the formulation and the films were prepared. However, crystallization of the drug was observed over a period of time and hence, the drug amounts were adjusted to 30mg per batch. The formulae of different SAL MDFs were prepared using HPMC E5, HPMC E15 as per the formulae given in Table 1. Totally a 5g batch size of formulation gave approximately 120cm^2 film area. In the case of SAL MDFs with PVPK30 the films were not peeled off from the glass plate after drying and are not included in the studies. Different homogenous films of SAL were prepared; all the films are transparent, colorless, and soft with no spots found on them.

Morphological properties:
SAL MDFs were visually tested for homogeneity, transparency, color and smoothness and results were given in Table 1. All the formulations showed no change in the properties at the end of 6 month time period when compared to initial properties and especially no crystallization of the drugs was observed.

Drug content:
Films of 1cm^2 were cut from different places of the whole films and SAL content was estimated. The results were given in Table 2. These results indicate a good uniformity of SAL within films and overall, good solubilization of SAL in the formulations was observed.

Thickness:
The thickness was measured with screw gauge at different places of MDFs in order to evaluate the reproducibility of preparation method. Around 60% of wet film thickness was lost during drying. The results are given in Table 2 and a good uniformity of thickness was observed.

Disintegration time:
The results of disintegration time are given in Table 2. These results indicated that the E5 formulations disintegrated faster than the E15 formulations. The SAL MDF formulations with SLS disintegrated faster than the MDFs without SLS formulations. With Petri dish method F2 and F4 formulations disintegrated/ dissolute faster than the other formulations.

Variation of mass:
Films of (4×4cm2) were cut from different batches and weighed. The results are given in Table 3. Same mass of film was obtained with three batches of films indicating reproducibility of preparation method and formulation.

Tensile Strength:
Mouth dissolving films should possess moderate tensile strength, high % elongation (% E), low EM, and high percent of drug release. The results revealed that all the films showed moderate tensile strength values, films of F2 and F4 showed highest % E compared with other formulae and F2 has lowest EM when compared with other formulae. The results are given in Table 3.

Table 2. Physico-mechanical properties of different SAL MDFs

Formulae	Appearance	Drug Content/cm^2 (mg) (n=3)	Thickness (µm) (n=6)	Disintegration time (sec)	
				Drop Method (n=3)	Petri Dish Method (n=3)
F1	Homogeneous, transparent, colorless, both sides smooth Transparent	0.250 ± 0.020	70.6 ± 1.15	1.66 ± 0.50	33.66 ± 1.52
F2	Homogeneous, transparent, colorless, both sides smooth Transparent	0.250 ± 0.020	70.33 ± 1.15	2.33 ± 1.15	33.00 ± 2.00
F3	Homogeneous, transparent, colorless, both sides smooth Transparent	0.252 ± 0.002	71.33 ± 1.52	2.00 ± 1.00	32.33 ± 1.52
F4	Homogeneous, transparent, colorless, both sides smooth Transparent	0.250 ± 0.002	71.33 ± 2.00	1.66 ± 0.50	33.33 ± 1.52

** No change in properties even after 6 months of storage period*

Table 3. Physico-mechanical properties of different SAL MDFs

Formulae	Mass variation (mg)	Tensile Strength (N/cm^2)	% Elongation (cm %)	Elasticity Modulus	Folding Endurance
F1	45.33 ± 0.57	2.93 ± 0.152	85.53 ± 3.60	3.38 ± 0.244	101
F2	44.66 ± 0.57	1.93 ± 0.152	94.83 ± 3.22	1.86 ± 0.151	139
F3	45.00 ± 1.00	3.53 ± 0.251	84.43 ± 3.66	3.28 ± 0.102	99
F4	45.00 ± 0.00	2.19 ± 0.173	89.16 ± 3.18	1.99 ± 0.218	112

***In vitro* Dissolution Studies:**

The *in vitro* dissolution profile of SAL films are shown in Figure 2. Totally 4 different formulations of SAL were prepared using HPMC E5 and HPMC E15 as film forming polymers with and without SLS. With Method I i.e., beaker stirring method for F1 (only E5) the cumulative percent SAL released at the end of 10sec is 22.85 ± 0.60 whereas, with F3 (only E15) 18.90 ± 0.50 percent of SAL was released. However with both the formulations complete SAL release was obtained at 50sec. These results are an indication of requirement of more sampling points in dissolution profile pattern. The comparative release profiles are shown in Figure 2.

Effect of solubilizing and or wetting agents on SAL release was also tested. SLS was added to the formulations at 0.04% levels. The cumulative percent of SAL released at the end of 10sec is 48.98 ± 0.26 for F2 (E5 with SLS) whereas, with F4 (E15 with SLS) 22.44 ± 0.88 percent of SAL was released. Complete SAL release was obtained at 50sec for both the formulations. The SAL release from F2 is significantly higher when compared to F4 and also when compared to the F1 and F3. The comparative release profiles are shown in Figure 2. Overall, the E5 formulations (F1, F2) with and without SLS gave superior dissolution properties when compared to E15 formulations (F3, F4). This could be due to the low viscosity of the HPMC E5 polymer when compared to E15 polymer.

Dissolution studies were also carried out with type 5 dissolution apparatus where a 600mL of dissolution medium was used (artificial saliva) for comparison. All the formulations followed similar dissolution behavior when compared to the method I. However, the initial percent SAL released at 10sec is significantly different for both the methods. Method II gave higher release when compared to method I. The dissolution data was very well supported by the disintegration time data obtained with all 4 formulations.

Drug Release Kinetics

The first order release rate constant 'k' (sec^{-1}) values for SAL MDFs calculated from Method I dissolution data (0-20sec) were given in Table 4. When compared to the F1 the 'k' value was significantly higher for F2. The 'k' value for F4 is higher when compared to that of F3 whereas; the 'k' values are significantly higher for HPMC E5 MDFs when compared to HPMC E15 MDFs. A 1.67 folds increase in 'k' values for F2 when compared to F1 and 1.16 folds increase in 'k' values for F4 when compared to F3 was obtained. Based on the above results the MDF of formula F2 showed the highest dissolution rate and lowest *in vitro* disintegration time is suitable for fast-dissolving dosage form.

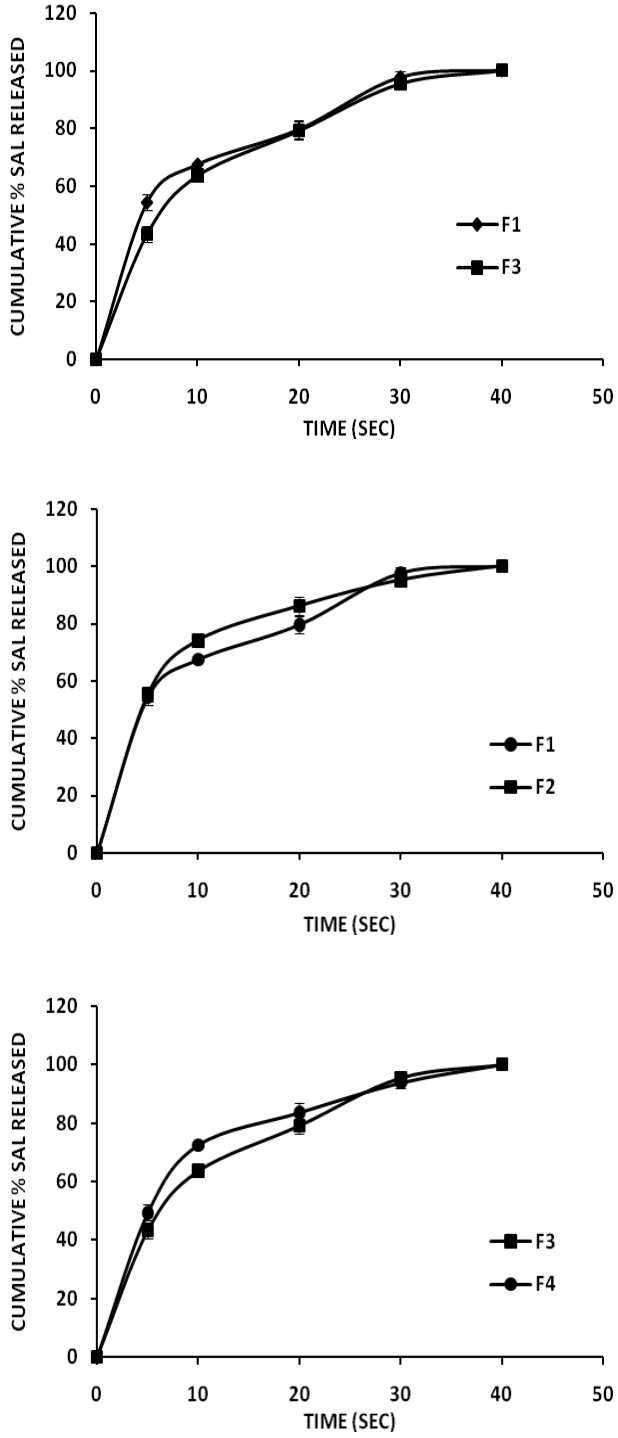

Fig 2. Comparative Dissolution Profiles of F1- F4 (Method II)

Table 4. Dissolution parameters of SAL MDFs

Formulation	DP_{10} (Mean ± SD)		Mean 'k' (sec^{-1})- 0-20sec	
	(Method I)	(Method II)	(Method I)	(Method II)
F1	22.85 ± 0.60	67.44 ± 0.25	0.029	0.073
F2	48.98 ± 0.26	74.11 ± 0.89	0.050	0.094
F3	18.90 ± 0.50	63.58 ± 2.80	0.028	0.076
F4	22.44 ± 0.88	72.48 ± 2.27	0.032	0.088

DP_{10} – percent drug released at 10 sec.

CONCLUSION

The SAL MDFs were prepared using different film-forming materials showed satisfactory drug dissolution and acceptable physico-mechanical characteristics. Amongst 4 formulae, the film prepared using HPMC E5 and SLS showed the highest dissolution rate, suitable *in vitro* disintegration time and satisfactory physico-mechanical properties.

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