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Original Article

SODIUM CROMOGLYCATE MUCOADHESIVE BUCCAL PATCHES: DESIGN, FABRICATION, *IN VITRO* AND *IN VIVO* CHARACTERIZATION

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ABSTRACT

Objective: The purpose of this study was to design and formulate mucoadhesive buccal patches of sodium cromoglycate (SCG) as an alternative way to overcome its poor oral absorption and short half-life.

Methods: Mucoadhesive patches were prepared by solvent casting technique using cellulose acetate butyrate (CAB) alone or in combination with mucoadhesive polymers like SCMC (sodium carboxymethyl cellulose), HPMC 100M (hydroxyl propyl methyl cellulose) and Cbp934P (carbopol) in different concentrations. The successful patches were evaluated for thickness, weight variation, folding endurance, tensile strength, drug content, surface pH, moisture uptake, swelling percentage, mucoadhesion strength, residence time, *in vitro* release study, ex vivo permeation and *in vivo* pharmacokinetic studies.

Results: The thickness of all prepared patches ranged from 0.210±0.006 to0.355±0.012, folding endurance was more than 300, weight variation did not exceed 0.179±0.015, tensile strength and % elongation ranged from 6.4±0.018 to 13.1±0.024, and from 30.4±0.88 to 53.4±0.78respectively. The swelling percentage after one hour was from 20.8±0.99 to 53.2±1.5. pH of all prepared patches did not exceed 6.8, the drug content was about 99 to 101%, moisture uptake did not exceed 10%. Mucoadhesion strength and residence time ranged from 17.2±0.14 to 51.2±0.26, and from 3.35±0.25 to 7.45±0.28 respectively. The cumulative release percentage of SCG was in the following descending order CAB>CAB with Cbp934P>CAB with HPMC>CAB with SCMC. The optimized patch (F9) decreased the C_{max} and increased T_{max} compared to the parenteral solution.

Conclusion: It can be concluded that mucoadhesive buccal patch is a promising dosage form to prolong the release of SCG and enhance its poor oral bioavailability.

Keywords: Buccal patches, Sodium cromoglycate, Solvent casting

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INTRODUCTION

Although oral drug delivery remains the most common and preferred route for delivery of many drugs, it suffers from several important drawbacks such as enzymatic degradation along the gastrointestinal tract, first pass metabolism, delayed onset of absorption and sometimes poor absorption. These defects necessitate the importance of designing alternative dosage forms to be administered through alternative routes such as pulmonary, transdermal, ocular, rectal, vaginal and buccal. The buccal route overcomes the disadvantages associated with the oral route for systemic drug delivery [1, 2]. These include avoidance of first-pass metabolism and enzymatic degradation, rapid onset of absorption, prolonged release of certain drugs and ease administration of drugs [3]. Buccal patches suffer from certain limitations which include [4]: certain drugs which have undesirable taste, irritate buccal mucosa, unstable in buccal pH, discolor the teeth and drugs with large dose could not be formulated as buccal patches. Mucoadhesive buccal patches are more recent dosage form which is designed to give systemic or local drug delivery and fabricated to overcome the short residence time of oral gel which is easily washed by saliva [5] and discomfort of solid dosage forms like tablets. Sodium cromoglycate is a mast cell stabilizer that inhibits the release of inflammatory mediators and prevents the immediate onset and delayed onset asthma [6, 7]. It suffers from poor oral absorption, which is found to be 0.5% of the total administered dose and short plasma half-life which is 60-90 min [8]. This research work aims to design, formulate and evaluate mucoadhesive buccal patches of SCG to overcome its poor oral absorption and prolonged its release and consequently enhances its bioavailability.

MATERIALS AND METHODS

Materials

Sodium cromoglycate was kindly supplied by sigma company, Egypt. Phosphoric acid and Potassium-dihydrogen phosphate were purchased from El Nasr Company Egypt. HPLC grade acetonitrile, SCMC, Cbp934 P and HPMC100M were purchased from Sigma-Aldrich Chemie, Germany. All other chemicals and solvents are of analytical grade. Diethyl ether was purchased from Fine Chem. Ltd. (India).

Methods

Preparation of mucoadhesive buccal patches

The solvent casting technique was used for the preparation of SCG mucoadhesive patch [9-12]. The composition of the successful patches was illustrated in table 1. The calculated amount of the drug and polyethyleneglycol 600 as a plasticizer (50% W/W of dry polymer weight) were dissolved in a 20 ml mixture of absolute ethanol and methylene chloride (1:1) as casting solvent. The calculated amount of the polymer or polymer mixture was sprinkled onto the solution with occasional shaking. The casting solution was then adjusted to 25 ml to give 4% W/V polymeric solution and left for 24 h for complete dissolution and removal of suspended air bubbles. The solution was then cast in a glass petri dish (area=50.24 cm^2) covered with inverted glass funnel to control the rate of evaporation and prevent patch blistering. The solvent was allowed to evaporate for 24 h at ambient room temperature. The dry patch was isolated and cut into square sections of 2x2 cm, each containing 20 mg of SCG and finally wrapped in an aluminium foil and stored in a desiccator.

Evaluation of mucoadhesive buccal patches

Physical appearance

All prepared buccal patches were visually inspected for clarity, smoothness and flexibility.

Thickness

The thickness of three patches of each formulation was measured with a digital micrometre (Cole-Parmer Instrumental Co., Japan) at five different places and the mean thickness was determined [13].

Table 1: Composition of successful sodium cromoglycate buccal mucoadhesive patches

Formula code	SCG (mg)	CAB (mg)	Cbp934p (mg)	CMCS (mg)	HPMC100M (mg)
F1	20	1000			
F2	20	800	200	----	----
F3	20	700	300	----	----
F4	20	600	400	----	----
F5	20	500	500	----	----
F6	20	800	----	200	----
F7	20	700	----	300	----
F8	20	600	----	400	----
F9	20	500	----	500	----
F10	20	800	----	----	200
F11	20	700	----	----	300
F12	20	600	----	----	400
F13	20	500	----	----	500

SCG: sodium cromoglycate, CAB: cellulose acetate butyrate, Cbp934p: carbopol934p, SCMC: sodium carboxymethyl cellulose, HPMC100M: hydroxyl propyl methyl cellulose

Weight variation

All prepared patches were subjected to weight variation test by individually weighing three randomly selected patches (2x2 cm) for each formula [14] using an electronic digital balance (Metter-Toledo, Ag, CH 8606, Greifensee, Switzerland).

Tensile strength and percent elongation

Tensile strength and percent elongation were determined using JJ load cell instrument 100n, j. j LIoyd instruments limited (warash, Southampton, England). The dried piece of each patch with uniform size 8x100 mm was clamped using an upper and lower flat faced metal grip. The distance between the grips and the effective length of the patch under stress was kept constant at 40 mm. A crosshead speed of 3 mm/min was started. When the film broke, the force and elongation were measured [15, 16]. The average of three measurements for each formula was determined. Tensile strength can be calculated according to the following equation:

$$\text{Tensile strength} = \frac{\text{breaking load}}{\text{cross sectional area } (\mathbf{mm2})}$$

Percent elongation can be determined according to the following equation:

$$\text{Percent elongation} = \frac{\text{increasing in length}}{\text{original length}} \text{x} 100$$

Surface pH

SCG patch of each formula (2x2 cm) was soaked for 1 h in 5 ml distilled water at ambient room temperature. pH was determined by mounting the electrode of pH meter300 (Jenway LTD, UK) on the patch surface and permitting equilibration for 1 min. The experiment was conducted in triplicate [17].

Drug content uniformity

SCG patch 2x2 cm of each formula was dissolved in 100 ml phosphate buffer pH 6.8 with occasional stirring and then filtered. SCG was determined spectrophotometrically at 326 nm using UV-Spectro-photometer Shimadzu UV-1201, Japan against phosphate buffer pH 6.8 as a blank. The experiment was performed in triplicate [18].

Folding endurance

Folding endurance of each formula was conducted by folding section of 2x2 cm size repeatedly at the same place till it broke or folded up to 300 times.

The value of folding endurance is expressed as the number of times the film could be folded at the same position without breaking. Folding endurance is given as the average of three determinations [19, 20].

Moisture uptake

The patches of all prepared formulations were placed in a desiccator containing 200 ml saturated solution of potassium chloride to give relative humidity of 84% for 3 d. At the end of the experiment, the patches were removed and weighed [21]. The percent moisture uptake of each patch was calculated according to the following equation:

$$\text{Percent moisture uptake} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \text{x} 100$$

Percent swelling

Square section of each patch measuring 2x2 cm was carefully weighed, then immersed in 50 ml phosphate buffer pH 6.8 in a glass petri dish. The patch section was removed carefully at 5, 10, 15, 20, 30 and 60 min interval, dried carefully with the aid of filter paper and accurately weighed [22, 23]. Swelling percentage was calculated according to the following equation.

$$\text{Swelling percentage} = \frac{Wt - W0}{W0} \text{x } 100$$

Where

W0= the initial weight at zero time

Wt = the weight of the swollen patch at time t.

Swelling percentage expressed as the average of three determinations.

Ex-vivo mucoadhesion strength

A modified physical balance was used for the determination of mucoadhesion strength of the prepared patches using the porcine buccal mucosa. The buccal mucosa was cut carefully into pieces and washed with pH 6.8 phosphate buffer. A piece of the porcine buccal mucosa was firmly tied to the open mouth of a glass vial which was completely filled with pH 6.8 phosphate buffer. The glass vial was firmly fitted to the centre of a glass beaker which was filled with pH 6.8 phosphate buffer kept at 37±0.5 °C to the level that just touches the mucosal surface. The patch was tightly stuck to the lower surface of the rubber stopper using cyanoacrylate adhesive. 5 g weight was put on right side pan for balancing the two pans. The weight was then removed, which lowered the pan along with the film over the mucosa. The balance was kept for 5 min at such position. Water then added slowly at a rate of 100 drops/min with the aid of the infusion set. The weight of water in grams that completely detached the patch from the surface of buccal mucosa was used in the calculation of mucoadhesion strength [24-26] according to the following equation:

$$\text{Detachment stress (dyne/cm}^2) = \frac{m.gr}{A} [27]$$

Where m is the weight of water in g

gr equal 980 cm/sec^2 the acceleration due to gravity

A is the area of porcine mucosa equal to πr^2 where r is the radius of the exposed porcine buccal mucosa.

Ex-vivo mucoadhesion residence time

Ex-vivo determination of mucoadhesion time was conducted using porcine buccal mucosa. The segment of the porcine mucosa was glued onto the internal side of a glass beaker using cyanoacrylate adhesive. The patch which was previously hydrated with pH 6.8 phosphate buffer was then attached to the mucosa by applying light force for 20 Sec with a fingertip. The beaker was then filled with 200 ml pH 6.8 phosphate buffer and was kept at 37±0.5 °C and 50 RPM in a thermostatic shaker

water bath (Julabo SW-20 C, Germany). Ex-vivo mucoadhesion time is the time taken by the patch to erode or dislodge from the mucosa. The experiment was performed in triplicate [28].

***In vitro* release study**

The cumulative drug release percent of SCG from different patches was conducted using USP type II dissolution apparatus paddle type. 2x2 cm section of each formula was attached to a glass slide using cyanoacrylate adhesive. The glass slide was placed in the bottom of dissolution vessel. 500 ml pH 6.8 phosphate buffer was used as the release medium and maintained at 37±0.5 °C and 50 RPM. 5 ml sample was withdrawn at 1, 2, 3, 4, 5, 6, 7, 8 h and replaced with an equal volume of fresh buffer. The samples were filtered, accurately diluted and analyzed spectrophotometrically at 326 nm. The experiment was conducted in triplicate [29].

Ex-vivo drug permeation study.

Franz diffusion cell was used for the permeation study. The porcine oral mucosa was used as the model mucosal membrane. The buccal mucosa was washed and stabilized in phosphate buffer pH 6.8 to remove any soluble component. The porcine mucosa was mounted between the donor and receptor compartments. 20 ml phosphate buffer pH 6.8 was filled into the receptor compartment maintained at 37±0.5 °C and stirred using magnetic bead at 50 RPM. 3 ml sample was withdrawn at a predetermined time interval and replaced with fresh buffer. The amount of SCG was estimated spectrophotometrically at 326 nm. The experiment was performed in triplicate [30, 31].

***In vivo* pharmacokinetic study**

SCG was estimated in rabbit plasma by simple and sensitive RP-HPLC method described by paparajusowjanya *et al.* [32] with certain modifications.

Experimental design

White male albino rabbits (2-2.5 kg) were used for the pharmacokinetic study. Animals were housed at the standardized condition of the animal house of faculty of pharmacy, Zagazig University, Zagazig, Egypt. All animals were acclimatized and kept constant at ambient room temperature. All animal procedures were performed in accordance with the approved protocol for the use of experimental animals set by the standing committee on the animal care of the faculty of pharmacy, Zagazig University, EgyptP3-12-2016. Animals were divided into three groups, each group of six rabbits. Group 1 act as a control, group 2 received the optimized patch F9 and group 3 received SCG solution parenterally. Group 2 and group 3 received a dose of 5 mg/kg, which was determined by trials. Blood samples were withdrawn from the sinus orbital at 0.5, 1, 2, 4, 6, 8, 10, 12, 24 h. The blood samples were centrifuged at 3000 RPM for 10 min. SCG was extracted from rabbit plasma by adding 100 µl of 10% perchloric acid to precipitate the protein. 1 ml rabbit plasma was vortexed for 1 min, then 2 ml diethyl ether was added. The mixture was centrifuged at 5000 RPM and 4 ° C for 10 min, then 2 ml of the supernatant was taken and dried in a vacuum oven at 40 ° C. The residue was reconstituted with 20 µl mobile phase and injected into the column.

HPLC conditions

HPLC (Waters Instrument, Germany) with the reverse phase C18 column. The UV detector was set at 240 nm for sample detection. The mobile phase consisted of acetonitrile and potassium di hydrogen ortho phosphate adjusted to pH 1.5 with orthophosphoric acid in the ratio of 25:75 at a flow rate of 1 ml/min. 10 mg of SCG was dissolved in 10 ml of mobile phase and suitably diluted to produce a stock solution of 1 mg/ml. Dilution of stock solution was performed to give 10, 15, 20, 25, 30, 35 µg/ml.100 µl of spiked plasma was added to each of the above concentrations and the samples were analyzed as previously described.

Kinetic data analysis

The cumulative drug release percentages were plotted according to the different kinetic models such as Higuchi diffusion, zero order, first order, Korsmeyer-Peppas, and Hixson and Crowell to determine the best kinetic model of the drug release [33].

Statistical analysis

The resulting data of different evaluated parameters were expressed as the average mean±standard deviation of the mean. One way analysis of variance (ANOVA) was employed for the data analysis using SPSS program, version 16. The data were significant at a level P<0.05.

RESULTS AND DISCUSSION

Physical appearance and thickness

All prepared patches were translucent and smooth. The average thickness of all patches was found in the range from 0.21±0.006 to 0.355±0.012 mm (table 2).

Weight variation

The weight of all prepared patches (2x2 cm) ranged from 0.155±0.025 to 0.179±0.015 mg. The results in table 2 demonstrate the uniformity of weight of all prepared patches.

Folding endurance

The folding endurance of all prepared patches was more than 300 irrespective to the type of the polymer which ensures flexibility and toughness of all prepared patches (table 2) [34].

Tensile strength and percent elongation

Tensile strength and percent elongation give an indication for the elasticity and strength of the prepared patches. Soft and tough patches have the high tensile strength and percent elongation. Data recorded in table 2 show that the tensile strength of CAB patch (F1) was 6.4±0.018 and percent elongation was 30.4±0.88. The addition of mucoadhesive polymers increased both mechanical parameters. The effect of the mucoadhesive polymers can be ranked in the following order: SCMC>HPMC 100M>CbP934P. The amount of the mucoadhesive polymers had a non-significant effect. This was in a good correlation with patel *et al.* and Qadir *et al.* [13, 28]. They found that the tensile strength of the buccal patches increased with increasing the percentage of HPMC 15 cp.

Table 2: Physico mechanical characterization of SCG patches.

Formula code	Thickness (mm) ±SD	Folding endurance	Tensile strength (N/MM2)±SD	% elongation ±SD	Weight variation±SD
F1	0.210±0.006	>300	6.4±0.018	30.4±0.88	0.155±0.025
F2	0.230±0.012	>300	7.5±0.053	39.5±0.71	0.155±0.015
F3	0.235±0.015	>300	8.6±0.185	39.9±0.88	0.158±0.025
F4	0.240±0.006	>300	10.5±0.172	43.5±0.55	0.160±0.009
F5	0.250±0.006	>300	10.6±0.125	45.2±0.92	0.157±0.013
F6	0.240±0.002	>300	11.6±0.006	47.9±0.75	0.160±0.015
F7	0.250±0.015	>300	11.8±0.120	50.7±0.66	0.158±0.009
F8	0.305±0.023	>300	12.6±0.080	51.5±0.68	0.175±0.009
F9	0.320±0.012	>300	13.1±0.024	53.4±0.78	0.169±0.019
F10	0.235±0.015	>300	9.8±0.085	43.2±0.88	0.155±0.011
F11	0.250±0.006	>300	10.4±0.006	47.6±0.68	0.157±0.019
F12	0.312±0.025	>300	11.2±0.085	49.1±0.92	0.170±0.015
F13	0.355±0.012	>300	12.1±0.120	51.2±0.73	0.179±0.015

*Data are expressed as mean±standard deviation of the mean (SD), n=3

Percent swelling

Swelling of the polymer is an important property for the prolonged release of the drug and good mucoadhesion. Table 3 demonstrates the percent swelling of different patches. It is observed that there was an increase in the percent swelling with time. The obtained results revealed that the addition of mucoadhesive polymers increased the percent swelling of all prepared patches compared to CAB (F1) alone which had the lowest percent swelling. It is clear that SCMC had the highest percent swelling (F6-F9) followed by HPMC100M (F10-F13) and finally Cbp934P (F2-F5) that had a poor influence on the percent swelling. This could be ascribed to the presence of more hydroxyl group in SCMC compared to both HPMC100M and Cbp934P [35].

Table 3: Swelling percentages of SCG patches

Formula code	5 (min)	10 (min)	15 (min)	20 (min)	30 (min)	60 (min)
F1	3.7±0.006	5.2±0.01	8.6±0.08	10.2±0.09	15.6±0.82	20.8±0.99
F2	4.8±0.006	6.2±0.01	10.7±0.05	13.5±0.06	18.6±0.54	24.9±1.5
F3	4.8±0.009	7.8±0.008	11.8±0.01	14.6±0.08	19.7±0.35	25.9±0.85
F4	5.6±0.08	9.2±0.006	12.6±0.009	15.8±0.01	19.6±0.85	24.6±1.9
F5	4.5±0.06	8.9±0.01	13.2±0.08	16.7±0.009	20.1±0.96	26.2±0.58
F6	3.5±0.006	9.4±0.008	16.8±0.08	23.1±0.06	25.5±0.54	35.5±0.85
F7	2.8±0.008	8.6±0.006	17.2±0.009	27.1±0.09	32.5±0.96	40.4±1.5
F8	3.5±0.006	10.6±0.08	19.2±0.006	28.6±0.09	35.2±0.87	45.4±1.9
F9	2.8±0.01	8.2±0.08	18.6±0.009	26.8±0.04	35.4±0.58	53.2±1.5
F10	2.6±0.008	5.8±0.006	10.2±0.08	14.2±0.08	18.2±0.99	31.5±0.85
F11	3.1±0.006	7.2±0.008	13.8±0.06	15.6±0.09	19.8±0.96	35.4±0.96
F12	3.5±0.01	7.8±0.06	14.5±0.06	16.8±0.04	20.5±1.5	39.4±0.54
F13	2.8±0.01	9.4±0.08	15.7±0.009	18.2±0.04	21.2±1.5	41.5±0.85

*Data are expressed as mean±standard deviation of the mean (SD), n=3

Surface pH

The surface pH of all prepared patches was found to be in the range from 6.4 to 6.9, which indicates that the prepared patches are non-irritant to the buccal mucosa and expected to be palatable (table 4).

Drug content

Drug content of SCG buccal patches (2x2 cm) was observed to be in the range from 97.8±0.08 to 101.8±0.018 (table 4) which ensures homogeneous and uniform distribution of the drug throughout the prepared patches.

Moisture uptake

The moisture uptake of all prepared patches ranged from 3.2±0.08 to 10.8±0.25 (table 4) which indicates that all prepared patches will remain stable and non-brittle with a poor chance of microbial attack [36]. It was found that the addition of mucoadhesive polymers increased the film hydrophilicity and resulted in a significant increase in moisture uptake [37]. Both HPMC 100M and SCMC increased moisture uptake more than Cbp934P compared to CAB alone (F1). The amount of mucoadhesive polymer had a non-significant effect on moisture uptake of the prepared patches.

Ex-vivo mucoadhesion strength

Table 4 illustrated the results of mucoadhesion strength of all prepared patches. It is clear that patch which was prepared from CAB alone (F1) had the lowest mucoadhesion strength (17.2±0.014). The addition of mucoadhesive polymers increased the mucoadhesion significantly and their effect arranged in the following order SCMC>HPMC100M>CbP934P. It was observed that SCMC had the highest effect and Cbp934P had the lowest effect. Also, the results showed that the mucoadhesion behaviour is greatly influenced by the type of mucoadhesive polymer and increased with an increase in the concentration of hydrophilic polymer. The effect of SCMC could be attributed to the higher hydration and higher swelling. Shilpa *et al.* [38] found that buccal strips of pravastatin which were prepared from SCMC showed high mucoadhesion. Also, it was observed that HPMC had a lower effect on mucoadhesion compared to SCMC and this could be ascribed to the lack of proton donating carboxyl group which results in a decreased ability to form hydrogen bonds [39].

Ex-vivo mucoadhesion residence time

Ex-vivo mucoadhesion residence time of all prepared patches is presented in table 4. It is obvious from the results that incorporation of both HPMC 100M and SCMC increased the residence time while Cbp934P had no effect compared to CAB alone (F1). It was found that as the amount of SCMC increased from 200 mg (F6) to 500 mg (F9), there was an increase in the residence time from 6.75±0.28 to 8.3±0.25. The same behaviour was observed in case of HPMC 100M (F10-F13). The residence time of the prepared patches arranged as follows: SCMC>HPMC100M>CbP934P>CAB. From the obtained results of both percent swelling and mucoadhesion strength, it can be predicted that there was a good correlation between them, this means that patch with higher percent swelling had higher mucoadhesion and remain attached to the buccal mucosa for a longer time.

Table 4: Physico mechanical characterization of SCG patches

Formula code	Surface pH±SD*	Drug content (%)±SD	Moisture uptake (%)±SD	Mucoadhesion strength (*dyne/cm^2)±SD	Residence time(h)±SD
F1	6.5±0.021	100.8±1.2	3.2±0.08	17.2±0.14	3.35±0.25
F2	6.7±0.019	98.6±0.08	5.2±0.16	19.1±0.26	3.55±0.28
F3	6.4±0.021	99.7±0.08	4.2±0.18	21.6±0.21	3.75±0.25
F4	6.4±0.021	101.0±1.5	3.8±0.15	24.2±0.26	3.75±0.18
F5	6.7±0.016	97.8±0.08	4.8±0.15	25.6±0.18	3.5±0.22
F6	6.5±0.019	98.8±0.06	6.2±0.16	31.6±0.25	6.75±0.28
F7	6.4±0.015	99.5±1.6	8.1±0.18	37.6±0.18	7.15±0.18
F8	6.5±0.012	99.2±0.08	9.8±0.19	41.1±0.15	7.45±0.28
F9	6.8±0.015	98.2±0.18	10.8±0.25	51.2±0.26	8.3±0.25
F10	6.8±0.015	99.4±1.8	6.3±0.25	23.2±0.18	4.5±0.21
F11	6.8±0.012	101.2±1.7	7.2±0.21	25.1±0.11	4.7±0.18
F12	6.8±0.019	99.8±1.9	9.1±0.28	28.5±0.22	5.7±0.15
F13	6.6±0.011	101.8±0.018	10.4±0.21	30.2±0.17	6.7±0.25

*Data are expressed as mean±standard deviation of the mean (SD), n=3

In vitro release study

In vitro release studies were performed in phosphate buffer pH 6.8 to simulate buccal cavity. The release profiles of the prepared patches are clearly illustrated in figs. (1-3). It is obvious from the figs. that 95.2±1.4 % of the incorporated dose released from F1 after 8 h. The addition of Cbp934P had non-significant effect at low concentration as observed in F2 (92.4±1.5) and F3 (90.1±0.8) but upon increasing its concentration there was a slight but significant reduction in the amount of drug released after 8 h, as observed in F4 (89.1±1.3) and F5 (87.2±1.5) (fig. 1). It is clear from fig. 2 that incorporation of SCMC significantly retarded the release of SCG from F7 (87.1±0.8), F8 (82.1±1.5) and F9 (75.2±1.1) after 8 h. Similar behaviour was observed with HPMC100M (fig. 3). From the previous, it can be concluded that the mucoadhesive polymers retarded the release in the following order SCMC>HPMC100M>CbP934P. The retarding effect of SCMC and HPMC100M could be attributed to the fact that upon contact of both polymers with the dissolution medium, they undergo swelling forming a thick gel layer on the surface of the swollen patch which lead to an increase in the diffusional path length [40, 41] in addition to the prevention of the matrix disintegration by retarding penetration of the dissolution medium into the patch [42]. Magdy *et al.* found that montelukast released slowly from patches which were prepared from either SCMC or HPMC [14], Also, Mishra *et al.* found that incorporation of HPMC retarded the release of simvastatin from Eudragit RS-100 patches [43].

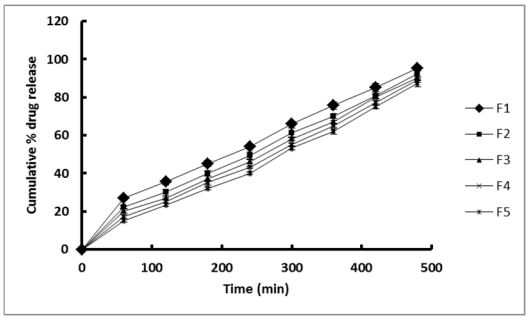

Fig. 1: Cumulative drug release percent of SCG from CAB±CbP934P different patches, n=3±SDM (standard deviation of the mean)

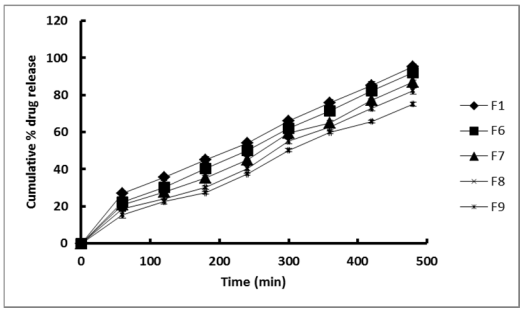

Fig. 2: Cumulative drug release percent of SCG from CAB±SCMC different patches, n=3±SD

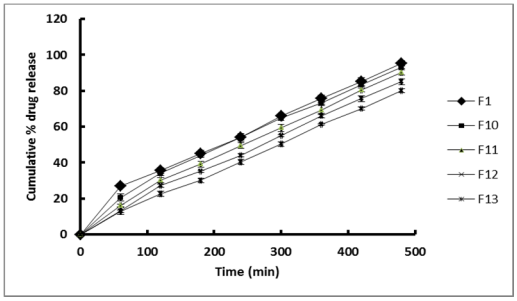

Fig. 3: Cumulative drug release percent of SCG from CAB±HPMC different patches, n=3±SD

Kinetic data analysis

The *in vitro* release profile of all prepared mucoadhesive patches follow Higuchi diffusion model.

Ex-vivo drug permeation study

F5, F9 and F13 were selected for ex-vivo permeation through the porcine buccal mucosa based on their physicomechanical characters, release profiles and the used mucoadhesive polymer. It was found that 82.1±1.7, 70.1±0.8 and 75.6±1.5 of the incorporated dose were permeated through the porcine buccal mucosa from F5, F9 and F13 respectively (fig.4). By comparing the release profile and permeation profile of each formula, it can be concluded that there was a good correlation between the release and permeation of SCG which gives a good evidence for the effective therapeutic response of the prepared patches. Mehraj udin *et al.* found that there was a good correlation between *in vitro* release data and ex-vivo permeation data of methyldopa from HPMC K47-PVP K30 patches [18].

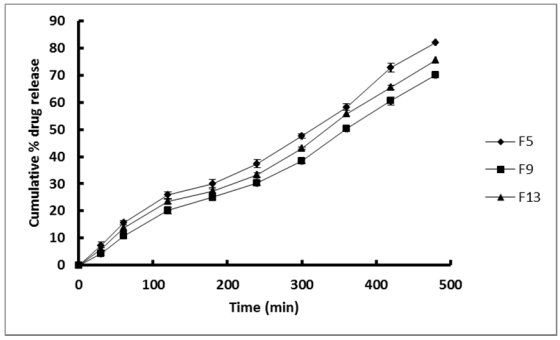

Fig. 4: Cumulative drug release percent of SCG permeated through the porcine buccal mucosa, n=3±SDM

In vivo pharmacokinetic study

Fig.5 shows the chromatogram of the rabbit plasma of SCG. It can be observed that well-resolved peak obtained at 5.4 min for SCG. Fig.6 represents the plasma profile of SCG optimized patch (F9) and parenteral solution as a function of time. It is clearly observed that there was a significant difference in the mean plasma concentration of both parenteral solution and mucoadhesive patch at all-time intervals. Table 5 depicts the mean pharmacokinetic parameters of tested formulae. From the illustrated results, it can be noticed that after administration of parenteral solution of SCG the peak plasma concentration was14.2±1.2 µg/h/ml and reached rapidly after 1.15±0.06 h, whereas peak plasma concentration of mucoadhesive patch was 9.9±0.08 µg/h/ml and reached after 3.85±0.008 h. The increase in T_{max} and the decrease in C_{max} of SCG patch compared to parenteral solution suggests a sustained release effect with a good bioavailability.

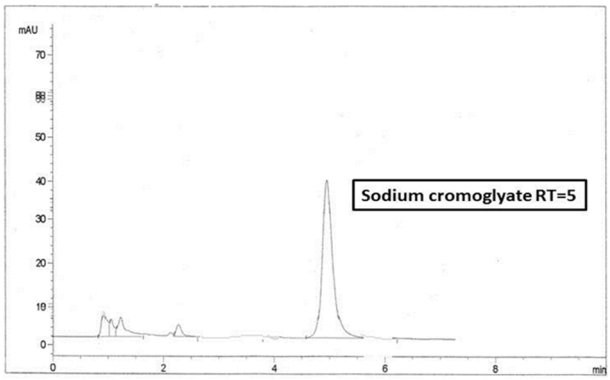

Fig. 5: Typical HPLC chromatogram of SCG in rabbit plasma

Table 5: Pharmacokinetic parameters of SCG patch and parenteral solution

Formula	Cmax (µg/h/ml)±SD*	Tmax (h)±SD	AUC_{0-24}±SD
SCG patch (F9)	9.9±0.08	3.85±0.008	10.76±0.85
Parenteral solution	14.2±1.2	1.15±0.06	10.12±0.56

*All results are expressed as the mean of six determinations±standard deviations of the mean (SD)

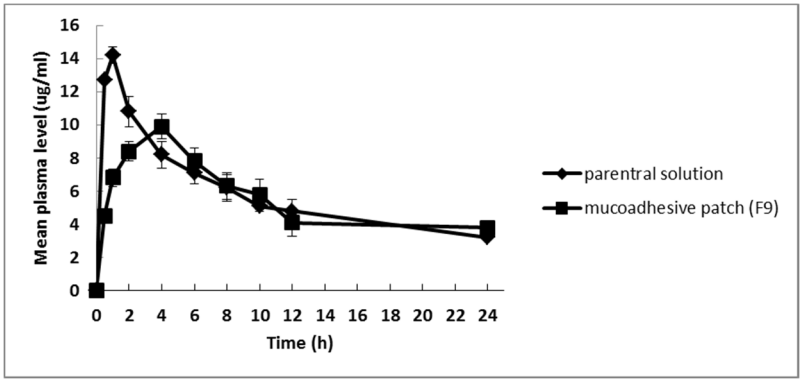

Fig. 6: Mean plasma levels of SCG of the parenteral solution and optimized mucoadhesive buccal patch F9, Sample size= 6±SD

CONCLUSION

From the previous results it can be concluded that mucoadhesive buccal patches which were prepared from cellulose acetate butyrate and carboxy methyl cellulose sodium (F9) showed a good *in vitro* characteristics, an enhanced bioavailability and considered a promising dosage form to solve the poor oral absorption and short half-life of the drug.

AUTHOR CONTRIBUTION

All the work have been carried out by me

CONFLICT OF INTERESTS

No conflict of interest

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