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Levosalbutamol Sulphate mucoadhesive buccal thin film formulation design and characterization: Effect of polyethylene glycol 400 as a plasticizer

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Polyvinyl pyrrolidone K-30 (PVP K30).

Abstract

The present study aimed to design and evaluate mucoadhesive buccal thin films of levosalbutamol sulphate to circumvent pre-systemic elimination due to gastrointestinal degradation and hepatic first-pass metabolism. Films were prepared using four water-soluble polymers in varying proportions with PEG-400 as a plasticizer. A total of five formulations were developed and characterized for physicochemical parameters including surface pH, film thickness, folding endurance, mass and content uniformity, density, swelling index, disintegration time, percent moisture absorption/loss (PMA/PML), in vitro drug release kinetics, and ex vivo mucoadhesion time. All evaluations were performed in triplicate to ensure data reliability. The prepared films exhibited high folding endurance (>300), uniformity in mass and thickness, and a surface pH compatible with salivary fluid. Disintegration time and content uniformity met standard criteria. Drug release kinetics followed zero-order in two formulations, Higuchi model in two, and first-order in one. Mucoadhesion times ranged from 2 to 9 minutes, and the films demonstrated satisfactory stability under both dry and humid conditions.

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1. Introduction

For most active pharmaceutical ingredients (API), the enteral route is the most favored and acceptable in terms of patient compliance. When taken orally, numerous APIs have significant pre-systemic

clearance due to digestive tract breakdown and/or hepatic metabolism. Inadequate systemic bioavailability, a short degree of therapeutic effectiveness, and the production of noxious and inactive metabolites are all common side effects. The idea of mucoadhesion or oral thin films has received a lot of focus in pharmaceutical technology since the early 1980s (Chickering & Mathiowitz, 1999)

Beneficial impacts of oral thin films' mobility and ease of use have increased both the geriatric and pediatric groups' acceptability of this dose type (Gavaskar, Kumar, Sharan & Rao, 2010). Many variables contributed to the necessity for rapid-dissolving oral thin films (Bandari & Gannu, 2008). Rapid-dissolving oral thin films are among the dosage forms that have a good patient compliance rate, particularly for patients who have trouble chewing or swallowing (Biradar, Bhagavati & Kupassad, 2006; Dixit & Puthli, 2009). You can administer drugs orally anywhere, at any time, and without the need for water. Additionally, oral thin films are free of the friability concerns that are common with orodispersible tablets (Patel & Poddar, 2009).

As an alternative to conventional dosage forms, thin films provide a flexible platform that can produce immediate, local, or systemic effects (Ozakar, 2021). Drugs' ability to stick to mucosa in the mouth is affected by things like molecular weight, flexibility, hydrogen bonding capacity, swelling behaviour, and pH range in the environment (Lalla & Gurnancy, 2002). There are various benefits to administering medications through the oral mucosa (Barnhart, Rathborne, Hadgraft, Roberts & Lane, 2013). Depending on whether local or systemic action is required, administering medication via buccal drug delivery presents some difficulties (Mitra, Alur & Johnston, 2002). The medicine itself, or other formulation ingredients, may cause toxic effects (Smart, 2005).

Drugs that are broken down before they reach the liver can quickly get into the bloodstream through the internal jugular vein, which makes them very bioavailable (Jasti, Xiaoling & Gary, 2004). Additionally, buccal films have better patient compliance because they are smaller and thinner than other common dosage forms like

tablets. They can be used as an alternative drug delivery method for a variety of therapeutic classes (Karki, Kim, Na, Shi, Jo & Lee, 2016).

HPMC E15 was found to be a suitable film-forming agent, while PEG 400 possesses outstanding plasticizing properties in the development of buccal films of meloxicam (Zaman, Hanif, & Qaiser, 2016). Morales (2011) proposed that rizatriptan-benzoate-loaded mucoadhesive buccal films might represent a viable option for achieving optimal medication release for migraine treatment. Mashru (2005) developed quick sublingual dissolving films for the administration of polyvinyl alcohol polymer-based salbutamol sulphate. A novel mucoadhesive oral film of levosalbutamol sulfate based on propylene glycol as a plasticizer was developed, and in vitro as well as additional studies have revealed that this is a promising drug delivery approach with good physicochemical properties and a consistent release profile (Morshed, Mallick, Islam, Sohel & Kawsar, 2017)

Levosalbutamol sulphate's physicochemical and pharmacokinetic properties make it a promising option for the development of a buccal system of drug delivery. As a result, the aim of this research was to formulate mucoadhesive buccal oral thin films of levosalbutamol sulphate to ensure optimal drug release and avoid pre-hepatic first-pass metabolism that increases bioavailability of this drug in asthma and COPD patients which can assist young and elderly people, as well as unconscious individuals who have difficulties swallowing. Among the several polymeric plasticizer options, polyethylene glycol (PEG 400) was chosen to observe its effect on the formulation development of mucoadhesive levosalbutamol sulphate buccal oral thin film.

The chirally pure R-enantiomer of levosalbutamol, also known as levalbuterol, is a selective β2-adrenoceptor agonist, which is twenty-nine times greater in its preference for β2-receptors than β1-receptors, suggesting that it is more selective for the broncho-receptor than the β1-receptor of the heart. Salbutamol has both R- and S-isomers, as shown in Figure 1, and hence is considered a racemic mixture. Salbutamol's R-isomer has fifty times more selective affinity for the β2-adrenoceptor than S-isomer, though S-isomer is responsible for showing its adverse effects. That resulted

in the discovery of levosalbutamol, which is an R-isomer of salbutamol (Schreck & Babin, 2005)

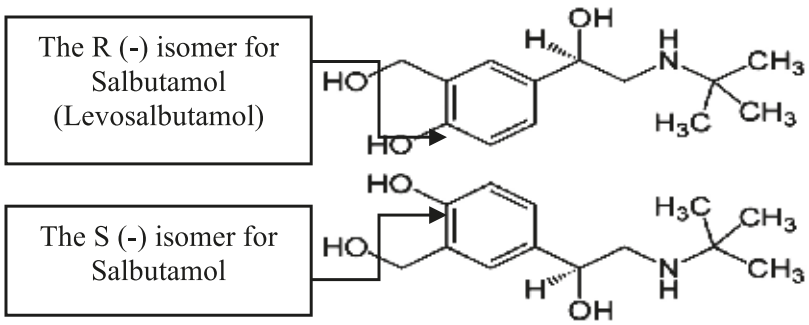

Figure 1
Salbutamol enantiomer's structural formulas

It is thought that the (S)-enantiomer of racemic salbutamol may cause airway hypersensitivity reactions in asthma patients, even though it is not useful for treatment. A comprehensive clinical experiment found that inhaling 0.625 mg or 1.25 mg of levosalbutamol three times per day provided excellent relief from asthmatic symptoms. Racemic salbutamol (2.5 mg) was more effective than levosalbutamol (0.625 mg). Levosalbutamol showed greater potency and effective tolerance in most of the clinical trials than racemic salbutamol (Khairwa & Jat, 2013)

2. Materials and methods

The Department of Pharmacy, Advanced Pharmaceutical Technology Research Laboratory, State University of Bangladesh, Dhaka, conducted the overall experiment. We collected Levosalbutamol sulfate INN from Beximco Pharmaceuticals Limited in Bangladesh. Les Laboratories SERVIER in France provided the polymers Carbopol 934p (Cp), Polyvinyl Pyrolidone (PVP K30), and Hydroxypropyl Methylcellulose (HPMC-K4M). We procured PEG-400 polyethylene glycol from Merck, Germany. Every other material, including reagents, was of analytical grade. We collected fresh oral mucosa from a nearby slaughterhouse within two hours of the sheep's slaughter.

2.1 Preparation and analysis of standard levosalbutamol sulphate

The standard stock solution was made by dissolving about 20 mg of levosalbutamol sulphate into phosphate buffer pH 6.8 to achieve a

final concentration of 200 g/mL. We obtained different aliquots of the stock solution and successively diluted them with phosphate buffer pH 6.8 to produce a series of concentrations ranging from 10 to 100 g/mL. The maximum wave length (λmax, 276 nm) for levosalbutamol sulphate in a phosphate buffer of pH 6.8 was measured by UV spectroscopy. The calibration curve was generated by graphing absorbance against different levosalbutamol sulphate solution concentrations (μg/mL). Absorbance found in solutions of different concentrations was taken three times, and an average value was taken for analysis.

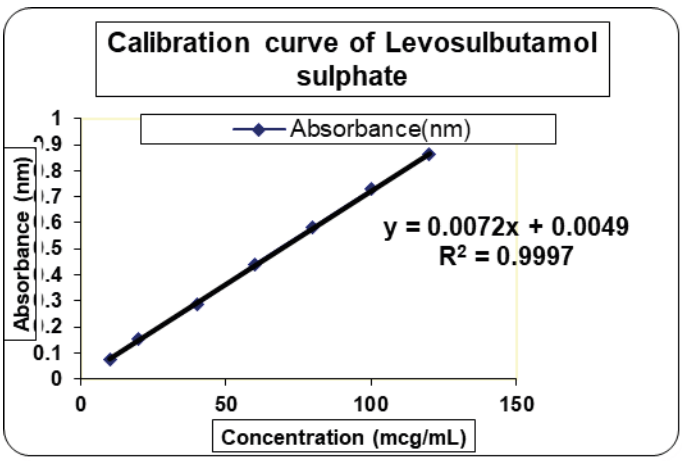

Figure 2
Linear calibration curve of levosalbutamol sulphate

Levosalbutamol sulphate has been shown to obey linearity utilizing the suggested method in the concentration range of 10 to 100 μg/mL (Table I). The method is highly reproducible, as evidenced by the fact that the RSD is less than 2%.

Table I
Analytical validation parameters of prepared calibration curve of levosalbutamol sulphate

Parameter	Findings
Absorption maxima(nm)	276
Range of linearity (μg/mL)	10-120
Standard regression equation	y=0.0072x+0.0049
Correlation coefficient (r^2)	0.9997

2.2 Formulation of levosalbutamol sulphate oral thin films

The solvent casting approach was employed to manufacture buccal thin films of levosalbutamol sulphate due to its simplicity and

inexpensive cost (Buanz, Belaunde, Soutari, Tuleu, Gul & Gaisford, 2015). Water has been employed as the solvent in the solvent casting method to formulate the oral thin films of Levosalbutamol sulphate. We tried multiple polymeric combinations, including Hydroxy Propyl Methyl Cellulose/Sodium Carboxy Methyl Cellulose, Hydroxy Propyl Methyl Cellulose/Carbopol, Hydroxy Propyl Methyl Cellulose/Carbopol/Sodium Carboxy Methyl Cellulose, Hydroxy Propyl Methyl Cellulose/Carbopol/Polyvinylpyrrolidone, and Hydroxy Propyl MethylCellulose/Polyvinylpyrrolidone. We incorporated aqueous solutions of polymers of multiple concentrations into the ratios stated in Table II. We obtained an aqueous solution containing 1% m/V CP 934 P and SCMC and 2% m/V HPMC K4M and PVP K30 by dissolving in an appropriate proportion of distilled water. To dissolve the medication, 1 mL of pure methanol was employed (Patel, Prajapati & Ravel, 2010; Prasanth & Mathew, 2011).

Table II

Design and arrangement of levasalbutamol sulphate oral thin film formulations.

Formulation code	Levosalbutamol sulphate (mg)	PEG-400 (mL)	HPMC- K4M (2% m/V mL)	CP 934P (1% m/V mL)	SCMC (1% m/V mL)	PVP K30 (2% m/V mL)
F-1	117.6	5	50	-	25	-
F-2	117.6	5	50	25	-	-
F-3	117.6	5	50	-	-	25
F-4	117.6	5	40	20	-	15
F-5	117.6	5	40	20	15	-

To this polymeric solution, an appropriate quantity of medication equivalent to 2.4 mg levosalbutamol sulphate was slowly added, followed by a thorough mixing with PEG 400. We used sodium saccharine as a sweetener to mask the bitter taste. We stirred the suspension for 30 minutes with a high-shear propeller mixer to obtain a homogeneous drug-polymer mixture. We allowed the films to undergo vacuum drying in vacuum desiccators for 30 minutes at room temperature to eliminate any unwanted bubbles, after sufficient mixing. We carefully dispensed the prepared drug-polymer mixture into a 14 x 14 cm^2 specially designed glass plate, covering all of the square plate's ends. The film settlement was done

at room temperature for 1 hour prior to being dried for 18 hours at 60◦ with a hot air oven (Daihan Sci, Korea). Afterwards, after careful inspection, dried films were taken out, checked for flaws or the presence of air bubbles, and then cut into 2x2 cm2 of film by means of a stainless steel cutter. The prepared films were subjected to sealing by using high-density polyethylene (HDPE) sheets and preserved at room temperature in desiccators. According to International Conference on Harmonization (ICH) rules, prepared film samples were also preserved for accelerated stability assessments (Morshed, Mallick, Islam, Sohel & Kawsar, 2017).

2.3 Prepared levosalbutamol sulphate films evaluation

2.3.1 Film thickness

Film thickness was assessed on ten films, and thickness readings of four random areas for each film were examined with a micrometer screw gauge (Mitutoyo Corporation, Japan).

2.3.2 Mass uniformity

From each batch, at least three individual films were randomly selected and tested for mass uniformity using an electronic balance (Mettler Toledo, Japan).

2.3.3 Folding endurance

The flexibility of a film is connected to its folding endurance and tensile strength, both of which indicate the film's physical stability throughout manufacturing, packaging, and use. We manually measured the film's folding endurance by repeatedly and firmly folding it in the middle. The degree of folding endurance was assessed by quantifying the number of folds on the bending that were needed to form a crack in the film (Shinde & Garala, 2008).

2.3.4 Surface pH:

By dissolving agar of 2% (m/V) in a warm, phosphate buffer (isotonic) with pH 6.8 g with continuous stirring, place the solution into an 80 mm petri dish, and leave it to cool until it gels at room temperature. Over the course of two hours, films swelled on the outermost layer of these plates. To determine the surface pH, a pH paper (Merck, Germany) was positioned on the exterior part of the expanded films.

2.3.5 Density

The following formula was applied to figure out how dense the prepared film is:-

$$Density = \frac{Mass\ of\ the\ film}{\text{Volume}}$$

Here, Volume = thickness of the film X total area of the film

2.3.6 In vitro disintegration time

Two basic approaches involving a small amount of medium were used. The first step was to add a single drop of water to the securely clamped film using a 10 mL pipette. Disintegration time (DT) was the amount of time it took to create a hole in the film. In the second approach, a few drops of distilled water were placed on a petri plate, a film was positioned on the water surface, and the time it took for the film to disintegrate was taken as disintegration time. The test has been performed at least three times since the average value was used for determining disintegration time.

2.3.7 Drug content uniformity assessment

The produced film was allowed to dissolve for two to three hours while being occasionally shaken in a 10 mL volume of simulated saliva solution, which was set at pH 6.2. The resulting solution was allowed to filter via 0.45 mm whatman filter paper; subsequently, the quantitation of Levosalbutamol sulphate present in the film was done spectrophotometrically at wavelength maxima of 276 nm, followed by proper dilution (Nidhi, Vaishali, Anwar & Minal, 2011).

2.3.8 Swelling index

Agar plates were produced as indicated in the section on measuring surface pH for the purpose of the swelling investigations. The prepared film has been allowed to swell on the plate top. We thoroughly mixed 50 mL of phosphate buffer (pH of 6.8) and 2% agar, then poured them onto the petridish, which we kept in an incubator at 37 °C. (Nidhi, Vaishali, Anwar & Minal, 2011).

When the individual films had gelled, the initial weight of all formulations was recorded and then allowed to be placed again on the agar plate. The film's weight allowed it to grow over a 60-minute period. At intervals of 15 minutes, the swallon weight of the

films was measured. The swelling percentage was calculated using the formula below:

Swelling index (SI) = { $\frac{Wt - Wo}{Wo}$ } x 100

Here, W_t = at time t, mass of swollen films

W_0 = at time t=0, mass of dry films

2.3.9 *In vitro* release study

Dissolution assessment of films was conducted by means of a USP 23 rotating paddle-type Type-II dissolution test apparatus (Electrolab, India). We used 200 mL of simulated saliva solution (pH 6.2) as the dissolution medium at 37.2 °C and 50 rpm. The film was adhered to the specially constructed stainless steel disk using cyanoacrylate glue. The disk was placed at the dissolution tank's bottom, with the levosalbutamol sulphate film remaining on the disk's upper surface. At predetermined time intervals, samples (15 mL) were taken out and restored with an equivalent volume of dissolution medium. The samples were filtered through 0.45-mm Whatman filter paper; the resulted filtrate was diluted with a simulated saliva (pH 6.2) solution; and they were assessed by spectrophotometric analysis (Shimadzu Corporation, Japan) at a maximum wavelength of 276 nm (Nidhi , Vaishali, Anwar & Minal, 2011).

2.3.10 Percentage of moisture absorption (PMA)

The percentage of moisture absorption test was performed to evaluate the physical durability of the films under highly humid conditions. Three films were precisely weighed before being placed in a desiccator holding a saturated aluminum chloride solution, keeping the level of moisture inside the desiccator at 79.5%. After three days, the films were removed, weighed, and the moisture absorption was calculated. The average percentages of moisture absorption for three films were identified in (Lohani, Prasad & Arya, 2011).

For determination of percent of moisture absorption, the following formula was used.

$$Percent\ of\ moisture\ absorption = \frac{Final\ weight - Initial\ weight}{Initial\ weight}\ x\ 100$$

2.3.11 Percentage of moisture loss (PML)

The strength of the films in dry conditions was further checked by measuring the percentage of moisture loss. In desiccators filled with fused anhydrous calcium chloride, three films were accurately weighed and preserved. The films were taken off after passing of 72 hours and reweighed. The average proportion of moisture loss calculated (Lohani, Prasad & Arya, 2011).

For determination of percent of moisture loss, the following formula was used.

$$Percent\ of\ moisture\ loss = \frac{Initial\ weight - Final\ weight}{Final\ weight}\ x\ 100$$

2.3.12 Residence time (ex vivo mucoadhesion time)

The USP dissolving apparatus II was used to test the strength of mucoadhesion of the produced levosalbutamol sulphate films. The buccal mucosa of sheep was utilized in this investigation because it is structurally and permeability-wise similar to the human buccal membrane. By getting rid of the loosened tissues and underlying fat, the mucosal membranes were separated. Phosphate buffer (pH 6.8) was used to wash the membrane. Initially, the sliced mucosa sample was attached to the inside wall of the beaker, just about 2.5 cm above the bottom of the beaker. The buccal mucosal membrane was attached to a sample of film by applying light pressure with finger tips for 30 seconds after wetting one side of the film with phosphate buffer (pH 6.8) to make it sticky. The beaker was then filled with 500 mL of phosphate buffer pH 6.8 while keeping at a temperature of 37.2 °C and a rotation of 50 rpm. The value of ex vivo mucoadhesion time is the period of time required for separating the film from the buccal mucosal membrane (Prasanth & Mathew, 2011).

3. Result

3.1 Formulation of levosalbutamol sulphate thin films

In this study, films of levosalbutamol sulphate were made utilising the solvent casting method using multiple polymer mixers of hydroxypropyl methyl cellulose K4M, carbopol 934 P, sodium carboxymethyl cellulose, and polyvinyl pyrrolidon. To evaluate the effect of PEG-400 as a plasticizer, a total of five formulations (F-1

to F-5) were developed. To avoid any undesirable residual solvent difficulties, organic solvents were not applied. Water was used as a solvent for the lengthy drying period during the formulation process (20 hours).

3.2 Thickness, mass uniformity and folding endurance of developed films

Table III showed the average thickness readings of all formulated films. From F-1 to F-5, the film thickness varied between 0.179 and 0.224 mm. The weight of the films ranged from 100 mg to 114 mg (F-1 to F-5).

Table III

The physicochemical properties of levosalbutamol sulphate thin films

Formulation Code	Thickness (mm)	Mass Uniformity (mg)	Disintegration Time (min)	Surface pH	Folding Endurance	Density
F-1	0.224±0.67	114±0.34	3.50±0.13	6.8	>300	0.104±0.15
F-2	0.224±0.67	102±0.30	4.50±0.08	6.0	>300	0.093±0.09
F-3	0.179±0.53	89±0.26	3.30±0.10	6.3	>300	0.092±0.08
F-4	0.209±0.62	100±0.30	4.50±0.12	6.5	>300	0.062±0.06
F-5	0.204±0.61	103±0.30	5.00±0.06	6.0	>300	0.065±0.06

We manually assessed the folding endurance by folding the film continuously at a point until it broke. We calculated the folding endurance by counting the number of times we could fold the film at the same point without it breaking. Consequently, we determined the breaking time at the finish point (Table III).

3.3 Surface pH of films

The pH range of all prepared formulations falls within the salivary pH range, i.e., 6.0 to 7.0 (Table III).

3.4 Density of films

The highest density was found for F-1 (0.104±0.15) using the polymer combination Hydroxypropyl methyl cellulose K4M/Sodium carboxy methyl cellulose. The lesser density was found for F-4 (0.062±0.06) using a combination of hydroxypropyl methyl cellulose, carbopol 934 P, and polyvinyl pyrrolidon, F-4 had a lower density (0.062±0.06). The density was obtained in the following order: F-4<F-5<F-3<F-2<F-1 (Table III).

3.5 Drug content uniformity of films

The observed content uniformity findings showed a uniform distribution of the medication throughout the film. However, F-4 had the highest drug loading of 2.6504 mg (110.25%), while F-1 had the lowest drug loading of 2.0508 mg (85.41%).

3.6 Disintegration time of films

We found that the disintegration time for the developed formulation batches fell within the limits. Formulation F-3 demonstrated the quickest disintegration (about 3 minutes) with the polymer combination HPMC-K4M/PVP K30 (Table II). We found that the maximum disintegration time for F-5 is approximately 5 minutes. The use of suitable disintegrants in the formulation may accelerate disintegration time.

3.7 Swelling index studies of the prepared films

The films' swelling indices ranged between the various polymer compositions and reached up to 334.37% for F-1 after 45 minutes. In the following order, the swelling index increased: F4<F2<F5<F3<F1.

3.8 *In vitro* dissolution study of levosalbutamol sulphate films

Using phosphate buffer (pH 6.8) as the dissolution medium and analysing the amount of drug UV spectrophotometrically at λmax 276nm, which was previously calculated, in vitro drug release tests have been carried out for all the developed formulations. We took six samples from each formulation for the investigation to ensure accurate results. We continued the studies for 150 minutes, recording each absorbance's data in triplicate. Figure 4 shows the outcomes of the (F-1 to F-5) in vitro release tests. The graph was prepared by plotting cumulative percentage release vs. time (min). F-2 demonstrated a quicker release than the others. The various release rate kinetics of levosalbutamol sulphate thin films were also investigated (Figures 4 (a), 4 (b), 4 (c), and 4 (d) in succession).

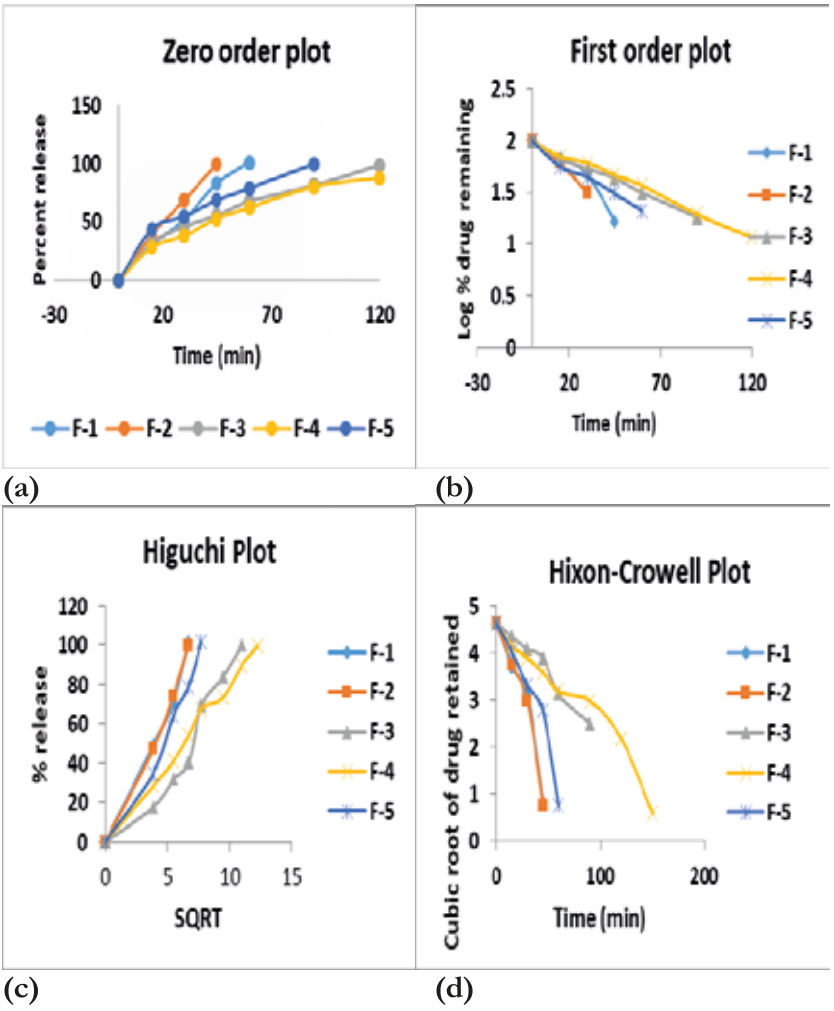

Figure 3

Release profile of LS buccal film formulation 1 to 5 using PEG 400 as plasticizer a) zero order plot b) first order plot c) higuchi plot d) hixon-crowell plot

Table IV: Respective linear regression equation (Y=mx+c) & correlation coefficient (R^2) value

Code	Zero Order		First Order		Highuchi		Hixon Crowell	
	Y=mx+c	R^2	Y=mx+c	R^2	Y=mx+c	R^2	Y=mx+c	R^2
F1	1.70x+2.04	**0.994**	-0.016x+2.06	0.920	12.97x-8.45	0.933	-0.044x+4.74	0.959
F2	2.19x+2.35	**0.996**	-0.017x+2.01	0.993	14.24x-5.42	0.951	-0.088x+5.04	0.884
F3	0.74x+16.12	0.928	-0.008x+1.97	0.994	8.963x-2.04	**0.996**	-0.027x+4.68	0.948
F4	0.62x+16.59	0.933	-0.007x+2.00	**0.995**	8.521x-3.56	0.992	-0.019x+4.52	0.990
F5	1.00x+17.39	0.902	-0.010x+1.96	0.984	10.31x+0.44	**0.996**	-0.029x+4.47	0.965

From Table IV, F-1 and F-2 followed zero-order release kinetics, F-3 and F-5 followed Higuchi release, but only F-4 followed first order based on the value of the correlation coefficient. It has to be noted that no formulation meets the Hixon-Crowell release criteria. F-1 and F-2 are polymeric combinations of two polymers, HPMC K4M/SCMC and HPMC K4M/CP 934P.F-3, a mixture of the two polymers HPMC K4M and PVP K30, and F-5, a combination of the three polymers HPMC K4M, CP 934, and SCMC, followed the higuchi release. Only the F-4 with the HPMC K4M/CP 934/SCMS combination followed the first order release.

3.9 Percent PMA and PML

We assessed the formulated films of levosalbutamol sulphate for percentage absorption of moisture (PMA) and percentage loss of moisture (PML), respectively, to determine the film's physical strength under both highly moist and dried conditions (Figure 4). The observed PMA for F-1 to F-5 was in the order of F3>F1>F2>F4>F5. On the contrary, the PML values of F-1 to F-5 were in the order of F3>F1>F2>F5>F4.

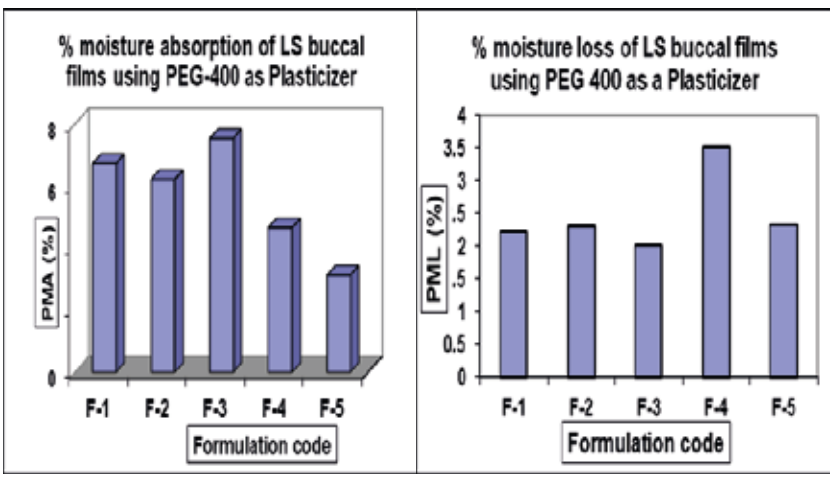

Figure 4
Effect of Plasticizer PEG 400 in percent moisture absorption and loss of LS buccal film

3.10 Residence time (*ex vivo* mucoadhesion time)

In F-5 (8.10 min), where the polymer combinations were HPMC K4M/CP 934P/SCMC, the mucoadhesive strength had been found

to be at its highest, and the lowest period of residence was reported in F-1 (5.20 min).

4. Discussions

Mucoadhesive buccal films are preferred over other forms because to their high flexibility, lack of adverse effects, more accurate dosage than drops or syrup formulations that having wider area of contact for drug absorption (Khan, Trivedi & Boateng, 2016; Scarpa, Stegemann, Hsiao, Pichler, Gaisford & Bresciani, 2017).

We successfully made five formulations of levosalbutamol sulphate buccal thin film by adopting different polymeric configurations and using PEG-400 as the plasticizer. A very low standard deviation number suggests the method employed in film formulation is reproducible and produces films of consistent thickness, ensuring dose precision in each film. This study found that the thickness and mass of the films were almost reproducible. The consistency of thickness and content of drug is related to the reliability of drug concentration in various parts of each film (Dixit & Puthli, 2009).

The surface pH of films revealed that there is no significant variation in surface pH across all film formulations, implying that no mucosal discomfort was expected. Results show that surface pH of films is in the range of healthy human saliva, which is 6.3–7.3 (Aframian, Davidowitz & Benoliel, 2006). Folding endurance was used to assess the cracking resistance and mechanical resilience of buccal films. When folding endurance grew, mechanical strength also increased. The folding durability for every formulations was determined more than 100 times, indicating good flexibility (Liew, Tan & Peh, 2012).

We determined the percentage of drug concentration in all prepared formulations to be within 85%–110%, which complies with regulatory compendia (Chaudhary, Gauri, Rathee & Kumar, 2013; United States Pharmacopeia, 2011).

As expected, raising the polymeric concentration increases disintegration time, whereas increasing the content of plasticizer results in quicker film disintegration for a certain polymer quantity. The existence of water-soluble polymers may be the reason for higher swelling indices. The swelling behavior provides insight into how well different types of polymers absorb moisture and whether

the formulations retain their integrity after doing so. The resistance of the matrix network varies due to the presence of hydrogen bonds. The flow of water-soluble molecules may account for variations in the swelling of the tested hydrophilic polymers. Additionally, the inclusion of a water-soluble medication may have enhanced the matrix's surface wetting.

The various release rate kinetics showed that, among the five formulations based on the value of the correlation coefficient, two followed zero-order release kinetics, two followed higuchi release, and only one followed first-order, ensuring a predictable drug release profile. Adhesion residence times for the studied films were found between 2 to 9 minutes. The mechanical and mucoadhesive qualities associated with these dosage forms are essential for their efficacy in delivering the active medication ingredient across the oral mucosa and reducing saliva washout of the medication (Alaei, Omidi & Omidian, 2021).

The relatively low standard deviation of the results indicates the relative stability of the film in both dry and humid conditions. The ex vivo mucoadhesion time showed that carbopol 934P had a greater effect than SCMC, and increasing carbopol 934P concentrations had a favourable impact on in vivo mucoadhesive ability.

Lastly, it should be mentioned that more effort is needed in addition to developing new methods of evaluating adhesion or refining the current procedures in these two domains:

i) comparing different procedures side by side. Different methods should be used to test the adherence of different substrate-film combinations.

ii) measuring thin polymeric film adhesion. Therefore, a thorough investigation of how these and other polymeric film properties affect their adhesion strength needs to be done.

5. Conclusion

The impact of the plasticizer has been studied on the physical and chemical properties of the mucoadhesive levosalbutamol sulphate oral thin films, aiming to combat the pre-hepatic first-pass metabolism and the resulting reduced bioavailability of the drug.

Based on results from tests in vitro and other sources, it may be a good way to deliver levosalbutamol sulphate because it has better physicochemical properties and a predictable release profile. We need further research to scale up formulations, confirm these findings in vivo, and examine additional film properties such as the film's tensile strength, dryness/tack test, Young's modulus, percent elongation, and so on. We can also research another appropriate plasticizer for potential use.

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