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CONTROLLED RELEASE OF CARVEDILOL FROM HYDROPHILIC POLYMER MATRICES

RangaPriya M*, Punitha B, Sasikala S, Shanmugapriya Dharshini M, Sindhuja L

Dept. of Pharmaceutical Research, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode-637 205. Namakkal Dist., Tamilnadu, India.

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***Correspondence for Author**
Dr. RangaPriya M
Dept. of Pharmaceutical Research, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode-637 205. Namakkal Dist., Tamilnadu, India.

ABSTRACT

Transdermal drug delivery system is being extensively investigated as a viable alternative to drug delivery with improved bioavailability. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drug because drug is delivered through the skin at a predetermined and controlled rate. The aim of the present investigation is to formulate Carvedilol loaded transdermal patches by solvent evaporation method using varying concentrations of hydrophilic polymers like ethyl cellulose and hydroxy propyl ethyl cellulose and to evaluate the feasibility of hydrophilic polymers in the formulation of TDDS. The Carvedilol transdermal patches were found to be uniform in their weight and thickness with low SD values. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage. Although the moisture uptake of the formulations was also low, this could protect the formulations from microbial contamination and reduce bulkiness. As the concentration of hydrophilic polymer was increased, the amount of drug release was increased. After dissolution experiment the film showed the presence of pores/channels indicating the drug release is diffusion controlled. The present study concludes that the successful formulation of Carvedilol loaded transdermal patches can be done by using ethyl cellulose and hydroxyl propyl methyl cellulose as polymers.

KEYWORDS: Transdermal patches, Carvedilol, HPMC, Solvent casting.

INTRODUCTION

Transdermal drug delivery system is defined as the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and the controlled rate. Transdermal patches deliver the drug through the skin in order to increase the therapeutic efficacy of drug and reduce side effect of drug. Controlled drug release can be achieved by transdermal drug delivery systems which can deliver the drug via the skin portal to systemic circulation at a pre-determined rate over a prolonged period of time. Through effective TDDS, the drug is able to penetrate the skin easily and reach the target site. TDDS increases the patient compliance and reduces the load as compared to oral route.[1-3] Transdermal drug delivery system has gained popularity over the past decades and the major penetration pathway of drug molecules through the stratum corneum of intact human skin is by diffusing through lipid envelopes of the skin cell.[4-8] Carvedilol is a novel, multiple action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. Carvedilol is widely used for the therapeutic management of hypertension, congestive heart failure. The reduction in blood pressure of Carvedilol results primarily from beta-adrenoceptor blockage and vasodilatation. The multiple action of Carvedilol may also provide the underlying rationale for the use of the drug in the treatment of coronary artery disease and congestive heart failure. Carvedilol is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver. Its absolute bioavailability is about 25%. It has a half-life of 2.2±0.3h, longer half-lives of about 6h have been measured at lower concentrations.[9]

MATERIALS AND METHODS

Carvedilol was received from Zydus cadila, Ahmadabad, India as a gift sample. Hydroxy propyl methyl cellulose (K15M), Ethyl cellulose and Polyvinyl alcohol was obtained from Loba chemie, Mumbai. Polyvinyl Pyrrolidine (K30) was received from SD fine chemicals. All other materials and reagents were of laboratory grade.

METHODS

Drug-Excipient compatibility study[10]

The drug-excipient compatibility study was performed in 1:1 ratios. About 1/8” of the solid sample was taken on a micro spatula and about 0.25-0.50mg of KBR was mixed thoroughly in a mortar with a pestle. Enough quantity of sample was placed just to cover the bottom in pellet die and pressed at 800-1000psi pressed sample was carefully removed from the die

and placed in the FTIR sample holder.

Formulation of Carvedilol loaded Transdermal Patches[11]

Drug free film was prepared by using the solvent evaporation method. The bottom of Petridish was wrapped with aluminum foil on which the backing membrane was cast by Pouring 5ml of polyvinyl alcohol solution (4 % w/v) prepared by dissolving in double distilled water followed by drying at 60^0c for 6 hrs in hot air oven. After the drying of backing membrane, different polymers were mixed in chloroform containing PEG (30% w/w) in total polymer composition and 5ml polymer solution was poured in the petridish and inverted funnel was Placed to facilitate the evaporation of solvent at controlled manner over a drying period of 6hrs at 40^0c. The film was retrieved by cutting with surgical knife and kept in desiccators for further evaluation. All the parameters optimized during preparation of placebo polymeric film were remaining same for the drug loaded polymeric films except amount of the drugs. Drug loaded polymeric film prepared in similar manner except that 16mg (2.5%w/v of polymer composition) of Carvedilol dissolved in 5ml chloroform and is was added in the polymer solution containing plasticizers .

Table 1: Composition of Carvedilol loaded transdermal patches.

S.no	Ingredients	F1	F2	F3	F4
1	**Carvedilol**	16mg	16mg	16mg	16mg
2	**Ethyl Cellulose**	375mg	375mg	375mg	375mg
3	**HPMC K15**	125mg	150mg	175mg	200mg
4	**PVA**	5ml	5ml	5ml	5ml
5	**PVP K30**	0.2ml	0.2ml	0.2ml	0.2ml
6	**Chloroform**	15ml	15ml	15ml	15ml

EVALUATION OF CARVEDILOL LOADED TRANSDERMAL PATCHES

Weight Variation[10]

Weight variation was studied by individually weighing 10 randomly selected Patches (46.5cm^2). Such determination was performed for each formulation.

Thickness[10]

Patches were selected randomly and their thickness was measured using the calibrated Vernier calipers.

Flatness Study[10]

Three longitudinal strips were collected by cutting off three zones from each film: one from the left side and one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness.

% constriction = $(1_1\text{-}1_2/1_2) \times 100$

Where, 1_1= initial length of each strip

1_2= final length of each strip

Moisture content[10]

The patches were weighed individually and kept in a desiccator containing activated silica at room temperature for 24h. Then, the final weight was noted when there was no further change in the weight of the individual patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

Folding Endurance[11]

Folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be the same place without breaking/cracking gave the value of folding endurance.

Content Uniformity[11]

The longitudinal strips were collected by cutting of three zones from each film: one from the centre, one from the left side and one from the rights side. Films of 0.64 cm^2 areas from each zone were dissolved in 200 ml of methanol and the volume was made up to 100ml with same solvent and placed in electronic shaker for 1h to dissolve completely films in methanol. The solutions were filtered through a 0.45µm membrane, diluted suitably and absorbance were noted at 242 nm in a double UV –Visible spectrophotometer against a blank that was prepared using a drug –free patch treated similarly after that drug content was calculated.

Scanning Electron Microscopy (SEM)[12]

Sample, for the SEM was prepared by sprinkling the film on one side of a double adhesive stub. The stub was then coated with gold under vacuum (Fine Coat, in sputter, EC-1100). The films were then observed under the scanning electron microscope (JEOL, JSM-6360 Scanning Electron Microscope, and Japan) at 15Kv. The samples include blank film (without drug), film before and after carrying out the permeation studies.

In Vitro drug release study[13]

Carvedilol release from the transdermal system was evaluated using the USP paddle over disc dissolution apparatus prescribed for TDDS. The dissolution test apparatus was thermo stated at 32 ± 0.5 °C and stirred at 50 rpm. The film was fixed on inverted glass petriplate using cyanoacrylate adhesive allowing drug to release only from upper surface and was placed at the bottom of the vessel containing 500 ml of phosphate buffer, pH 7.4. Aliquots of 5 ml of sample were withdrawn at every half an hour up to 2 h, and thereafter periodically up to 24 h, replacing with equal volume of buffer. The samples were analyzed spectrophotometrically at 242 nm.

RESULTS AND DISCUSSION

The standard curve of Carvedilol of phosphate buffer pH 7.4.the method obeys the beer's law limits in concentration ranges 4to24µg/ml.

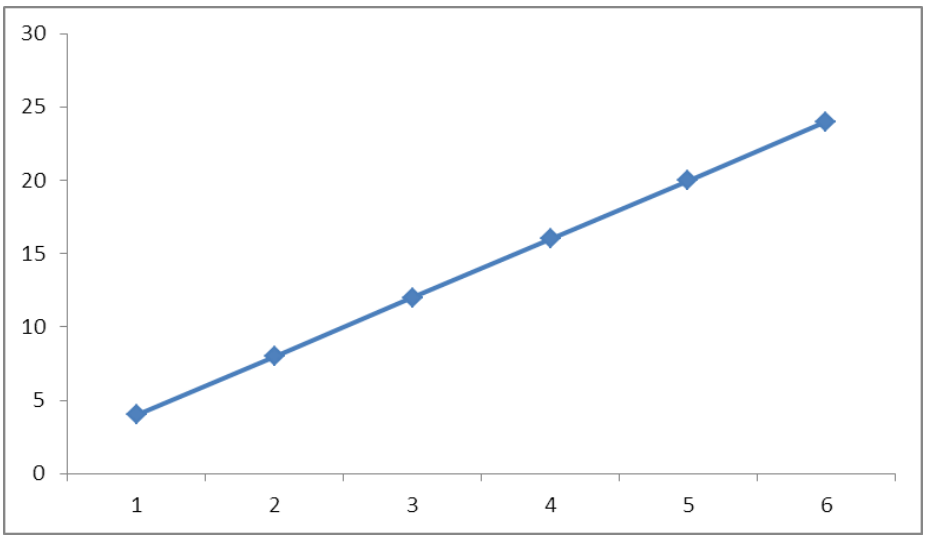

Fig 1: Standard curve of Carvedilol in pH7.4

In the present study, transdermal patches of Carvedilol were formulated using different ratios of hydrophilic polymer (HPMC) and evaluated them to select the suitable formulation.

The physicochemical properties of the drug was analysed and found to be suitable for the study as shown in table 2. Carvedilol transdermal patches were subjected to various evaluations and the results are presented in the Table 3. They were found to be uniform in their weight and thickness with low SD values.

Table 2: Properties of Drug

Parameter	Standard	Result
Color	White or all most white	white
Odour	Pungent	pungent
State	Crystalline	solid, powder form
Solubility	Soluble in methanol, methylene chloride, Freely soluble in DMSO Sparingly soluble in alcohol	soluble in methanol, DMSO, acetone Insoluble in water, gastric fluid Sparingly soluble in ethanol

Table 3: Post formulation studies of Carvedilol TDDS

Formulation code	Weight variation (%)	Thickness (mm)	%moisture absorbed	%moisture Loss	Folding endurance	Drug content (%)
F1	0.350±0.05	0.086±0.005	1.6±0.21	1.4±0.22	10	98
F2	0.365±0.03	0.146±0.011	1.7±0.15	1.6±0.21	12	96
F3	0.374±0.05	0.173±0.005	1.3±0.05	1.5+0.11	15	98
F4	0.455±0.03	0.183±0.003	1.5±0.25	1.3±0.25	11	85

The thickness for various formulations ranged between 0.086±0.005 to 0.191±0.01. The deviation in the thickness was within the limits, as it gets confirmed by low standard deviation for thickness. In case of F1 and F2, it has been seen with increase in HPMC content, thickness was increased consistently. It may be due to the gel forming properties of the polymer with the other excipients.

The weight variation for various formulations ranged between 0.350±0.05 to 0.513±0.02. The deviation in the weight was within the limits as it is confirmed by low standard deviation for weight. It was observed that the weight of the patches was increasing gradually with increase of HPMC content. The weight of the patches increased with increase in thickness of the respective patches as the weight and thickness are directly proportionate to each other.

The folding endurance measures the ability of patch to withstand rupture. The folding endurance was found to be increased with increasing HPMC concentration. The formulation F3 was having better folding endurance compared to other carvedilol films.

Moisture content studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content of the patches.

Moisture absorption of films was found in the range of 1.3±0.05 to 2.1±0.11 % which shows that the formulation F3 has least moisture content compared to other films. Moisture loss of the films was found in the range of 1.3±0.25 to 2.3±0.11 %.

The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage. Although the moisture uptake of the formulations was also low, this could protect the formulations from microbial contamination and reduce bulkiness.

It was found that the %MA and %ML was increased with increasing in HPMC concentration; which might be attributed to the hydrophilic nature of the HPMC. The results reveal that the drug content was almost uniform in all the patches with low SD values.

For various formulations, the drug content was between 85.99±1.01 to 98.78±0.11%. The drug content of the prepared formulations has shown that the process employed to prepare transdermal films in this study was capable of producing films with a uniform drug content and minimum batch variability.

The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 100% flatness. Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin.

The process of drug release in most controlled release device is governed by diffusion, and the polymer matrix has a strong influence of the diffusivity as the motion of small molecules is restricted by the three-dimensional network of polymer chains.

The alteration of the cross linking and the modification of structural arrangements of polymers by using different blends of polymer already reported.

Drug release profiles from different formulations are shown in table 4 and Figure 2. *In vitro* release of carvedilol from F3 and F4 formulation showed increment in the drug release when compared to F1 and F2 at the end of 24h.

Table 4: Comparative *in vitro* drug release of formulations F1-F4.

Time (hrs)	Cumulative % drug release			
	F1	F2	F3	F4
0	0	0	0	0
1	17.450±0.574	14.923±0.940	14.814±0.815	14.730±1.069
2	21.797±0.675	21.464±0.894	21.530±0.758	21.270±0.801
3	28.601±0.168	26.874±0.894	26.758±0.564	27.641±0.178
4	35.296±0.798	32.544±0.554	34.313±0.972	34.338±0.970
5	47.074±0.926	38.580±0.462	40.451±1.182	38.472±1.393
6	52.140±0.905	47.159±0.855	47.888±0.773	47.618±0.674
7	57.560±0.590	55.934±0.866	56.190±0.397	61.225±0.587
8	66.077±0.364	62.935±0.865	65.301±0.736	66.957±0.763
9	71.402±1.109	75.830±0.659	74.528±0.887	72.588±1.354
10	78.854±0.593	80.830±0.659	82.508±1.078	79.444±1.400
11	87.554±0.498	81.153±0.340	91.712±1.417	87.136±0.728
12	89.666±0.433	90.124±0.713	97.593±1.072	91.084±0.930

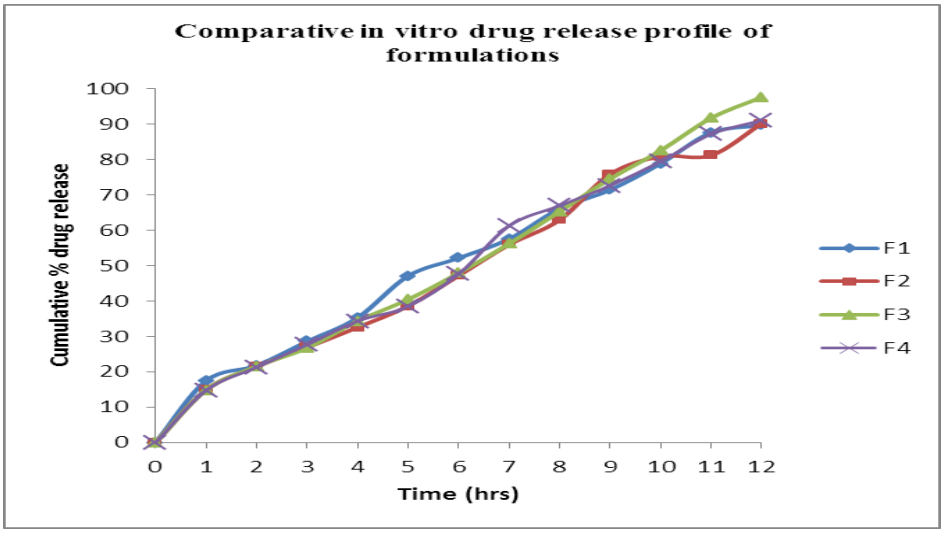

Fig 2: Comparative in-vitro drug release profile of formulations F1 – F4.

It is evident from the above result that with increasing in the concentration of HPMC the cumulative % release of Carvedilol also increased. It might be attributed due to the hydrophilic nature of HPMC. However, with further increase in the polymer, there was a decrease in the drug release as seen in the formulations F3 and F4, which could be attributable to the varied cross linking networks of polymeric chains of the different blends of polymeric transdermal experimental formulations as tortuosity and diffusion pathway varied, and they thereby have been reported to vary the release of drug.

As the concentration of hydrophilic polymer was increased, the amount of drug release was increased. This may be a result of the initial rapid dissolution of the hydrophilic polymers

when the patch is in contact with the hydrated skin, which results in accumulation of high amount of drugs on the skin surface and thus leads to the saturation of the skin with drug molecules at all time. The rapid dissolution of the aqueous soluble fraction of the film also leads to the formation of pores, and hence higher release rate.

The drug release data of all the formulations were subjected to kinetic analysis to know the mechanism and it is tabulated in table 5 which indicates that all the formulations showed controlled and steady drug release pattern.

Table 5: Kinetic data of different formulations (F1– F4)

F.code	Zero-order plot	First-order plot	Higuchi's Plot	Korsemeyer Peppa's plot		Possible Drug Release mechanism
	Regression Coefficient (R^2)	Regression Coefficient (R^2)	Regression coefficient (R^2)	Slope (n)	Regression coefficient (R^2)	
F1	0.990	0.847	0.968	0.856	0.991	Zero order Fickian
F2	0.992	0.842	0.945	1.041	0.994	Zero order Fickian
F3	0.997	0.812	0.964	0.957	0.996	Zero order non-fickian
F4	0.995	0.889	0.972	0.992	0.995	Zero order Non-fickian

Figures 3 and 4 represents the SEM photographs of Carvedilol loaded transdermal patches before dissolution and after dissolution study respectively. The SEM of the drug loaded patch clearly indicates that Carvedilol is molecularly dissolved in the patch. After dissolution experiment the film showed that the presence of pores/channels indicating the drug release is diffusion controlled. Therefore, it could be concluded that the formulation F3 is suitable for the transdermal delivery of Carvedilol.

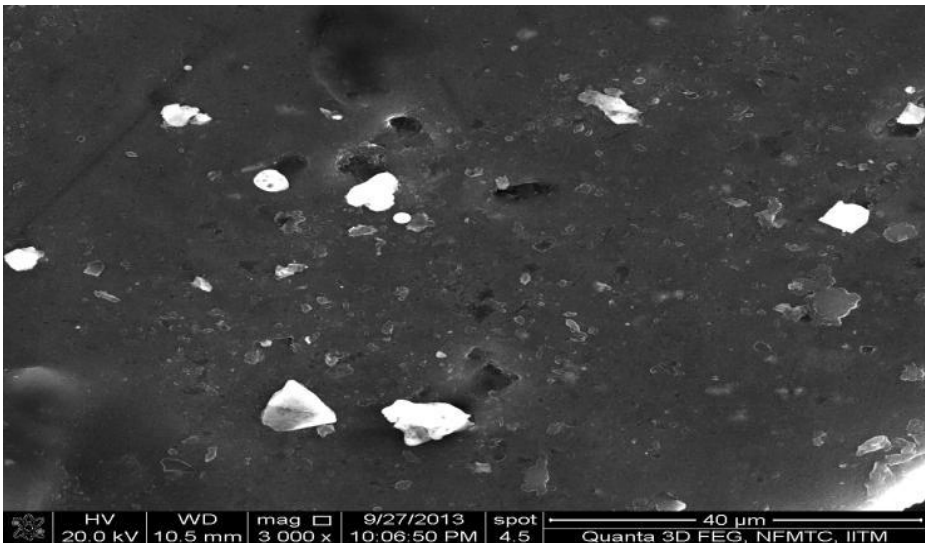

Fig 3. SEM image of the formulation F3 before dissolution

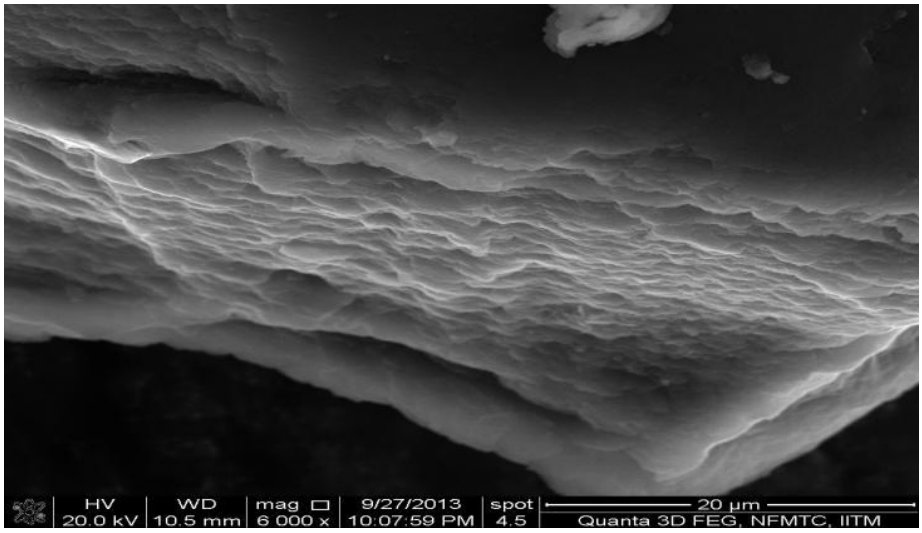

Fig 4. SEM image of the formulation F3 after dissolution

SUMMARY AND CONCLUSION

Transdermal drug delivery system is a most suitable system for a long-term treatment or for a multi dose treatment because different transdermal patches are prepared for a long period of time in a suitable dose proving treatment from a day to even up to seven days. Lower molecular weight, good lipid solubility, lower elimination half-life, and lower melting make Carvedilol an ideal candidate for transdermal formulation.

The present study concludes that the successful formulation of Carvedilol loaded transdermal patches can be done by using ethyl cellulose and hydroxyl propyl methyl cellulose as polymers. Thus an ideal TDDS can be prepared for improving patient acceptabilility. The concept is suitable for other drugs of the same category also. Various evaluatory studies have shown promising results; hence, there is a scope for further pharmacodynamic and pharmacokinetic evaluation.

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