Research Article

Formulation and *In vitro* Evaluation of Buccal Mucoadhesive Tablets of Promethazine HCl

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ABSTRACT

This study is concerned with the formulation and evaluation of muco-adhesive buccal tablets containing promethazine HCl antiemetic drug; to achieve prolong duration of action and improve patient compliance. The study developed mucoadhesive buccal tablets consist of drug containing mucoadhesive layer and drug free backing layer to allow unidirectional release of the drug. Tablets of promethazine HCl were prepared by direct compression method using carbopol 940P (Cb 940P) as primary polymer and sodium alginate (Na Alginae), sodium carboxymethylcellulose (Na CMC) and hydroxypropyl methylcellulose K15 M (HPMC K15M) as secondary polymers. The tablets were evaluated for weight variation, hardness, friability, surface pH, drug content uniformity, swelling index, bioadhesive strength, *ex vivo* residence time and *in-vitro* drug dissolution study. Fourier transform infrared spectroscopy (FT-IR) studies showed no evidence for interactions between drug, polymers, and excipient. Among the prepared formulation, the formula that contains carbopol 940P as primary polymer in concentration (3% w/w) and sodium alginate as secondary polymer in concentration (27% w/w) was found to be promising; with pH value (6.11), mucoadhesive strength (15.6±0.62 gm), residence time (7.45 hr), cumulative percent drug release was 88 % after 6 hr and the release kinetic was found to follow zero order kinetic, F1 selected as optimum formula. The *in vivo* evaluation of the prepared buccal tablet showed successful results. The optimum formula may avoid the 1st pass effect of Promethazine HCl and improving its bioavailability and consequently may reduce its dose and dosing frequency leading to reduce its side effects.

Keywords: Buccal mucoadhesive tablets, *In-vitro* dissolution study, Mucoadhesive strength, Promethazine HCl, Residence time, Swelling index.

INTRODUCTION

The most common method of drug administration is via oral route in which the drug is swallowed and enters the systemic circulation primarily through the membrane of the small intestine.[1] However, oral administration of drugs has disadvantages like hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract (GIT).[2] Because of these obstacles there has been a growing interest in delivering of therapeutic agent through various transmucosal routes to provide the required amount of drug to the proper site in body. Buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage form. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability.[3] In the development of these buccal drug delivery systems, mucoadhesion of the device is a key element.[4] "Mucoadhesion" is defined as the interaction between a mucin surface and a synthetic or natural polymer.[5] These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucous and optimal fluidity that permits the mutual adsorption and interpenetration of polymer.[6] mucoadhesive polymers can guarantee an intimate contact with the absorption membrane, providing the basis for a high concentration gradient as a driving force for passive drug uptake.[7] Promethazine hydrochloride is used for the symptomatic relief of allergic conditions to prevent or treat motion sickness, vertigo, nausea and vomiting and in certain type of anesthesia and surgery.[8] Promethazine is well absorbed after oral or intramuscular doses. Peak plasma concentrations have been seen 2 to 3 hours after a dose by these routes, although there is low systemic bioavailability after oral doses, due to high first-pass metabolism in the liver.[9] In the current study, the aim is to prepare mucoadhesive buccal tablets of promethazine HCl to extend the residence time of the buccal tablets, which guarantee satisfactory drug release to a mucosa and avoid consequential loss of drug from wash out with saliva in order to improve patient compliance and improve the systemic bioavailability of the drug.

MATERIALS AND METHODS

Promethazine HCl was purchased from SDI, Iraq. Carbopol 940P, HPMCK15M and PVP were purchased from Alladin Industrial Corporation, Shanghai, China. Sodium Alginate was purchased from Sinopharm Chemical Reagent Co.,Ltd. China. PEG 6000 BDH Ind. China, Sodium carboxymethylcellulose, Ethyl Cellulose, Lactose, Avicel, Sodium Saccharine, Talc and Magnesium stearate were purchased from SDI, Iraq. All other reagents and chemicals used were of analytical grade.

Tablet Formulation

Bilayer tablets (consisting of a backing layer and adhesive: drug reservoir layer) were made by covering one side of

the single-layer tablet with an inert ethyl cellulose layer. Ethyl cellulose was selected as a backing material because it has very low water permeability thus providing an impermeable backing layer that prevents drug loss.[10] Different formulas were prepared as shown in table 1.

Table 1: Composition of buccal mucoadhesive tablets of Promethazine HCl

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Promethazine HCl	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Carbapol 940P	5	10	15	5	10	15	5	10	15	5	5	5	5	5
Na Alginate	45	40	35	-	-	-	-	-	-	45	45	45	45	45
Na CMC	-	-	-	45	40	35	-	-	-	-	-	-	-	-
HPMCK15M	-	-	-	-	-	-	45	40	35	-	-	-	-	-
PVP	-	-	-	-	-	-	-	-	-	5	10	-	-	-
Mannitol	-	-	-	-	-	-	-	-	-	-	-	76.5	-	-
Avicel	-	-	-	-	-	-	-	-	-	-	-	-	76.5	-
Ethanol	-	-	-	-	-	-	-	-	-	-	-	-	-	QS
Na Saccharine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Lactose	76.5	76.5	76.5	76.5	76.5	76.5	76.5	76.5	76.5	71.5	66.5	-	-	76.5
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mg Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2
EC	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Total	165	165	165	165	165	165	165	165	165	165	165	165	165	165

Table 2: Rheology Parameters of the Prepared Powder Blend

Formula code	Angle of repose	Carr 's index	Flow Character
F1	26	16.6	Good/ Fair to passable
F2	25.1	15.7	Good/Good
F3	24.3	15	Excellent/ Excellent
F4	30.34	18.75	Passable/Fair to passable
F5	29.7	17.6	Good/Fair
F6	28.14	16.6	Good/Fair
F7	31.37	20	Passable/ Fair to passable
F8	30.8	19	Passable/ Fair to passable
F9	29.7	18	Good/ Fair to passable
F10	26.9	15.8	Good/ Good
F11	27.3	15.5	Good/ Good
F12	30	16.8	Passable/Good
F13	28.5	15.3	Good/ Good
F14	22.5	13.1	Excellent/ Good

Table 3: Physico-mechanical Characteristics of Promethazine HCl Tablets

Formula No.	Thickness (mm)	Hardness (Kg/cm^2)	% Friability	Surface pH	Weight Variation
F1	3.64±0.005	4.5±0.06	0.24	6.11	Passed
F2	3.64±0.02	6.2±0.221	0.36	5.88	Passed
F3	3.62±0.02	7.65±0.13	0.48	5.73	Passed
F4	3.73±0.02	5±0.1	0.38	6.34	Passed
F5	3.72±0.01	6.2±0.26	0.4	6.05	Passed
F6	3.7±0.005	7.7±0.22	0.43	5.92	Passed
F7	3.73±0.005	5.6±0.12	0.28	6.13	Passed
F8	3.72±0.01	6.5±0.1	0.30	5.83	Passed
F9	3.68±0.01	8.5±0.2	0.34	5.65	Passed
F10	3.63±0.005	5.1±0.12	0.26	5.92	Passed
F11	3.62±0.01	5.9±0.15	0.28	5.75	Passed
F12	3.65±0.005	4.4±0.06	0.33	5.88	Passed
F13	3.64±0.05	8.9±0.21	0.29	6.12	Passed
F14	3.64±0.01	5.1±0.17	0.21	6.15	Passed

Direct Compression Method

All the ingredients including drug, polymer and excipient were weighed accurately and passed through 0.630 mm sieve to get uniform particle size. The drug and all the ingredients except lubricants were mixed in the order of ascending weights and blended for 15 min. After uniform mixing of ingredients, lubricant was added and again mixed for 5 min. The prepared blend of each formulation was compressed by using 8mm punch on a single punch tablet machine (Riva, Germany).[11] After compression of tablet, the upper punch was removed carefully without disturbing the set up and the ingredient of the backing layer was added over the tablet and compressed again.[12] This method applied for formulas (F1-F13).

Wet Granulation Method

Formula 14 was prepared by mixing promethazine HCl, polymers (Carbopol 940P and Na Alginate), lactose and Na Saccharine thoroughly for 15 minutes; the powder was granulated using the sufficient quantity of selected granulating solvent (ethanol) till a wet mass was formed. The cohesive mass obtained was passed through 1.25 mm sieve and the granules were dried at 40ºC for 2 hr.[13] The dried granules were reduced in size by screening through 0.630 mm mesh size sieve.[14] Then the granules were mixed for 5 minutes with mg stearate and talc. The tablets were obtained using the same machine as described above.

Evaluation of the flow Properties for Pre-compressed Powder

Angle of Repose

The angle of repose for the physical mixtures was determined by fixed funnel and petri dish method, where the sample powder poured into fixed funnel and allow to flow gently over fixed diameter Petri dish, the angle of repose were calculated as follow :

$$\text{Tan } Ø = h/r$$

Where Tan Ø is the tan of the angle of repose, h is the height of the resulted con after pouring, r is the radius of the fixed Petri dish.[15]

Compressibility Index (Carr's index)

A sample of each formula powder was poured into10 ml graduated cylinder to occupy the initial bulk volume (V_0) which was then subjected to constant standard tapping procedure until a constant volume was achieved (V_t). Compressibility index was then calculated using the following equation.[15]

$$\text{Compressibility Index} = \frac{V_0 - V_t}{V_0} \times 100$$

Evaluation of the Prepared Buccal Mucoadhesive Tablets

Tablet Thickness

The thickness of three tablets from each formula (F1-F14) (selected randomly) was measured by means of a digital micrometer caliper. The average thickness was determined.[16]

Tablet Hardness

Tablets require certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using electrical hardness tester (Coslab, India). It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. [17]

Tablet Friability

Friability is the measure of tablet strength. Roche type friabilator (Guoming CS-2, China) was used for testing the friability. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min, the tablets were weighed and the percentage loss was determined.[18]

$$\text{Percentage Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. Since an acidic or alkaline pH may cause irritation to the buccal mucosa, so it was determined to keep the surface pH as close to neutral as possible.[19] A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.[20]

Weight Variation

Twenty buccal tablets were weighted individually. The requirement met the USP 30 if not more than two tablets differ from the average weight by more than 7.5 % and no tablet differs in weight by double that percentage, the tablets will be accepted.[15]

Content Uniformity

Five tablets of the selected formula were powdered in a glass mortar and the powder equivalent to 10 mg of drug was placed in a Stoppard 10 ml conical flask. The drug was extracted with 60% methanol with vigorous shaking and filtered into 10 ml volumetric flask. Further appropriate dilution were made by using phosphate buffer pH 6.8 to make 10 mcg/ml concentration and absorbance was measured at 253 nm by UV-Visible spectrophotometer (Shimadzu, Japan).[21]

Swelling Study

Buccal tablet was placed on glass cover slide, weighed and its weight was recorded.[22] The tablet together with the cover slide was placed in Petri dish containing 15 ml of phosphate buffer (pH 6.8) solution. At regular intervals (1, 2, 4 and 6 hr), the tablet together with the cover slid were removed from the Petri dish, and excess surface water was removed carefully using the filter paper. The swollen tablet was then reweighed (W2**)**. This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following equation.[23]

$$\text{Swelling Index} = \frac{W_1 - W_0}{W_0} \times 100$$

Mucoadhesive Strength Study

A modified balance was used for determining the *ex vivo* mucoadhesive strength. Fresh sheep intestinal mucosa was obtained from a local slaughterhouse (Small intestine mucosa was used as model membrane since the intestine provide flat and uniform surface[24], and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer 6.8 solutions. The sheep intestinal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of intestinal mucosa was tied to a glass vial; the vial was tightly fitted into a glass beaker filled with phosphate buffer pH 6.8, so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a glass stopper with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 2 minutes contact time; a force was applied to the left pan of balance by pouring water drop wise to the beaker till complete detachment of tablet achieved. The mucoadhesive strength represent the amount of water added minus the weight of the preload, and the mucoadhesive force was calculated from the following equation:[25]

Mucoadhesive Force = mucoadhesive strength x 0.0098

Mucoadhesion Time Study

The *ex vivo* mucoadhesion time was performed after application of tablets on fresh cut sheep intestinal mucosa. The sheep intestinal tissues were fixed in the internal side of the beaker with cyanoacrylate glue. A side of each tablet was wetted with 1 ml of phosphate buffer (6.8) and was attached to the sheep intestinal tissues by applying a light force with finger tip for 20 sec. The beaker was filled with 800 ml of phosphate buffer (pH 6.8), after 2 min a stirring rate of 150 revolutions per minutes (rpm) using magnetic stirrer (Barnstead Thermolyne, (UK) was applied to simulate the movement of buccal cavity. Tablet behavior was monitored until complete detachment or dissolution occurred.[26]

In vitro Release Study

The drug release from buccal tablets was studied by using USP type II (paddle type) (Copley scientific, UK.), dissolution test apparatus. Tablets were designed to release the drug from one side only; therefore an impermeable backing membrane was placed on one side of the tablet. The tablet was further fixed to a 2 × 2 cm glass slide with a solution of cyanoacrylate adhesive as shown. Then it was placed in the dissolution apparatus containing 500 ml of pH 6.8 phosphate buffers and paddle was rotated at 50 rpm at a temperature of 37 ± 0.5°C. Samples of 5 ml were collected at different time intervals up to 6 hrs and analyzed by spectrophotometer at 248 nm.[27]

Mathematical Modeling of Drug Release Profile

The cumulative amount of promethazine HCl release from the prepared tablets at different time interval was fitted to zero order kinetics, first order kinetics, Higuchi model, Hixson-Crowell and Koresmeyer-Peppas model to characterize the mechanism of drug release.[28]

Drug Excipient Compatibility Study

FT-IR studies were conducted for studying the compatibility of drug, polymers and other additives in the selected optimized formulation (F1). FT-IR spectra (4000-400 cm^{-1}) for the drug alone, physical mixture of the drug and other ingredients of the formula and the compressed tablet were obtained by potassium bromide disks.[29]

Statistical Analysis

Statistical analysis was done by using one-way analysis of variance (ANOVA).The difference is statistically significant when ($P < 0.05$).

RESULTS AND DISCUSSION

Angle of repose and Carr's index

The result in table 2 for angle of repose and Carr's index showed that the powder blends and granules were compressible and had acceptable flow characters.[15]

Tablet thickness, hardness, friability, surface pH and weight variation

Physico-mechanical characteristics of the prepared buccal tablets are shown in table 3.The thickness of the prepared tablets ranged between 3.61 to 3.73 mm and the hardness was in range of 4.1±0.1 kg/cm^2 to 8.9±0.21 kg/cm^2 indicating that the tablets are of adequate strength property to resist handling and mechanical stress and it was increased as the concentration of carbopol 940P increases this is due to its binding capacity.[30] Friability test shows that the weight loss resulted was lower than 1% (0.12–0.48%) for all tablets indicating good compactness and mechanical resistance .The values of surface pH were ranged between 5.73 to 6.31 which indicate that all the formulation provide an acceptable pH

in the range of salivary pH 5.5 to 7.0.[37] Weight variation evaluation shows all the prepared tablets met the USP requirements.

Swelling study

Appropriate swelling behavior of a buccal adhesive tablet is essential for uniform and prolonged release of the drug and effective mucoadhesion.[32] Swelling index of various formulations (F1-F9) performed for a period of 6 hours. The obtained results are summarized in table 4. The highest swelling index for the formulation contains sodium alginate and Na CMC as secondary polymers along with carbopol 940P as primary polymer. This is due to easy hydration with less contact time and fast swelling properties of these polymers as compared to other cellulose derivatives.[22] Lowest hydration percentages was observed with formulas containing HPMCK15M as secondary polymers .These findings correlated with the hydrophilicity of HPMCK15M, although cellulose derivatives are water soluble, their hydrophilicity usually varies according kind and degree of substitution and to some extent with the polymer viscosity.[33] The swelling index was affected by the concentration of carbopol 940P too as shown in figure 1. Non significant increase (P>0.05) was observed with increasing carbopol 940P concentration due to the ionization of the carboxylic acid group of the carbopol 940 that occurs at higher pH values (6.8) and causes the ionic repulsion of the polymer, which is manifested on a macro level as swelling.[34]

Table 4: Swelling Index of Different Formulation

Formula No.	Swelling Index			
	1hr	2hr	4hr	6hr
F1	20.3	37.2	45.2	53.8
F2	24.7	38.98	45.8	59.4
F3	27	42.6	53.6	64.5
F4	18.7	33.4	42.2	50.35
F5	21.6	35	43.7	53.8
F6	24.19	39.13	49.7	60.3
F7	13.7	17.7	22.7	28.3
F8	15.7	18.7	24.3	30.7
F9	17.7	21.3	28.1	36.2

Bioadhesion study

Bioadhesion study was preformed for F1-F9 and the results are shown in table 5. High force of mucoadhesion was observed for formulation containing Na alginate and formulation containing Na CMC as secondary polymer this may be due to opening of the polymer chain as a result of rapid swelling properties of Na alginate which led to initial rapid hydration, so the ionizable functional groups become available for mucoadhesion.[35] Mucoadhesion force for formulation containing HPMCK15M as secondary polymer is lower than that of Na alginate and Na CMC. This is due lower hydration rate that lowered the mucoadhesive force and also due to the non ionic nature of HPMCK15M. [36] Significant increase ($p < 0.05$) in mucoadhesive strength was observed with the increase in the concentration of carbapol 940P as represented in figure 2, which is due to the ability of carbapol 940p to form secondary mucoadhesion bonds with the mucin where the polymer chains undergo rapid swelling and interpenetration into the interfacial region while other polymers exhibit only superficial adhesion.[37]

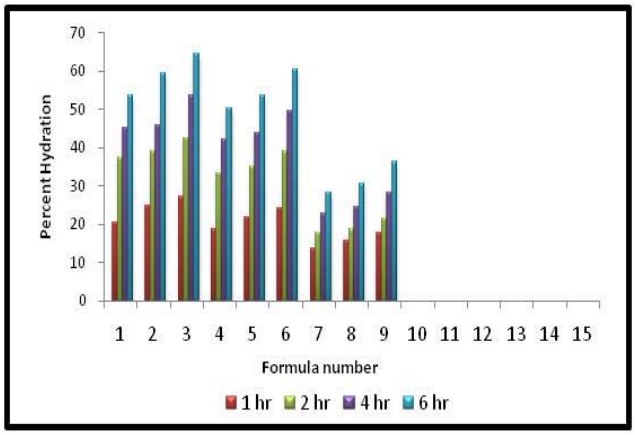

Figure 1: Swelling Index of Formulation F1 to F9

Table 5: Mucoadhesive Strength of Different Formulation

Formula Code	Mucoadhesion Strength(gm)	Force of Adhesion (N)
F1	15.6±0.62	0.15288
F2	17.9±0.79	0.17542
F3	19.8±0.7	0.19404
F4	14.3±0.50	0.140467
F5	16.4±0.75	0.161047
F6	18.5±0.50	0.180973
F7	12.5±0.31	0.1225
F8	14.1±0.25	0.13818
F9	16.2±0.75	0.15876

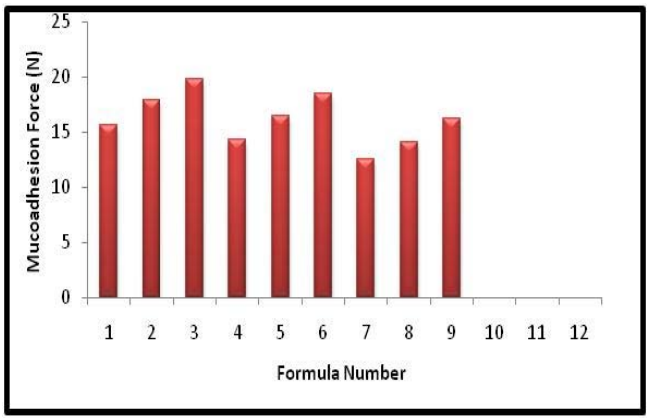

Figure 2: Mucoadhesive Strength of Formulation F1 to F9

Ex-vivo residence time study

The Ex-vivo residence time is the time required for complete erosion and/or detachment of the tablet from the mucosal surface.[32] The results in table 6 indicated that

the residence time for (F1-F9) was between (6.10 - > 12 hrs). The difference could be due to the combination of various amounts of polymers that might have affected mucoadhesion. Mucoadhesion time was found to be increased with formulation containing higher concentration of carbopol 940P. This is because of the high mucoadhesive nature of the carbopol and inter-penetration of polymeric chains in to the mucus membrane.[39]

Table 6: Residence Time of Different Formulations

Formula Code	Residence Time (hr.min)
F1	7.45
F2	8.40
F3	9.55
F4	6.10
F5	7.0
F6	8.30
F7	>12
F8	>12
F9	>12

In vitro Release Study

The in vitro release study was performed in phosphate buffer pH 6.8 and illustrate in table 7. Formulas containing Na alginate as secondary polymer showed higher drug release, this may be due to the fact that Na alginate is water soluble polymer that undergo dissolution and lead to the formation of pores and channels within the viscous gel layer which is tightly cross linked. The penetration of the dissolution media within the matrix tablet lead the drug to diffuse out through the device. Formulas with Na CMC as secondary polymer show a cumulative percent drug release lower than that of Na alginate. This is may be due to the low viscosity of Na CMC that facilitate the penetration of the dissolution media within the highly viscous gel layer of carbopol 940P and allow drug to release. Formulas containing carbopol 940P in combination with HPMCK15M shows relatively low cumulative percent drug release as compared to formulas containing Na alginate and Na CMC, which is due to synergistic increase in the viscosity as a result of competent water uptake of HPMCK15M and carbopol 940P resulting in the formation of strong gel layer and consequently slower diffusion and erosion rate (40). Increasing carbopol 940P concentration cause significant ($P<0.05$) reduction on drug release which is due to the acid weakening inductive effect of ionized carboxylate residues of carbopol 940P that affect the ionization potential of neighboring groups. This may result in high coiling and proximity of carboxylic groups (compare with linear polymer) which led to intermolecular hydrogen bonding. This cross linking leads to entrapment of the drug inside the cross linked network of the polymer (41). Effect of addition of PVP as a binder in concentration (3% and 6% w/w) on the drug release is shown in figure 3, increasing PVP concentration lead to non significant ($P > 0.05$) retardation in drug release. The cumulative release of promethazine HCl after 6 hr was 88%, 82.9% and 75.4% for F1, F10 and F11 respectively. This is due to the binding effect of PVP that resulted in increasing the hardness of the tablets which led to reduce the drug release as its concentration increased[42] as well as reduction in lactose concentration which act as channeling agent. Mannitol and Avicel (F12 and F 13) have been used instead of lactose in F1 to study the effect of diluents on drug release. Figure 4 showed that higher drug release was obtained from F1 that contain lactose as diluents due to the high solubility of lactose in water that lead to pores formation in the matrix and allow the penetration of the dissolution medium into the matrix by channel formation.[43] The effect of the method of preparation on the drug release was studied by comparing F 1 which prepared by direct compression and F14 which was prepared by non aqueous wet granulation technique as shown in figure 5. Greater retardation effect was obtained in F 14 which is due to coating of drug particles by carbapol 940 P and Na alginate during granulation process which in turn slows down the penetration of water into the granules and/or reduces the direct contact of the drug with dissolution medium.[44]

Table 7: Dissolution Parameter of Different Prepared Formulations

Formula No.	$T_{50\%}$ (hr)	$T_{80\%}$ (hr)	Cumulative % Drug Release at 6 hr
F1	3.3	5.57	88
F2	5.33	> 6	57.4
F3	> 6	> 6	36
F4	4	5.79	85
F5	> 6	> 6	48
F6	> 6	> 6	31
F7	5.29	> 6	55
F8	> 6	> 6	35
F9	> 6	> 6	19.3

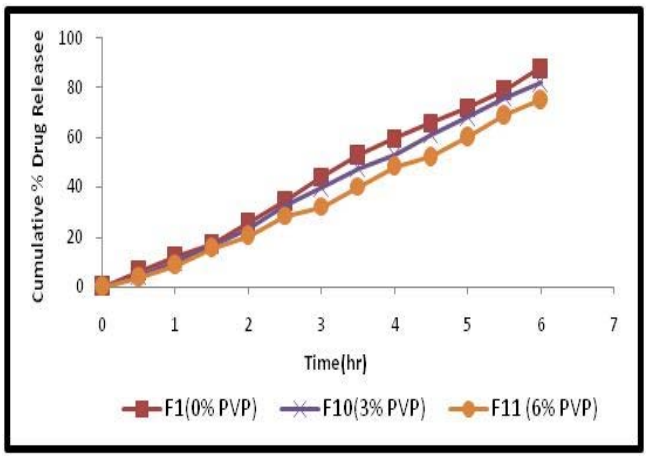

Figure 3: The effect of PVP and its concentration on the cumulative drug release

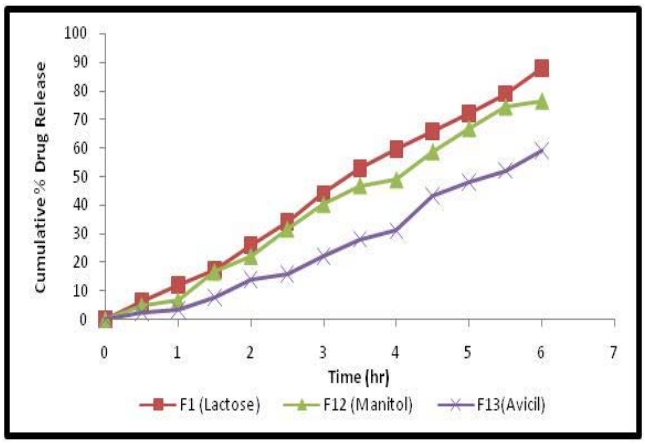

Figure 4: Effect of different filler excipient on cumulative drug release.

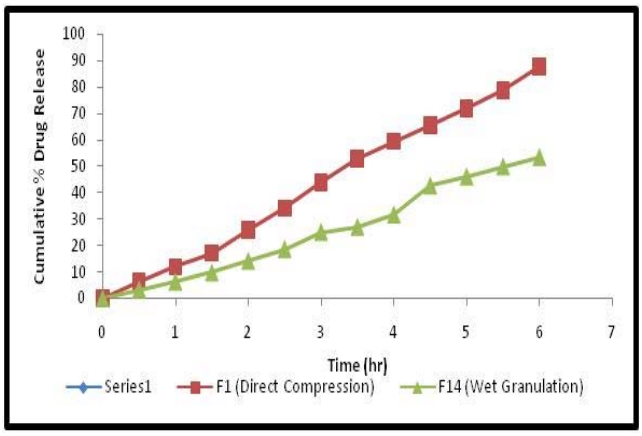

Figure 5: Effect of method of preparation on cumulative drug release.

Table 8: Promethazine HCl Release Kinetic from Different Formulations

Formula Number	Zero Order		First Order		Higuchi		Korsmeyer Pappas		
	K_O (h^{-1})	R^2	K_1 (h^1)	R^2	K_H ($h^{1/2}$)	R^2	n	K_{KP} ($h^{1/3}$)	R^2
F1	9.4776	0.9939	0.1476	0.9303	48.942	0.9732	1.0974	12.5	0.9934
F2	6.0669	0.9815	.0609	0.9438	29.966	0.9205	0.8727	9.457	0.9696
F3	1.1569	0.9891	0.0333	0.9832	13.737	0.9453	0.9613	6.997	0.953
F4	14.53	0.9727	0.1294	0.8569	54.703	0.9029	1.047	10.95	0.9477
F5	7.8119	0.9896	0.0465	0.9699	24.847	0.9393	0.9106	8.294	0.9646
F6	4.9105	0.989	0.0258	0.979	15.604	0.9369	0.8382	6.001	0.9588
F7	7.9037	0.9962	0.0531	0.9928	25.645	0.984	0.6604	16.15	0.9945
F8	5.172	0.9963	0.0285	0.989	16.569	0.9592	0.6828	9.330	0.97
F9	2.6608	0.9932	0.0132	0.9931	8.5975	0.9727	0.5695	6.563	0.9727
F10	14.503	0.9991	0.1281	0.9458	46.717	0.9727	0.2104	7.286	0.8779
F11	13.085	0.9965	0.1023	0.9462	41.944	0.9607	1.2023	8.889	0.9985
F12	13.984	0.9928	0.1147	0.9641	45.661	0.9678	0.9795	16.24	0.9788
F13	10.748	0.9819	0.0685	0.9502	34.083	0.9246	1.3822	4.865	0.9791
F14	9.609	0.9878	0.0598	0.9699	30.701	0.946	1.1585	6.697	0.9344

Kinetic of Drug Release and Mechanism

In-vitro release data were fitted to various mathematical models such as Zero order, First order, Higuchi and Korsemeyer-Peppas model in order to understand the mechanism of drug release from dosage forms. From table 8, a good fitting to zero order model was observed with all formulations (F1-F14), indicated by highest regression value (R^2). For Korsmyer-Pappas model ,the value of release exponent (n) defines the release mechanism, the n value of F2,F6,F7,F8 and F9 are between 0.45 to 0.89 indicating anomalous(non –Fickian) transport which refer to combination of diffusion and erosion controlled drug release. F10 shows n value less than 0.45 pointing a Fickian diffusion release[45] which occurs when the liquid diffusion rate is slower than the relaxation rate of the polymeric chains.[26] F1, F3, F4, F5, F11, F13 and F14 show n value more than 0.89 indicating super case II transport where the drug release involves polymer relaxation and chain disentanglement.[46]

Selection of Optimum Formula

F1 has a good release profile (88%) after 6 hr, sufficient mucoadhesive strength (15.6±0.62) to remain in the buccal cavity for sufficient time parallel to the time that required for dissolution study, in addition to surface pH value (6.11) which is within the range of salivary pH so no irritation would be expected from this formulation, in addition to acceptable tablet mechanical properties like hardness and friability. Accordingly it was selected as optimum formula.

Drug Content Uniformity

The tablets of the selected formula (F1) were evaluated for its content uniformity and the concentration of drug was calculated and was found to be 99.4 indicating that promethazine HCl was uniformly distributed within all the tablets of the optimum formula.

Drug–polymer compatibility study

The FT-IR spectra of pure promethazine HCL alone and for its physical mixture with the excipient and additives, in addition to FT-IR spectrum for the optimum tablet formula (after grinding)shows similar absorption bands indicating the absence of any interaction.

CONCLUSION

The overall study revealed that promethazine HCl can be prepared as buccal mucoadhesive tablets that release the drug through the buccal mucosa for prolong duration that may reduce its 1st pass metabolism leading to improve its bioavailability.

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