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Formulation and Evaluation of Losartan Potassium Buccal Tablets

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ABSTRACT

The Mucoadhesive tablet is one of the delivery system that can be used for different drugs in order to improve the efficiency of drugs in patients. Hydrophilic polymers are using to prepare these types of tablets with appropriate adhesion and stability in order to deliver the drugs for a prolonged period of time. The aim of the study is to formulate and evaluate mucoadhesive tablets of Losartan potassium using different viscosity grades of poly ethylene oxides (PEO). The tablets were evaluated for various physicochemical properties such as weight variation, hardness, friability, disintegration, surface pH, Muccoadhesive strength, moisture content and invitro drug release. The invitro dissolution studies of the prepared formulations were extended up to 14 hours. The surface pH of all tablets found to be satisfactory, close to neutral pH hence no irritation would observe with these tablets. The maximum bio-adhesive strength was observed in tablets formulated with high content of PEO-303. DSC and FTIR studies showed no drug polymer interaction

Key words: Buccal Tablets, Losartan Potassium, PEO, In-vitro release, DSC, FTIR

1. INTRODUCTION

Traditional dosage forms like tablets, capsules, injections, solutions, suspensions, creams, ointments etc unfortunately all the above are unable to do the facilitate adequate drug absorption and access to target site, prevent non-specific drug distribution (side effects) and premature metabolism, excretion and match drug input with dose requirement [1] . Therefore an alternative root of drug administration and advanced drug delivery systems are needed to meet these drug delivery challenges and improve the drug therapy.

Advanced Drug delivery systems like, buccal drug delivery is a potential alternative to the conventional therapy especially for drugs that undergo extensive first pass metabolism or for drugs that undergo degradation due to environment in the stomach or for those drugs that have poor bioavailability when given by oral route. This offers a great potential for commercial application. Mucoadhesive drug delivery systems may be defined as which utilize property of bio-adhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time. The mucosal layer lines a number of regions in the body including gastro intestinal track, urogenital track, airway, ear, nose and eye. These represent potential sites for attachment of any bio-adhesive systems and hence the mucoadhesive drug delivery system includes the Buccal, oral, vaginal, rectal, nasal, ocular delivery systems.

The oral mucosa mainly the buccal site rather attractive for drug for delivery in the combination of several aspects, [2,3,4] like easily accessible, so dosage forms can be easily administered and even removed from the site of application. Since patients are well adapted to the oral administration of drugs in general patients acceptance and compliance is expected to be good. The oral mucosa is routinely exposed to a multitude of different external compounds and therefore is supposed to be rather robust and less prone to irreversible irritation or damage by a dosage form and its ability to recover after local treatment is pronounced and hence allows a wide range of formulations to be used eg., bio-adhasive ointments and patches.

Hypertension is the leading cause of mortality in the world after malnutrition. Losartan is a competitive antagonist of Angiotension –II (AT II), devoid of partial agonistic activity and 10,000 more selective for AT1 and AT2 receptor, does not block any other receptor or iron channel. It blocks all over action of AT II, the main adverse effect is dose related hypotension.

Losartan is readily absorbed from the gastrointestinal track following oral administration. However oral bioavailability is about 33% due to first

pass metabolism. The terminal elimination half life of losartan is 1.5 to 2.5 hours. Hence, critical dose adjustment is required in patient with hepatic impairment [5,6]. Thus formulation of losartan potassium into bio-adhesive tablet will overcome bioavailability problems due to first pass effect and use of controlled drug delivery will optimize therapeutic effect.

The work of Chen and Cyr [7] together with other works by park and robinson [8] and smart et al [9] detailed the investigation of a range of polymers of varying molecular characteristics required for mucoadhesion. The properties that are exhibited by such a molecule are detailed by Peppas & Buri [10] and may be summerised as Generally, hydrophilic molecules, that contains numerous hydrogen bond formation groups bond –OH, -COOH, strong anionic charges containing many carboxyl groups, Surface tension characteristics suitable for wetting mucous/mucosal tissue surface, usually have a high molecular weight i.e.,>1,00,000 and sufficient flexibility to penetrate the mucous network or tissue crevices.

To develop an intimate contact between the interacting molecules, the mucous membrane has sufficient water content. The mucous has 95% of water [11]. A low water polymer contact angle will encourage hydration of the polymer chains and increase segmental mobility, spreading of the polymer over the mucous also occurs promoting an intimate contact. The polymer must have a sufficient linear chain length to ensure interpenetration can occur [12]. As the hydration increased, adhesive properties were found to be reduced since mucoadhesive bonds became over extended.

2. MARERIALS AND METHODS

2.1. Chemicals

Losartan Potassium, Polyethylene oxides three viscosity grades such as 301, 303, N750, Microcrystalline cellulose and Aerosil were gift samples from Aurobindo Pharmaceutical Industry, Hyderabad. All other reagents and chemical used in the present study were of analytical grades

2.2. Preparation Losartan potassium muco-adhesive tablets

Losartan potassium, microcrystalline cellulose was mixed manually in poly bags with different viscosity grades of polyethylene Oxide (301,303,N750), in the concentrations 10%, 20% and 30% of polymers to drug ratios mixture for about 10 minutes , then the above blend was pre lubricated with aerosol and talc and then finally lubricated with magnesium stearate. Then mixed blend was compressed into tablets by direct compression method using 7mm punches a sixteen station rotary tablet punching machine.

2.3 Evaluation of Buccal Tablets

The prepared Losartan Potassium Buccal tablets were evaluated for physiochemical parameters, in vitro dissolution, DSC and FTIR.

2.3.1 Weight Variation

For weight variation, 20 tablets of each type of formulation were weight individually on an electronic balance, average weight was calculated and individual tablet weight was then compared with the average value to find out the deviation in weight. The % Weight variation also calculated.

% deviation = (Individual weight – Average weight / Average weight) X 100

2.3.2 Thickness

The thickness of buccal tablets was determined using digital micrometer. Ten individual tablets from each batch were used and the results averaged.

2.3.3 Friability

It is a measure of mechanical strength of tablets. Roche friabilator was used to determined the friability by following procedure. Pre-weighed tablets (10 tablets) were placed in the friabilator. This device consists of a plastic chamber that is set to revolve around 100 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. At the end of test, tablets were reweighed; loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$F\ (\%) = [1-Wo/W] \times 100$$

Where,
Wo is the weight of the tablets before the test and
W is the weight of the tablets after test.

2.3.4 Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage, depends on its hardness. For each formulation, the hardness was determined using Monsanto hardness tester and the average was calculated and presented with standard deviation.

2.3.5 Assay

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in 100ml of water by sonication for 30 min and filtered through filter paper. The drug content was analysed spectrophot- ometrically at 250 nm using an UV spectrophotometer.

Table **1** Formulation and physico chemical properties of the prepared Losartan potassium tablets

Froamulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	50	50	50	50	50	50	50	50	50
PEO N 750	12.5	25	37.5						
PEO 301				12.5	25	37.5			
PEO 303							12.5	25	37.5
MCC PH 200	52.5	40	27.5	52.5	40	27.5	52.5	40	27.5
Aerosil	6	6	6	6	6	6	6	6	6
Talc	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25
Mg.stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Properties									
Thickness in mm	3.81	3.81	4.52	3.69	3.65	3.78	3.81	3.76	3.83
Friability in %	0.69	0.92	0.83	0.7	0.76	0.67	0.72	0.88	0.82
Assay in %	99.85	100.28	99.17	99.13	100.43	99.56	100.02	99.74	98.56

2.3.6 In Vitro Mucoadhesion Studies

Porcine Buccal tissue from domestic pigs was obtained from a local slaughterhouse and used within 2 hours of slaughter. The tissue was stored in pH 7.4 phosphate buffer at 4^0C after collection. The epithelium was separated from the underlying connective tissue with a surgical technique and the de-lipidized membrance was allowed to equilibrate for approximately one hour in receptor buffer to regain lost elasticity.

Muco-adhesive strength of Losartan potassium Buccal tablets with porcine Buccal mucosa was measured using a modified 2-arm balance apparatus. The design of apparatus used while measuring the mucoadhesive strength.

The experiment was performed within the 3 hrs of procurement of the mucosa. The porcine Buccal mucosa was fixed to the stainless steel piece with cyanocrylate adhesive and placed in a beaker. pH 7.4 phosphate buffer was added into the beaker up to the upper surface of the Buccal mucosa to maintain Buccal mucosal viability during the experiment. The tablet was attached to the upper clamp of the apparatus and then the beaker was raised slowly until contact between porcine Buccal mucosa and tablet was established.

A preload of 50 gm was placed on the clamp for 10mins to establish adhesion bonding between the tablet and porcine Buccal mucosa. The preload and preload time were kept constant for all the formulations. After completion of preload time, preload was removed from the clamp and water was added into the beaker placed on another clamp, from the burette at a constant rate of 100 drops/min. the addition of water was stopped when tablet was detached from porcine Buccal mucosa. The weight of water required to detach the tablet from Buccal mucosa was noted as mucoadhesive strength and experiment was repeated with fresh mucosa is an identical manner.

2.3.7 Moisture Absorption

Agar (5 %, W/V) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six Buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37^0 C for one hour. Then the tablets were removed and weighted and the percentage of moisture absorption was calculated by using following formula.

% Moisture absorption = [(final weight – initial weight)/initial weight] X 100

2.3.8 Surface pH Study

The bio-adhesive tablet was allowed to swell by keeping it in contact with 1ml distilled water for 2 hr at room temperature.

The pH was measured by bringing the pH paper, in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

2.3.9 In Vitro Release Studies

The drug release rate from Buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug

from one side only; therefore an impermeable backing membrance was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500ml of water at 50 rpm at a temperature of 37±0.5^{o}C samples of 5ml were collected at different time intervals up to 12 hrs and analysed spectrophotometrically.

2.3.10 DSC and FTIR studies

Thermal properties of pure drug and the formulation were evaluated by Differrential scanning colorimetry (DSC) using a diamod (DSC) (Mettler star sw8.10). The analysis was performed at a rate 50c min-1 to 2000C temperature range under nitrogen flow of 25 ml min-1.

The FT-IR spectrum of pure drug and formulation were determined. A FT-IR (Thermo nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 - 400cm-1 and 4cm-1 resolutions. A quality equivalent to 2mg of pure drug was used for the study.

4. RESULTS AND DISCUSSION

Prepared tablets were evaluated to weight variation study. The results of weight variation test are shown in the table and the values are with in the pharmacopoeial limits. The tablets thickness of the various formulations was observed to be in the range of 3.52mm to 4.52 mm. The hardness of all the tablets was found to be in the range of 5 to 6 kg/cm^2. The friability of the prepared tablets was below 1% clearly indicates the good mechanical strength of the tablets. Good mucoadhesive strength was obtained for the prepared tablets. The drug content ranged from 99.13±0.87 in formulation to 100.28±0.66 in formulation clearly indicating good content uniformity. The results of the physico chemical properties were summarized in Table 1.

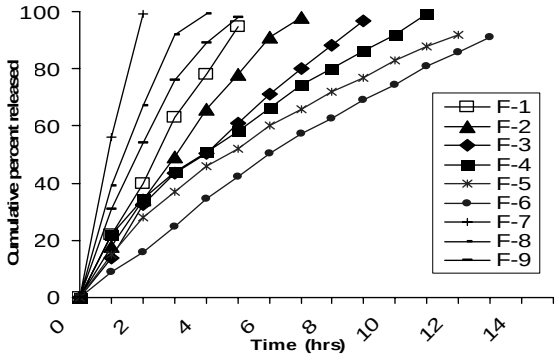

Figure1 Cumulative percent drug release vs time plot of Losartan potassium buccal tablets

Surface pH evaluation of oral mucosal dosage forms is an important characterization study an acidic or alkaline pH may cause irritation to the oral mucosa. It was therefore necessary to determine if any extreme surface pH changes occurred with the tablets during the drug release period under investigation. Attempts were made to keep the surface pH as close as to Buccal / salivary pH as possible by proper selection polymer for developing the Buccal tablets. Surface pH of all the formulations is in an acceptable pH range of 6.5 to 7 (salivary pH). Hence they may not produce any local irritation or damage to the mucosa.

In vitro dissolution studies showed that the drug release was extended up to 14 hours in the matrix tablets prepared with PEO 303, the drug release was extended up to 7 hours in the formulations prepared with PEO 301. Faster drug release was observed in the formulations prepared with the PEO N 750. The drug release was mainly depends up on the polymer viscosity and polymer proportion. As the viscosity and polymer proportion increases the drug release was retarded. The dissolution profile were fitted to various kinetic models such as zero order, first order and higuchi. The drug release was zero order with diffusion mechanism in all the formulations.

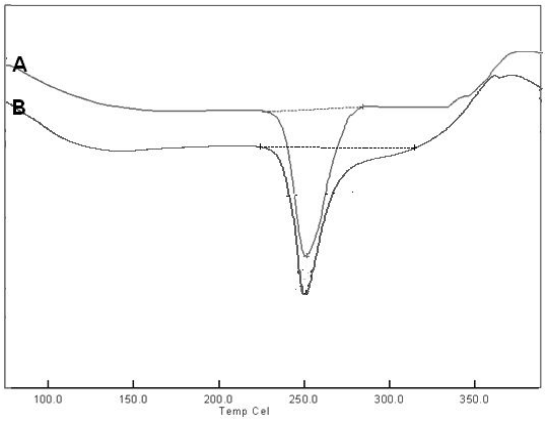

Figure **2** DSC thermogram of (A) pure Losartan potassium (B) Losartan potassium –PEO 303 buccal tablets.

DSC studies were performed to investigate the physical state of the drug in the tablets and to know the interactions of drug with polymers in the formulation. The DSC results shows sharp endothermic peak for the pure Losartan at 255 ^{o}C. Similar sharp endothermic peaks were observed in the formulations at almost similar temperatures. This clearly indicates that there is no drug excipients interaction. FTIR spectrum shows similar spectrum peak points with that of the pure drug clearly

indicates that there is no drug polymer interaction in the prepared formulations.

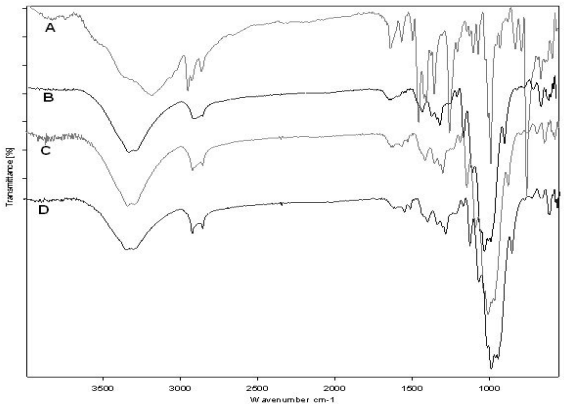

Figure **3** FTIR spectrum of (A) pure Losartan potassium (B) Losartan potassium –PEO 301 (C) Losartan potassium –PEO 303 (D) Losartan potassium –PEO **N** 750 buccal tablets.

5. CONCLUSION

Mucoadhesive Buccal tablets of Losartan Potassium were prepared by direct compression method. Good mucoadhesive strength was observed with the different grades of the PEO. PEO 303 showed the more extended drug release then other PEO grades used in the present study. DSC and FTIR study shows no drug polymer interaction. The prepared formulation have good industrial applications.

6. ACKNOWLEDGEMENT

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