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DESIGN AND EVALUATION OF BUCCAL MUCOADHESIVE TABLETS OF PANTOPRAZOLE SODIUM

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ABSTRACT

Introduction: Drug delivery via buccal route using mucoadhesive dosage forms offers a novel route that can improve bioavailability of many drugs. Pantoprazole sodium is a proton pump inhibitor indicated for erosive esophagitis associated with gastroesophageal reflux disease (GERD). It is completely absorbed after oral administration, has short half life and low bioavailability because of first pass metabolism. It is a suitable candidate for administration via buccal route. **Materials and methods:** Various synthetic and natural bioadhesive polymers were studied for suitability as mucoadhesive buccal delivery. Bilayer mucoadhesive buccal tablets were prepared by direct compression. The tablets were evaluated for *in vitro* drug dissolution and *ex vivo* mucoadhesion. **Results:** Hydroxyl propyl methyl cellulose and sodium alginate were found to be most suitable mucoadhesive polymers. Drug release and *ex vivo* mucoadhesion was observed for 8 hours.

KEYWORDS: buccal, mucoadhesive, esophagitis, hydroxyl propyl methyl cellulose, sodium alginate.

INTRODUCTION

Oral route offers more flexibility in the designing of dosage forms and is most convenient as compared to other routes. But it has some disadvantages like extensive first pass metabolism, degradation of drugs in GIT and poor bioavailability. Drug delivery via buccal mucosal route eliminates these problems and offers various advantages like increased bioavailability, improved patient compliance and dose reduction.[1] Drugs penetrate the mucous membrane by simple diffusion and are carried into systemic circulation via the jugular veins. Buccal route provides a potential route for delivery of large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides as well as conventional small drug molecules. Basic components of buccal drug delivery system in addition to the drug are, mucoadhesive polymer, backing membrane and penetration enhancers.[2]

Buccal tablets are intended to be inserted in the buccal pouch. The tablet erodes or dissolves slowly and the active ingredient is absorbed directly through the oral mucosa. Buccal delivery of drug has many advantages such as prolonged residence time ensuring drug release in unidirectional way thus avoiding loss of drug, good accessibility, facile removal of dosage form in case of need, less susceptibility to enzymatic activity, prevent drug degradation in gastrointestinal tract and avoid hepatic first-pass metabolism. It also has the same challenges namely; drug delivery system should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period, therefore necessitates the use of mucoadhesive polymers.[3,4,5]

Mucoadhesive polymers form viscous liquids when hydrated with water that increases their retention time over mucosal surfaces and may lead to adhesive interactions. These polymers possess certain physicochemical features like hydrophylicity, numerous hydrogen bond forming groups, flexibility for interpenetration with mucous and epithelial tissue and visco-elastic properties. These polymers can be naturally occurring e.g. chitosan and pectin or synthetic e.g. polyacrylic acid derivatives and cellulose derivatives. They are classified as anionic (Carbopol®, Sodium carboxymethylcellulose), cationic (Chitosan) or non-ionic (hydroxypropylmethyl cellulose). Pectins are non-toxic, low cost hydrophilic polysaccharides derived from plant cell walls.[6,7,8]

Gastroesophageal reflux is the return of stomach's contents back up into the esophagus. It occurs when the lower esophageal sphincter (LES) is weak or relaxes inappropriately, allowing the stomach's contents to rise up into esophagus. The severity of GERD depends on the type and amount of fluid brought up from the stomach and on LES dysfunction.[9] The prevalence of GERD is very common in world. Approximately 8 -20% of the total Indian Population suffers from GERD.[10,11]

Antacids, Histamine receptor antagonists (e.g. cimetidine, ranitidine), proton pump inhibitors (e.g. PS, omeprazole), prokinetics (e.g. cisapride) are used for the treatment of GERD. Avoidance of tobacco, alcohol, chocolate, and citrus juice may also help relieve the GERD symptoms.[1]

Pantoprazole sodium (PS) exhibits potent and long lasting inhibition of gastric acid secretion by selectively interacting with gastric proton pump in the parietal cell secretory membrane. However, the bioavailability of PS following oral administration is usually very low, since it degrades very rapidly in the acidic environment of stomach and undergoes hepatic first pass metabolism. To improve bioavailability of PS various formulations have been developed but they have been known to have a wide individual variation of plasma concentration. Thus, attempts were made to develop buccal mucoadhesive tablets to overcome these problems.[1]

MATERIALS AND METHODS:

Materials

Pantoprazole sodium and Carbopol® 974P was obtained as a gift sample from Wanbury Ltd, Mumbai. HPMC K4M CR was obtained from Colorcon Asia. sodium alginate, xanthan gum, ethyl cellulose, mannitol and all other chemicals were obtained from S. D. Fine Chemicals.

Methods

Preformulation

Preformulation studies were carried out on the PS and excipients. PS was authenticated by FTIR, UV and DSC. A calibration curve of absorbance against concentration was constructed by accurately weighing PS (50 mg) and dissolving in 100 mL of phosphate buffer pH 6. A series of dilution were made from the above stock solution to get a solution of concentration ranging from 5 to 30 µg/mL. The absorbance was recorded at 288nm and plotted against concentration (Figure 1.). PS and excipients were evaluated for their flow properties and compatibility. Compatibility was studied by placing a 1:1 sample of PS and excipients in stability chambers at 40±2°C/75±5% RH for a period of 1 month. Any change in physical appearance and assay value was assessed.

Preparation of bilayered tablets by direct compression

Ethyl cellulose was used to form the backing layer. PS and all excipients, other than ethyl cellulose, were homogenously blended as per the formula mentioned in Table 1. Accurately weighed 70 mg of the powder blend was pre-compressed on single station tablet punching machine to form a single layered flat bevelled tablet of 6mm diameter. Further, accurately weighed 10mg of ethyl cellulose powder was added and final compression was done to get a bilayer tablet.

The effect of different concentrations of polymer and penetration enhancer was studied on rate of drug release from the tablet and time of mucoadhesion. Developed formula was screened for its robustness from design of experiments in accordance with a full factorial design model. Three levels of HPMC K4M (controlled release and mucoadhesive polymer) and SLS (permeability enhancer) were selected for the study. Software, Design Expert 8.0.7, was used to analyse the data (Table 2.). The full factorial design revealed that an alteration in formula was desired hence further tablets were prepared using a modified formula containing a combination of HPMC K4M and sodium alginate to improve mucoadhesion and drug release. (Table 3).

Physiochemical evaluation of tablets

The tablets were evaluated for physicochemical parameters like tablet thickness, hardness, weight variation, assay. Thickness of tablets was measured by vernier callipers. Hardness was measured by Monsanto tester and friability was determined in a Roche friabilator.

Assay

Ten tablets from each batch were powdered together and a quantity equivalent to 30mg of PS was accurately weighed and extracted with methanol. Each extract was suitably diluted and analysed spectrophotometrically at 288 nm.[14]

In vitro dissolution studies

Drug release rate of tablets was determined by carrying out dissolution study using USP apparatus type 2 (paddle type). The test was performed in 500 mL phosphate buffer solution of pH 6 maintained at 37±0.5°C at 50 rpm. Aliquots of 5 mL were collected at predetermined time intervals and replaced with 5 mL dissolution medium. The drug content was analysed by measuring the UV absorbance at 288nm using UV spectrophotometer.[15]

In vitro Mucoadhesion/Retention time study

The *in-vitro* retention time is one of the important physical parameter of buccal-mucoadhesive tablet. The prepared tablet was pressed over excised porcine buccal mucosa for 30s after previously being secured on glass slab. It was immersed in a basket of the dissolution apparatus containing 750 mL of phosphate buffer pH 6, at 37° C. The paddle of the dissolution apparatus as adjusted at 5cm from the tablet and rotated at 25 rpm. The time for complete erosion or detachment from the mucosa was recorded as given in Table 8.[16]

Ex vivo permeability study

Ex vivo permeability study was performed using a dialysis membrane placed in a glass Franz diffusion cell of capacity 25 mL. Assembly was placed in water circulation maintained at 37± 0.5° C. Dialysis membrane was stabilized for 1 h. The receiver chamber was maintained by stirring with magnetic bead at 50rpm. After 1 h the tablet was kept on dialysis membrane and 2 mL of phosphate buffer of pH 6 was added in donor

chamber. Aliquots of 1 mL were withdrawn at the time intervals of 1 h till the end of 8 h and replaced with equal volume of fresh dissolution medium to maintain sink conditions. The withdrawn sample was diluted to 5 mL. The amount of PS diffused into the receiver chamber was determined by UV spectrophotometry at λ_{max} 288 nm.[17]

***In vitro* swelling studies**

Tablets were weighed individually (w_1) and placed separately in petri dishes containing phosphate buffer pH 6. At regular intervals (0.5, 1, 2 h) samples were removed from the petri dish and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (w_2).[18]

The swelling index of each system was calculated using the following formula.

Swelling index= $(w_2 – w_1)/w_1$ *100

***In vitro* mucoadhesion force**

A mucin disc was fixed to the glass vial using cyanoacrylate adhesive. The disc was hydrated with distilled water. Each tablet was placed on the lower vial. The lower vial was then elevated till the surface of the tablet came in contact with the mucin disc. Both the tablet and the mucin disc were left in contact for 2 min using a preload of 10 g to allow formation of an adhesive bond then water was added from an infusion set into a pre-weighed plastic jar at a constant rate of 30 drops/min. The addition of water was stopped when the mucin disc was detached from the tested sample, the filled plastic jar was reweighed and the weight of water required to detach the tested sample from the mucin disc was calculated by difference.[19]

Bioadhesive force (F) = 0.00981 w/2

Where w= weight of water**.**

Determination of surface pH

A combined glass electrode was used for determination of surface pH. The tablets were first allowed to swell by keeping them in contact with 5 mL phosphate buffer pH 6 for 2 h in 10 mL beakers. The pH was noted. The experiment was performed in triplicate and average value was calculated.

Drug release from backing layer

The bi-layered buccal tablet was placed between the donor and receptor compartment of the Franz diffusion cell in such a manner that the backing layer was in contact with the dialysis membrane. The complete unit was maintained at 37° C. The donor compartment and the receptor compartment were filled with phosphate buffer pH 6 with synchronous stirring. Aliquots of 2 mL were withdrawn at a predetermined interval from the donor compartment and analysed at 288 nm by UV spectrophotometric analysis to check the release of drug from the backing layer of the tablets.[20]

Stability studies

To determine the change in physical properties and *in vitro* release profile on storage, optimized batches were stored at 25 ± 2° C/60 ±5 % RH, 40± 2° C/75% RH and 30 ± 2°C/65±5% RH for duration of three months. Samples were evaluated at the end of 1, 2 and 3 months for physical appearance, assay and dissolution.

RESULTS AND DISCUSSION

The FTIR spectrum of the PS matched with the reported spectrum and certificate of analysis. The DSC thermogram of PS showed a melting point of 157.1 ºC. A linear response (r^2= 0.9986) was observed between concentration and absorbance in the range of 5 to 30 µg/mL at a λ_{max} of 288nm (fig 1). PS was found to be compatible with selected excipients and polymers. The results showed no changes in physical appearance and there was no change in the assay values.

Mucoadhesive tablets of PS were formulated using HPMC, Carbopol® and sodium alginate as mucoadhesive polymers. SLS and polysorbate 80 were used as penetration enhancers.

The prepared tablets were subjected to physicochemical evaluation. The results are depicted in Table 4. The parameters like thickness, diameter, hardness, friability were within predetermined limits. The batches D1-D4 were made using Carbopol® as mucoadhesive polymer and SLS and polysorbate 80 as permeability enhancers. However, all the batches had poor stability. Stability of PS was increased by adding magnesium oxide as pH adjuster to maintain the micro-environmental pH in a range that will improve stability during manufacture and storage. Drug release of PS from these formulations was 94-98% in 4 h, hence further tablets were prepared with altered formula to get a quicker drug release. The tablets were formulated using HPMC K4M. HPMC K4M has lower molecular weight and viscosity compared to other grades like HPMC K15M, HPMC K100M etc. The lower degree of entanglement would increase the effective molecular diffusion area and hence the drug permeation across the matrix gel. The batch H2 containing HPMC K4M and sodium alginate was chosen as optimized batch amongst all the prepared batches. This batch demonstrated optimum mucoadhesion time (>8h) and promising *in vitro* release (95.04%) in 6 h. This is in accordance with the reported data that sodium alginate provides good mucoadhesion and HPMC K4M retards the release.

Optimization studies were carried out as per 3^2 factorial design. Two parameters namely drug release rate and mucoadhesion time were optimized. The software Design Expert 8.0.7. was used to analyse the data.

The batches A1-A4 containing HPMC K4M showed 58.68-76.36% release at the end of 4 hours. HPMC K4M is a high viscosity polymer and hence higher the amount of polymer leads to lower the rate of release. The percent

cumulative release of B1-B4 was 80-97%. Carbopol® forms a high viscosity gel on hydration in environment of buccal cavity thereby inhibiting the drug release from the tablet. As Carbopol® concentration was increased drug release was found to reduce. The percent cumulative release of PS from batch B1-B4 was found to be 75-91 % at 4 h. The Batches E1 to E9 containing HPMC K4 M as release retarding polymer and SLS as permeation enhancer were formulated as per the formula obtained from design expert software. The prepared batches were subjected to physicochemical evaluation. All the parameters were with the desired range. The results of dissolution study portrayed that batches E1 to E3 containing highest amount (8%) of HPMC K4 M showed 74.24-77.02% release in 6 hours, E4 to E6 (containing 6% of HPMC K4M) showed 75.71-80.4 % release and E7- E9 containing lowest amount of polymer (4% HPMC K4M) showed 81.43-89.08 % release at the end of 6 hours. Thus it was observed that the release of drug varied greatly on changing the polymer-polymer ratio. The drug release in hydrophilic matrix tablets occurs through the hydrophilic gel formed around the tablets, and the drug release rate depends on the formation and viscosity of gel layer, the extent of swelling and erosion of the polymer chains. Erosion occurs as the polymer chain becomes more hydrated resulting in disentanglement and subsequent erosion. On comparing the release profile of the batches maximum release was observed for batches D1-D4 since penetration enhancers SLS and polysorbate 80 were used. Batches A1-A4 showed lowest release which may be attributed to high viscosity of HPMC K4M.

***In vitro* mucoadhesion time study**

Higher concentration of HPMC K4M gives higher mucoadhesion time. When the polymer concentration is too low, the number of penetrating polymer chains per unit volume of mucus is small and the interaction between polymer and mucus is unstable. Sodium alginate shows higher mucoadhesion time because the polymer, although manifesting higher swelling is less water bound and hence it tends to retain its structure.

***Ex vivo* permeability study**

The result of *ex vivo* permeability studies are given in table 9. From the results it was found that higher the concentration of polysorbate 80 higher the permeability of drug. This may be due to the adsorption and fusion of drug molecules onto the surface, resulting in the high thermodynamic activity gradient of drug at the interface, which is the driving force for drug permeation.

***In vitro* swelling studies**

Swelling index is used to study the swelling ability of polymer. As time increased, the swelling index was increased because the weight gained by tablet was increased proportionally with rate of hydration. From the swelling index study it was observed that the increase in the concentration of polymers increases the swelling property of the tablets, this might be due to increased absorption of water in the polymer matrix. (Table 10)

***In vitro* mucoadhesion force**

The bioadhesive strength of the mucoadhesive polymer was determined by measuring the force required to detach the formulation from a mucin disc.

Mucoadhesive strength of all the formulations was found to increase as the concentrations of polymer was increased. The high bioadhesive strength of sodium alginate may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of polymeric chains in the interfacial region. Polymers like HPMC and sodium alginate undergo superficial bioadhesion. Bilayer tablets containing HPMC K4M and sodium alginate in the ratio 1:3 exhibit higher bioadhesive strength.

Determination of surface pH

The surface pH was determined in order to investigate the possibility of any side effects in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mocosa. Surface pH of all formulations was found to be very close to neutral pH hence these formulations cause no irritation in buccal cavity.

Drug release from backing layer

It was found that no drug was released in 6 hours in the donor compartment of Franz diffusion cell. This indicated that ethyl cellulose membrane was impermeable to PS and the swelling of mucoadhesive layer did not change the integrity of backing layer. Hence tablet was found to be efficient for unidirectional release of PS through buccal mucosa.

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2	Drug release profile of batch A1-A4
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Table 1: Formulation and development of bi layered PS tablet.

Ingredients	Formulations and quantity (mg)											
	A1	A2	A3	A4	B1	B2	B3	B4	D1	D2	D3	D4
PS	15	15	15	15	15	15	15	15	15	15	15	15
HPMC K4M	6.4	4.8	4	3.2	-	-	-	-	-	-	-	-
Carbopol® 974P	-	-	-	-	6.4	4.8	4	3.2	6.4	6.4	6.4	6.4
Sodium alginate	-	-	-	-	-	-	-	-	-	-	-	-
Lactose	6.4	6.4	8	6.4	6.4	6.4	8	6.4	6.4	6.4	6.4	6.4
Mannitol	39.4	41	41.16	42.6	39.4	41	41.16	42.6	38.68	39.08	38.68	39.08
SLS	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.6	1.2	-	-
Talc	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.04
Aspartame	0.48	0.48	0.48	0.48	0.48	0.48	0.48	0.48	-	-	-	-
Flavour	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.28	0.64	0.64	0.64	0.64
Polysorbate 80	-	-	-	-	-	-	-	-	-	-	1.6	1.2
Sucrose	-	-	-	-	-	-	-	-	0.24	0.24	0.24	0.24
Backing layer												
Ethyl cellulose	10	10	10	10	10	10	10	10	10	10	10	10
Total (mg)	80	80	80	80	80	80	80	80	80	80	80	80

Table 2: 3^2 FullFactorial design for optimization of HPMC K4M and SLS quantities

Batches	Coded Values	
	X_1	X_2
E1	1	-1
E2	1	0
E3	1	1
E4	0	-1
E5	0	0
E6	0	1
E7	-1	-1
E8	-1	0
E9	-1	1
X1: HPMC K4M (%) X2: SLS (%) -1: low level (X1=4, X2=1) 0:middle level (X1=6, X2= 1.5) +1:high level (X1= 8, X2= 2)		

Table 3: Formulation and development of tablets using HPMC K4M and sodium alginate (batch H1)

Ingredients	Formulations and quantity (mg)
PS	15
HPMC K4M	4
Sodium alginate	12
Lactose	4
Magnesium oxide	31.48
Polysorbate 80	1.6
Talc	1.04
Sucrose	0.24
Orange	0.64
Ethyl cellulose	10
Total	**80**

Table 4: Physical parameters of buccalmucoadhesive tablets of PS tablets of batches A1-C4.

Formulation	Thickness (n=10)	Diameter	Hardness	Friability (n=3)	Weight Variation (n=7.5)	% assay (n=3)
A1	2.1±0.01	6	4-5	0.8±0.02	80.02±0.17	97.03±0.01
A2	2.1±0.01	6	4-5	0.82±0.01	80.01±0.01	93.19±0.01
A3	2.1±0.04	6	4-5	0.8±0.05	80.04±1.02	95.69±0.03
A4	2.1±0.05	6	4-5	0.84±0.07	80.11±0.35	94.49±0.04
B1	2.1±0.03	6	4-5	0.9±0.02	80.07±1.21	96.79±0.02
B2	1.9±0.17	6	4-5	0.86±0.03	80.03±0.15	98.98±0.04
B3	1.9±0.19	6	4-5	0.81±0.03	80.05±1.21	96.99±0.03
B4	2.0±0.14	6	4-5	0.88±0.01	80.21±1.01	95.10±0.01

Table 5: Physical parameters of D1-D4 formulation batch.

Formulation	Thickness (n=10)	Diameter	Hardness	Friability (n=3)	Weight Variation (n=7.5)	% assay (n=3)
D1	1.9±0.01	6	4.5	0.82±0.34	80.04±0.30	96.99±0.02
D2	1.9±0.02	6	4.5	0.82±0.95	80.13±1.26	96.99±0.19
D3	1.9±0.01	6	4.5	0.8±0.45	80.01±1.05	96.54±0.94
D4	1.9±0.01	6	4.5	0.8±0.63	80.71±1.05	93.48±0.21

Table 6: Physical parameters of H1 and H2 formulation batch

Formulation	Thickness (n=10)	Diameter	Hardness	Friability (n=3)	Weight Variation (n=7.5)	% assay (n=3)
H1	1.9±0.4	6	4.5	0.82±1.29	80.03±1.21	99.98±0.05

Table 7: *In vitro* dissolution study.

Batch	% cumulative drug release at 4 hours	Inference
A1-A4	58-76%	As the polymer concentration increases the drug release decreases.
B1-B4	80-97%	As Carbopol® 974P concentration increases the drug release decreases
D1-D4	**94-96%**	**SLS and polysorbate 80 slightly increase % cumulative release**
E1-E9	69.89-75.83%	Increase in SLS concentration increases drug dissolution
H1-H2	65.86-70.89%	As polysorbate 80 increases % cumulative release increases

Table 8: *In vitro* mucoadhesion time for batches E1-E9, H1-H2.

Batch	Polymers used	Mucoadhesion time	Result
E1-E9	HPMC K4M	< 6 h	Unsatisfactory
H1-H2	HPMC K4M and sodium alginate	>8 h	Satisfactory

Table 9: Results of *Ex vivo* permeability study.

batch	%cumulative release at the end of 8 h	Inference
D1-D4	41.98-50.04	Brown discolouration was observed in donor chamber at the end of 6 hrs. Thus in further batches Magnesium oxide was added to enhance the stability and polysorbate 80 was added to increase permeability.
E1-E9	40.56-72.21	Higher the concentration of SLS higher the permeability of drug.
H1-H2	82.42-89.94	Higher the concentration of polysorbate 80 higher the permeability of drug

Table 10: results of *in vitro* swelling, mucoadhesive force and surface pH

Formulation	% swelling index (n=3)	Mucoadhesion strength (n=3)	Surface pH (n=3)
H1	60±1.03	26.9±2.34	7.1±2.1
H2	61±1.75	26.9±2.46	7.1±1.42

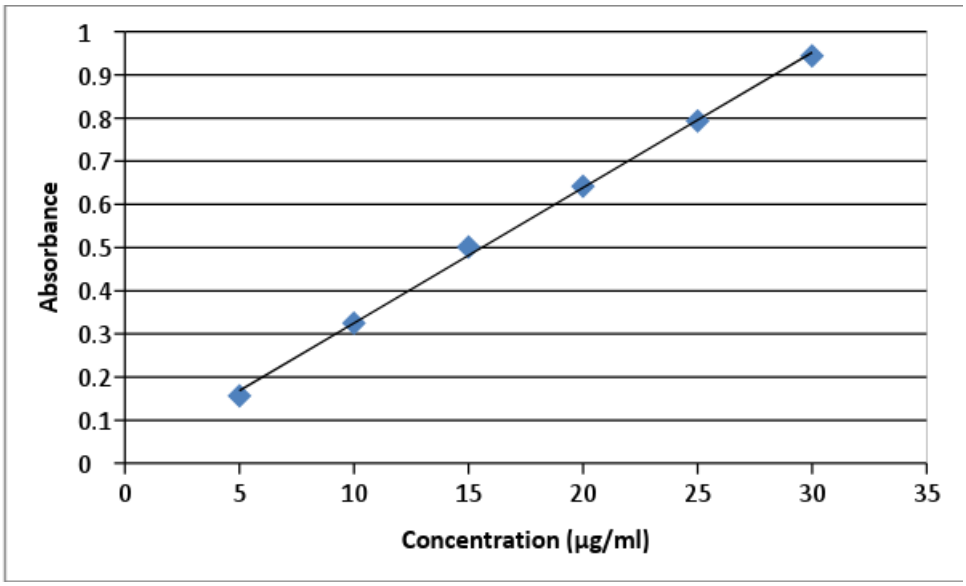

Figure 1: Calibration curve of PS prepared by UV spectroscopy in Phosphate buffer pH 6

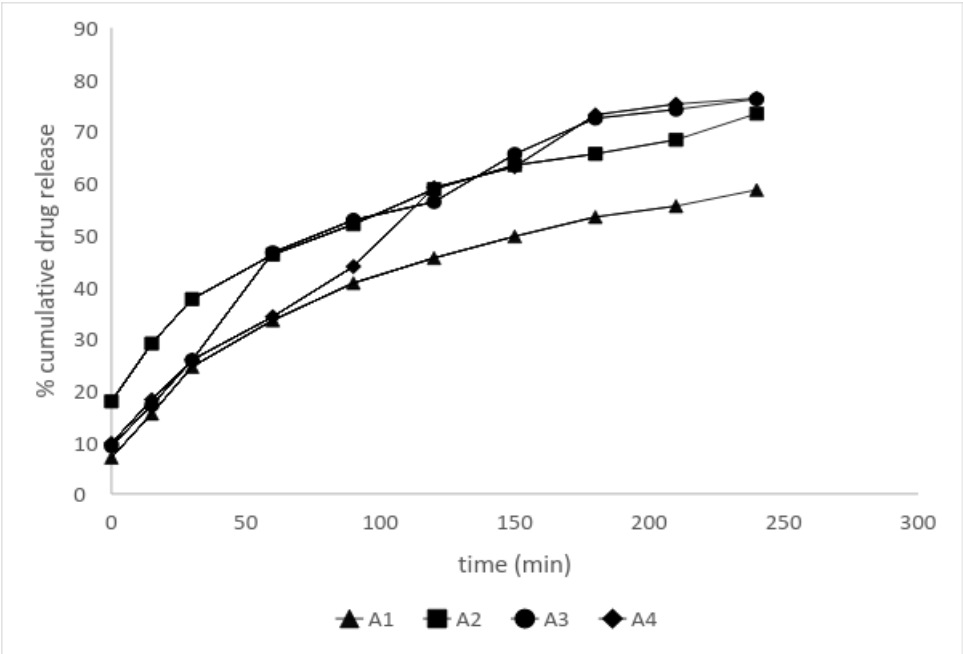

Fig 2: Drug release profile of batch A1-A4.

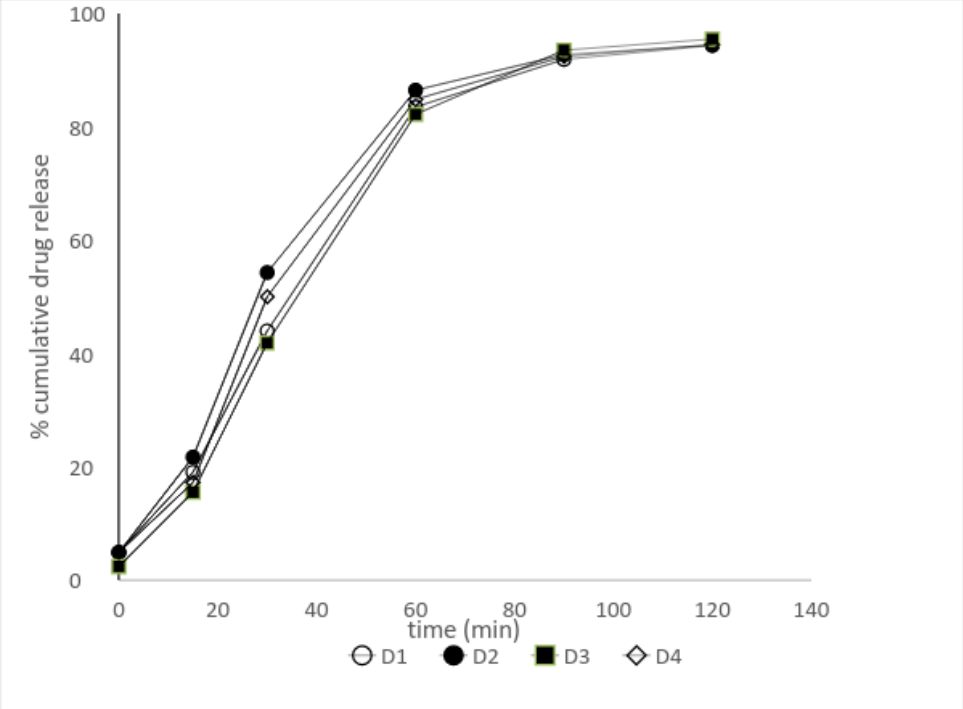

Fig 3: **Drug release profile of batch D1-D4**

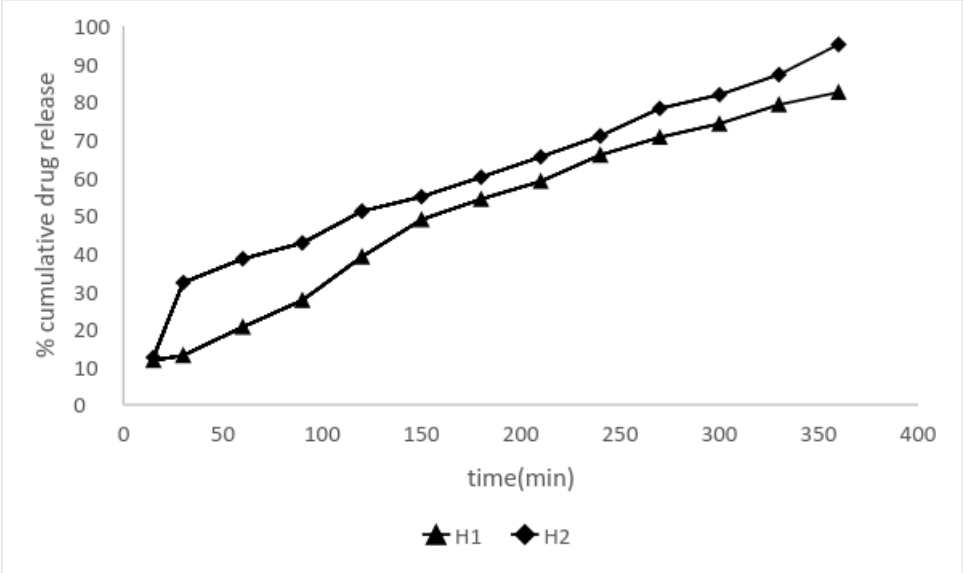

Fig 4: Drug release profile of batch H1-H2.

CONCLUSION

The developed PS mucoadhesive tablets can be beneficial in reducing multiple dosing, provide unidirectional release and avoid extensive hepatic first pass metabolism encountered during systemic therapy. The main advantage of developed buccal tablets is that it contains lower drug dose that is sufficient for therapeutic effect. Thus the formulation can be used for better bioavailability and improved patient compliance.

HPMC and sodium alginate were found to be ideal candidates among various bioadhesive polymers. Polysorbate 80 was found to be effective as a penetration enhancer while ethyl cellulose formed an excellent backing membrane.

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