Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com

A RESEARCH ARTICLE ON FORMULATION AND EVALUATION OF MOUTHDISSOLVING FILMS OF SALBUTAMOL SULPHATE USING SODIUM ALGINATE AND METHYL CELLULOSE

C.H. Jyothirmai[*1], B. Nagendra Babu[1], Uma Maheswara rao[1], J. Sushmitha[2], C.H.V. Alekhya[3]

[1*]Department of Pharmaceutics, St Mary's College of Pharmacy, Chebrolu, Tenali, Andhra Pradesh, India.
[2]Department of Pharmacology, Hindu College of Pharmacy, Guntur, Andhra Pradesh, India.
[3]Department of Pharmaceutics, ASN College of Pharmacy, Andhra Pradesh, India.

ABSTRACT

Buccal drug delivery has lately become an important route of drug administration. Various bio adhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. The present study involves formulation and evaluation of Salbutamol Sulphate oro dissolving films using film forming polymers (methyl cellulose and sodium alginate) in different ratios for the treatment of Asthma.

KEYWORDS

Salbutamol sulphate, Mucosal dosage forms, Buccal delivery, Methyl cellulose and Sodium alginate.

Author for Correspondence:

Jyothirmai C H,
Department of Pharmaceutics,
St Mary's College of Pharmacy,
Chebrolu, Tenali, Andhra Pradesh, India.

Email: jyothirmai.pharmacy@gmail.com

INTRODUCTION[1]

Various bio adhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films[1]. Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. 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. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets[2].

Asthma is a chronic inflammatory disease, which includes bronchial hyperactivity and bronchospasm. Characterised by hyper responsiveness of tracheo bronchial smooth muscle to variety of stimuli resulting in narrowing of air narrowing air tubes, often accompanied by increased secretions and mucosal edema resulting in breathlessness or dyspnea, wheezing cough, chest congestion and anxiety about being unable to breathe[2].

Asthma affects over 5-10% of population in industrialized countries. It afflicts approximately 53 million people across world mostly in United states, France, Germany, Italy, Spain, United Kingdom, and japan. More than people die every year in India as result of complications arising from serious asthma attacks through there are several recommendations and treatments being reported.

The treatments of asthmatic symptoms generally includes conventional oral dosage forms like tablets, capsules, oral liquids etc. inhalation therapy includes meter dose inhalers with or without spacers, dry powder inhalers, and other aerosol systems. Oral administration is the most widely accepted route of delivery due to its ease of administration, convenience, versatility and most importantly patient compliance. Several new technologies for oral delivery have recently been available to address the problems of physicochemical and pharmacokinetic characteristic of drugs, while improving patient compliance. One of these include fast dissolving technology which offers the advantages and dissolution of tablets, no residue in mouth, require no water intake, provides a pleasant mouth feel and even allows high drug load[3].

Adults For the relief of acute asthma or before exercise 100-400mcg. The recommended dose for maintenance treatment or prophylactic therapy is 100-400mcg three to four times a day. Maximum dose is 1.6mg/day.

Children in the treatment of episodic asthma or before exercise 100-200mcg. The recommended dose for maintenance treatment or prophylactic treatment is 100-200mcg three to four times a day. Maximum dose is 0.8mcg/day[4].

For treatment of asthma various conventional oral dosage forms like tablets, capsules, oral suspension, syrups etc are available in market but the major drawbacks with these are many patients find to difficult to swallow (dysphasia) tablets and hard gelatine capsules. The difficulty experienced in particular by paediatrics and geriatrics patients because of tremors of extremities, due to a fear of chocking and this also applies to the patients who are bed in travelling.

For this reasons, oro-disintegrating drug delivery systems have attracted a great deal of attention. A dosage form that dissolves disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water is known as mouth dissolving films/tablets. When this type of film is placed in to the mouth, the saliva will serve to rapidly dissolve the film. Recently, fast dissolving drug delivery systems have stated gaining popularity and acceptance as new drug delivery systems, because some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down in to the passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

In the oro dissolving drug delivery systems mouth dissolving films gained popularity rather than oro dissolving tablets because of its benefits over oro dissolving tablets.

MATERIALS AND METHODS

Salbutamol sulphate, Sodium alginate, Methyl cellulose, Cellulose acetate phthalate, Mannitol, Glycerol, Sodium lauryl sulphate, Sucrose and Citric acid.

Method

Salbutamol sulphate raw material and the required quantity of all the excipients were weighed according to listed in Table No.1 and passed through sieve No.44. The polymer solution prepared by dissolving the film forming polymer in the required quantity of water by vigorous stirring, to this cellulose acetate phthalate added and made it into semi solid by adding required quantity of glycerol, to this solution of sodium lauryl sulphate added then drug, Salbutamol sulphate added to the mixture by dissolving in water and stirred gently, then the remain excipients were added one after another after made them into solution with water, finally colouring agent added by dissolving it in water, then the resultant solution stirred gently for 5 minutes. Then the mixture is subjected to degassing by a vacuum pump to remove the entrapped air bubbles. After degassing the resultant solution poured into Petri plates and placed them in hot air oven at 45^0C for 24 hours. Then the films are carefully removed and cut into desired shapes and in uniform sizes.

EVALUATION

Thickness

The thickness of the polymer films was measured by using screw gauge. The thickness of each strip at six different areas was determined and standard deviation was calculated[5].

Moisture loss studies

The percent moisture loss studies were carried out to check the physical stability and integrity of the films. In the present study the moisture loss capacity of the films was determined by placing the known weight and predetermined size (1x1) of films in dessicator containing anhydrous calcium chloride (inside the dessicator) for three days. The films were removed and reweighed, and the percentage moisture loss of the films was measured by using the formula.

$$\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Folding Endurance

The folding endurance was measured manually for the prepared films. A strip of film was repeatedly folded at the same place till it broke[6]. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. The folding endurance of prepared films was measured in triplicate.

In vitro disintegration time

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. The disintegration time of prepared films was measured in triplicate.

Uniformity of drug content

The film of area 1x1 cm2 was cut and dissolved in 6.8 phosphate buffer solution and made up to 100 mL in a volumetric flask. Then 1 mL was withdrawn from the solution and diluted to 10mL. The absorbance of the solution was taken at 276 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated. The test was performed in triplicate.

In-vitro dissolution studies

Dissolution study was carried out in USP paddle type apparatus using 300 mL of stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rpm. Temperature of the dissolution medium was maintained at 37±0.5ºC. Samples of 5ml were withdrawn at every 4 minute interval, filtered (through 0.45µ) and replaced with 5ml of fresh dissolution medium. The samples were suitably diluted and estimated spectrophotometrically at 276 nm by using ELICO-164 double beam UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate. Dissolution rate was studied for all designed formulations and dissolution parameters were calculated.

Drug-Excipients Interaction studies

Interaction of Salbutamol sulphate with the respective polymers that is, MC and Sodium

Alginate and individual excipients formulation was established by Infrared Absorption Spectral Analysis (FTIR). Any changes in the chemical composition after combining with the excipients were investigated with IR spectral analysis. Infra-red spectra were obtained by using Shimadzu FTIR-281 spectrophotometer.

RESULTS AND DISCUSSION

Salbutamol sulphate was subjected to the following evaluation tests and has passed all the tests. The results are listed in Table No.2.

Evaluation of Films

Films are evaluated by different tests like Thickness, Folding endurance, Moisture loss, Disintegration time, Drug content (%) and *In Vitro* Release Study, The results were tabulated in Table No.3 and 4.

***In vitro* dissolution test reveals the following results in ascending order as follows**

Sodium alginate+ methyl cellulose>Sodium alginate>Methyl cellulose.

The maximum *in vitro* dissolution was found to be with formulation F-VIII which is combination of sodium alginate and methyl cellulose in 2:1 ratio. Alone alginate shows good results but in combination with methyl cellulose it shows best results in releasing drug from the film. The methyl cellulose alone shows poor results with the combination of alginate it shows better results and in the combination of sodium alginate and methyl cellulose different ratios were prepared among those 2:1 shows best results compared to the other ratios.

In this work, from the above results and discussions, the best formulation selected among the different formulations is F-VIII. The reason is it has rapid disintegration and maximum amount of drug compared with other formulations.

Table No.1: List of Ingredients

S.No	Ingredients	Quantity per tablet(mg)								
		F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
1	Salbutamol sulphate	120	120	120	120	120	120	120	120	120
2	Sodium alginate	500	400	300	-	-	-	250	333.3	166.6
3	Methyl cellulose	-	-	-	500	400	300	250	166.6	333.3
4	Cellulose acetate phthalate	125	125	125	125	125	125	125	125	125
5	Glycerol	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml
6	Mannitol	250	250	250	250	250	250	250	250	250
7	Sodium lauryl sulphate	50	50	50	50	50	50	50	50	50
8	Sucrose	100	100	100	100	100	100	100	100	100
9	Citric acid	100	100	100	100	100	100	100	100	100
10	Flavoring agent	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
11	Coloring agent	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
12	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table No.2: Physical Characterisation of Salbutamol Sulphate

S.No	Test	Limits as per monograph	Observation
1	Description	White crystalline powder	Complies with U.S.P
2	Solubility	Freely soluble in water, very slightly soluble in alcohol and in methylene chloride.	Complies with U.S.P
3	Melting point	158-161 ºC	159-161 ºC
4	Identification	IR absorption spectrum concordant with reference spectrum.	Complies with U.S.P
5	Assay	98.0-101.0%	99.79%

Table No.3: Evaluation of Films

S.No	Formulations	Thickness ± S.D (mm)	Folding endurance	Moisture loss (%)	Disintegration time(min)	Drug content (%)
1	F-1	0.18 ± 0.6	85	20.5	1.20	95.6
2	F-2	0.15± 0.6	100	19.0	1.10	97.3
3	F-3	0.14 ± 0.6	150	17.25	0.55	98.7
4	F-4	0.20 ± 0.6	75	22.3	1.30	95.5
5	F-5	0.19± 0.6	90	20.7	1.20	96.9
6	F-6	0.16 ± 0.6	125	19.4	1.0	98.3
7	F-7	0.15 ± 0.6	90	19.3	1.10	98.2
8	F-8	0.14 ± 0.6	165	17.0	0.45	98.5
9	F-9	0.17 ± 0.6	130	18.2	1.0	98.9

Table No.4: *In Vitro* Release Study of All Formulations

S.No	Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	4	50.56	58.97	59.37	44.49	50.56	57.23	59.08	61.33	59.08
3	8	66.32	63.91	68.21	50.56	57.23	61.06	71.35	79.76	63.68
4	12	70.93	77.93	79.76	57.23	77.93	77.93	84.37	93.16	89.59
5	16	77.93	88.69	89.28	74.65	80.38	87.18	93.11	96.97	90.16

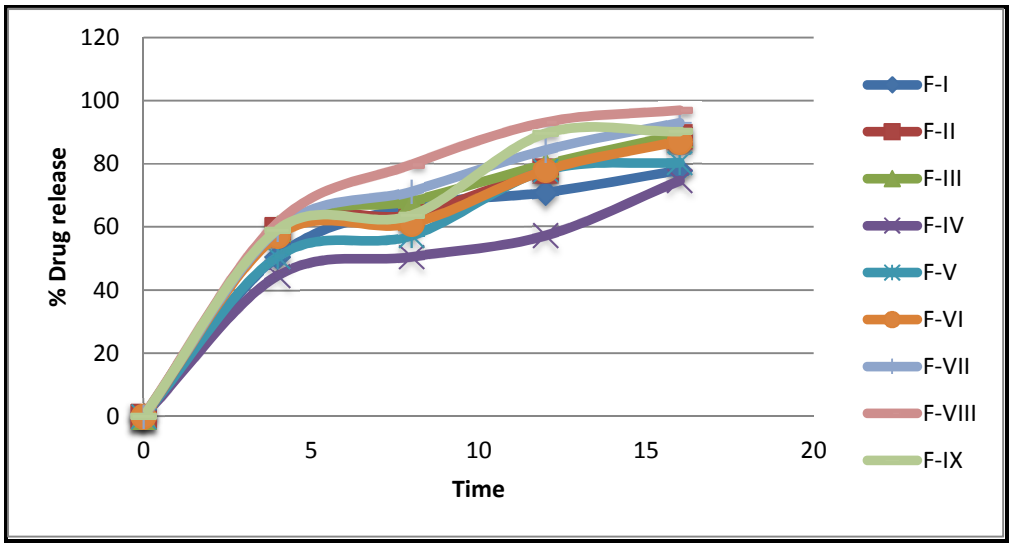

Figure No.1: Comparison of Percentage Drug Release for All Prepared Formulations

CONCLUSION

The results have shown that the dissolution rate of the drug increases with increase in concentration of the sodium alginate with respect to methyl cellulose. The dissolution rate increases in the following order with increase in concentration of sodium alginate in sodium alginate and methyl cellulose combination. Sodium alginate + methylcellulose (1:2) < Sodium alginate +methyl cellulose (1:1) <sodium alginate +methyl cellulose (2:1). The evaluation studies show all the formulations passes all the tests. The IR studies have proved that there is no interaction between drug and the Excipients. Sodium alginate and methyl cellulose in the ratio 2:1 shows fast disintegration of film and fast dissolution of film (96% within 16 min). To conclude, sodium alginate and methyl cellulose in the ratio of 2:1 suitable for preparing rapid dissolving films of Salbutamol sulphate.

ACKNOWLEDGEMENT

Our college St Mary's College of Pharmacy, Chebrolu, Tenali, Andhra Pradesh, India supports for doing this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: C.H. Jyothirmai *et al.* A Research Article on Formulation and Evaluation of Mouth dissolving Films of Salbutamol Sulphate using Sodium Alginate and Methyl Cellulose, *International Journal of Research in Pharmaceutical and Nano Sciences,* 4(5), 2015, 276 - 281.