Research Article

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DESIGN AND EVALUATION OF CARVEDILOL TRANSDERMAL PATCHES BY USING SOLVENT EVAPORATION TECHNIQUES

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Abstract

Transdermal patches of carvedilol with an Ethylcellulose, HPMC-drug reservoir were prepared by the solvent evaporation technique. In this investigation, the membranes of Eudragit RL100 and Eudragit RS100 were cast to achieve controlled release of the drug. The prepared patches possessed satisfactory physicochemical characteristics. Thickness, mass and drug content were uniform in prepared batches. Moisture vapour transmission through the patches followed zero-order kinetics. In vitro permeation studies were performed using a K-C diffusion cell across hairless guinea pig skin and followed the super case II transport mechanism. The effects of non-ionic surfactants Tween 80 on drug permeation were studied. The non- -ionic surfactants in the patches increased the permeation rate, Tween80 exhibiting better enhancement. The patches were seemingly free of potentially hazardous skin irritation.

Keywords: Carvedilol, Transdermal patches, In vitro permeation, Permeation rate-enhancers.

Introduction

Carvedilol is a novel, multiple-action cardiovascular drug that is currently approved in many countries for the treatment of hypertension. The reduction in blood pressure produced by carvedilol results primarily from beta-adrenoceptor blockade and vasodilation, the latter resulting from alpha 1 adrenoceptor blockade. These actions as well as several other carvedilol activities are associated with cardioprotection in animal models that occurs to a degree that is greater than that observed with other drugs. The multiple actions 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[1]. 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 ± 0.3 h; longer half-lives of about 6 h have been measured at lower concentrations[2]

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 mass, high lipid solubility, effective in low plasma

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concentration as well as a high degree of first-pass metabolism. It also means multiple daily administration with subsequent lack of patient compliance. The aim of this study was to develop and evaluate transdermal patches of carvedilol so as to prevent its first-pass metabolism and achieve controlled release

Materials

Carvedilol was a gift from ShaSun Pharmaceutical Industries Ltd. (India). Eudragit RL100 was kindly supplied by loba chemical. Pvt. Ltd. (India). HPMC, Ethylcellulose, Ethanol, Glycerine, Acetone, Tween-80, were purchased from Sd Fine chemicals (Mumbai). All the other chemicals were of analytical grade[3].

Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form.

Identification of drug by IR Spectra

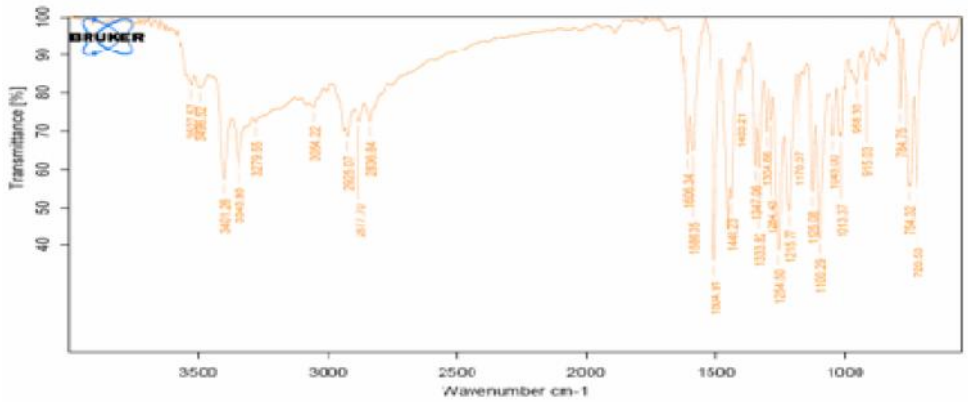

Fig. No. 01: IR Spectrum of carvedilol

The IR spectrum of famotidine in KBr dispersion was analysed using AB Bomen model MB 104 Fourier Transform Infrared Spectrophotometer. From the IR spectrum obtained interpretations were made and compared with that of standard.

Observation

The IR Spectrum of drug sample found to complies with that of standard carvedilol USP.

Procedure for standard calibration curve of carvedilol

In a 100 ml standard flask, stock solution was prepared by dissolving 100 mg of carvedilol in 5 ml methanol and made up to the volume with 7.4 phosphate buffer. From this stock solution (1%w/v), serial dilutions were made by withdrawing 1 ml, 2 ml, 3 ml, 4 ml and 5µg/ml and transferred individually into 10 ml standard flask and the volume was made up to the mark using 7.4 phosphate buffer. The absorbance of resulting solutions was measured using shimadzu UV-1601 spectrophotometer at 241 nm and the values are given in table- 1.

Table No. 01: Values of calibration curve of carvedilol

S.No	Concentration (µg/ml)	% of Absorbance 241nm
1.	1	0.110
2.	2	0.238
3.	3	0.366
4.	4	0.471
5.	5	0.601

Table No. 02: Formulation flow chart

Chemicals	F1	F2	F3	F4	F5	F6	F7	F8
Carvedilol(mg)	60	60	60	60	60	60	60	60
HPMC(mg)	500	400	300	200				
Ethly cellulose(mg)					500	400	300	200
Glycerol(ml) 4drops	117.6	117.6	117.6	117.6	117.6	117.6	117.6	117.6
Dibutyl phthalate(ml)	1	1	1	1	1	1	1	1
Ethanol (ml)	19ml	14	14	14				
Acetone(ml)		5	5	5		5	5	5
Methyl chloride (ml)					19	14	14	14
Tween-80(ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Eudragit RL-100/ RS-100	250	250	250	250	250	250	250	250

Preparation of Transdermal patches

Transdermal films containing carvedilol were prepared by the solvent evaporation technique[6] for the formulations shown in Table-6. Solution of HPMC and ethylcellulose were prepared separately in ethanol and acetone, respectively. The two polymeric solutions were mixed to which weighed amount of carvedilol was added slowly. To the mixture, 4 drops of glycerin (117.6 mg), 1 drop of dibutyl phthalate (27.4 mg), and 0.25 ml of surfactant (PEG 400 / Tween 80) and permeation enhancer (DMF / DMSO) were added and mixed. The drug-polymer solution was casted in a glass mould of 40 cm^2 (4 x 1 0 cm^2). The mould was kept aside for drying at room temperature for 24 h. Inverted plastic funnel was placed over the mould to prevent the current of air. After drying, the films were peeled from glass mould, wrapped in aluminium foil and preserved in desiccator for further studies.

Determination of Partition Coefficient

The oil-water partition coefficient is a measure of lipophilicity of a molecule, which can be used to predict its capability to cross biological membrane. One of the most common ways of measuring partition coefficient is shake flask method.[4,5] The carvedilol was added little at once in to 5 ml of n-octanol until saturated solution was obtained. This solution was filtered to get a clear solution. Three ml of the saturated solution was mixed with 2 ml of fresh octanol. In total, 5 ml of octanol containing carvedilol was mixed with 15 ml of water. Then, two phases were allowed to equilibrate at 37 ℃ for 24 h, in cryostatic constant temperature shaker bath (Research and Test Equipments, Bangalore, India). The concentration of the drug in the aqueous phase and organic phase was determined by UV spectroscopic method after necessary dilution. The apparent partition coefficient (K_p) was calculated as the ratio of drug concentration in each phase by the following equation.

$$K_P = \frac{C_{0rg}}{C_{aq}}$$

Where,

C_{org} is concentration of drug in organic phase

C_{aq} is the concentration of drug in aqueous phase.

Drug-Excipient Compatibility Studies

In the preparation of film formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer

Evaluation of Patches

Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies.

Thickness Uniformity

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.[6]

Folding Endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times manually, which is considered satisfactory to reveal good patch properties.[7] The number of times of patch

could be folded at the same place without breaking gave the *value* of the folding endurance. This test was done on all the patches for three times.

Uniformity of Weight

Patch of size l x l cm^2 were cut. The weights of three patches were taken using Shimadzu balance of ^sensitivity *0.0001* g (Shimadzu, Tokyo, Japan) and the weight variation was calculated.[7]

Drug Content Uniformity

The films were tested for the content uniformity.[8] A film of size 2 x 2 cm^2 was cut and placed in a volumetric flask. Ten ml of methanol was added and the contents were stirred in a shaker bath for 24 h to dissolve the film. Subsequent dilutions were made with phosphate buffer (pH 7.4). The absorbance of the solution was measured against the corresponding blank solution at 241 nm using UV-VIS spectrophotometer (UV-1601,. Shimadzu Corporation, Tokyo, Japan).

Swelling Studies

Weight and area increase due to swelling were measured.

***In- vitro* Release Studies of Carvedilol Patches in Phosphate Buffer (pH** 7.4)

The drug release was determined using U.S.P. dissolution tester (TDT-08L, Electrolab, Bombay, India) thermostated at 37 ±1 C and stirred at a rate of 50 rpm.[9,10] Sink condition was maintained throughout the study.

Each film was fixed on a glass slide with the help of cyanoacrylate adhesive, so that the drug could be released only from upper face. The slide was immersed in the vessel containing 900 ml of phosphate buffer (pH 7.4) solution. Aliquots of 5 ml of samples were withdrawn with graduated pipette at every one hour time intervals up to 24 h replacing with equal volume of phosphate buffer (pH 7.4) solution. The sample was analyzed spectrophotometrically at 241 nm and the cumulative amount of drug released at various time intervals was calculated. The test was carried out in triplicate.[11]

Kinetics of drug release[12]

To study the study kinetics, data obtained from in vitro release were plotted in various kinetic models.

Zero order equation

The graph was plotted as % drug released Vs time in hours.

$$C=K_0t$$

Where,

K_0 – Zero order constant in concentration/time

t – Time in hours

First order equation

The graph was plotted as log % cumulative drug remaining Vs Time in hours.

$$\text{Log } C = \log C_0 - Kt/2.303$$

Where,

C_0 - initial concentration of drug.

K- First order constant.

t- Time.

Higuchi kinetics

The graph was plotted as % Cumulative drug released Vs square root of time

$$Q = Kt^{1/2}$$

Where,

K – constant reflecting design variable system.

t - time in hours

Hixson and crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and crowell rate equation. The graph was plotted by cube root of % drug remaining Vs time in hours.

$$Q_0^{1/3} - Qt^{1/3} = K_{HC} X t$$

Where,

Qt – Amount of drug released in time t.

Q_0 - Initial amount of drug .

K_{HC} – Rate constant for Hixon crowell equation.

Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs time

$$M_t / M_\alpha = Kt^n$$

$$\text{Log } M_t / M_\alpha = \log K + n \log t$$

Where,

$M_t / M\alpha$ - fraction of drug released at time t

t – Release time

K – Kinetic constant (incorporating structural and geometric characteristics of preparation)

n - Diffusional exponentindicative of the mechanism of drug release.

If n value is 0.5 or less, the release mechanism follows " Fickian diffusion" and higher values of 0.5 < n< 1 for mass transfer follow a non- fickian model (anamalous transport). The drug release follows zero-order drug release and case – II transport if the value is 1. For the values of n higher than 1, the mechanism of drug release is regard as super case II transport. This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time. The results are tabulated in Table:6 fig no-4,5.

- Zero Order Reaction - % Cumulative drug release Vs Time in hrs
- Korsmeyer – Peppas equation - log cumulative % of drug released Vs log time
- Higuchi kinetics - % Cumulative drug release Vs square root of time
- First Order Reaction – Log % Cumulative drug remaining Vs Time in hours
- Hixon and crowell erosion equation- cube root of % drug remaining Vs time in hours.

Stability Studies

Optimized medicated films were subjected to short term stability testing. Films were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2 C and 75 ± 5% RH for 1 month as per ICH guidelines.[13] Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week. The data presented were the mean of three determinations. Interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between carvedilol and the selected polymers. The pure drug and drug with excipient were scanned separately.[14]

Results

Table No. 03: Physicochemical Characteristics Of Transdermal Patches Containg Carvedilol

Formulation	TN (mm)	Swelling		Weight uniformity	Content uniformity	Folding endurance
		% weight increase after 30 min	% area increase after 60 mins			
F1	0.262	431.31	61.60	22.33	96.10	>300
F2	0.199	406.11	59.39	21.80	95.90	>300
F3	0.190	386.07	52.11	19.63	96.06	>300
F4	0.186	291.93	44.09	14.56	96.09	>300
F5	0.261	430.11	60.12	21.89	96.10	>300
F6	0.200	403.09	58.19	20.56	96.09	>300
F7	0.177	384.01	50.09	18.80	96.07	>300
F8	0.161	290.0	43.01	13.89	96.09	>300

Table No. 04: Comparison of formulation F1 to F8

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Time in Hrs	% of drug release ± S.D	% of drug release ± S.D	% of drug release ± S.D	% of drug release ± S.D	% of drug release ± S.D	% of drug release ± S.D	% of drug release ± S.D	% of drug release ± S.D
1	4.02±0.12	5.04±0.12	4.02±0.12	3.52±0.12	3.02±0.08	3.02±0.10	2.51±0.10	2.51±0.10
2	6.06±0.13	6.57±0.09	5.56±0.013	4.55±0.13	4.55±0.11	4.55±0.11	5.05±0.12	5.55±0.12
3	9.12±0.09	6.57±0.08	9.12±0.11	8.61±0.11	10.12±0.10	10.12±0.12	9.61±0.11	11.13±0.11
4	16.74±0.10	15.24±0.11	12.20±0.10	14.68±0.09	16.22±0.11	14.21±0.11	15.21±0.11	13.21±0.12
5	25.25±0.11	18.92±0.09	17.62±0.09	19.52±0.10	18.27±0.11	21.74±0.12	25.54±0.09	20.79±0.09
6	32.36±0.12	23.14±0.12	21.51±0.08	26.91±0.11	21.22±0.12	33.89±0.10	33.60±0.10	31.34±0.11
7	41.72±0.08	32.13±0.13	30.82±0.09	36.88±0.12	28.30±0.11	41.68±0.11	39.80±0.11	37.86±0.12
8	48.91±0.09	47.82±0.09	38.58±0.10	40.25±0.14	33.53±0.09	48.88±0.10	42.57±0.10	47.57±0.14
9	54.16±0.09	54.42±0.12	48.93±0.09	50.50±0.15	40.99±0.10	59.91±0.09	54.85±0.11	57.30±0.09
10	62.46±0.12	66.75±0.08	53.31±0.11	58.16±0.09	53.88±0.10	65.94±0.09	73.52±0.12	65.88±0.14
11	73.88±0.08	72.82±0.12	62.15±0.12	63.54±0.09	67.79±0.08	71.27±0.08	78.99±0.11	70.35±0.12
12	81.88±0.09	81.45±0.08	74.21±0.11	77.19±0.12	76.08±0.09	80.30±0.10	84.05±0.09	78.97±0.11
20	90.56±0.09	87.59±0.12	83.80±0.12	84.89±0.10	87.26±0.10	87.39±0.11	93.19±0.08	86.36±0.13
24	98.56±0.12	91.88±0.12	90.33±0.11	95.17±0.09	95.65±0.10	99.57±0.12	97.49±0.08	96.65±0.09

Table No. 05: Comparison of formulation F1 & F5

Time in minutes	F1	F5
1	4.02±0.12	3.02±0.08
2	6.06±0.13	4.55±0.11
3	9.12±0.09	10.12±0.10
4	16.74±0.10	16.22±0.11
5	25.25±0.11	18.27±0.11
6	32.36±0.12	21.22±0.12
7	41.72±0.08	28.30±0.11
8	48.91±0.09	33.53±0.09
9	54.16±0.09	40.99±0.10
10	62.46±0.12	53.88±0.10
11	73.88±0.08	67.79±0.08
12	81.88±0.09	76.08±0.09
20	90.56±0.09	87.26±0.10

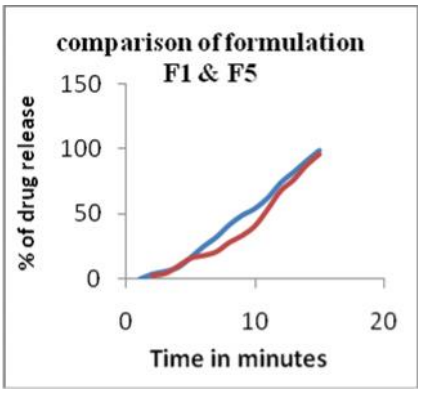

Fig. No. 02

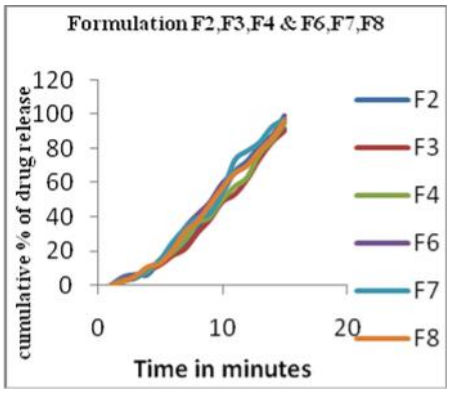

Fig. No. 03

Table No. 06: Pharmacokinetic studies

Time (hours)	% of Cumulative drug release	%cumulative drug remaining	Log% cumulative drug remaining	Square root of time	log time	log % cummulative drug release	Cube root of % drug remaining
0	0	0	0	0	0	0	0
1	4.02	95.98	1.982181	0.707107	-0.30103	0.604226	4.57
2	6.56	93.44	1.970533	1	0	0.816904	4.53
3	11.6	88.4	1.946452	1.224745	0.176091	1.064458	4.45
4	16.1	83.9	1.923762	1.414214	0.30103	1.206826	4.37
5	23.74	76.26	1.882297	1.732051	0.477121	1.375481	4.24
6	29.57	70.43	1.847758	2	0.60206	1.470851	4.12
7	37.03	62.97	1.799134	2.236068	0.69897	1.568554	4.01
8	45.1	54.9	1.739572	2.44949	0.778151	1.654177	3.8
9	52.03	47.97	1.68097	2.645751	0.845098	1.716254	3.63
10	61.03	38.97	1.59073	2.828427	0.90309	1.785543	3.39
11	69.02	30.98	1.491081	3	0.954243	1.838975	3.14
12	79.09	20.91	1.320354	3.162278	1	1.898122	2.75
20	87.77	12.23	1.087426	3.316625	1.041393	1.943346	2.3
24	98.93	1.07	0.029384	3.4641	1.079181	1.995328	1.02

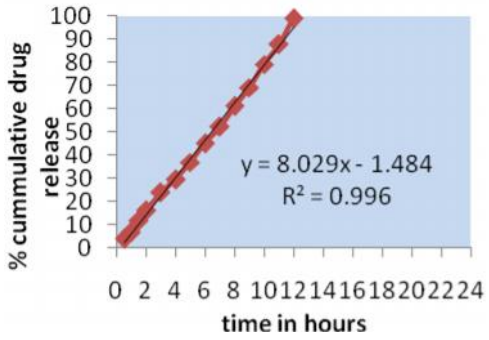

Fig. No. 04: Zero order kinetics release

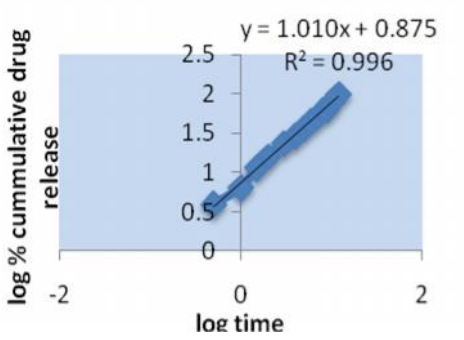

Fig. No. 05: Korsmeyer-peppas equation

Discussion

In the preset study transdermal patches of carvedilol were formulated using the hydrophilic polymer matrix of hydroxypropyl methyl cellulose and Ethylcellulose polymers was compared. The prepared patches were characterized for physicochemical properties. *Invitro* release studies. The physicochemical properties of carvedilol transdermal patches are presented in table -3.

All the patches had uniform thickness throughout with the standard deviation ± 0.005µm. the thickness results are given in table no-3 . The results indicated that there was no much difference in the thickness within the formulations. The order of the thickness of films is F4<F3<F2<F1 & F8<F7<F6<F5.The addition of tween 80 in the all formulation increased the thickness of film. Tween 80 decreases interfacial tension and increases wetting of polymer by solvent. This results in more swelling during casting even after complete drying, the swollen polymer gave thicker film.

Drug loaded patches (1x 1cm^2) were tested for uniformity of weight and the results of weight uniformity are given in table-3 . the order of the weight of the film is F4<F3<F2<F1 & F8<F7<F6<F5. The F1 & F5 exhibited highest weight. It could be because of the reason explained in the thickness uniformity. Patch did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between dummy patches and drug-loaded patches. The result of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 82.1 to 98.53 % for all formulation F1 to F8. The swelling of the drug loaded pathes of size 1x1 cm^2 was studied upto 30min in case of change in weight and 60 min in case of change in area. The swelling of the patches were observed in phosphate buffer solution (pH 7.4). The data for increase in weight due to swelling are given in table-3.

Swelling was more pronounced in patch F1 and F5 compared to F3 ,F4, F6, F7, F8. Which contain more of HPMC & ethyl cellulose and rate controlling polymer in the all Patches ,F4, F6, F7,F8 showed lesser swelling, may be due to the presence of higher concentrations of ethyl cellulose, hydrophilic polymer. The order of patches for their increases in weight due to swelling is F4<F3<F2<F1 & F8<F7<F6<F5this must be due to the presence of higher concentration of HPMC & Ethyl cellulose. (The tensile strength of drug films were higher than dummy films). The drug release formulation F1 & F5 are shown in Fig-3. where as F2,F3,F4 & F6,F7, F8 are shown in fig-4. The slower drug release rate is due to the use of high rate controlling polymeric membrane. Of Eudragit RS100, were cost with the aim to achieve controlled release of carvedilol from drug reservoir of HPMC. The cumulative amount of drug released after 10hrs, from F1 & F5 was found to 95 to 98% when compared drug release from F2,F3,F4 & F6, F7, F8. This effect because of the co-polymer, Eudragit RS100, which act as a rate controlling polymer. However , the target is to get drug release upto 24hrs. The sustained release could be achieve by increasing the co-polymer concentration in the formulation by maintaining the total polymer concentration same i.e 500mg. in the formulation F2,F3,F4 & F6, F7, F8 increased. (formulation table chart) given in table -2 from. Fig -4. it, was found that only 81% of carvedilol was released

from F2, F3, F4, & F6, F7, F8 at the end of 24 hrs. further was a needed to improve the formulation.

In the all formulations F1 to F8 an attempt was made by adding surfactant (Tween-80) to get the required release rate. The increased drug release rate from 81 to 91.53. this was applicable improvement. In the literature study given us an idea of using permeation enhancer as an surfactant to improve the formulation as the former helps in the permeation of drug through the skin. DMF & DMSO were the most popularly used permeation enhancers in the research reported for transdermal drug delivery. This was significant improvement as DMF along with surfactant improve the performance 98.56%**.** In the formulation F5 to F8 , DMSO was used instead of DMF as permeation enhancer and observe the response. It was clearly indicated from the fig-F1-98.56% of the carvedilol was released in 24 hrs. when compared to all the earlier formulations, The F1 formulation gave a maximum drug release in 24hrs. The regression value of films F1 & F5 follows zero order and therefore the release kinetics followed by zero-order. According to Korsemeyar- peppas model a value of slope between 0.1 to 0.5 indicates, an anomalous behavior. fickian diffusion. So it indicates that release mechanism from the all films fickian diffusion. However F1 film follows case –I transport(n<1)

Conclusion

On the basis of the invitro characterization it was concluded that carvedilol could be administered transdermally through matrix type tdds developed in our laboratory. Transdermal patches consisting of permeation enhancer demonstrated sustained and controlled release. The drug remained intact and stable in the TDDS during storage with no significant chemical interaction between the drug and excipients. Further work is to establish my Future research studies.

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