Available online at www.ijpsdronline.com
International Journal of Pharmaceutical Sciences and Drug Research 2010; 2(3): 193-198

Research Article ISSN 0975-248X

Development and Evaluation of Epichlorohydrin Cross-linked Mucoadhesive Patches of Tamarind Seed Polysaccharide for Buccal Application

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ABSTRACT
In this study, buccal patches of metronidazole were formulated by solvent casting method using tamarind seed polysaccharide (TSP). The patches were crosslinked with epichlorohydrin and different batches were prepared following 2^3 factorial design. The patches were evaluated with respect to their *ex-vivo* drug permeation characteristics, mucoadhesive strength, folding endurance, and buccal residence time. At lower level of cross linker and plasticizer, the drug permeation was the highest (72.72%). The drug release from the patches was dominated by a dissolution-controlled mechanism rather than diffusion. The folding endurance did not vary widely (201-254), however the mucoadhesive strength (6.1-36.5 g) and the residence time (~2-6 h) deviated widely depending upon the formulation variables. The FT-IR spectroscopy revealed no interaction between drug and polymer. Thus the TSP could be a promising vehicle for the fabrication of buccal patches.

Keywords: Tamarind seed polysaccharide, propylene glycol, Buccal patches, Metronidazole, Folding endurance, *Ex vivo* permeation.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the oral administration. It has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable, for administration of retentive dosage forms. [1-2] The direct entry of the drug into the systemic circulation avoids the first-pass hepatic metabolism leading to increase in bioavailability. [3-4] Various mucoadhesive formulations were suggested for buccal delivery that includes buccal patches, adhesive tablets and adhesive gel. [5] Buccal patches overcome some of the drawbacks of other dosage forms. They have unique characteristics including flexibility, relative rapid onset of drug delivery, sustained drug release and rapid decline in the serum drug concentration when the patch is removed. The patch is confined to the buccal area over which it is attached and therefore the absorption profile may have less inter and intra-individual variability. Tamarind kernel powder (TKP) is derived from the seeds of *Tamarindus indica* Linn, a common and most important tree of India and South East Asia. Tamarind seed polysaccharide (TSP) has xyloglucan and glucose backbone with xylose and galactose decoration as side chains. [6] Refined TSP is used as a thickening, stabilizing and gelling agent in the food industry, particularly in Japan where it is a permitted food additive. The polysaccharide is composed of (1→4)-β-D-glucan backbone substituted with side chains of α-D-xylopyranose and β-D-galactopyranosyl (1 to 2)-α-D-xylopyranose linked (1→ 6) to glucose residues. The glucose, xylose and galactose units are present in the ratio of 2.8:2.25:1.0. [7-8] In India, TKP is one of the cheapest gums available. TSP has excellent stability over the acid pH range. [9] Tamarind seed polysaccharide has the ability to form the gels in the presence of sugar or alcohol. The molecular weight of the polysaccharide is reported to the range from 115,000 to 2,500,000 Da. [10]

TSP has been described as a viscosity enhancer showing mucomimetic, mucoadhesive, and bioadhesive activities. [11] TSP is noncarcinogenic, biocompatible and has high drug holding capacity. These led to its application as excipient in hydrophilic drug delivery system. [12-14] Since TSP is an important excipient, the release kinetics of both water-soluble and water insoluble drugs from this matrix were investigated

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and high thermal stability was also observed. [11] It is used as binder in tablets, gelling agent, thickening agent, as emulsifier and as stabilizer in food, and pharmaceutical industries. Due to its hydrophilic and mucoadhesive property, it can be used in mucoadhesive drug delivery system. [14] TSP has a promising pharmaceutical uses and is presently under research as a carrier material in colon-specific drug delivery systems. [15]

Literature survey reveals that buccal formulation made from TSP was not till studied. The lack of hydrogel delivery devices for hydrophobic drugs also observed that might be due to low attention paid to the incorporation of relatively hydrophobic drugs into hydrogels. So in the present study we aimed to develop a buccal delivery of TSP patch with metronidazole as model drug.

Scientists often face the challenge of finding the appropriate combination of variables that will produce the product with optimum properties. [16] The optimization technique encompasses designing a set of experiment that will reliably measure the response variables, fitting a mathematical model to the data and conducting appropriate statistical test to assure that the best possible model is chosen [17] and determining the optimum value of independent variables that produce best response and this is the another aspect of this study that is to use the principles of quality by design (QbD) along with appropriate design of experiments to obtain a comprehensive knowledge about effect of different variables on the formulations. QbD aims at making the regulatory approval process more flexible without compromising patient safety. Regulatory agencies such as the US FDA, have championed QbD principles to ensure rapid availability of high quality pharmaceutical products. [18]

The use of statistical formula optimization methodology has been commonly used for designing and optimization of different pharmaceutical formulations. [19-20]

Thus, the objectives of the studies are i) to develop different TSP buccal patches using different concentration of cross-linkers and plasticizers and optimize the effect of these independent variables on the *ex-vivo* drug permeation by 2^3 factorial designs. ii) to characterize them physically and iii) to observe their *ex-vivo* mucoadhesivity, drug incorporation capability etc.

MATERIALS AND METHODS

Metronidazole (Medopharm, Chennai, India) was obtained as a gift sample. Tamarind seed was purchased from local market. Propylene glycols (PG), epichlorhydrin were purchased from Merck. All other reagents and ingredients were of analytical grade.

Isolation of tamarind seed polysaccharide

Raw seeds of Tamarind were dried in sun light for a day or two and the whole seed was broken into small pieces and ground into a fine powder. Distilled water was taken in a beaker and the required amount of fine powder of Tamarind seed was added to give a solution concentration of 4% (w/v). The solution was heated to 80-100°C with a constant stirring to avoid layer formation on the surface for 2 h, and subsequently filtered using glass wool to throw away the un-dissolved fraction. The un-dissolved material contained approximately 25% of the dry weight substance. Then the dried materials are called Tamarind kernel powder (TKP). TSP was prepared according the method described by Rao et al. [21] In brief, 20 g of tamarind kernel powder, 200 ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800 ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibers settled out. The solution was then centrifuged at 5000 rpm for 20 minutes. The supernatant was separated and poured into twice the volume of absolute ethanol by continuous stirring. The product was pressed between felt. The precipitate was washed with absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60°C under vacuum

Experimental design

A three-factor, two-level factorial design (2^3) was employed for optimization procedure with TSP amount (X_1), amount of epichlorhydrin (X_2), the cross linker and amount of propylene glycol (X_3), the plasticizer in the synthesis as three prime selected independent variables, which were varied at two levels, low level –1 and high level +1. The values of two coded levels of three factors were assumed after preliminary trials and are mentioned with the description of different formulation batches in Table 1. The percentage cumulative permeation of the drug was used as dependent variable. Design-Expert® DX 7 Software was used for the generation and evaluation of the statistical experimental design.

Preparation of gel and patch

Gel of TSP was prepared according to the method of cross linking of TSP with epichlorhydrin. [22] Tamarind seed polysaccharide and sodium hydroxide (1N, 54°C) were mixed thoroughly and epichlorhydrin was slowly added with continuous homogenization (15 min). Then the formed gel was diluted with water. After solubilization of metronidazole in acetic acid, the solution was added to the gel and mixed properly. After that the gel was neutralized with acetic acid solution and required amount of propylene glycol as plasticizer were added as mentioned in the formula. The patches were prepared using solvent casting technique. The metal rings having diameter of 4.5 cm and thickness 0.5 cm were used for holding the polymer solution on aluminum foil. The resulting gel was poured in the ring and dried at 50°C at an oven. After drying the patch was taken out from the metal ring and cut into circular shapes and stored in desiccators. The ratio of TSP to 1N NaOH solution (i.e. 0.5 ml NaOH per 100 mg of TSP) and amount of metronidazole loaded (i.e. 100 mg) were kept constant for all formulation including the optimized formulations (i.e. Formulation no. F9-F11)

Ex vivo permeation study

Tissue preparation

Buccal membrane of goat was collected from local slaughter house in Krebs ringer solution. The epithelium was separated from the underlying connective tissue with surgical technique immediately after collection. Then buccal mucosa was stored in a Krebs buffer solution at -20°C until used. Just before the experiment, it was thawed at room temperature and checked for any damage.

Ex vivo study

Drug permeation study was carried out with acetate buffer (pH 6) using Franz diffusion cells. The Patches were kept on stratum cornium side of cells and this patch complex sandwiched between donor and receptor compartment. The receiving compartment contains blank 35 ml of buffer and touches the dermal side of the buccal tissue. The whole the

assembly was kept on magnetic stirrer, which thermostatically controlled at 37°C at 60 rpm. Samples were withdrawn at pre set time interval from the receiving compartment and analyzed at 256 nm using UV-visible spectrophotometer (Spectronic, England, model-UV1-094022). The fresh buffer in receiving compartment was replaced after each withdrawal. The permeation studies continued for period of 9 h and calculated as cumulative percent drug permeated (CAP %).

Statistical and kinetic analysis

The *ex vivo* permeation profiles were tested for their kinetic behavior in order to establish the kind of mechanism possibly involved in metronidazole permeation through the buccal membrane. When the cumulative amount of drug permeated was plotted against time, the permeation profiles of the drug followed mixed zero-order/first-order kinetics. The in vitro release profiles of the formulations were fitted into zero-order kinetics (r^2 = 0.9739-0.9980) or first-order kinetics (r^2 = 0.9400-0.9892). However, the release profile of the formulated patches did not follow Higuchi's equation (r^2 = 0.6754-0.8780), which indicates that the permeation of the drug from the patches was not governed by a diffusion mechanism. Since many release processes can be represented by a coupling of a Fickian and non-Fickian mechanism. Korsmeyer and Peppas introduced the following power law equation (equation1) to characterize the controlled-release behavior of a drug from polymer matrices. [23]

$$Mt/ M\infty = Kt^n \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where $Mt/M\infty$ is the fraction of drug released at time t, k is a constant depending upon structural and geometric characteristics of the system and n is an exponent used to characterize the transport mechanism. For example, $n = 0.45$ for Case I or Fickian diffusion, $0.45 < n < 0.89$ for anomalous behaviour or non-Fickian transport, $n = 0.89$ for Case II transport, and $n > 0.89$ for Super Case II transport. [24] Case II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. [25]

Characterization of mucoadhesive patches

***Ex vivo* mucoadhesive strength**

The patch's bioadhesive strength was measured using a modified physical balance. [26] The fresh goat buccal mucosa was cut into pieces and washed with acetate buffer (pH 6). A piece of buccal mucosa was tied in the open mouth of a glass vial, filled with acetate buffer (pH 6). This glass vial was tightly fitted into a glass beaker filled with acetate buffer (pH 6) so it just touched the mucosal surface. The patch was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of the balance were balanced with a 5 gm weight on the right-hand side pan. The 5 gm weight was then removed from the left-hand side pan, which lowered the pan along with the patch over the mucosa. The balance was kept in this position for 5 minutes of contact time. The water was added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. Weight in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength.

Folding endurance test

The folding endurance of patches was determined by repeatedly folding 1 patch at the same place till it broke or was folded up to 200 times without breaking. [5]

***Ex vivo* residence time determination**

The *ex vivo* residence time was studied (n = 3) after application of patches on freshly cut goat buccal mucosa. The fresh goat buccal mucosa was fixed in the inner side of a beaker, about 2.5 cm from the bottom, with cyanoacrylate glue. One side of each patch was wetted with 1 drop of acetate buffer (pH 6) and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 200 ml of acetate buffer (pH 6) and was kept at 37°C ± 1°C. After 2 minutes, a 50 rpm stirring rate was applied to simulate the buccal cavity environment, and patch adhesion was monitored for 12 h. The time required for the patch to detach from the goat buccal mucosa was recorded as the residence time

Fourier transform infrared (FT-IR) spectroscopy

Fourier transform infrared (FT-IR) spectrum was recorded on Perkin Elmer (USA) FT-IR spectrophotometer (Spectrum Rx-1). Sample were prepared as KBr pellet and scanned against a blank KBr pellet background at wave number range 4000-400 cm^{-1}.

Table 1: Different Formulations of buccal patches of metronidazole according to 23 factorial design

Formulation	TSP (X1) mg	Epichlorohydrin (X2), ml	Propylene glycol (PG) (X3) ml	Cumulative % permeation
F1	100.00(-1)#	50.00(+1)	0.00(-1)	46.47
F2	500.00(+1)	10.00(-1)	0.40(+1)	53.91
F3	500.00(+1)	50.00(+1)	0.00(-1)	43.18
F4	100.00(-1)	10.00(-1)	0.40(+1)	51.85
F5	500.00(+1)	50.00(+1)	0.40(+1)	38.65
F6	500.00(+1)	10.00(-1)	0.00(-1)	72.72
F7	100.00(-1)	50.00(+1)	0.40(+1)	33.48
F8	100.00(-1)	10.00(-1)	0.00(-1)	67.28

coded values are given in parentheses; In all formulations, 0.5 ml of NaOH per 100 mg of TSP and 100 mg of metronidazole were added.

RESULTS AND DISCUSSION

***Ex vivo* permeation study**

The purpose of using a full factorial experimental design was to conduct a comprehensive study of the effect of the process parameters and their interactions using a suitable statistical tool (Design–Expert® DX 7 Software) by applying one-way ANOVA at 0.05 levels. Individual response parameters were evaluated using the F-test. A mathematical modeling was carried out by using equation 2 to obtain a first–order polynomial equation depending on significant influences among three factors (X_1, X_2 and X_3) of the factorial design model.

$$Y = b_o + b_1 X_1 + b_2 X_2 + b_3X_3 + b_4 X_1X_2 + b_5X_1X_3 + b_6X_2X_3 + b_7X_1X_2X_3 \ldots\ldots\ldots\ldots (2)$$

Where Y = the dependent variable, while b_o = the intercept, b_1, b_2, b_3, b_4, b_5, b_6 and b_7 = regression coefficients; X_1, X_2 and X_3 = main effects; X_1X_2, X_2X_3, X_1X_3 and $X_1X_2X_3$ = interactions between main effects.

The values of the drug permeation data in 2^3 factorial designs (Table 1) were fitted to a first order polynomial model based on response surface regression. Model simplification was carried out by eliminating non-significant parameters ($p<0.05$) in the polynomial equation resulting from multiple regression analysis and the model equation became:

$$Y= +72.35250+2.68750E\text{-}003*X_1-0.52487*X_2-37.11250*X_3+0.015875* X_1X_3 \ldots (3)$$

The results of the ANOVA, as shown in Table 2, indicated that the model was significant for all response parameters

investigated with an F-value of 43.05 (p> F 0.0007) and R^2 value of 0.9999.

The influence of the main effects like TSP amount (X_1), amount of epichlorhydrin, the cross linker (X_2) and amount of propylene glycol, the plasticizer in the synthesis (X_3) as three prime selected independent variables on the response i.e. the cumulative % drug permeation (Y), was further elucidated using perturbation plot (Fig.2). Cumulative amount of metronidazole permeated through the different buccal patches (formulation F1 to F8) are shown in Fig.1. It was observed from the response that formulation F6 had the highest drug permeation in 9 h. This may be attributed to lowest amount of cross linker and no plasticizer. But the permeation of drug from F8 in 9 h (67.28%) suggested that decreasing amount of TSP also decrease the drug permeation. A numerical optimization technique using the desirability approach was employed to develop new formulations with desired response. Constraint of optimizing the metronidazole permeation through buccal patch in 9 h was to set as goal to locate the optimum settings of independent variables in the new formulation, as shown in Table 5, formulation F9-F11. The optimized buccal patch formulation was evaluated for drug permeation again. Table 5 listed the values of the observed responses and those predicted by mathematical model. The observed value of drug permeation of the optimized buccal patch formulation was almost similar to the predicted value by using mathematical model. This reveals that the mathematical model obtained by the 2^3 factorial experimental designs to produce optimized response was well fitted. Model reduction by eliminating insignificant terms has already been reported to result in better prognosis of the performance of the optimized formulations. [25]

Release kinetics

Release kinetics of drug of different formulation follows zero order (R^2=0.9128-0.9985), first order (R^2 =0.9207-0.9813) and Koresmeyer-Peppas equation. Different formulations and their release kinetic models with regression co-efficient are reported in Table 3. To evaluate the drug release kinetics, formulations showing a significant slow release, formulations F3, F5 and F7 were chosen. In general, the mechanism of drug release from polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a "front" defined at an exact speed; simultaneously, the thickness of the area increases with time in the opposite direction. The mechanism of drug release can be described by a second phenomenon that involves the disentanglement and erosion of the polymer and for tamarind xyloglucan patches, the release process involves the penetration of water into the dry matrix, followed by hydration and swelling of the polymer, and release of the drug that dissolved in the matrix. By using the Korsmeyer and Peppas model equation [26], the *n* values were obtained between 1.21 and 1.65 (Table 3) for all formulations. These values are characteristic of super case II transport, suggesting that the contribution of polymer relaxation occurs throughout the entire dissolution period. The F6 and F8 formulations showed the highest contribution of polymer relaxation, and swelling/erosion. In this context, the results obtained from the fitting the data in Higuchi's equation and zero order kinetics also supported the theory that the release of the drug from the patches was by a dissolution-dominated mechanism rather than diffusion dominated.

Mucoadhesive strength, folding endurance, and residence time

The *ex vivo* mucoadhesive strength, residence time and folding endurance are shown in Table 4. The results obtained explained that amount of TSP has a prominent effect on mucoadhesive strength and residence time of the patches. The effect of propylene glycol on folding endurance was also observed in different formulations of buccal patches.

Table 2: Analysis of variance table

Source	Sum of Squares	df	Mean Square	F value	Prob >F	p-value
Model	1216.47	2	608.23	43.05	0.0007	
B-amt of epichlorohydrin	881.58	1	881.58	62.40	0.0005	significant
C-amt of PG	334.89	1	334.89	23.70	0.0046	
Residual	70.64	5	14.13			
Cor Total	1287.11	7				

The model F-value of 43.05 implies the model is significant. There is only a 0.07% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, C are significant model terms.

Table 3: Regression coefficient of various formulation patches in different release kinetic model

Formulation	Zero order (R^2)	1st order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas model equation	
				(R^2)	n
F1	0.9227	0.9249	0.7909	0.9810	1.3700
F2	0.9852	0.9729	0.8100	0.9997	1.2814
F3	0.9295	0.9490	0.7013	0.9964	1.5640
F4	0.9873	0.9813	0.8037	0.9992	1.2123
F5	0.9128	0.9388	0.6937	0.9988	1.6369
F6	0.9985	0.9777	0.8780	0.9971	1.0059
F7	0.9348	0.9613	0.7300	0.9967	1.6532
F8	0.9744	0.9555	0.7663	0.9923	1.2964
F9	0.9249	0.9409	0.6754	0.9967	1.8770
F10	0.9836	0.9719	0.7932	0.9994	1.2248
F11	0.9335	0.9207	0.7061	0.9826	1.3170

Table 4: Mucoadhesive strength, folding endurance and *ex vivo* residence time of different patches

Formulations	Adhesive strength Mean±SD	Folding endurance (Mean±SD)	Residence time (min) Mean±SD
F1	7.50 ± 0.50	208 ± 3.15	139±1.00
F2	29.23 ± 0.24	236 ± 1.73	353±3.05
F3	16.10 ± 0.10	201 ± 1.00	339±2.70
F4	9.15 ± 0.25	225 ± 2.50	149±2.25
F5	36.5 ± 0.50	238 ± 1.50	325±5.45
F6	28.25 ± 0.50	203 ± 3.45	335±0.05
F7	10.06 ± 0.25	254 ± 2.66	140±4.50
F8	6.10 ± 0.56	207 ± 1.50	136±2.50
F9	26.40 ± 0.85	207 ± 2.11	237±3.40
F10	24.73 ± 0.27	229 ± 1.73	218±2.20
F11	28.71 ± 0.35	217 ± 1.00	257±4.30

Table 5: *Ex vivo* % cumulative amount permeation of optimized formulations (including their formula) through buccal skin of goat

Formulation	TSP (X_1), mg	Epichlorhydrin (X_2), ml	Propylene glycol (X_3), ml	Cumulative% permeation predicted	Cumulative% permeation observed
F9	313.80	25.0	0.00	60.04	59.1
F10	256.30	30.00	1.00	54.17	58.2
F11	379.00	20.00	0.50	61.04	63.4

Fourier transform infrared (FT-IR) spectroscopy

The FT-IR spectra of TSP, metronidazole and TSP-metronidazole composite have been cited in Fig.3. FT-IR spectra of TSP revealed the following data: 1401.12 cm^{-1} C-O-C stretching, 2927.38 cm^{-1} aliphatic C-H stretching,

3320.16 cm^{-1} O-H stretching. FT-IR spectra of metronidazole revealed the following data: 1265.28 cm^{-1} C-O stretching ,1369.22 cm^{-1} N-O stretching , 1536.23 cm^{-1} C=N stretching , 3223.21 cm^{-1} O-H stretching. FT-IR spectra of TSP-metronidazole revealed the following data: 1265.28 cm^{-1} C-O stretching, 1369.23 cm^{-1} N-O stretching, 3217.05 cm^{-1} O-H stretching, 2958.21 cm^{-1} aliphatic C-H stretching. FT-IR spectra of TSP, metronidazole and TSP-metronidazole showed chemical stability of polymer matrix as well as non-existence of interaction between TSP and metronidazole. So the TSP- metronidazole matrix might be used as a buccal formulation.

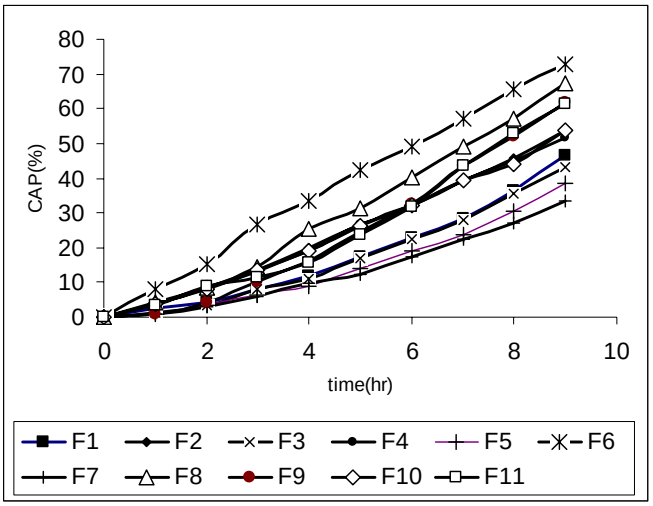

Fig. 1: *Ex-vivo* cumulative amount of metronidazole permeation (CAP %) as a function of time through goat buccal skin from the different buccal patch formulations

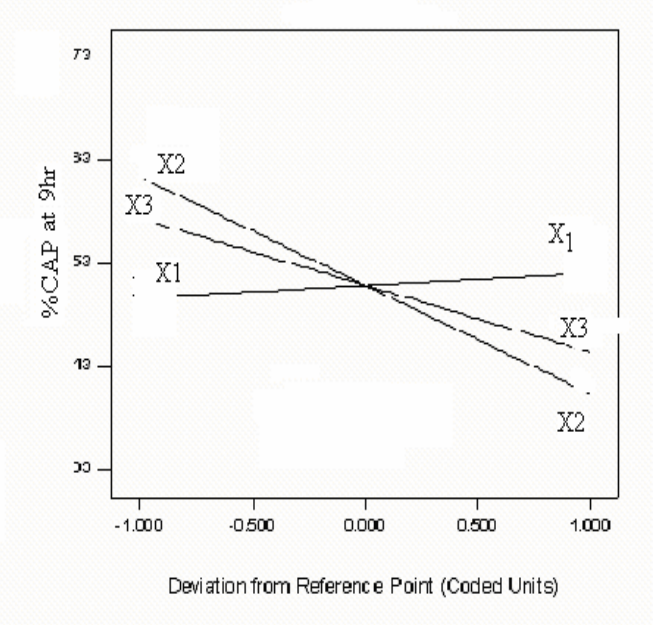

Fig. 2: Perturbation Plot showing the effect of three factors on %CAP at 9h

In conclusion, it can be stated that the buccal patches prepared from gel of TSP and metronidazole was successful. The application of 2^3 factorial designs was useful in developing statistically optimized formulations of TSP as buccal patches. The use of 2^3 factorial experimental designs allowed us to describe the influence of the significant independent input variables by a simple first-order polynomial equation in experimental area studied. The reduced model equation also illustrated that the influence of the amount of epichlorhydrin, the cross linker (X_2) , amount of propylene glycol, the plasticizer (X_3) and their interactions were significant on the in-vitro permeation but the influence of the amount of TSP (X_1) was insignificant. The ex-vivo mucoadhesive study showed that the required mucoadhesive strength was attained by each formulation and folding endurance study revealed that TSP alone had a good plasticizing effect that decreased the need of adding other plasticizer. It can be finally concluded that TSP might be well utilized to develop a buccal drug delivery system with required mucoadhesive strength.

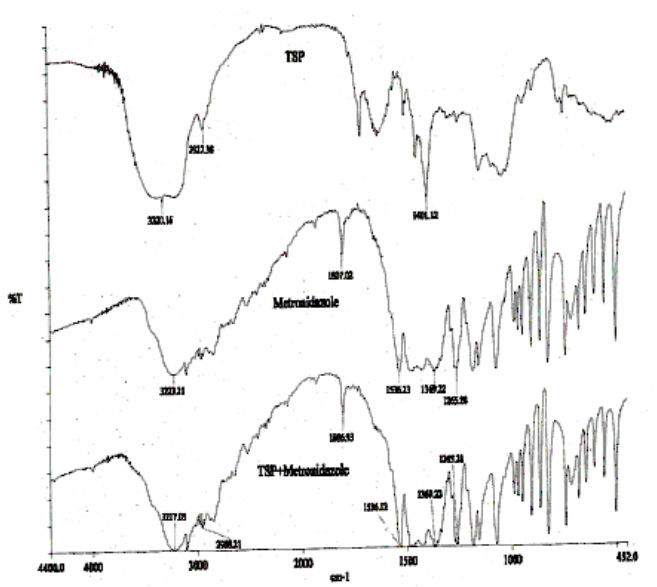

Fig. 3: FT- IR spectra of TSP , metronidazole and TSP- metronidazole

ACKNOWLEDGMENTS

The study was sponsored by Gupta college of Technological Sciences, Ashram More, G.T. Road, Asansol-713301, West Bengal; India. The authors also acknowledge the help of Mr. H.S. Maji for conducting FTIR studies.

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