**FORMULATION AND EVALUTION OF FAST DISSOLVING BUCCAL PATCHES OF ACYCLOVIR**

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**ABSTRACT**

Acyclovir is a anti-retroviral agent. It is used in the treatment of HIV-1infection. The present work is designed to prepare and evaluate mucoadhesive buccal patches of Acyclovir as a novel form of fast releasing dosage form. Buccal patches of Acyclovir were prepared by solvent casting method. The prepared films were evaluated for the various evaluation parameters like thickness, surface pH, weight uniformity, content uniformity, folding endurance, swelling index, in vitro drug release study. All the formulations exhibited good results for physicochemical characterizations. In In-vitro drug release study, the patches exhibited fast release within 5 hours. The formulation F1 (containing HPMC and croscarmellose) showed no irritant effect on buccal mucosa. It was revealed that Superdisintegrants composition had significant influence on drug release. Thus, conclusion can be made that stable dosage form can be developed for Acyclovir for fast release by buccal patches.

**Keywords:** Fast dissolving Buccal patches, Acyclovir, superdisintegrants, % Cumulative drug release

1. **INTRODUCTION**

Oral route has been the commonly adopted and most convenient route for drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes, ease of administration as well as traditional belief that by oral administration the drug is well absorbed as the food stuffs that are ingested daily [1,2] Rich blood supply, robust nature, short recovery times after stress or damage, lower enzymatic activity of saliva, facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious visages of buccoadhesive systems.

Acyclovir is the most effective antiviral drug against HIV. The oral absorption of acyclovir is dose dependent and highly variable, with bioavailability ranging from 15-30%. Percutaneous absorption of acyclovir is poor. [3] The main drawbacks associated with this drug are gastric irritation, first pass metabolism and low oral bioavailability. Side effects associated with topical application of drug consist of stinging and burning sensation. However, on oral application, the drug is well tolerated. In case of intravenous administration, rashes, sweating and emesis are observed. Therefore, there is a need to formulate an oral delivery system for acyclovir that promotes systemic delivery, bypass of first pass metabolism and improved bioavailability.

The present study is aimed at formulating fast dissolving mucoadhesive Buccal patches loading acyclovir to act as transmucosal drug delivery systems in order to improve oral bioavailability.

1. **MATERIALS AND METHODS**

Acyclovir was purchased from yarrow chemicals Mumbai, Glycerol, HPMC K4M, Croscarmellose, Crospovidone, Sodium Starch Glycolate, Citric acid, Sodium Lauryl Sulphate, Methanol, Ethanol, Chloroform was purchased from SD Fine chem. Ltd. All other materials used and received were of analytical grade.

**Methodology:**

**Drug-polymer-excipient compatibility studies**

This was carried out by infrared light absorption spectroscopy (IR). Infrared spectra of pure drug and mixture of formulations were recorded by dispersion of drug and mixture of formulations in suitable material (KBr) using Fourier Transform Infrared Spectrophotometer (FTIR). A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded on FTIR.

**Method of preparation of patches: [4]**

The mucoadhesive buccal patches were formulated using solvent casting technique. In this method, mucoadhesive polymers in required quantity are treated with solvent and polymer swell after vortexing. The measured quantity of plasticizer added in polymer mixture and again vortexed. The quantity of drug that is needed is liquefied in small volume of solvent system and added to the polymer solution and mixed well. The prepared solution is poured into a Petri dish containing glycerin and allowed to dry for overnight in order to evaporate the solvents. Finally, the patches are collected after drying.

**Table 1: Composition of buccal patches of Acyclovir**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ingredients** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
| Acyclovir (mg) | 50 | 50 | 50 | 50 | 50 | 50 |
| Glycerol(mg) | 200 | 194 | 200 | 194 | 200 | 194 |
| HPMC(mg) | 400 | 400 | 400 | 400 | 400 | 400 |
| Croscarmellose(mg) | 20 | 26 | - | - | - | - |
| Crospovidone(mg) | - | - | 20 | 26 | - | - |
| SSG(mg) | - | - | - | - | 20 | 26 |
| Citric acid (mg) | 6 | 6 | 6 | 6 | 6 | 6 |
| SLS(mg) | 1 | 1 | 1 | 1 | 1 | 1 |
| Orange spirit(mg) | 5 | 5 | 5 | 5 | 5 | 5 |
| Methanol:Ethanol:Chloroform(solvents) | 6:9:12 | 6:9:12 | 6:9:12 | 6:9:12 | 6:9:12 | 6:9:12 |

**Evaluation tests for patches:**

**Weight Variation: [5]**

The patches were cut in the required sizes and weights were calculated individually.

**Thickness: [5]**

The thickness of each patch was measured using thickness tester (screw gauge) at different positions of the film and the average was calculated.

**Moisture Absorption:[6]**

The buccal patches were weighed (w1) and placed in desiccators having anhydrous Aluminium chloride. After 3 days, the patches were reweighed (w2). The % moisture absorption was calculated using

**% Moisture absorption = X 100**

**Moisture Loss: [6]**

The buccal patches were weighed (w1) and placed in desiccators having anhydrous calcium chloride. After 3 days, the patches were reweighed (w2). The % moisture absorption was calculated using

**% Moisture loss = X 100**

**Folding Endurance: [7]**

Folding endurance of the buccal patches was determined by taking 20mmdiameter of patch was repeatedly folding at the same place till it broke. The no oftimes of patch could be folded at the same place without breaking gave the value ofthe folding endurance.

**Drug content uniformity:**

The films were tested for the content uniformity. A film of size 1 cm2 was cut and placed in the beaker containing 100 ml of 6.8 pH phosphate buffer. The films were allowed to dissolve in the solution. The contents were transferred to a volumetric flask. The absorbance of the solution was subjected to spectrophotometric analysis (UV-Visible) to determine absorbance at ƛmax of 252 nm.

**Surface pH: [8]**

For surface pH determination, the patches were left to swell for 2 hours in 6.8 pH phosphate buffer. The surface pH was measured by means of pH paper placed on the surface of the patches. The mean of three readings was recorded.

**Swelling Index:** A drug loaded film of 1 cm2 was weighed and then placed in the 50 ml of 6.8 pH phosphate buffer. After 2 hours the patch was removed and again reweighed. The difference in the final and initial weights gave the results of weight increase due to the absorption of water and swelling of film.

**Swelling index = X 100**

**Disintegration time:** It is an important tool in designing the dosage form. It is the time required for the dosage form to break up into granules of specified size under carefully specified conditions.

**Diffusion Studies:** The prepared patches were cut according the required size and the attached to the open-end glass test tube; it is placed in the beaker containing 6.8 pH phosphate buffer. The beaker is kept on the magnetic stirrer and temperature of 37±0.50 C was maintained. Aliquot amount of samples are withdrawn at an interval of 1 minute and same amount of fresh medium was replaced. The absorbance of the solution was subjected to spectrophotometric analysis (UV-Visible) to determine absorbance at ƛmax of 260 nm.

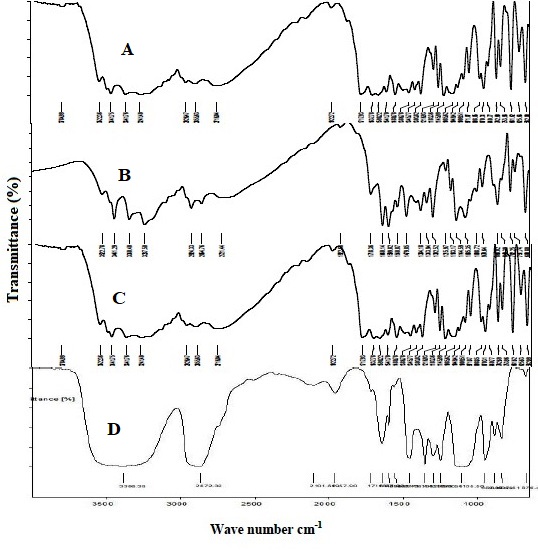
**Kinetic study:**

The matrix systems were reported to follow the zero order release rate and the Diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into, Zero order, First order, Higuchi matrix and peppa’s model. In this by comparing the r2 Values obtained, the best fit model was selected.

1. **RESULTS AND DISCUSSION**

**Drug polymer compatibility studies:**

The IR spectrum of pure drug was found to be similar to that of standard spectrum of Acyclovir. The spectrum of Acyclovir shows the following groups at their frequencies shown in 1037, 1330, 1412, 1586, 2923, 3108 cm-1.

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**Figure 1: A) FTIR Spectrum of Acyclovir B) FTIR Spectrum of Acyclovir with HPMCK4M C) FTIR Spectrum of Acyclovir with crospovidone D) FTIR Spectrum of Acyclovir with SSG**

**Preparation of fast dissolving mucoadhesive Buccal patches:**

Buccal patches acyclovir is prepared by solvent evaporation method.

**Figure 2: Acyclovir fast dissolving mucoadhesive Buccal patches**

**Evaluation Results of Prepared Acyclovir Buccal Patches:**

**Weight variation: [5]**

Weight variation test was performed. The weights of the patches were between 0.30 gm to 0.35 gm. Hence all patches formulations passed weight variation test. Results are shown in table 2.

**Thickness: [5]**

Thickness of all the formulations was between 0.21 mm to 0.28 mm. Results are shown in table 2.

**% Moisture absorption: [6]**

% Moisture absorption of all formulations was between 6.45 % to 14.70 %. Results are shown in table 2.

**% Moisture loss: [6]**

% Moisture loss of all the formulations was between 9.09 % to 16.12 %. Results are shown in table 2.

**Folding endurance: [7]**

The number of times the strip could be folded at the same place without breaking gives the exact value of folding endurance (a measure of fragility). The folding endurance was measured manually for the prepared films. A strip of 2×2 cm was cut evenly and repeatedly folded at the same place till it broke.

**Drug content:**

Percentage drug content of all formulations was between 85.34 to 96.73%. The results are shown in table 2.

**Surface pH: [8]**

The surface pH of prepared inserts was found be in range of 6.7 to 7. This indicated that the prepared inserts would not alter the pH of the tear fluid in the eye. Results are shown in table 2

**Swelling index:**

Swelling index of all the formulations was between 0.52% to 0.86%. Results are shown in table 2.

**Disintegration time:**

Disintegration time of all the formulations was between 32 to 59. Results are shown in table 2.

**Table 2: Evaluation studies of formulated buccal patches**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Formula No. | Weight variation  (mg) | Thickness  (mm) | % of Moisture absorption | % of Moisture loss | Folding endurance | Drug content  (%) | Surface pH | Swelling  Index  (%) | Disintegration  Time  (sec) |
| F1 | 0.30 | 0.21 | 9.10 | 9.09 | 295 | 98.34 | 7.0 | 0.86 | 32 |
| F2 | 0.33 | 0.26 | 15.23 | 15.74 | 267 | 96.73 | 6.8 | 0.65 | 34 |
| F3 | 0.33 | 0.23 | 14.60 | 11.87 | 285 | 91.63 | 6.7 | 0.61 | 40 |
| F4 | 0.31 | 0.24 | 10.52 | 16.48 | 191 | 88.16 | 6.8 | 0.69 | 46 |
| F5 | 0.35 | 0.28 | 12.35 | 12.20 | 199 | 94.49 | 6.9 | 0.84 | 59 |
| F6 | 0.34 | 0.23 | 6.45 | 16.12 | 205 | 91.54 | 7.0 | 0.86 | 54 |

**In vitro drug release studies:**

**Table 3: % Cumulative drug release studies for all formulations**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Time in min** | **F 1** | **F 2** | **F 3** | **F 4** | **F 5** | **F 6** |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 25.12 | 22.43 | 23.37 | 19.46 | 24.45 | 24.36 |
| 1 | 41.49 | 37.63 | 33.65 | 24.63 | 34.42 | 35.42 |
| 1.5 | 50.17 | 49.47 | 49.34 | 39.58 | 43.67 | 45.43 |
| 2 | 69.38 | 65.14 | 57.48 | 64.45 | 58.62 | 65.88 |
| 3 | 77.64 | 74.63 | 68.36 | 71.31 | 69.71 | 75.43 |
| 4 | 87.73 | 83.63 | 79.49 | 80.41 | 84.97 | 85.66 |
| 5 | 97.14 | 92.15 | 94.59 | 87.98 | 95.67 | 96.74 |

**Figure 3: Percentage cumulative drug release of F-F6**

In all formulations, formulation prepared with croscarmellose showed better release compared with above five (F2, F3, F4, F5 and F6). In these formulation F1release 97.14% drug in 5 mis. Whereas F2, F3, F4, F5 and F6 were released 92.15%, 94.59%, 87.98%, 95.67% and 96.74% release respectively.

**In vitro release kinetics:**

**Table 4*: In vitro* Drug release kinetics of F1 formulation**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Formulation code** | **Zero order** | | **First order** | | **Higuchi model** | | **Korsmeyer-peppas** | | **Release Mechanism transport** |
| **Slope** | **R2** | **Slope** | **R2** | **Slope** | **R2** | **n** | **R2** |
| F1 | 17.97 | 0.899 | -0.279 | 0.949 | 45.22 | 0.986 | 1.072 | 0.314 | Super case II Transport |

Best formulation F1 were subjected for four different models viz. Zero order, First order, Higuchi order and Peppas model equations and all the formulations best fit in to the higuchi model by giving the values of diffusional exponent (n) in the range of 0–98.57that indicate the formulation had release the drug by diffusion followed by erosion mechanism.

**4. CONCLUSION**

These results indicated that F1 (drug 50 mg) with croscarmellose of Acyclovir buccal patches has achieved the objective of considerable influence on the physio chemical characteristics and releasing property. The concentration of Croscarmellose in the formulation determines the drug release from the patches. As the concentration of Croscarmellose increases, drug release also increases. So, finally the best concentration of Croscarmellose was found to be 20 mg and formulation F1 gave the best results.

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