ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Development and Characterization of an Orodispersible Film Containing Terbutaline Sulphate.

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ABSTRACT

The aim of present research was to develop a fast releasing oral film avoiding first pass metabolism and thus improving bioavailability of Terbutaline Sulphate with good mechanical properties, fast disintegration and dissolution, producing an acceptable taste when placed on tongue. Terbutaline sulphate, an anti-asthmatic, was incorporated to relieve the symptoms of acute asthma. Solvent casting method was used to prepare oral films.The polymers selected were HPMC E 15, Sodium alginate and PVP K-30 and sorbitol as a plasticizer. Drug-excipient compatibility study was was carried out. Different batches of films were prepared using different combinations and concentrations of polymers by using solvent casting method. The resultant films were evaluated for tear resistance, folding endurance, thickness, surface pH, moisture content, transparency, swelling test, in vitro disintegration and dissolution. Most efficient film was of 4% HPMC E 15.The selected film which was disintegrated in less than 3 minutes and releasing 100% of drug within 5 minutes..There were no interference found between drug and excipients. Scanning Electron Microscopy was done to check the surface topography of the film. The selected film was found to beporous . X-ray Diffraction was done to check the crystallinity of the film.X-ray spectra of the film shows the formation of the amorphous structure leading to increasing the solubility of the drug.

Keywords: Differential Scanning Calorimetry ,Fast releasing oral film , Scanning Electron Microscopy,Terbutaline Sulphate , X-ray Diffraction.

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ISSN: 0975-8585

INTRODUCTION

Terbutaline Sulphate is a selective β2 receptor agonist which is widely used as bronchodilator. Commercially, it is available in formulations for Syrup, inhalation, and injection. In healthy subjects the bioavailability of oral Terbutaline Sulphate is 14−15%. This low bioavailability is due to various factors, including stereoselective absorption, but the main factor is hepatic first pass metabolism.[1] Food impairs the bioavailability by about one third because of reduced absorption.[2] Terbutaline Sulphate is available commercially in Egypt as syrup, conventional tablets, and inhalation. Drug delivery via oral mucousa is a promising alternative to the oral route for avoiding presystemic metabolism or instability in the GIT. The relatively less thickness and the higher blood flow of the sublingual area of the oral cavity makes it more permeable than the buccal and palatal areas.[3,4] In some cases, the sublingual route provides an alternative to invasive intravenous dosing if rapid delivery to the systemic circulation is required. It is safer and more comfortable for the patient.[5] Sublingual pharmaceuticals are acceptable as drug delivery systems for patients with swallowing problems. Furthermore, sublingual drug administration is simple and relatively cost effective. [6,7] Fast dissolving films have several advantages over the conventional dosage forms. They are of great importance during the emergency cases whenever an immediate onset of action is desired. [8]

The recent literature survey showed that only one method was reported for formulation and evaluation of sublingual film containing Terbutaline sulphate [9].Some methods were reported for formulation and evaluation of Terbutaline sulphate as a tablet and transdermal system [10,11]. Several methods were reported for formulation and evaluation of Mosapridefilm, Ondansatron film, Ranitidine and salbutamol films respectively [12-15]. Several review articles of fast dissolving films were also referred [16-19].

This work aimed to formulate Terbutaline Sulphate as orodispersible films to improve its bioavailability and to improve patient compliance. A fast dissolving property could help in the management of acute asthmatic attacks.

MATERIALS AND METHODS

The materials and suppliers were as follows: Terbutaline Sulphate (ZydusCadila healthcare Ltd. Ahmedabad); Hydroxypropyl methylcellulose (HPMC E15) purchased from s d fine-chem limited (Mumbai), Sodium alginate supplied from central drug house (new Delhi.), Polyvinylpyrrolidones (PVP K-30) from s d fine-chemlimited (Mumbai), Sorbitol supplied from Research lab fine chem industries (Mumbai), Potassium dihydrogenorthophosphate (KH_2PO_4) supplied from MerkPvt. Ltd (Mumbai), Sodium hydroxide (NaOH) supplied from Rankem lab (Delhi).

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Compatibility Studies of Terbutaline Sulphate with the Suggested Excipients:

Ultraviolate spectroscopy, Fourier transform infrared spectroscopy (FT-IR) studies were conducted to screen excipients commonly used asfilm forming polymers and plasticizers for drug compatible ones. Solid state characterization was done for Terbutaline Sulphate, each excipient, and 1:1 physical mixtures of drug-excipient.

Differential Scanning Calorimetry (DSC Study)

Samples (2.0 mg) were placed in aluminium pan and heated in the rate of 10 ˚C/min, to a temperature of 300 ˚C (differential scanning calorimeter DSC-50,). The instrument was calibrated with indium, and dry nitrogen was used as a carrier gas with a flow rate of 25 mL/min.

Compatibility study by using IR spectrophotometer

The IR spectra were recorded for drug, polymers and film discs after grinding with about 100 mg of dry KBr powder and compression.

Spectroscopic analysis ofTerbutaline sulphate:

In the present work, Terbutaline sulphate was estimated by UV-Visible Spectrophotometric method using distilled water.

Determination of UV absorption maxima

Solution of Terbutaline sulphate (10µg/ml) was prepared in the distilled water. The solution was scanned for absorbance between 200-400 nm using spectrophotometer. Terbutaline sulphate exhibits UV absorption maxima at 282 nm.

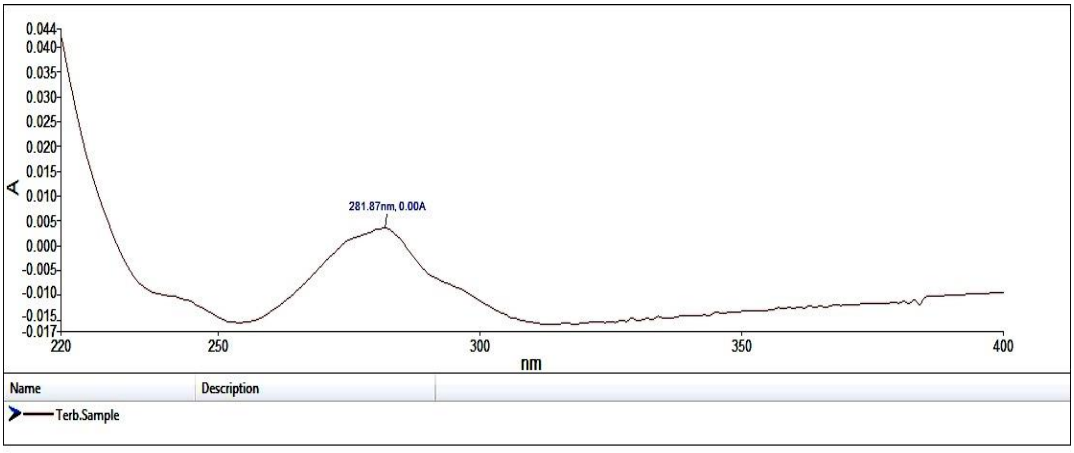

Fig.1 : Wavelength maxima for Terbutaline sulphate

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Preparation of standard curve

Stock solution of 100 µg/mlTerbutaline sulphate was prepared. Aliquots of the stock solution were serially diluted with distilled water to 10 ml to get 2, 4, 6, 8, 10 µg/ml concentrations. The absorbance was measured at 282 nm against distilled water as a blank. The results are shown in Table 3. The data were subjected to weighted linear regression analysis.

UV absorbance was measured for drug – excipients solutions and compared it with that of pure drug solution absorbance.

Preliminary Experiments:

Experiments were done to determine the optimum concentration of each polymer .For each polymer, a series of different concentrations was tested at a fixed plasticizer 1%. The total preparation volume was fixed at 30 mL, The tested concentrations were 3, 4, 5 g/plate for HPMC E15, PVA, Sodium alginate.Different polymer combinations were also tried, and the obtained films were evaluated for their appearance, colour, elegance, continuity, texture, presence of air bubbles, stickiness to Petri dish, cracks, cuttings, and imperfections.

Preparation of Terbutaline SulphateOrodispersible Films.

Table 1. Composition for the Prepared Terbutaline Sulphate Sublingual Fast Dissolving Placebo Films

Ingredients	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13
	% w/w												
HPMC E15	3%	4%	5%	-	-	-	-	-	-	3%	2%	2%	-
Sodium Alginate	-	-	-	3%	4%	5%	-	-	-	1%	2%	-	2%
PVP K30	-	-	-	-	-	-	3%	4%	5%	1%	-	2%	2%
Sorbitol	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Water	96%	95%	94%	96%	95%	94%	96%	95%	94%	94%	95%	95%	95%

According to dose of Terbutaline sulphate (2.5 mg), amount required for film of 70.1 cm^2 area was calculated so that each portion of 3 cm × 2 cm will contain the required dose.Films of single polymer and their combinations were prepared by solvent casting method. The polymer was dissolved in 30ml distilled water. The solution was stirred for 20 min using glass rod and was kept undisturbed till the entrapped air bubbles were removed. Drug was dissolved in 20 ml of distilled water and plasticizer was added in drug solution. This aqueous solution was added to the polymer solution. The final solution was stirred for 10 min by using glass rod and was kept undisturbed till the entrapped air bubbles were removed. The final solution was casted in a petridish having 70.1 cm^2 surface area and was dried at room temperature or in Oven at 50 ˚C. The film took approximately 48 hr to dry at room temperature and 10 to 12 hours in Oven. The dried films were carefully removed from the petridish and was cut into size required for testing. The films were stored in airtight plastic bags till further use.

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Table 2: Composition of the Selected film

Ingredients	Strength
Terbutaline Sulphate	0.03%
HPMC	4%
Sorbitol	1%
Distilled water	Q.S to 100%

***In Vitro* Characterization of the Prepared Films: [20-25]**

Visual Inspection: The prepared films were tested visually for their appearance, colour, and elegance, as well as for drug precipitation, air bubble entrapment, or cracks. The ease of removal from the Petri dish was also evaluated.

Film Thickness Uniformity: The thickness of the prepared films was measured at five places (centre and four corners) using Vernier Caliperand the mean thickness and % RSD were calculated.10

Determination of Tear resistance: The maximum stress applied to a point at which the film specimen breaks. It was measured at laboratory.

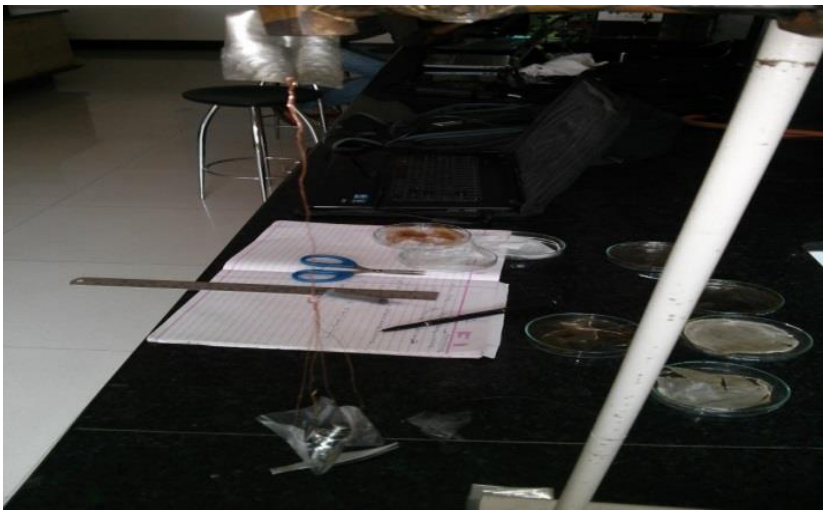

Fig 2: Measurement of Tear Resistance

***In Vitro* Disintegration Time:** The *in vitro* disintegration time was measured (n=3) for film of each batch in 20 ml of Phosphate buffer (pH 6.8). Film sample (2 cm x 2 cm) was placed in 20 ml of Phosphate buffer (pH 6.8). The medium was kept mildly agitated using a magnetic stirrer. The time for complete disintegration of the film was recorded as disintegration time. The average of three measurements was taken into consideration.

Determination of Moisture Content: Moisture content of the freshly prepared films wasdetermined using a Karl Fischer Titrator apparatus 787KF Titrino. Films were pulverized,

inserted in the titration vessel containing dried Karl Fischer grade methanol, and titrated with Hydranal composite 5 reagent . % moisture content was measured.

Measurement of folding endurance:

Folding endurance was determined by repeatedly folding the film at the same place till it break. The numbers of times the film can be folded at the same place without breaking give the value of folding endurance.

***In Vitro* Dissolution Study:**

The dissolution study was carried out using USP I basket apparatusat 37˚C ± 0.5˚C using 300 ml of phosphate buffer (pH 6.8) as a dissolution medium. The agitation rate of basket was 50 rpm. The drug loaded film (2cm× 2cm) was hanged in the basket. 3.0 ml samples were withdrawn at 5 , 10 , 15 , 20 , 25 , 30 minute time and were filtered through whatman filter paper and analysed spectrophotometrically at 282nm. An equal volume of the fresh dissolution media, maintained at the same temperature, was added after withdrawing the sample to maintain the volume.

Transparency: It was measured be putting a 3*2 film inside the UV cell and took the transmittance at 600 nm. %T was calculated.

pH: It was measured by putting a wetted film (wetted with water) on the pH strip and colour change of the pH strip was observed .

Swelling test: It was measured be putting a 3*2 film in the glass cylinder of 50 ml. took distilled water in the cylinder up to 40 ml. then the cylinder was kept aside at room temperature . The level of the water at the end of 5 minutes was observed. Difference in the level of water after 5 minutes was calculated.

Scanning Electron Microscopy: SEM was done by using Flex Scan F520 instrument. 15 KV electro beam was passed to the sample and surface of the film was observed.

X-ray Diffraction: It was done by using PANALYTICAL X'Pert PRO instrument. The sample was placed in an aluminium pan and passed X-rays in the range of 5 to 60 at 2thita angle. The Spectra was observed and compared with that of pure Terbutaline drug.

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RESULTS AND DISCUSSION

Spectroscopic Analysis of Terbutaline Sulphate

Table 3: Results of Spectrophotometric analysis of Terbutaline sulphate

Concentration(µg/ml)	Absorbance
2	0.016
4	0.033
6	0.052
8	0.068
10	0.083

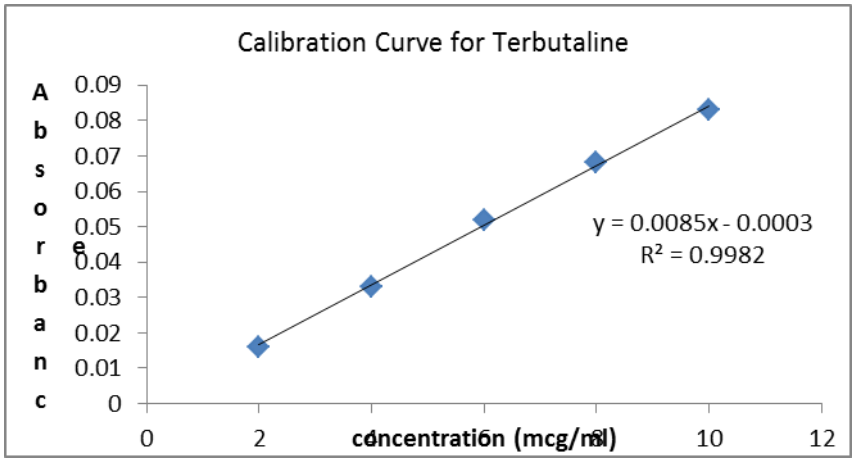

Fig. 3: Calibration curve for Terbutaline sulphate

Results of DSC study:

The DSC thermogram of terbutalinesulphate containing orodispersible filmwas measured. No endothermic peak corresponding to its melting point was observed which proving the absence of physical interaction between drug and all the tested excipients.

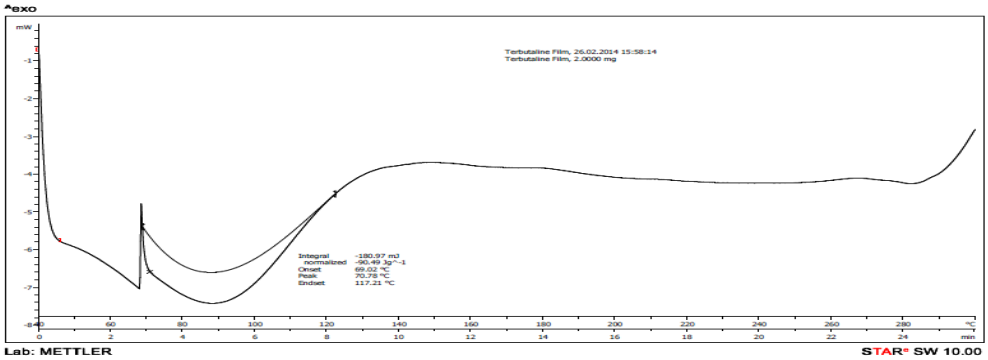

Fig 4: DSC thermogram of Terbutaline orodispersible film.

ISSN: 0975-8585

Results of Compatibility studies by Infrared spectroscopy

Similarly, the characteristic IR absorption peaks of Terbutaline were persistent in the drug/excipients physical mixtures. No extra peaks were observed in such IR spectra, showing no chemical interaction and indicating good drug excipients compatibility.

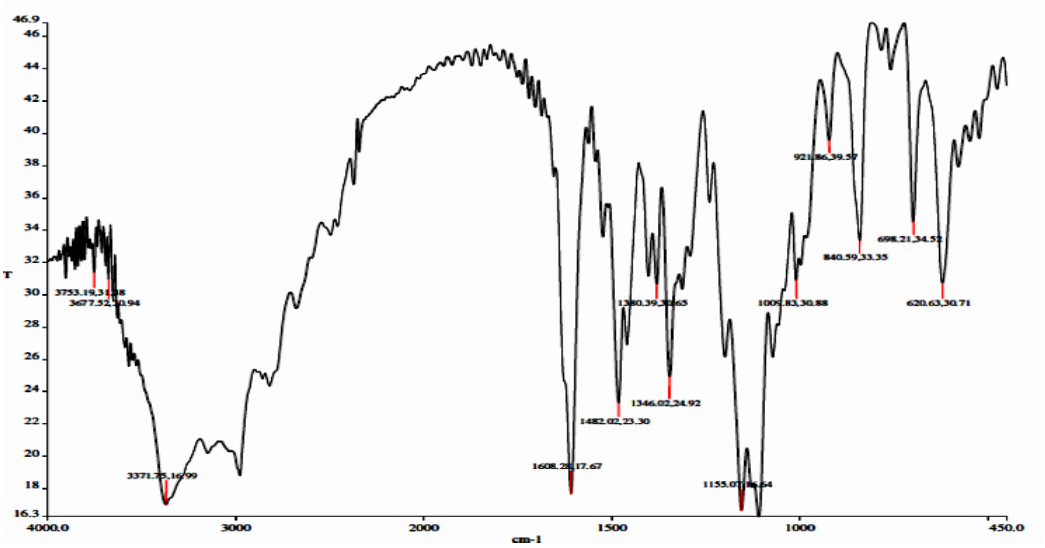

Fig 5: IR spectra of Terbutaline sulphate API

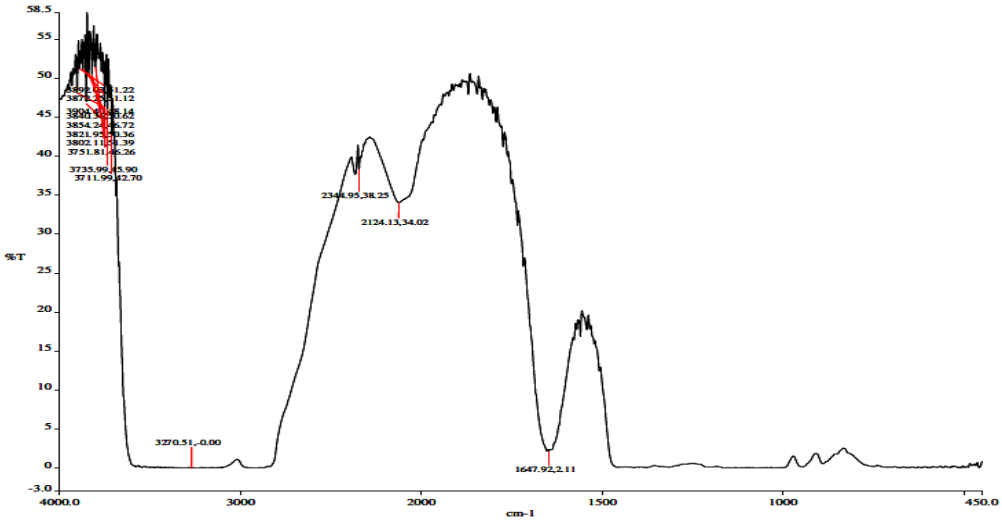

Fig 6: IR spectra of Terbutaline Orodispersible film

Observation: There were no interference of excipients found.

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DISCUSSION

It was found that all the functional groups which were appear in the IR spectra of Terbutaline Sulphate film that were of same present in the IR spectra of pure Terbutaline drug.

Table 4 Results of Compatibility studies by UV Spectrophotometer:

Days	HPMC + API at RT.		HPMC + API at Refrigerator		HPMC + API at Stability chamber	
	Absorbance	Amount of drug (%)	Absorbance	Amount of drug	Absorbance	Amount of drug
1	0.079	95.1	0.083	100	0.083	100
2	0.081	97.5	0.079	95.1	0.080	96.3
3	0.081	97.5	0.084	101.2	0.081	97.5
4	0.080	96.3	0.081	97.5	0.081	97.5
5	0.079	95.1	0.085	102.4	0.079	95.1
6	0.081	97.5	0.079	95.1	0.078	93.9
7	0.082	98.7	0.082	98.7	0.081	97.5
8	0.084	101.2	0.083	100	0.079	95.1
9	0.079	95.1	0.083	100	0.083	100
10	0.081	97.5	0.080	96.3	0.084	101.2
11	0.083	100	0.079	95.1	0.081	97.5
12	0.080	96.3	0.083	100	0.085	102.4
13	0.079	95.1	0.081	97.5	0.083	100
14	0.082	98.7	0.080	96.3	0.078	93.9
15	0.080	96.3	0.079	95.1	0.080	96.3

Observation: There were no interference of excipients found.

Discussion: Compatibility data was compared with the standard drug. It was found that there was no such difference after 15 days storage.

Preliminary Experiments.

Table 5: Results of Evaluation parameters for Placebo films

Parameters	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13
Tear Resistance (gm)	-	18.57	26.19	-	20.47	27.87	-	-	-	-	45.72	-	38.37
Thickness (upper) mm	-	0.07	0.05	-	0.06	0.04	-	-	-	-	0.06	-	0.08
Thickness (middle) mm	-	0.07	0.05	-	0.06	0.04	-	-	-	-	0.06	-	0.08
Thickness (lower) mm	-	0.07	0.05	-	0.06	0.04	-	-	-	-	0.06	-	0.08
Disintegration time (min)	-	3.4	3.8	-	3.5	3.9	-	-	-	-	3.1	-	3.3
pH	-	7	7	-	7	7	-	-	-	-	7	-	7

Moisture %	-	14.8	8.8	-	10.0	6.0	-	-	-	-	9.4	-	16.7
% transmittance	-	84.4	60.3	-	54.7	58.7	-	-	-	-	3.1	-	40.9
Folding endurance	-	967	945	-	776	3	-	-	-	-	4	-	5
Swelling (ml)	-	0.2	0.3	-	0.2	0.1	-	-	-	-	0.1	-	0.3

Table 6: Results of Selected Oro Dispersible Film of Terbutaline Sulphate (A2)

Parameters	Results
Tear Resistence (gm)	98.5
Thickness (upper) mm	0.04
Thickness (middle) mm	0.04
Thickness (lower) mm	0.04
Disintegration time (min)	3.1
pH	7.0
Moisture %	6.0
% transmittance	85.5
Folding endurance	917
Swelling (ml)	0.1
% Drug release(5 min) n=3	100.3%

Observations:

A1: Film was not peelable from the Petri plate.
A2: Film was easily peelable and passed all the criteria.
A3: Film was easily peelable but the transparency of the film was not good enough.

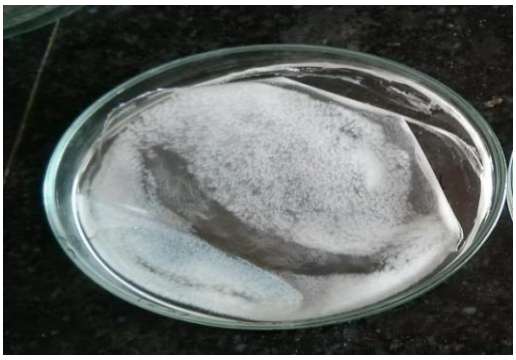

Fig 7: Image of Film Containing composition of A3

A4: Film was not peelable from the Petri plate.
A5: film was peelable but transperancy was not good enough.

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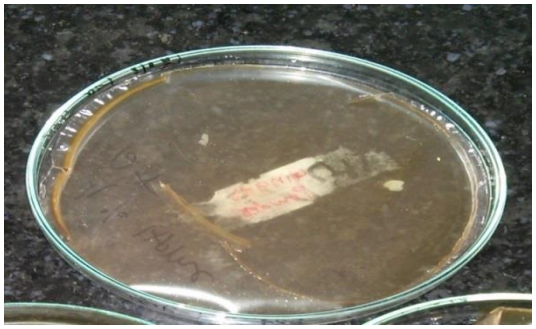

Fig 8: Image of Film Containing composition of A5

A6: film was peelable but folding endurance not passed and transparency was also not good.

Fig 9: Image of Film Containing composition of A6

A7 , A8, A9, A10: Films were not formed.

Fig 10: Image of Film Containing composition of A7 , A8 , A9.

Fig 11: Image of Film Containing composition of A10

A11: Transparency of the film was not good enough and folding endurance not passed.

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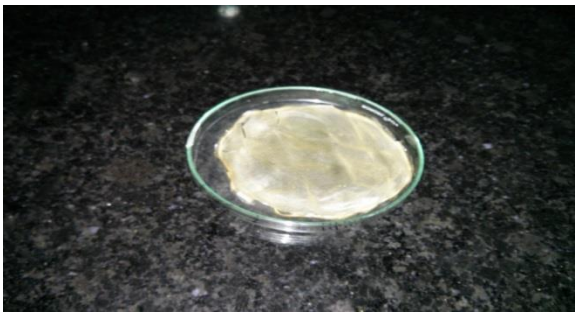

Fig 12: Image of Film Containing composition of A11

A12: film was not formed.

Fig 13: Image of Film Containing composition of A12

A13:Transparency of the film was not good enough and folding endurance not passed

Fig 14: Image of Film Containing composition of A13

Table6 : Results of Selected Oro Dispersible Film of Terbutaline Sulphate (A2)

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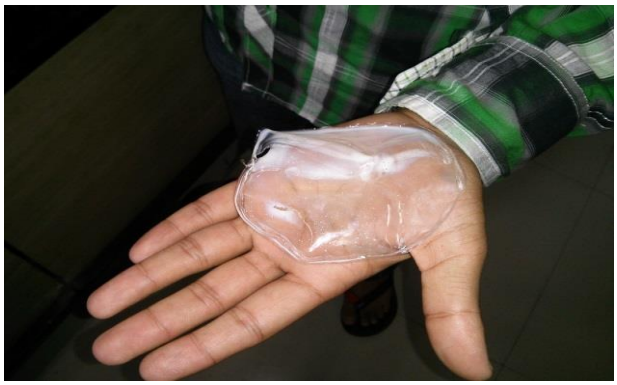
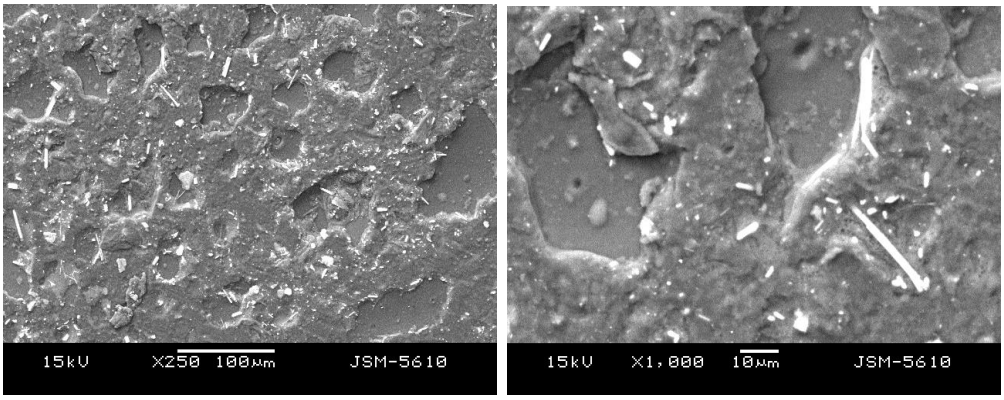


Fig 15: Image of Selected Film dried in Oven

Fig 16: Image of Selected Film dried at controlled room temperature

Discussion: Thirteen **t**rials of placebo films containing different polymers and concentrations were evaluated. From that it was found that placebo Film containing A2 formula passed all the criteria regarding to the evaluation parameters so that A2 film was selected. Selected film was prepared again by adding the terbutaline sulphate. & evaluated (3*2 film) all the parameter. It was found that all the criteria passed. After that Assay and Dissolution study was carried out and it was found that all drug content was released within the 5 minutes.

Scanning Electron Microscopy:



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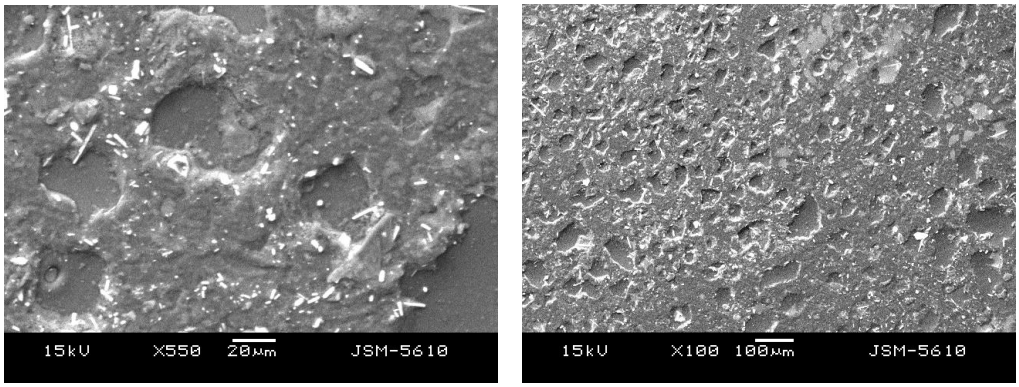

Fig. 17: Images of Scanning Electron Microscopy of film.

Observation: Images of SEM of film showed that the film was found to be porous . Surface of the film was rough and thickness uniformity varies.

Discussion: The film was found porous due to the air entrapment. Actually the porosity and rough surface helped the film to release its content as fast as possible.

X-ray Diffraction:

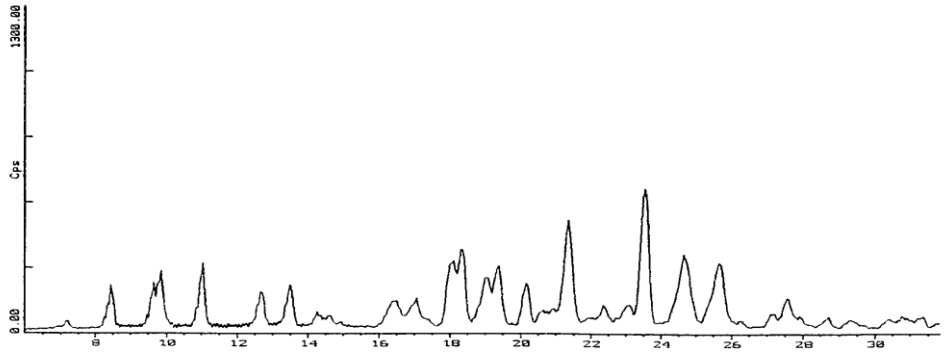

Figure 6c

Fig. 18: X-ray spectra for Terbutaline pure drug

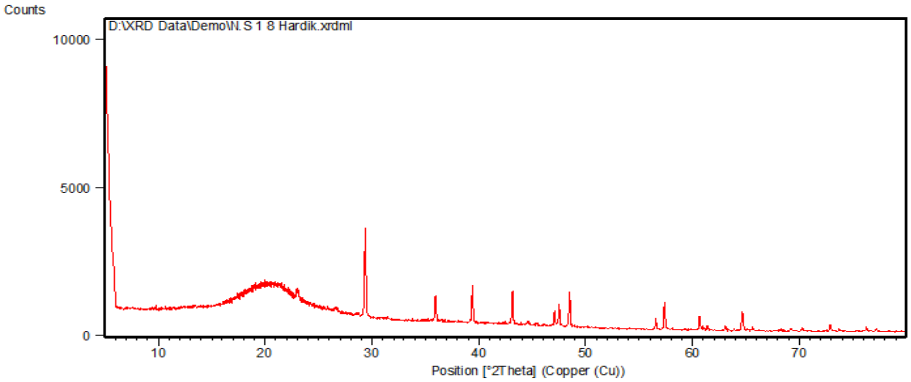

Fig. 19: X-ray spectra for Selected Terbutaline Film

The intensity of the peaks in the X-ray spectra of Selected film shows the formation of the amorphous structure of the drug that leads to the increasing the solubility of the drug.

CONCLUSION

Terbutaline Sulphate films were successfully prepared using affordable excipients and an easy reproducible method of preparation. A sublingual route of delivery is promising for avoiding the metabolism of the drug in the gut wall and liver. The fast disintegration and dissolution introduces the optimized film formula as a promising convenient delivery system for the management of acute episodes of asthma.

ACKNOWLEDGEMENT

The authors are thankful to Zyduscadila Healthcare Pvt. Ltd., Ahmedabad for the gift sample of Pure Terbutaline Sulphate.

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