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A Study on Combined Effect of Polymers in Physical Characterization of Placebo Buccal film

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ABSTRACT

A novel buccal film can be applied to the oral mucosal surface which can be retained there for few hours, even where it is challenged with fluids. Polymers play an important role in designing such buccal films so as to increase the residence time of the active agent at the desired location. Hence the objective of our study was to optimize a suitable formula which comprises a best combination of polymers in suitable ratio to produce buccal film with desirable physical and mechanical properties. The study was carried out in chitosan film with three other different combination of polymers such as PVPK 30 (polyvinyl pyrolodine 30) PVPK 90 (polyvinyl pyrolodine 90) and HPMC (Hydroxy propyl methyl cellulose) at various concentrations. The effect of each concentration of the particular polymer in combination with the other polymers in making buccal film by solvent casting method was evaluated through twelve different batches of buccal film like F1,F2,F3,F4,F5,F6,F7,F8,F9,F10,F11,andF12.The physical and mechanical properties of formulated films were studied in terms of its appearance, texture, average weight, thickness, folding endurance, swelling index, surface pH, tensile strength, percentage elongation and bioadhesive strength. Overall results of our investigation reveals that the combination of PVPK30 at a concentration of 0.6%w/v with 1% concentration of chitosan is found to be effective in producing film with better bioadhesiveness and further addition of 0.2% of HPMC with 0.4% PVPK90 to this combination could enhances its elastic properties without having any added effect on its bioadhesive strength.

Keywords: Buccal film, effect of polymers, evaluation of mechanical and physical property.

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INTRODUCTION

The novel type buccal dosage forms include buccal adhesive tablets, patches, tapes, semisolids and powders. Buccal adhesive tablets are dry dosage forms that need to be moistened prior to placing in contact with buccal mucosa. Bioadhesive gels or ointments have less patient acceptability than solid dosage adhesive forms, and most are used only for localized drug therapy within the oral cavity[1]. Buccal patches consist of two ply laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut the required oval shape. A novel mucosal adhesive film called 'Zilactin' consist of an alcoholic solution of hydroxyl propyl cellulose and three organic acids, forms a film which is applied to the oral mucosal surface which can be retained in place for at least 4 hours, even where challenged with fluids. The drug selected for buccal film must have critical characteristics like low conventional single dose and hepatic first pass metabolism. The drug should have passive oral absorption and it should not have bad taste and be free from irritancy[2]. The polymer used in formulation should have good film property. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers. Anionic polyelectrolytes, e.g. poly acrylic acid and carboxymethyl cellulose, have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer.[3]Chitosan provides an excellent example of cationic polyelectrolyte which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties[4] hence in our study the main objective was to optimize a suitable formula and also to develop a balanced combination of polymers so as to produce a buccal film of desirable mechanical and physical property, which in turn enhances the intended release characteristics from the patch and reduces formulator's optimization time for the selection of polymer and formula.

MATERIALS AND METHOD

Chitosan 150cps was procured from central institute of fisheries and technology, Cochin, kerala, India. PVPK 30 (Polyvinyl pyrolodine 30) PVPK 90 (Polyvinyl pyrolodine 90) and HPMC (Hydroxy propyl methyl cellulose) were purchased from Hi media laboratories, Mumbai, India. All chemicals and solvents used were of analytical grade. Modified physical balance was specially designed and assembled at Aimst University, Kedah, Malaysia.

Formulation of buccal patch by solvent casting method[5] using combination of Chitosan and PVPK 30 as film formers

To study the effect of increasing concentration of PVP K 30 in film characteristics of buccal film having chitosan, four different batches of buccal films namely F1, F2, F3 and F4 were prepared by using different concentration of PVP K 30 such as 1.2%, 1%, 0.8 %and 0.6% and a constant concentration of chitosan solution 1%w/v as the main film former and 5% V/V of propylene glycol as plasticizer.

Procedure

Polymeric solution of film was prepared by dissolving 1 gm chitosan dissolving in 100 ml of 1.5% acetic acid by stirring in a mechanical stirrer for 24 hours. This solution was filtered through a muslin cloth to remove debris. For preparing formula F1, 15ml of chitosan solution was taken and 1.2%w/v PVP K30 and 5%v/v propylene glycol was added and stirred for 2 hours. This polymeric solution was kept overnight to remove air bubbles, it was added uniformly to a Petri plate containing mercury as substrate.

The plate was then kept in an oven at 40^0C for 24 hours. After drying, the film was peeled off with a sharp blade and kept in a self sealed cover. Similarly three other batches were prepared where the concentration of PVPK30 was varied. It was maintained at 1%w/v, 0.8 %w/v and 0.6 %w/v respectively for F2, F3 and F4. The combination of polymers and its concentration is given. (Table 1) In all these batches the chitosan and propylene glycol concentration were constant. All four batches of the buccal films were subjected to evaluation of physical and mechanical characteristics.

Table -1 Composition of buccal patch of chitosan in combination with PVPK30

Ingredients	BatchF1	Batch F2	Batch F3	Batch F4
Chitosan (% W/V)	1	1	1	1
PVPK 30 (% W/V)	1.2	1	0. 8	0.6
Propylene glycol (V/V)	5	5	5	5

Formulation of buccal patch by solvent casting method using combination of Chitosan PVPK 30 and HPMC as film formers

To study the effect of different concentration of HPMC in buccal film which was produced through the combination of chitosan and PVPK30, the film which produced the best physical property in the previous combination was selected from the previous study. In addition to those polymers, HPMC (Hydroxy propyl methyl cellulose) was added at four different concentrations such as 0.2%, 0.4 %, 0.6% and 0.8%. The effect of increasing concentrations of HPMC on film made up of chitosan and PVPK30 was studied through its physical and mechanical properties.

To study the combined effect of HPMC with other polymers, four different polymeric batches namely F5, F6, F7 and F8 were prepared by using the different concentration of HPMC. For the

preparation of batch F5 1%w/v of chitosan solution was prepared by dissolving 1G of chitosan in 100ml of 1.5 % acetic acid, stirred for 24 hours this solution was filtered through a muslin cloth to remove debris. 15ml of chitosan solution was taken and 0.6%w/v PVP K30, 0.2%w/v HPMC and 5%v/v propylene glycol were added and stirred for 2 hours. This polymeric solution was kept overnight to remove air bubbles, and then it was added uniformly to a Petri plate containing mercury as substrate. The plate was then kept in an oven at 40^0C for 24 hours. After drying, the film was peeled off with a sharp blade and kept in a self sealed cover.

Similarly batches F6, F7 and F8 were prepared by the same method where the PVP K30 and chitosan concentration were constant and the concentration of HPMC was varied. It was maintained at 0.4%, 0.6%and 0.8% respectively for batches F6, F7 and F8 .the amount of plasticizer remained same for all batches throughout the study. The combination of polymers and their concentration is given.(Table 2) All four batches of the buccal films were subjected to evaluation of physical and mechanical characteristics.

Table-2 Composition of buccal patch of chitosan, PVPK30 and HPMC

Ingredients	Batch F5	Batch F6	Batch F7	BatchF8
Chitosan (% W/V)	1	1	1	1
PVPK 30(% W/V)	0.6	0.6	0.6	0.6
HPMC(%W/V)	0.2	0.4	0.6	0.8
Propylene glycol % V/V	5	5	5	5

Formulation of buccal patch by solvent casting method using combination of Chitosan PVPK 30 and HPMC and PVPK 90 as film formers

To study the effect of different concentration of PVPK 90 in combination with other polymers in the preparation buccal patch, the film which produced the best physical property in the previous combinations were selected. In addition to those polymers PVPK90 was also added at a concentration of 0.2%, 0.4% 0.6% and 0.8% and named as F9, $F_{10,}$ F_{11}, andF_{12} respectively. The method of preparation was same as above. The concentration of polymers like chitosan, PVPK30, HPMC and plasticizer were same as the best batch which was selected in the previous stage. Set of polymers and its concentration (table 3).

Table- 3Composition of buccal patch of chitosan, PVPK30, HPMC and PVPK 90

Ingredients	Batch F9	Batch F10	Batch F11	Batch F12
Chitosan (% W/V)	1	1	1	1
PVPK 30 (% W/V)	0.6	0.6	0.6	0.6
HPMC (% W/V)	0.2	0.2	0.2	0.2
PVPK 90 (% W/V)	0.2	0.4	0.6	0.8
Propylene glycol(%V/V)	5	5	5	5

EVALUATION OF BUCCAL PATCHES[6]

The buccal patches were evaluated for their physical, mechanical and bioadhesive properties.

Physical Properties:

Physical appearance and surface texture evaluation includes the visual inspection and evaluation of texture by feel or touch.

Weight variation:

Ten patches of $1cm^2$ were weighed individually and average weight of those patches was measured.

Thickness:

The thickness of the patch was measured using screw gauge with a least count of 0.01 mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

Percent Swelling Index[7]

Diameter method

The polymeric patches were cut in to small patches of 1.5 cm diameter. This patch was placed on the surface of the agar plate and the diameter at different time intervals where taken up to 5 hrs and the percentage swelling index was calculated using the formula,

SD% = Dt – Do/Do X 100

SD% = % swelling by diameter method, DT = diameter of swollen patch after time t

Do = original patch diameter.

Folding Endurance: [8]

The flexibility of patches can be measured quantitatively in terms of folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times at which the patch could be folded at the same place, without breaking gives the value of folding endurance.

Surface pH [9]

Buccal patches were left to swell for 1 hour on the surface of the agar plate. The agar plate was prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring. The solution was poured into the petridish, and allowed to stand until it solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

II. MECHANICAL PROPERTIES: [10-11]

Tensile Strength:

The tensile strength of buccal patch refers to tension or force required to tear of the patch apart into two pieces. Tensile strength was determined using an instrument assembled in the laboratory.

Design of the Instrument

The instrument used to measure the tensile strength was designed in our laboratory especially for buccal patches. The instrument is a modification of usual chemical balance. One pan of the balance was replaced with one specially made thin metallic plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the patch could be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan.

Method of Calculation:

The definition of tensile strength as per American Standard for Testing Material (ASTM) standard tests principles is, "the maximum load during the tensile strength test divided by the original minimum cross-sectional area of the specimen". Thus, tensile strength,

$$T = \frac{M \times g}{B \times t} \quad \text{Dynes/cm}^2$$

T= force at break/ initial cross-sectional area of sample.

Where, m = mass in grams

g = acceleration due to gravity 980 cm/sec^2

b = breadth of the specimen in cm

t = thickness of sample in cm.

b. Percent Elongation at Break [12]

The percent elongation at break is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100.

Percent elongation at break = LB – L0/ L0 X 100

LB = length of the specimen in cm when it breaks.

L0 = original length of the specimen in cm.

The instrument and procedure is similar to the one used for tensile strength.

Bioadhesive strength [13 -15]

Measurement of Bioadhesive Strength:

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance.

Instrument:

The apparatus was locally assembled and it was a modification of the physical balance .The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended. At the same side, a platform was maintained in the bottom in order to fix the model mucosal membrane.

Method:

The fabricated balance described above was used for the bioadhesion studies.[16- 17] The bovine cheek pouch excised and washed was fixed to the platform. The mucoadhesive patch of 3 cm^2 was fixed to the stainless steel lamina using an adhesive. The exposed patch surface was moistened with 1 ml of isotonic phosphate buffer for 30 seconds for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into the contact with the mucosal surface. A preload of 20gm was placed over the stainless steel lamina for 3 minutes as initial pressure. And then weights were slowly increased on the right pan, till the patch detaches from the mucosal membrane. Force required to detach the patch from the mucosa gave the bioadhesive strength of the mucoadhesive patch. The procedure is repeated for 3 times (n=3) for each patch and mean value of the 3-trials was taken for each set of formulation. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 10 minutes before taking next reading.

RESULTS AND DISCUSSION

The effect of various concentration of PVPK30 in buccal film of chitosan was investigated where the concentration of chitosan and the plasticizer propylene glycol were constant. But the concentration of PVPK30 was only changed.

Table -4 Physical characteristics of chitosan buccal patch in combination with PVPK30

Formulation code	F1	F2	F3	F4
Appearance	Smooth	Smooth	Smooth	Smooth
texture	Brittle	Brittle	Brittle	Flexible
Folding endurance	300 ±2	90±3	80±1.2	335±2
Swelling index After 5hrs	80± 1.2	86.6± 0.4	80±0.3	123±0.6
Average Weight(mg)	7.2 ± 0.2	7.4 ±0.11	7.3 ±0.23	7.2 ± 0.22
Thickness (mm)	0.06± 0.2	0.06± 0.4	0.06±0.3	0.06± 0.4
Surface PH	6.8± 0.2	6.6 ± 0.4	6.8 ± 0.6	7.0 ± 0.3

N=3 average of 3 determinations ± Standard deviation

The results are shown in (Table 4) it is clear that all the four batches of buccal film prepared through this particular combination of polymer produces film with uniform thickness, surface PH, and weight. The texture of films was smooth only for the batch F4 which was prepared

through 0.6%w/v of PVPK30. This batch produced film of relatively higher folding endurance and swelling index. Similarly batch F4 was found to have relatively higher percentage elongation, tensile strength, and bio adhesive strength than other batches. It is evidenced in film's flexibility.

Table-5 Physical characteristics of buccal Patch of chitosan, with PVPK30 and HPMC

	F5	F6	F7	F8
Appearance	Smooth	Smooth	Smooth	Smooth
Texture	Flexible	Flexible	Flexible	Flexible
Folding Endurance	341±1.4	321± 1.2	306± 2.1	311± 1.3
Swelling-index After 5 hrs	86 ±0.2	75.1± 0.3	78.9± 1.1	81.2±0.3
Average Weight(mg)	8.9±1.1	8.8± 0.2	9.2 ± 0.3	9.2 ±0.1
Thickness(mm)	0.03± 0.1	0.03± 0.2	0.03±0.1	0.03 +0.2
Surface pH	7±0.1	7.2± 0.8	6.8±0.4	7.2±0.2

N=3 average of 3 determinations ± Standard deviation

The other batches of patches like F1, F2, and F_3 were found to have no marked effect on the mechanical and physical property of film. Hence it may be concluded that among various selected concentration of PVPK30, the conc. of 0.6%w/v in combination with 1% of chitosan produces a film with desirable physical and mechanical characteristics. It has also been understood that there is no proportional increase in film's strength like folding endurance, swelling index, and bioadhesive strength with increase in concentration of PVPK30 which is reflected in (Table 7).To study the added effect of various concentrations of HPMC in buccal film of chitosan and PVPK30, a study was carried out in subsequent stage where the concentration of chitosan and the plasticizer propylene glycol were constant. But the concentration of PVPK30 was selected through the previous stage, it was 0.6% for all four batches, but the concentration HPMC were different like 0.2%, 0.4% 0.6%and 0.8% respectively F5, F6, F7and F8 batches. The data obtained in the physical characterization study (Table no 5). It can be observed that all the four batches of buccal film prepared through various concentration of HPMC in combination with other two polymer produces film with uniform thickness, weight, smoothness, surface PH and texture. But the batch F5 prepared with 0.2 %w/v of HPMC produced film of relatively higher folding endurance and swelling index. Similarly batch F5 was found to have relatively higher percentage elongation, tensile strength, and bio adhesive strength than other batches. (Table 7) it was also evident that bioadhesive strength of all the four films produced through the previous combination such as chitosan, PVPK30 exerted relatively better bioadhesive strength than all the films produced through the combination of chitosan, PVPK30 and HPMC. It can be concluded that the combination of PVPK30 and chitosan has more

prominent effect on film's bioadhesive strength than the combination of all three polymers at the selected concentrations. The combined effect of HPMC in buccal film has better effect on film's elastic properties such as elongation and tensile strength. It may be attributed to its water absorbing nature and subsequent increase in swelling and thickness of film. A similar effect of HPMC in film's elasticity has been reported by other investigators where they used HPMC chitosan and HEC [18]

Figure1 F10 batch of buccal film with better elastic properties

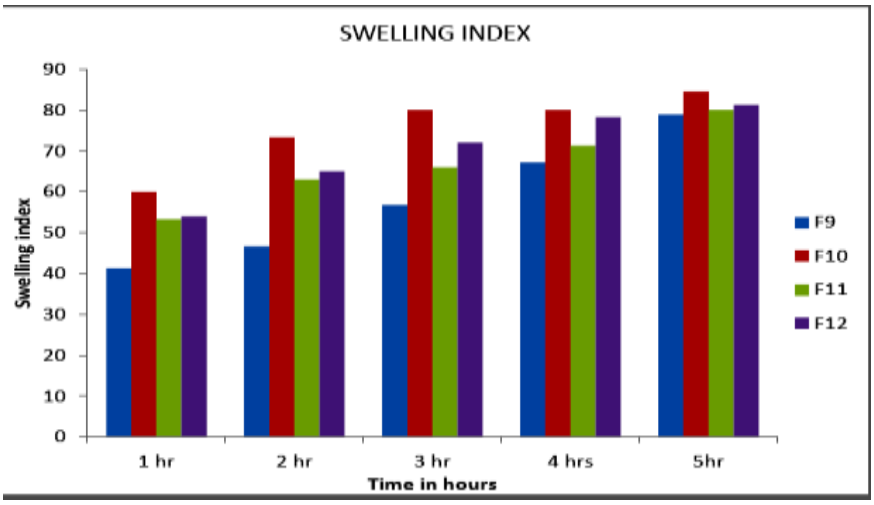

Figure 2 swelling index of formulations with combination of Chitosan, PVPK30, HPMC, and PVPK90

To study the combined effect PVPK90 along with other two polymers, the best concentration of each polymer selected from the previous study was included in this stage like 0.6% of PVPK 30, 0.2% of HPMC, along with the standard concentrations of chitosan and plasticizer, the combined effect of PVPK90 in film characteristics was explored through batches such as F_9, $F_{10,}$ and $F_{11}$and $F_{12.}$ The physical characteristics of the film (Table 6). It is evident that all the selected concentration of PVPK90 produces film of smooth and flexible nature. It has also been observed that this combination produces films with uniform thickness, weight and surface PH. Amongst

all batches the batch F10 produced film with relatively higher folding endurance and swelling index as shown in table: 6.and also there was a marked increase in percentage elongation, tensile strength and bioadhesive strength compared to other batches. It was also evident that the combination of PVPK90 at a concentration of 0.4% was more effective in improving the film's physical and mechanical properties. (Table No 5 and 6) it is understood that the addition of both HPMC and PVPK90 has marked effect in enhancing the film's elastic properties such as elongation and tensile strength. Folding endurance and tensile strength were found to be 341± 1.4, 9.6 ± 0.4 respectively for batch F4. The batch F10 produced film with a folding endurance of 345±1.8 and tensile strength of 8.7±0.1, these values were found to be relatively higher than other batches prepared through the combination of PVPK30 and chitosan alone. But the addition of both HPMC and PVPK90 has no distinct effect on the bioadhesive strength of film at the particular selected concentrations. The combination of PVPK30 at a conc. of 0.6%w/v and 1% of chitosan produces a film with maximum swelling index and better bioadhesive strength

Table-6 Physical characteristics of patch of Chitosan with PVPK30 HPMC & PVPK90

Formulation code	F9	F10	F11	F12
Appearance	Smooth	Smooth	Smooth	Smooth
Texture	Flexible	Flexible	Flexible	Flexible
Folding Endurance	310±2.1	345± 1.8	330±1.4	320 ±2.8
Swelling-index After 5 hrs	78.9± 0.2	84.6± 0.1	80±0.1	81.3±0.2
Average Weight(mg)	7± 0.2	7.2± 0.4	6.8±0.3	7.1± 0.3
Thickness(mm)	0.04 ±0.1	0.038 ±0.2	0.04± 0.2 1	0.036±0.2
Surface pH	6.9±0.18	7±0.88	7.1±0.2	7.2 ±0.24

N=3 average of 3 determinations ± Standard deviation

Table-7 Mechanical & bioadhesive strength of buccal patch with various combinations of polymers

Batch code	Tensile strength Kg/cm^2	Percentage Elongation at break	Bioadhesive strength gm/cm^2
F1	4.1±0.1	4±0.2	9.8±1.1
F2	4.4 ±0.4	6±0.3	9.6±0.8
F3	5.6±0.2	4±0.1	9.2±0.6
F4	6.4±0.2	9±0.3	10.8±0.8
F5	9.6±0.3	10±0.2	8.7 ±0.2
F6	4.2±0.2	8±0.4	8.4±1.2
F7	6 ±0.1	7±0.2	8.6±0.6
F8	6 ±0.6	6± 0.1	8.2±0.4
F9	4.4 ±0.4	6±0.3	9.2±0.8
F10	8.7±0.1	12±0.2	10.2 ±0.6
F11	5.1 ± 0.2	8±0.2	9.4 ±0.2
F12	5.2 ±0.3	7±0.6	9.8 ±0.4

N= 3 average of 3 determinations ± Standard deviation

CONCLUSION

Overall results of our investigation reveals that the combination of PVPK30 at a concentration of 0.6% with 1% concentration of chitosan is found to be effective in producing film with better bioadhesiveness, and further addition of 0.2% of HPMC with 0.4% PVPK90 to that was found to enhance its elastic properties without having any added effect on its bioadhesive strength. It may be concluded that for formulation of buccal film with desirable mechanical and physical characteristics, the selection of combination of polymers and optimization of their concentration must be prudent in turn it may influence the film's drug loading, *in vitro* and in vivo performances.

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