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Research Article

STUDY THE EFFECTS OF SECONDARY POLYMERS ON THE PROPERTIES OF BUCCOADHESIVE POLYVINYL ALCOHOL PATCHES OF 5-FLOUROURACIL

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ABSTRACT

Objectives: The aim of this study is to formulate and evaluate buccoadhesive patch of 5-Fluoruuracil (5-FU) for local treatment of oral squamous cell carcinoma (OSCC)

Methods: The buccoadhesive patches were prepared using polyvinyl alcohol (PVA) as patch forming polymer with hydrophilic or hydrophobic polymers as secondary polymer include Polyvinylpyrrolidone (PVP K30), Na CMC, sodium alginate, HPMC, chitosan, or Eudragit E100. The patches were prepared by solvent casting method and evaluated for weight variation, surface pH, mucoadhesive strength, mechanical properties, content uniformity, mucoadhesive residence time, and drug release study.

Results: The measured surface pH values of all prepared patches were close to the saliva pH in range of (5.9-7.3), the folding endurances were found to be within the recommended value (>300). Incorporation of hydrophilic polymer with PVA increases the swelling index and the maximum was observed for PVA: Na CMC (4:1) patch. There is a decrease in elongation percent (EB %) and tensile strength (TS) with using of secondary polymers except Eudragit E 100 that increase the TS. Although PVA: SALG (4:1) patches show the highest mucoadhesive strength, the PVA: Eudragit E100 (4:1) patches show longest adhesion time and release over 4hrs.

Conclusion: It can be concluded that the incorporation of secondary polymer to PVA patches of 5-FU improves the properties of patches regarding the mucoadhesion, mechanical properties, and release profile which make the patch as a mucoadhesive system good candidate for local treatment of OSCC.

Keyword: Oral squamous cell carcinoma, Buccal patches, 5-Fluoruuracil, Polyvinyl alcohol

INTRODUCTION

Over the past several decades, targeting drug delivery of therapeutic agents through various transmucosal routes has received significant attention to minimize the side effect or the achieving high drug concentration at the site of action [1].

Treatment of oral squamous cell carcinoma (OSCC) has primarily relied on classical modalities encompassing surgery, radiation, and chemotherapy or a combination of these methods [2]. Most of the patients are still treated with chemotherapy, in order to improve the tumor control and long survival rate [3] .The current treatment of OSCC is not still satisfactory in terms of patient survival and the role of chemotherapy in the management of patients with oral cancer is not well established yet.

Systemic regimens with high doses of chemotherapeutic agents appear to be efficient but they are also associated with severe toxicity and morbidity, potentially relevant to the survival rate. In addition, the high doses of chemotherapeutic agents could cause the development of resistant cell lines [4]. Solid tumor cells *in vivo* are often exposed to hypoxic conditions due to limited blood supply from surrounding tissue. This phenomenon could induce resistance to chemotherapeutic agents [5].

Topical Administration of 5-FU close to cancerous lesion could be a useful means to improve treatment of OSCC due to the high level of 5-FU that can be achieved in the tumor area and decrease resistance to chemotherapeutics agent with reduced systemic side effect[6].

The purpose of this work is to study the effect of hydrophobic polymer like Eudragit E 100 and hydrophilic polymer like PVP K30, Na CMC, HPMC, and sodium alginate (SALG) on the *in vitro* drug release and other characteristics of PVA buccoadhesive patch.

MATERIALS AND METHODS

Materials

The 5-FU was purchased from Ampla Pharmaceutics Inc., USA. Polyvinylalcohol (PVA) and sodium carboxymethylcellulose (Na CMC) were purchased from (Panreac, Espana). Polyvinylpyrolidine (PVP) was purchased from (Fluka analytica Co., USA). Chitosan (M.wt 400, 00) was purchased from (Himedia Lab. India). Hydroxypropylmethylcellulose (HPMC) was purchased from (Sigma-Aldrich, USA). Sodium alginate (SALG) was purchased from (BDH, UK). All other reagents and chemicals used were of analytical grade.

Table 1: Formulas composition of 5-FU mucoadhesive buccal patches

Ingredient (gm)	Formula Code						
	F1	F2	F3	F4	F5	F6	F7
5-Flourouracil	0.283	0.283	0.283	0.283	0.283	0.283	0.283
PVA	5	4	4	4	4	4	4
HPMC		1					
Sod. Alginate (SALG)			1				
PVP K30				1			
Chitosan					1		
Eudragit E 100						1	
Na CMC							1
Water (ml)	150	150	150	150	75	120	150
Acetic Acid 2% Solution (ml)					75		
Ethanol(ml)						30	
Propylene glycol	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Methods

Preparation of buccal patches

The calculated amount of polymer was dissolved in distilled water with magnetic stirring for 24 hrs, and then the drug (5-FU) was incorporated into the polymeric solution with continuous stirring. Desired quantity (30% of the polymeric weight) of the plasticizer (propylene glycol) was added and kept aside for 1 hr at room temperature. The mixture of the polymeric solution and drug of all formulas was poured on aluminum foil in a glass petri dish having 15 cm diameter. The Petri dishes were kept on leveled surface and covered by inverted funnel to allow controlled evaporation of solvent at room temperature till a flexible patch was formed. Dried patches were carefully removed, checked for any imperfections or air bubbles and cut into small patches. The patch was packed in aluminum foil and stored in desiccator to maintain the integrity and elasticity of the patches. The formulations were prepared so that each 2.5×2.5 cm patch contains 10 mg of 5-FU using petri dish with a surface area (176.7cm^2). The composition of buccoadhesive patches is listed in table (1).

Evaluation of 5-FU buccal patches

Weight variation

Three patches from each formulation were weighed using an electronic digital balance and the average weight was calculated [7].

Patch thickness

Three patches each formulation was taken and the film thickness was measured using digital vernia and the average was calculated [7].

Folding endurance

Folding endurance of the patches was measured by repeated folding of the patch till it broken, the number of time that the patch will folded without breaking consider as folding endurance, the test repeated in triplicate[8] .

Surface pH

The surface pH of the patches was determined using litmus paper, three patches (2.5×2.5 cm^2) from each formulation were kept in contact with 5 mL of distilled water for 6 h, in test tubes and then litmus paper was placed for pH reading after equilibrating for 1 min [9].

Swelling Index

The studies for swelling index of the patches were conducted in simulated salivary fluid of pH 6.8. The patch was weighted using digital balance and immersed in 50ml phosphate buffer (pH 6.8), and then reweighed at different time interval [10].

The percentage swelling was calculated using the following equation:

Percentage swelling = $((W2) - (W1))/W2$ **X 100**

Where, W1: initial weight (before swelling) , W2: weight after swelling

Drug content uniformity

Drug content uniformity was determined by dissolving the patch in 100 ml of phosphate buffer (pH 6.8) for 24hrs with stirring. From the solution 5ml was diluted with phosphate buffer pH 6.8 up to 10ml. The drug content was then determined after proper dilution of filtered solution at λmax266 nm using a UV spectrophotometer (Carry win UV, Varian, Australia) [11].

Mucoadhesive Strength

The mucoadhesion test of films was performed by using modified physical balance method described by Gupta *et al* [12]. In this method the physical balance was modified to measure the weight required to detach the film from mucosal membrane. The mucosal side of chicken pouch was used to study the mucoadhesion. The chicken pouch was collected from the local slaughter house and preserved at 4° C and used within 24 hours. Average of three patches of each formulation was calculated for mucoadhesive strength [13]. The following parameters were calculated from the mucoadhesive strength:

$$\text{Force of adhesion (N)} = \frac{\text{mucoadhesive strength (g)} \times 9.81}{1000}$$

$$\text{Bond strength (N m}^{-2}\text{)} = \frac{\text{Force of adhesion}}{\text{Disk surface area}}$$

Mucoadhesive residence time

The mucoadhesive test medium consisted of 200 ml of SSF pH 6.8, maintained at 37±2°C and 50 rpm stirring rate. The chicken pouch membrane was cut and fixed on the internal side of a beaker by cyanoacrylate glue with mucosal surface facing out. The time required for complete erosion or detachment of the film from the mucosal surface was recorded [14].

In vitro drug release

USP dissolution apparatus type II was used throughout the study. One patch of 2.5x2.5 cm^2 was fixed to a glass slide using cyanoacrylate glue. The slide was put in the bottom of beaker at angle 45^o containing 250 ml of phosphate buffer pH 6.8 as dissolution medium. The drug release study was performed at 37±0.5º C at a rotation speed of 50 rpm for 360 min. At different time intervals, the sample was withdrawn from the dissolution medium and the same volume of fresh medium maintained at 37±0.5ºC was replaced. Each withdrawn sample was filtered and analyzed spectrophotometrically at 266 nm [15].

Tensile Strength Measurement

Mechanical properties of the prepared patches were evaluated using (tensometer 10, Monsanto, USA); Patches strips free from air imperfections were held between two clamps positioned at a distance of 3cm. The patch strips were pulled by the top clamp at a rate of 100 mm/min. TS and %EB were measured in triplicate when the patch broke using the following formulas.

$$\text{Tensile strength} = \frac{\text{Force at break (N)}}{\text{Initial cross sectional area of the sample (mm2)}}$$

$$\text{Elongation percent} = \frac{\text{Increase in length}}{\text{original length}} \text{X100}$$

Percentage moisture absorption (PMA)

The percentage moisture absorption test was carried out to evaluate the physical stability of the buccal patches at high humidity condition. Three patches of 1cm diameter were cut out and weighed accurately, and then the patches were placed in desiccator containing saturated solution of potassium chloride keeping the humidity inside the desiccator at 75 %.

After 3 days the patches were removed, weighed and percentage moisture absorption was calculated using the following equations [16].

$$\textit{Percentage moisture absorption} = \frac{(\textit{Final weight} - \textit{Initial weight})}{\textit{Initial weight}} X100$$

Water vapor transmission rate (WVTR)

Water vapor transmission rate was used for the determination of vapor transmission from the patch. Glass vial filled with 1 g anhydrous calcium chloride and an adhesive (cyanoacrylate) spread across its rim. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of potassium chloride and maintained at 37 °C. The difference in weight after 1st, 3rd and 7th days was calculated. The experiments were carried out in triplicate and vapor transmission rate was obtained as follow [17].

$$\textit{Water Vapor transmission rate (WVTR)} = \frac{\textit{Amount of moisture transmitted}}{(\textit{Area} \times \textit{Thickness})}$$

Drug polymer compatibility study

The drug and polymer compatibility was studied using FTIR (Shimadzu S-1601, Japan). Pure drug, physical mixture, and prepared formulas were analyzed at 400 to 4000cm^{-1} using a KBr disk

RESULT AND DISCUSSION

The characterization parameters of the prepared patches are shown in table (2). All formulas show uniform weight with higher practical than theoretical weight in patches contains hydrophilic polymers was observed. Acceptable thickness, drug content, and surface pH value in range of 5.9-7.3 which means that they have no irritancy to the buccal mucosa and therefore it comfortable to patient. The folding endurance was found to be within the recommended value (>300) which means that it flexible enough to be handle and transport without destroyed.

Incorporation of hydrophilic polymer with PVA increase the swelling index as in PVA :Na CMC (4:1) patches which have the highest value due to the presence of large number of hydroxylic groups in NaCMC that can absorb and retain water and thus increasing weight and swelling index while incorporation of hydrophobic polymer like Eudragit E 100 decrease the swelling index due to the hydrophobic nature of Eudragit E 100 that have poor swelling capacity because of lack of quaternary ammonium group in their chemical structure (figure 1) [18].

Addition of secondary polymers in all formulas shows a decrease in the %EB and TS except patches contain Eudragit E 100 caused an increase in the TS, this may be due breakage of the bonds between PVA molecular network that make it easy to breaks (figure 2).

The mucoadhesive strength was varies according to the type of polymer that added to the PVA as shown in Table (3). The results indicate that the PVA: SALG (4:1) produced the highest mucoadhesive strength due to high number of polar groups in SALG and therefore gets hydrated easily and forms a strong gel that entangles tightly with the mucin molecules [19].

Table 2: Physical evaluation parameters for 5-FU mucoadhesive buccal patches

Formula code	Surface pH	Weight variation(mg)	Thickness (mm)	Folding endurance	Content uniformity%
F1	6.40±0.173	239±2.17	0.276±0.023	>300	90.3±1.02
F2	6.00±0.173	243±6.42	0.296±0.025	>300	93.0±0.67
F3	6.00±0.173	260±10.6	0.200±0.015	>300	98.3±0.12
F4	6.26±0.208	273±4.25	0.250±0.015	>300	90.0±0.99
F5	5.90±0.152	267±1.76	0.350±0.045	>300	96.4±0.56
F6	7.00±0.200	215±5.78	0.266±0.025	>300	94.6±0.98
F7	7.30±0.360	287±3.24	0.370±0.010	>300	99.0±0.19

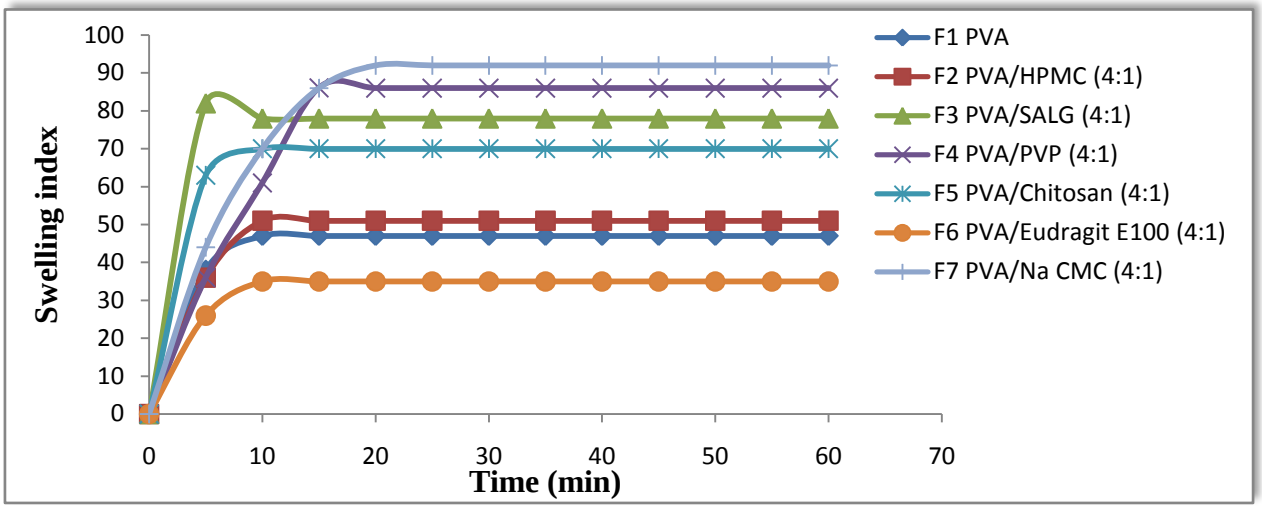

Fig.1: Effect of polymer type on the swelling of 5-FU from prepared patches of different formulas

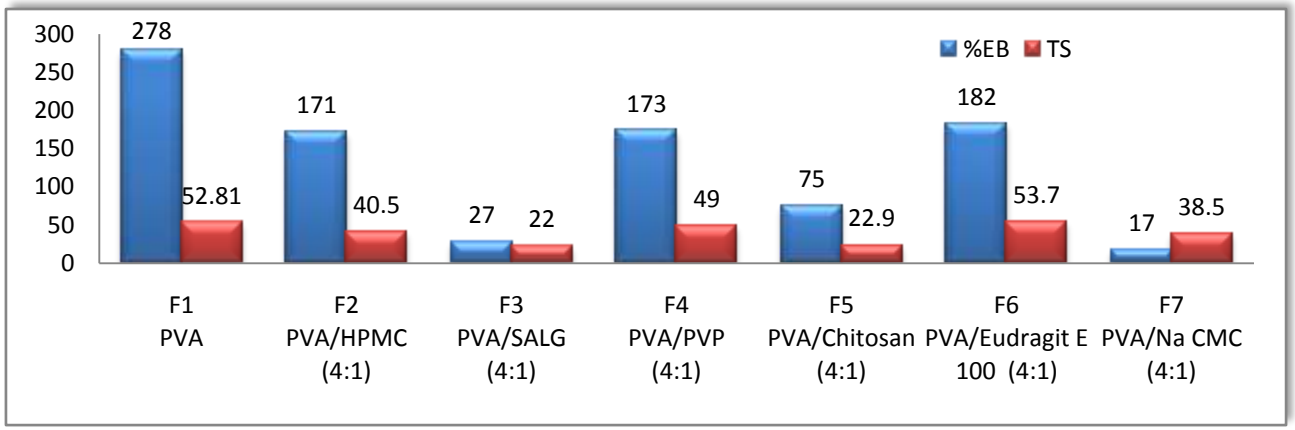

Fig. 2: Effect of polymer type on the mechanical properties of prepared 5-FU buccal patches of different formulas

The high mucoadhesive strength of chitosan containing patches may be due to numerous amino and hydroxyl groups that may increase the electrostatic interaction of chitosan with the mucin [20]. On the other hand PVA: Eudragit E 100 (4:1) shows the longer adhesion time among the secondary polymers.

Water vapor transmission rate (WVTR) studies indicated that all the patches were permeable to water vapor with highest value observed for PVA: PVP (4:1) patches (Table4).

Figure (3) indicates a burst drug release during the first 30 minutes (> 20%) of all formulas. The drug release rate appeared to increase by addition of hydrophilic polymers. The slow release of PVA: PVP (4:1) patches may be due to the complex formation between PVP and drug [21]. Formula PVA: Eudragit E 100 (4:1) showed the much lower burst release followed by slowest percent release over 4 hrs which may be due to hydrophobic property of Eudragit [22].

There is no significant changes ($p<0.05$) in the characteristic peaks of drug in the FTIR spectra (Table 5) after patches preparation which indicates that there is no incompatibility between 5-FU and the excipients.

Table 3: Mucoadhesive properties of prepared 5-FU mucoadhesive buccal patches

Formula	Mucoadhesive strength (gm)	Force of adhesion (N)	Bond strength (Nm^{-2})	Ex-vivo residence time (hrs)
F1	8.70±0.17	0.085	212	3.22±0.56
F2	9.10±0.14	0.089	222	4.07±0.86
F3	18.3±0.24	0.179	447	4.28±0.46
F4	9.23±0.09	0.090	225	3.44±0.56
F5	14.5±0.70	0.142	355	3.77±0.33
F6	10.6±0.12	0.103	257	4.94±0.54
F7	12.9±0.23	0.126	315	3.55±0.99

Table 4: Water permeation data of formulated 5-FU mucoadhesive buccal patches

Formula code	Water vapor transmission rate g cm^{-2} h^{-1} $\times 10^{-3}$ (mean ± SD)			Percentage Moisture absorption (%) at day3
	Day 1	Day 3	Day 7	
F1	0.68 ± 2.03	0.77 ± 0.56	0.45 ± 0.68	8.40±1.09
F2	0.28 ± 3.12	0.29 ± 0.17	0.24 ± 0.19	7.50±0.21
F3	1.47 ± 1.33	0.93 ± 1.45	0.86 ± 0.10	5.20±0.12
F4	1.63 ± 0.97	0.91 ± 2.61	0.65 ± 0.81	8.00±0.65
F5	1.06 ± 0.46	0.86 ± 0.83	0.67 ± 0.33	11.7±0.61
F6	1.00 ± 0.98	0.53 ± 2.11	0.21 ± 0.12	10.7±0.89
F7	0.53 ± 0.97	0.54 ± 0.22	0.46 ± 0.21	7.40±0.54

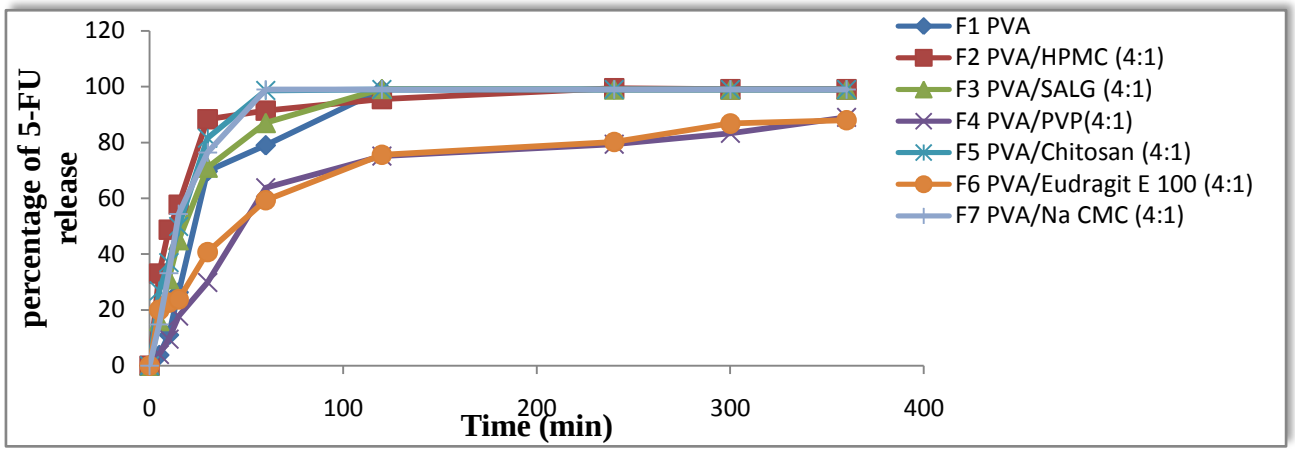

Fig. 3: Effect of secondary polymers on the *in vitro* release of 5-FU from prepared buccal patches of different formulas

Table 5: FTIR spectra bands of 5-FU mucoadhesive buccal patches

Formula code	Frequency cm^{-1}						
	N-H Stretch	ν(C=O) Amide I band	C-F stretch	Aromatic C-H bend	Amide ν(N-H) wag	N-H in plane bend	N-H amide bend (amide II band)
Pure 5-FU	3138	1728 / 1649	1246	950/937	811/752/642	1431	1506
Prepared formula (F3)	-----	1720 / 1653	1283	950/926	850/750/650	1436	1510
Physical mixture of formula (F3)	-----	1653	1249	930	810/745650	1440	1510
Physical mixture of formula (F6)	3140	1728/ 1653	1246	980	810/750/640	1431	1510

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