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Formulation, And Evaluation of Fast Dissolving Sublingual Films Ofterbutaline Sulphate

Ms. Reena Thakur, Rupali, Shivali Singla, Sachin Goyal
Assistant Professor, HOD Associate Professor
Department of M. Pharm (Pharmaceutics)
Himalayan Institute of Pharmacy, Kala-Amb, Himachal Pradesh-173030, India
Corresponding author's email id: *reenathakur511@gmail.com*

Abstract

Terbutaline sulfate fast dissolving sublingual films were prepared using drug compatible film formers in different combinations and proportions. The film polymers are maltodextrin, HPMC E15, PVP K-25. Propylene glycol and sorbitol were used as plasticizers and mannitol as filler. The optimum polymer concentrations and the plasticizer amount were selected on the basis of flexibility, tensile strength, and stickiness of the films. The prepared films were evaluated for their tensile strength, thickness uniformity, disintegration time (in vitro), in vitro dissolution, and moisture content. Polymer type rather than total polymer concentration or plasticizer amount showed a significant effect on the tested film properties Sublingual films could be promising as a convenient delivery system for terbutaline sulfate in patientswith swallowing problems. Among all, the formulation F9 showed release up to 97.8% of the drug in 10 min.

Keywords: *sublingual; convenient delivery; swallowing; tensile strength*

INTRODUCTION

The oral route of drug administration is the most common and suitable for patient use. Tablets and capsules are the most popular conventional solid oral dosage form. However, many patients have complexity in swallowing of tablets and hard gelatin capsules and therefore do not take medication as prescribed by physicians.[1]

Novel oral drug delivery systems have advantage to dissolve or disperse quickly in a few seconds after placement in the

mouth without water can improve the problem of swallowing tablets[2]. Fast dissolving films have many benefits over the conventional dosage forms.[3] They are more suitable to administer, and improved patients compliance who have difficulty in taking tablets also have great importance during the emergency cases whenever an immediate onset of action is desired. A fast dissolving property could help in the management of acute asthmatic attacks.

Asthma is a disorder in which patient get attack in which bronchi constricts making it difficult to swallow a solid content[5]. Asthma is incurable so patient need to take medicine for preventive measure daily, now dosage form which don't need water and which can be consumed anywhere without water will make it easy for patient. Terbutaline sulphate is a selective β2 adreno receptor agonist widely used in the acute and chronic treatment of bronchial asthma, chronic bronchitis, emphysema and other obstructive lung diseases.[6] In healthy subjects the bioavailability of oral terbutaline sulfate is 14−15%. This low bioavailability is due to various factors, including stereoselective absorption, but the main factor is hepatic first pass metabolism. Food impairs the bioavailability by about one third because of reduced absorption.[7]

Drug delivery via the oral mucous membranes is a promising alternative to the oral route for avoiding presystemic metabolism or instability in the GIT. [8] The relatively less thickness and the higher blood flow of the sublingual area of the oral cavity make it more permeable than the buccal and palatal areas. [9, 10]

Fast dissolving film have got all advantages of tablets, but in addition to it, it is easy to swallow and preferable for paediatric and geriatric patients (ease of application).It leads to precise dosing, rapid bioavailability, easy application (no need of water), easy to carry. [11]

The fast dissolving sublingual film of terbutaline sulphate will disintegrate into the mouth and the saliva containing the TBS is then partially swallowed and the drug is absorbed in the normal way. Higher sublingual mucosal permeability leads to more and more drug will directly reaches to the systematic circulation via huge blood supply as well as absence of organized lipid lamellae in the intercellular spaces of the non keratinized oralsublingualmucosa and Some fraction of the drug may be absorbed from pregastric sites such as the mouth, pharynx, and esophagus as the saliva

passes down into the stomach. In these cases, the bioavailability of drugs from fast dissolving sublingual film may be greater compared to the standard oral dosage forms.[12,13]

This work aimed to formulate terbutaline sulfate as sublingual films in a trial to improve its bioavailability and to improve patient compliance.

EXPERIMENTAL SECTION

Materials - The materials and suppliers were as follows: terbutaline sulfate (AMercuryLab Pvt. Ltd., Baroda); Maltodextrin from Lincolnpharma Pvt Ltd, Aspartame- from Himedia Laboratory Pvt.Ltd, Mumbai, India, PVP K30 from S. D. Fine Chemicals Ltd. Mumbai, India, HPMC E15 from Torrent pharmaceutical Ltd., Citric acid, Ammonium acetate, Potassium-di-hydrogen phosphate, Sodium Hydroxide supplied from Finar Chemicals Ltd. Ahmedabad, India.

Compatibility Studies of Terbutaline Sulfate with the Suggested Excipients

Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR) studies were conducted to screen excipients commonly used as film forming polymers and plasticizers for drug compatible ones. DSC study was performed for Terbutaline sulphate and physical mixture of al lingredients of optimized film. (HPMCE15+CitricAcid+Aspartame+Drug. Samples (2−4 mg) were placed in aluminum pan and heated in the rate of 10 °C/min, to a temperature of 300 °C (DSC TA-60WS). The instrument was calibrated with indium, and dry nitrogen was used as a carrier gas with a flow rate of 25 mL/min. The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch were measured using Fourier transform infrared spectrophotometer (Model FTIR-8400S, Shimadzu, Japan).

Preparation of Terbutaline Sulfate Sublingual Films

The solvent casting technique was used for preparation of fast-dissolving sublingual films of terbutaline sulfate.[14] Aqueous solutions were prepared by dissolving the specified polymer(s) amounts by magnetic stirring. Amount and composition of casting solution remained Constant (15ml) but the drying rate can be changed by altering the drying temperature as well as drying time, so we considered these two variables, drying time and drying temperature. The plasticizer, the filler (mannitol), and the drug were then added and mixed. The obtained solutions were

casted onto plastic Petri dishes, previously cleaned, and dried. Prepared nine batches at three different temperature (room temperature (30°C), 55°C and 80°C) and time period of drying (10, 20 and 30 hrs) of final formulation. The obtained solutions were casted onto plastic Petri dishes, previously cleaned, and dried. Plates were kept in oven at 50°C for 24 h. Dried films were carefully removed, checked for any imperfections, and cut into squares of different dimensions for further characterizations using sharp razor blade. They were individually sealed in airtight packets and stored at 25 °C until use.[15]

EVALUATION OF THE FAST DISSOLVING FILM

Separability

The ease of film separation from the mould (separability) and in vitro dissolving time were considered for the selection of best film from various batches prepared (preliminary batches) as well as for the selection of the polymer for further studies.[16]

Table 1 Formulation composition of batches

Ingredients	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Terbutalinesulphate (mg)	68	68	68	68	68	68	68	68	68
HPMCE 15 cps(%W/V)	1.75	1.75	1.75	2.25	2.25	2.25	2.75	2.75	2.75
Glycrol(% w/wof polymer)	15	20	25	15	20	25	15	20	25
Citricacid(%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame(%w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Applegreencolour	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Distilled water	Up to15 ml								

Thickness of film

The thickness of each sample was measured using a micrometer (Digimatic Micrometer, Mitutoyo, Tokyo, Japan) at five locations (center and four corners),

and the mean thickness calculated.[16]

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.[17]

Drug content uniformity

The film unit (n=3) of the dimensions 2cm×2cm was placed in 100ml of distilled water. After complete solubilization, the solution was diluted appropriately, filtered and analyzed by HPLC. The average of three films was taken as the content of drug in one film unit. [17]

Measurement of in vitro disintegrating

The invitro dissolving time was measured (n=3) for film of each batch in 20ml of simulated saliva (pH6.8) in glass petri dish. Film sample (2cmx2cm) was placed in 20ml of simulated saliva. The medium was kept mildly agitated using a magnetic stirrer. The time for complete dissolution of the film was recorded as dissolving time. The average of three measurements was taken into consideration.[18]

In Vitro Dissolution Study

The dissolution study was carried out using USP paddle apparatus (Model TDT-00T, Electro lab, Mumbai, India), at 37ºC±0.5ºC using 300ml of simulated saliva (pH6.8) as a dissolution medium. The agitation rate of paddle was 50 rpm. In order to sink the film, each prepared film of the dimensions 2×2cm2 was affixed to a paper clip and put into the vessel at initial time. Sampling was done after 1.5 minutes. The sample was filtered through What man filter paper, diluted suitably if required and analyzed by HPLC. An equal volume of the fresh dissolution media, maintained at the same temperature was added after withdrawing the sample to maintain the volume. [18]

Measurement of Mechanical Properties

The mechanical property of the film gives idea about to what extent the film can with stand the force or stress during processing, packaging, transport and handling. The measurement of mechanical properties gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and elongation break.[19]

Tensile Strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks. The tensile strength (TS)

can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it is expressed in force per unit area (N/mm^2).[19, 20]

Percent Elongation at break (%E)

Percent elongation at break (%E) is calculated by dividing the extension at the moment of rupture of the specimen by the initial length of the specimen and multiplying by100.[20]

Morphology study by SEM

The surface morphology and texture were studied by scanning electron microscopy (SEM, PhilipsXL-30environment). Simple photograph of film were also taken by camera. The samples for SEM were prepared by sticking film formulation on a double-sided adhesive tape stuck to an aluminum stub. The film samples were then randomly scanned and microphotographs were taken on different magnification and higher magnification was used for surface morphology, homogencity of polymer and drug distribution and texture of film. The accelerator voltage was set at30.0KV during scanning.

RESULTS

Drug- excipients compatibility study (FT-IR)

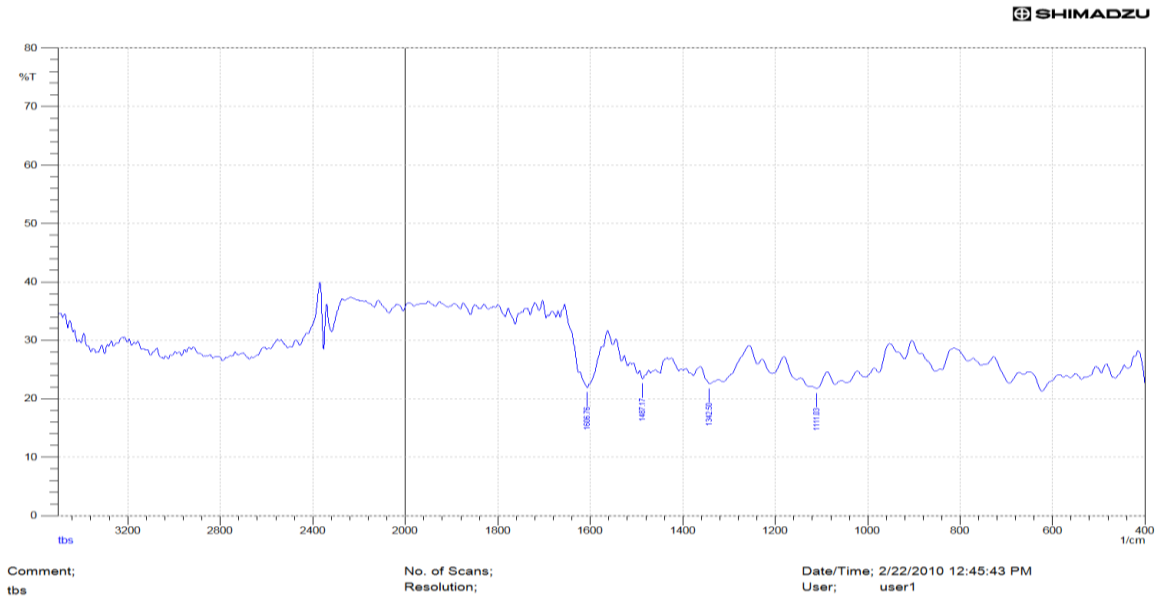

Figure: 1 FTIR Spectraofpure Terbutaline Sulphate.

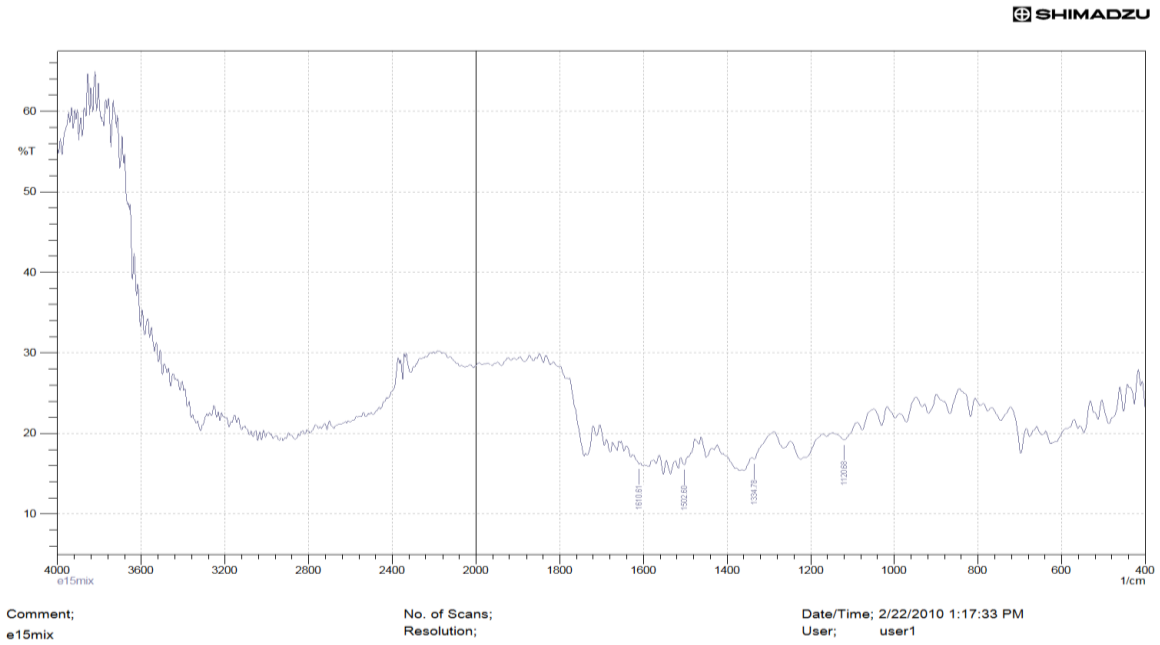

Figure: 2 FTIR Spectra of physical mixture of film formulation.

From FTIR spectra of pure TBS in figure 6indicate that four principle peaks observed at wave numbers 1606, 1487, 1342 and 1111 cm-1 according to mentioned in terbutaline protocol these wave numbers match with the standard drug wave numbers. In case of physical mixture of final optimized film formulation containing Drug, HPMC E15, aspartame and citric acid also show same FTIR wave numbers peak as pure TBS in figure so these results suggest that there is no any functional group changes of TBS incase final formulation of film. So all ingredients are chemically compatible with eachother'sin film

DSC study

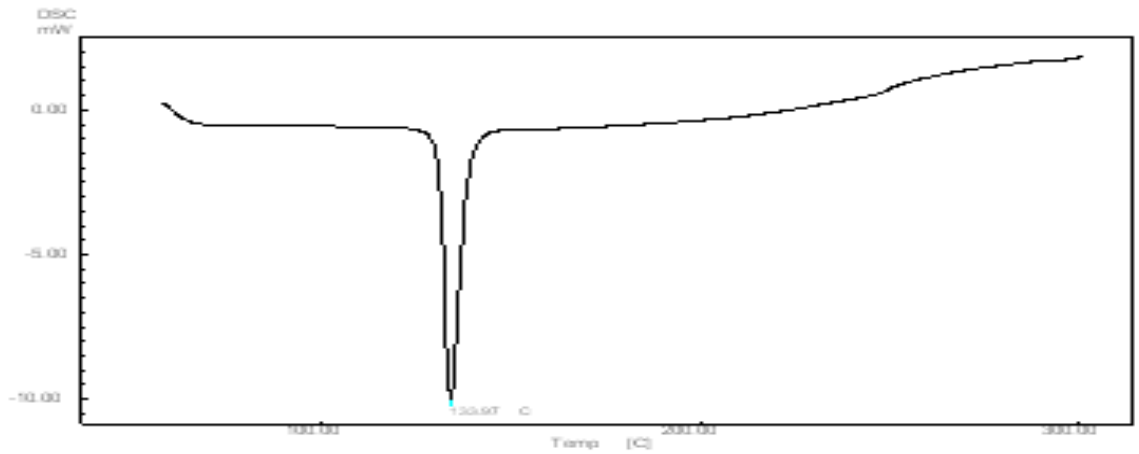

Figure: 3 DSC Thermograms of Puredrug

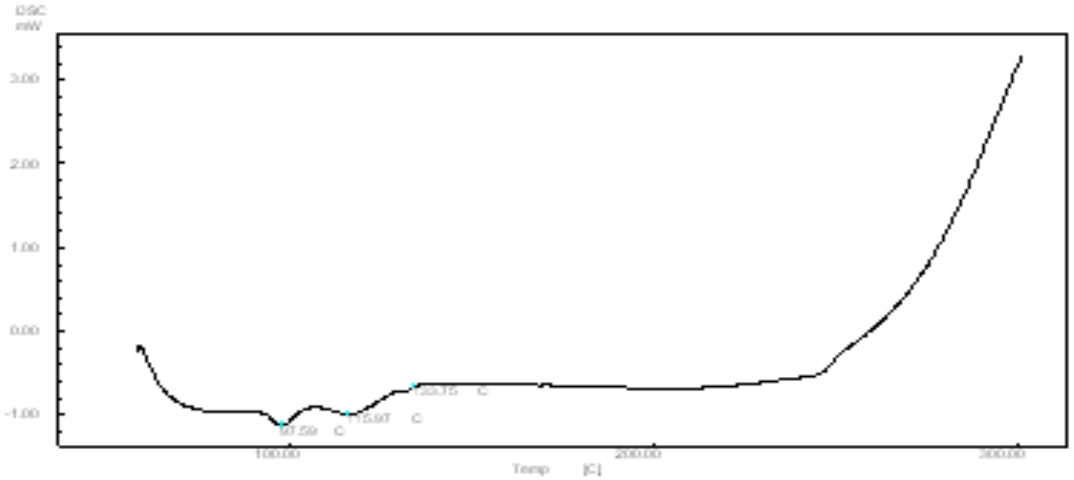

Figure: 4 DSC Thermograms physical mixture of Optimized film formulation

The DSC curves of pure drug (TBS) and physical mixture of final optimized film formulation containing drug (TBS), HPMC E15, aspartame and citric acid is shown in figure 3 and 4. Terbutaline sulphate showed endothermic peakat133.90 corresponding to its melting point. Physical mixture of final optimized film formulation except glycerin and water show same intact endothermic peak at133.70C but peak intensity was less since amount of drug was very low as compared to the excipients. These results indicate that the drug did not interact with the excipients used in the film formulation.

Results of films: In vitro DT, thickness, content uniformity and palatability

Table 4.1FactorialDesign batches Results:*in vitro* DT, thickness, content uniformity and palatability

Batch Code	*In vitro*D.T time (Min) (mean±S.D) (n=6)	Thickness (µm) (mean±S.D) (n=6)	Content uniformity (mean±S.D) (n=6)	Palatability grade
F1	12.50±1.52	64.17±4.40	94.11±4.0	A
F2	12.00±1.67	63.00±4.86	92.77±3.4	A
F3	12.00±2.10	63.33±2.94	95.33±4.2	B
F4	22.00±3.79	76.33±3.61	95.96±3.51	A
F5	20.67±2.34	76.17±5.00	95.60±4.37	A
F6	19.67±1.75	77.17±3.31	92.74±6.86	A
F7	36.50±4.42	102.50±5.82	94.57±2.29	B
F8	35.33±4.97	100.50±7.53	94.03±4.17	A
F9	33.67±3.08	101.17±6.52	96.80±1.81	A

As results shown in the table 4.1 various parameters like thickness, invitro, DT Time as well as content uniformity were checked. Seeing the data of thickness value of prepared film of nine batches, as the concentration of polymer HPMCE 15 increase from 1.75-2.75%, increase in the thickness of prepared film. So there is direct linear relationship observed between thickness of film and amount of HPMC E15LV present. There was no such relationship observed with amount of glycerin and thickness of film. So by optimizing the amount of polymer we can control the thickness and that will further be optimized Invitro DT time indirectly.

Invitro DT is main key parameter to determine the amount of drug release in shorter period of time and simultaneously faster onset of action. Results shown in table indicate that as the amount of polymer increase, invitro DT time increased proportionally since thickness of film increased.

Content uniformity is also important consideration in administering the precise dose inpatient and thus content uniformity were evaluated for all factorial design batches and results are shown in table 4.1.Contentuniformityissolelydependenton the manufacturing process. Results indicate that all batches had content uniformity more than90%.Therewere no significant changes observed for content uniformity with respect to polymer and plasticizer concentration in this experiment.

Morphology study of prepared film

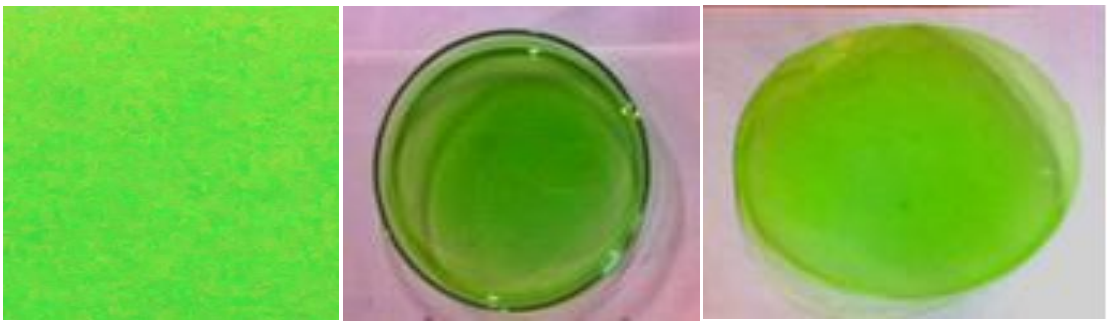

Figure 4.5: Photograph of optimizedbatch (F9) films:

(1) 2×2cm2film

(2)Petri dish containing the solution of film

(3)Complete film that was separated from petridish after drying.

SEM of optimized TBS film

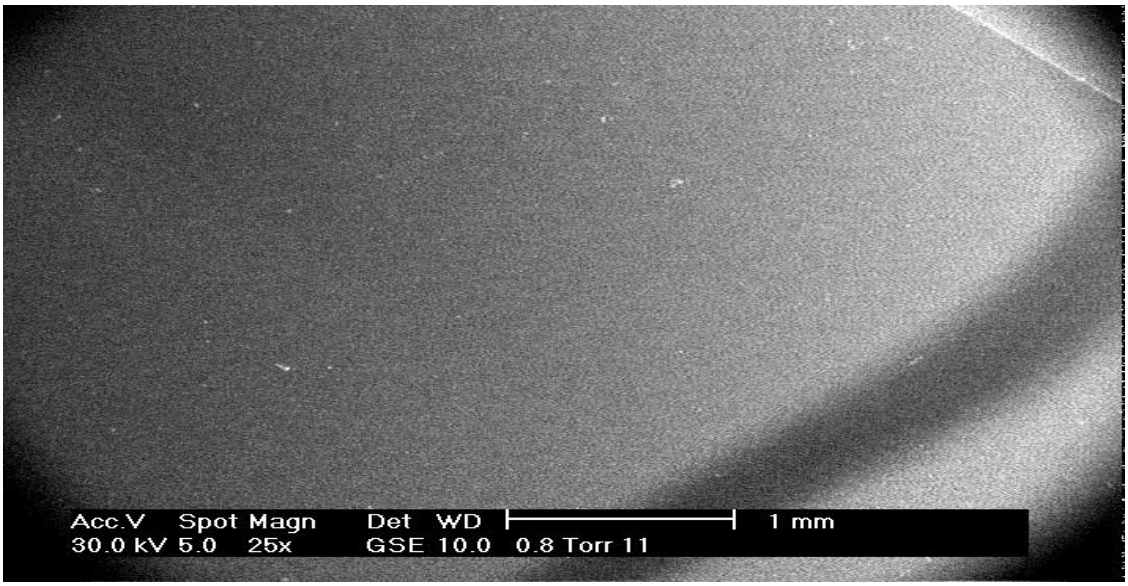

Figure 4.6: Scanning electron photo micrograph of optimized TBS film (batch F9).

4.6 In vitro dissolution

Table 4.2: In vitro dissolution profile of formulations F1-F9

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	33.85	37.75	41.98	43.65	45.13	46.19	34.31	39.41	46.98
2	49.85	51.25	53.59	54.98	55.88	55.89	49.98	51.38	59.89
4	55.39	64.8	66.45	66.89	67.67	68.25	55.9	53.76	69.78
6	63.89	69.7	71.65	71.9	73.63	74.76	63.51	68.98	78.31
8	75.89	76.5	77.67	78.59	79.93	81.98	76.38	77.78	85.13
10	81.74	83.18	86.7	87.9	89.31	91.17	82.56	85.13	97.8

Stability Study results of optimized batch (F9) films

Table 4.3 : Results of stability data for F9 batch

Stability condition	Sampling time	Observations			
		Folding endurance	*In vitro* DT	Visual appearance	Drug content
Room storage (30±2^{0}C and 65±5% RH)	Initial (0 day)	>50	20.14±0.12	Clear homogeneous film	95.60±4.37
	After 10 days	>50	21.45±0.45		95.45±3.88
	After 20 days	>50	20.11±0.55		95.94±4.78
	After 30 days	>50	22.12±0.14		94.89±3.98
Accelerated condition (40±2^{0}C and 75±5% RH)	Initial (0day)	>50	20.14±0.12	Clear homogeneous film	95.60±2.98
	After 10 days	31	22.14±0.34		94.67±3.67
	After 20days	19	24.12±0.23	Slight hazy film	93.87±2.88
	After 30days	5	25.12±0.17	Slight recrystalization	94.78±1.98

Results illustrated in table 4.3 proved that the films stored under two different conditions did not show any changes with respect to content uniformity thus no problem of drug dose variation in the prepared film formulation. In case of physical appearance of film that were stored in room temperature condition clear homogeneous film remained throughout 30 days of film formulation so films were stable at room temperature condition. Results of in-vitro DT and folding endurance also suggest that as temperature increase amount of moisture in the film that remain less and duet on sufficient amount of moisture presence it will diminish the film. Forming properties of HPMC, so hard and brittle film formed.

That also results into more DT time. By this way final formulation was stable in normal room temperature condition as compare to accelerate condition (75% RH and 40ºC). There are so many water soluble components in the FDFs so problem of recrystallization become more pronounced as time go on so stability is one of the main issue with regards to prepared FDFs.

CONCLUSION

The formulation of fast dissolving oral films of Terbutaline sulphate from design of experiment and optimization with the help of response surface methodology involving the factors as amount of film forming polymer(HPMC E15LV) and super disintegrant (sod. Starch glycolate) and responses taken as disintegration time, tensile strength, folding endurance and percent drug release at 10 minutes. The formulation F9 was found to be optimized formulation with desirable disintegration time, tensile strength, folding endurance and maximum cumulative percent drug release at 10 minutes in the oral cavity. One major advantage of the fast dissolving oral films is that they dissolve in oral cavity within seconds without leaving any residue. Patients for pediatric and geriatric or patients with dysphasia can use Terbutaline sulphate fast dissolving oral films that give an immediate relief from asthmatic attacks.

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