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FORMULATION AND EVALUATION OF DILTIAZEM HCL BUCCAL PATCHES BY USING Lannea GUM

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ABSTRACT

The present investigation involves formulation and evaluation of buccal patch of Diltiazem Hydrochloridean calcium channel blocker drug to bypass the first pass metabolism. The buccal patch of Diltiazem Hydrochloride was prepared by solvent casting technique. Six formulation were prepared with concentrations of bioadhesive polymers like e.g Solvent acetone was used with cellulose acetate. Drug-polymer interaction was investigated using FTIR. The prepared patches were evaluated for thickness, Surface pH, drug content uniformity, Ex vivo Mucoadhesive strength, % swelling index, folding endurance and in vitro drug release, Determination of Residence Time, Ex Vivo Permeation Study which produced satisfactory results with low standard deviation. After evaluation of all parameter, on the basis of results obtained batch F6 as found to be a optimize batch. This batch shows 98.6% Controlled Drug Release after 6hrs and best fitted in Higuchi model for drug release kinetic.

KEYWORDS: Mucoadhesive, Diltiazem Hydrochloride, Drug delivery, Controlled Drug Release, lannea Gum.

INTRODUCTION

The drugs that are administered orally are subjected to first pass metabolism. To overcome this first pass metabolism, there are different techniques which are applied for the protection of drug against the first pass metabolism. The techniques that include are administration of drug through transdermal route, parentral route, buccal route, and sublingual route etc.

Among the novel drug delivery system, buccal drug delivery is the main and extensive acceptable drug delivery systems. The orally disintegrating tablets are available in the market

providing one to two minute of disintegrating tablets of disintegration time. Among fast dissolving drug delivery systems.

The administration of drugs to buccal and sublingual requires adhesion of drugs to buccal and sublingual layers. Hence majority of buccal and sublingual drug deliveries are prepared by using hydrophilic polymers which are having bioadhesion property. Hence buccal delivery is one of the most favourable drug deliveries.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was supplied as a gift sample by primal Science Solution Pharmaceutical Limited, Mumbai. Lannea gum, Poloxamer 407, Cellulose acetate, glycerin, Acetone purchased from Yarrow Chem Product, Mumbai.

Fabrication of Medicated Patches

Required amounts of polymer, drug and permeation enhancer were dissolved in water separately. The composition of different patches prepared are shown in table The solution containing drug and permeation enhancer was added to the prepared polymer solution and stirred continuously using homogenizer. The prepared solution was poured uniformly in to a petridish containing the dried backing layer by solvent casting technique and allowed to dry in oven at 40℃.

Formulation of diltiazem HCl Buccal patches using Lannea.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Diltiazem HCl	290	290	290	290	290	290
Lannea gum	290	435	580	580	580	580
Poloxamer 407	-	-	1	3	5	6
Cellulose acetate	600	600	600	600	600	600
Glycerin (mL)	0.5	0.5	0.5	0.5	0.5	0.5
Acetone (mL)	30	30	30	30	30	30

Evaluation of patches

Measurement of mucoadhesive strength

Detachment force was measured on modified balance in which the right pan was removed. A plastic beaker was kept in left pan and both the sides were balanced by weights. The buccal mucosal tissue of porcelain was collected from the local slaughter house and stored in normal saline solution, the underlying connective tissue was separated and washed with pH6.8

phosphate buffer. The mucosal membrane was cut and attached to the glass slide with the mucosal side facing outwards using cyanoacrylate glue and this slide was attached to the Petri plate and it was placed on the right side of the balance. The patch was attached to the glass slide facing the drug polymer layer outwards using a non elastic thread and the height of thread was adjusted. The mucous layer and patch were wetted with pH6.8 phosphate buffer and the patch was fixed to the mucus layer by applying a little pressure with thumb and kept undisturbed for 5 min. on left hand side, water was added slowly in to a plastic beaker with help of a burette till the patch just separated from the membrane surface. The weight of water in grams required to detach the patch was noted and results. The mucoadhesive strength determination was shown**.**

Mucoadhesion strength was calculated in Newtons by using formula:

Force of adhesion (N) = mucoadhesive strength×9.81/1000

- **Determination of *ex vivo* residence time**

The *ex vivo* residence time was determined using USP dissolution apparatus II. The buccal mucosa of porcine which was previously washed was attached to the glass slide with the mucosal side facing outwards using cyanoacrylate glue. This was horizontally fixed to paddle of the dissolution apparatus. Drug polymer layer of patch was wetted with 0.5 mL of pH6.8 phosphate buffer and attached to the mucus tissue with a little pressure to develop initial contact. 900mL of pH 6.8 phosphate buffer was used as medium maintained at 37℃ at 20 rpm. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded.

- **Swelling studies**

2% agar gel was prepared and poured in to a petri dish and allowed to solidify. Buccoadhesive patches were weighed individually (W1) and placed in petri dish and allowed to swell. The patches were removed at time intervals of 30min, 1, 2, 3, 4, 5, 6, and 7hrs from the petri dish and excess surface water was removed carefully with the tissue paper. The swollen patches were weighed (W2). This experiment was calculated according to the following equation,

Swelling index = (W2-W1)/W1×100

Weight variation and thickness

For the evaluation of weight variation three patches (each of 1sqcm) of every formulation were taken and weighed individually on a digital balance. The average weights were calculated. Similarly, three patches (each of 1sqcm) of each formulation were taken and film thickness was measured using micrometer screw gauge at three different places and the mean value was calculated and shown

Surface pH study

To evaluate the surface pH, buccal patches were left to swell for 2hrs in the 6.8 phosphate buffer. The surface pH was measured by means of pH paper (range of 2-14) placed on the surface of the swollen patch and pH was measured and values are shown

Folding endurance

The folding endurance of patches were determined by folding a patch repeatedly at the same place till it broke or was folded up to 300 times without breaking.

Estimation of drug content

To estimate the drug content for lannea gum (5mg/sq.cm), three patch units from each formulation were taken and dissolved in 100mL of pH 6.8 phosphate buffer by continues stirring using magnetic stirrer. The solution was diluted suitably with the pH6.8 phosphate buffer and analyzed at 240 nm using U.V. spectrophotometer.

***In vitro* drug release studies**

USP dissolution apparatus type II (paddle) was used to study the drug release from patch formulation under sink condition at 37℃± 0.5℃ and 50 rpm. A single patch was placed in 500ml dissolution media containing pH6.8 phosphate buffer. A was applied on glass slide in such a way that mucoadhesive layer of the patch was in contact with dissolution medium and non-adhesive backing layer was fixed on the slide with the help of two-sided adhesive tape. Samples(5mL) were withdrawn at suitable intervals and replaced with fresh dissolution medium maintained at the same temperature. The amount of diltiazem hydrochloride was determined by UV spectrophotometer at 240 nm.

RESULTS AND DISCUSSION

Lannea gum was used to study its applicability in the formulation of mucoadhesive buccal patches. Mucoadhesive buccal patches each containing 5 mg of Diltiazem Hcl were prepared

by usin glannea gum as a controlled release polymer by solvent casting technique. Poloxamer 407 is used as a penetration enhancer (0.5-5%). Twelve formulations (F12) were prepared with drug polymer ratios of 1:1, 1:2, 1:2 (0.5 - 5% poloxamer (407).

- **Physico-chemical properties of lannea gum:**

The physico-chemical characteristics of lannea gum like swelling index, moisture content, loss on drying and pH were evaluated and the results are shown in **Table.**

Physico-chemical properties of Lannea gum

Property	Mean ± s.d., n=3
Swelling index (%)	436 ± 0.94
Moisture content (%)	8.5% ± 0.02
pH	6.5
Loss on drying (%)	3.6 ± 0.05

By observing the above results lannea gum has high swelling nature with slightly acidic nature pH 6.5. The swelling nature of the gum was increased about 4 times than the actual amount of the gum.

- **Calibration curve for diltiazem hydrochloride**

The results of absorbance vs. concentration are shown in table. and the calibration curve is shownGood correlation was observed between concentration vs. absorbance and the correlation coefficient was found to be 0.9997. The regression equation was found to be y=0.0447X+0.1015

Concentartion vs. Absorbance

Concentration (µg/mL)	Absorbance at 240 nm (mean±s.d n=3)
2	0.147 ± 0.035
4	0.19 ± 0.043
6	0.236 ± 0.043
8	0.278 ± 0.038
10	0.326 ± 0.046

Evaluation of mucoadhesive properties of Diltiazem Hcl buccal patches

The prepared Buccal patches were evaluated for weight variation, thickness, surface pH, folding endurance, drug content uniformity, swelling index, *ex-vivo*mucoadhesive time and mucoadhesive strength.

Weight variation

Three films each of 1 sq.cm was cut at three different places and weighed individually on analytical electronic balance and weights of each film was noted and calculate weight variation. It was found to be in the range of 0.022 ± 0.00004 to 0.0458 ± 0.00004. The weight of all the films was found to be uniform. From all the formulations it has been observed that increase in concentration of polymer increases weight of the film. The values were shown in tabel.

Thickness

The thickness of buccal patch was measured by screw gauge at three different locations. It was found to be in the range of 0.0216 ± 0.0012 to 0.0406 ± 0.0012. The thickness of the buccal patches was increased with increase in the amount polymer. The maximum thickness was observed for the formulation F6 whereas minimum thickness was observed for the formulation F1. The average thickness of backing layer was 0.3 mm. The results were shown in tabel.

Surface pH

The surface pH of the patches was measured with pH paper, the values were found to be in the range of 6-7. This shows that formulations were suitable for buccal drug delivery as pH was within the range of buccal cavity. Results were shown in table.

Folding endurance

All patches did not show any deformation after 250 times folding, which results that all are having satisfactory flexibility. Results were shown.

Drug Content

Drug content for all the formulations was found to be uniform from 4.46 ± 0.111 to 4.893 ± 0.004 and shows favourable drug loading efficiency. This indicated that the drug was dispersed uniformly throughout the patch. Results were shown in table.

Swelling Studies

Swelling behavior for all the patches as a function of time is showed in the table. The swelling index of the patches was increased up to 476.15±0.02 for formulation F6 after 4hrs. F6 shows maximum swelling index due to high swelling nature of lannea gum and increase in

the concentration of penetration enhancer. During the study all patches maintained its integrity and did not show any changes in shape.

Characteristics of Mucoadhesive Buccal Patches of Diltiazem Hcl.

Batch no	Weight variation (mean±s.d n=3)	Thickness (mean±s.d n=3)	Drug content (mean±s.d n=3)	pH	Folding endurance
F1	0.022±0.00004	0.021±0.001	4.46±0.11	6-7	>250
F2	0.025±0.00008	0.025±0.0004	4.43±0.15	6-7	>250
F3	0.032±0.00049	0.027±0.0012	4.61±0.08	6-7	>250
F4	0.034±0.00102	0.029±0.0009	4.71±0.03	6-7	>250
F5	0.037±0.0019	0.031±0.0016	4.70±0.04	6-7	>250
F6	0.038±0.0004	0.030±0.0012	4.51±0.05	6-7	>250

Swelling Index Values for Mucoadehsive Buccal Patches of Diltiazem Hcl.

Batch no	Swelling index (mean±s.d. n=3)					
	Time (hr)					
	0.5	1	2	3	4	5
F1	102±0.03	199±0.03	256±0.04	305±0.01	305±0.01	-
F2	104±0.01	211±0.02	246±0.05	262±0.03	333±0.03	-
F3	104±0.03	149±0.04	174±0.08	216±0.01	283±0.02	347±0.03
F4	105±0.04	153±0.03	159±0.06	176±0.02	270±0.03	355±0.02
F5	108±0.03	138±0.03	153±0.07	217±0.01	323±0.02	376±0.02
F6	107±0.02	141±0.03	241±0.03	293±0.03	372±0.03	372±0.01

Swelling indices of mucoadhesive buccal patches

***Ex-vivo* Mucoadhesion Time**

The values of ex-vivo mucoadehsion time are shown in Themucoadhesion time for all the patches ranges from 7.16 ± 0.23 to 10.5 ± 0.01 hrs. All patches retained on the rat buccal mucosa over the study period which indicates that the mucoadhesion time for all the patches was sufficient to retain on the buccal mucosa. The maximum mucoadhesion time was seen in formulation F6.

Measurement of Mucoadhesive Strength

Mucoadhesive strength was performed for all the formulations. The values for mucoadhesive strength are shown in Mucoadehsive strength of the buccal patches was increased due to increase in the concentration of the penetration enhancer. The maximum mucoadhesion force was observed for the formulation F6.

***ex-vivo* Mucoadhesion Time and Mucoadhesive Strength of Diltiazem Hcl Buccal Patches**

Batch no	*Ex-vivo*mucoadhesion time (mean±s.d n=3)	Mucoadhesion force(N) (mean±s.d n=3)
F1	7.16±0.23	0.113±0.0009
F2	7.6±0.14	0.127±0.0016
F3	8.16±0.23	0.147±0.0001
F4	8.33±0.23	0.166±0.0004
F5	8.16±0.23	0.186±0.0004
F6	7.33±0.23	0.185±0.0009

***in-vitro* drug release**

In-vitro drug release for all the patches were shown in and the values were shown in Drug release mechanism was determined by plotting release data to huguchi and korsmeyer peppas model. Buccal patch prepared by using drug to polymer ratio of 1:2 – 5% (poloxamer 407) shows 98.7% cumulative drug release in 6 hrs. Hence the formulation F6 was taken as optimized formulation for the study.

By observing the diffusion data that the drug release from the prepared buccal patches depends on the concentration of penetration enhancer.

Drug release kinetics

In order to establish the mechanism of drug release the experiment data was fitted to four exponential equations.

The drug release from all the formulations followed first order kinetics which was indicated by slightly higher ´r´ values of first order release model when compared to those of zero order release model.

The relative contribution of drug diffusion to drug release was further confirmed by subjecting the dissolution data to higuchi and korsemeyar-peppas model. It was found that formulation F6 follows diffusion mechanism and it follows.

SUMMARY AND CONCLUSIONS

Mucoadhesive polymers shown prolong residence time and mucoadhesive polymers are either natural or synthetic in nature. The present work is based on the applicability of lannea gum in the design of mucoadhesive systems and their capacity to form controlled release. Lanneagum is naturally obtained neutral polysaccharide.

The preliminary characterization studies on the lannea gum were found that it is having good swelling nature and viscosity. Lannea gum was first time tried as mucoadhesive polymer. Diltiazem HCl is a calcium channel blocker with peripheral and coronary vasodilator properties.

It has elimination half life of 3-4.5 hrs. To avoid the first pass metabolism and to improve the bioavailability of diltiazem it was formulated as buccoadhesive patches and it was formulated by solvent casting method using poloxamer 407 as permeation enhancer. One side of the patch was coated with impermeable backing layer cellulose acetate inorder to get unidirectional release.

Lannea gum showed good swelling property and the patches were prepared with different ratios of drug and polymers there was less drug release for F1 and F2 for 6 hrs to overcome this poloxamer 407 was added to increase the release rate.

Weight variation, thickness, folding endurance and uniformity of the dosage forms of the prepared buccoadhesive patches of diltiazem HCl were complied with the compendia requirements of the patches.

Optimized formulation prepared with lannea gum (F6). This formulation has shown N= 0.197 mucoadhesive force, 0.185% swelling index and *exvivo*residence time of 9.5 hrs.

Release kinetics and mechanism of drug release was established by fitting the dissolution data into popular kinetics models like zero order, first order, and Higuchi and erosion models. Drug release for optimized formulation follows first order kinetics with diffusion mechanism.

FT-IR studies were conducted for pure drug, polymer and polymer-drug mixture. It was observed that there were no interactions between the polymer and drug.

The results of the present work indicated that the formulations had high swelling nature and mucoadhesive properties.

The mucoadhesive buccal patches of diltiazem HCl were successfully formulated and evaluated. There were no reports on the applicability of lannea gum in the development mucoadhesive buccal patches.

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