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MODIFIED RELEASE OF DILTIAZEM HYDROCHLORIDE USING TRANSDERMAL DRUG DELIVERY SYSTEM

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Abstract

The objective of present study was to investigate the suitable polymeric films for the development of diltiazem hydrochloride (diltiazem HCl) transdermal drug delivery systems. Hydroxypropyl methylcellulose (HPMC) and ethyl cellulose (EC) were used as hydrophilic and hydrophobic film formers, respectively. Effects of HPMC/EC ratios and plasticizers on mechanical properties of free films were studied. Matrix films were evaluated for their physicochemical characterization followed by *in vitro* evaluation. The Thickness and weight of patch increase with the increase in polymeric grade and content. Fourier transforms infrared spectroscopy results confirmed that there is no interaction between drug and polymer used. The *in vitro* drug release followed Higuchi kinetic as its coefficient of correlation values predominates over first order kinetics. Comparison of skin permeation rate between hairless rat and human cadaver skin was done by using diffusion cells. Out of the various formulations made, the selected formulations are better in their *in vitro* dissolution thus holds potential for transdermal delivery.

INTRODUCTION

Most of the chronic diseases have genetic, hereditary cause or lifestyle borne like hypertension, asthma, diabetes, addiction etc. It is desirable, from the standpoint of pharmacodynamic to maintain the drug concentration in plasma within a therapeutic effective range for long periods [1]. However, even if the drug is well absorbed orally, it will run through entero-hepatic cycle. In some cases it will decrease the systemic availability of drug as it undergoes hepatic first pass metabolism. This effect will establish a significant difference between claimed (theoretical) and attained (practical) bioavailability of drug moiety [2]. To compensate the loss, massive dosing is being done but that makes the product bulkier, process uneconomical and may cause toxicity in some cases. Among conventional dosage forms, continuous i.v. infusion is the sole exception that will bypass the hepatic cycle and also releases the drug following zero order kinetics for long term, hence minimizes overdosing [3,4].

Diltiazemhydrochloride [DL-HCL] is rapidly and completely absorbed from the gastrointestinal tract but is subject to saturable first pass hepatic metabolism. Following oral administration of DL-HCL was shown to be rapidly and extensively metabolised in the liver and to be rapidly eliminated from plasma through urine and faeces, mainly as inactive metabolites. Bioavailability of about 35% has been reported after a 30 mg dose at steady state. Administration of DL-HCL following a meal reduced the bioavailability. The pharmacokinetics of DL-HCL is non-linear due to the saturable first-pass hepatic metabolism and an increase in dose may produce a disproportionate increase in plasma concentration. The terminal plasma half-life is about 8.6 hours. TDDS is considered to be the ideal method which can bypass the difficulties of first-pass metabolism, enable absolute elimination of GIT toxic effects, maintain the steady plasma level of drug for a prolonged period and deliver the drug at predetermined rate without the hazards of specialist care as is required in the intravenous infusion. Since transdermal patches offer a better quality of life, they are more popular than the oral dosage form. The aim of the present study

was to prepare transdermal patches of DL-HCL using hydrophilic and hydrophobic polymer and the purpose was to provide steady state plasma concentration of the drug with improved bioavailability when compared to conventional dosage forms and to meet the patient compliance.

MATERIALS & METHODS

Materials:

DL-HCL was received as a gift samples from Wokchardt pharma limited Aurangabad, India. Hydroxypropyl methylcellulose (HPMC E5) and ethyl cellulose (EC) were procured from Shreeji chemicals and Rolex chemical industries Mumbai, India, respectively. Dimethyl sulfoxide (DMSO) and dibutyl phthalate (DBP) were procured from S.D Fine chemical ltd. (Mumbai, India). All other laboratory chemicals used in the study were of analytical reagents grade. Double distilled water was used throughout the study.

Investigation of physicochemical compatibility of drug and polymer:

The physicochemical compatibility between DL-HCL and polymers used in the films was studied by using Fourier transform-infrared (FTIR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy. The pellatization was done by the KBr pellet method. The FT-IR spectra were recorded in the wavelength region between 4000 and 400 cm^{-1}. The spectra obtained for DL-HCL and physical mixtures of DL-HCL with polymers were compared.

Preparation of transdermal patch:

In the present study, drug loaded matrix type transdermal films of DL-HCL were prepared by solvent evaporation method. A mould (Teflon plate) of 6 cm radius with a total area of 28.26 cm^2 as fabricated was used. 360 mg of the polymer(s) was accurately weighed and dissolved in 7 ml of acetone: methanol (4:3) and kept aside to form clear solution. Dibutyl phthalate was used as plasticizer and dimethyl sulfoxide was used as permeation enhancer. 40 mg of DL-HCL was dissolved in the above solution and mixed for 10 min. The resulted uniform solution was cast on the mould and dried at 40°C in the hot air oven for 24 hrs. An inverted funnel was placed over the mould to prevent fast evaporation of the solvent. After 24 hrs the dried films were taken out and stored in a desiccator's for further studies. Compositions of different formulations are represented in Table 1.

EVALUATION OF TRANSDERMAL PATCH:

Physical appearance

All the prepared patches were visually inspected for colour, clarity, flexibility and smoothness.

Thickness uniformity

The thickness of the formulated film was measured at 3 different points using a digital calliper and average thickness of three reading was calculated [5, 6].

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually and the average weight was calculated [7, 8].

Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (5 x 5 cm) was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

Percentage moisture uptake

The films were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80-90% RH. The final weight was noted when there was no change in the weight of individual patch. The study was performed at room temperature. The percentage moisture absorption was calculated using the formula: Percentage moisture uptake= [(Final weight- Initial weight)/ Initial weight] ×100.

Percentage moisture content

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. The final weight was noted when there was no change in the weight of individual patch. The moisture loss was calculated using the formula: Percentage moisture content = [(Initial weight- Final weight) / Final weight] ×100.

Water vapour permeability (WVP) evaluation: [9] water vapour permeability can be determined by a natural air circulation oven. The WVP can be determined by the following formula; WVP=W/A Where, WVP is expressed in gm/m^2 per 24 hrs, W is the amount of vapour permeated through the patch expressed in gm/24 hrs, A is the

surface area of the exposure samples expressed in m^2.

Tensile strength and % Elongation [10]

The films were casted on mercury and taken in rectangular containers using proportionate quantity of the solution calculated on the basis of area. The films were cut into strips of 1cm width and 15cm length. The films were fixed onto the Tensile strength apparatus in such a way that the length of film between the jaws was initially 10 cm. The trials where the breakage occurred at the jaw were invalid and the result was repeated on another strip. The Tensile strength was calculated by the formula, Tensile strength =Break force [1 + change in length]/ (width) (breadth) [initial length of the film]. The percent elongation was determined by noting the length just before the break point and substituting the formula % Elongation = [Final length - Initial length] * 100 / Initial length.

Drug content uniformity of films [11]

The patches ($1cm^2$) were cut and added to a beaker containing 100 ml of phosphate buffered saline of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 236 nm spectrophotometrically. The experiment was repeated to validate the result.

***In vitro* drug release studies**[12]

In vitro skin permeation studies were performed by using a modified Franz diffusion cell with a receptor compartment capacity of 20 ml. The synthetic cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 1 cm^2 and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37 ± 0.50°C. The samples of 5 ml were withdrawn at time interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hrs (For F2 up to 16 hrs), analyzed for drug content spectrophotometrically at 236 nm against

blank. The receptor phase was replenished with an equal volume of phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug permeated per square centimeter of patches were plotted against time.

RESULTS AND DISCUSSION

Physicochemical compatibility of drug and polymer

The FT-IR spectral analysis of DL-HCL, HPMC E5 and EC alone showed that the principal peaks were observed that confirming the compatibility of the drug and polymer respectively.

Evaluation of transdermal patch

The prepared transdermal patches were evaluated for their physicochemical characteristics such as weight variation, thickness, % moisture loss and % moisture absorption, water vapour transmission rate, folding endurance (Table 2), tensile strength, drug content and *in vitro* drug release (Table 3). The transdermal patches were transparent, smooth, uniform and flexible. The thickness of the patches was varied from 0.14 ± 0.010 mm to 0.19 ± 0.015 mm. Low standard deviation values in the film thickness measurements ensured uniformity of the patches prepared by solvent evaporation. The weights ranged between 0.432 ± 0.002 mg and 0.473 ± 0.023 mg, which indicates that different batches patch weight, were relatively similar. The % moisture loss was found to be between 7.46 ± 0.52 to 10.20 ± 0.27 and % moisture absorption was found to be 2.77 ± 0.13 to 6.94 ± 0.14. The result revealed that the moisture absorption and loss was found to increase with increasing concentration of hydrophilic polymers. The small moisture loss in the formulations helps the film to remain stable, brittle and free from complete drying. Again low moisture absorption protects the material from microbial contamination and bulkiness of the patches. The patches prepared from HPMC E5 (F1) show more tensile strength than the patches prepared from EC (F2). As the concentration of hydrophilic polymer HPMC E5 was increased there is increase in tensile strength. The tensile strength measures the ability of a patch to withstand rupture. Presence of DBT and DMSO has shown good tensile strength. The mean value was found to vary between 2.96 **±**

0.005 to 3.95 ± 0.015 kg/mm^2. Drug content was found to be 1.291 ± 0.005 mg/cm^2 to 1.363 ± 0.005 mg/cm^2. The cumulative % drug permeated and % drug retained by the individual patch in the *in vitro* skin permeation studies were based on the mean amount of drug present in the respective patch.

***In vitro* drug release studies**

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. The result indicated that the release of drug from patches increases with increasing concentration of HPMC E5. The cumulative percent of drug release in 7 hrs was found to be the highest (98.1887 ± 0.5689) from formulation F1 carrying HPMC E5 and minimum (67.9393 ± 1.8120) from formulation F2 carrying EC. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate. Formulation F3 containing HPMC E5: EC (1:1) showed cumulative % drug release of 99.1887 ± 0.1758 in 24 hrs, emerging as a best formulation by fulfilling the requirement of better and sustained release which was not possible with HPMC E5 and EC alone. The diffusion kinetics of the drug DL-HCL was analyzed by graphical method for Zero order, First order, Higuchi and Peppas exponential equation. The r^2 value (Table 4) of fitting model indicates that the drug release kinetics of formulations (F1 and F3) follows zero order kinetics and formulation (F2) showing first order release kinetics.

DISCUSSION

Transdermal drug delivery system is a most suitable system for a long term treatment or for a multi dose treatment because transdermal patches are prepared for a long period of time in a single dose providing treatment from a day to even up to seven days. TDDS also increases the bioavailability of drug by avoiding the first pass metabolism and increases the therapeutic efficacy of drug by reaching into the

systemic circulation. Polymers HPMC E5 and EC were selected on the basis of their adhering property and non toxicity. The result of the finding showed excellent adhering property and controlled release. Result from present study concluded that DL-HCL in combination with HPMC E5, EC and with incorporation of DBT and DMSO produced smooth, flexible and transparent film. FT-IR studies showed characteristic peaks of DL-HCL, confirming the purity of the drug. FT-IR spectral studies indicated there was no interaction between DL-HCL and polymers used. DL-HCL patches were prepared with combination of these polymers and evaluated it for physical parameters such as thickness, drug content, weight variation, and % moisture loss and % moisture absorption. From the results, it was observed that thickness, drug content, weight variation, low moisture loss, low moisture absorption, tensile strength were suitable for maximum stability of the prepared formulations. The drug content of TDDS patches ranged from 1.390 ± 0.005 mg/cm^2 to 1.460 ± 0.005 mg/cm^2. The drug release rate increased when the concentration of hydrophilic polymer was increased. The cumulative percentage drug release for F1 was found to be 98.1887 ± 0.5689 % at 7 hrs and for F2 it was found 67.9393 ± 1.8120 % at 24 hrs. The formulation, F3 [HPMC E5: EC (1:1)] is considered as a best formulation, since it shows maximum *in vitro* drug release as 99.1887 ± 0.1758 % at 24 hrs.

CONCLUSION

In conclusion, controlled release TDDS patches of DL-HCL can be prepared using the polymer combinations, HPMC E5: EC (1:1) with DBT and DMSO as plasticizer and enhancer, respectively. The release rate of drug through patches increased when the concentration of hydrophilic polymer was increased. The drug release kinetics of formulations (F1 and F3) follows zero order kinetics and formulation (F2) showing first order release kinetics. Further, *in vivo* studies have to be performed to correlate with *in vitro* release data for the development of suitable controlled release patches for DL-HCL.

Table 1

Composition of different formulations containing DL-HCL

Compositions	F1	F2	F3
DL-HCL (mg)	40	40	40
HPMC E5 (mg)	360	-	180
EC (mg)	-	360	180
Dibutyl phthalate (ml)	0.15	0.15	0.15
Acetone : Methanol (4:3) (ml)	7	7	7

Table 2

Results of Thickness (mm), Weight uniformity (g), Folding endurance, % Moisture absorption, % Moisture loss, Water vapour transmission rate

Formulation code	Thickness (mm)	Weight (g)	Folding endurance	Moisture absorption (%)	Moisture loss (%)	Water vapour transmission rate
F1	0.15±0.010	0.473±0.023	293	6.94±0.14	10.20±0.27	0.0051±0.0010
F2	0.19±0.015	0.493±0.020	269	7.99±0.13	8.22±0.23	0.0049±0.0003
F3	0.14±0.010	0.445±0.027	289	3.23±0.10	9.10±0.17	0.0031±0.0007

Table 3

Results of tensile strength, drug content and *in vitro* drug release

Formulation code	Tensile strength (kg/mm2)	Drug content (%)	% Drug released
F1	3.95±0.015	96.38±0.3906	98.1887 ± 0.5689
F2	3.65±0.012	98.38±0.3906	67.9393 ± 1.8120
F3	2.85±0.017	95.36±0.8152	99.1887 ± 0.1758

Table 4

R^2 value of model fitting of DL_HCL

Formulation code	Zero order	First order	Higuchi matrix	Peppas kinetics
F1	0.9976	0.9476	0.8851	0.9935
F2	0.9816	0.9326	0.9851	0.9645
F3	0.9845	0.9136	0.9351	0.9255

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