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Research Article

FORMULATION AND EVALUATION OF VERAPAMIL HYDROCHLORIDE BUCCOADHESIVE TABLETS

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ABSTRACT

Verapamil hydrochloride (Vp-HCl) is a calcium channel blocker and class IV antiarrythmic drug. Its oral bioavailability is about 20-30% because of the extensive first-pass metabolism, so it is advisable to prepare the drug in a buccoadhesive dosage forms to bypass first-pass metabolism and thus achieving constant plasma concentrations during treatment of chronic hypertension. Certain bioadhesive polymers were used either singly or in combinations at different ratios in order to select the best matrix forming tablets with satisfactory drug release, characteristic bioadhesiveness and swelling properties.

It was found that the drug release decreased by increasing the concentration of the polymer in all the studied formulations and the drug release from using polymer blends is slower than those containing single polymer. Tablet formula containing either 30% (w/w) hydroxypropyl methyl cellulose 15000(HPMC 15000) & 10% (w/w) sodium carboxymethyl cellulose (SCMC), or containing 5% (w/w) carbopol 934P (Cp934P) with either 15% (w/w) HPMC 15000 or 30% (w/w) sodium alginate (NaAlg) was developed to a satisfactory level in terms of drug release, bioadhesive performance and swelling properties.

Plasma concentration time curves obtained following buccal administration of the optimal prepared buccoadhesive tablets to rabbits showed evidence of sustained release of Vp-HCl. Bioavailability of Vp-HCl formulated tablets formulae (T31, T35 & T38) was approximately two times higher than that achieved after oral administration of commercial tablets.

Keywords: Verapamil Hydrochloride, Antiarrhythmic, Buccoadhesive, Bioavailability, Plasma Concentration.

INTRODUCTION

Verapamil hydrochloride is a phenyl alkylamine calcium-channel blocker and class IV antiarrhythmic that is widely used in the management of hypertension, ischemic heart disease such as angina pectoris, mycocardial infarction and arrythmias[1].

Verapamil is subjected to presystemic hepatic metabolism with up to 80% of the dose eliminated in this way. The bioavailability is therefore 20-30%[2]. Since this drug has a short elimination half-life about 2-7 hours and is eliminated rapidly, repeated daily administration are required to maintain effective plasma levels[3].

The buccal mucosa may be a more favourable site of absorption of verapamil than the digestive tract[4,5]. Non-keratinized and strongly supplied with blood buccal mucosa, with a dense capillary vessel network, constitutes a relatively large drug absorption area. Drug can thus reach the systemic circulation directly through capillary vessels, bypassing the first-pass metabolism in the intestine and liver or avoiding inactivation in the stomach[6]. That in turn contributes to higher bioavailability parameters after administration of a smaller dose of the drug than in conventional tablets.

Accordingly, there is a particular interest in this study for the development of buccoadhesive tablets as the short half life and extensive first pass metabolism of Vp-HCl makes it a suitable candidate for administration via a buccal delivery system that provides controlled drug delivery without pre-systemic metabolism.

Therefore, the first step in the development of a buccal delivery system is selection of appropriate adhesives. These tablets were formulated using different polymers Cp934P, HPMC 15000, NaAlg and SCMC either single at different concentrations or in combinations.

MATERIALS AND METHODS

Materials:

Verapamil Hydrochloride powder (T3A, Egypt). Cp934P, HPMC 15000, anhydrous lactose and sodium hydroxide (El-Gomhouria Co., Cairo, Egypt). NaAlg (The general chemical & pharmaceutical co Ltd, Sudbury Middlesex, England). SCMC (Elnile co., for pharmaceutical and chemical industry, Egypt). Magnesium stearate, Potassium dihydrogen phosphate (El-Nasr Pharmaceutical Chemicals Co., Egypt). Agar (Chemi-search for chemi-trade & laboratory supp., Egypt). Porcine stomach mucin (Sigma Aldrich Chem., Germany).

All chemicals used were of analytical grade, and were used as received.

Equipment:

- Electronic balance, Sartorius TE214S, Germany.
- Digital pH meter, Jenway-model 3310, England.
- UV-Visible spectrophotometer, Jenway-model 6305, England.
- Single punch tablet machine, Erweka, Germany.
- Erweka tablet hardness tester, type TAB, G.m.b.H., Germany.
- Micrometer, Mitutoyo Corporation, Japan.
- Incubator, Binder, Germany.
- Dissolution apparatus, Erweka, Germany.

Methods:

Preparation of Verapamil Hydrochloride Buccoadhesive Tablets:

Controlled-release buccoadhesive tablets containing Verapamil Hydrochloride were prepared by the direct compression technique using the formulae shown in Tables (1-3). Different ratios of Cp934P, HPMC, NaAlg, SCMC, anhydrous lactose, fixed amount of Vp-HCl and 1% magnesium stearate were passed through a No. 100 sieve and mixed by trituration in a glass mortar with pestle to obtain uniform mixture. The blended powder were compressed into tablets weighing 200 mg using a single punch tablet machine having a flat-faced non-beveled punch and die set of 8 mm diameter.

The prepared verapamil HCl buccoadhesive tablets were evaluated for the following parameters: tablet weight uniformity, drug content uniformity, tablet diameter, tablet thickness and tablet hardness.

Swelling of Buccoadhesive tablets using Agar-Gel Plate[7]:

The swelling procedure was evaluated using agar - gel (1% w/v of agar in phosphate buffer pH 6.8). The average weight of each four tablets was calculated (W_1). The tablets were placed on the gel surface in seven Petri dishes (each containing four tablets) which were placed in an incubator at 37°C. Four tablets were removed at time intervals of 0.5, 1, 2, 3, 4, 5, 6 and 8 hrs; excess water on the surface was carefully removed using filter paper, and the swollen tablets were weighed.

The average weight (W_2) was calculated and then the swelling index was calculated by the following formula:

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1}$$

Where the W_1 and W_2 are the weights of dry and swollen tablets at different time intervals.

The surface pH was measured by placing the electrode in contact with the surface of the swollen tablet (after 8 hours). The mean of three determinations was recorded.

***In-vitro* Bioadhesion Test[8]:**

The mucoadhesive strength of the formulated buccoadhesive tablets was determined by measuring the force required to detach the formulation from a mucin tablet using our locally assymbelled device (Fig. 1). At the right arm of the balance (B), mucin tablet (E) was glued to moving lower platform (C) and tablet formulation (D) was glued to the upper clamp of the balance using cyanoacrylate glue. The mucin tablet was hydrated with few drops of phosphate buffer pH 6.8 prior to test. The lower stage (C) was then elevated till the surface of the sample became in contact with the hydrated mucin tablet using a preload of 10 grams for 5 minutes to establish a perfect contact and formation of an adhesive bond. On the other side of the used device, water was dropped from a glass bottle (I) through an infusion set (H) into a preweighed plastic jar (G) in the pan (F) at a constant rate of 60 drops/min. The addition of water was stopped when mucin tablet was detached from the buccoadhesive tablet. The volume of dripped water was considered as the weight required for detachment and taken as a measure of bioadhesion strength.

The detachment force was determined using the following equation:

$$\text{Detachment Force (dyne/cm}^2\text{)} = m \times g/A$$

Where; m: is the weight of water in grams required for detachment. g: is the acceleration gravity taken as 980 cm/sec^2. A: is the surface area of mucin tablet (area of the contact) which is equal to πr^2 (r is the radius of mucin tablet).

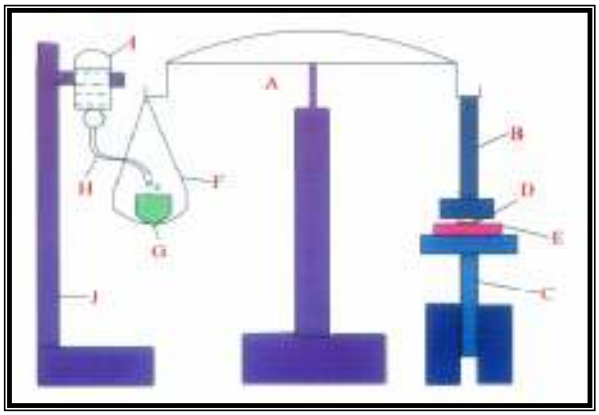


Figure 1: Modified balance method.

In-vitro Drug Release:

The drug release from the prepared buccoadhesive tablets was determined using a dissolution apparatus which, according to USP method II (paddle), consists of six polycarbonate vessels placed in a water bath maintained at 37±0.5°C and stirred at a rate of 50 rpm. Each tablet was immersed in the vessel containing 250 ml of phosphate buffer pH 6.8, three tablets were examined at the same time. A drug-free tablet, used as control, was introduced in the fourth vessel. With the aid of pipette, after 5, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360, 480 minutes an aliquot of dissolution medium was drawn and the content of verapamil hydrochloride was determined spectrophotometrically at λ_{max} 278 nm.

Kinetic Analysis of the Drug Release Data:

The release data were kinetically analyzed using different kinetic models (zero order, first order and Higuchi diffusion model) to determine the mechanism of drug release from the different buccoadhesive formulations.

The release data were analyzed using the equation proposed by Korsmeyer[9]:

$$M_t / M_\infty = Kt^n$$

Where M_t / M_∞ is the fractional release of the drug at time t, K is the release rate constant and n is the diffusional exponent that characterizes the type of release mechanism during the

dissolution process. For non-Fickian release, the value of n falls between 0.45 and 0.89; while in case of Fickian diffusion, n= 0.45; for zero order release(case II transport), n= 0.89 and for supercase II transport, n > 0.89.

In-vivo Evaluation of Buccal Tablets in rabbits:

For both oral and buccal administrations, the dose level of 2.5 mg/kg of the drug corresponding to 50 mg human dose was used. The equivalent dose for rabbits was calculated by the aid of surface area ratio. To more directly correlate the efficacy of absorption from the buccal cavity and gastrointestinal tract with that by intravenous dosing, the tested drug was given in the same doses by all three routes (2.5 mg/kg)[10].

Treatment of Animals:

Fifteen healthy rabbits, weighing 1.8-2 kg, were divided into five groups, each group consists of three animals. The rabbits were fasted for 24 hrs with free access to water before drug administration and anaesthetized with intraperitoneal injection of urethane solution for buccal dosing and maintained on urethane for 2 hrs to allow adhesion of the tablets to the buccal mucosa.

The rabbits were divided into 5 groups, each received one dosage form. The first group was fasted and received I.V. Vp-HCl saline (2.5 mg/kg) through the indwelling femoral ear vein cannula for the determination of the AUC of the drug after I.V. administration for the calculation of the absolute bioavailability of the drug from other extravascular dosage forms. The second group received oral Vp-HCl (2.5 mg/kg) (Isoptin®). And the other groups received the selected medicated buccal tablets (T31, T35 & T38) which also contain 2.5 mg/kg of the drug, by attaching this mucoadhesive tablet on the cheek pouch of rabbits.

Assay of Verapamil Hydrochloride in the tested rabbits[11]:

The extraction from rabbit plasma was carried out as follows: To 0.5 ml of plasma 50.0 ng of propranolol HCl as an internal standard (30 µl of a standard solution in the mobile phase) and 2.0 ml of acetonitrile were added. The extraction was carried out over 10 min by shaking in glass test-tubes with teflon caps Chromacol. The organic layer was separated by centrifugation at 5000 rpm for 10 min and then transferred into a Pyrex conical tube then aliquots of 20 µl was injected directly in HPLC column consisting acetonitrile / 0.05 M phosphate buffer pH 3 (40/60 v/v) as the mobile phase.

A flow rate of 1.2 ml/min was adopted and verapamil HCl and propranolol HCl (internal standard) was detected using fluorescence detector (model Fp 2020, Jasco, Japan) at 204 nm (excitation) and 314 nm (emission) chromatograms were recorded and analyzed using Young Lin Autochro-3000 software. Standard curves were developed in plasma for the Vp-HCl within a range of 100 to 6000 ng/ml. The peak area was plotted as a function of Vp-HCl concentration. The linearity of the method (r > 0.998) was determined to show a directly proportional relationship between the peak response and the concentration of Vp-HCl. All experiments were run as triplicates and the mean values ± SD were taken.

Pharmacokinetic Analysis of Vp-HCl in rabbits:

Pharmacokinetic parameters of verapamil HCl following oral and buccal administration were determined from plasma concentration-time data. The maximum plasma concentration (C_{max}) and the time to attain the peak concentration (T_{max}) were obtained directly from the plasma concentration-time curve. The area under the plasma concentration-time curve from time zero to 24 hour ($AUC_{0\text{-}24\ hr}$) was calculated by using linear trapezoidal rule[12]. Relative bioavailability F_R (%):

$$F_R\,(\%) = \frac{AUC_{0-24}\ (\text{tested formula})}{AUC_{0\text{-}24}\ (\text{commercial product})} \times 100$$

The absolute bioavailability F was evaluated by using the following equation:

$$F(\%) = \frac{AUC_{0-24}\ (\text{tested formula})}{AUC_{0\text{-}24}\ (T.V)} \times 100$$

Statistical analysis was performed using Student's t-test at traditional level ($p < 0.05$).

RESULTS AND DISCUSSION

Verapamil HCl buccoadhesive tablets prepared using the investigated polymers were uniform in weight and tablet weights and drug content of all the studied formulations were found to be within the pharmacopeial limits (B.P. 2009). Vp-HCl buccoadhesive tablets were uniform in thickness and diameter.

The hardness of tablets of each batch was within the range that ensures good handling characteristics for all batches. Tablets with the highest hardness were obtained with carbopol 934P while tablets containing sodium alginate showed the lowest hardness. The drug is released from buccal tablets by diffusion through the gel layer and/or erosion of this layer and thus independent of the dry state of the tablet.So the differences in the tablet hardness had no effect on the release of the drug from hydrophilic matrices[13].

Swelling Studies of Buccoadhesive Tablets:

The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The agar plate model used in this study resembles the secreting fluid around the buccal mucosa[14].

The amount of water absorbed by the polymer is a function of its hydrophilicity, the network structure and number of ionized groups on the polymer[15]. The swelling increases as the time proceeds where the outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or dispersed, the hydration swelling release process is continued towards new exposed surfaces, thus maintaining the integrity of the dosage form[16].

Table (4) shows the swelling index of different Vp-HCl buccoadhesive tablets after 8 hrs. In general, it is evident that, the normalized swelling values increase by increasing polymer concentration. Taking the results at 40% w/w polymer concentration as a representative example for swelling, the order of swelling was:

NaAlg > SCMC > HPMC 15000 > Cp934P

Tablets containing Cp934P showed the least swelling than the other polymers. This is attributed to the property of Cp934P to retain water forming thick swollen mass[17]. Tablets containing HPMC or SCMC showed more swelling than those with Cp934P due to the hydrophilicity of cellulose derivative polymers[18], also the hydroxyl group in the molecules play an

important role in the matrix integrity of the swollen hydrophilic cellulose derivatives[19]. The highest swelling was obtained from tablets containing NaAlg. This may be due to the high water solubility of this polymer[20].

It is obvious that, the swelling index buccoadhesive tablets containing different ratios of the mixture of each two polymers that tablets with high ratios of Cp show the lowest swelling index and that with high ratios of NaAlg show the highest swelling index.

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, in-vivo. All formulations exhibited surface pHs within satisfactory limits (6-7) except the surface pH of formulations containing high concentration or ratio of Cp934P was slightly acidic (5-6).

In-vitro Bioadhesion Test:

It is clear that the bioadhesive strength varied considerably with polymer structure and concentration. An increase in polymer concentration resulted in an increase in bioadhesion strength as shown in table (4) and this can be explained by the increased sites of bond formation[21].

The order of the tested polymers was as follows:

Cp 934P > SCMC > Na Alg > HPMC 15000

Cp934P was found to have the maximum bioadhesive strength compared to other polymers. Carbopol 934P contains greater number of carboxylic acid groups (-COOH) that can provide the ability to form hydrogen bonds and could bind more strongly with oligosaccharide chains than other investigated polymers. Also, it was reported that the high bioadhesive strength of Cp may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region[22].

NaAlg, SCMC and HPMC 15000 have hydroxyl group in the polymer molecules and thus can bind with the oligosaccharide chains of the buccal membrane by forming hydrogen bonds[19].

The results revealed that tablets containing Cp934P with either HPMC 15000, NaAlg or SCMC, the highest adhesion force and residence time was possessed by formulations containing 10% Cp934P, increase in Cp934P content beyond this proportion resulted into a decrease in bioadhesion. This may be attributed to high polymer chain entanglement and complexation; thus leading to reduced availability of free functional groups of polymers to substrate and consequent low bioadhesion[23]. Moreover, bioadhesive property of Cp934P is known to decrease beyond pH 6[24]. The adhesion force in the formulation containing Cp934P with either HPMC 15000, NaAlg or SCMC at a weight ratio of 1:1 was improportionally less than those with other mixing ratios in this group. This could be attributed to the possible interpolymer complex formation between Cp and these polymers which in turn inhibited, at least in part, the adhesion force of the tablet. This interaction results from hydrogen binding between the OH groups of these polymers and the carbonyl groups of Cp in the acidic medium[25,26]. Although an interpolymer complexation for Cp934P with these polymers at weight ratio of 1:3 and 3:1 has been reported[25], the bioadhesion did not decrease significantly. Also, it should be mentioned that the bioadhesion strength decreased with increasing the concentration of the filler.

In-vitro Drug Release Studies:

The in-vitro release profiles of Vp-HCl from buccoadhesive tablets containing different concentrations of bioadhesive polymers (10, 20, 30 and 40% w/w) was found to be dependent on the type and concentration of polymer used.

Generally, an increase in polymer concentration results in decreasing the percent of drug released. This may be attributed to the increased tortousity of the polymer matrix which retards diffusion of the drug molecules from the polymer network by increasing diffusion pathway[27].

The order of drug release using various bioadhesive polymers was:

NaAlg > SCMC > HPMC > Cp.

Figure (2) shows the in-vitro release profiles of verapamil HCl from buccoadhesive tablets containing different bioadhesive single polymers.

Retardation of the release of Vp-HCl from buccoadhesive tablets containing Cp934P is due to entrapment of the drug in the glassy core of carbopol matrix in the dry state. On hydration of the surface, a gelatinous layer is formed that consists of discrete microgels made up of many polymer particles in which the drug is dispersed. When the hydrogel is fully hydrated, it does not dissolve, but osmotic pressure from within works to break up the structure mainly by sloughing off discrete pieces of the hydrogel. The hydrogels remain intact, and the drug continues to diffuse through the gel layer at continuous rate. As the concentration of the drug becomes high within the gel matrix and its thermodynamic potential increases, the gel layer around the disc core act as a rate-controlling membrane[21].

The process of drug release from a HPMC-drug matrix is affected by the rate of water uptake and the diffusion rate of the drug through the swollen gel. Water uptake rate into the matrix is enhanced by the presence of HPMC due to its high hydrophilicity[20].

The observed release profiles of buccoadhesive tablets containing NaAlg can be attributed to the high water solubility and swelling property of this polymer which result in formation of porous channels leading to less compact polymer formation[20] and so faster drug release is expected.

SCMC is a swellable cellulose ether that upon hydration, behaved as a gel-like system, thereby producing a gelatinous barrier through which the drug diffuse during the dissolution process[28].

Figures (3-9) show the in-vitro release profile of Vp-HCl from buccoadhesive tablets containing mixture of polymers. It is evident from the figures that the lowest release rate was obtained by formulations containing higher amounts of Cp934P and the rate increased as another polymers was mixed with it.

Figures (3-5) show the release profiles of verapamil hydrochloride from buccoadhesive tablets containing different ratios of Cp:HPMC, Cp:NaAlg and Cp:SCMC, respectively.

Although matrices containing Cp-SCMC exhibited greater swelling values than matrices containing Cp-HPMC, they showed lower release rates which maybe due to the higher hydrophilicity and water uptake of Cp and SCMC compared to HPMC, which creates a water-swollen gel-like state that may decrease the penetration of dissolution medium into the tablets and as a result the drug release rate[14].

Figures (6-8) show the release profiles of verapamil hydrochloride from buccoadhesive tablets containing different ratios of HPMC:NaAlg, HPMC:SCMC and NaAlg:SCMC respectively.

The release rates from tablets containing HPMC-SCMC are much slower than those from tablets containing HPMC alone. This may be due to that verapamil hydrochloride, a cationic drug, might be forming a complex with the anionic SCMC and the complex might be diffusing from the swollen gel at a much slower rate[29]. Similarly, this happens with the other two mixtures.

Figure (9) shows the in-vitro release profiles of Vp-HCl buccoadhesive tablets containing 5% Cp934P and different ratios of HPMC, NaAlg and SCMC, respectively, where it was found that the optimum concentration of Cp934P for sustaining the release of Vp-HCl for 8 hours together with sufficient swelling and bioadhesion was 5%(w/w).

Kinetic Analysis

The release of verapamil HCl from all the prepared buccoadhesive tablets containing single polymers are best fitted to simplified Higuchi model as indicated from the highest regression coefficient (r^2) except for Cp934P which follows zero order kinetics. This means that the release rate of verapamil HCl from the prepared buccoadhesive tablets (formulae 5-16) is dependent on the diffusion mechanism.

The release data of verapamil HCl from tablets containing different polymer blends in dissolution medium of pH 6.8, followed zero-order release mechanism. This may be attributed to the sufficient sustaining of the drug release due to the presence of polymer blends that leads to increase in the total polymer content resulted in highly viscous gel layer around the drug leading to zero-order drug release.

To understand the mechanism of diffusion of Vp-HCl from these tablets the dissolution data were analyzed using the equation proposed by Korsmeyer.The obtained values of n (release exponent) lie between 0.45 and 0.89 in all the formulations exhibiting a non-fickian release behaviour controlled by a combination of diffusion and chain releaxation mechanism.

In-vivo Bioadhesion of the Selected Formulae (Tolerance and Residence Time):

Good adhesion and tolerance were used as criteria for selecting the formulation to be used for clinical assessment. The prepared plain buccoadhesive tablets (T31, T35 & T38) were evaluated for their tolerance and contact time on five human volunteers.

The results revealed that all the selected buccoadhesive tablets had an acceptable taste and no signs of local irritation were observed. With respect to contact time, the tablets retained readily on buccal mucosa, but the polymer type and nature appeared to have great impact on retention time. The mean residence time of T31 and T38 was more than 8 hours while T35 was retained for more than 6 hours.

In-vivo Evaluation of Buccal Tablets in rabbits:

Under the condition of analytical procedure previously mentioned, the retention time of propranolol HCl and verapamil HCl were 4 and 7 minutes, respectively.A good resolution was obtained without interference with the endogenous plasma components, indicating efficient extraction of both the drug and the internal standard by the assay procedure[11].

The mean plasma levels profiles versus time obtained after buccal dosing of formulation T31, T35 and T38 are shown in Figures (10-12) for comparative purpose, the plasma concentration-time profile after oral and intravenous administration of Vp-HCl is also shown in these figures.

Absorption of Vp-HCl from buccoadhesive tablets was much more sustained and extended over a longer period of time compared with oral and intravenous Vp-HCl. The plasma concentration curves for buccoadhesive tablets showed evidence of a more sustained release of Vp-HCl.

The pharmacokinetics parameters derived from these plasma concentration-time curves after buccal administration of the tested buccoadhesive formulation in comparison with the commercial immediate release tablets are listed in Table (5).

CONCLUSION

The absolute bioavailability of Vp-HCl was 75.5, 67.2 and 71.4% for buccoadhesive tablets T31, T35 and T38 respectively, which compares favourably with a value 28.81% calculated for oral bioavailability. These results clearly indicate that the bioavailability of Vp-HCl from buccoadhesive tablets is significantly improved (more than two folds) than the bioavailability observed after oral administration of the drug. This is attributed to avoidance of the first-pass metabolism through the buccal route. Further delayed T_{max} and C_{max} values from the formulated buccoadhesive tablets compared to commercial oral tablets and maintainance of higher blood levels until the last sample from the buccoadhesive tablets than for the oral tablet clearly indicate that the buccoadhesive dosage form not only improved the bioavailability of the drug, but also gave prolonged and controlled blood level profiles of Vp-HCl.

Table 1: Composition of formulated buccoadhesive tablets of verapamil hydrochloride containing single polymer

Formula no.	Drug (mg)	Cp934P (mg)	HPMC (mg)	NaAlg (mg)	SCMC (mg)	Lactose (mg)	MgSt (mg)	Polymer % tablet
T1	50	20	--	--	--	128	2	10%
T2	50	40	--	--	--	108	2	20%
T3	50	60	--	--	--	88	2	30%
T4	50	80	--	--	--	68	2	40%
T5	50	--	20	--	--	128	2	10%
T6	50	--	40	--	--	108	2	20%
T7	50	--	60	--	--	88	2	30%
T8	50	--	80	--	--	68	2	40%
T9	50	--	--	20	--	128	2	10%
T10	50	--	--	40	--	108	2	20%
T11	50	--	--	60	--	88	2	30%
T12	50	--	--	80	--	68	2	40%
T13	50	--	--	--	20	128	2	10%
T14	50	--	--	--	40	108	2	20%
T15	50	--	--	--	60	88	2	30%
T16	50	--	--	--	80	68	2	40%

Table 2: Composition of formulated buccoadhesive tablets of verapamil hydrochloride containing mixture of two polymers

Formula no.	Drug (mg)	Cp934P (mg)	HPMC (mg)	NaAlg (mg)	SCMC (mg)	Lactose (mg)	MgSt (mg)	Polymers ratio
T17	50	20	60	--	--	68	2	1:3
T18	50	40	40	--	--	68	2	1:1
T19	50	60	20	--	--	68	2	3:1
T20	50	20	--	60	--	68	2	1:3
T21	50	40	--	40	--	68	2	1:1
T22	50	60	--	20	--	68	2	3:1
T23	50	20	--	--	60	68	2	1:3
T24	50	40	--	--	40	68	2	1:1
T25	50	60	--	--	20	68	2	3:1
T26	50	--	20	60	--	68	2	1:3
T27	50	--	40	40	--	68	2	1:1
T28	50	--	60	20	--	68	2	3:1
T29	50	--	20	--	60	68	2	1:3
T30	50	--	40	--	40	68	2	1:1
T31	50	--	60	--	20	68	2	3:1
T32	50	--	--	20	60	68	2	1:3
T33	50	--	--	40	40	68	2	1:1
T34	50	--	--	60	20	68	2	3:1

Table 3: Composition of formulated buccoadhesive tablets of verapamil hydrochloride containing 5%(w/w) Cp-934P and different ratios of the other mucoadhesive polymers.

Formula no.	Drug (mg)	Cp934P (mg)	HPMC (mg)	NaAlg (mg)	SCMC (mg)	Lactose (mg)	MgSt (mg)	Polymers percentage
T35	50	10	30	--	--	108	2	5%:15%
T36	50	10	60	--	--	78	2	5%:30%
T37	50	10	--	30	--	108	2	5%:15%
T38	50	10	--	60	--	78	2	5%:30%
T39	50	10	--	--	30	108	2	5%:15%
T40	50	10	--	--	60	78	2	5%:30%

Table 4: Swelling index, in-vitro buccoadhesive properties of the prepared buccoadhesive tablets of verapamil hydrochloride

Formula no.	Swelling index at 8 hrs	Bioadhesive strength (g ± SD)	Bioadhesive force x 10^2 (dyne/cm^2)
T1	0.42 ± 0.063	24.570 ± 2.121	4.789855
T2	0.56 ± 0.087	28.985 ± 1.874	5.650547
T3	0.59 ± 0.028	38.685 ± 4.440	7.541536
T4	0.63 ± 0.034	59.350 ± 3.140	11.57012
T5	0.63 ± 0.033	20.467 ± 1.546	3.989921
T6	1.11 ± 0.003	23.485 ± 1.209	4.578337
T7	1.16 ± 0.001	25.913 ± 1.607	5.051572
T8	1.25 ± 0.200	31.500 ± 0.871	6.140839
T9	0.90 ± 0.001	20.615 ± 1.520	4.018838
T10	1.08 ± 0.028	23.815 ± 1.534	4.64267
T11	1.41 ± 0.038	29.255 ± 4.603	5.703183
T12	1.88 ± 0.058	32.620 ± 1.768	6.35918
T13	0.87 ± 0.098	23.017 ± 0.129	4.487037
T14	1.06 ± 0.111	28.115 ± 2.666	5.480943
T15	1.36 ± 0.084	30.076 ± 5.304	5.863527
T16	1.51 ± 0.189	39.280 ± 3.060	7.657529
T17	0.83 ± 0.010	51.443 ± 2.301	10.02874
T18	0.59 ± 0.113	28.710 ± 1.004	5.596937
T19	0.33 ± 0.065	38.940 ± 5.006	7.591247
T20	1.20 ± 0.062	52.760 ± 4.271	10.28542
T21	1.18 ± 0.036	30.120 ± 3.540	5.871812
T22	0.44 ± 0.023	39.665 ± 2.793	7.732584
T23	0.93 ± 0.045	53.883 ± 4.286	10.50441
T24	0.80 ± 0.256	32.755 ± 0.969	6.385498
T25	0.36 ± 0.035	48.315 ± 4.122	9.418878
T26	1.71 ± 0.097	51.167 ± 0.551	9.974803
T27	1.32 ± 0.098	45.793 ± 5.367	8.927286
T28	1.20 ± 0.082	37.467 ± 1.168	7.304025
T29	1.58 ± 0.301	52.430 ± 5.530	10.22109
T30	1.23 ± 0.062	46.243 ± 1.165	9.015012
T31	1.17 ± 0.054	42.955 ± 4.335	8.373961
T32	1.63 ± 0.383	58.767 ± 1.204	11.4564
T33	1.64 ± 0.072	51.045 ± 1.450	9.951084
T34	1.78 ± 0.020	43.845 ± 0.361	8.547464
T35	0.84 ± 0.054	30.775 ± 1.195	5.999503
T36	0.93 ± 0.043	32.533 ± 0.551	6.342285
T37	1.05 ± 0.013	33.517 ± 1.206	6.533983
T38	1.55 ± 0.059	49.533 ± 1.002	9.656389
T39	0.97 ± 0.026	28.457 ± 0.506	5.54755
T40	1.38 ± 0.023	53.650 ± 4.172	10.45892

Table 5: Pharmacokinetic parameters of verapamil HCl in rabbits following buccal administration of the prepared verapamil HCl buccoadhesive tablet formula (T31, T35, T38) in comparison with the commercial oral tablets (Isoptin®).

	C_{max}	T_{max}	AUC_{0-24}	F_R (%)	F%
Intravenous	---	---	34.73862	----	100
Oral (Isoptin)	0.995	2	10.0001	-----	28.81
Buccal(T31)	2.188	4	26.21613	262.1	75.50
Buccal(T35)	2.165	4	23.33826	233.3	67.20
Buccal(T38)	2.3965	4	24.78894	247.8	71.40

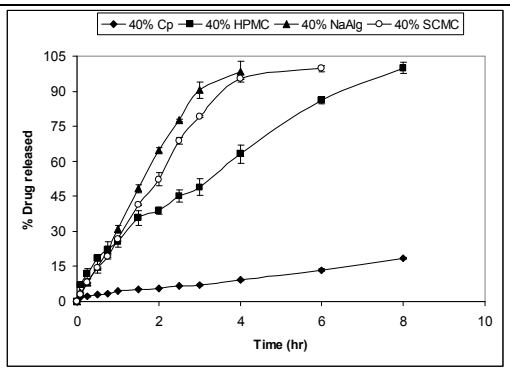


Figure 2: Release profiles of verapamil HCl from buccoadhesive tablets containing different bioadhesive single polymers.

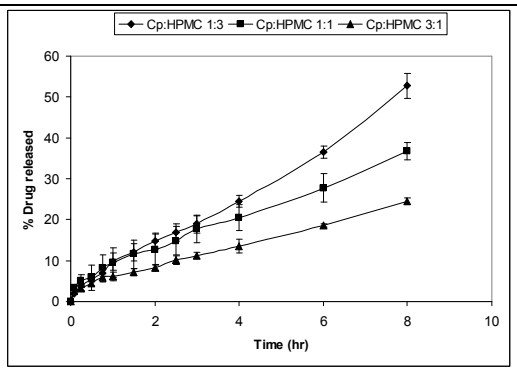


Figure 3: Release profiles of verapamil HCl from buccoadhesive tablets containing different ratios of Cp934P : HPMC.

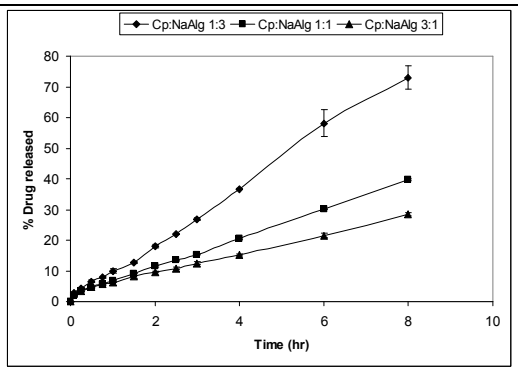


Figure 4: Release profiles of verapamil HCl from buccoadhesive tablets containing different ratios of Cp934P : NaAlg.

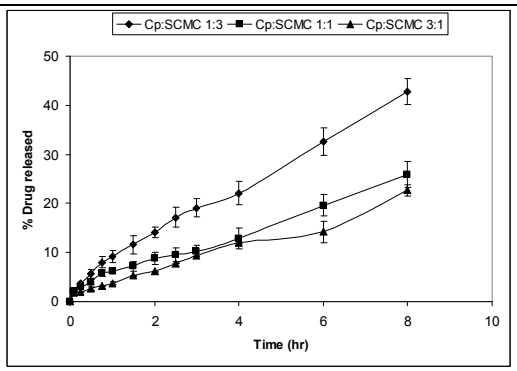


Figure 5: Release profiles of verapamil HCl from buccoadhesive tablets containing different ratios of Cp934P : SCMC.

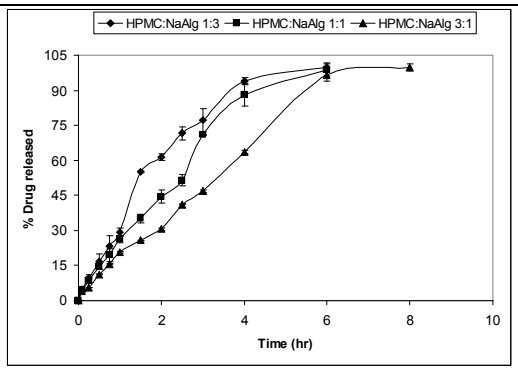


Figure 6: Release profiles of verapamil HCl from buccoadhesive tablets containing different ratios of HPMC : NaAlg.

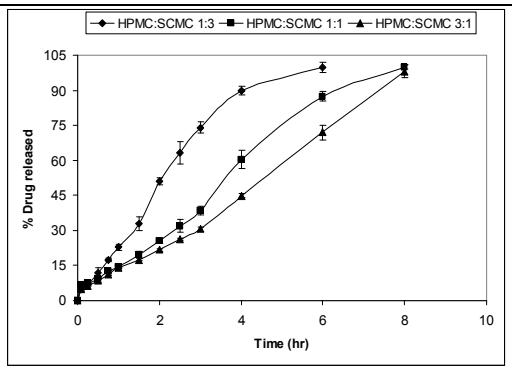


Figure 7: Release profiles of verapamil HCl from buccoadhesive tablets containing different ratios of HPMC : SCMC.

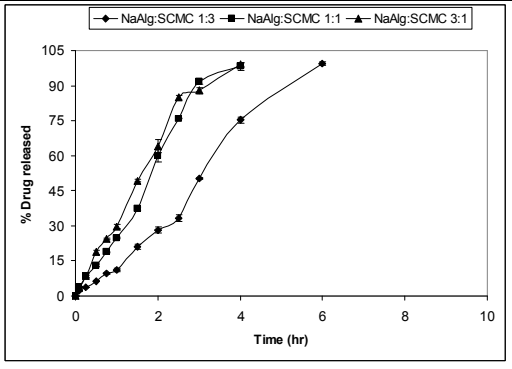


Figure 8: Release profiles of verapamil HCl from buccoadhesive tablets containing different ratios of NaAlg : SCMC.

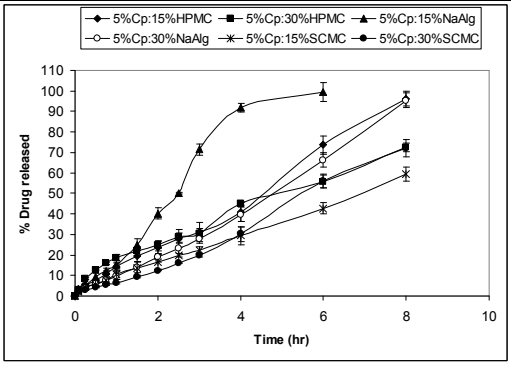


Figure 9: Release profiles of verapamil HCl from buccoadhesive tablets containing 5% (w/w) Cp934P and different ratios of the other mucoadhesive polymer.

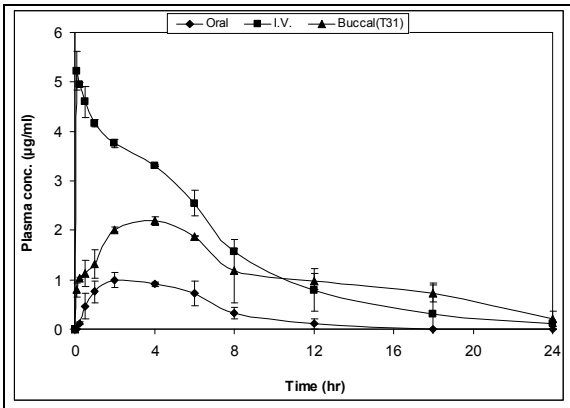


Figure 10: Plasma concentrations of verapamil hydrochloride at dose level (2.5 mg/kg) after oral administration of the commercial ampoules (Isoptin®) and the commercial tablets (Isoptin®) and the prepared verapamil HCl buccoadhesive tablets (T31).

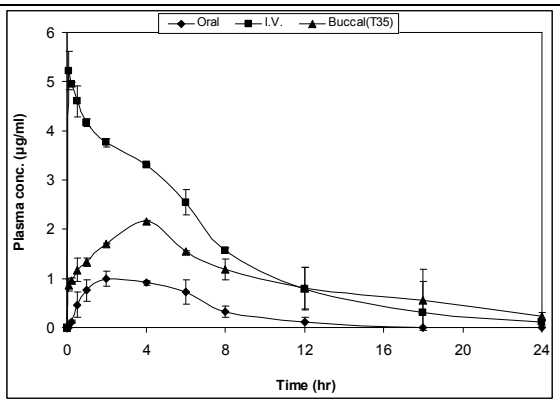
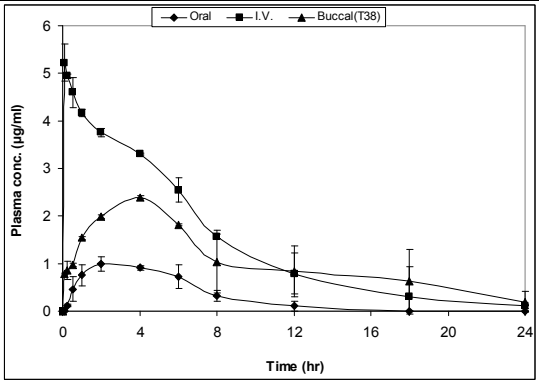


Figure 11: Plasma concentrations of verapamil hydrochloride at dose level (2.5 mg/kg) after oral administration of the commercial ampoules (Isoptin®) and the commercial tablets (Isoptin®) and the prepared verapamil HCl buccoadhesive tablets (T35).



: **Figure 12: Plasma concentrations of verapamil hydrochloride at dose level (2.5 mg/kg) after oral administration of the commercial ampoules (Isoptin®) and the commercial tablets (Isoptin®) and the prepared verapamil HCl buccoadhesive tablets (T38).**

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