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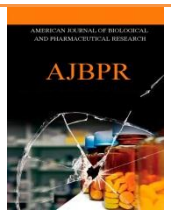

FORMULATION AND EVALUATION OF IBUPROFEN BUCCAL PATCHES USING DIFFERENT POLYMERS

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ABSTRACT

The aim of the study is to formulate buccal patch to maintain the site specific concentration of ibuprofen thereby to reduce the cost of therapy and to improve patient compliance. Buccal patch thickness in between 0.11-0.13 mm was prepared by solvent casting technique. Physicochemical evaluations such as weight uniformity (8.68-8.78 mg) folding endurance (270 to 290 times), drug content (87.42- 92.60%), swelling index (13.2 to 27.5), surface pH of the films were determined. The patches were prepared using three different combinations: Chitosan-HPMC, Chitosan - Gelatin, Chitosan-PVA incorporating ibuprofen as the drug. From different polymer combinations ibuprofen incorporated chitosan gelatin combination show a sustain release upto a maximum of 93.16% in 8 hrs. The optimized formulation subjected to microbiological analysis for confirmation of activity against *S.aureus.* It can be concluded that the buccal patches can be helpful for effective management of oral hygiene with sustained and localized release of ibuprofen.

INTRODUCTION

Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery. Oral route is perhaps the most preferred for the patients. Within the oral mucosal cavity, the buccal region offers an attractive route of administration for a systemic drug delivery. A buccal route of drug delivery offers distinct advantages over oral administration for systemic drug delivery [1]. These advantages include possible bypass of first pass effect, avoidance of pre systemic elimination within the GI tract, these factors make the oral mucosal cavity as very attractive and feasible site for systemic drug delivery [2]. The buccal film was designed particularly for anti-inflammatory and analgesic therapies in the oral cavity. The advantage resides on the reduction of drug dose because of its localization in the inflammatory process site. The advantages of buccal patches include: the drug gains direct entry into the systemic circulation thereby bypassing the first pass effect the area of buccal membrane is sufficiently large to allow a delivery system to good accessibility to the membranes that lying the oral cavity control the period of administration better patient compliance. One particular problem that is common to many drug delivery systems is the short residence time at the site of application. This problem may be resolved by using bioadhesive polymers [3] i.e. polymers that exhibit characteristic adhesive interaction with biological membrane. Buccal patches can be prepared either by solvent casting or direct milling method. Polymer combinations are tried in this work to increase the effectiveness of buccal patches. Chitosan is a deacetylated chitin derivative containing amino sugar used as a component of mucoadhesive forms [4]. HPMC is used as a binder in film coating and extended release matrix. Polyvinyl alcohol (PVA) is a water soluble used in multiples studies especially in membrane technology [4].

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Gelatin is soluble and used in the preparation of bacteriological culture medium, gelatin film. Administration of drug along with polymer combination will improve the disease management. Here ibuprofen is used as the drug and it have analgesic, antipyretic and anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2. It is available in 200-800 mg dose as ibuprofen tablets, gels and infusions [6].In this study, a new buccal formulation of ibuprofen was prepared to treat buccal infections and ulcers with a sustained action over 8 hrs.

MATERIALS AND METHODS

Materials

Ibuprofen, Poly vinyl alcohol, Mueller Hinton Agar Medium were purchased from Hi Media Laboratories, Mumbai. Chitosan (polymer) was gifted by Kerala state co-operative fed for fisheries development ltd. Alappuzha. Hydroxy propyl methyl cellulose, Methanol, Glacial acetic acid, Sodium hydroxide, pH paper, Potassium dihydrogen phosphate were purchased from Spectrum chemicals, Ernakulam. Gelatin and propylene glycol obtained from Nice chemicals Pvt. Ltd. Cochin. All other reagents used are of high purity.

METHODS

Preparation of Ibuprofen Buccal Patches

Ibuprofen buccal patch were prepared by solvent casting technique. Different polymers are used to get good controlled release of drug. Acetic acid solution 1.5% was prepared in which weighed quantity of chitosan was properly dissolved. The solution was filtered through muslin cloth to remove debris. Polymers are added at different ratios to get different combinations of patches. Propylene glycol was added as plasticizer. The polymers were weighed accurately and dissolved properly. 5% propylene glycol was added. Required quantity of ibuprofen was added and stirred well for uniform mixing. This polymeric solution was kept overnight to remove air bubbles, and then it was added uniformly to a petri plate. The plate was then kept in an oven at 45ºC for 24 hrs. After drying the film was peeled off with a sharp blade and kept in a self- sealed cover.

Various patches of ibuprofen were prepared by solvent casting method. 800 mg of ibuprofen was loaded in patches and various combinations were tried to get patches which have excellent characteristics, 800 mg of ibuprofen was loaded to glacial acetic acid solution which containing chitosan as one of the polymers are added and 0.2 ml of glycerine (as plasticizer). After the drug got dissolved, the polymer solutions was poured into petri dishes having area of 70cm^2 and allowed to dry for three days by placing an inverted funnel over it. After that the dried films were peeled off and cut into pieces of 1×1cm^2 patches, stored it and further used for evaluations.

EVALUATION STUDY

Uniformity of Weight

Three patches of the size 1 cm diameter were weighed individually using digital balance and the average weights were calculated [7].

Thickness

The thickness of patches were determined by selecting randomly patches and using screw gauge, the patch was measured at three different places and mean value was calculated.

Folding Endurance

The folding endurance was determined by repeatedly folding the patch at the same place until it broke. The number of times the patch could be folded at the same place without breaking was consider as folding endurance value [8].

Swelling index

A piece of 1 cm² size were cut out from the prepared patches and kept in a petri dish containing 50ml phosphate buffer pH 6.8. The weight is taken at 0, 15, 30, 45, 60, 75, 90, 100&120 minutes.

From that determine the swelling index.

Swelling index = $(w_2-w_1)/w_1$ x100

Where SI is percent swelling, w_2 is the swollen patch weight, w_1 is the initial weight of patch.

Surface pH

Buccal patches were left swell for 1 hr on the surface of agar plate, the agar plate prepared by dissolving 2% w/v agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and the solution was poured into the petri dish .It was 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 swollen patch.

Drug Content

The drug contents in the buccal patches were determined by dissolving 1cm² patch in 100ml phosphate buffer (pH 6.8) and shaken vigorously for 24 hours at room temperature. These solutions were filtered through filter paper. After proper dilution, the amount of drug present in per patch was determined by using UV spectrometer at 265nm against blank.

Tensile Strength

It 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.

Instrument

The instrumentation is modification of chemical

balance. One pan of the balance was replaced with one metallic plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the right pan. The instrument is modified in such a way that patch can be fixed up between two hooks of horizontal beams to hold the rest film. A film of 2.5 cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan.

Tensile strength, $T = \frac{M \times g}{B \times t}$ Dynes /cm^2

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

***In-vitro* Dissolution study**

The *in-vitro* release study was carried out by using IP dissolution apparatus type 2(basket) in 400ml phosphate buffer at pH 6.8 at 100rpm 37±0.5ºC.A 2x2 cm patch was taken and attached to a glass slide inorder to prevent floating over the dissolution media. The *in-vitro* release study was carried out for 8 hours. 5ml sample was withdrawn at various time intervals, replacing with fresh medium each interval, absorbance of the sample were measured at 265 nm, and the cumulative % release was calculated.

***In-vitro* diffusion study**

In-vitro drug diffusion study was carried out by using Franz diffusion cell. In this pre-hydrated cellophane membrane is used as the model membrane. The membrane was placed between the donor compartment and the reservoir compartment (phosphate buffer pH 6.8).The patch was placed on the membrane and the compartments clamped together. The receptor compartment (20 ml capacity) was filled with phosphate buffer pH 6.8 and hydrodynamics in the receptor compartment was maintained by stirring with magnetic bead at 100 rpm.1 ml of sample is withdrawn and replaced with receptor medium. 1ml sample was diluted up to 100 ml with phosphate buffer pH 6.8 to get concentration in between 2-20 µg/ml and assayed spectrophotometrically at 265 nm and amount of drug diffused at various time intervals was calculated [9].

Microbiological Analysis

Microbiological analysis of Ibuprofen was performed by agar diffusion method based on comparison between the growth inhibition zones produced by standard solutions and those produced by test samples. For the microbiological assay of Ibuprofen, the medium used is Mueller Hinton agar medium and the organism used is *S. aureus*.

Agar diffusion assay

Agar diffusion assay was done by surface spread method using petri dishes 9 -10 cm in diameter. Inoculated *S. aureus* into Mueller Hinton agar medium .Added 50 ml of medium at 37°C to petri dishes and allowed to solidify. Then wells were obtained with help of cork borer and 50 µl of ibuprofen in methanol solution used as standard and various ibuprofen loaded polymer combinations were placed in wells. Leave the dishes for 1-4 hours at room temperature as a period of pre incubation diffusion to minimize the effects of variation in time between the applications of different solutions. Incubated the petri plates for 24 hr and measured the diameter or area of the circular inhibition zone and calculated the result. To compare the product efficacy an ibuprofen suspension MIC also compared with the standard.

RESULTS

The prime objective of the work was to investigate the feasibility of ibuprofen polymer combinations were prepared from chitosan, gelatin, HPMC and PVA for buccal cavity.

Identification by FTIR spectroscopy

IR spectrum of Ibuprofen was compared with the standard spectrum (fig.1) and the sample spectrum (fig.2) showed all the characteristic peaks in the relevant region. So IR spectra verified the authenticity of the procured sample.

Formulation of Ibuprofen Buccal Patches Using Polymer Combinations

Ibuprofen buccal patches with various polymer combinations were prepared by solvent casting method. For that 800 mg of ibuprofen was loaded in various polymer solution, so as to get a concentration of12 mg/cm^2. Biodegradable polymers such as chitosan, HPMC, gelatin, PVA were used as polymers and IB1,IB2,IB3 prepared by incorporating respectively.

Evaluation of Films

Formulated patches were subjected to preliminary evaluation tests. Patches with any imperfections, entrapped air or differing in thickness and weight uniformity were excluded.

Weight uniformity

The weight of various patches was determined as shown in table 2 and variation observed was very low and all the films were within the limits.

Thickness uniformity

All the films have a thickness ranges from 0.11 mm to 0.14mm.The thickness of the films was increased with

increase in polymer concentration. The thickness of the film showed a high value in IB2 formulation.

Folding endurance

Formulations showing folding endurance >200 indicate that films have good physical properties and listed in table 2. The formulation prepared alone with chitosan and HPMC showed least folding endurance and highest in formulation. From the results it was found that chitosan gelatin film was easy to handle and use. Based on folding endurance study, formulations swelling index showing highest folding endurance (IB2) were subjected to other evaluation tests.

Swelling index

Swelling index of the prepared films was performed at 30 min,1,2,3 and 5 hrs. Swelling behavior is an important property for uniform and prolonged release of the drug and effective bioadhesion. The swelling index increases with increase in the concentration of chitosan and gelatin. It ranges from 13.2 to27.5 in table 2.The formulation IB2 has shown maximum swelling index.

Surface pH

The surface pH of the formulations was found to be around 7, which was within the range of buccal pH, hence no irritation was expected and will achieve patient compliance.

Tensile strength

DRUG CONTENT UNIFORMITY

Drug content of all the formulations were determined by using UV spectrophotometer at 265 nm. The drug was uniformly distributed throughout the films within the limits. The batch showed a high drug content of 92.60%.

***In-vitro* DIFFUSION STUDIES**

In-vitro diffusion studies were performed to ensure the release of drug from the patches and its permeation into buccal cavity. *In-vitro* diffusion studies of all drug loaded batches were carried out using pH6.8 phosphate buffer as the medium. The buccal patches produced a sustained release in its formulations. Maximum diffusion was found to be 92.44% with IB2 formulation and minimum of 83.16%with IB1 formulation.

***In-vitro* drug dissolution studies**

In-vitro dissolution studies were performed to ensure the dissolution of film and the release of ibuprofen in buccal cavity. Formulation prepared with chitosan and gelatin has shown of 93.16% drug dissolution in 8hrs. *In-vitro* drug dissolution studies has showed that formulation chitosan with gelatin has maximum *in-vitro* drug dissolution rate of 93.16% (Table 6). Hence based on *in-vitro* drug diffusion and drug dissolution studies formulation IB2 has shown maximum drug release and drug dissolution.

Microbiological analysis

Formulation prepared with chitosan gelatin, chitosan PVA and chitosan HPMC respectively having 12mg/cm^2 dose of ibuprofen were subjected to microbiological analysis. The zone of inhibition obtained by various ibuprofen combinations were determined in gram positive organism and compared with ibuprofen standard. It was found that chitosan gelatin ibuprofen loaded patch have similar zone diameter as those of ibuprofen standard

C- IBUPROFEN STANDARD

Also found that ibuprofen chitosan gelatin patch have similar zone diameter as that of ibuprofen marketed suspension. Moreover the presence of chitosan in all formulations can also contribute to prevent the development of mycoses because it inhibits Candida adhesion to buccal mucosa.

Table 1. Composition of Ibuprofen Buccal Patch

S. No	Ingredients	IB1	IB2	IB3
1	Drug(Ibuprofen) mg	800	800	800
2	Chitosan (%)	1	1	1
3	Hydroxyl propyl methyl cellulose (%)	0.8	---	---
4	Gelatin (%)	---	10	---
5	Polyvinyl alcohol (%)	---	---	0.8
6	Propylene glycol(ml)	5	5	5
7	Ethanol(ml)	10	10	10

Table 2. Evaluation data of formulations

Formulation code	IB1	IB2	IB3
Appearance	Smooth	Smooth	Smooth
Texture	Less flexible	Flexible	Flexible

Folding endurance	270	290	274
Swelling index	13.2	27.5	22.2
Thickness(mm)	0.13	0.14	0.11
Surface pH	7	7	7
Weight uniformity(mg)	8.68	8.78	8.73

Table 3. Tensile strength of the formulations

Batch	IB1	IB2	IB3
Elongation at break (%)	18%	32%	30%
Tensile strength (N/m^2)	1.6×10^3	3.2×10^3	2.6×10^3

The tensile strength is in the range of 1.6 to 3.2 [N/m2]. The percentage elongation was at the range of 10 to 30%.

Table 4. Drug content uniformity of the formulations

BATCH	% DRUG CONTENT[%]
IB1	87.42
IB2	92.60
IB3	88.68

Drug content of all the formulations were determined by using UV spectrophotometer at 265 nm. The drug was uniformly distributed throughout the films within the limits. The batch showed a high drug content of 92.60%.

Table 5. *In-vitro* drug release of batches

Time (hr)	IB1 %CDR*	IB2 %CDR*	IB3 %CDR*
0	**0**	**0**	**0**
0.5	7.25	3.33	3.78
1.0	12.22	12.26	5.88
2.0	24.33	18.43	17.89
3.0	41.24	37.94	29.70
4.0	56.23	55.66	51.43
5.0	71.32	73.27	71.26
6.0	78.23	83.54	76.22
8.0	83.16	92.44	85.32

Table 6. *In-vitro* drug dissolution of batches

Time(hr)	F1%CDR	F2%CDR	F3%CDR
0.5	15.30	16.32	15.49
1.0	23.38	28.25	24.65
2.0	30.45	33.45	32.52
3.0	48.56	49.56	49.55
4.0	57.10	63.25	59.12
5.0	62.26	72.16	63.85
6.0	78.15	84.29	72.43
8.0	82.18	93.16	84.22

Fig 1. FTIR-Ibuprofen

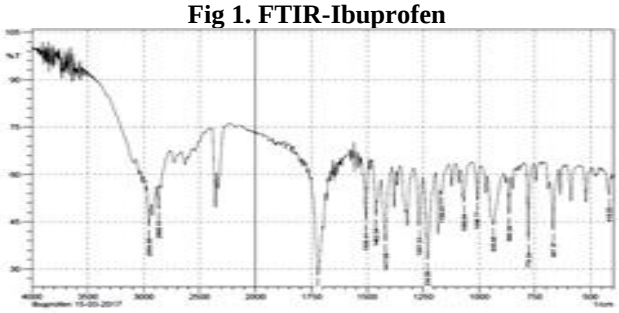


Fig 2. FTIR-Ibuprofen chitosan gelatin combination

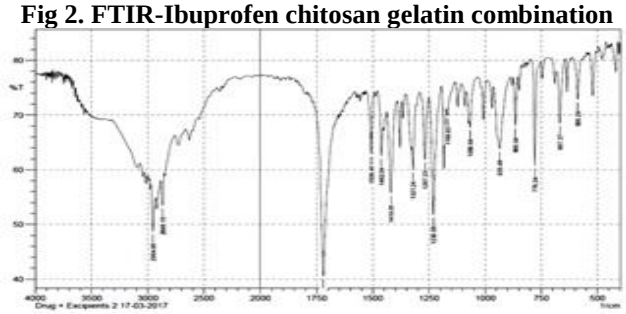
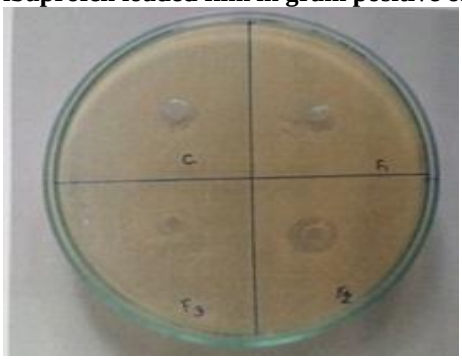


Fig 3. Antimicrobial activity of various ibuprofen loaded film in gram positive organisms



F1-Chitosan HPMC Ibuprofen patch
F2-Chitosan Gelatin Ibuprofen patch
F3–Chitosan PVA Ibuprofen patch

SUMMARY AND CONCLUSION

Localised treatment of oral diseases with buccal patches seems to be a promising alternative among the novel drug delivery systems with number of advantages in terms of accessibility, site specific delivery, economy and high patient compliance. In the last decade, localized targeted delivery system achieved immense advancements.

IR spectra of ibuprofen together with polymers indicated no interaction between ibuprofen and all the three selected combinations. Three different polymer combinations of ibuprofen patches were prepared by solvent casting method.

Physicochemical evaluations of all the three formulations showed satisfactory end up in weight uniformity, thickness uniformity, drug content, folding endurance, swelling index, surface pH etc.

The cumulative drug release data show sustained release of drug upto a maximum of 93.16% in 8 hours. The optimized formulation subjected to microbiological analysis for confirmation of its activity against *S.aureus*.

From the study, it is evident that the polymer combination patches of ibuprofen should deliver the drug in the buccal cavity to maintain the site specific concentration of drug to achieve minimum inhibitory concentration. Developing such a system should improve patient compliance with improved buccal activity. The cost of the therapy can be significantly reduced. *In-vivo* studies have to be performed to confirm the *in-vitro* data. Thus it can be concluded that the buccal patches can be helpful for the effective management of oral hygiene with sustained and localized release of ibuprofen.

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Nil

CONFLICT OF INTEREST

No interest

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