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Formulation, Physico-chemical characterization and Release kinetic study of antihypertensive Transdermal Patches

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ABSTRACT

The objective of the present study was to develop the matrix type transdermal patches of Carvedilol Phosphate (CP) using polymeric combination of polyvinylpyrrolidone (PVP) and ethylcellulose (EC) by solvent casting method over a backing membrane of polyvinylalcohol. All the prepared formulations were subjected to physicochemical studies like drug content, thickness, weight variation, moisture content, moisture uptake, water vapor transmission, flatness and folding endurance. The drug-polymer compatibility was ascertained by Fourier Transform Infrared spectroscopy (FTIR). The surface morphology and drug distribution in the patch was studied by Scanning Electron Microscopy (SEM). The release profile of the drug was evaluated by in-vitro dissolution study in 6-stage USP dissolution apparatusII, and in-vitro permeability study was done in 6 stage diffusion cell apparatus (FDC-06, Orchid Scientifics, Nashik) through dialysis membrane-70(LA 393, Hi Media). The results of physicochemical studies indicate the suitability of patch formulation of CP with the polymeric combinations of PVP and EC. The in-vitro drug release and permeation studies indicate that the required rate of drug release can be adjusted by selecting proper ratio of PVP and EC. Highest correlation was observed with Higuchi plot rather than first order or zero order. The present study has demonstrated the potential of the fabricated matrix transdermal patches of CP for sustained delivery through transdermal route.

Keywords: Transdermal Patch, Carvedilol phosphate, Release Kinetics, SEM, FTIR.

INTRODUCTION

Carvedilol phosphate is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is safe and effective in the treatment of hypertension, left ventricular dysfunction and heart failure. Carvedilol is rapidly and extensively absorbed following oral administration of immediate-release carvedilol tablets, with an absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism [1]. Carvedilol also has a short plasma half-life of 6 hours [2]. Long-term therapy of hypertension by carvedilol oral administration may result in poor patient compliance because of low bioavailability and short plasma half-life, leading to increased frequency of administration [3]. Extended release carvedilol formulation is therefore necessary for improving patient compliance and reducing frequency of administration. The release of carvedilol can be extended and controlled by making it in Transdermal drug delivery systems (TDDS), which are a class of novel drug delivery systems because of their so many advantages such as reduced side effects, less frequent administration to produce the desired constant plasma concentration associated with improved patient compliance, elimination of the first-pass effect, sustained drug delivery and interruption of treatment when necessary [4, 5]. Ubaidulla et.al had shown the effect of hydrophilic and hydrophobic polymer on in-vitro and in-vivo characteristics of matrix type transdermal patches of carvedilol [6]. Here the phosphate salt of carvedilol was chosen as it is being already selected in extended release capsule formulation as well as it possesses the ideal characteristics for formulation a drug in transdermal drug delivery system like low molecular weight (513.5), high lipid solubility, low daily dose (10mg daily) as well as high degree of first-pass metabolism [7]. The present study envisaged the physicochemical characterization of transdermal patches containing carvedilol phosphate in combination with different ratio of polyvinylpyrrolidone (PVP) and ethylcellulose (EC) [8]. The drug release kinetics and permeation profiles were also investigated from different patches.

MATERIAL AND METHODS

Materials

Carvedilol Phosphate was received as a gift sample from Sun Pharmaceuticals Ltd.(Baroda,India) EC (ethoxyl content 48-49.5% and viscosity range 18-22 cp), PVP (M.W. 40,000 approx., viscosity of 5% aqueous solution at 25° C about 2.4cp) were procured from Loba Chemie Pvt. Ltd. Mumbai, India. Other materials used in this study like chloroform, di-n-butylphthalate, potassium chloride, calcium chloride are of analytical grade.

Drug-polymer compatibility study

The physicochemical interactions between carvedilol phosphate and the polymers used in the formulation of transdermal patches PVP and EC were studied using Fourier transform infrared spectroscopy (FTIR). The infrared spectra were recorded in the FTIR (Perkin Elmer) instrument in the wave length region between 4400 and 600cm^{-1} by KBr pellet method. The spectra obtained for drug, polymer and physical mixture of drug and polymer were compared.

Preparation of Transdermal Patches

The matrix type transdermal patches containing carvedilol phosphate were prepared using solvent casting method. The PVP and EC were used in different proportion; total quantity of

polymer in the patches were remain constant (500mg). The proportion of two polymers is varied in different formulations (Table 1). The drug load is also constant (5mg) in each formulation. Di-n-butyl-phthalate is used as plasticizer. The polymers were dissolved in chloroform. The drug and plasticizer were added and dispersed homogeneously over a magnetic stirrer. Then the polymeric dispersion was poured over a backing membrane of polyvinyl alcohol. The patches were dried overnight at room temperature and then stored in desiccators for evaluation. [9]

Table1. Composition and physicochemical characterization of Carvedilol phosphate transdermel patches*

Formulation Code	PVP : EC	Total weight (mg)	Thickness (mm)	% Moisture content	% Moisture uptake	Folding Endurance	Moisture vapor transmission ($gm/cm^2/h$) $\times 10^{-4}$
FCP-1	1:1	532.85±3.25	0.855±0.036	5.16±0.12	6.57±0.25	16±02	8.35 ±.0.63
FCP-2	2:3	525.56±5.69	1.015±0.042	4.19±0.16	5.13±0.36	17±03	7.24±0.59
FCP-3	1:2	542.12±4.92	0.855±0.029	3.09±0.14	4.9±0.35	15±02	11.03±0.69
FCP-4	1:3	514.65±9.65	0.895±0.056	2.86±0.24	4.12±0.29	15±03	3.89±1.46
FCP-5	1:4	524.12±5.23	0.895±0.047	2.23±0.19	2.58±0.15	10±02	6.4±0.98

**All values expressed as mean ± SD (n=6)*

Table 2 Different parameters of the model equations on the in vitro release kinetics

Formulation code	Zero order		First order		Higuchi model		Korsmeyer Peppas model	
	r^2	K_0	r^2	K_1	r^2	K_h	r^2	n
FCP-1	0.922	5.612	0.9668	0.18	0.9677	23.80	0.971	0.42
FCP-2	0.832	3.442	0.8592	0.0628	0.9328	15.12	0.955	0.366
FCP-3	0.937	2.081	0.9418	0.0315	0.9493	8.69	0.914	0.263
FCP-4	0.908	1.514	0.939	0.018	0.974	6.503	0.945	0.241
FCP-5	0.923	1.391	0.939	0.018	0.9667	5.906	0.947	0.217

Drug Content

Individual films of 3.14cm^2 areas containing 5mg of drug theoretically were cut into thin slices and kept in a 100 ml of phosphate buffer pH7.4 and shaken continuously in a mechanical shaker for 24 hrs. Next day it was sonicated for 15 minutes and after filtration the drug content was assayed spectrophotometrically at 240 nm against the blank solution prepared by same method using the patch of the same formulation having no drug. [6]

Thickness Measurement

The thickness of the prepared patches was measured using slide calipers (DIAL CALIPER, Aerospace) by taking measurement at 6 different places of each formulation and average thickness was recorded. [10]

Weight Variation

Weight variation was studied by taking individual weight of ten randomly selected patches for each formulation prepared in different batches. The weights were taken in Mettler Toledo balance. [11]

Moisture Content Determination
6 patches of each formulation were weighed individually and kept in desiccators containing activated silica gel 5-8 mesh at room temperature. The weights were taken periodically until two successive weights remain constant. The percentage moisture content was calculated as a difference between initial and final weight with respect to final weight [12].

Moisture Uptake Capacity
Moisture uptake capacities of each formulation was determined by exposing the formulations in high relative humidity at room temperature; prepared in desiccators using supersaturated solution of potassium chloride (84.3%RH) The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [13].

Water vapor transmission rate
Conical flasks of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in each flask and the prepared transdermal patches of each formulation were fixed over the brim with the help of adhesive. The cells were accurately weighed and kept in closed desiccators containing saturated solution of potassium chloride to maintain a relative humidity of 84%. The cells were taken out and weighed after 6, 12, 24, 36, 48 and 72 hrs of storage. Water vapor transmission rate is usually expressed as the number of grams of moisture gained/h/cm^2 [14].

Flatness
The longitudinal strips were cut from the centre and both sides of each patch. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured as % constriction, and a 0% constriction was considered to be equivalent to 100% flatness [9].

Folding Endurance
Folding endurance was determined by repeatedly folding the formulations at the same place until it broke. The number of time, the patch could be folded at the same place without breaking is considered as the folding endurance value. The average of the three readings was calculated [12].

Scanning Electron Microscope (SEM) study
The external morphology of the transdermal patches before and after permeation was studied by using a SEM (JSM 6100, JEOL, Tokyo, Japan).the samples were mounted on stubs and coated with gold palladium alloy and photographs are taken at proper resolution.

In Vitro Release (Dissolution) Studies [13]
The dissolution of the patches was performed using 6stage dissolution test apparatus USP type II (rotating paddle type). The backing membrane side of the patches was fixed on the glass disc facing their drug matrix towards the dissolution medium phosphate buffer pH 7.4. The disc was then placed at the bottom of the dissolution flask keeping the patches on its upper side. The rotation of the paddles was adjusted at 50 rpm and 900 ml of dissolution medium was taken in each dissolution flask. 5 ml of samples were withdrawn and analyzed for drug content

spectrophotometrically at 240nm. The cumulative percentage drug release was plotted against time in hr.

In-Vitro Permeation Studies

In vitro permeation studies were performed through dialysis membrane-70 (LA393, Hi Media) by using 6 stage diffusion cell apparatus (FDC-06, Orchid Scientifics, Nashik) with a receptor compartment capacity of 20 ml and cross sectional area of 3.14cm$^{2.}$ The formulated patches were placed over the membrane facing the matrix side in contact with the membrane. It was then mounted in the donor compartment so that the membrane facing towards the receiver compartment. The phosphate buffer pH 7.4was filled in the receptor compartment. The receptor solution was constantly and continuously stirred using magnetic beads at 500 rpm; the temperature was maintained at 32 ± 0.5-C by circulating the constant temperature water through outer jacket of the diffusion cells. The samples were withdrawn at different time intervals and analyzed for drug. One ml of receptor solution was withdrawn and an equal volume of fresh buffer was replaced. The samples are analyzed for drug content in spectrophotometer (Shimazhu UV-Vis, Model -1800) at 240nm.The cumulative amounts of drug permeated per square centimeter of patches were plotted against time in hr. under similar experimental condition another set was run with the dialysis membrane but without the transdermal formulation. The samples of which is being treated as blank for the corresponding time intervals.

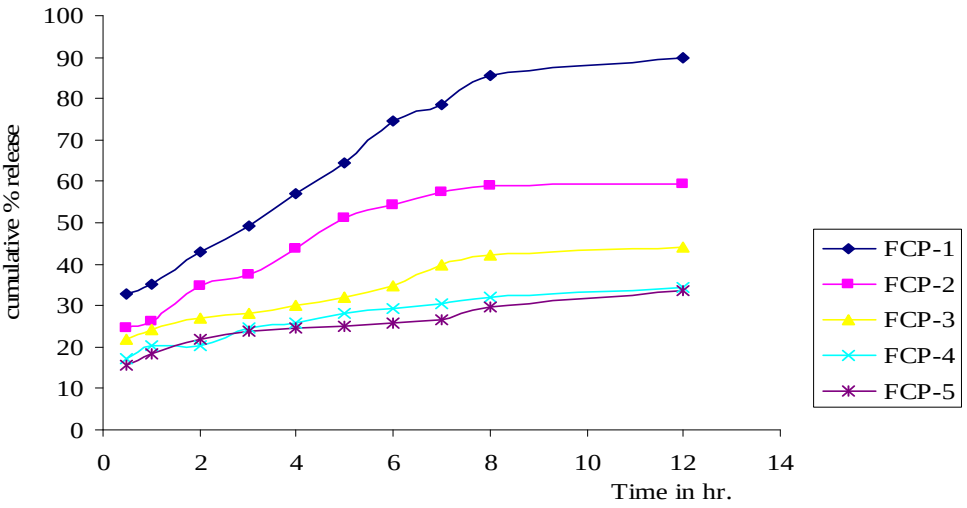

Fig.1 Zero order release profile of carvedilol phosphste (n=6) from different transdermal matrix patches having different ratios of PVP and EC

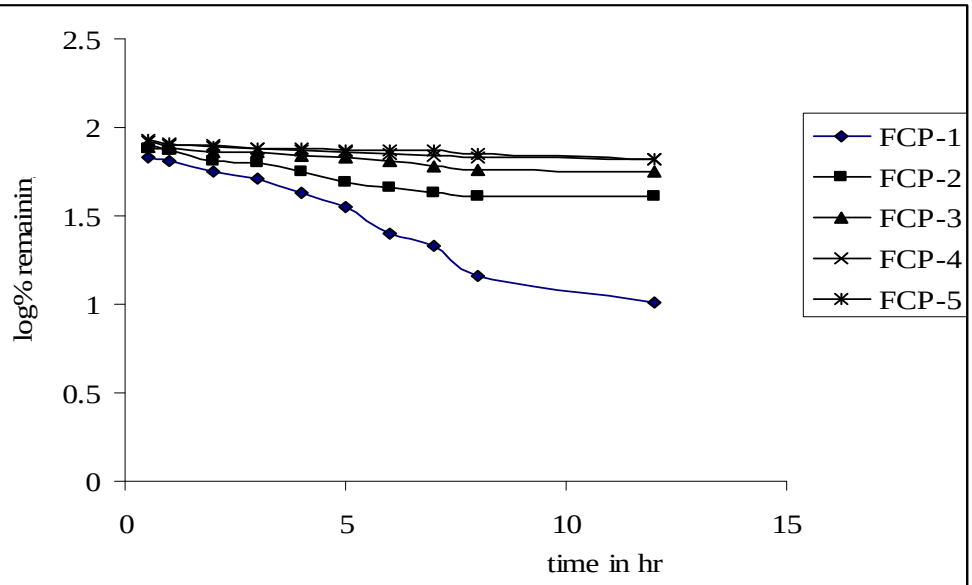

Fig.2 First order release profile of carvedilol phosphate from transdermal matrix patches having different ratio of PVP and EC

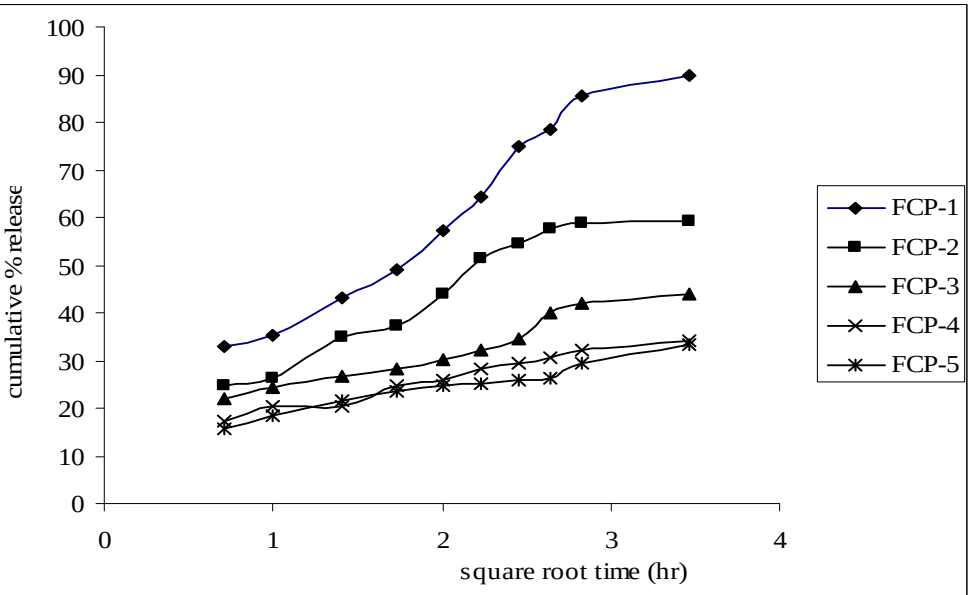

Fig.3 Higuchi plot of cavedilol phosphate release from different transdermal matrix patches having different ratios of PVP and EC

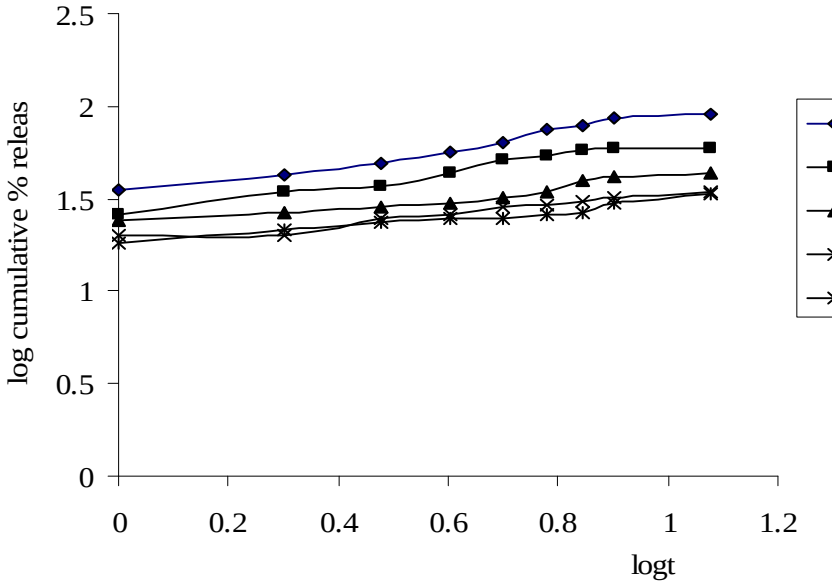

Fig.4 Korsmeyer-Peppas model for in-vitro release of carvedilol phophate from transdermal patches.

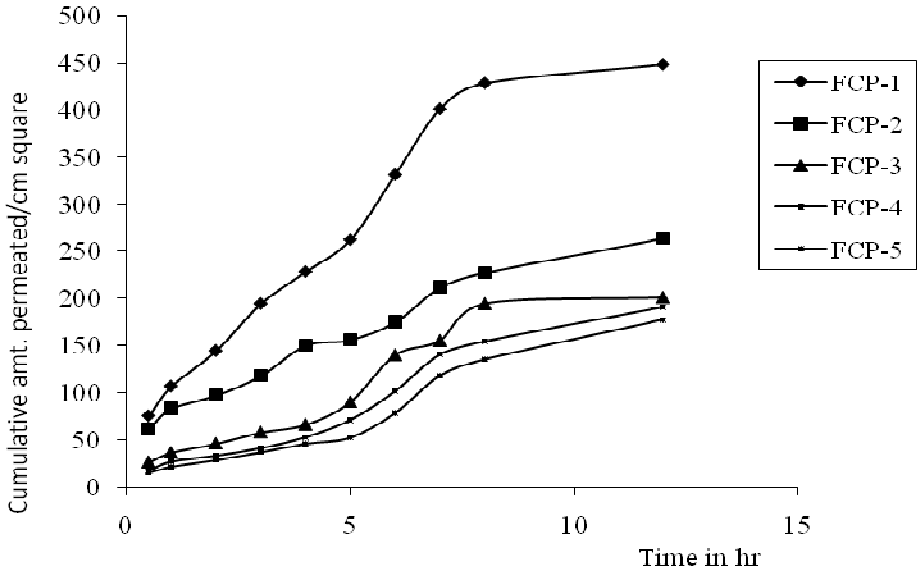

Fig.5 Permeation profile of Carvedilol phosphate through dialysis membrane from transdermal patches having different ratio of PVP and EC

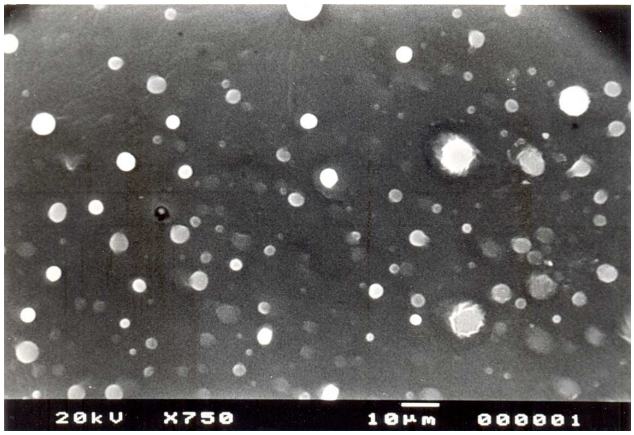

Fig.6 Scanning electron micrograph of carvedilol phosphate transdermal patch (FCP-3) before permeation study.

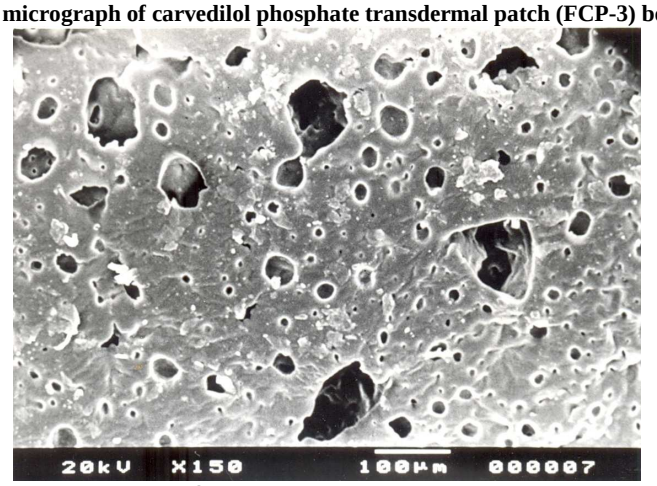

Fig.7 Scanning electron micrograph of carvedilol phosphate transdermal patch (FCP-3) 12 hrs after permeation study

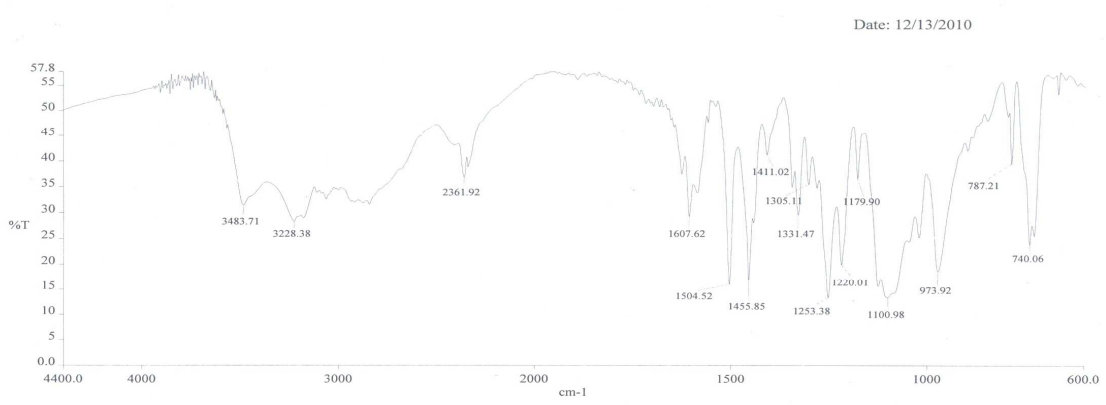

Fig.8 FTIR Spectra of the pure drug, carvedilol phosphate.

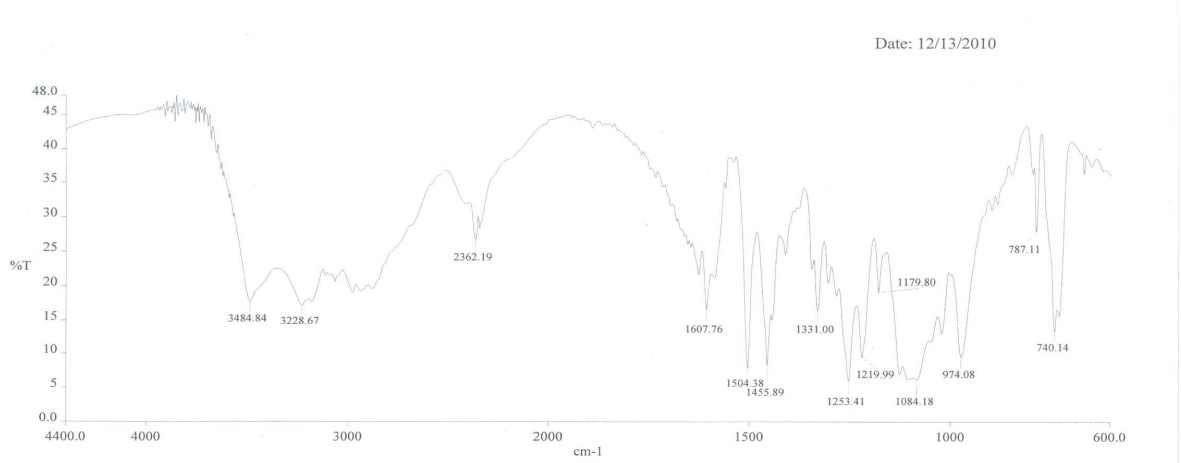

Fig.9 FTIR Spectra of the physical mixture of drug with matrix forming polymers, carvedilol phosphate along with PVP and EC

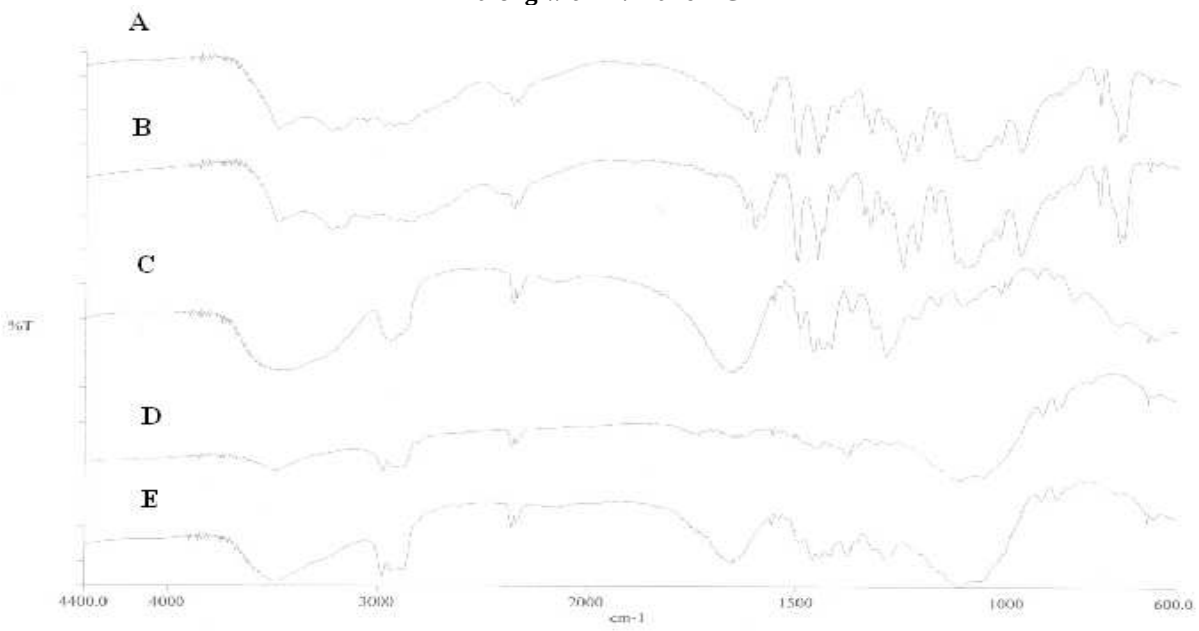

Fig.10 FTIR Spectra of A) pure CP, B) physical mixture of CP with PVP and EC, C) PVP D) EC and E) physical mixture of PVP and EC

RESULTS AND DISCUSSION

The IR spectra of carvedilol phosphate alone (Fig.8) showed the presence of principal peaks at wave numbers 974, 1100, 1179, 1220, 1253, 1331 and 1411 cm^{-1} in the fingerprint region (1430-910 cm^{-1}) which confirmed about the purity of the drug. The IR spectra of the physical mixture of the drug with the matrix polymers (PVP and EC) also contain the principal peaks (Fig.9) which were present in the fingerprint region of the pure carvedilol phosphate. The presence of the characteristic peaks at the wave numbers 1084 cm^{-1} i.e. due to the stretching vibrations of primary alcohols and 1331 cm^{-1} i.e. due to the stretching vibrations of aromatic primary amine in both the pure drug spectra and the spectra of drug-polymer mixture indicates

the compatibility of carvedilol phosphate with the matrix forming polymers like PVP and EC. Fig 10 shows the FTIR spectra of physical mixture of CP with PVP and EC (A); pure drug, CP (B), PVP (C), EC (D) and the physical mixture of PVP with EC (E) all together in the same scale for better understanding of appearance, disappearance or shifting of IR peaks.

The physicochemical characteristics of the matrix type transdermal patches containing carvedilol phosphate along with different combination of PVP and EC were presented in table1. The percentage of drug content in the different formulations varied within a narrow range from 98.78% to 99.76%, which indicates that good content uniformity and less variation between batch to batch. The prepared patches were found to be uniform in thickness (thickness below 01mm) and low weight variation. The thickness of the patches varied from 0.855 to 1.015mm and the weight of the individual patches varied from 514-542 mg. The thickness uniformity and low weight variation indicates dosage uniformity in the patches. The results of moisture content (2-5%) and moisture uptake capacities (2-6%) revealed that these properties were increased with the increase in hydrophilic polymer (PVP) content in the films. The highest level of moisture present is 5.16% (FCP-1 where the ratio of PVP and EC is 1:1), which helps them to remain stable and prevent from being completely dry and brittle. Low moisture uptake capacities protect the patches from microbial contamination and bulkiness during high humid conditions. There was found no difference in the length of the strips before and after cutting in longitudinal strips. This indicates zero constriction and 100% flatness. Hence these patches will maintain a smooth and uniform surface when they were placed onto the skin. The folding endurance (10-17) results indicate the ability of the patch to withstand mechanical pressure. Low water vapor transmission rate is also indicating high degree of stability even in high humid conditions.

The in vitro drug release studies were performed in using 6stage dissolution test apparatus USP type II (rotating paddle type). The release profile for all the five formulations were fitted to zero order kinetics (cumulative % drug release vs. time plot) in Fig.1, first order kinetics (log% remaining to be released vs. time plot) in Fig.2, Higuchi model (cumulative % release vs. square root of time plot) in Fig.3 and Korsmeyer-Peppas model in Fig.4 (log cumulative % release vs. log time plot). The rate constants were calculated from the slope of the respective plots. The regression coefficients and the release rate constants of different kinetic models were tabulated in table 2 [15]. Highest correlation was observed with Higuchi plot rather than first order or zero order. The data obtained were also fitted to Korsmeyer-Peppas model in order to find out the ‘n’ value, which describes the release mechanism. The ‘n’ value for all formulations lies between 0 and 0.5 indicating the mechanism of drug release to be diffusion controlled The results of release profile also indicated that as the concentration of hydrophilic polymer (PVP) increased in the films FCP-1>FCP-2>FCP-3>FCP-4>FCP-5; the drug release from the patches is also increased significantly. The initial burst release was found with the patch FCP-1 (33% at 0.5 hr), which is having PVP/EC ratio1:1. Whereas the other patches showed comparatively controlled and sustained release as the concentration hydrophilic polymer goes down. Highest release was found in the formulation FCP-1 (90%) after 12 hrs study containing highest proportion of PVP. At the same time the release is gradually decreasing with increase in EC concentration up to 33% with the formulation FCP-5 after the same time period.

Homogeneous distribution of the drug throughout the matrix is one of the important criteria to get the reproducible release rate from a definite area of patch on application over the skin. It can be ascertained by Scanning Electron Micrograph (SEM). The surface morphology of the transdermal patches was studied before and after skin permeation of drug from the patches. The SEM photograph of the patch before permeation (Fig.6) showed that the drug is homogenously dispersed throughout the matrix patch. The SEM photograph of the patch after skin permeation (Fig.7) showed the presence of number of holes. Drugs that had diffused from the drug clusters might form holes.

The cumulative amount of drug permeated per cm^2 area through the membrane was plotted against time and results of in vitro skin permeation study shown in Fig.5. The results also indicated that increase in proportion of hydrophilic polymer (PVP) increase the amount permeated with time and highest permeation was found with formulation FCP-1 (448µ/cm^2) after 12 hr. and the lowest (178µ/cm^2) at the same time with FCP-5.

CONCLUSION

The carvedilol transdermal patches developed in this study using PVP and EC in combination are physicochemically stable and are a viable option as extended release formulation in effective management of hypertension.

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