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Feasibility of Polyvinyl Alcohol as a Transdermal Drug Delivery System for Terbutaline Sulphate

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A series of terbutaline sulphate drug incorporated polyvinyl alcohol (PVA) matrix films were produced by the solvent evaporation method. The effect of xanthan gum and plasticizers (propylene glycol and dibutyl phthalate) on the rate and amount of drug diffusion from PVA membrane across the hydrated cellophane membrane has been evaluated, using an open glass diffusion-tube. The obtained films were clear, smooth and flexible having sufficient mechanical strength. The mechanical performance of the dry PVA films with xanthan gum and plasticizers were also ascertained. Polyvinyl alcohol-xanthan gum blends showed a high rate of drug release compared to that of polyvinyl alcohol film alone. Among the two plasticizers employed, propylene glycol showed better permeability. Among different formulations studied, the formulation PVA/xanthan gum/propylene glycol (F7) was found to be an optimized composition for efficient transdermal delivery of the model drug, terbutaline sulphate. The mechanism of drug diffusion has been evaluated using the Peppas model. Stability studies carried out on polymer-drug formulations revealed that the drug is stable at 40°C and 75% RH for a period of 6 weeks.

Keywords: Poly(vinyl alcohol); xanthan gum; transdermal drug delivery systems; terbutaline sulphate.

1 Introduction

Controlled drug delivery by using polymers is one of the emerging technologies, which is generating significant interest because the therapeutic effectiveness of many drugs can be improved by combining them with polymers (1). Furthermore, polymeric moieties will be key components of controlled and targeted delivery systems. There are at least two main approaches to combine drugs into polymers. One is the chemical crosslinking of the polymer and drug, to achieve targeted drug release such as prodrugs. But, the second and simplest way involves the formation of polymer matrices in which drugs are mixed physically or blended, and the release of drug is achieved by diffusion from the surrounding polymeric matrix or by disintegration of the polymeric matrix (2). Recently, much attention has been focused on developing controlled drug delivery using hydrophilic polymers. These developments led to the formulation of transdermal drug delivery systems (TDDS). Transdermal application of drugs have attracted pharmaceutical scientists and gained considerable momentum during the last few years. The law of passive diffusion governs the release of active ingredient from these systems and permeation through the skin. In addition to its simplicity, the main advantage of this type of delivery system is that the drug remains unchanged in the polymer matrix and therefore, retains its pharmacological properties after release. TDDS not only provides controlled, constant administration of the drug, allowing continuous input of drugs with short biological half-life, but also can eliminate pulsed entry into the systemic circulation, which often cause undesirable side effects (3, 4). Among the various types of TDDS available for different ailments, one of the major systems used is incorporation of drug in polymer matrix, which releases the drug in a controlled rate. The rate of release from polymer carrier can be tailor-made by selecting a suitable polymer-polymer composition and drug concentration (5, 6).

PVA is a yellowish-white powder or a translucent granule, which is a non-toxic (7), water soluble, biocompatible (8) and biodegradable (9) material. It is a non-ionic surfactant, used in pharmaceutical manufacturing as a stabilizing agent, viscosity modifier and lubricant. Recently, it is being extensively used in ophthalmic films (8), implants (9), controlled release tablets (10), hydrogels, etc. PVA based transdermal drug delivery systems (TDDS) have been developed for

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drugs such as testosterone (11), progesterone (12), indomethacin (13), ketorolac tromethamine (14), isosorbide-5-mononitrate (15), verapamil (16), etc. Studies have also been reported in modifying PVA membranes for drug delivery using poly(N-vinyl pyrrolidone) [PVP] (12–14, 16).

Xanthan gum is a naturally occurring white or yellowish white, free-flowing powder; soluble in hot and cold water; practically insoluble in organic solvents. It is a high molecular weight polysaccharide gum produced by pure fermentation of carbohydrate with X*anthomonas campestris*, then purified by recovery with isopropyl alcohol, dried and milled (3).

Xanthan gum was used as a suspending agent for delivering anti-spasmodics topically along the length of the esophagus in patients with esophageal spasm. Xanthan gum is widely used in pharmaceuticals as a suspending (17), stabilizing (18) and thickening (19) agent. It is also used as an additive in the food industries.

Terbutaline sulphate is a highly selective β_2 agonist, which is commonly used as a bronchodilator for the treatment of asthma. It is usually administered by inhalation from pressurized aerosol or drug powder devices (20). The recommended dose of terbutaline sulphate is 2.5 to 5 mg, two to three times a day for adults and has a half-life of about 3–4 h. In order to achieve an optimal clinical effect, it is most important that the drug should be taken regularly at an interval of 6–8 h. Terbutaline sulphate is metabolized by hepatic first pass effect in the liver and as a result, about half of the administered dose is inactivated (21). Therefore, TDDS are designed to exclude hepatic first pass metabolism and control the delivery of the drug to systemic circulation (22, 23). A thorough literature study revealed lack of literature on the influence of plasticizer and xanthan gum on PVA based transdermal films.

The PVA/xanthan gum blend was chosen in order to study the release profile of a drug from membranes made both from synthetic and natural polymers, respectively. The proposed system may be more viable to traditional systems such as inhalation devices, since they are easy to prepare and are cheap. This research article deals with the mechanical properties such as tensile strength and percent elongation at break of the prepared PVA/xanthan gum blends. The drug incorporated polymer blends have been characterized for content uniformity, drug release, and stability studies.

2 Experimental

2.1 Materials

Terbutaline sulphate (Figure 1) was obtained from M/s Astra-IDL, Bangalore, India as a gift sample. It is a white, odorless crystalline powder, which is freely soluble in water, sparingly soluble in ethanol and insoluble in chloroform and ether. It has a molecular weight of 548.65 and melting point is 119–122°C. Poly(vinyl alcohol) [PVA] procured from M/s Otto Kemi, Mumbai had a molecular weight (MW) of about 1,25,000, density of about 1.27 g/cm^3, T_g is 75–85°C and T_m is greater than 200°C. Xanthan gum was procured from M/s Sigma Labs, USA. PVA and xanthan gum were used without further purification.

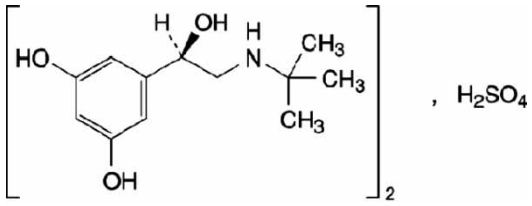

Fig. 1. Chemical structure of terbutaline sulphate, H_2SO_4.

2.2 FTIR Spectrophotometry

In order to evaluate the integrity and compatibility of the drug with the carrier polymer in the polymer-drug matrix formulations, IR spectra of the drug and its formulations were obtained by FTIR spectrophotometer (Perkin Elmer-1000, Japan), using a potassium bromide pellet method.

2.3 Preparation of Terbutaline Sulphate-Polymer Films

Poly(vinyl alcohol) (7.4% w/v) was dissolved in a known amount of water by heating on a water bath at 75 ± 5°C for 45 min. Similarly, xanthan gum (0.4% w/v) was dissolved in a known amount of water by stirring at 100 rpm on a magnetic stirrer maintained at 40°C. The two polymer solutions were then mixed as per requirement. To this mixture, the calculated amount of drug, terbutaline sulphate and the plasticizer (20% w/w of the polymers) were added with constant stirring.

The prepared polymeric solution was poured on to cleaned glass molds and kept in a vacuum drier until the solvent has evaporated. The cast polymer films with different formulations were then peeled off from the glass molds, covered with aluminium foils and stored in a desiccator until further study. Terbutaline sulphate in two different concentrations (2 and 4 mg/cm^2) was incorporated into the PVA matrix, with and without xanthan gum and by using two different plasticizers (propylene glycol and dibutyl phthalate). Eight different PVA-drug formulations were prepared. The formulations of polymer-drug systems along with the sample code are given in Table 1.

2.4 Measurements

Mechanical properties, such as tensile strength and percentage elongation at break of PVA and its blends, were measured as per ASTM D 685 using Universal Testing Machine (UTM) (Model 4309, Instron). A minimum of six samples were tested for each composition and the average value was recorded.

Table 1. Formulations of PVA/xanthan gum-drug films

	Formulation code							
Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Terbutaline sulphate		2 mg/cm^2				4 mg/cm^2		
PVA	yes	yes	yes	yes	yes	yes	yes	yes
Xanthan gum	—	—	yes	yes	—	—	yes	yes
Propylene glycol	yes	—	yes	—	yes	—	yes	—
Dibutyl phthalate	—	yes	—	yes	—	yes	—	yes

2.5 Content Uniformity

The wavelength of maximum absorbance (λ_{max}) of terbutaline sulphate drug was determined by scanning a known concentration of a drug solution in the wavelength region 200–400 nm by using a Shimadzu 1601 UV/Visible spectrophotometer. The λ_{max} was found to be 277 nm. In order to ascertain the uniform distribution of the drug in the polymer membrane, the content uniformity test was performed. A specimen sample of 1 cm^2 was cut from the film at three different places and dissolved separately in 100 ml of normal saline by slightly warming. After cooling, the drug concentration of the polymer membrane was determined by measuring the absorbance at 277 nm.

2.6 Drug Diffusion Studies

Drug diffusion studies were carried out in an open glass diffusion tube (Figure 2). A specimen dimension of 4 cm^2 was fixed to the hydrated cellophane membrane at one end of the open glass tube and placed in the receptor compartment containing buffer solution (normal saline). The assembly was placed on a magnetic stirrer and stirred at 100 rpm. The temperature of the system was maintained at 37 $\pm$ 1°C. A known amount of receptor medium (buffer) was withdrawn at regular intervals (for 8 h) and sink condition was maintained by replacing equal volume of fresh saline. The drug concentration was determined by measuring the absorbance of the solution at 277 nm.

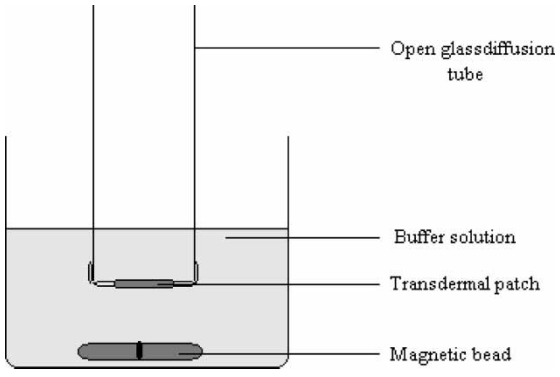

Fig. 2. Schematic representation of a diffusion cell.

2.7 Peppas Model Fitting

The Koresmeyer-Peppas model (24) is one of the mathematical expressions used to evaluate the mechanism of drug delivery. The Koresmeyer-Peppas equation is as follows:

$$M_t/M_\infty = 1 - A(\exp^{-kt}) \quad (1)$$

$$\log(1 - M_t/M_\infty) = \log A - kt/2.303 \quad (2)$$

where, M_t/M_∞ is the fractional amount of drug released and t is the time in hours. In this study, the release constant k and constant A were calculated from the slopes and intercepts of the plot of ln $(1 - M_t/M_\infty)$ vs. time t.

2.8 Stability of the Transdermal Films

The stability of the drug incorporated polymer matrix membrane was confirmed by exposing the 4 cm^2 size specimens at 40°C $\pm$ 1°C and at 75% RH (relative humidity) for 6 weeks. The membranes were then evaluated for its content uniformity initially and at weekly intervals for six weeks.

2.9 Differential Scanning Calorimetry (DSC)

DSC studies were carried out in the temperature range ambient to 250°C at a heating rate of 10°C/min in air media by using DuPont DSC. The sample size used for each analysis was 6–8 mg.

3 Results and Discussion

3.1 FTIR Spectrophotometry

The FTIR spectra of terbutaline sulphate and its formulations are shown in Figure 3. The FTIR spectra of terbutaline sulphate and its formulations were found to be identical. The characteristic IR absorption peaks of terbutaline at 3330 (OH stretch), 2837 (O-CH_3 stretch), 2393 (amine), 1679 (lactam, C═O stretch), 839 (o-substituted aromatic C-H out of plane deformation) and 781 cm^{-1} (p-substituted aromatic C-H out-of-plane deformation) were obtained. The FTIR spectra of the pure drug, as well as drug incorporated PVA formulations indicated that no chemical interaction occurred between the drug and the polymers used. But, a slight change in absorption peaks position was noticed. This result revealed that some kind of physical interaction might have occurred between the drug and the polymer.

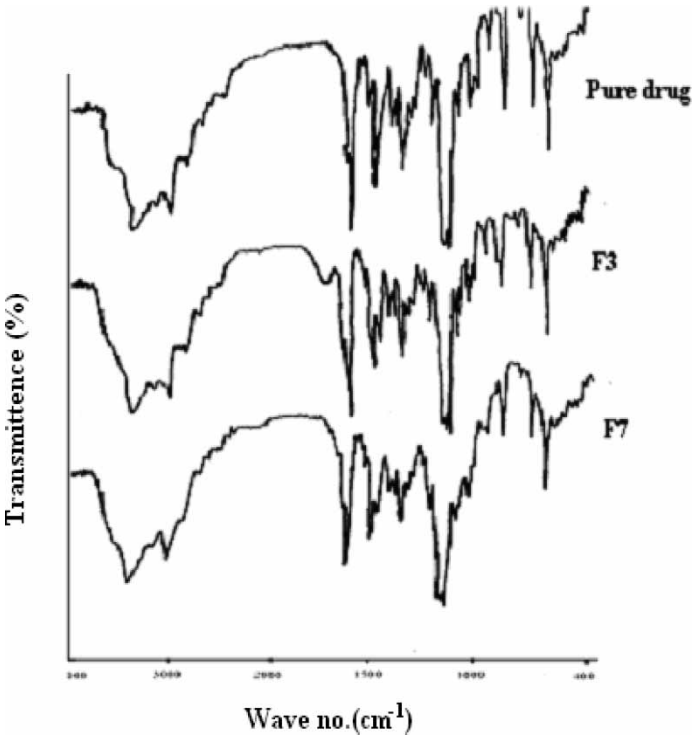

Fig. 3. FTIR spectra of terbutaline sulphate and its formulations.

3.2 Mechanical Properties

The measured mechanical properties, such as tensile strength and percentage elongation at break for the PVA and its formulations are given in Table 2. From the table, it is observed that the tensile strength decreased and percentage elongation increased after incorporation of both xanthan gum and dibutyl phthalate (plasticizer).

Propylene glycol incorporated PVA films showed high tensile strength as compared to dibutyl phthalate added systems. A drastic reduction in tensile strength was noticed after blending PVA with xanthan gum. This is attributed to low molecular weight of xanthan gum compared to PVA, also poor interaction between them and/or their immiscible nature.

Table 2. Mechanical properties of modified PVA membranes and content uniformity data

Formulation	Tensile strength (N/mm^2)[a]	% Elongation at break[a]	Content Uniformity[a] (mg/cm^2)
F1	64.9 ± 2.50	211 ± 16.21	2.17 ± 0.018
F2	49.5 ± 2.37	240 ± 17.98	2.16 ± 0.032
F3	44.4 ± 1.94	318 ± 15.18	1.96 ± 0.056
F4	43.8 ± 1.69	328 ± 16.46	1.94 ± 0.037
F5	67.2 ± 2.85	207 ± 15.90	4.14 ± 0.124
F6	54.0 ± 2.33	225 ± 15.74	4.14 ± 0.082
F7	50.8 ± 2.25	250 ± 14.96	4.08 ± 0.226
F8	45.7 ± 1.83	286 ± 16.72	4.24 ± 0.226

[a]Mean ± SD, n = 3.

The influence of plasticizer on mechanical performance of PVA systems with or without xanthan gum are same. That means propylene glycol loaded systems showed better tensile strength. This result clearly indicates that propylene glycol is more compatible with PVA than dibutyl phthalate.

Table 2 shows the enhancement in percentage elongation at break after the incorporation of plasticizer to the PVA membranes. This can be attributed to the plasticization effect. Higher percentage elongation at break was noticed for dibutyl phthalate incorporated membranes compared to propylene glycol incorporated membranes. Xanthan gum blended PVA systems have also shown higher percent elongation at break than without xanthan gum. That means a reverse trend of percent elongation at break with tensile strength for all formulations was noticed.

3.3 Content Uniformity

From Table 2, it was observed that the content uniformity value lies in the range 1.94–4.24 mg/cm^2. The results of content uniformity studies clearly indicate that the drug was uniformly distributed throughout the polymer membranes. These values are in the expected range as per Indian Pharmacopoeia (IP) standards (1–9 mg/cm^2).

3.4 Diffusion Studies

Diffusion studies were carried out in an open glass diffusion tube, using hydrated cellophane as a diffusion membrane. Diffusion studies for all the formulations of PVA-terbutaline sulphate films were carried out for 8 h in normal saline.

The plot of cumulative drug release vs. time for the low dosage of drug (2 mg/cm^2) and high dosage of drug (4 mg/cm^2) are given in Figures 4 and 5, respectively. Diffusion studies of terbutaline sulphate films indicated that the order of diffusion is as, F3 > F4 > F1 > F2 and F7 > F8 > F5 > F6 for 2 and 4 mg/cm^2 drug filled membranes, respectively. From the figures, it is noticed that two stages of drug release occurred. In the first 2 h, there was a fast drug release indicated by a steep increase in the

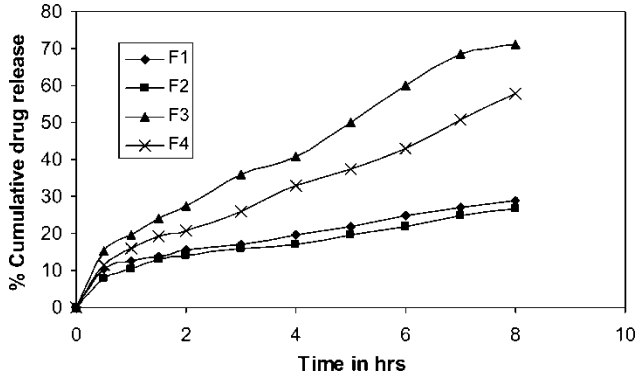

Fig. 4. Drug release profiles of modified PVA membranes for low drug dosage systems (formulations F1-F4).

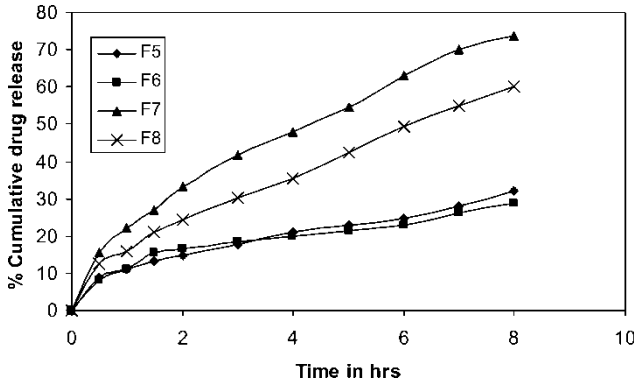

Fig. 5. Drug release profiles of modified PVA membranes for high drug dosage systems (formulations F5-F8).

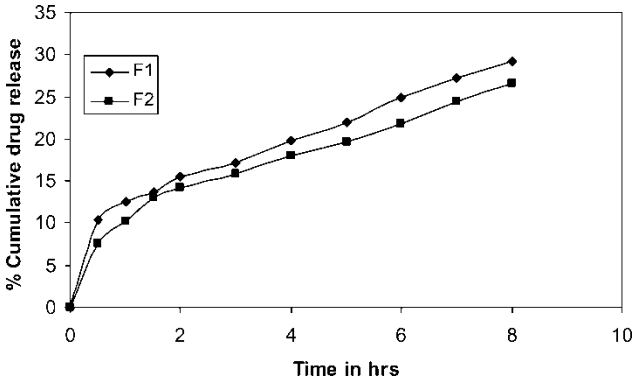

Fig. 7. Drug release profiles of modified PVA membranes with different plasticizers like propylene glycol and dibutyl phthalate (formulations F1 and F2).

slope of the curve, this is due to the drug molecules present over the surface of the membranes which gets released. Later, a linear slow release of drug from the membrane was observed for the next 6 h.

The effect of drug content on the rate of drug release from PVA formulations F2 (low dosage of drug) and F6 (high dosage of drug) are shown in Figure 6. From the figure, it is indicated that the drug release increased with an increase in drug dosage. This result clearly revealed that the rate of drug delivery is directly related to the drug concentration.

The effect of plasticizer on the rate of drug release from the polymer-drug films can be studied by the drug release profile plots of formulations F1 and F2 (Figure 7). From the figure, it is clear that drug release was more from the formulation in which propylene glycol was incorporated (F1) compared to the films in which dibutyl phthalate was used (F2).

A plot of percent cumulative drug release vs. time for the films with (F3) or without xanthan gum (F1) is shown in Figure 8, to evaluate the influence of xanthan gum on the rate of drug release profiles. From Figure 8, it was noticed that films cast with xanthan gum showed a higher rate of drug release as compared to the formulation without xanthan gum. This is attributed to the hydration of xanthan gum, which is more than PVA.

3.5 Peppas Model Fitting

The data obtained from *in vitro* drug release studies was fit into Peppas model (24). From the plot of log M_t/M_∞ vs. t, the parameters such as release constant (k), constant (A) and the regression coefficient (R^2) were calculated and are given in Table 3. In all cases, the value of A were found to be between 0.5 and 1. This result indicates that the release of drug from the polymer matrix formulations was found to be non-Fickian diffusion.

3.6 Stability Studies

Stability studies of the drug formulations are performed to ascertain whether the drug undergoes any physical/chemical change or degradation during its shelf life. In the present study, the formulations F3 ($2\ mg/cm^2$) and F7 ($4\ mg/cm^2$) that have shown maximum drug release were selected for stability studies. The stability studies were carried out by exposing the drug incorporated membranes at $40^\circ \pm 1^\circ C$ and at 75% RH for 6 weeks. The obtained results of the stability studies are given in Table 4. From the stability study data, it was concluded that the films were stable in the formulations for the study period.

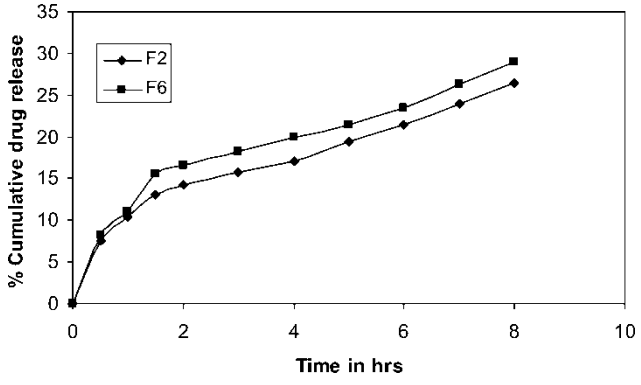

Fig. 6. Drug release profiles of modified PVA membranes for low and high dosage of drug (F2 and F6).

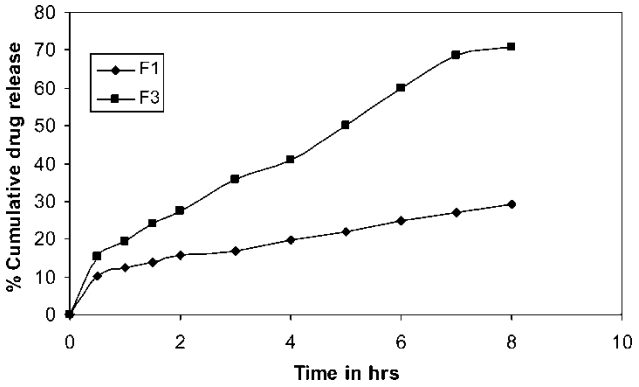

Fig. 8. Drug release profiles from PVA membranes with and without xanthan gum (formulations F1 and F3).

Table 3. Data obtained from Peppas model fitting curves for all the PVA-drug formulations

	Parameters		
Formulations	Release constant (k) $\times 10^2$	Constant (A)	Regression coefficient (R^2)
F1	0.58	0.9118	0.9862
F2	0.54	0.9205	0.9897
F3	2.71	0.9566	0.9915
F4	1.73	0.9457	0.9885
F5	0.69	0.9209	0.9967
F6	0.57	0.9310	0.9970
F7	2.93	0.9266	0.9989
F8	1.88	0.9290	0.9972

Table 4. Stability study data of optimized formulations F3 and F7

Time in weeks	Drug content in F3 (mg/cm^2) mean $\pm$ SD[a] at $40^\circ \pm 1^\circ C$ and 75% RH	Drug content in F7 (mg/cm^2) mean $\pm$ SD[a] at $40^\circ \pm 1^\circ C$ and 75% RH
Initial	1.97 $\pm$ 0.4320	3.92 $\pm$ 0.160
1	1.98 $\pm$ 0.0188	3.92 $\pm$ 0.000
2	1.94 $\pm$ 0.0188	3.89 $\pm$ 0.009
3	1.94 $\pm$ 0.2828	3.87 $\pm$ 0.009
4	1.92 $\pm$ 0.0188	3.86 $\pm$ 0.016
5	1.89 $\pm$ 0.0094	3.83 $\pm$ 0.009
6	1.89 $\pm$ 0.0094	3.80 $\pm$ 0.282

[a]Standard deviation n = 3.

3.7 Differential Scanning Calorimetry (DSC)

DSC is a fast and reliable method to screen drug compatibility and provides information about the possible interaction between the drug and the polymers used in the formulation. DSC thermograms of the pure drug and its formulations after stability studies were recorded to evaluate whether the drug has undergone any degradation during the study period. From the DSC data (Table 5), it was evident that the melting point of terbutaline sulphate is not changed after exposing the specimens to stability measurement. Hence, it may be inferred that there is no interaction between terbutaline sulphate and polymers used in the preparation of compacts and films. From DSC results it can be concluded that the drug maintained its chemical identity throughout the process.

Table 5. Data obtained from DSC curves for formulations F3 and F7

Composition (wt/wt,%)	Melting range ($^\circ C$)	$T_m(^\circ C) \pm 1\%$
F3	104–132	121
F7	103–130	123
Drug	102–130	121

4 Conclusions

FTIR spectrograms of the terbutaline sulphate incorporated PVA films indicated no reaction between the drug and polymers used. From the content uniformity studies, it was found that the drug is uniformly distributed throughout the modified polymer membrane. The PVA films prepared without xanthan gum has high tensile strength compared to films with xanthan gum. From the tensile strength studies, it was observed that films prepared with propylene glycol as plasticizers have high tensile strength compared to dibutyl phthalate systems.

The drug diffusion data revealed that the formulation without xanthan gum showed a low release rate compared to formulation with xanthan gum. Among the two plasticizers used, namely propylene glycol and dibutyl phthalate, the rate of drug delivery is fast in the films containing propylene glycol. The formulations F3 and F7 showed drug release of about 70.4 and 73.8%, respectively, which may be a result of the presence of xanthan gum and propylene glycol.

Films containing a higher dosage of drug (4 mg/cm^2) in the PVA matrix showed controlled release over a prolonged period of time as compared to the system with lower dosage (2 mg/cm^2) of drug.

From the stability studies, it is clear that the terbutaline sulphate/PVA formulations were stable for six weeks and the data obtained from DSC thermograms indicated no change in chemical identity of the drug. The data obtained from the Peppas model fitting, indicates that the mechanism of drug release was non-Fickian. The diffusion of terbutaline sulphate from PVA membranes can be significantly improved by the addition of xanthan gum as a copolymer and by using propylene glycol as plasticizer. However, further release studies on animal membrane and *in vivo* percutaneous absorption studies may be carried out.

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