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DESIGN AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF SALBUTAMOL SULPHATE BY USING HUPU GUM AND LANNEA GUM

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ABSTRACT: The purpose of the present investigation is to evaluate the applicability of hupu gum and lannea gum in the design of buccoadhesive patches for extended-release over a period of 6 hours, using Salbutamol sulphate as a model drug. The efficiency of these polymers was compared with already established synthetic polymer PEO coagulant. The patches were prepared by using the solvent casting method in which, initially backing layer with cellulose acetate was formed on which patches were cast for unidirectional drug release to buccal mucosa. *In-vitro* drug diffusion studies were done by using Franz diffusion cells. The kinetics of both the phases were calculated, and both the phases followed zero-order for the majority of the patches. Based on the swelling Index (%), buccoadhesive strength, *ex vivo* residence time and in vitro diffusion studies SHG9 (hupu gum), SLG9 (lannea gum) and SPEO6 were considered as optimized formulations as they could extend the drug release over a period of 6 hours as contemplated. Among three optimized patches, SHG9 and SLG9 were found to be superior compared to SPEO6 due to significantly higher swelling index, buccoadhesive strength, and *ex vivo* residence time.

INTRODUCTION: Over the past few decades, the oral route has been the major route for the administration of therapeutic agents due to low cost, ease of administration, and high level of patient compliance. However, the drugs administered through the oral route have certain limitations like gastric irritation and first-pass metabolism leading to poor bioavailability [1]. Buccal drug delivery has high patient acceptability, bypasses hepatic first-pass metabolism, and also avoids acid hydrolysis in the gastrointestinal (GI) tract, compared to other non-oral transmucosal routes of drug administration [2].

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Salbutamol sulphate was selected as model drug as it is a suitable candidate for the buccoadhesive drug delivery. Salbutamol sulphate is with a short biological half-life and suffers with the first-pass metabolism which requires increased frequency of administration. Drugs which are having a short biological half-life and hepatic first-pass metabolism are frequently administered with higher doses than the dose required to maintain blood concentrations within the therapeutic range. Decreased frequency of administration and fewer doses reduces adverse effects and improves patient compliance. Hence, salbutamol sulphate was selected as the model drug in the design of buccoadhesive patches [3].

Hupu gum or Kondagogu gum is a naturally occurring polysaccharide derived as an exudate from the deciduous tree *Cochlospermum religiosum* belongs to the family *Bixaceae.* Lannea gum or

gumpena gum is a naturally occurring poly-saccharide obtained from *Lannea coromandelica* tree belongs to the family Anacardiaceae [4-6].

MATERIALS AND METHODS: Salbutamol sulphate is obtained as a gift sample from M/s. Hetero Drugs Ltd., Hyderabad. PEO coagulant, cellulose acetate, acetone, glycerine was provided by M/s. Qualigens Fine Chemicals Pvt. Ltd., India. Hupu gum and lannea gum purchased from M/s. Palaniappa Chettiar Traders, Chennai. All other chemicals used were of analytical grade.

Preparation of Backing Layer: Initially backing layer was casted in the petri dish by using cellulose acetate as polymer by solvent casting method1. Cellulose acetate was dissolved in acetone and backing layer was casted in the petri dish with 8.6 cm. The thickness of the backing layer varied with concentration of cellulose acetate and the volume of acetone used for dissolving the polymer. Initial trials were made and finally the composition of the backing layer was optimized with 600 mg of cellulose acetate in 20 mL of acetone for the selected petri dish. 600 mg of cellulose acetate was weighed and dissolved in 20 mL of acetone and added with 0.2 mL of glycerine as plasticizer. The thickness of the patch was found to be 0.092±0.001 mm. The prepared solution was poured into a petri dish of 8.6 cm diameter and kept at room temperature (~26ºC) and allowed to dry for 6-8 hours.

Solvent casting method was used for the preparation of patches using a different drug to polymer (hupu gum/lannea gum/PEO coagulant) ratios. The buccoadhesive patches were casted on the dried backing layer in the petri dish. These patches were prepared in the drug and polymer ratio of 1:2, 1:2.5, and 1:3 for two natural gums and in the ratio 1:2.5 and 1:3 for PEO coagulant.

Formulae of salbutamol sulphatebuccoadhesive patches are presented in **Table 1-3**. Initially, the polymer was weighed accurately, and it was swollen in half quantity of distilled water. Salbutamol sulphate and penetration enhancer were weighed and dissolved in the remaining quantity of distilled water. This solution was added to the above polymer mucilage and stirred well using a magnetic stirrer (100 rpm) to obtain a homogenous solution. This solution was allowed to stand for 30 minutes for deaeration of the solution. The solution was then casted into a petri dish containing a backing layer and kept in a hot air oven for 8-10 hours at 60ºC. After drying, patches were removed with the help of scalpel. The obtained patch was cut into pieces of 1 cm length x 1 cm breadth with an area of 1.0 cm^2.

TABLE 1: FORMULATION OF HG- SALBUTAMOL SULPHATEBUCCOADHESIVE PATCHES

Ingredients	SHG1	SHG2	SHG3	SHG4	SHG5	SHG6	SHG7	SHG8	SHG9
Salbutamol sulphate(mg)	232	232	232	232	232	232	232	232	232
Hupu gum (mg)	464	464	464	580	580	580	696	696	696
Poloxamer 407 (mg)	-	0.007	0.013	-	0.007	0.013	-	0.007	0.013
Glycerine (mL)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Distilled water (mL)	20	20	20	25	25	25	30	30	30

TABLE 2: FORMULATION OF LG- SALBUTAMOL SULPHATEBUCCOADHESIVE PATCHES

Ingredients	SLG1	SLG2	SLG3	SLG4	SLG5	SLG6	SLG7	SLG8	SLG9
Salbutamol sulphate(mg)	232	232	232	232	232	232	232	232	232
lannea gum (mg)	464	464	464	580	580	580	696	696	696
Poloxamer 407 (mg)	-	0.007	0.013	-	0.007	0.013	-	0.007	0.013
Glycerine (mL)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Distilled water (mL)	20	20	20	25	25	25	30	30	30

TABLE 3: FORMULATION OF SPEO–SALBUTAMOL SULPHATEBUCCOADHESIVE PATCHES

Ingredients	SPEO1	SPEO2	SPEO3	SPEO4	SPEO5	SPEO6
Salbutamol sulphate(mg)	232	232	232	232	232	232
PEO coagulant (mg)	580	580	580	696	696	696
Poloxamer 407 (mg)	-	0.007	0.013	-	0.007	0.013
Glycerine (mL)	0.5	0.5	0.5	0.5	0.5	0.5
Distilled water (mL)	25	25	25	30	30	30

Evaluation of Buccoadhesive Patches [7-10]: The prepared unidirectional buccoadhesive patches were evaluated for uniformity of weight, thickness, folding endurance, drug content, swelling index (%), surface pH, and mucoadhesive properties like buccoadhesive strength, *ex-vivo* residence time, and *in-vitro* drug release studies.

Uniformity of Weight and Thickness: Five patches (each of 1 cm^2) from each formulation were selected randomly and weighed individually on a digital balance to determine the uniformity of weight. The average weights and % deviation from the average weight were calculated. Five patches were randomly selected, and the thickness of each patch was measured at five points, and mean thickness is calculated.

Folding Endurance: Folding endurance is essential to determine the mechanical properties of patch and was measured by repeatedly folding the patch at the same place till it broke or was folded up to 300 times without breaking. The number of times the patch is folded without breaking is calculated as the folding endurance value.

Uniformity of Drug Content: Five patches (each of 1 cm^2) from each formulation were randomly selected and each patch was dissolved separately in a 30 mL of pH 6.8 phosphate buffer with vigorous shaking on a mechanical shaker for 2 hours. The contents were transferred into a 50 mL volumetric flask and made up to the volume with pH 6.8 phosphate buffer and thoroughly shaken for 5 minutes and filtered through 0.45 µm Millipore filter disc. The collected filtrate was suitably diluted and estimated for salbutamol sulphate content by measuring absorbance at 276 nm against reagent blank (pH 6.8 phosphate buffer). The patches complies the pharmacopoeial test for uniformity of content of salbutamol sulphate if all the tested units fall within the range of 98 – 101% as per IP[11-13].

Swelling Index (%): 2% (w/v) agar solution was prepared in warmed pH 6.8 phosphate buffer and poured into the petri dish and allowed for gelling at room temperature. Buccoadhesive patches were weighed individually (W_1) and placed in petri dish sufficient for carrying out the study for a period of 6 hours with the drug-polymer layer facing agar gel and allowed to swell. One patch was removed from the petri dish at regular intervals of 1, 2, 3, 4, 5, and 6 hours and excess water was removed carefully with tissue paper. The swollen patches were then reweighed (W_2). The swelling index (%) values were calculated using the following equation[14-26].

$$\text{Swelling index} = [(W_2-W_1)/W_1)] \times 100$$

Each experiment was repeated three times, and average values are reported.

Determination of Surface pH: 2% (w/v) agar solution was prepared in warmed pH 6.8 phosphate buffer and poured into the petri dish, and allowed for gelling at room temperature. Patches from each formulation were kept on the agar gel with the drug-polymer layer facing the agar gel and were allowed to swell for 1 hour on the surface of the agar plate. The patches were carefully removed, and pH paper (BDH 8510 Indicator paper range of 1-14) was placed on the surface of the drug-polymer layer for measuring pH. This experiment was performed in triplicate (n=3), and the surface pH range was reported [27-28].

Buccoadhesive Strength: A modified balance method is designed with a similar concept used for determining the buccoadhesive strength, as illustrated by Ch'Ng Hung Seng *et al.* [7] Fresh buccal mucosa of swine is obtained from the slaughterhouse. The mucosal membrane was collected after separating the underlying fat and loose tissues. The membrane obtained was washed with distilled water and then with phosphate buffer pH 6.8 and cut into pieces. A piece of buccal mucosa was attached to the glass slide with the mucosal side facing outwards using rubber band, which was fixed over a heavy stainless steel object using cyanoacrylate glue and placed in petri dish filled with pH 6.8 phosphate buffer so that the membrane used in the experiment was kept wet throughout the experimental conditions. During the study, an empty glass beaker was kept in the left pan. The right pan of the physical balance was removed and fixed with 2 × 2 cm glass side in place of the pan using non-elastic thread. The two sides of the balance were made equal before the study by placing the required weight on the right-hand side of the balance over the fixed 2 × 2 cm glass slide. The non-elastic thread was tied to the glass slide of 2 × 2 sizes. This 2 × 2 cm glass side was hanged from the right-hand side of the balance

to which the coated side of the patch was attached with cyanoacrylate glue, and the core side of the patch touches mucosal side of the buccal membrane placed in the petri dish [29-30].

The mucus layer and the patch were wetted with pH 6.8 phosphate buffer, and the patch was fixed to the mucus layer by applying a little pressure. This was kept undisturbed for 5 min. On the left-hand side, water was added with a slow infusion rate from the burette into the glass beaker placed in the left pan until the patch placed on right-hand side detached from the membrane surface. Experiment was performed in triplicate (n=3), and the weight of water in grams required to detach the patch was measured. The detachment force can be measured from the following equation and the values were expressed in Newton (N).

$$\text{Detachment force (F)} = W\ (Kg) \times 9.8\ m/sec^2$$

***Ex-vivo* Residence Time:** The *ex-vivo* residence time was measured using modified USP dissolution apparatus in which paddles were tied with glass slide to which buccal membrane fixed with cyanoacrylate glue with mucosal side facing outwards to affix buccoadhesive patches. This was vertically fixed to the shaft of the dissolution apparatus with the help of elastic threads. Core side of patch was wetted with 0.5 mL of pH 6.8 phosphate buffer and attached to the mucosal membrane with a little pressure to develop initial contact. 500 mL of pH 6.8 phosphate buffer was used as medium and maintained at 37°C and the patch was completely immersed in the buffer solution and allowed to run under continuous agitation of the paddle at 50 rpm speed during the study period. Time taken for the complete detachment of the patch from the mucosal surface was recorded. The experiment was performed in triplicate (n=3) and mean was determined.

***In-vitro* Drug Diffusion Studies:** *In-vitro* drug diffusion studies were performed on prepared salbutamol sulphatebuccoadhesive patches using vertical Franz diffusion cells consisting of donor compartment and receptor compartment which are clamped together with the help of a holder clamp. The donor compartment and receptor compartment were separated by a semipermeable membrane. In the Franz diffusion cell, the effective diffusion area of3.63 cm^2 is available to the (diameter of diffusion cell: 2.15 cm) core patch placed in the donor compartment. The semipermeable membrane with a molecular weight cut off 12,000 to 14,000 Daltons is used in the present study (Himedia, dialysis membrane 50, LA 387). The semipermeable membrane was soaked in pH 6.8 phosphate buffer overnight before the experiment. The patch of 1 cm^2 was placed in such a way that the uncoated surface of the patch will be facing the semipermeable membrane. 25 mL of pH 6.8 phosphate buffer was used as diffusion medium maintained at a temperature of 37±0.5°C using a magnetic stirrer with 200 rpm. During the study, 2 mL sample was withdrawn at predetermined intervals using a syringe with cannula from the receptor compartment and replaced with fresh medium maintained at the same temperature. The samples collected were diluted suitably wherever necessary and analyzed at 276 nm using UV spectrophotometer against a reagent blank.

Drug Diffusion Studies from Backing Layer of the Patches: Drug diffusion studies from cellulose acetate backing layer were performed on prepared salbutamol sulphatebuccoadhesive patches using vertical Franz diffusion cell. In this experiment, the 1 cm^2 patch was placed in the Franz diffusion cell in such way that the backing layer was facing the semipermeable membrane. The samples collected were analyzed at 276 nm using UV spectrophotometer against a reagent blank.

Mean Steady-State Flux: Mean steady-state flux is the average of individual flux values at all sampling points. The flux across the membrane was calculated using the following formula:

$$J = V\ (dc/dt)$$

Where, J = Flux of the drug across the membrane; V = Volume of receptor compartment; (dc/dt) = Rate of change of concentration.

Establishment of Release Kinetics and Mechanisms: The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in matrix systems. As a model-dependent approach, the dissolution data were fitted to popular release models such as zero order, first order, Higuchi, erosion, and Peppas equations. The order of drug release from the matrix systems

was determined by using zero order kinetics or first order kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi, erosion and Peppas equation [31-32].

RESULTS AND DISCUSSION: Uniformity of weight was conducted for all the prepared patches. Average weight of all the formulations was found to be in the range of 19.38±0.2 to 23.57±0.4 mg. The low % deviation from the average weight clearly indicated the uniformity of weight for all the prepared patches.

The thickness of the buccoadhesive patch should be uniform for patient compliance. Patches with more thickness pose problems like irritability and inconvenience due to retention of patches for a prolonged period of time. The mean thickness of all the formulations was found to be in the range of 0.125±0.003 to 0.151±0.001 mm, and the results are shown in **Table 4** to **6**.

The low standard deviation values indicated the uniformity in the thickness of the patches, indicating their suitability for buccal delivery.

Mechanical strength with flexibility is an important character for buccoadhesive patches for ease of administration and for attaining the required mechanical strength with flexibility. Plasticizers are used during the preparation of the patches.

All the prepared patches were analyzed for uniformity of drug content, and the results of all the formulations were found to be in the range of 99.52±0.51 to 100.92±0.73 **Table 4** to **6,** which are well within the specified range of 98%-101% Pharmacopoeial limits as per IP for salbutamol sulphate. Thus salbutamol sulphatebuccoadhesive patches prepared with the selected polymers were observed as good quality fulfilling the entire official and other requirements of patches.

TABLE 4: PHYSICO-CHEMICAL CHARACTERISTICS OF HG-SALBUTAMOL SULPHATE PATCHES

Formulation	% Drug content (mean ± S.D., n=5)	Uniformity of weight (mean ± % deviation, n=5)	Thickness (mm) (mean ± S.D., n=25)	Folding endurance (up to 300)
SHG1	99.52±0.43	19.89±0.25	0.125±0.003	No cracks
SHG2	99.82±0.36	20.24±0.33	0.127±0.002	No cracks
SHG3	99.60±1.14	19.76±0.49	0.127±0.009	No cracks
SHG4	100.07±0.55	21.74±0.26	0.134±0.003	No cracks
SHG5	99.85±0.52	21.66±0.37	0.135±0.005	No cracks
SHG6	100.19±0.25	21.83±0.20	0.135±0.004	No cracks
SHG7	100.26±0.73	23.33±0.33	0.147±0.006	No cracks
SHG8	99.77±0.83	23.37±0.11	0.146±0.001	No cracks
SHG9	99.92±0.51	23.46±0.40	0.147±0.008	No cracks

TABLE 5: PHYSICO-CHEMICAL CHARACTERISTICS OF LG-SALBUTAMOL SULPHATE PATCHES

Formulation	% Drug content (mean ± S.D., n=5)	Uniformity of weight (mean ± % deviation, n=5)	Thickness (mm) (mean ± S.D., n=25)	Folding endurance (up to 300)
SLG1	99.97±0.26	19.38±0.20	0.129±0.004	No cracks
SLG2	99.92±0.14	19.78±0.36	0.127±0.001	No cracks
SLG3	100.92±0.73	19.73±0.34	0.128±0.005	No cracks
SLG4	98.84±0.62	21.33±0.57	0.130±0.005	No cracks
SLG5	100.55±0.38	21.49±0.41	0.131±0.004	No cracks
SLG6	99.48±0.36	21.84±0.75	0.132±0.003	No cracks
SLG7	100.43±0.45	22.84±0.23	0.150±0.002	No cracks
SLG8	99.55±0.35	23.13±0.32	0.149±0.010	No cracks
SLG9	100.09±0.56	23.46±0.35	0.151±0.001	No cracks

TABLE 6: PHYSICO-CHEMICAL CHARACTERISTICS OF PEO-SALBUTAMOL SULPHATE PATCHES

Formulation	% Drug content (mean ± S.D., n=5)	Uniformity of weight (mean ± % deviation, n=5)	Thickness (mm) (mean ± S.D., n=25)	Folding endurance (up to 300)
SPEO1	99.78±0.21	21.20±0.40	0.130±0.006	No cracks
SPEO2	99.74±0.10	21.23±0.25	0.131±0.003	No cracks
SPEO3	100.04±0.73	21.73±0.38	0.133±0.002	No cracks
SPEO4	99.43±0.44	22.78±0.38	0.149±0.004	No cracks
SPEO5	100.07±0.35	23.57±0.40	0.148±0.002	No cracks
SPEO6	99.97±0.22	23.53±0.20	0.148±0.007	No cracks

All the prepared formulations were evaluated for their swelling index (%) for 6 h as the objective of the study is to complete the drug release over a period of 6 hours and the results are shown in the **Fig. 1.** The swelling index (%) values were increased both with time as well as polymer concentration for the formulations prepared with hupu gum and lannea gum. Swelling index (%) values for PEO coagulant patches were decreased after 4 h as PEO started spreading on the surface of the agar plate. The swelling index (%) of patches prepared with hupu gum, lannea gum was found to be in the range of 6.65±0.65 to 83.12±0.83 and 7.11±0.56 to 77.62±0.84, respectively. Gradual swelling was observed for the patches prepared with hupu gum, lannea gum, and the patches maintained an intact contact with the backing layer without any detachment. Among all the formulations prepared with three polymers, formulation SHG9 (hupu gum), SLG9 (lannea gum), and SPEO6 (PEO coagulant) indicated high swelling index. The comparative and swelling behaviour of these patches are shown in **Fig. 1**. A linear relationship was observed between swelling index (%) and time for both the hupu gum (r = 0.9964) and lannea gum (0.9962) formulations other than PEO coagulant (r = 0.864). The comparative swelling studies confirmed that, among all the prepared patches hupu gum has shown high swelling index (%) than patches prepared with lannea gum and PEO coagulant. The swelling index (%) of the patches prepared with PEO coagulant were increased up to 4 hours and decreased thereafter.

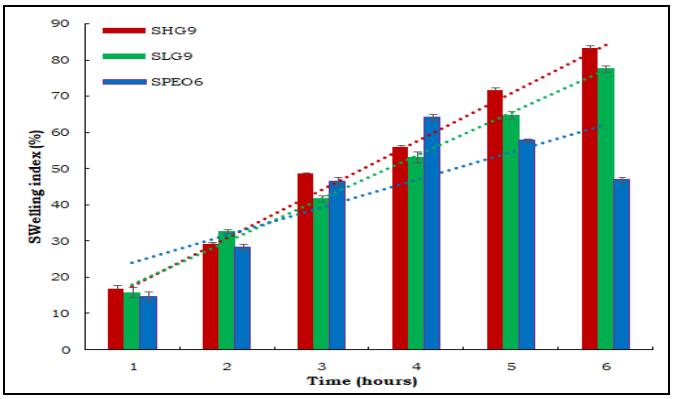

FIG. 1: COMPARATIVE STUDIES OF SWELLING BEHAVIOUR OF SHG9, SLG9 AND SPEO6

The surface pH of the prepared patches was measured with pH paper, and the values were found to be in the range of 5-7 **Table 7** to **9**. This showed that the formulations were appropriate to the buccal drug delivery as pH was within the range of the buccal cavity.

Measurement of Buccoadhesive Strength: Buccoadhesive strength of the patches prepared with hupu gum, lannea gum, and PEO coagulant was found to be 0.215±0.011 to 0.284±0.008, 0.205±0.002 to 0.275±0.012, and 0.196±0.004 to 0.244±0.011 N, respectively. Irrespective of the polymer used, the mucoadhesive strength was increased with increase in polymer concentration and the results are shown in **Table 7** to **9**. At the same polymer concentration (drug to polymer ratio 1:3) buccoadhesive strength of 0.284±0.008, 0.275 ±0.012 and 0.244±0.011 N was observed for hupu gum, lannea gum and PEO coagulant, respectively. Hupu gum showed good mucoadhesive strength than the other two polymers at the same drug-polymer ratio and the order of buccoadhesive strength was hupu gum > lannea gum > PEO coagulant.

***Ex-vivo* Residence Time:** *Ex-vivo* residence time of 7-10, 6.5-8.5, and 3-5.2 hours was observed for the patches prepared with hupu gum, lannea gum and PEO coagulant respectively and the results are shown in **Table 7** to **9.** A higher residence time of 10 h was observed for the formulation SHG9, whereas lower residence time of 3 h was observed for the formulation SPEO1. Results indicated that irrespective of the polymer used, *ex vivo* residence time of all the polymers increased with an increase in the polymer concentration and penetration enhancer used. The order of *ex vivo* residence time of three polymers was hupu gum>lannea gum>PEO coagulant. Among all the formulations SHG9 (hupu gum), SLG9 (lannea gum) and SPEO6 (PEO coagulant) showed higher *ex-vivo* residence times.

TABLE 7: BUCCOADHESIVE STRENGTH, *EX-VIVO* RESIDENCE TIME AND SURFACE pH VALUES OF HG-SALBUTAMOL SULPHATE PATCHES

Formulation code	Buccoadhesive strength (N) (mean ± S.D., n=3)	*Ex-vivo* residence time (hours) (mean ± S.D., n=3)	Surface pH
SHG1	0.215±0.011	7.01±0.14	6-7
SHG2	0.225±0.004	7.53±0.32	6-7
SHG3	0.245±0.001	7.76±0.37	6-7
SHG4	0.225±0.003	8.10±0.33	6-7
SHG5	0.248±0.005	8.60±0.15	6-7
SHG6	0.264±0.002	9.06±0.46	6-7
SHG7	0.245±0.004	9.25±0.16	6-7
SHG8	0.274±0.005	9.66±0.28	6-7
SHG9	0.284±0.008	10.02±0.23	6-7

TABLE 8: BUCCOADHESIVE STRENGTH, *EX-VIVO* RESIDENCE TIME AND SURFACE pH VALUES OF LG-SALBUTAMOL SULPHATE PATCHES

Formulation code	Buccoadhesive strength (N) (mean ± S.D., n=3)	*Ex-vivo* residence time (hours) (mean ± S.D., n=3)	Surface pH
SLG1	0.205±0.002	6.48±0.46	6-7
SLG2	0.215±0.003	6.70±0.15	6-7
SLG3	0.225±0.005	6.82±0.44	6-7
SLG4	0.231±0.002	6.48±0.34	6-7
SLG5	0.235±0.007	7.01±0.45	6-7
SLG6	0.254±0.002	7.16±0.24	6-7
SLG7	0.249±0.001	7.91±0.52	6-7
SLG8	0.268±0.006	8.1±0.26	6-7
SLG9	0.275±0.012	8.52±0.36	6-7

TABLE 9: BUCCOADHESIVE STRENGTH, *EX-VIVO* RESIDENCE TIME AND SURFACE pH VALUES OF PEO-SALBUTAMOL SULPHATE PATCHES

Formulation code	Buccoadhesive strength (N) (mean ± S.D., n=3)	*Ex-vivo* residence time (hours) (mean ± S.D., n=3)	Surface pH
SPEO1	0.196±0.004	3.0±0.22	5-6
SPEO2	0.215±0.005	3.4±0.33	5-6
SPEO3	0.221±0.003	4.1±0.35	5-6
SPEO4	0.205±0.002	4.7±0.16	5-6
SPEO5	0.235±0.002	5.0±0.40	5-6
SPEO6	0.244±0.011	5.2±0.37	5-6

An examination of the swelling index (%), buccoadhesive strength and *ex-vivo* residence time values, it was observed that more the swelling index, higher the buccoadhesive strength and *ex vivo* residence time values. The swelling index (%) values for patches prepared with PEO coagulant were increased up to 4 h and decreased thereafter and accordingly the buccoadhesive strength and *ex-vivo* residence time values were also decreased. Among all the formulations SHG9, SLG9 and SPEO6 indicated high swelling index up to 6 hours. The results of these three parameters clearly indicated the interrelationship between swelling index, buccoadhesive strength and *ex vivo* residence time.

***In-vitro* Diffusion and Flux Studies of the Patches:** Diffusion studies were performed on all the prepared patches, and the results are shown in **Fig. 2** to **4**. The *in-vitro* diffusion studies of the formulated patches revealed that the drug release was influenced by the concentration of polymer and the penetration enhancer used. The drug release was increased with an increase in penetration enhancer and was extended by enhancing the polymer concentration. Hupu gum-based formulations were prepared in different drug to polymer ratios of 1:2, 1:2.5, and 1:3. SHG1, SHG4 and SHG6 were without penetration enhancer, SHG2, SHG5 and SHG7 with 0.3% penetration enhancers and SHG3, SHG6, and SHG9 with 0.6% penetration enhancer. Out of these formulations, SHG9 (hupu gum), containing a drug-polymer ratio of 1:3 with 0.6% (w/v) penetration enhancer released 100.34% of drug over a period of 6 hours with an initial 25% drug release.

The formulations prepared with lannea gum in the same manner also exhibited a similar pattern of drug release based on polymer and permeation enhancer concentration. Among all the prepared patches, SLG9 (drug-polymer ratio of 1:3 with 0.6% (w/v) penetration enhancer showed 100.65% drug release for a period of 6 h with an initial 29% drug release and hence considered as optimized formulation.

PEO coagulant, an established synthetic polymer, was chosen to compare the mucoadhesive properties of natural gums. The formulations prepared with PEO coagulant in the drug-polymer ratio of 1:2.5 and 1:3 as the ratio of 1:2 drug-polymer ratio failed to give good films. Out of these formulations, SPEO6 containing a drug-polymer ratio of 1:3 with 0.6% (w/v) penetration enhancer showed a good release profile with 99.87% of the drug in 6 hours.

The swelling studies of the patches that are prepared with three different polymers indicated the hydration period during the first two hours. Once the polymer is hydrated completely, the rate of swelling is increased and showed maximum swelling during the remaining 3-4 h. The swelling index values are low, i.e., 30-35% for SHG9, SLG9, and SPEO6 during the initial period and released the adhered drug on the surface of the patch, which served as a loading dose. Once the patch was fully swollen, the drug release was slowed down and released the drug in a consistent rate over a period of 6 h. As a result of the hydration and swelling behaviour of the polymers, the drug release was found to be biphasic in nature, *i.e.*, initial burst release followed by controlled release. The patches with low polymer concentration released 70-80% of the drug within 2-3 h before the polymer is completely swollen due to low concentration of polymer, and with an

increase in the concentration of polymer, the initial drug release during the first 2-3 h was reduced and extended over a period of 4-6 h. Hence, the results clearly indicated that the concentration of polymer is playing an important role in extending the drug release.

Irrespective of the polymer used, the flux values were increased with an increase in penetration enhancer. The mean flux values reported in the study was ranging between 0.177-0.618 mg/min.

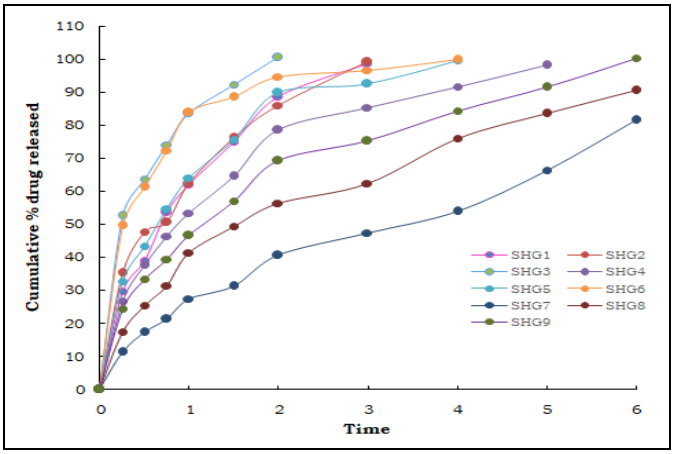

FIG. 2: DIFFUSION PROFILES OF HG-SALBUTAMOL SULPHATE PATCHES

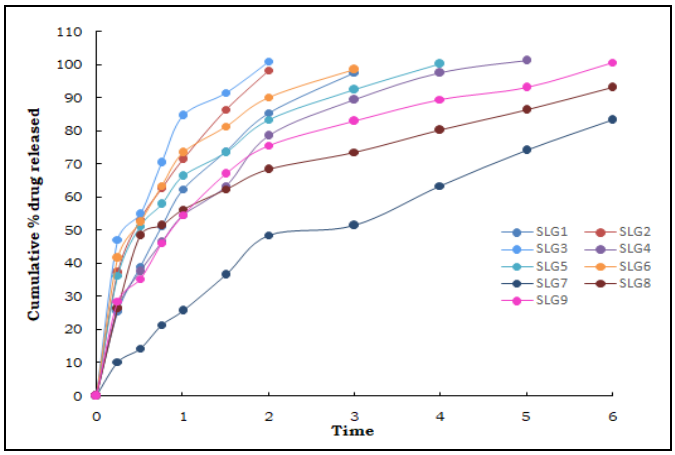

FIG. 3: DIFFUSION PROFILES OF LG-SALBUTAMOL SULPHATE PATCHES

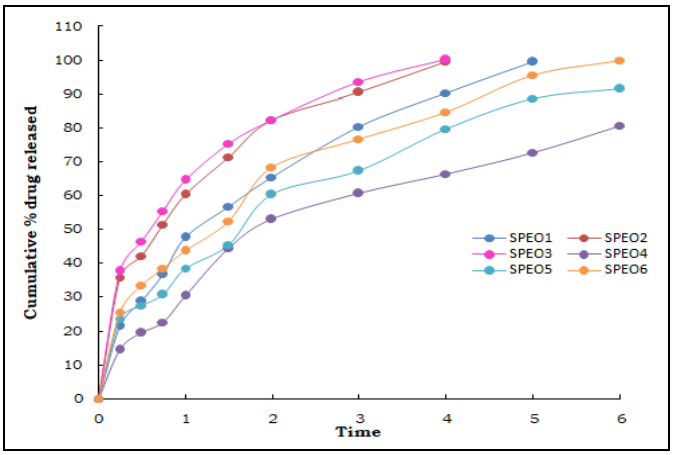

FIG. 4: DIFFUSION PROFILES OF PEO-SALBUTAMOL SULPHATE PATCHES

The percentage drug diffused over a period of 6 h was found to be not more than 10%. This study clearly indicated the suitability of cellulose acetate as a backing layer for preventing the release of the drug from the coated side of the patch. The diffusion data was fitted to zero and first-order kinetic models and the respective rate constants and the correlation coefficient values 'r' of release kinetics. For the establishment of a mechanism of release from the patches, the diffusion data was fitted to Higuchi, erosion, and Korsmeyer-Peppas equations. The appropriate correlation coefficient values are highlighted in bold letters indicating the order and release mechanism followed by the respective formulations. A biphasic release pattern was observed during the diffusion studies due to higher drug release before the complete swelling of polymer followed by controlled release of the drug. Accordingly, the kinetic data was separated as the first phase and second phase, and the appropriate drug release kinetics were calculated for zero-order and first order.

The formulations prepared with hupu gum followed zero order in both the phases except in formulation SHG1, which followed first-order kinetics in both phases. All the formulations followed non-Fickian diffusion mechanism except SHG6, which followed erosion mechanism was found to be dominant compared to diffusion. Lannea gum-based formulations followed zero-order kinetics in both phases except SLG1, SLG5, and SLG8 as they

followed first order in the first phase and zero order in the second phase. All the prepared formulations followed the non-Fickian diffusion mechanism. All the formulations prepared with PEO coagulant followed zero-order kinetics in both phases with non-Fickian diffusion mechanism. One formulation from each polymer was selected among all the formulations prepared, which could extend the drug release over a period of 6 hours. They are SHG9 from hupu gum, SLG9 from lannea gum, and SPEO6 from PEO coagulant. Swelling index (%) values of hupu gum and lannea gum were increased with time whereas, the values of PEO coagulant was increased up to a certain extent. Buccoadhesive characteristics like buccoadhesive strength, *ex-vivo* residence time were compared for the optimized formulations. It was observed that SHG9 showed higher values compared with other optimized formulations and was in the order of hupu gum>lannea gum>PEO coagulant. From the above results, it was observed that SHG9 formulation prepared with a drug-hupu gum ratio of 1:3 was giving superior performance compared to the remaining optimized formulations. Though PEO coagulant could extend the release up to 6 hours with the same drug-polymer ratio, its mucoadhesive properties were inferior to hupu gum and lannea gum. SLG9 is having lesser mucoadhesive properties than hupu gum but it is showing good adhesion nature compared with the PEO coagulant. Hence hupu gum formulation SHG9 and lannea gum formulation SLG9 were considered as optimized formulations.

CONCLUSION: In the present investigation natural polymers hupu gum and lannea gum were evaluated for their buccoadhesive property and compared with that of the established mucoadhesive synthetic polymer PEO coagulant. Formulated salbutamol sulphatebuccoadhesive patches were evaluated for their physico-chemical and muco-adhesive characteristics and were found to be good. Based on the diffusion profile, buccoadhesive properties SHG9, SLG9, and SPEO6 at the drug to polymer ratio of 1:3 were considered as optimized formulations. Among the optimized formulations hupu gum is found to have good mucoadhesive characteristics. The pH of all the formulations was found be in the range of 5-7, which is a suitable pH for buccal drug delivery. By comparing the above results buccoadhesive strength of selected polymers is in the order of hupu gum>lannea gum>PEO coagulant. Though the mucoadhesive strength of lannea gum was found to be less at the same drug-polymer concentration compared to hupu gum it also showed promising results for suitability as a buccoadhesive polymer. Results of the present study clearly indicated the suitability of hupu gum and lannea gum in the design of buccoadhesive drug delivery systems compared to established synthetic polymers like PEO coagulant.

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