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Research Article

Metoprolol tartrate Containing Glutaraldehyde Cross-linked Chitosan- Polyvinyl pyrrolidone Matrix Transdermal Patch: Preparation and Characterization

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Abstract

The present study was undertaken to develop a suitable transdermal matrix patch of Metoprolol tartrate with different proportions of polyvinyl pyrrolidone (PVP) and chitosan crosslinked with glutaraldehyde (GA). The prepared transdermal patches were subjected to different physicochemical evaluations such as thickness, tensile strength, folding endurance, drug content, swellability, surface pH, water vapour transmission, *in vitro* permeation and skin irritation studies. The permeability of drug was increased with increase in PVP content. The *in vitro* drug permeation followed Korsmeyer-Peppas model with non-Fickian diffusion mechanism. The patches were found to be free of any skin irritation.

Keywords: Matrix patch, Polyvinyl pyrrolidone, Chitosan, Metoprolol tartrate, Skin permeation

1.Introduction

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs.[1] It offers many advantages over conventional administration such as enhanced efficacy, increased safety, greater convenience, improved patient compliance and absence of hepatic first pass metabolism.[2] It excludes the variables that affect drug absorption from the gastrointestinal tract such as pH, enzymatic activity and drug food interactions.[3] This approach of drug delivery is more pertinent in case of chronic disorders, such as hypertension, which require long term dosing to maintain therapeutic drug concentration.[4]

The present work is aimed at developing glutarldehyde (GA) cross-linked chitosan-Poly vinyl pyrolidine (PVP) hydrogel matrix dispersion type transdermal drug delivery of Metoprolol tartrate to ensure satisfactory drug release with the use of optimum polymer and prolong duration of action.

Metoprolol tartrate is a cardio selective beta blocker. It is used in the management of hypertension, angina pectoris, cardiac arrhythmia and myocardial infarction. It is almost completely absorbed after oral administration, although the systemic bioavailability varies widely owing to extensive presystemic metabolism. Peak plasma concentrations are achieved after 2-3 h. The plasma half life is about four hours, which makes frequent dosing necessary to maintain the therapeutic blood levels of the drug for a long term treatment. The transdermal route of administration is capable of avoiding the hepatic first pass effect, thus achieving higher systemic bioavailability of drugs.[5]

Chitosan is used as a carrier material for drug delivery because of its biodegradable and nontoxic in nature.[6] It is a linear polysaccharide composed of α-1,4- linked 2 - amino- 2-deoxy- α- D-glucose (N-acetyl glucosamine). It is obtained from the N-deacetylation of chitin with a strong alkali.[7-9]

Generally PVP hydrogels are excellent candidates for biomaterials as they exhibit a high degree of swelling in water, a rubbery elastic nature are non-toxic, non-carcinogenic and can be readily accepted in the body.[10]

2. Materials and Methods

2.1. Materials

Metoprolol tartrate was obtained as a gift sample from Torrent Pharmaceuticals, Gandhinagar, India. Chitosan was purchased from Everest Edward, Cochin, India. PVP was obtained from SD fine-Chem. Ltd., Mumbai, India. Polyethylene glycol 400 was obtained from Merck Specialities Private Ltd., Mumbai, India. Glutaraldehyde was obtained from Loba chemie Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

2.2. Preparation of transdermal patch

Matrix type transdermal patches composed of different concentrations of PVP, chitosan and drug were prepared by solvent evaporation method. A petridish with a total area of 44.15cm^2 was used. PVP were accurately weighed and dissolved in 10ml of hot water. Drug was dissolved in the above solution and mixed until clear solution was obtained. Chitosan solution added to the different formulation and blended well. GA solution added drop wise .Then the entire mixture stirred well for 30 min. Simultaneously 2 to 3 drops of concentrated sulphuric acid was added. Polyethylene glycol was used as plasticizer. The resulted uniform solution was cast on the petridish, which was lubricated with glycerin and dried at room temperature for 24h. An inverted funnel was placed over the petridish to prevent fast evaporation of the solvent. After 24h, the dried patches were taken out and stored in desiccators for further studies. The composition of transdermal patches is shown in Table 1.

2.3. Characterization of transdermal patches

2.3.1. Folding endurance

A strip of specific area (4cm^2) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance.[11]

2.3.2. Moisture absorption study

The films were weighed accurately and placed in a desiccator containing 100 ml of saturated solution of aluminium chloride (75%

RH). After 3 days, the films were taken out and weighed, the percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight.[12]

2.3.3. Moisture content

The patches were weighed and kept in a desiccator containing calcium chloride at 40°C for 24h. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight.

2.3.4. Thickness

Patch thickness was measured using micrometer screw gauge at three different places of each patch and the mean value was calculated and reported.[13]

Table 1. Composition of Transdermal patches.

Formulation code	Drug (mg)	PVP (%w/v)	Chitosan (%w/v)	Glutaraldehyde (ml)	Poly ethylene glycol(%v/v)
F-1	10	-	0.5	1	2
F-2	10	1.0	0.5	1	2
F-3	10	1.5	0.5	1	2
F-4	10	2.0	0.5	1	2

2.3.5. Tensile strength

The tensile strength of the patch was evaluated by using the tensiometer. It consists of two load cell grips. The lower one was fixed and upper one was movable. Film strips with dimensions of 4 cm^2 were fixed between these cell grips, and force was gradually applied till the film broke. The tensile strength was taken directly from the dial reading in kg.[14]

2.3.6. Swellability

The patches of 2.5 cm^2 was weighed and put in a petridish containing 10 ml of double distilled water and were allowed to imbibe. Increase in weight of the patch was determined at preset time intervals, until a constant weight was observed.

The degree of swelling (S) was calculated using the formula: $S\ (\%) = (W_t - W_0)/W_0 \times 100$

where S is percent swelling, W_t is the weight of patch at time *t* and W_o is the weight of patch at time zero.[15]

2.3.7. Surface pH

The patches were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1h in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the patch and allowing it to equilibrate for 1 min.[16]

2.3.8. Water vapour transmission

In water vapour transmission study, glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried to constant weight in an oven. Fused calcium chloride (1g) as a desiccant was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape. These pre-weighed vials were stored in a humidity chamber at an RH of 80 % with the temperature set to 30ºC for a period of 24 h. The weight gain was determined every hour up to a period of 24 h.

Water vapour transmission (Q) usually expressed as number of grams of moisture gain per 24h per cm^2, was calculated using the equation:

$Q = WL/S$

Where W is gm of water transmitted/24h, L is patch thickness in cm and S is surface area in cm^2.[17]

2.3.9. Drug entrapment efficiency

Specified area of patch (4 $cm^{2)}$ was dissolved in 100 ml. saline phosphate buffer pH 7.4 and shaken continuously for 24 h. Then the whole solution was ultrasonicated for 15 min. After filtration, the drug was estimated spectrophotometrically at wavelength of 223 nm and determined the drug content.

2.3.10. Drug permeation study

Drug permeation study was carried out with saline phosphate buffer (pH7.4) using Franz diffusion cells. Full thickness abdominal skin of male Wister rat weighing 200 to 250 g was used. Hair from the abdominal region was removed carefully by using an electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrate for an hour in saline phosphate buffer pH7.4 The isolated rat skin piece was mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. The whole assembly was kept on magnetic stirrer, which thermostatically controlled at 37°C at 50 rpm. Samples were withdrawn at regular time interval from the receptor compartment and analyzed at 223 nm using UV-visible spectrophotometer (Spectronic,model -UV1,England). The fresh buffer in receptor compartment was replaced after each withdrawal. The permeation studies continued for period of 8h. Cumulative amounts of drug permeated [Q] in $\mu g/cm^2$ were calculated and plotted against time. Drug flux [J] ($\mu g\ min^{-1}cm^{-2}$) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface ($2.54cm^2$).[18]

2.3.11. Analysis of drug permeation kinetics and mechanism

In order to predict and correlate the *in vitro* permeation of drug from formulated transdermal paches containing Metoprolol tartrate, it is necessary to fit into a suitable mathematical model. The *in vitro* release data were evaluated kinetically using various important mathematical models like zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models.

Zero-order model: $Q = kt + Q_0$; where Q represents the drug released amount in time t, and Q0 is the start value of Q; k is the rate constant.

First-order model: $Q = Q_0 e^{kt}$; where Q represents the drug released amount in time t, and Q_0 is the start value of Q; k is the rate constant.

Higuchi model: $Q = kt^{0.5}$; where Q represents the drug released amount in time t, and k is the rate constant.

Hixson-Crowell model: $Q^{1/3} = kt + Q_0^{1/3}$; where Q represents the drug released amount in time t, and Q_0 is the start value of Q; *k* is the rate constant.

Korsmeyer-Peppas model: $Q = kt^n$; where Q represents the drug released amount in time t, k is the rate constant and *n* is the diffusional exponent, indicative of drug release mechanism.

Again, the Korsmeyer-Peppas model was employed in the *in vitro* drug release behaviour analysis of these formulations to distinguish between competing release mechanisms: Fickian release (diffusion-

controlled release), non-fickian release (anomalous transport), and case-II transport (relaxation-controlled release).[19]

2.3.12. Primary skin irritation test

Primary skin irritation and corrosion are evaluated most often by modification described by Draize and his colleagues in 1994, which is based on scoring method. Scores as assigned from 0 to 4 based on the severity of erythema or oedema formation. The safety of the patch decreases with increase in scoring. The skin irritation study permission was obtained from Institutional Animal Ethics Committee (955/A/06/CPCSEA). The hair on the dorsal side of Wister albino rats was removed 1day before the initiation of this study. The rats were divided into three groups. Group I served as the control, group II received transdermal patch, and group III received a 0.8% (v/v) aqueous solution of formalin as a standard irritant. A new patch or new formulation was applied daily for 7 days. Finally the application sites were graded always by the same investigator.[20]

3. Results and Discussion

In this study, it was desired to design a transdermal paches of Metoprolol tartrate using a polymeric matrix film. This allows one to control the overall release of the drug *via* an appropriate choice of polymers and their blends studied here, utilizing the different diffusion pathways created due to the blend of polymers to produce overall desired steady and sustained drug release. Here efforts have been made to prepare Metoprolol tartrate containing Transdermal patches using solvent evaporation technique. The films were prepared by using different hydrophilic polymers such as PVP and chitosan in presence of glutaraldehyde and Polyethylene glycol. The physicochemical evaluation data in Table 2 and 3 reveals that all formulations measured with low standard deviation values. These values assured that the process used for preparing the delivery system is capable of giving reproducible results.

The thickness of the films varied from 0.21 ± 0.11 to 0.37 ± 0.14 mm. The results indicated that the film thickness measurement ensured uniformity of the patches prepared by solvent evaporation technique. The folding endurance measures the ability of patch to withstand rupture. It was found to be satisfactory. The values in the range of 58±0.44 to 84±0.32 were observed. The result indicated that the patches would not break and would maintain their integrity with general skin folding when used.

The surface pH of all the formulations was in the range of 7.2 - 7.4 and hence no skin irritation was expected. The tensile strength of the patches was found to vary with the nature of polymer and plasticizer. Formulation F4 (2% w/v PVP, 0.5% w/v chitosan) showed highest tensile strength of 2.88±0.58 kg cm^{-2}.

Data of percentage moisture absorption indicates that the formulation F4 (2% w/v PVP, 0.5% w/v chitosan) has shown maximum absorption than the other formulations. This may be due to the presence of hydrophilicity of PVP. The same patch showed more pronounced swelling as compared to other patches. It varied between 14.22±0.54 to 26.42±0.18%. The swellability varied with nature and composition of patches. Increasing the concentration of PVP showed considerable increase in swelling, as it increased the surface wettability and consequently water penetration within the matrix.

The results of moisture content revealed that the moisture content was found to increase with increasing the concentration of hydrophilic polymers in all the formulations. The results indicated that the hydrophilic polymers are directly proportional to the percentage of moisture contents. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage. The low moisture absorption protects the material from microbial contamination and bulkiness of the patches.

Table 2. Evaluation of transdermal films of Metoprolol tartrate.

Formulation code	Folding Endurance	Tensile Strength (kg cm^{-2})	Water vapour transmission (gm-cm/cm^2.24h)	Moisture content (%)
F-1	58±0.44	2.54±0.12	2.66 x10^{-4}	2.14±0.88
F-2	59±0.68	2.68±0.34	3.42 x10^{-4}	2.36±0.24
F-3	71±0.72	2.74±0.64	4.28 x10^{-4}	2.58±0.56
F-4	84±0.32	2.88±0.58	4.85 x10^{-4}	2.91±0.38

Table 3. Evaluation of transdermal films of Metoprolol tartrate

Formulation code	% moisture absorption	Thickness (mm)	Swellability (%)	Surface pH
F-1	17.68± 0.42	0.21± 0.11	14.22± 0.54	7.2± 0.22
F-2	18.42± 0.18	0.26± 0.14	18.37± 0.23	7.3± 0.16
F-3	19.84± 0.26	0.28± 0.09	23.51± 0.62	7.3± 0.12
F-4	21.73± 0.34	0.37± 0.14	26.42± 0.18	7.4± 0.08

Release of the drug from transdermal patches is controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. The process of drug release in most controlled release devices is governed by diffusion and the polymer matrix has strong influence on the diffusivity as the motion of a small molecule is restricted by the three-dimensional network of polymer chains. Table 4 indicates the cumulative percent of drug permeated from formulations F1, F2, F3 and F4 were found to be 28.63, 47.34, 59.56 and 71.32 % respectively after 8h. The increase of release with increase of PVP content in the patch may be due to the leaching of PVP and pore formation. This leads to an increase in the external film area exposed to the solvent, increased internal porosity and decreased the tortuosity. Drug flux (µg/cm^2/h) of F4 was also higher

than other formulations. The possible mechanism of enhancement of skin flux with increase of PVP in the patches may be due to its co enhancing property in aqueous vehicle system. The rapid leaching of hydrophilic fraction of polymers resulted in the formation of pores and thus leads to the decrease of mean diffusional path length of the drug molecules to permeate into dissolution medium. Diffusion in the polymer occurs through the amorphous polymeric regions and diffusivity of the drug molecule is related to the mobility of polymer chains.

Table 4. Data of cumulative percentage of drug permeated, Q value, drug flux and % drug entrapment efficiency of different formulations.

Formulation code	Cumulative % of drug permeated after 8 h	Q value (µg/cm^2)	Drug flux (µg/cm^2/h)	% drug entrapment efficiency
F-1	28.63	0.5122	0.00202	76.66
F-2	47.34	0.8234	0.00294	81.23
F-3	59.56	1.1050	0.00329	82.44
F-4	71.32	1.2410	0.00389	87.58

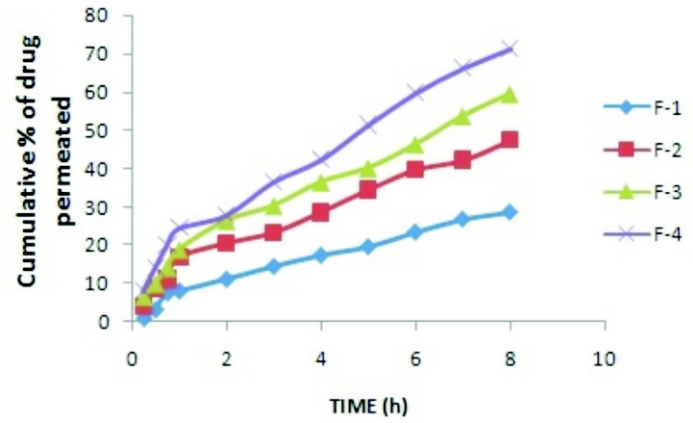

Fig.1.: Results of permeation study for F1, F2, F3 and F4.

Fig. 1 shows the results of permeation study of different formulations The in vitro skin permeation data were fitted to different equations and kinetic models to explain permeation profiles (Table 5). The coefficient of correlation of each of the kinetics was calculated and compared.

The *in vitro* permeation profiles of all the different formulations of transdermal patches could be best expressed by Korsmeyer-Peppas model for the release of drug from a homogeneous polymer matrix type delivery system that depends mostly on diffusion characteristic. The slope *(n)* values obtained by Korsmeyer-Peppas equation indicated that the drug released by non-fickian diffusion predominated with all formulations. The skin irritation study indicated that neither the polymer nor the drug caused any noticeable irritation or inflammation on or around the patch area, either during the period of study or after removal of the patch.

Table 5. Various kinetic models for TDDS of Metoprolol tartrate

Formulation code	Zero order model (R^2)	First order model (R^2)	Higuchi model (R^2)	Hixson–Crowell model (R^2)	Korsmeyer-Peppas model	
					R^2	*n*
F-1	0.812	0.934	0.946	0.848	0.971	0.58
F-2	0.826	0.828	0.928	0.956	0.982	0.54
F-3	0.916	0.918	0.854	0.972	0.986	0.66
F-4	0.844	0.936	0.938	0.948	0.988	0.72

4.Conclusion

Based on the results of this study, it can be concluded that a well-controlled release and effective skin permeation of the drug was achieved by the formulation containing 2% (w/v) PVP and 0.5% (w/v) chitosan (F4). The physicochemical evaluation indicated the stability of the developed transdermal patches. The controlled release of drug from the transdermal patches suggested that the frequency of administration can be reduced. The formulation which contains highest concentration of PVP showed greater tensile strength and swellability. Permeation results of optimized formulation revealed Korsmeyer-Peppas model release pattern. Further work is to establish the therapeutic utility of this system by pharmacokinetics and pharmacodynamic studies on animal models.

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Conflicts of Interest

The authors report no conflict of interest.

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