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Research Article

Formulation and Evaluation of Buccal Patches of Terbutaline Sulphate

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ABSTRACT

The purpose of this study was to develop and optimize formulations of mucoadhesive patches of Terbutaline sulphate. The patches were prepared by the solvent casting method using Hydroxyl propyl methyl cellulose(HPMC cps50) as basic polymer and Carbopol 934, Eudragit RL 100, and Ethyl cellulose were taken in various ratios and 6 different formulations were made. The patches were found to be smooth in appearance, uniform in thickness, weight uniformity, drug content, swelling behaviour, and surface pH. The BP3 formulation containing Terbutaline sulphate, HPMC: Eudragit RL100 (4:1) Glycerine, Acetone and Tween 80 showed a release of 96.36% after 12 hours in phosphate buffer (pH, 6.8). This formulation was further optimized by varying HPMC cps50 and Eudragit RL100 and other variables and 9 new formulations F1 to F9 were prepared. Among the nine formulation, F6 formulation showed maximum desired properties and release 96.89%.

Keywords: Buccal patches; Terbutaline sulphate; Eudragit; Mucoadhesive.

INTRODUCTION

Asthma is one of the most common diseases affecting the human race, with 2%–10% of the adult population suffering from asthma or symptoms of asthma (Kumar V *et al*., 1992). Asthma has a diurnal rhythm and, in a large percentage of patients, the pulmonary function is reduced from midnight until 8 h. Thus, the ideal therapeutic agent should be effective in preventing bronchospasm for the 6–8 h period during which most individuals are sleep. A limiting factor is the relatively short duration of bronchodilator activity of Terbutaline sulphate (TBS).

TBS is a selective β2 adrenceptor agonist widely used in the acute and long-term treatment of bronchial asthma, chronic bronchitis, emphysema and other chronic obstructive lung diseases with reversible bronchial hyperreactivity. Terbutaline sulphate is a short-acting bronchorelaxant which can be given orally, parenterally or by inhalation. Orally administered terbutaline is absorbed incompletely (Tripathi KD, 2004). TBS undergoes high first pass metabolism in the gut wall and liver and the bioavailability is only 15% (Borgstrom L *et al*., 1989). Peak plasma levels are 1.2 µg/ml for every mg of an oral dose, reached within 2–3 h. After inhalation, only about 10%–20% of inhaled dose reaches the lungs and the rest is swallowed. There are also reports about the harmful effects of aerosol bronchodilator therapy (Multu GM *et al*., 2000, Nagabhushana S, 2000). Hence, there is a need to develop controlled drug delivery systems which can overcome the first pass effect, reduce the frequency of dosing and improve bioavailability (Chidambaram N *et al*., 1995).

The buccal region, within the oral cavity, offers an attractive route of administration for systemic drug delivery (Bremecker KD *et al*., 1984, Bouckaert S *et al*., 1993). Consequently, buccal drug delivery requires the use of mucoadhesive polymers as these dosage forms should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period of time.

The buccal route was chosen because of its good accaccessibility, robustness of the epithelium, facile removal of the dosage form, relatively low enzymatic activity, and natural clearance mechanism for elimination of the drug from buccal area, satisfactory patient compliance, and avoidance of hepatic first pass metabolism (Nagai T *et al*., 1985).

The purpose of this study was to develop formulations and systematically evaluate in-vitro & *Ex vivo* permeation performances of buccoadhesive patches of Terbutaline sulphate using different polymer and chose the polymer to develop the release of drug in immediate and sustained manner.

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Table 1: Composition of different buccal mucoadhesive patch

Ingredients	Patch code					
	BP 1	BP 2	BP 3	BP 4	BP 5	BP 6
Terbutaline sulphate, mg	60	60	60	60	60	60
HPMC (50 cps), mg,	250	150	200	150	200	200
Eudragit-Rl-100, mg	-	100	50	-	-	-
Carbopol - 934, mg	-	-	-	100	50	-
Ethyl cellulose, mg	-	-	-	-	-	50
Glycerin (1 drop), g	0.0588	0.0588	0.0588	0.0588	0.0588	0.0588
Ethanol, ml	10	8	8	7	7	10
Acetone, ml	-	2	2	-	-	-
Tween80, ml	o.1	o.1	o.1	o.1	o.1	o.1
Water, ml	-	-	-	3	3	-

Table 2: Optimization of patch containing Terbutaline sulphate

Patch code	Amount of Drug (mg)	Total amount of polymer (mg)	Amount of HPMC		Amount of RL-100		Amount of Tween 80	Amount of glycerin	Solvents		
			%	mg	%	mg	ml	ml	Water ml	Alcohol ml	Acetone ml
F1	10	150	100	150	0	0	0.1	0.1l	1	10	0
F2	10	250	100	250	0	0	0.2	0.3	1.5	15	0
F3	10	350	100	350	0	0	0.3	0.5	2	20	0
F4	10	150	80	120	20	30	0.1	0.1	1	8	2
F5	10	250	80	200	20	50	0.2	0.3	1.5	11	4
F6	10	350	80	280	20	70	0.3	0.5	2	14	6
F7	10	150	66.6	100	33.3	50	0.1	0.1	1	7	3
F8	10	250	66.6	166	33.3	84	0.2	0.3	1.5	9	6
F9	10	350	66.6	232	33.3	118	0.3	0.5	2	11	9

MATERIALS

Terbutaline sulphate was gifted from Kwality Pharmaceuticals Ltd., Amritsar. Carbopol 934 and Hydroxypropylmethylcellulose 50cps (HPMC), ethylCellulose, Eudragit RL100 and Other chemicals used were of analytical grade and procured from S.D. Fine Chemicals (Mumbai, India).

METHODS

Preparation of Patches

The buccal mucoadhesive patches of Terbutaline sulphate BP1 were prepared by solvent casting method (Anders R *et al*., 1989) using film forming polymers for the patches mentioned in table 1.HPMC polymer (250 mg) was weighed accurately and dissolved in 2 ml of ethanol. The beaker-containing polymer was kept aside for 5 minutes for swelling of polymer. 60 mg of Terbutaline sulphate was weighed and dissolved in 2 ml of ethanol. Further 6 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then one drop of (0.0294 g) glycerin was added to the polymer solution. The drug solution was added to the polymer solution. The whole solution was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5×3 cm^2 was placed over a flat surface. The whole solution was poured into the glass mould. An inverted funnel was placed over the mould to avoid sudden evaporation. Similarly patch BP2, BP3, BP4 BP5 BP6 were prepared. For preparing patch BP2 and BP3, Eudragit was dissolved in 2 ml acetone and HPMC was dissolved in 6 ml ethanol and kept for drying 24 hours. The two polymeric solutions were mixed. For preparing patch BP4 and BP5, Carbopol 934 was placed in 3 ml of water, and stirred for 60 min. HPMC was dissolved in 5 ml of ethanol. The two polymeric solutions were mixed. For preparing patch BP6 both Ethyl cellulose and HPMC were dissolved in ethanol. The moulds were kept 24 hours for drying of patch for formulations, BP1 BP2, BP3, and BP6. Whereas for formulations BP4 and BP5 moulds were kept aside for 72 hours. Formulations F1 to F3 prepared same as patch BP1 and Formulations F4 to F9 prepared same as patch BP2(Table 2).

Optimization of buccal mucoadhesive patch

In this study three factor namely, Amount of polymer (HPMC and RL-100) Amount of Tween 80 and Amount of glycerin were selected as independent variables while thickness, weight uniformity, drug entrapment efficiency, surface pH, mucoadhesive strength, permeation studies and In vitro drug release were the dependent variables used for optimization of process

variables (independent variables) in preparation of buccal mucoadhesive patch.

Optimization of HPMC and Eudragit RL-100 ratio

Table 2 shows different concentration ratio of HPMC (100-350mg) and Eudragit RL-100 (0-118mg) used in different formulations. Formulation F6 containing 280mg HPMC and 70mg Eudragit RL-100 shows best in-vitro drug release 96.89% in 12 hour (as shown in Table 5).

Optimization of Tween -80 concentration

Table-2 shows that three concentration of tween-80 0.1 ml, 0.2ml and 0.3ml used for formulation of buccal patches and Table 5 shows that the as the amount of tween 80 increased rate of permeation also increased simuntaneously. Formulation containing 0.3 ml tween 80 shows better permeation rate than formulation containing 0.2ml or 0.3ml tween 80.

Evaluation Parameters

Uniformity of weight of the patches: Patch size of 1 x 1 cm^2 was cut. The weight of each patch was taken and the weight variation was calculated.

Thickness uniformity of the patch: The thickness of each patch was measured using thickness tester at different positions of the patch and the average was calculated (Attama AA *et al*., 2008).

Swelling studies of the patches: Weight and area increase due to swelling were measured (Gua J H et al., 1995). A drug-loaded patch of 1 x 1 cm^2 was weighed on a pre weighed cover slip. It was kept into a Petri dish and 50 ml of phosphate buffer, pH 6.8 was added. After 10 minutes, the cover-slip was removed and weighed again same readings are taken up to 30 min. The difference in the final and initial weight gives the weight increase due to absorption of water and swelling of patch.

Surface pH: Buccal patches were left to swell for 1 hour in phosphate buffer of pH 6.8 in a petredish. The surface pH was measured by pH meter placed on the surface of the swollen patch. The mean of three readings was recorded**.**

Drug Entrapment and Content Uniformity of Patches: The patches were tested for the content uniformity. A patch of size 1×1 cm^2 was cut and placed in a 100 ml volumetric flask containing 100ml pH 6.8 phosphate buffer solution. The contents were kept for 24 hours to complete dissolve the patch. After making proper dilution to the stock solution if necessary, the absorbance of the solution was measured against the corresponding blank solution at 276 nm.

Measurement of Mucoadhesive strength: The goat mucosal membrane was used as the model membrane and isotonic phosphate buffer pH 6.8 was used as the moistening fluid. The goat mucosal membrane was then stuck on to the inner surface of the beaker using suitable glue such that mucosal surface faces upwards. Then the phosphate buffer pH 6.8 was added in to beaker such that the buffer is contacted with the mucosal membrane. Two sides of the balance were made equal before the study, by keeping a 5 g weight on the left side. A beaker containing mucosal membrane was kept below the right hand set up of the balance. The patch was stuck on to a lower flat side of arm balance. 25 µl of phosphate buffer pH 6.8 was added to the mucosal surface. Five grams weight from the left pan was removed. This lowered arm balance assembly along with patch over the membrane with weight of 5 g. This was kept undisturbed for 3 min. Then the weights on the left hand side were slowly added till the patch just separated from the membrane surface. The excess weight on the left pan i.e. total weight minus 5 g was taken as adhesive strength (Gupta A *et al*., 1992).

Measurement of Mucoadhesive Time: The mucoadhesive performance of the buccal patch was evaluated using goat buccal tissue. The time for patch to detach from the goat buccal tissue in a well-stirred beaker were used to assess the mucoadhesive performance. The fresh goat buccal tissue was fixed on the side of the beaker with glue. Before addition of the buffer, the patch was attached to goat buccal tissue by applying light force with fingertip for 20 second. The beaker was then filled with 800 ml phosphate buffer and kept at 37°. A stirring rate of 50 rpm were used to simulate buccal and saliva movement. The time for the patch to detach from the goat buccal tissue was recorded as the mucoadhesion time (Han RY *et al*., 1999).

Folding endurance: folding endurance of the patches was determined (Khanna R *et al.,* 1997) by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance.

In-Vitro Release Studies of Terbutaline sulphate patches in Phosphate Buffer (pH 6.8)

A patch of 1x 1 cm^2 size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.8). This slide was kept in a dissolution apparatus containing 200 ml phosphate buffer (pH 6.8) solution and temperature was maintained at 37^oC. A non-agitated system was selected to eliminate any effect of turbulence on the release rate. Samples were withdrawn periodically. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool (as a filter). 5 ml of the buffer was replaced immediately. The samples were taken periodically and analyzed for drug content at 276 nm. The release studies were conducted for three times and average was determined (Patel VM *et al*., 2007).

Kinetic of drug release

The result of in-vitro dissolution studies of buccal patches were fitted with various kinetics models, like zero order (% cumulative drug release vs. time), Higuchi's model (% cumulative drug release vs. square root of time) but these models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer and Peppas semi-empirical model to ascertain the mechanism of drug release.

$$\log (Mt/M\infty) = \log k + n \log t$$

Where, M∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the buccal patches; and n is the diffusional exponent; indicative of the mechanism of drug release. Table3 shows an analysis of diffusional release mechanism obtained by various value of n. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

Table 3: Release Mechanism with Variation of n Values

n value	Mechanism
n≤0.5	Quasi-fickian diffusion
0.5	fickian diffusion
0.5≤n≤1.0	Anomalous(non-fickian) diffusion
n≥1.0	Non –fickian super case II
1	Non –fickian case II

Ex vivo permeation through goat buccal mucosa

From the local slaughterhouse the buccal mucosa was collected and immediately transported to the laboratory in cold normal saline solution. Then buccal epithelium was isolated from the underlying tissue. The buccal epithelium was used within 2 h upon removal. The modified K. C. cell was used to permeation studies, it consists of two compartments, one is donor compartment and another is receptor compartment .The receptor compartment was covered with water jacket to maintain temperature 37°. The separated buccal epithelium was mounted between two chambers and in receptor chamber PBS pH 6.8 was filled and buccal epithelium was allowed to stabilization. After stabilization of buccal epithelium, the patch was kept on buccal epithelium and donor compartment filled with PBS pH 7.4 .Periodically samples were withdrawn and same volume fresh medium was replaced. The aliquots were analyzed spectrophotometrically.

Stability studies

Optimized formulations were stored in screw capped small glass bottles at room temperature and in stability chamber at 40±1ºC and 75 % relative humidity. Samples were analyzed for physical appearance, residual drug content and in vitro release after a period of 15, 30, 45 days. Initial drug content was taken as 100% for each formulation (Yoshika S *et al*., 2006).

RESULTS AND DISCUSSION

Drug estimation

Calibration curves of Terbutaline sulphate in phosphate buffer (pH 6.8) solutions were obtained at λmax 276 nm with a UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 0-10 µg/ml. Analyses were done in triplicate.

Drug-polymer compatibility

IR spectra of Terbutaline sulphate alone and its combination with polymers are shown in figures. An IR spectrum of pure Terbutaline sulphate showed the peaks 1601 cm^{-1}, 907 cm^{-1}. These peaks can be considered as characteristic peaks of Terbutaline sulphate and were not affected and prominently observed in IR spectra of Terbutaline sulphate along with polymers as shown in the figure, indicated no interaction between Terbutaline sulphate and polymers (Figure 1-4). Further, the interference was also verified using UV spectrometric method.

Weight uniformity

Weight uniformity for formulation BP-1 to BP-6 varied from 36.1±0.26 mg to 62.5±0.47 mg (table 4) and formulation F1 to F9 varied from 32.3±0.34 mg to 69.9±0.18 mg (table 5). The patches were found uniform.

Table 4: Result of different buccal patches containing Terbutaline sulphate

Patch code	Thickness (mm)	Weight uniformity (mg) (mean±SD)	% Entrapment	Content Uniformity (mean±SD)	Surface pH (mean±SD)	Muco adhesive strength (gm)	Muco adhesive time (min)	Permeation studies at 9 hours (%)	In vitro drug release at 12 hours (%)
BP 1	0.28±0.02	62.5±0.47	90.94	8.96±0.12	6.85±0.01	8.189	273	83.74	96.13
BP 2	0.24±0.03	43.5±0.31	93.91	8.89±0.17	6.66±0.04	8.53	287	69.46	91.81
BP 3	0.20±0.01	54.5±0.21	96.00	9.41±0.04	6.69±0.01	8.89	312	73.74	96.36
BP 4	0.12±0.03	37.9±0.19	94.67	9.29±0.11	6.71±0.03	7.28	285	71.25	98.81
BP 5	0.15±0.02	36.1±0.26	98.00	9.43±0.15	6.64±0.02	7.63	314	75.53	97.11
BP 6	0.26±0.02	51.0±0.41	96.69	9.35±0.16	6.67±0.05	7.78	319	71.96	96.37

Table 5: Result of optimization of patches containing Terbutaline sulphate

Patch Code	Thickness (mm) (mean±SD)	Weight uniformity (mg) (mean±SD)	% Entrapment	Content Uniformity (mean±SD)	Surface pH (mean±SD)	Muco adhesive strength (gm)	Muco adhesive time (min)	Permeation studies at 10 hr (%)	In vitro drug release at 12 hour (%)
F1	0.10±0.01	48.8±0.21	96.68	9.19±0.16	6.85±0.01	8.189	273	70.89	96.91
F2	0.23±0.03	69.9±0.18	97.37	9.6±0.08	6.66±0.04	8.53	287	78.92	95.14
F 3	0.25±0.02	89.2±0.40	98.01	9.74±0.17	6.69±0.01	8.89	312	81.25	96.19
F4	0.09±0.01	43.0±0.27	95.52	9.43±0.12	6.71±0.03	7.28	285	62.32	94.67
F 5	0.15±0.01	48.2±0.31	94.76	9.4±0.11	6.64±0.02	7.63	314	69.99	88.19
F 6	0.20±0.03	64.4±0.16	96.79	9.55±0.04	6.67±0.05	7.78	319	74.64	96.89
F7	0.09±0.01	32.3±0.34	95.23	9.52±0.18	6.54±0.02	6.15	295	60.53	90.88
F8	0.12±0.02	36.8±0.29	93.98	9.34±0.09	6.81±0.04	6.39	325	63.57	88.24
F9	0.14±0.02	46.9±0.19	97.62	9.7±0.15	6.88±0.03	6.97	343	68.74	82.63

Thickness uniformity

As the total amount of polymer increases the thickness of the film were found to be increased. The thickness for formulation BP-1 to BP-6 varied from 0.12±0.03 mm to 0.28±0.02 mm (as shown in table 4) and formulation F1 to F9 varied from 0.09±0.01 mm to 0.25±0.02 mm (as shown in table 5).

Swelling studies

Any polymer with good swelling property is expected to be a good candidate for bioadhesive application. When bioadhesive comes in contact with aqueous medium they swell and form a gel. The faster this phenomenon occurs more rapid will be the polymer adherence to the buccal mucosa. The swelling of the patches were observed in phosphate buffer solution (pH 6.8) and shown in table 4,5. Swelling was more pronounced in patches BP4 and BP5 which contain HPMC and Carbopol in a ratio of (1.5:1) and (2:0.5) respectively. Patches BP2, and BP6 showed less swelling (weight basis), may be due to the presence of Eudragit RL 100 and ethyl cellulose, respectively. These results were in agreement with the increase in area due to swelling.The results revealed that all the formulations provide an acceptable swelling index in the range of formulation BP-1 to BP-6 varied from 345.65% to 643.01% (as shown in table 4) and formulation F1 to F9 varied from 390.25% - 470.67% (as shown in table 5, figure 5).

Surface pH

An acidic or alkaline formulation is bound to cause irritation on the mucosal membrane. Surface pH of formulation F1 to F9 varied from 6.54 ± 0.02 to 6.88 ± 0.03 (table 5). Each sample is analyzed in triplicate (n=3). The surface pH of all formulations was within ± 0.5 units of the neutral pH and hence no mucosal irritation was expected and ultimately achieves patient compliance.

Drug Content Uniformity and Drug Entrapment

Drug entrapment of formulation BP-1 to BP-6 varied from 90.94% to 98% (as shown in table 4) and formulation F1 to F9 varied from 93.98 to 98.01 %(table 5). Drug content uniformity formulation BP-1 to BP-6 varied from 8.89±0.17to 9.43±0.15 and formulation F1 to F9 varied from 9.19±0.16 to 9.74±0.17 (as shown in table 4 and 5).Which is within the desirable range.

Mucoadhesion strength

As the amount of mucoadhesive polymer increases the mucoadhesion was found to be increase. In formulation BP-1 to BP-6 four different polymer was used in which Carbopol 934P have better mucoadhesion property than other so BP4 shows greater mucoadhesion strength (10.37 gm). Mucoadhesion strength of formulation BP-1 to BP-6 varied from 7.15 gm to 10.37 gm (table 4). In formulation F1 to F9 mucoadhesion strength increases with increase in the amount of HPMC so F3 shows greater mucoadhesion strength (8.89 gm). Mucoadhesion strength of formulation F1 to F9 varied from 5.15 gm to 8.89 gm (table 5).

Mucoadhesion Time

In formulation BP-1 to BP-6 four different polymer was used in which Carbopol 934P have better mucoadhesion property than other so BP4 shows greater mucoadhesion time 385 min than the formulation containing Eudragit RL-100 and ethyl cellulose. Mucoadhesion time of formulation BP-1 to BP-6 varied from 293minute to 385 minute (table 4).Mucoadhesion time of formulation F1 to F9 varied from 273minute to 345 minute (table 5).

Folding Endurance

As the amount of glycerin increases the folding endurance was found to be increases. The folding endurance for all the formulation was found more than 300 times which was satisfactory to reveal good film properties for all the formulation.

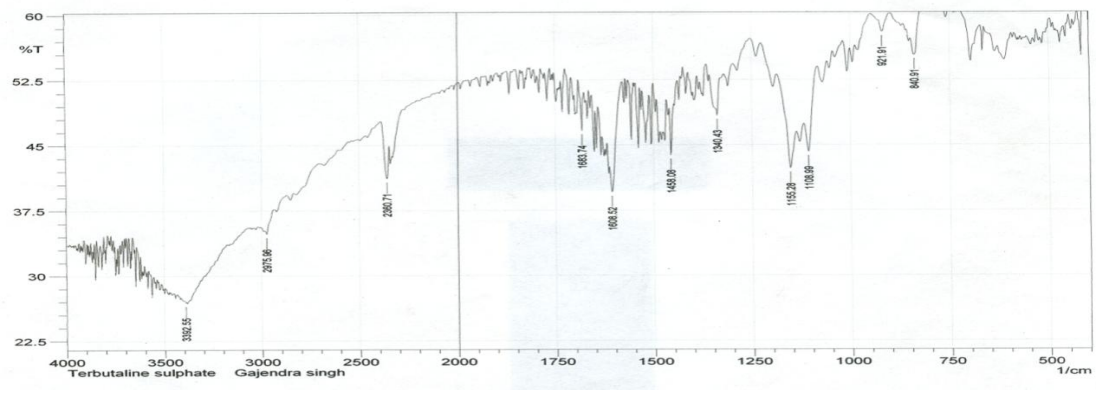

Figure 1: I.R spectra of pure drug of Terbutaline sulphate

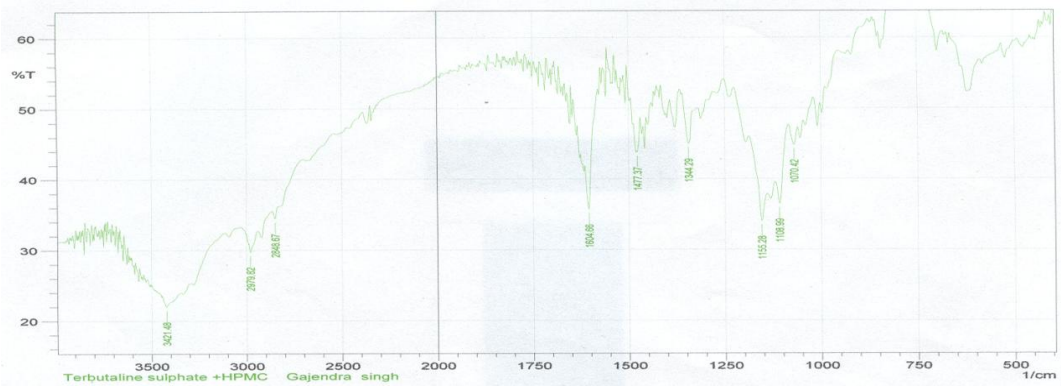

Figure 2: IR spectrum of Terbutaline sulphate and HPMC

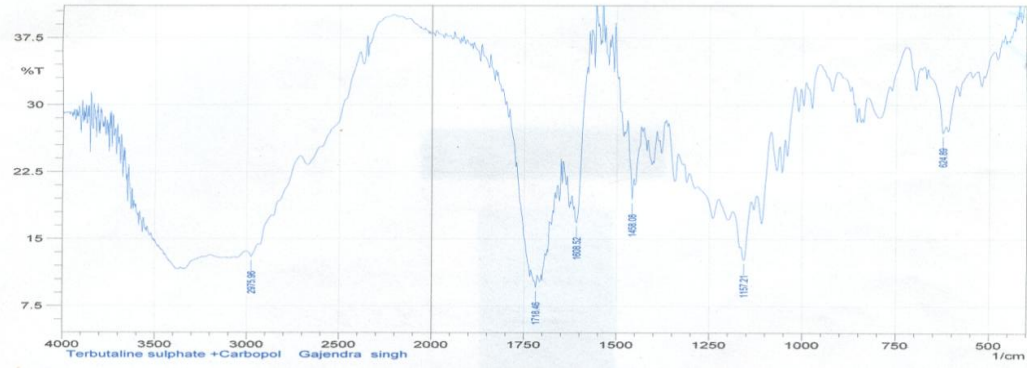

Figure 3: IR spectrum of Terbutaline sulphate and Carbopol

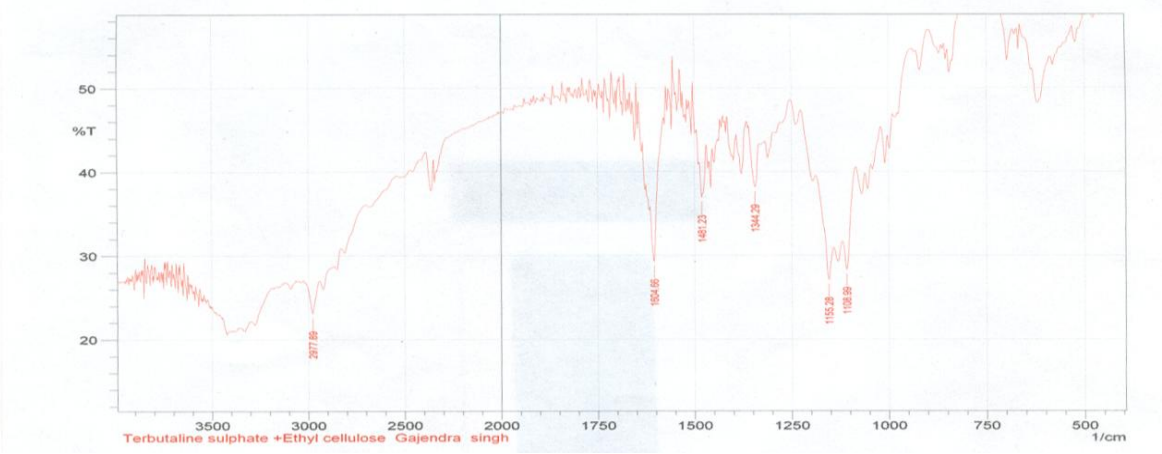

Figure 4: IR Spectrum of Terbutaline sulphate and Ethyl cellulose

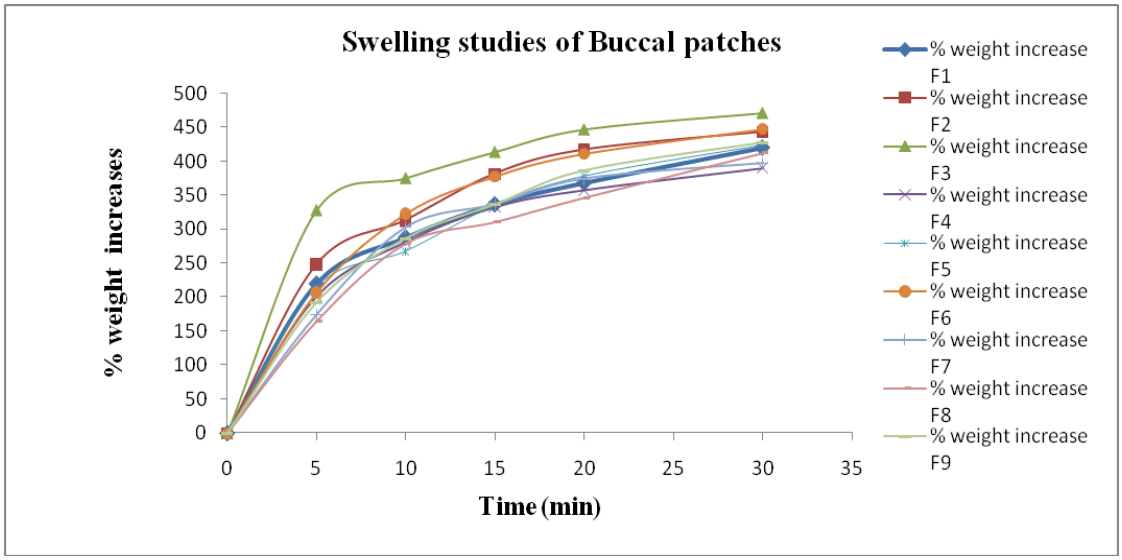

Figure 5: Swelling studies of buccal patches

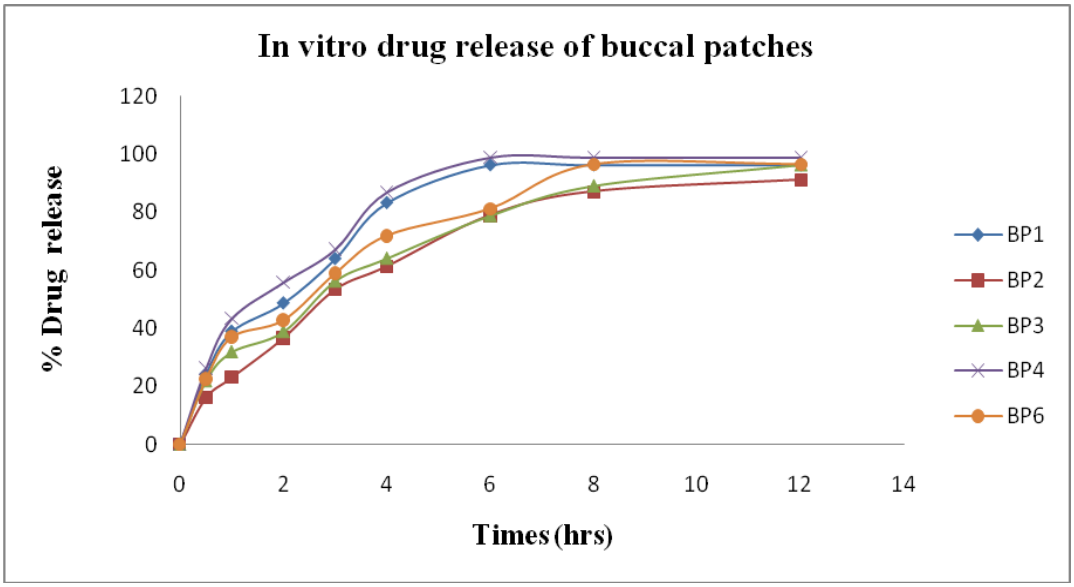

Figure 6: In- vitro drug release of buccal patches containing different polymer

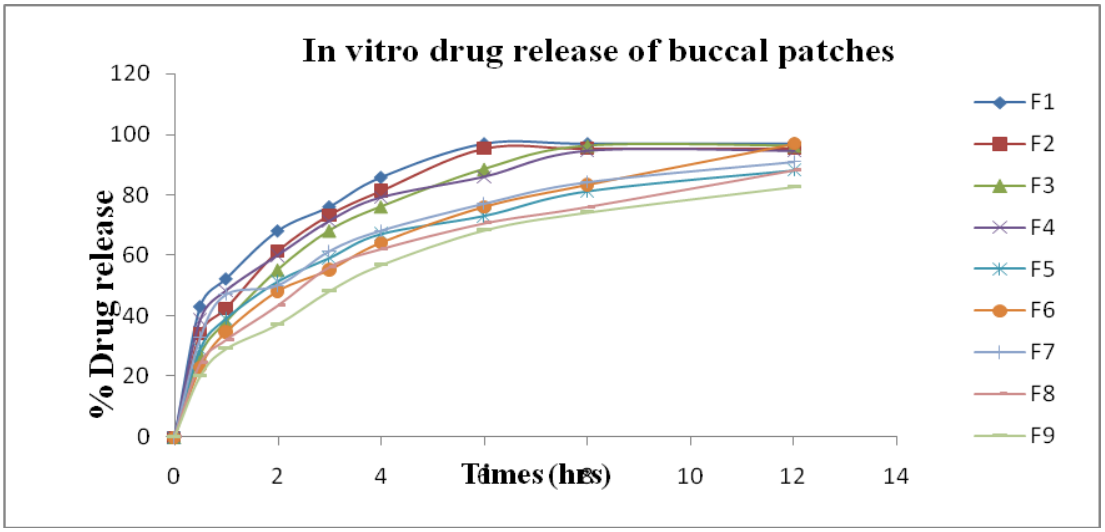

Figure 7: In- vitro drug release behaviour of buccal patches

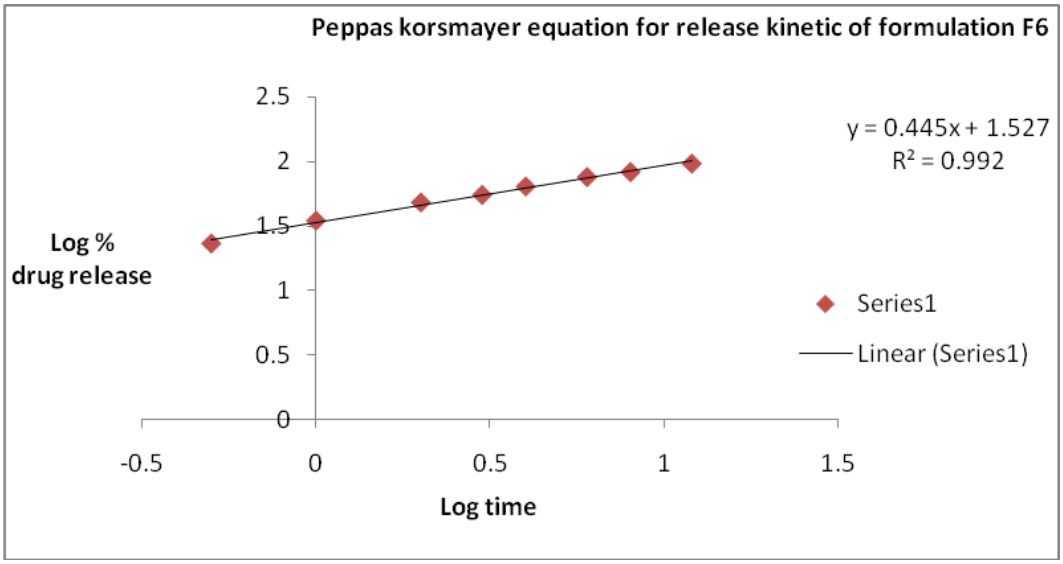

Figure 8: Peppas korsmayer equation for release kinetic of formulation F6

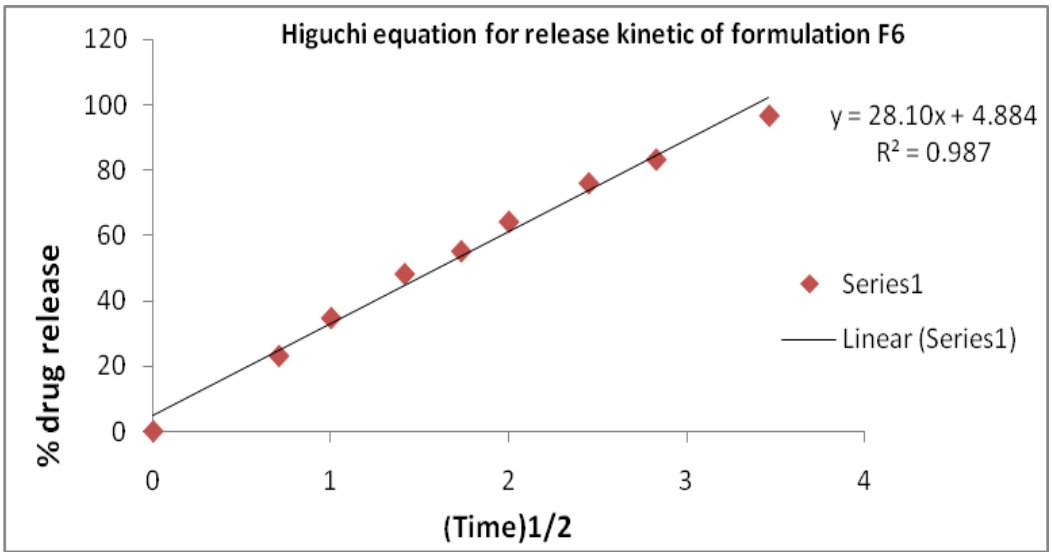

Figure 9: Higuchi equation for release kinetic of formulation F6

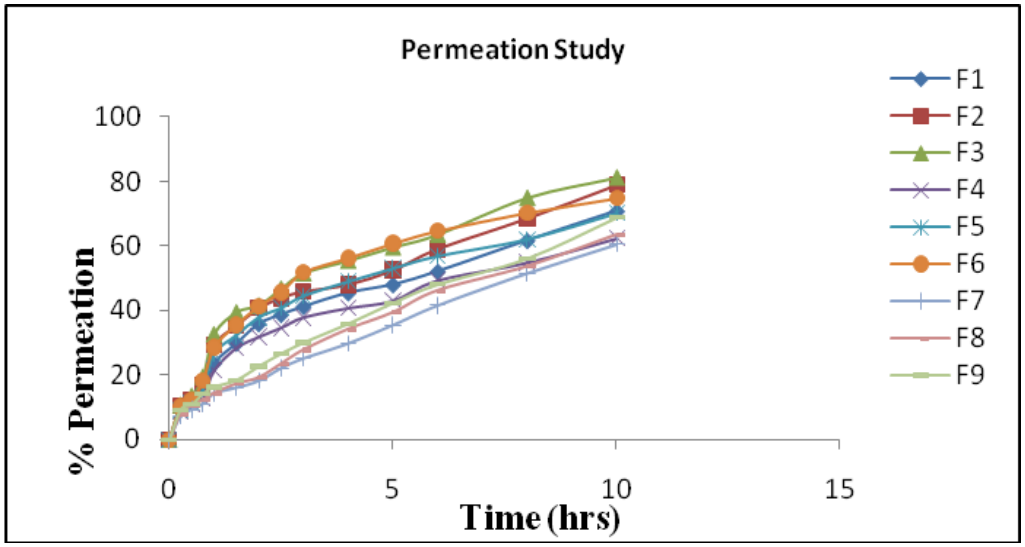

Figure 10: Ex- vivo permeation studies of buccal patches

In-vitro drug release study

The release data of Terbutaline sulphate from all the patches are given in (table 4, 5). A perusal to table 4 indicated that In case of formulation BP-1 to BP-6 the release data of Terbutaline sulphate from all the patches indicated that the drug release was higher in HPMC (patch BP1) and HPMC-Carbopol combinations (patches BP4 and BP5) at pH 6.8, Carbopol is present in the ionized state and as a result the polymeric network gets loosened comparatively, attributing for the higher drug release .Eudragit retarded the release rate of drug from HPMC patches (patch BP2 and BP3). An increase in the polymer content was associated with a corresponding decrease in the drug-release rate BP-3 shows in-vitro drug release 96.36% in 12 hours (Figure 6). In formulation F1 to F9 in-vitro drug release varied from 82.63% to 96.89% in 12 hours. In formulation F1-F3 which was made of HPMC alone gave faster drug release as compared to which have HPMC in combination with Eudragit RL-100. Formulation F1 release 96.91% drug within 6 hours, while formulation F6 uniform and sustain drug releases 96.89% drug in 12 hours (Figure7).

Kinetic of drug release

The data were processed for regression analysis using MS EXCEL statistical function. The values of release exponent (n) were calculated from Korsmeyer and Peppas equation and the 'n' values was determine to be 0.4452 indicating Anomalous (Quasi-fickian) diffusion (Figure 8)**.**

Ex-vivo drug diffusion studies

In the formulations BP1 to BP6 Ex-vivo drug diffusion varied from 69.46% to 83.74%. Faster permeation is shown by patch BP1 83.74% and slower permeation by patch BP2 69.46% in 9 hour (table 4).In case of formulation F1 to F9 faster permeation is shown by formulations F1 to F3 which has HPMC alone as compare to other formulations which have HPMC in combination with Eudragit RL-100 which retard the drug release from the buccal patch. Ex-vivo drug diffusion varied from 60.53% to 81.25% in 10 hours. Formulation F7 diffuses 60.53%drug in 10 hours, while formulation F3 diffuses 81.25% drug in 10 hour (table 5 and figure 10).

Stability studies

Terbutaline sulphate buccal patches showed no significant change in the physical appearance, percent residual drug content, In-vitro dissolution and Ex-vivo drug diffusion studies was determined at 0, 15, 30 and 45 days which showed no significant change at room temperature and in stability chamber at 40±1ºC and 75 % relative humidity this indicate that optimized formulations were stable.

CONCLUSION

The main advantage of this formulation is that it contains a lower drug dose, sufficient for therapeutic effect as it bypass first pass metabolism. The results showed that mucoadhesive buccal patch containing 280mg HPMC and 70mg Eudragit RL-100 produced buccal patches having good mucoadhesive strength and 96.89% drug release in 12 hr .Good results were obtained both *in vitro* and *ex- vivo* conditions for bioadhesive buccal patch for Terbutaline sulphate so It may be concluded that buccal route is one of the alternatives available for administration of Terbutaline sulphate.

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