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Research Article

Development and evaluation of sustained release matrix transdermal patches of Nano carvedilol

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ABSTRACT

Transdermal drug delivery system of nano carvedilol has been formulated by solvent casting method. Nano sized carvedilol was prepared by high pressure homogenization technique and morphology of nano particles confirmed by scanning electron microscopy. Sustained release nano carvedilol matrix patches were prepared by using hydroxyl propyl methyl cellulose (HPMC) and poly vinyl pyrrolidone (PVP). Physicochemical parameters like thickness uniformity, folding endurance, elongation break, weight variation, drug content uniformity, percentage moisture content, percentage moisture uptake, water vapor transmission rate (WVTR) were evaluated. On the basis of *in vitro* drug release studies (12 hours) and *ex vivo* permeation performance, formulation code CT2 was found to be better than other formulation and it was selected as the optimized formulation. *In vitro* kinetic studies results followed higuchi (r^2=0.9948), and the mechanism of release was diffusion. The optimized patch was found to be stable at 40°C ± 2°C and 75 ± 5 % RH for six month with respect to their physicochemical parameters and drug content.

Keywords: Nano carvedilol; Transdermal patches; Physicochemical parameters; *In-vitro* study

INTRODUCTION

Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver medicines via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. TDDS has gained a lot of interest during the last decade as it offers many advantages over the conventional dosage forms and oral controlled release delivery systems notably avoidance of hepatic first pass metabolism, less frequency of administration, reduction in gastrointestinal side effects and improves patient compliance. For transdermal products the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin (Sivakumar T *et al*., 2010).

Carvedilol, a cardiovascular drug that is currently used for the treatment of hypertension in many countries. The reduction in blood pressure produced by carvedilol results primarily from beta-adrenoceptor blockade, vasodilatation and alpha 1- adrenoceptor blockade. The multiple action of carvedilol may also provide that underlying rational for the use of the drug in the treatment of coronary artery disease and congestive heart failure (Ruffolol RR and Feuerstein GZ., 1997). Carvedilol is well absorbed from the gastrointestinal tract but is subjected to significant first pass metabolism in liver. Oral bioavailability of the drug has been about 25%. It has a short biological half-life 2.2±0.3hour; longer half-lives of about 6hours have been measured at low concentration (Thummel KE and Shen DD., 2001).

Carvedilol was chosen as the model candidate for this study since it possesses near ideal characteristics that a drug must have in formulating a transdermal drug delivery system: low molecular weight, a favorable logarithmic partition coefficient, smaller dose range, short plasma half-life, poor oral bioavailability (due to poor solubility). It also means multiple daily administrations with subsequent lack of patient compliance (Shashikant D Barhate and Mrugendra B. Potdar., 2011). Reservoir type transdermal patch of carvedilol has been already reported based on the use of HPMC, combination of PVA and PVP (Yuveraj singh tanwar *et al*., 2007; Shashikant D. Barhate *et al*., 2009). The reported transdermal formulation of carvedilol did not involve any attempt to use of nano particle.

In the present study envisaged to select the suitable polymer composition of HPMC and PVP for the transdermal delivery and the effect of nano carvedilol in sustained release formulation.

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Table 1: Composition of different formulations

S.No.	Ingredients	Formulation code				
		CT1	CT2	CT3	CT4	CT5
1	Nano carvedilol (mg)	10	10	10	10	10
2	HPMC (mg)	96	92	88	84	80
3	PVP (mg)	04	08	12	16	20
4	Glycerine (mg)	57	57	57	57	57
5	Dibutyl phthalate (mg)	26.5	26.5	26.5	26.5	26.5
6	PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5
7	Ethanol (ml)	3	3	3	3	3
8	Acetone (ml)	2	2	2	2	2
9	Castor oil (ml)	1	1	1	1	1

MATERIALS AND METHODS

Materials

Carvedilol (Code No J50000025) provided as a gift sample by Dr Reddy's Laboratories (Hyderabad, India), Sodium dodecyl sulphate (SDS), Poly vinyl pyrrolidone (PVP) K-90, Acetone and Hydroxy propyl methyl cellulose (HPMC) K 100M (LOBA Chemie Pvt Ltd, Mumbai). All other chemicals were of analytical grade and were used as procured.

Preparation of nano carvedilol

Carvedilol nano pareticles was prepared by emulsion-diffusion (solvent exchange) method, further homogenized by high pressure homogenization using PVP K 30/SDS as stabilizer. Scanning electron microscopy (SEM) image of carvedilol and nano carvedilol were recorded for particle size (morphology) analysis using scanning electron microscopy (Kitachi 3000, Japan).

Compatibility study

The physicochemical compatibility between carvedilol and polymers used in the patches were studied by using Fourier transform-infrared (FT-IR-2500, Analytical, Germany) 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 carvedilol and physical mixtures of carvedilol with polymers were compared.

Preparation of nano sustained release transdermal patches

The matrix transdermal patches of carvedilol were prepared by the solvent casting technique. The casting solution was prepared by dissolving the polymers (HPMC: PVP) in ethanol. The plasticizers (glycerine and dibutyl phthalate), Surfactant (PEG 400), permeation enhancer (castor oil) and drug (nano carvedilol dissolved in acetone) were dispersed in the polymeric solution using thermostatically controlled magnetic stirrer.

Backing membrane was cast by pouring 4% aqueous solution of polyvinyl alcohol to petridish drying at 60°C. The patches were prepared by pouring the homogenous dispersion was cast on a backing membrane and dried at 40°C for 5-6 hours. The dried patches were peeled from glass mould, wrapped in aluminium foil and preserved in desiccators until further studies. Compositions of different formulation are represented in table 1.

Evaluation of transdermal patches

Formulated patches were evaluated for their physicochemical characteristics such as thickness uniformity, folding endurance, elongation break, weight variation, drug content uniformity, percentage moisture content, percentage moisture uptake, water vapor transmission rate (WVTR), *in vitro* drug release, *ex vivo* permeation study, kinetic studies and stability studies. Patches with any imperfection, entrapped air, differing in thickness, weight or content uniformity were excluded from further studies. The results of physicochemical characterization of the patches are shown in table 2.

Thickness uniformity

The thickness of the formulated patches were measured at three different points using a digital caliper and the average thickness of three reading was calculated (Sivakumar T *et al*., 2010).

Folding endurance

This was determined by repeatedly folding one patch at the same place till it broke. The number of times the patgh could be folded at the same place without breaking/cracking gave the value of folding endurance (Devi VK *et al*., 2003).

Elongation break

The percentage elongation break was determined by noting the length just before the break point and substituted in formula

$$\text{Elongation } \% = \left(\frac{\text{Initial length} - \text{Final length}}{\text{Final length}} \right) \text{X } 100$$

Weight variation

Each formulation, three randomly selected patches were weighed individually and average weight of three patches was found out (Sivakumar T *et al*., 2010).

Table 2: Physicochemical characterization

Parameters	CT1	CT2	CT3	CT4	CT5
Thickness (mm)	0.22±0.042	0.25±0.037	0.24±0.034	0.26±0.028	0.27±0.036
Folding endurance	> 186	> 192	> 180	> 175	> 174
Elongation break (%)	85.52±2.24	86.66±4.12	83.32±3.23	83.40±2.24	82.15±4.32
Weight variation (mg)	197±2.36	198±1.58	199±1.42	194±2.21	195±3.40
Drug content (%)	98.13±0.65	98.75±0.54	97.50±0.35	96.00±0.84	96.25±0.48
Moisture content (%)	11.96±1.42	10.84±1.56	8.78±0.82	8.64±0.81	7.64±0.73
Moisture uptake (%)	6.25±0.46	4.82±0.58	3.44±0.32	3.31±0.48	3.25±0.42
WVTR (mg cm^{-2} h^{-1})	0.63±0.08	0.55±0.17	0.05±0.04	0.33±0.03	0.25±0.03

Table 3: Kinetic modeling of drug release

Formulation code	Zero order	First order	Higuchi	Hixo crowel
CT1	0.9037	0.7864	0.9522	0.9306
CT2	0.9399	0.8675	0.9848	0.9862
CT3	0.8961	0.9475	0.9982	0.9780
CT4	0.9235	0.9537	0.9965	0.9860
CT5	0.9324	0.9565	0.9963	0.9883

Drug content uniformity

A fabricated patch was cut into small pieces and placed in a 100ml of pH 6.8 phosphate buffer. The contents were stirred in a mechanical stirrer to get a homogenous solution and filtered using whatmann filter paper. The filtrate was examined for the drug content against the reference solution consisting of placebo patch (contains no drug) at 242 nm spectrophotometrically. The experiment was repeated to validate the result. (Jayaprakash S *et al*., 2010)

Percentage of moisture content

The patches were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hours. Individual patch was weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight (Gupta R and Mukherjee B., 2003).

Percentage moisture uptake

The patches were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of potassium chloride, which maintains 80-90% RH. After 24 hours, the patches were taken out and weighed. The percentage moisture absorption was calculated using the formula:

$$\% \text{ Moisture uptake} = \left(\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \right) X\ 100$$

Water vapour transmission rate (WVTR)

WVTR is defined as the quantity of moisture transmitted through unit area of film in unit time. Glass cells were filled with 2gm of anhydrous calcium chloride and a patch of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2 °C for 24 hours (Krishna R and Pandit JK., 1994).

$$WVTR = \frac{WL}{S}$$

Where, W is the water vapor transmitted in 'mg', L is the thickness of the film in 'cm' and S is the exposed surface area in square cm.

***In vitro* release studies**

The drug release was determined using USP II dissolution tester maintained at 37± 0.5°C and stirred at 50 rpm. Each one forth of patch was mounted on the glass slide at the bottom of the dissolution vessel containing 900 ml of phosphate buffer pH 6.8. Aliquots of 5 ml of samples were withdrawn with graduated pipette at 1, 2, 4, 8, 10 and 12 hour time intervals, replacing with equal volume of buffer solution to maintain the sink condition. The sample was analyzed spectrophotometrically at 242 nm and the cumulative amount of drug released at various time intervals was calculated and plotted against time (Costa P and Lobo JS., 2001).

***Ex vivo* permeation studies**

Ex vivo permeation studies were performed by using an open ended glass tube (both side open), with receiver compartment capacity of 50 ml. The sigma dialysis membrane (grade 70) was activated in phosphate buffer pH 6.8 by soaked in it for 2 hours. A section of membrane was cut, measured and placed on the dermal side of the membrane. Membrane in the donor compartment facing the drug matrix side of the patch to the membrane and backing membrane upward. The holder containing the membrane and formulation was then placed on the receiver compartment of the cell, containing phosphate buffer pH 6.8. The whole assembly was fixed on a magnetic stirrer, and the solution in the receiver compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 37±0.5°C. The sample were withdrawn at different time intervals and ana-

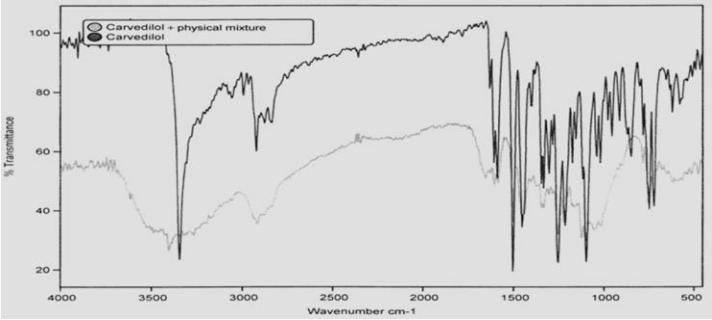

Figure 1: Compatibility study (FT-IR)

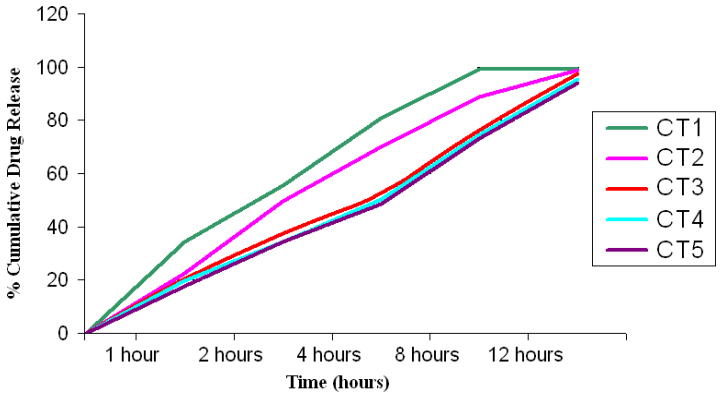

Figure 2: In vitro cumulative drug release

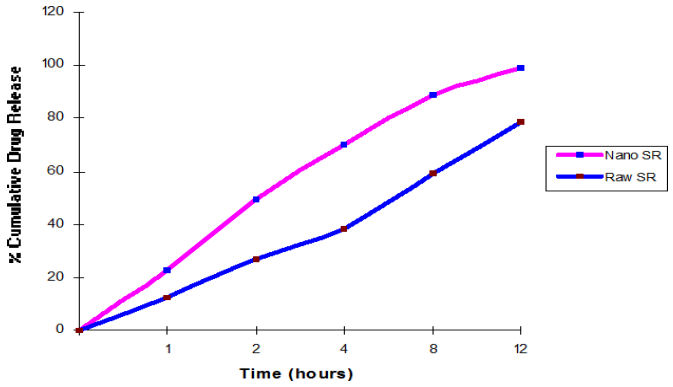

Figure 3: Comparative in vitro release of raw and nano carvedilol patch (CT2)

lyzed for drug content spectrophotometrically (Umesh D Mathur *et al*., 2009).

Kinetic modeling of drug release

To analyze the mechanism of drug release from the patches, the release data were fitted to the following equations (Rakesh P Patel *et al*., 2009),

Zero-order equation

$$Q = k0t$$

Where Q is the amount of drug released at time t, and k0 is the release rate.

First-order equation

$$\ln (100-Q) = \ln 100 - k1t$$

Where Q is the percent of drug release at time t, and k1 is the release rate constant.

Higuchi's equation

$$Q = k2\sqrt{t}$$

Where Q is the percent of drug release at time t, and k2 is the diffusion rate constant

Stability study of optimized formulation

Optimized patches were subjected to short term stability testing. Film were pleased in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained 40°C ± 2°C and 75 ± 5 % RH for six month as per ICH guidelines. Changes in the appearance and drug content of the stored patches were investigated after storage at the end of every two months (Mathews BR., 1999).

RESULT AND DISCUSSION

Preparation of nano carvedilol

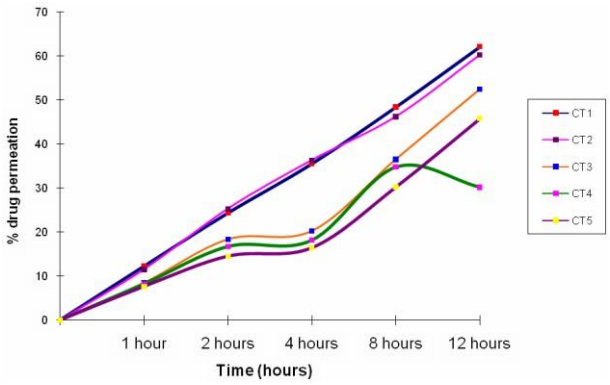

Figure 4: Ex vivo permeation studies

Carvedilol nanoparticles are focused on the emulsion-diffusion method, combination of PVP and SDS was used for stabilization of nanosuspension. The Carvedilol nanoparticles have been successfully prepared by high pressure homogenization techniques. SEM imaging was performed to characterize the morphology of raw and nanosized carvedilol patches. Particles size below 100 nm was observed with this homogenization technique, which is confirmed by SEM.

Compatibility study

Fourier transform infrared spectra of carvedilol alone and its combination with polymer shown in figure 1. FT-IR spectra of the pure (nano) carvedilol and the drug-polymer mixture showed characteristic bands at 3344.93cm^{-1} (N-H Stretching), 2922.59cm^{-1} (O-H Stretching), 2630.43cm^{-1} (C-H Stretching) and 1099.83cm^{-1} (C=O Stretching) due to functional group, indicating the chemical stability of carvedilol in the chosen polymeric mixture. This also indicated the carvedilol is not involved in any chemical reaction with polymer used.

Preparation of nano sustained release transdermal patches

In the present study, five different formulations of nano carvedilol transdermal patches were prepared using HPMC and PVP by solvent casting method. The prepared patches were characterized for physicochemical properties, *in vitro* release, *ex vivo* permeation studies, *in vitro* kinetic studies and stability studies.

Physicochemical characterization transdermal patches

The thickness of patches varied from 0.22±0.042 to 0.27±0.036 mm, high concentration of PVP increase the thickness of patch. The percentage elongation was measured by using the instrument designed in the laboratory. The formulation CT2 showed the maximum elongation where as the least value was found with CT5. The decrease in percent elongation at break with CT5 containing 10% w/v PVP might be due to precipitation during the process of solvent evaporation. The percent elongation at break was found to vary between 82.15±4.38 to 86.66±4.12.

Folding endurance was found to vary between >174 to >192. It was observed that the patches formulated by used plasticizer were free from brittleness. Weight variation in the formulated transdermal patches of carvedilol was between 194±2.21 to 199±1.42 mg / patch. Content uniformity of various formulations was between 96±0.84 to 98.75±0.54%. The content analysis of the prepared formulations has shown that the process employed to prepare patches in this study was capable of giving films with uniform drug content and minimum batch variability.

Moisture content and moisture uptake studies indicated that the increase in the concentration of HPMC polymer was directly proportional to the increase in moisture content and moisture uptake of the patches. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage.

The moisture uptakes of patches were observed in the range of 2.1±0.48 to 3.5±0.46%. Moisture uptake was more pronounced in patch CT1 and CT2 which contain higher percentage of HPMC compare to others patches. The moisture uptake of the formulations was low, which could protect the formulations from microbial contamination and reduce bulkiness (Mutalik S and Udupa N., 2004). The patches formulated with high HPMC polymer concentration showed maximum WVTR of 0.63±0.08 mg cm^{-1}h^{-1}, which can be attributed to the hydrophilic nature of polymers.

***In vitro* drug release studies**

Release studies are required for predicting the reproducibility of rate and duration of drug release from matrices has been know for ensuring the sustained release performance. The results indicated that the release of drug from patches increase with increasing concentration of HPMC. The cumulative percentage of drug release in 12 hours was found to the highest (98.94%) from formulation CT2 carrying HPMC and PVP in ratio of 23:2 and minimum (93.86%) from formulation CT5 carrying HPMC and PVP in ratio of 20:5 (Figure 2). *In vitro* release of optimized nano carvedilol (CT2) compared with raw carvedilol patch, which was prepared with same composition. It was observed that the nano carvedilol optimized patch have shown release more than 98% in 12 hours, where as the raw carvedi-

lol have shown cumulative release of below 79% (Figure 3).

***Ex vivo* permeation studies**

The result of *ex vivo* permeation studies of nano carvedilol from transdermal patches are shown in figure 4. Formulation CT1 exhibited greatest 62.15% of drug release value, while formulation CT4 exhibit lowest 30.25% of drug release value. The cumulative amount of drug released from formulations CT1 and CT2 is much higher than formulations CT3, CT4 and CT5. The optimized formulation CT2 also achieved a high cumulative amount 60.25% of drug permeation at the end of 12 hours.

Kinetic modeling of drug release

The cumulative amount of *in vitro* drug release was plotted against time was fitted to zero, first and higuchi kinetic model. As indicated in Table 3, the release profile of carvedilol followed mixed zero-order and first-order kinetics in all formulations. However, the release profile of the optimized formulation CT2 (r^2=0.9948 for Higuchi) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism.

Stability studies

Optimized patches were placed in humidity chamber for short term stability studies, which were withdrawn every two months and analyzed for their drug content. Decrease in the drug content from the patches ranged from 98.75 to 94.48 %. It was found that the drug loss is less though the patches were stored for six month. The patches were also observed for their appearance and texture. These properties did not change in patches during the period of study. Transdermal patches containing carvedilol using HPMC and PVP polymers showed satisfactory characteristic without being drastically influenced by ageing.

CONCLUSIONS

In conclusion, sustained release transdremal patches of nano carvedilol in combination with HPMC and PVP produced smooth, flexible and transparent patches. All formulation showed good physicochemical properties like thickness uniformity, folding endurance, elongation break, weight variation, drug content uniformity, percentage moisture uptake, water vapor transmission rate (WVTR). The *in-vitro* release of drug through patches and permeation across dialysis membrane increased when the concentration of HPMC polymer was increased. The drug release kinetics of all patches follows higuchi except CT1, whereas, the mechanism of drug release were diffusion. Stability studies of the optimized batch at 40^{o}C ± 2^{o}C and 75 ± 5 % RH showed no significant alteration in drug content. The finding of this result revealed that the problems of carvedilol on oral administration like dissolution rate limited absorption can be overcome by applying topically in the form of transdermal patch.

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