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Buccal Patches with Combination drugs: Tramadol and Paracetamol

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ABSTRACT

Aim Present study aims at preparation and evaluation of buccal patches for combination drugs for Paracetamol and tramadol which are used in pain management. The patches were developed by using HPMC, Carbopol as polymers. Such dosage forms helps in repeated administration of dosage forms and patient acceptance.

Method Buccal Patches of combination drugs Paracetamol and Tramadol were prepared by using Solvent casting method using HPMC and Carbopol as polymers individually and in combination. The patches were developed along with different plasticizers to understand their effect too. The prepared patches were evaluated for folding endurance, swelling index, surface pH, weight variation, thickness, drug content and Invitro release by dissolution studies.

Results The patches were developed as F1 to F14 with different compositions. All the physical parameters were found to be at par with standard values. Among these formulations F1, F9, F13 and F14 were selected for evaluation tests for different reasons. FTIR also says that polymer and drugs were compatible with each other.

Conclusion form the results obtained it was evident that the patches for the above said drugs i.e. Paracetmol and tramadol will be promising dosage form in pain management and among the all the formulations the drug release from formulation F14 was promising as the release was slow and sustained manner. Further the patches have to be tested for optimization and bioadhesive tests.

Key words: Paracetamol, Tramadol, Buccal Patches, HPMC, Carbopol, Mucoadhesive Patches.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit the oral administration of certain classes of drugs especially peptides and proteins [1].

The Parenteral route is not routinely used for self-administration of medication. Consequently, other absorptive mucosa is considered as potential sites for

drug administration. Transmucosal routes of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular and oral cavity) offer distinct advantages over per oral administration for systematic drug delivery. These advantages include possible by pass of first pass effect, avoidance of pre-systemic elimination within the G.I. tract, and depending on the particular drugs, a better enzymatic flora for drug absorption.

The nasal cavity as a site for systemic drug delivery, however, the potential irritation and the irreversible

damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms, as well as the large intra- and inter-subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal and ocular mucosa all offer certain advantages, the poor patient acceptability associated with these sites render them reserved for local application rather than systemic drug administration [2, 3].

The oral cavity on the other hand is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage and the virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens. The oral mucosal drug delivery systems can be localized easily and well accepted by patients. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectables and enterable methods. Difficulty is experienced in particular by pediatrics and geriatric patients, but it also applies to people who are ill bedridden and to those active working patient who are busy or travelling, especially those who have no access to water. In these cases oral mucosal drug delivery is most preferred.

The total surface of the oral cavity is about 100 cm. The mucosal membranes of the oral cavity can be divided into five regions such as the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingival), palatal mucosa, and the lining of the lips [3, 4]. These oral mucosal regions are different from each other in terms of anatomy, permeability to drug, and their ability to retain a system for a desired length of time. Although the buccal mucosa is less permeable than the sublingual mucosa and it does not yield a rapid onset of action as seen with sublingual delivery, mucosa of the buccal area has an expanse of smooth and relatively immobile surface, which is suitable for placement of retentive system. These characteristics make the buccal mucosa a more appropriate site for prolonged systemic delivery of drugs.

The present investigation deals with the formulation of buccal patches with combination of drugs i.e. Paracetamol and tramadol by using polymers like HPMC and Carbopol. The prepared patches were evaluated for Weight variation, folding endurance, thickness, dissolution test, drug content, swelling index and surface P^H and understanding compatibility between drug and polymers.

MATERIALS AND METHODS

Paracetamol and Tramadol were obtained as gift sample from Sun Pharma Ltd, Mumbai. HPMC and Carbopol were purchased from HIMEDIA, Mumbai. The other chemicals and reagents were of analytical grade.

Compatibility Studies by FTIR

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepared were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra.

Preparation of Buccal patches

Buccal patches were formulated by initially preparing a polymer solution. Accurately weighed amount of drugs i.e. tramadol and paracetamol (1:10) were dispersed in the polymer solution. This was followed by adding plasticizer (glycerin or Propylene glycol). The mixture was then subjected to magnetic stirring for 45 minutes for getting a lumps free viscous liquid. After 45 minutes it was given sufficient time to remove the entrapped air. The viscous mixture was then poured in to petridishes and allowed to dry. Drying rate was controlled by placing an inverted glass funnel on petridish [9]. After complete drying the patches were removed and cut into 2 X 2 patches. The buccal patches were supported by backing layer which was again prepared in two formulations. One with ethyl cellulose and other was with Poly vinyl pyrrolidone in alcohol. Dummy patches were also prepared i.e. without drug. The compositions of patches were tabulated in Table. 1.

Preparation of backing membrane

The backing membrane was prepared by dissolving 200mg of ethyl cellulose in 10ml of ethanol and mixed well. 1ml of glycerin was added then and mixed well. The solution was kept aside for overnight and dried films were collected. It is also prepared by using another polymer Poly vinyl pyrrolidone [5].

Characterization of Buccal Patches

Weight of Patch

All the patches of different formulations were cut into 2cm x 2cm square and weighed individually [7].

Folding Endurance

The patches of selected formulations were folded at a particular area till they break. The number of times a patch can be folded at same place before breaking was taken as its folding endurance. All patches were tested for 3 times and average was reported [8].

Thickness

The thicknesses of selected patches were measured of three different spots on a single patch and average was calculated [6].

Swelling Index

The studies on swelling rate in terms of weight were conducted on selected patches, formulations up to 30min and the results were noted [6,7].

Table 1: Composition of Buccal patches.

Sl.no	Tramadol (mg)	Paracetamol (mg)	Ethanol (ml)	HPMC (mg)	Carbopol (mg)	Glycerin (mg)	Propylene glycol	PVP (mg)
F1	10	100	12	400	-	5%	-	-
F2	10	100	12	200	-	5%	-	-
F3	10	100	12	100	-	5%	-	-
F4	10	100	12	200	200	5%	-	-
F5	10	100	12	100	100	5%	-	-
F6	10	100	12	50	50	5%	-	-
F7	10	100	12	300	-	5%	-	-
F8	10	100	12	150	150	5%	-	-
F9	10	100	12	400	-	-	5%	-
F10	10	100	12	300	-	-	5%	-
F11	10	100	12	200	-	-	5%	-
F12	10	100	12	100	-	-	5%	-
F13	10	100	12	400	-	5%	-	100
F14	10	100	12	400	-	-	5%	100

Surface pH

The selected patches were placed in phosphate buffer pH 6.8 and pH was checked by placed the pH paper on surface of the patch [8].

Drug Content

Drug content in the patches was determined by suitably diluting after crushing the total patch in phosphate buffer pH 6.8. A dummy patch (without drug) of some formulation was also treated in the same manner to get blank. The drug content was tested on selected patches and average was calculated [9, 10].

In Vitro Drug Release

The selected patches were undergoes to measure the drug release by using USP rotating basket method of dissolution apparatus. And the samples of different time intervals 5, 10, 15, 20, 30, 40, 50 and 60min were analyzed after dilution by UV spectrophotometer at 248nm & 273nm for paracetamol and tramadol respectively [12].

RESULTS AND DISCUSSION**Fourier Transform Infrared Spectrophotometry**

By observing the IR spectra of pure drug and the all physical mixtures of drug and polymers, it was found that none of the above mentioned groups were affected by those polymers. Thus it can be said that there was no interaction between the drug and any of the polymers. The FTIR spectra's of pure drug and physical mixture of drug and excipients are shown in Figures 1-3.

Weight of Patch

All the patches of different formulations were cut into 2cm x 2cm square and weighed. The average weight of

patches was in between 0.027 to 0.056 gms. The individual weights are shown in Table 2.

Folding Endurance

The patches of selected formulations were folded at a particular area till they break and noted as folding endurance. The results are shown in Table 2.

Thickness

The thickness of patches was measured of three different spots on a single patch by screw gauge and average was found to be as thickness. The results are shown in Table 2.

Table 2: Weight, thickness and folding endurance of the buccal patches

Formulation	Weight of the patch	Folding endurance	Thickness
F1	0.045	132.33	0.6
F9	0.027	162	0.566
F13	0.056	147.66	0.633
F14	0.037	144	0.33

Swelling Index

The studies on swelling rate in terms of weight were conducted on selected patches, formulations up to 30min.

Surface pH

The pH of surface patches was determined by pH paper. The patches were placed in phosphate buffer pH 6.8 and pH was checked and found that all the patches have pH nearly neutral.

Figure. 1: FTIR Spectra of Pure Drug.

Figure 2: FTIR Spectra of Polymer

Figure. 3: FTIR Spectra of formulation

Table. 3: Drug content of selected patches.

Formulations	Tramadol (mg)	% Release	Paracetamol (mg)	% Release
F1	0.083	92.2	0.91	101.1
F9	0.087	96.6	0.89	98.8
F13	0.081	90	0.80	88.8
F14	0.084	93.3	0.89	98.8

Drug Content

Drug content in the patches was determined by suitably diluting after crushing the total patch in phosphate buffer pH 6.8. A dummy patch (without drug) of same formulation was also treated in the same manner to get blank. The drug content was tested on selected patches and average was tabled in Table 3.

Dissolution studies

The formulations selected were F1, F9, F13, and F14. The buccal patch of F13 was heavier than other formulations, which is may be because of presence of PVP as release enhancer. But the folding endurance was more in the buccal patch of F9 because of propylene glycol is responsible for additional strength for the patch. The thickness of the patch F13 was found to be more as it has an additional ingredient i.e. Poly Vinyl Pyrrolidone even though PVP is present in F14 as the composition varies in plasticizer the thickness of F13 was high.

Swelling index was found larger in the patch of F1 which means drug release may be at faster rate than other patches of other formulations. This was also evident from the dissolution studies of the patches. Patch of F1 was exhibiting drug release at faster rate and patch of F14 was found to be releasing drug at slower rate. Drug content of the patches was also found to be encouraging as it ranges from 88.8% to 101.1%. Even the surface pH of all the patches was near to neutral which is very clear that the presence of patch do not generate any irritation to buccal mucosa. The drug release profile of Paracetamol and tramadol were explained in Figures 6 & 7.

SEM Analysis:

The SEM photographs of the Formulation F14 was clearly showing the morphology of the patches given in Figures 4 & 5

Figure. 4: SEM image of Patch F14 (Side view) **Figure. 5:** SEM Image of the Patch F14 (Top View)

Figure. 6: Drug release profile form Selected patches (Tramadol)

Figure. 7: Drug Release profile from selected buccal patches (Paracetamol)

Conclusion

The buccal patches with multiple drugs i.e. tramadol and paracetamol were prepared using hydroxy propyl methyl cellulose and carbopol as polymer. The patches were also formulated with combination of polymers. Two different plasticizers i.e. glycerin and Propylene glycol were also tried to understand their effect. The patches with sufficient thickness i.e. F1, F9, F13 and F14 were selected and evaluated for their characteristics. The selected patches were tested for their weight, thickness, swelling index, folding endurance, surface pH, drug content and dissolution studies and found that weight and amount of drug present was high in F1 but drug dissolution studies reveal that drug release from the patch of F14 was slower and at a sustained rate.

The prepared patches were further tested to understand bioadhesive behavior and further the drug release has to be optimized by understanding the effect of various release enhancers.

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Conflict of interest: None

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