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STUDYING THE EFFECT OF CHANGING PLASTICIZER ON THE FORMULATION OF MUCOADHESIVE BUCCAL PATCHES OF CAPTOPRIL

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ABSTACT

Drug delivery through buccal mucosa is a novel method for local and systemic treatment because buccal mucosa is permeable with rich blood supply and allow long- time retention of dosage from. The objective of this study is to prepare captopril as mucoadhesive buccal patch by solvent casting method and studying the effect of changing plasticizer type and increasing the drug amount on the physical and mechanical behavior of film and in vitro drug release study .The patch was prepared using hydroxylpropyl methyl cellulose K4 (HPMC) as patch forming polymer with secondary polymer (carbopol 934) and propylene glycol as plasticizer (30% of total polymer weight). The patches were prepared by solvent casting method and evaluated for weight variation, surface pH, mechanical properties, content uniformity, ex-vivo mucoadhesive strength and in-vitro drug release study. Formula F5containing HPMC as primary polymer with carbopol 934 as secondary polymer was chosen as selected formula since Surface pH(6.44), Tensile strength (16.06), percentage Elongation at break (34.14), Ex-vivo residence time (hrs) 6.12±0.06, Mucoadhesive strength(26.2gm)with invitro drug release around 94.73% of 6hrs. The research showed in-vivo drug release of 73.12% of captopril released after 6hrs for selected formula with acceptable correlation (R_2) value of (0.986) suggesting successful formulation that can be used to increase patient accessibility, increase the residence time of drug at absorption area which leads to increase drug absorption and avoidance of first pass metabolism that leads to increasing the drug bioavailability.

KEYWORDS: Captopril, buccal patches, mucoadhesion, propylene glycol.

INTRODUCTION

Among different routes of drug administration, oral route is highly preferred to the patients and physicians. According to our understandings of biochemical and physiological concept of drug absorption and metabolism, many drugs cannot be given through classical oral rout due to these drugs undergo per-systemic metabolism that lead to loss relationship between permeability of membrane, absorption and bioavailability of drug.[1] Bioadhesion is a case in which two phases one of them is of biological origin are joined with each other by interfacial bond for a long time interval. While mucoadhesion is used when the force arises with mucosal surface.[2]

Mucoadhesion drug delivery benefit the properties of some hydrophilic polymer that adhesive when exposing to water and therefore used for drug targeting to certain area of body for desired time interval.[3]

Captopril is substituted proline acts through decrease of angiotonsin II and increase of bradykinin production.[4] The mainly use of captopril in hypertension management and in patient suffering from heart failure when classical treatment unresponsive. Also in management left side heart failure after myocardial infarction and is renoprotective in diabetics nephropathy treatment.[5] A round 60-75% of captopril is absorbed through the elementary tract and the peak plasma concentrations are obtained through one hour[6], have two dissociation constant pka1 3.7 pka2 9.8, the $t_{1/2}$ around 1-2 hours.[7] The objective of this study is to prepare captopril as mucoadhesive buccal patch by solvent casting method and studying the effect of changing plasticizer type and increasing the drug amount on the physical and mechanical behavior of film and in vitro drug release.

MATERIALS AND METHODS

Chemicals

Captopril was obtained as a gift sample from Awamedica, Iraq. HPMC and Carbopol were obtained from Indian Fine Chemicals. Glycerin was obtained from Searle company. Propylene glycol (PG) was obtained from Evans Medical Ltd, Liverpool. Polyethylene glycol 400 was obtained from J.T Baker, China All other reagents and chemicals used were of analytical grade.

Formulation of captopril mucoadhesive buccal film

the mucoadhesive buccal patch was prepared by using HPMC K4M as primary polymer alone or in combination with secondary polymers (Carpabol 934) in different ratios of total polymer weight as shown in table (1), all formulas were dissolved in 50 ml of distilled water. HPMC K4 solution prepared by heating 20-30% of distilled water volume with stirring to 80-90ºC then the amount of HPMC K4 was added, after that complete the final volume with cold water under stirring[8], the secondary polymer carbopol was added after solubilization in sufficient amount of water with continues mixing, captopril was added after levigation with propylene glycol (30% of total polymer weight) while for formulas F5 and F6 glycerin and PEG 400 were added respectively instead of PG, The prepared solution leaved overnight to get ride air bubbles. Then these solutions were poured on aluminum foil(used as backing layer) in glass mould of diameter 9 cm and leaved to dry in hot air oven adjusted at 50°C until a flexible patches obtained. The dried patches divided in to 2×2 cm^2 diameter and then used for study.

Table1:- Composition of Formulated Captopril Mucoadhesive Buccal Patch

Ingredients (mg)	Formula code					
	F1	F2	F3	F4	F5	F6
captopril	12.5	12.5	12.5	12.5	12.5	17.5
HPMC	93.75	93.75	93.75	48.38	75	
Carbopol				9.37	18.75	
PG	28.125			28.125	28.125	28.125
Glycerin		28.125				
PEG400			28.125			

Physical Evaluation

A**. Weight Variation**

Three randomly chosen films were selected and weighed every one alone using digital balance, then take the mean value, this done for each formulation.[9]

B. Thickness

Three film randomly chosen from each formulation and measured the thickness at five point by using digital venire caliper, then take the average value.[10]

C. Surface PH

The surface PH of buccal film must be measured and maintain it neutral as possible when used in vivo. In this test the film allow in contact with 5 ml of distilled for 60 min at room

temperature and then the pH measured by using pH meter, this done in triplicate and take the mean value.[11]

D. Content Uniformity

This test was measured by dissolving the patch (2×2) cm^2 in 100 ml phosphate buffer PH 6.8.under magnetic stirrer for 60 min. Then the result solution filtered, diluted with phosphate buffer and determined drug content by UV spectrophotometer at λ max 206nm in triplicate.[12]

Tensile Strength and Percentage Elongation

Tensile strength is the maximum force required for breakdown of the film. The film which cut into dumbbell shape with size 5×2 cm^2 put between the two clamps of tens meter and pulled at a rate 5 mm/ min. The calculation of tensile strength is shown in this equation:

$$\text{Tensile strength} = \frac{\text{Load at break}}{\text{Width x thickness}} \times 100$$

While percentage elongation is the stretching and distortion of the patch when the force is applied and it calculated from this equation.[13]

$$\text{Percentage elongation} = \frac{\text{Final length} - \text{initial length}}{\text{Initial length}} \times 100$$

Ex- vivo mucoadhesive Strength

A modified physical balance as seen in figure 1 was utilized for measuring the mucoadhesive strength. Fresh chicken pouch was used as a model (taken from slaughter house and must use during 120min since slaughter).[14]

The pouch was washed with phosphate buffer solution pH 6.8 and attached on the bottom of the petridish by the help of cyanoacrylate glue, a glass stopper is hanged by threads at equal space from the left hand pan. To the lower end of the glass stopper, the film was attached by cyanoacrylate gum just above the pouch membrane. The right pan contain empty beaker, the two pan must balance by addition of a proper weight, after that a 5gm weight is removed from the right pan, in order to make the film in contact with pouch membrane. The balance was leaved in this situation for 5 min. Then distilled water was slowly added to the empty beaker till the film separate from the chicken pouch. The weight required to separate the film from the chicken pouch represent the measurement of mucoadhesive strength.

The force of adhesion and bond strength were calculated using following equation.[15]

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesion strength}}{1000} \times 9.8$$

$$\text{Bond strength (N/M2)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area}}$$

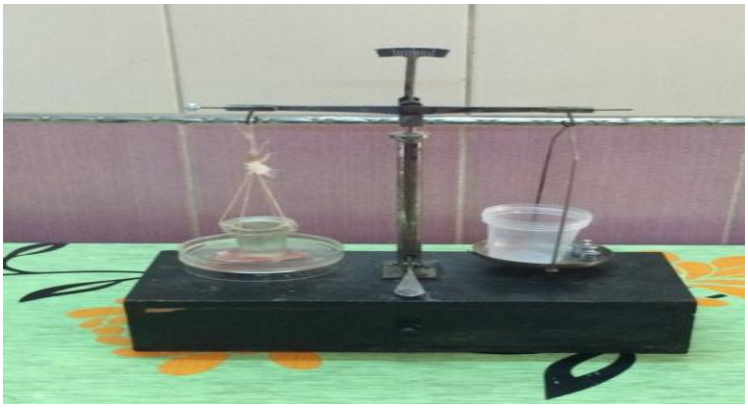

Figure 1: Modified physical balance used for mucoadhesive strength measurement.

Ex-vivo Residence time

The ex-vivo mucoadhesive time was determined by fix the prepared film on chicken pouch membrane (used as a model)[14]. figure 1.

After that the membrane was stuck on the inner face of a beaker around 2.5 cm from the bottom by using cyanoacrylate gum. Then the beaker which contain 500 ml phosphate buffer pH 6.8 stirred at 50 rpm and maintain the temperature at 37ºC for stimulation buccal environment.

The time require for the film to separate from chicken pouch membrane or complete erosion was consider as the mucoadhesion time.[16]

Percentage moisture Absorption and percentage moisture loss of patches

The percent moisture absorption (PMA) test was determined to check the film stability at high moisture environment. In this test three $2\times2cm^2$ diameter film were pre weight and put in a desiccators containing saturated solution of aluminum chloride to keep the humidity at79.6% for 72 hours. After that the films were taken from desiccators and reweight again the PMA was determined from this equation.[17]

$$PMA = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

While percentage moisture loss (PML) test was determined to check the film integrity at dry environment. There film (2×2) cm^2 pre weighed and put in desiccators containing fused anhydrous calcium chloride for three day. After that the film was taken from desiccators and reweight again. The PML was calculated this equation.[18]

$$PML = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

In vitro Release study

All the prepared captopril buccal patch was measured using U.S.P dissolution (paddle type) apparatus, adjusted at 37ºC, rotate at 50 rpm and the dissolution jar filled with 500 ml phosphate buffer pH 6.8.[19]

In order to produce unidirectional drug release, the patch (2×2) cm^2 was placed on glass slide by the help of cyanoacrylate glue, then the slide immersed in the dissolution apparatus jar. Aliquots of 5 ml sample were taken from the jar at regular time period (15, 30, 60, 120, 180, 240, 300, 360) min and replaced with equal volume of buffer solution since the drug is soluble. The sample suitably dilated and analyzed by UV spectrophotometers at 206nm, then the dissolution profile of captopril is constructed by plotting the percent of accumulative drug release against time.[20]

In– Vivo Drug Release Test

A patch 2×2 cm^2 (selective formula) containing 12.5mg captopril was fixed on cellophane paper which serve as backing membrane to produce unidirectional drug release. Five human volunteers aged (23-35) years, asked them to rinse their mouth with water before application of patch after that the selection patch were placed on volunteers buccal mucosa. Single patch for each time interval (30, 60, 120, 18, 240, 300 and 360 min) was taken at the end of each interval and added to beaker containing 10 ml of phosphate buffer pH 6.8 the subjects then rinsed their mouth with 10 ml buffer and the washing solution were added to previous one .After suitable dilution, their result solutions were analyzed spectrophotometerically at 206 nm for drug content, the result value considers as unabsorbed amount of drug.[21]

Stability studies (Determination of expiration Date)

Stability study was measured to study the effect of temperature on the captopril degradation in the final typical formulation.

This done by storing the selective patch in a sealed container and placed their in three oven in thermal condition (40, 50, 60°C).

Samples were taken each two weeks and the content of captopril measured by using UV-absorbance at λ max 206 min.

STATISTICAL ANALYSIS

The result of the experimental work were demonstrated as a mean of triplicate model ± SD and were examined in relation to the one way analysis of variance (ANOVA).

RESULT AND DISCUSSION

Physical evolution

The average weights for all prepared formulations were uniform and ranged (160.29-183.02) mg, All the captopril buccal patch showed an acceptable thickness(0.246-0.273) mm and the surface pH value (6.32-6.53), when compared to that pH of oral mucosa indicating that it doesn't cause un irritation to buccal mucosa, table 2.

Content uniformity

The formulated captopril buccal patch showed acceptable quantity of medicament ranged from (95.27-104.54%). This result met the accepted range of content uniformly labeled in BP which is ranged from 85% to 115%. According to that, captopril was spread uniformly throughout the 4 cm^2 constant area of buccal patch. as seen in table 2.

Table(2):- Result of physical Evolution Parameters of Prepared Captopril Mucoadhesive Buccal Patch.

Formula NO.	Weight uniformity(mg)	Thickness(mm)	surface pH	Content uniformity(%)
F1	160.29±5.23	0.246±0.075	6.53±0.23	95.27±0.032
F2	166.38±3.08	0.256±0.031	6.32±0.07	104.54±0.003
F3	183.02±1.33	0.273±0.046	6.43±0.12	100.06±0.014
F4	164.45±7.81	0.263±0.012	6.44±0.21	96.12±0.053
F5	168.33±5.12	0.266±0.009	6.38±0.05	95.39±0.042
F6	170.53±2.2	0.272±0.05	6.53±0.11	99.15±0.033

Mechanical Properties of Prepared Captopril Mucoadhesive Buccal Patches

This test involve both tensile strength and elongation at break which are give indication about the patch flexibility and elasticity ,an ideal buccal patch should have both high TS and EB% [22]. Formula F3 (PEG 400 as plasticizer) showed a significant increase ($P<0.05$) in both TS and %EB in comparison to F1 (PG) and F2 (glycerin), this is may due to PEG400 has large molecular weight with long carbon chain that permit it large flexibility and elasticity, so that it extend longer before ruptured[23], table 3.When drug amount increased from 12.5mg (F4) to 17.5mg (F6) led to a significant decrease ($P<0.05$) in TS and %EB, table3, this may be related to disrupt the bonding of functional group of polymer chains.

Table (3):- Mechanical properties of Prepared Captopril Mucoadhesive Buccal Patch.

Formula NO.	(TS)MPa	%EB
F1	19.5	24.06
F2	13.87	19.73
F3	26.09	30.1
F4	16.06	34.14
F5	10.15	26.8
F6	12.49	33.07

mucoadhesive strengths

The mucoadhesion describe the adhesion that occurs between the patch and the buccal mucosa. The mucoadhesive strengths are influenced by many factors such as biological membrane, molecular weight and rate of polymer swelling that used in the study.[24] Formula F2 which contained glycerin as plasticizer was found to have higher mucoadhesive strength than F1and F3 as seen in table 3, these result was in agreement with data found by Gardouh et al.[25] Also there is non- significant increased for F6(17.5mg captopril) when compared F4(12.5 mg captopril),as seen in table 4.

Table (4):- Mucoadhesive strength and Ex-vivo Residence Time of Prepared Captopril patch

Formula NO.	Mucoadhesive Strength (gm)	Force of adhesion (N)	Bond Strength (Nm^{-2})	and Ex-vivo Residence Time (hrs)
F1	**21.8±0.511**	**0.213**	**534.1**	**4.55±0.81**
F2	**25.63±0.101**	**0.251**	**627.39**	**5.10±0.39**
F3	**19.71±0.320**	**0.193**	**482.89**	**4.37±0.75**
F4	**26.2±0.256**	**0.256**	**641.9**	**6.12±0.06**
F5	**30.11±0.228**	**0.295**	**737.69**	**7.21±0.63**
F6	**26.11±0.166**	**0.264**	**660.27**	**5.53±0.51**

Percentage Moisture Absorption and Percentage Moisture Loss of Prepared Captopril Mucoadhesive Buccal Patches

This tests give an idea about the polymers abilities to absorb the moisture and if the dosage form maintained their stability after moisture absorption.[26]

If the films having large moisture content, this leads to microbial contamination and loss its integrity, while it became brittle, if it has low moisture content. An acceptable moisture content and fluid imbibitions are important for drug release because these fluids lead to solubilization and improving drug flow from the dosage from.[27] The highest values of PMA and PML obtained from F3 in which PEG 400 added as a plasticized, table 5, this is because of PEG 400 have high water uptake capacity when compared with PG.[28]

Table (5):- Percentage Moisture Absorption and Percentage Moisture Loss of Prepared Captopril Mucoadhesive Buccal Patches

Formula NO.	Percentage moisture absorption (PMA)	Percentage moisture loss(PML)
F1	6.53±0.9	6.06±0.11
F2	18.89±0.17	15.06±0.73
F3	20.88±0.75	16.10±0.08
F4	10.15±0.03	7.6±0.33
F5	14.74±0.08	8.94±0.96
F6	11.27±0.71	7.69±0.55

In-vitro drug release

The effect of plasticizer type on drug release was shown in figure 2, it was found that formula containing PG as plasticizer have a significant increase ($P<0.05$) in drug release than other plasticizer, this may due to PG increase the partition coefficient and so that increasing drug diffusion.[25] also it was found that the higher loading of captopril, the greater amount of drug would dissolve inside the hydrated polymer matrix leading to increasing the drug diffusion rate and release.[29]

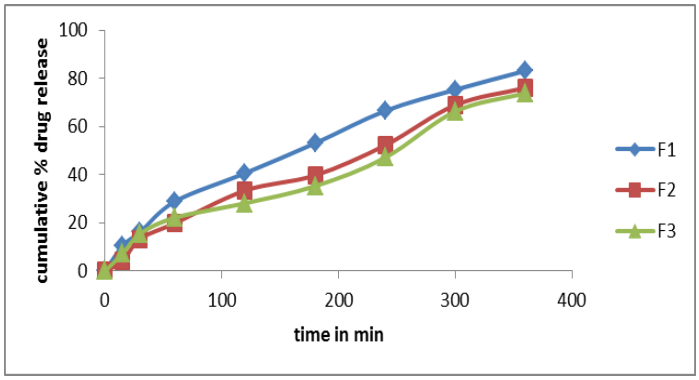

Figure 2: Effect of plasticizer type on in-vitro release of captopril in phosphate buffer pH6.8 at 37℃ from mucoadhesive buccal patches.

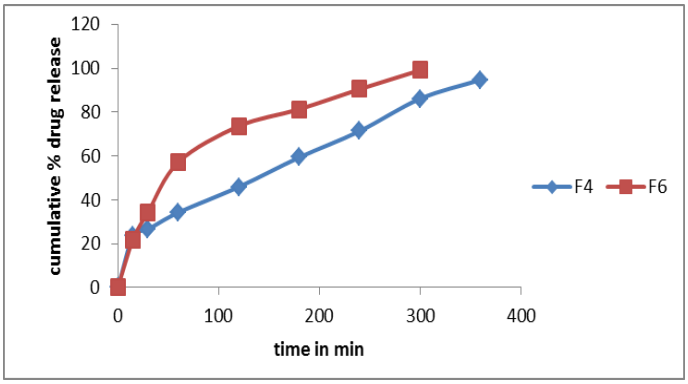

Figure 3:-Effect of increasing of drug amount on in-vitro release of captopril in phosphate buffer pH6.8 at 37°C from mucoadhesive buccal patches.

Determination of Selected Formula of Captopril Mucoadhesive Buccal Patch

Formula F4 was selected for further investigation and the selectivity was made since the patch had accepted value for mechanical properties (16.06MPa, 34.14%), surface PH(6.44±0.21), convenient mucoadhesive strength(26.2±0.256) and suitable ex-vivo time (6.12±0.06)hrs with high drug release 94.73% for 6hrs.

In-Vivo Drug Release Test

The selected formula (F_4) was chosen for in-vivo test on human cavity, the method used for determination the in-vivo release is the method of disappearance of the drug from the patch. It was found that 73.12% of captopril released after 6hrs, as shown in figure 4. The patch did not cause any discomfort or irritation to the human volunteers and no side effect, such as heaviness, or sever salivation were observed. The system claims the potential clinical usefulness in drug delivery.

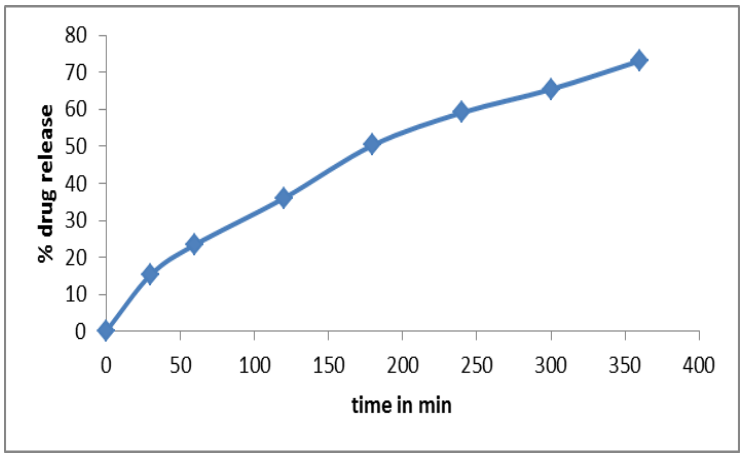

Figure 4: In-vivo release of captopril from buccal patches in human volunteers' buccal cavity for the selected formula F4

In-Vivo/ In vitro correlation (IVIVC)

The result of (IVIVC) was found to have acceptable correlation with (R_2) value of (0.986) as shown in figure 5.

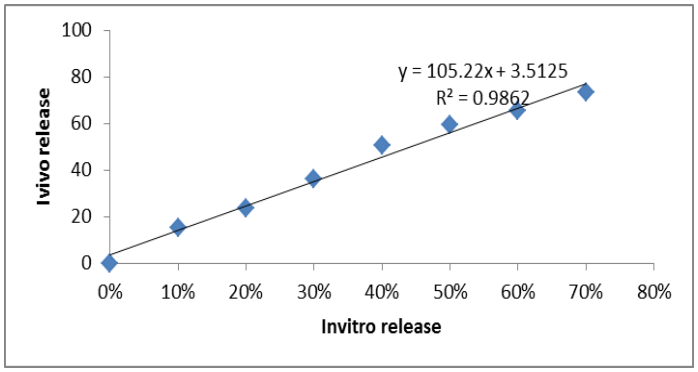

Figure 5:- In- vitro/in-vivo release correlation of captopril from buccal patches of selected formula F4

Stability Study

Formula F4 was chosen to be the selected formula because it gave satisfactory characteristic and the drug show stability in this formula with estimation expiration date 3.62 years at 25ºC.

CONCLUSION

The overall study revealed that captopril can be formulated as mucoadhesive buccal patch by using HPMC K4M as primary polymer and carbopol as secondary polymer that extend the drug release through the buccal mucosa for 6 hrs.

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