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Formulation and Evaluation of Mucoadhesive Buccal Patches of Resperidone

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ABSTRACT

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal formulations have been developed and are gaining in popularity and medical acceptance. To increase bioavailability and prevent first pass metabolism of drug. Resperidone patches were prepared using HPMC (15 & 47 cps), chitosan, poly vinyl alcohol, poly vinyl pyrrolidone. The patches were evaluated for their thickness, Uniformity content, folding endurance, weight uniformity, Swelling index, tensile strength and surface pH. In vitro loaded studies of resperidone-loaded patches in phosphate buffer(pH 6.6) exhibited drug release in the range of 67.32% to 98.28 in 60 min. Data of in vitro release from patches were fit in to different equations and kinetic models to explain kinetics. The models used were zero and first-order equations, Hixon-crowell, Higuchi and Korsmeyer-peppas models. The in-vitro release study showed that patches could deliver drug to the oral mucosa. The results indicate that the mucoadhesive buccal patches of resperidone may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of resperidone through buccal mucosa.

Key words: Mucoadhesion, Buccal patch, swelling study, buccal delivery, Resperidone.

INTRODUCTION

Buccal mucosa is an attractive route for systemic delivery of drugs since it is relatively permeable with a rich blood supply. (1) A drug can be easily applied and localized to the application site, and can be removed from there if necessary. Attempt has been made earlier to formulate various mucoadhesive buccal devices, including tablets (2), films (3), patches (4), disks (5), strips (6), ointments (7) and gels (8). Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Patches also ensure more accurate dosing of the drug compared to gels and ointments.

During the last decade, bioadhesive polymers received considerable attention as platforms for buccal controlled delivery due to their ability to localize the dosage form in specific regions to enhance drug bioavailability. Delivery of drug through buccal mucosa overcomes premature drug degradation within GI tract, as well as active drug loss due to the first pass metabolism, and inconvenience of parenterals administration. In addition, there is excellent acceptability and the drug can be applied localized, and may be removed easily at any time during the treatment period. A few drugs such as metoprolol tatarate, ibuprofen, sulbotamol sulphate, diltiazem hydrochloride, isosorbide dinitrate have been successfully administered via the buccal route.

Risperidone, a benzisoxazole derivative, is a novel antipsychotic drug which binds with high affinity to the serotonin type 2 (5-HT₂), dopamine D₂, and α 1-adrenergic receptors. Risperidone binds with a lower affinity to the α 2-adrenergic and histamine H₁ receptors. Risperidone does not bind to dopamine D₁ or muscarinic cholinergic receptors. Though it is rapidly absorbed after oral administration, the bioavailability of risperidone is 40-50% as it undergoes significant first pass metabolism and will be eliminated from body through the urine and feces. The log P value for risperidone has sufficient lipophilicity to pass through the buccal membranes. The t_{max} of risperidone is 3 hr by peroral route which is long and variable. The minimum dose of risperidone is 1 mg/day. By observing the above points, it is inferred that risperidone has need to formulate into buccal patches and the drug is suitable for it.

EXPERIMENTAL SECTION

Materials

Risperidone was a gift sample (Madras Pharmaceutical Ltd, Chennai), Chitosan, HPMC (15 & 47 cps) were obtained from Cadila Health care Ltd., Ahmadabad, India, PVA, PVP were obtained from S.D. Fine Chemicals Ltd,(Mumbai, India). Other chemicals were used of analytical grade and procedure S.D. Fine Chemicals (Mumbai, India)

Methods

Preparation of patches

Buccal mucoadhesive patches were prepared using polymer or polymers blends along with the drug and a suitable solvent. The buccal mucoadhesive films of risperidone were prepared using HPMC 47cps and HPMC 15 cps polymers by casting method. HPMC polymer (200 mg) was weighed accurately and placed in 3 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then the 3 drops (0.0882g) of glycerin were added to the polymer solution. Risperidone (10 mg) was weighed and dissolved in 3 m of ethanol and 3 drops of

tween 80 in an another beaker. The drug solution was added to the polymer dispersion. The whole mixture was mixed thoroughly with the help of a magnetic stirrer. The glass mould of size 5 x 3 cm² was placed over a flat surface. The drug-polymer mixture was poured into the glass mould. The mould was kept in hot air oven for 1 hour at 50°C for drying and sudden evaporation. After this period, an inverted funnel was placed over the mould overnight to remove the remaining solvent; the film was removed from the mould, packed in wax paper, and stored on a desiccators. Similarly film-II was prepared.

For preparing films-III and IV, PVA was dissolved in 6 ml water. For preparing film-V, Chitosan was placed in 5 ml of water followed by stirring for 60 min and HPMC was dissolved in 4 ml of ethanol. The two polymeric solutions were mixed. For preparing film IV, PVA and PVP were dissolved in hot water. The remaining procedure was same as explained earlier. Similarly, dummy patches were prepared without adding drug. Table 1 shows the composition of all repared patches.

Table1. Composition of different buccal mucoadhesive formulations containing Resperidone

Ingredients	Formulations				
	I	II	III	IV	V
Resperidone	10	10	10	10	10
HPMC(47cps),mg	-	200	-	-	-
HPMC(15cps),mg	200	-	-	-	150
PVA, mg	-	-	500	450	-
Chitosan, mg	-	-	-	-	50
PVP K30, mg	-	-	-	150	-
Glycerin ,mg	86.2	86.2	86.2	86.2	86.2
Ethanol, ml	7	7	4	4	4
Tween 80 , mg	33.5	33.5	33.5	33.5	33.5
Hot water , ml	-	-	6	6	6

Evaluation of the Patches

Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight or content uniformity were excluded from further studies.

Thickness

The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which is considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on all the patches for five times.

Uniformity of weight of the patches

Patches sizes of 1x1 cm² were cut. The weights of five patches were taken using Shimadzu balance of sensitivity 0.0001g (Shimadzu, Tokyo, Japan) and the weight calculated.

Drug content uniformity of the patches

The patches were tested for the content uniformity. A patch size 1x1 cm² was cut and placed in a beaker. Ten ml of a 0.1N hydrochloride acid solution was added. The contents were stirred in a cyclo-mixer to dissolve the film. The contents were transferred in to a volumetric flask (10 ml). The absorbance of the solution at 280 nm using UV-VIS spectrometer (UV-1601, Shimadzu Corporation, Tokyo, Japan).

Swelling percentage study

Swelling study of prepared buccal patch was calculated by function of weight and area increase due to swelling, which was measured for each formulation as follows.

Weight increase due to swelling:

A patch of 10 mm size (1 x 1 cm²) diameter from every batch was weighed on a preweighed cover slip. It was kept in a petridish and 10 ml of phosphate buffer, pH 6.6 was added. After one hour, the cover slip was removed and weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

Area increase due to swelling: similarly patch of 10 mm diameter from each batch was place on cover slip and this cover slip was placed in a petridish. Ten ml of phosphate buffer, pH 6.6, was poured into the petridish. A calibrated measuring scale was used to measure the increase in the area of each patch. An increase in the area in diameter of the patch was noted at one hour intervals for 6 hour and the area was calculated. The percentage weight and area swelling ratios was calculated from the average of three measurements using the following equation:

$$\% S = (X_t - X_o / X_o) / 100$$

Where,

X_t - weight or area of the swollen patch after time t

X_o - is the original patch weight or area at zero time.

Tensile strength

A tensile strength study of patch is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of Plexiglas's. The one plate is in front and is movable part of device and can be pulled by loading weights on the string, which is connected to movable part. The 1x1 cm² buccal patch equivalent to 50 mg drug from each formulation was fixed between the stationary and movable plate. The force needed to fracture the film was determined by measuring the total weight loaded in the string. The weight corresponds to break the patches were taken as tensile strength and the values were shown in table 2. The following equation was used to calculate the tensile strength (TS)

TS (g/cm²) = Force at break (g) / Initial cross sectional area of patch.

Surface pH study

The surface pH of the buccal patches was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The buccal patch was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 hour at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate, and average values were reported.

***In vitro* release studies of resperidone patches in phosphate buffer (pH 6.6)**

A patch of 3x 2.5 cm² size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.6). This slide was kept at an angle of 45°C in a 250 ml beaker containing 100 ml of phosphate buffer (pH 6.6) solution. The beaker was kept in circulating water bath in which temperature was maintained 37°C. A non-agitated system was selected to eliminate any effect of turbulence on the release rate. Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool. The slide was quickly reintroduced into a beaker. Five ml of the buffer was replaced immediately and the beaker was kept covered with a petridish to prevent evaporation of the fluid. The samples were taken after every 5 min and analyzed for the drug content after necessary dilution with phosphate buffer (pH 6.6) at 280 nm. The release studies were conducted for six times and average was determined.

RESULTS AND DISCUSSION**Drug Estimation**

Calibration curves of resperidone in 0.1 N HCl and phosphate buffer (pH 6.6) solutions were constructed at λ_{\max} 280 nm with a UV-VIS spectrometer (UV-1601, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 10-60 µg/ml. Analysis was done in triplicate.

Evaluation of Patches

Thickness: All the patches have uniform thickness throughout. Standard deviation of all the patches ranged from 0.0062 to 0.0421.

Weight uniformity: Drug loaded patches (1x1 cm²) were tested for uniformity of weight. The patches were found uniform. Standard deviation of the patches ranged from 0.02844-0.04638.

Folding endurance: Films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when comparison was made between dummy films and drug loaded films.

Tensile strength: The tensile strength of drug loaded patches were higher than dummy patches (table-2). This is justified because dissolved resperidone strengthened the bonding of polymer chains. The tensile strength of patches were in order of V < I < II < IV < III. This indicates PVA produces effective cross linking and higher viscosity supports these results.

Surface pH: The surface pH of all formulations was the neutral pH and hence no mucosal irritation was expected and ultimately achieved patient compliance.

In vitro release: The release data of resperidone from all the patches were given in Fig.1. It indicates that the drug release was highest in HPMC and HPMC-chitosan combinations. Data of the in vitro release were fit into different equations and kinetic models to explain the release kinetics of resperidone from the buccal patches. The release kinetics resperidone followed zero order from all the patches I to V. The better fit was observed in case of Higuchi's model than Hixon-crowel model except patch-I. Hence mechanism of drug release from the resperidone patches II to V followed are diffusion controlled and drug release from patch-I followed dissolution controlled.

Table 2: Characteristics of buccal mucoadhesive patches containing resperidone

Formulations	Thickness (mm)	Swelling		Tensile strength		Weight Uniformity (mg)	Content Uniformity	Folding endurance
		% Weight Increase After 30 min	% Area Increase After 30 min	Dummy patches	Drug Loaded patches			
I	0.213	769.21	37.91	3.412	4.213	13.73	85.07	>300
II	0.195	771.44	59.41	3.685	4.341	13.45	89.12	>300
III	0.291	362.67	49.35	5.181	5.413	29.17	88.61	>300
IV	0.272	251.17	67.61	4.616	5.213	37.91	87.13	>300
V	0.315	687.36	28.35	3.211	3.790	13.12	88.16	>300

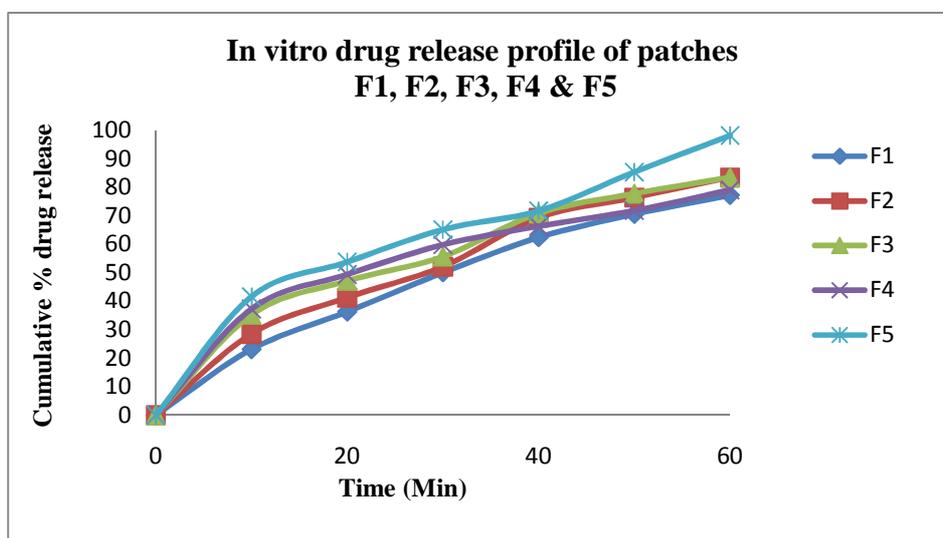


Fig. 1 *In vitro* release of resperidone from patches I to V.

CONCLUSION

It may be concluded that mucoadhesive patches for oral cavity are a promising drug delivery system for resperidone. The combination of polymers, Chitosan and HPMC showed good mucoadhesive and swelling characteristics. Medicated patches maintained a satisfactory residence in the buccal cavity. Hence the development of bioadhesive buccal formulations for resperidone may be a promising one as the dose of resperidone may be decreased and hence side effects may be reduced.

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