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Formulation and Evaluation of Salbutamol Sulphate Sublingual Films

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ABSTRACT

Salbutamol is a short-acting, selective beta-2-adrenergic receptor agonist used in treatment of asthma and COPD. In the present work, sublingual films of Salbutamol sulphate were developed with a view to enhance the patient compliance and provide quick onset of action. Salbutamol has a bioavailability of 53 - 60%. The goal of the study was to formulate sublingual films of Salbutamol sulphate to achieve a better dissolution rate and further improving the bioavailability of the drug. Sublingual films prepared by solvent casting method using film forming polymers HPMC-E5, HPMC-E15 and Maltodextrin in different ratios. The prepared batches of films were evaluated for the drug content, weight variation, film thickness, disintegration time and *in vitro* dissolution studies. Among all, the formulation B1 containing HPMC-E15 with a drug: polymer ratio (1:6) was found to be the best formulation which showed 98.36% of the drug release within 15 minutes and disintegration time 18 sec. This study shows the viability of developing sublingual films of salbutamol.

KEYWORDS: Sublingual Films; Salbutamol Sulphate; HPMC; Maltodextrin.

Introduction

Due to increased life expectancy, the elderly constitute a major portion of the world population today. Due to a decline in swallowing ability with age, many elderly patients complain that it is difficult for them to take some currently used dosage forms such as tablets, capsules or powders (Fusco et al., 2016). Oral disintegrating dosage forms are gaining prominence as new drug delivery system. These dosage forms dissolve or disintegrate in the oral cavity within a matter of seconds without the need of water or chewing .These are useful for pediatric, geriatric and dysphasia patients leading to improved patient compliance. They are also suitable for the mentally ill, the bedridden, and patients who do not have easy access to water.

Ease of administration, accurate dosing, no water required for swallowing made this dosage form more advantageous. Thin films ability to dissolve rapidly without the need for water provides an alternative to patients with swallowing disorders, and to patients suffering from nausea, such as those patients receiving chemotherapy. Thin film drug delivery is a process of delivering drugs of the systemic circulation via thin films that dissolves when in contact with liquid, often refered to as dissolving films or strips and dissolve within 1 minute when placed in mouth without drinking or chewing. (Nagaraju et al., 2013).

Salbutamol sulphate has a wide usage over treatment of asthma to children and also adults. (Briggs et al., 2006; Szefler et al., 2016). Polymers commonly used are HPMC E5, HPMC E15 and Maltodextrin. Plasticizer used in film formation is PEG 400, which imparts flexibility. Sublingual films are developed by using film forming polymers from the regulatory perspectives; all excipients used in formulation should be generally regarded as safe and should be approved for use in oral pharmaceutical dosage forms. (Dixit and Puthli, 2009).

The main goal of this study was to design sublingual film of salbutamol sulphate that disintegrate within few seconds.

Materials and Methods

Drugs and Chemicals

Salbutamol sulphate was a gift from New American Therapeutics, Inc. (Roseland, New Jersey). HPMC (all grades) Qualikems PvtLtd, Vadodara, PEG400 from Finar chemicals Ltd. (Ahmedabad, India). All the chemicals used were of analytical grade.

Methods

Determination of dose of Sulbutamol sulphate: Amount of drug required per film = 8mg of Sulbutamol sulphate.

Therefore, 4 films require 32 mg of drug

Area of the petridish (πr^2) = 3.14 × 4.5 × 4.5 = 63.5 cm^2

6 films of 4 cm^2 each i.e (2cm × 2cm) can be obtained freely per petridish.

Area not required is the one remaining after cutting the films from the centre of petridish. This is obtained as

Area considered = Sum of the areas of number of films taken = 4 cm^2 × 6 = 24 cm^2

Amount of drug in area considered = 48 mg

Area not considered = Total area of petridish-Area considered = 63.5 – 24 = 39.5 cm^2

4 cm^2 film contains 8mg of drug therefore 15 cm^2 contains mg of drug

Amount of drug in area not considered=316 mg

Therefore,

Total drug dose = (Amount of drug in area considered) + (Amount of drug in

Area not considered) = 32 + 316 = 348

Therefore, an approximate amount of 40mg drug was considered per petridish.

Preparation of Sublingual Films

Solvent casting method: Film is formulated using the solvent casting method, where by the water –soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution and combined with the bulk. This mixture was then added to the aqueous viscous solution. The entrapped air was removed by vaccum. The resulting solution is cast as a film and allowed to dry, which was then cut into pieces of the desired size.

Evaluation of Films

Thickness: The thickness of the patch was measured using digital Vernier calipers with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

Weight variation: Four centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variations was calculated.

Drug content: Drug content determination of the film was carried out by dissolving the film of 4cm in 100 mL of pH 6.8 phosphate buffer using magnetic stirrer for 1hour. The drug concentration was then evaluated spectrophotometrically at 276nm. The determination wascarried out in triplicate for all the formulations and average with standard deviation was recorded.

In vitro dissolution: The dissolution study was carried out using USP type I (basket type) dissolution apparatus. The dissolution was carried out in 900 mL of pH 6.8 phosphate buffer maintained at 37ºC at 50rpm. 5ml of samples were taken at various time intervals, which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37ºC. Salbutamol sulphate in the samples was then determined spectrophotometrically at 276nm. The results were expressed as mean of three determination.

In vitro disintegration: *In-vitro* disintegration time was determined visually in a petri plate containing 25ml of pH 6.8 phosphate buffer swirling every 10sec. The disintegrating time is the time when the film starts to break or disintegrates.

Folding endurance: *The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2.5 cm × 2.5 cm was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed, and the values were reported.*

Drug Excipient Compatability Studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectro-scopy (FTIR) method and Differential Scanning Colorimetry (DSC) method.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectro-photometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons.

Stability studies

The stability study of the optimized sublingual films was carried out under different conditions according to ICH guidelines. The film was packed in the aluminium foil and stored in a stability chamber for stability studies. Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 3 months. The films were characterized for the drug content and other parameters during the stability study period (Prabhu et al., 2011).

Surface pH

The film to be tested was placed in a Petri dish and was moistened with 0.5 mL of distilled water and kept for 30s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.

Results and Discussion

Films

The sublingual films were prepared by solvent casting technique using HPMC E5, HPMC E15, HPMC E5 + HPMC E15, Maltodextrin, Aspartame, PEG and flavor. (Table 1). HPMC is water soluble polymer, it is surface active agent and also enzyme resistant. E indicates a low viscous patch forming grade. PEG imparts good flexibility to films. (Newton & Lakshmanan, 2014). Maltodextrin is water soluble and acts as a film forming polymer. (Parikh et al). Aspartame is an artificial non-saccharide sugar used in foods and beverages. The strips were evaluated for drug

content, film thickness, average weight, *in vitro* disintegration time, *in vitro* dissolution studies. Results were formulated in (Table 2).

Assay was performed and percent drug content of all the batches were found to be 97.9±0.5, 99.8±0.08 & 99.1 ± 0.3 of salbutamol sulphate which was within acceptable limits. All the batches were evaluated for thickness using a screw gauge. As all the formulations contain different amount of polymers, hence the thickness gradually increases with the amount of polymers. The thickness was found to be 0.04 -0.2 mm.

In vitro Disintegration Time of Flms

Disintegration time was performed for all batches and the disintegration time was recorded less than 38 seconds for all batches. The disintegration time of formulation B1 containing HPMC E15 was found to be lower (18 sec) and was selected as the best formulation among the remaining formulations. (Fig. 1)

In vitro Dissolution Studies of Films

In vitro dissolution studies of prepared sublingual films was performed in 6.8 phosphate buffer using USP dissolution apparatus type 1. Results showed all the batches release more than 88% of drug within 15 minutes. Formulations A1, B1, and B2 have shown drug release 93.03 ± 0.13%, 98.36 ± 0.33%, 95.03 ± 0.26% respectively, at the end of 15 min. Therefore, film formulated with HPMC E15 (B1) is best formulation. (Fig. 2).

TABLE 1

Formulation of films

Ingredients (mg)	Formulation code								
	A1	A2	A3	B1	B2	B3	C1	C2	C3
Salbutamol sulphate	37.38	37.38	37.38	37.38	37.38	37.38	37.38	37.38	37.38
HPMC E5	224.28	261.66	299.04						
HPMC E15				224.28	261.66	299.04			
HPMC E5 + HPMC E15							112.4 112.4	130.83 130.83	149.52 149.52
Maltodextrin	20	20	20	20	20	20	20	20	20
PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame	2	2	2	2	2	2	2	2	2
Flavour	2	2	2	2	2	2	2	2	2
Water (ml)	15	15	15	15	15	15	15	15	15

TABLE 2

Physical evaluation of films.

Formulation code	Thickness (mm)	Average weight (mg)	Disintegration time (sec)	Drug content (%)
A3	0.05 ± 0.11	16 ± 1.22	32 ± 0.03	97.9 ± 0.5
B1	0.07 ± 0.01	15 ± 1.01	18 ± 0.01	99.8 ± 0.40
C3	0.09 ± 0.21	16 ± 0.14	38 ± 0.1	99.1 ± 0.3

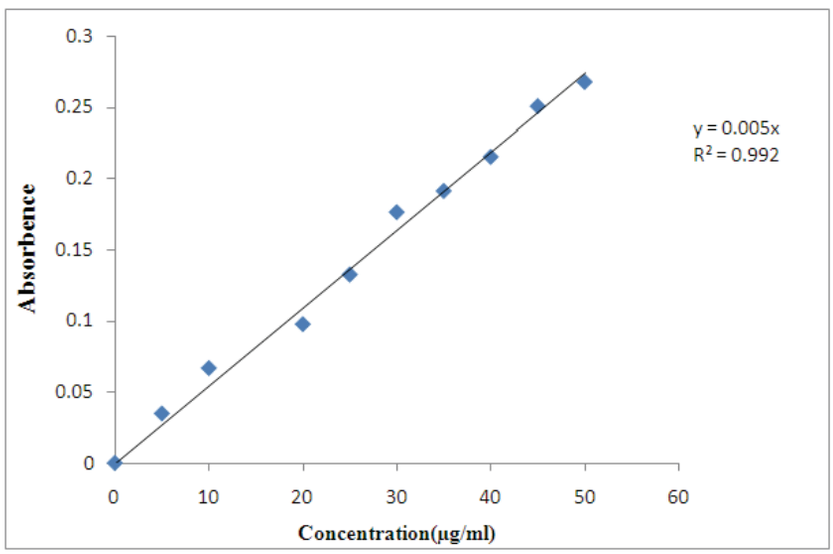

Fig. 1. Graphical representation of standard graph of Salbutamol Sulphate.

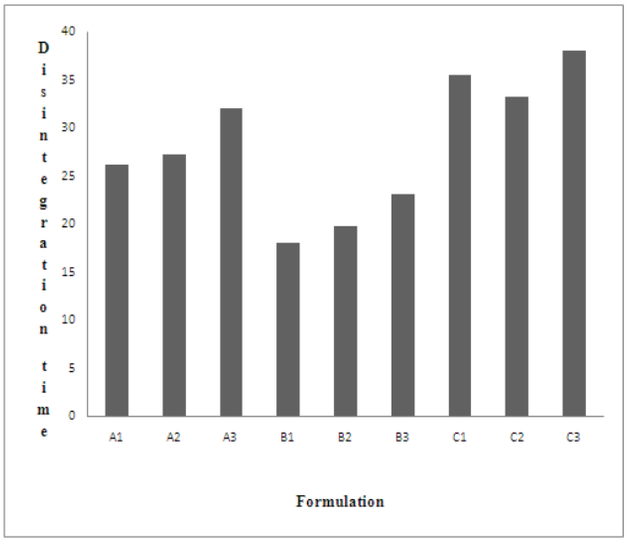

Fig. 2. Graphical representation of disintegration time.

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 mouth dissolving film increases. The folding endurance value of the prepared films ranged from 56 ± 2 to 116 ± 3 and results were formulated in (Table 3). The optimized film (B1) has folding endurance value of 116 ± 3, which was desirable.

TABLE 3
Values of Folding endurance and Surface pH

Code	Folding endurance	Surface pH
A1	56 ± 2	6.84 ± 0.1
A2	63 ± 1	6.65 ± 0.4
A3	99 ± 1	6.72 ± 0.5
B1	111 ± 5	6.64 ± 0.2
B2	116 ± 3	6.77 ± 0.1
B3	115 ± 1	6.78 ± 0.1
C1	104 ± 2	6.54 ± 0.3
C2	113 ± 1	6.71 ± 0.3
C3	106 ± 2	6.88 ± 0.2

Surface pH

Surface pH was conducted to all the formulations and was found to be in range of 6.8-7.2 and hence will not cause any irritation to oral mucosa (Patel et al., 2012). Results were formulated in (Table 3).

FTIR Studies

The drug-excipient compatability study was carried out using FTIR. The spectral data obtained showed that Salbutamol sulphate is compatible with all the excipients used in the formulation shown in Figure 3, 4, 5, 6, 7 and Table (4, 5).

Stability Studies

Stability studies were conducted following ICH guidelines following the temperature and humidity limitations. Obtained results are shown in (Table 6, 7, 8, 9).

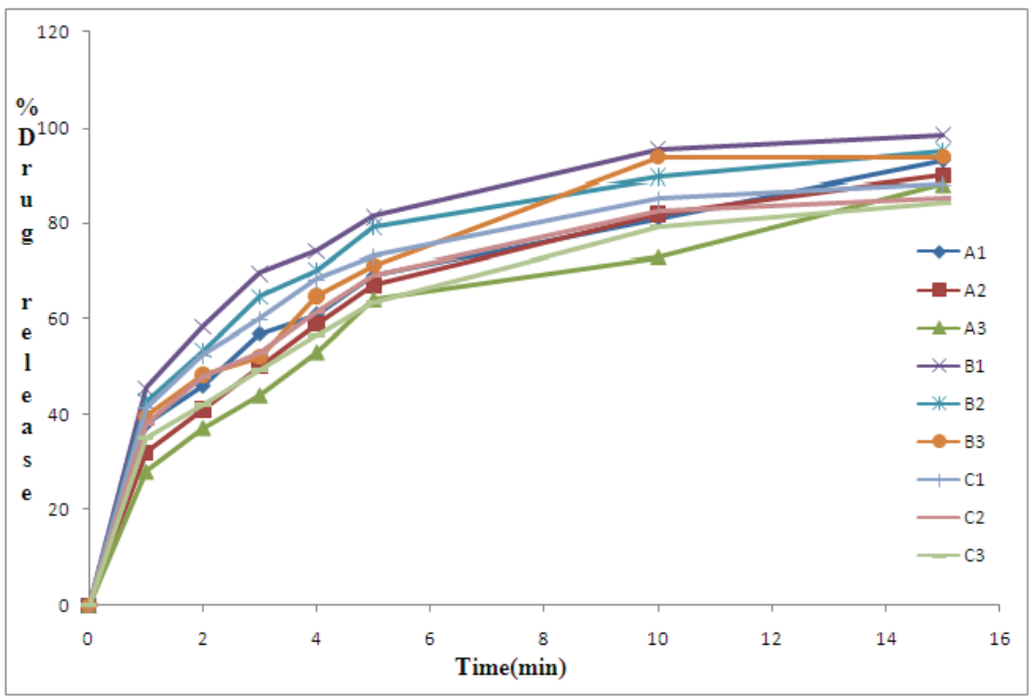

Fig. 3. Graphical representation of percentage drug release of salbutamol sulphate.

FTIR STUDIES

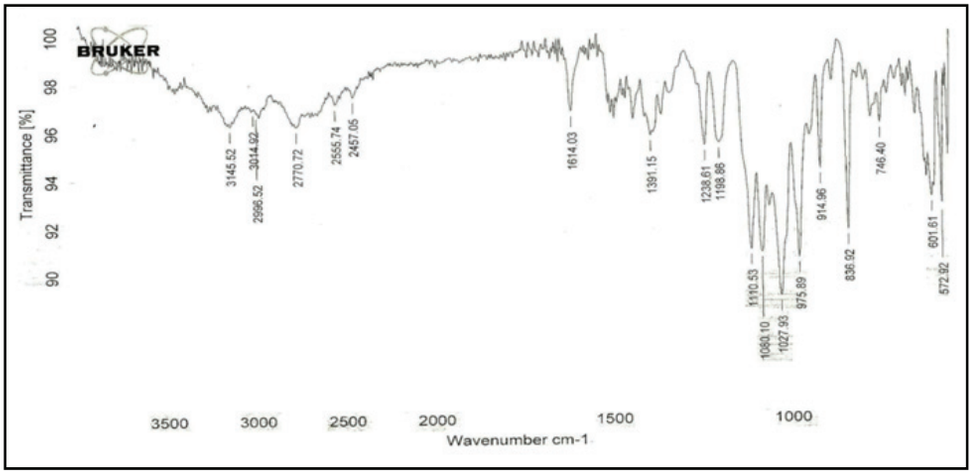

Fig. 4. IR Spectra of salbutamol sulphate.

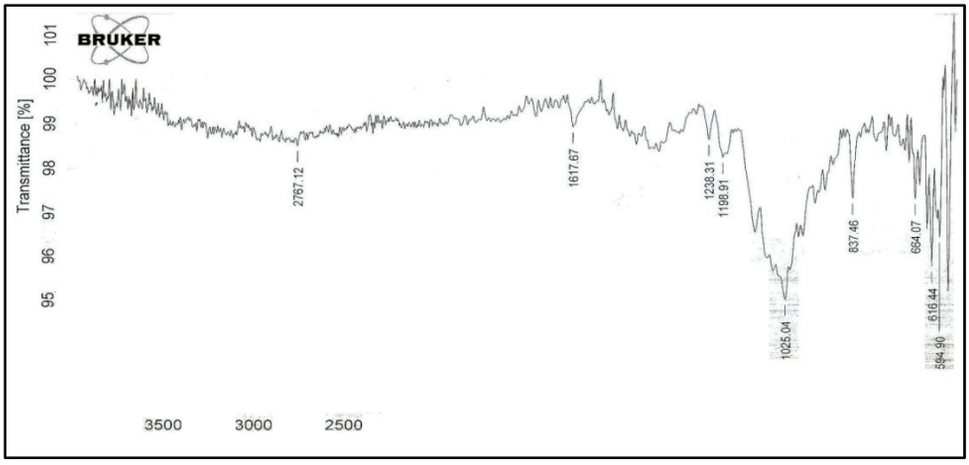

Fig. 5. IR Spectra of Drug+HPMC E15.

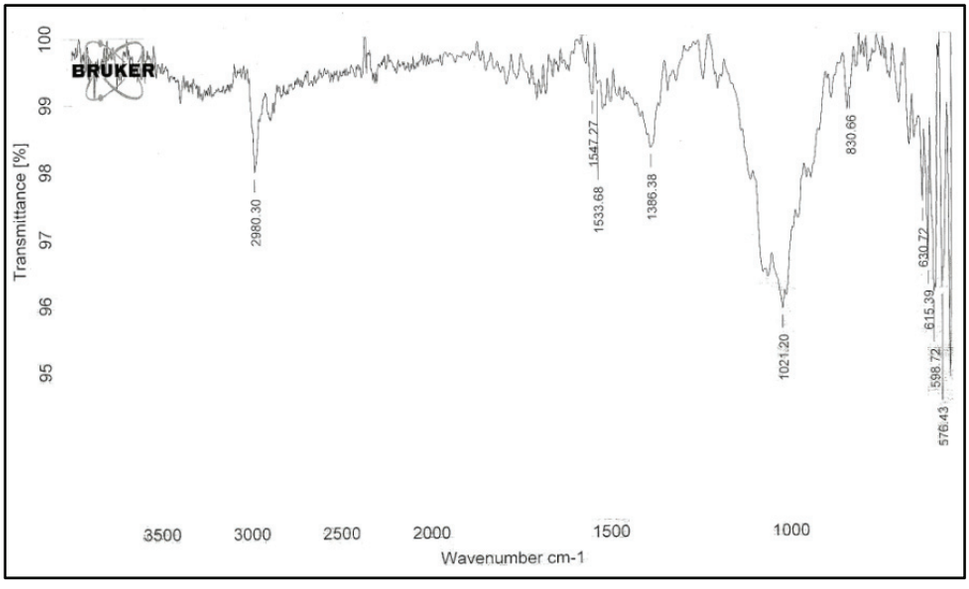

Fig. 6. IR Spectra of Drug+all excipients.

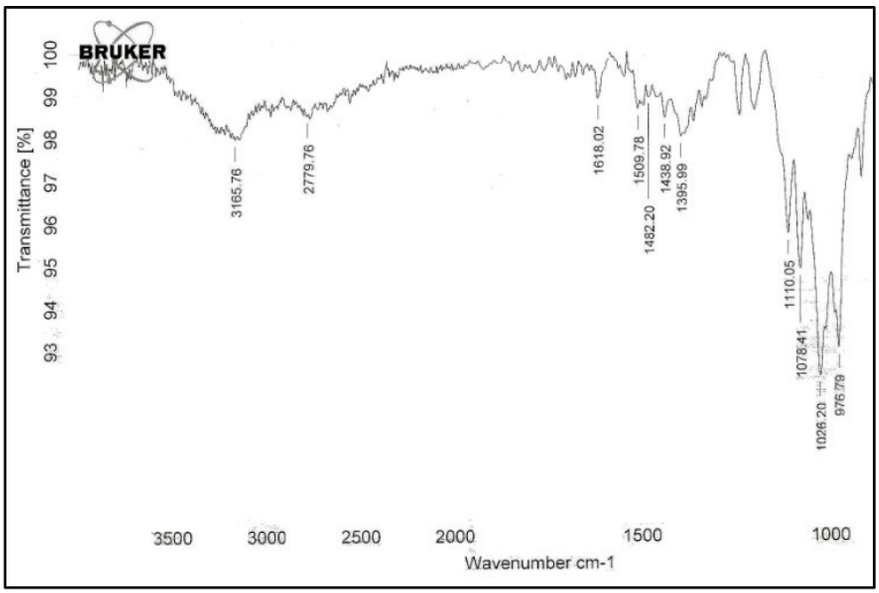

Fig. 7. IR Spectra of Drug +Maltodextrin.

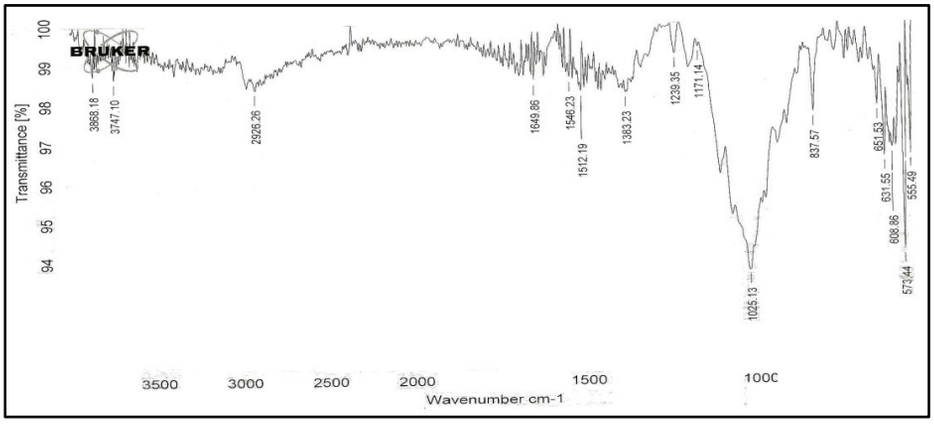

Fig. 8. IR Spectra of Drug+HPMC E5.

TABLE 4

Compatibility study of salbutamol with other excipients.

S.No.	Materials	Drug – excipient ratio	Physical description Initial	Results
1	Drug	-	White	
2	Drug + HPMC E15	1:1	White	Compatible
3	Drug + HPMC E5	1:1	White	Compatible
4	Drug + Maltodextrin	1:1	White	Compatible
5	Drug + All excipients	1:1	White	Compatible

TABLE 5

Values of FTIR spectra.

PEAK OF FUNCTIONAL GROUPS {WAVE LENGTH(cm-1)}				
IR Spectra	**O-H Stretching**	**C-O Stretching**	**C-H Stretching**	**N-H Streching**
Drug	3145	1438	836	3014
Drug + HPMC E 15	3145	1438	837	3014
Drug + MDX	3165	1438	837	3015
Drug + MDX + HPMCE15	s3155	1438	837	3014
Drug+All	3145	1438	830	3014

TABLE 6

Stability studies.

Storage Condition	Test Period
40°C± 2°C with RH 75%± 5%.	First month
	Second month
	Third month

TABLE 7

Stability studies for First month.

Formulation Code	Weight (mg)	Thickness (mm)	Disintegration time (sec)	Drug content
A1	15 ± 1.21	0.04 ± 0.21	26 ± 0.03	93.8 ± 0.37
A2	16 ± 0.11	0.05 ± 0.13	27 ± 0.3	97.3 ± 0.1
A3	16 ± 1.22	0.05 ± 0.11	32 ± 0.03	97.9 ± 0.5
B1	15 ± 1.01	0.07 ± 0.01	18 ± 0.01	99.8 ± 0.08
B2	17 ± 0.02	0.06 ± 0.11	19 ± 0.11	98.8 ± 0.40
B3	15 ± 2.1	0.08 ± 0.22	23 ± 0.21	98.8 ± 0.5
C1	16 ± 0.12	0.10 ± 0.14	35 ± 0.5	97.8 ± 0.1
C2	17 ± 0.13	0.12 ± 0.80	33 ± 0.2	98.4 ± 0.5
C3	16 ± 0.14	0.09 ± 0.21	38 ± 0.1	99.1 ± 0.3

TABLE 8

Stability studies for Second month.

Formulation Code	Weight (mg)	Thickness (mm)	Disintegration time (sec)	Drug content
A1	14.9 ± 1.21	0.04 ± 0.21	27 ± 0.03	93.4 ± 0.37
A2	15.8 ± 0.11	0.05 ± 0.13	26 ± 0.3	97.1 ± 0.1
A3	15.8 ± 1.22	0.05 ± 0.11	31 ± 0.03	97.6 ± 0.5
B1	15 ± 1.01	0.07 ± 0.01	19 ± 0.01	99.7 ± 0.08
B2	16.9 ± 0.02	0.06 ± 0.11	19 ± 0.11	98.6 ± 0.40
B3	14.8 ± 2.1	0.08 ± 0.22	24 ± 0.21	98.7 ± 0.5
C1	15.7 ± 0.12	0.10 ± 0.14	36 ± 0.5	97.7 ± 0.1
C2	17 ± 0.13	0.12 ± 0.80	33.7 ± 0.2	98.3 ± 0.5
C3	16 ± 0.14	0.09 ± 0.21	38 ± 0.1	99 ± 0.3

TABLE 9

Stability studies for Third month.

Formulation Code	Weight (mg)	Thickness (mm)	Disintegration time (sec)	Drug content
A1	14.8 ± 1.21	0.04 ± 0.21	27.3 ± 0.03	93 ± 0.37
A2	15.7 ± 0.11	0.05 ± 0.13	27 ± 0.3	97 ± 0.1
A3	15.6 ± 1.22	0.05 ± 0.11	32 ± 0.03	97.9 ± 0.5
B1	14.9 ± 1.01	0.07 ± 0.01	19.5 ± 0.01	99.5 ± 0.08
B2	16.8 ± 0.02	0.06 ± 0.11	19.8 ± 0.11	98.5 ± 0.40
B3	14.7 ± 2.1	0.08 ± 0.22	24.8 ± 0.21	98.5 ± 0.5
C1	15.8 ± 0.12	0.10 ± 0.14	36.5 ± 0.5	97.6 ± 0.1
C2	16.9 ± 0.13	0.12 ± 0.80	33.9 ± 0.2	98.1 ± 0.5
C3	15.8 ± 0.14	0.09 ± 0.21	38.5 ± 0.1	99 ± 0.3

Conclusions

Salbutamol sulphate films were prepared by solvent casting method using HPMC-E15 in various ratios like 1:6, 1:7, and 1:8. Among the all formulations, the formulation containing HPMC-E15 (1:6) resulted a least disintegration time of 18sec and a higher drug release of 98.89% in 15 minutes.

Taste masking of the films was also carried out by using Aspartame as a sweetener and vanilla as a flavoring agent. Usage of Aspartame resulted in the complete masking of the metallic taste of Salbutamol sulphate and hence, improved the patient compliance.

Based on disintegration and dissolution results, formulation B1 was the best one from prepared Sublingual film formulations. Sublingual films of Salbutamol sulphate were formulated with an aim to improve the versatility, convenience, patient compliance leading to an enhanced approach for the administration of drug to the pediatrics and geriatrics.

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