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Original article

Formulation and development of novel control release transdermal patches of carvedilol to improve bioavailability for the treatment of heart failure

Long Mo [a], Guijing Lu [a], Xiping Ou [a], Dongsheng Ouyang [b,*]

[a] Department of cardiology, Xiangya hospital central south university, Changsha, Hunan 410008, China
[b] Institute of clinical pharmacology, Central South University, Changsha, Hunan 410005, China

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ABSTRACT

The main aim of this study is to optimize and evaluate transdermal patch of Carvedilol by the use of different polymer and different permeation enhancers which help to release drug in controlled action and thereby increase the bioavailability of the drug. Main objective was to avoid first pass metabolism of Carvedilol. Transdermal patches were developed by solvent evaporation method. The combination of Eudragit RS-100 as rate controlling polymer and Span 80 as a permeation enhancer was found to be ideal formulation (Formulation F7) with maximum drug release i.e. 100.29 ± 0.44 % within 12 h. Formulation F7 showed maximum bioavailability and showed maximum drop of BP at 6 h. From this study the conclusion was, transdermal patch of Carvedilol which contains Eudragit RS-100 polymer and Span 80 as penetration enhancer produced sustained and continued drug release.

1. Introduction

Heart failure (HF) is a disease and which is occurring due to some abnormalities in myocardium. Its structural and functional strength becomes less and hence it leads to difficulty in pumping of the blood in heart. The overall syndrome leads to Heart failure. The most commonly due to the Heart failure, the function of left ventricular myocardium is get reduced. European Society of Cardiology in 2008 defined HF as "Due to the structural and functional abnormality of cardiac strength, it results in to failure of the heart and which results in improper delivery of oxygen which is needed for metabolism of tissues instead of pressure created by normal filling" The symptoms of HF are marked by chronic fatigue, intolerance to exercise, pulmonary congestion (Inamdar and Inamdar, 2016; Adebayo et al., 2017; Roger, 2013). There are two types of HF, Systolic Heart failure and Diastolic Heart Failure. The main cause of HF is hypertension, cardiomyopathy, and rheumatic heart disease and which is the leading cause and it has been documented from various studies from different regions. HF is a most commonly found problem in world, more than 26 million peoples affected with the same. In adult population about 1–3 % of HF is occupied in developed countries. About 6%–10% of people with age of 65 years and above are affected by HF. HF is having high mortality rate around 30–50 % over 5 years (Adebayo et al., 2017; Roger, 2013; Kveiborg et al., 2007; Katz, 2018). Different classes of drugs used in the treatment of HF such as, Diuretics e.g. Furosemide, Hydrochlorothiazide, Bumetanide, Spironolactone, Metolazone, Amiloride, Triamterene etc. Angiotensin converting enzyme inhibitors e.g. Enalapril, Lisinopril, etc. Beta blockers e.g. Carvedilol, Metoprolol, Bisoprolol etc. Digitalis etc (Kveiborg et al., 2007; Lonn and McKelvie, 2000). Different classes of cardiovascular drugs are prescribed in treatment of HF. Amongst them Carvedilol is most often prescribed drug having multiple action. It is potent beta-adrenergic blocking agent. The main mechanism of action of Carvedilol is it lowers the blood pressure which results primarily from blocking of beta-adrenoceptor and vasodilation, and then its results in blocking of alpha 1-adrenoceptor. Carvedilol administered orally in the form of tablet dosage form and its recommended dose is 3.125– 6.25 mg twice a day for 7–14 days for hypertension (Tanwar et al., 2007; Mounika et al., 2014; Aparna et al., 2013). Carvedilol is Freely soluble in dimethylsulfoxide;

* Corresponding author.
E-mail address: dongshengouyang123@gmail.com (D. Ouyang).
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soluble in methylene chloride, methanol; sparingly soluble in ethanol, isopropanol; slightly soluble in ethyl ether (Vahdati et al., 2013). The main characteristic of Carvedilol is, its absorption is done from GI tract and it has very low bioavailability around 23 % because it is having first pass hepatic metabolism. As carvedilol has low bioavailability and very shorten half- life (6hr) which leads to long term therapy ultimately result in poor patient compliance and leads to increase in dosing frequency. Hence alternate route is needed to improve patient compliance (Ubaidulla et al., 2007).

Low bioavailability is the very most common problem for the oral dosage forms of water-soluble drugs. Various chemical reactions reduce the drug absorption which results in low bioavailability. Solubility and permeability are the main aspect to improve the bioavailability. BCS classification plays an important role in the solubility and permeability and thereby in enhancing bioavailability. So, to improve solubility there are many methods like, co-solvent addition, micellar solubilization, and polymer loading, modification of drug dosage forms. In permeation approach, micro and nano emulsion, liposomes and niosomes, dry emulsion system, solid lipid nano particles are the different methods for enhancing the permeability (Allam et al., 2011). Polymer is the main backbone for the transdermal drug delivery system which controls the release of the drug from device. Whichever polymer is in formulation it should have biocompatibility and chemical compatibility with drug and other excipients. There are some criteria while choosing the polymer for TDDS formulation. The polymer should be stable and non-reactive with drug, its molecular weight and other chemical functionality of the polymer should be such that drug diffuses in proper manner and releases through it. Its degradation product must be non-toxic. There are many polymers used like natural polymers and synthetic polymers. Some of them are widely used polymers like Hydroxypropyl methyl cellulose, hydroxy propyl cellulose, ethyl cellulose. In this formulation Eudragit polymer has been used. Eudragit polymer can be used in the different formulations like microspheres, nanoparticles, liposomes, tablets, sustained release dosage forms, transdermal drug delivery systems. This polymer is used for bioavailability enhancement, drug release at intestine, and for sustained release of the drug (Patra et al., 2017; Oza et al., 2013; Kapoor et al., 2018; Rastogi and Yadav, 2014). Transdermal route is a best option for administration of carvedilol. As transdermal route has many advantages over oral dosage form, hence it is best suited for the delivery of Carvedilol. Transdermal drug delivery systems (TDDS) are the devices which contains the active ingredients of defined surface area that delivers the predetermined amount of active ingredient to the surface of intact skin at predefined rate. TDDS has many advantages over oral dosage forms like, it is a painless method to deliver the drug only by applying the drug on healthy skin, so the needle phobia can be avoided, it avoids gastric irritation, it avoids hepatic first pass metabolism and also increases bioavailability of drug, it improves the patient compliance by reducing the dosing frequency and also suitable the patients who are unconscious. Also, it reduces risk associated with side effects by systemic circulation. Its main advantage is, it releases the drug with sustained action and therapy can be easily and rapidly terminated. Skin provides the large surface area and it offers the ease of access which allows many placement options on the skin for transdermal absorption. The main purpose of this study is to provide the drug at a controlled rate across the intact skin thereby improving the bioavailability and hypertension can be controlled for longer period of time from the transdermal patches. (Oza et al., 2013; Kapoor et al., 2018; Rastogi and Yadav, 2014).

The main objective to choose the TDDS in the form of patch is because of drug characteristics and some biological properties of Carvedilol. Because of these Properties Carvedilol is considered as a challenging drug candidate for transdermal administration. Such properties are like high first pass metabolism, and also it is having high lipophilicity (log P 3.97) and low molecular weight (406.5) means having the capacity to cross the lipophilic skin barrier. A matrix type of design was selected for this formulation due to he ease of manufacturing. Therefore, it is possible to make transdermal patch to release the drug slowly through skin for long period of time and it will decrease the frequency of administration and will improve patient compliance which is helpful for the patient. Thus, objective of this study is prevention of first pass metabolism of Carvedilol and thereby increasing bioavailability by developing the transdermal patches of Carvedilol and also to control release of drug and to deliver the drug directly to systemic circulation in the treatment of Heart failure (Mounika et al., 2014).

2. Material and methods:

2.1. Materials:

Carvedilol was purchased from Hechemist Technology Co. ltd, (China). The polymer HPMC K4M & Eudragit RS-100 was purchased from Shouguang Fukang Pharmacy Factory (China). Polyethylene glycol 400 obtained from Merk (Germany). Propylene glycol and Span 80 were purchased from Food chem International Corporation (Shanghai). All the other chemicals were of pharmaceutical grade.

2.2. Development of transdermal patch:

The patches were developed by solvent casting evaporation technique. HPMC K4M and Eudragit RS-100 polymers were used. Different concentrations of polymers were added in 30 ml volume of solvent Methanol: Chloroform (3:2). The polymeric dispersion stirred with magnetic stirrer for about 10 min to form clear solution. Weighed amount of polyethylene Glycol 400 and Span 80 was added to above solution. 6.25 mg of drug was mixed thoroughly by the use of magnetic stirrer for few minutes. The uniform solution was formed which was poured into petri plate and placed inverted funnel which will help to control the evaporation of solvent and will avoid the cracking of patches. This was kept aside for overnight. Dried patches were separated from the plate, cut and stored in desiccator. All formulation batches are given in Table 1.

2.3. Evaluation of transdermal patches

The developed patches were evaluated by performing following tests.

2.3.1. Thickness:

Screw gauze was used for the determination of thickness of 10 selected patches. Thickness was measured at 5 different locations. And average was calculated (Mounika et al., 2014).

2.3.2. Uniformity of weight:

Uniformity of weight was calculated by weighing the patches on digital balance. The test was performed on 5 patches and average weight was calculated (Mounika et al., 2014).

2.3.3. Moisture content:

For moisture content, desiccator with fused calcium chloride was used. Patches to be evaluated were initially weighed and put in a desiccator for 24 h. After 24 h patches were reweighed and moisture content was calculated by subtracting the final weight from initial weight with respect to initial weight (Mounika et al., 2014).

Table 1
Development of Carvedilol transdermal patch.

Formulation code	Carvedilol (mg)	HPMC K4M (mg)	Eudragit RS-100 (mg)	PEG400 (%w/w)	Propylene glycol (%w/w)	Span 80 (%w/v)	Methanol: chloroform (3:2) ml
F1	6.25	300	–	30	30	–	30
F2	6.25	500	–	30	30	–	30
F3	6.25	700	–	30	30	–	30
F4	6.25	300	–	30	–	1	30
F5	6.25	300	–	30	–	1.5	30
F6	6.25	300	–	30	–	2	30
F7	6.25	–	700	30	–	2	30
F8	6.25	–	500	30	–	1.5	30
F9	6.25	–	300	30	–	1	30

2.3.4. Moisture uptake:

For maintaining the 84% Humidity in desiccator, Potassium Chloride solution was placed in Desiccator. Weighed patches were placed in the above desiccator for 24 h and after 24 hrs reweighed patches and % uptake moisture was calculated by subtracting the final weight from initial weight with respect to initial weight (Mounika et al., 2014).

2.3.5. Folding endurance

Folding endurance was determined by folding the patch several numbers of time at same time and at same place till patch broke. The number at which patch fold without breaking will give the value of folding endurance (Mounika et al., 2014).

2.3.6. Water vapour transmission (WVT) rate:

Glass vial is used as transmission cell in which Calcium Chloride was placed which act as a desiccant. A film which is to be evaluated was placed over cell. This cell was weighed and placed in desiccator which is filled with Potassium Chloride solution (saturated solution) to maintain the 84% RH. Glass vial was removed from desiccator & reweighed after 24 h for period of 72 h. The WVT rate was determined by below mentioned formula (Mounika et al., 2014).

$$\mathrm{WVT} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Area}}$$

2.3.7. Drug content determination

About 100 ml solution of Phosphate buffer with pH 7.4 was used to perform this test. A patch having dimension 1 cm × 1 cm was cut and added into buffer solution. Stirred the solution with magnetic stirrer for 5 h, filtered the solution and drug content analysis was done with dilution at 240 nm wavelength by using spectrophotometer (Mounika et al., 2014).

2.3.8. In vitro drug release study:

A glass diffusion cell was used to perform this test in which receptor compartment had the capacity of 20 ml and donor compartment had the capacity of 2 ml. Orifice had diameter of 4 mm. The patch was placed over semipermeable membrane which was attached to diffusion cell. A solution of Phosphate buffer with pH 7.4 was placed in receptor compartment and temperature was maintained at 37 ± 1 °C. This solution was continuously stirred. Samples (5 ml) were taken out from the medium at predetermined time and for maintaining sink condition same volume of fresh Phosphate buffer solution was replaced. The drug content was analysed spectrophotometrically at 240 nm wavelength and percentage drug release was calculated (Mounika et al., 2014).

2.3.9. In vitro skin permeation study

Franz diffusion cell was used to perform this study. Abdominal skin of rat was fixed in between the two compartments which was donor compartment and the receptor compartment. Receptor compartment had capacity 20 ml and it was filled with 7.4 pH Phosphate buffer. The patch was fixed on the skin. This set up was mounted on stirrer. The receptor compartment which was filled with Phosphate buffer solution was stirred with magnetic stirrer (temperature 32 ± 0.5 °C). The samples were taken out at different time intervals and drug content was analysed by spectrophotometer. After each sample withdrawal, the equal volume of buffer solution was replaced every time. The graph between cumulative amount of drug permeated and time was plotted (Mounika et al., 2014).

2.3.10. Skin irritation test:

Skin irritation test was done to check that the formulation is free from any skin irritation. Male Wistar rats were selected for this study. One day before of the experiment, hairs on back of rats were removed by clipping. 5 groups were prepared each of 6 Rats per group and were treated one time in a day over a period of 7 days.

Group 1- Normal, Group 2- control (application of commercially available formulation), Group 3–0.8% v/v aqueous solution of Formalin (Formalin was used as a standard irritant with concentration of 0.8% v/v.), Group 4- blank transdermal patch (without drug), Group 5- Transdermal patch with a drug. Application site will be evaluated on 8th day by same investigator for erythema and oedema (Oza et al., 2013).

2.3.11. In vivo studies

Wistar albino rats (adult male) were selected which were weighing average 230 to 250 g. These were kept at 25 ± 1-C and 55 ± 5% RH with 12-hour alternate light and dark cycle. All the rules followed as per the animal ethics committee guidelines. The rats were placed in polypropylene cages with 4 rats in each cage and having free access of laboratory food (Ubaidulla et al., 2007; Patra et al., 2017).

2.3.12. Pharmacokinetic evaluation of patches on animals

Adult rats (Wistar Albino species) were selected for bioavailability study and superficial skin was examined for any abnormality on skin surface of the rats. Only 230 to 250 g weight of rats were selected and shaving on dorsal side was done. Rats were kept under observation before application of the transdermal patches to avoid any unwanted effect of shaving. Rats were kept completely fasted in this period of time. Three groups were prepared. Group I was administered with drug Carvedilol orally (5 mg/kg), Group II was administered F6 formulation and group III was administered F7 formulation. The blood samples were taken out at various time intervals i. e. 2, 4 8 and 24 h. Till the analysis done, plasma samples were centrifuged by centrifugation and stored in

Table 2
Evaluation of Transdermal Patches of Carvedilol.

Formulation Code	Thickness uniformity Average (mm)	Weight variation Average (mg)	% Moisture content	% Moisture uptake
F1	0.20 ± 0.004	188.7 ± 0.52	3.18 ± 0.025	4.97 ± 0.05
F2	0.23 ± 0.002	198.25 ± 0.51	3.49 ± 0.05	4.21 ± 0.02
F3	0.25 ± 0.005	205.1 ± 1.6	4.19 ± 0.034	4.62 ± 0.01
F4	0.22 ± 0.01	197.4 ± 0.21	2.81 ± 0.01	5.18 ± 0.05
F5	0.237 ± 0.5	188.1 ± 0.49	2.35 ± 0.05	5.25 ± 0.01
F6	0.22 ± 0.5	198.6 ± 0.56	2.37 ± 0.01	4.38 ± 0.01
F7	0.198 ± 0.33	189.8 ± 0.89	2.34 ± 0.02	4.32 ± 0.022
F8	0.199 ± 0.88	194.6 ± 0.54	2.33 ± 0.044	4.32 ± 0.21
F9	0.22 ± 0.12	198.7 ± 0.52	2.22 ± 0.34	4.44 ± 0.56

vials at −70 °C. The drug plasma concentration was measured by reverse phase HPLC method. Chromolith column was used (column length: 100 × 4.6 mm, 2 μm), flow rate was 1.5 ml/min, Methanol: Acetonitrile: Phosphate buffer pH 3.0 (45:25:30 v/v) was used as a mobile phase. Injection of sample volume was 10 μL. and retention time was 5.5 min.(Alexander et al., 2012; Gannu et al., 2007; Alkilani et al., 2015; Zsikó et al., 2019)

2.3.13. Efficacy in rats against hypertension

Initial blood pressure (BP) of rats was measured by MUROMACHI MK2000ST with non-invasive tail cuff and digital BP display method. Initially BP was measured which was normal; Hypertension was induced by injecting Physostigmine 15 μg/kg/day intravenously for 2 weeks. Hypertension was induced after 14 days, mean BP of 150 mmHg was selected. Four groups (n = 5) were prepared for the Rats. Group 1- no treatment (control), group 2- treated with Carvedilol 5 mg/kg orally, group 3 was treated with Carvedilol transdermal patch of Formulation F6 and group 4 treated with transdermal patch of formulation F7. BP of rats was recorded at various time intervals (1, 2, 4,6,10, 24 Hrs) (Fröhlich et al., 2015).

3. Results and discussion

3.1. Thickness:

With the help of screw gauge thickness was measured and average was taken. Thickness of patches of formulation F1 to F9 varies from 0.199 ± 0.33 to 0.25 ± 0.005 mm. Results are tabulated in Table 2. F3 formulation with polymer HPMC K4M shows maximum thickness.

3.2. Uniformity of weight:

Uniformity of weight was calculated by weighing 5 patches and average was taken. Weight of the patches of formulation F1 to F9 varies from 188.1 ± 0.49 to 205.1 ± 1.6 mm Results are tabulated in Table 2**.**

3.3. Moisture content:

Moisture content of transdermal patches of formulation F1 to F9 ranges from 2.22 ± 0.34 to 4.19 ± 0.034 %. Formulation with HPMC K4M shows maximum moisture content whereas formulation with Eudragit shows less moisture content. Results are tabulated in Table 2.

3.4. Moisture uptake:

Moisture uptake of transdermal patch of formulation F1 to F9 ranges from 4.21 ± 0.02 to 5.25 ± 0.01%. Results are tabulated in Table 2

3.5. Folding Endurance:

This test was done and results indicated that patches would not break and would maintain their integrity with general skin folding when applied. Folding endurance of transdermal patch of formulation F1 to F9 ranges from 18.43 ± 0.0056 to 26.98 ± 0.11. Formulation with Eudragit polymer has provided a greater number of folding without cracks as compared to other formulation. Results are tabulated in Table 3

3.6. Drug content:

Drug content of transdermal patch of formulation F1 to F9 ranges from 91.45 ± 0.22 to 99.43 ± 0.004 %. Formulation with Eudragit (F7) shows the maximum drug content. But with increase in Eudragit concentration, the drug release was decreased. Results are tabulated in Table 3

3.7. Water vapour transmission rate:

It varies in the range from 1.56 ± 0.33 to 4.45 ± 0.22 (gm/ cm2/ hr) × 10–4 for formulation F1 to F9. Results are tabulated in Table 3

3.8. In vitro drug release study:

The formulation F1, F2, F3 containing different concentration of HPMC K4M, showed complete drug release within 10–11 hrs in which 30 % propylene glycol was used as penetration enhancer. Formulation F4, F5, F6 containing fixed concentration of HPMC K4 M with variable amount of Span 80 as a penetration enhancer, showed drug release within 11 h with 90.11%, 92.29% and 93.33%. Formulation F7, F8,F9 containing variable amount of Span 80 and variable amount of Eudragit polymer, showed drug release within 12 h with 100.29%, 94.25% and 92.12%. Formulation F7 had showed maximum cumulative % drug release within 12 h which indicated sustain release up to 12 h. All results has been tabulated in Table 4**.**

Table 3
Evaluation of Transdermal Patches of Carvedilol.

Formulation Code	Folding endurance (n = 3)	Drug content (%)	Water vapor transmission rate (gm/ cm^2/hr) × 10^{-4}
F1	14.45 ± 0.04	91.45 ± 0.22	3.46 ± 0.001
F2	18.98 ± 0.045	95.45 ± 0.57	3.67 ± 0.23
F3	23.34 ± 0.043	95.32 ± 0.45	4.45 ± 0.22
F4	20.93 ± 0.002	92.54 ± 0.11	3.33 ± 0.66
F5	18.43 ± 0.0056	94.67 ± 0.58	3.45 ± 0.56
F6	24.65 ± 0.005	93.99 ± 0.01	3.22 ± 0.76
F7	25.43 ± 0.55	99.43 ± 0.004	1.56 ± 0.33
F8	25.78 ± 0.12	98.42 ± 0.22	2.58 ± 0.45
F9	26.98 ± 0.11	97.56 ± 0.67	2.78 ± 0.21

Table 4
In vitro drug release profile for Carvedilol transdermal patch.

Time (Hrs)	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	17.3	13.9	11.3	14.	18.46	25.76	25.89	22.49	21.99
2	19.0	17.6	15.2	16.1	19.43	28.12	29.56	25.66	22.36
3	25.98	25.22	18.4	26.76	27.96	37.56	38.33	36.33	35.03
4	28.4	33.3	32.0	28.32	29.44	39.64	39.34	37.32	36.92
5	45.94	39.4	50.4	43.7	43.99	43.09	43.12	42.42	42.12
6	62.34	53.45	60.34	49.7	49.98	49.78	49.08	45.98	44.98
7	71.23	61.65	65.1	53.7	55.45	57.45	57.25	53.25	52.25
8	88.3	68.4	73.43	68.65	71.65	73.05	73.78	71.78	71.38
9	90.32	75.04	88.23	78.3	78.43	79.73	78.30	76.30	74.30
10	98.4	89.65	92.2	82.1	90.04	88.67	89.67	87.67	84.77
11	–	95.29	–	90.11	92.29	93.33	93.75	88.50	88.05
12	–	–	–				100.3	94.25	92.12

3.9. In vitro skin permeation study

In this study for formulation F1, F2, F3 indicated that % cumulative drug permeation decreased as the HPMC K4M polymer concentration increased in the formulation where propylene glycol was used as the permeation enhancer in fixed amount. In formulation F4, F5, F6, % cumulative drug permeated was found to be 89.15, 92.15 and 93.15 respectively where Span 80 was used as permeation enhancer in variable amount. It revealed that % cumulative drug permeation increased by increasing Span 80 concentration (Fig. 1). In formulation F7, F8, F9 % cumulative drug permeation was found to be 98.45, 95.10, and 94.32, in which Eudragit was used as a polymer. In formulation F7 maximum drug was permeated. It was observed that when Eudragit polymer concentration increased, and Span 80 concentration was decreased hence there was no more difference found in the drug permeation. All results showed in Table 5 and graphical representation showed in Fig. 2.

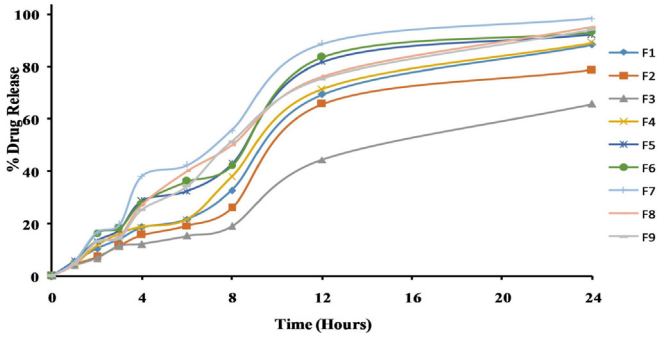

Fig. 1. Comparative In vitro drug release study of Carvedilol transdermal patches (F1 to F9) in buffer pH 7.4.

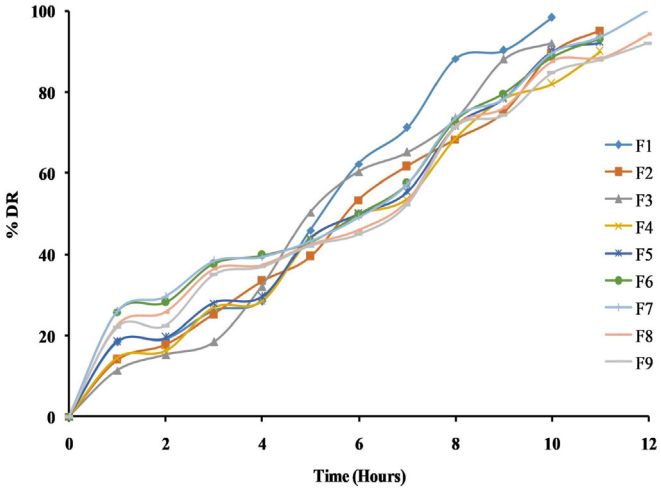

Fig. 2. In vitro drug permeation of F1 to F9 formulation.

3.10. Skin irritation study

Visual evaluation was done for skin irritation test. It was observed that erythema and edema observed in the group 5 was not more as compare to the group which was treated with standard irritant i. e. aqueous Formalin solution 0.8% v/v. So, it can be concluded that formulation having no skin irritation or very little amount of irritation (Fig. 3).

3.11. Pharmacokinetic effect on transdermal patches

In vivo studies results are presented in Table 7 which are pharmacokinetic effects of patches and were determined from blood plasma concentration. The results obtained for oral Carvedilol

Table 5
Cumulative % drug permeated.

Time (Hrs)	% cumulative drug permeated								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	5.25	4.43	4.0	4.34	5.65	4.99	5.34	4.33	4.54
2	10.45	7.32	6.71	11.75	13.43	16.22	16.72	13.21	13.13
3	14.23	11.67	11.45	16.23	17.66	18.32	19.66	15.22	14.44
4	18.67	15.66	12.22	18.87	28.65	28.05	38.25	27.33	25.34
6	21.78	19.22	15.33	21.78	32.38	36.18	42.38	40.22	34.33
8	32.65	25.98	19.0	37.75	42.75	42.11	55.75	50.09	51.33
12	69.32	65.66	44.43	71.32	81.76	83.66	88.74	76.32	75.45
24	88.45	78.65	65.76	89.15	92.15	93.15	98.45	95.10	94.32

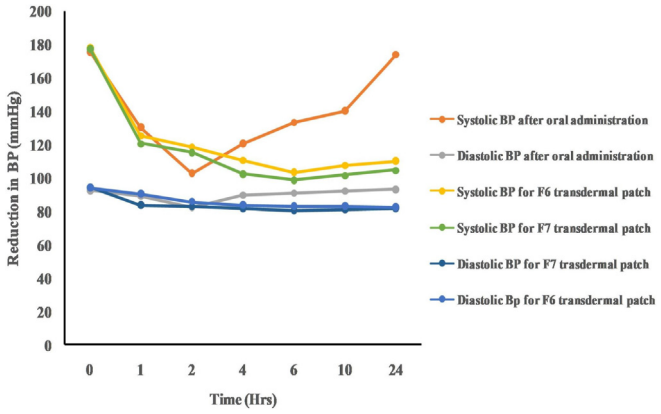

Fig. 3. Reduction of BP in comparison between transdermal patch and oral administration of Carvedilol.

administration was significantly different from results obtained from transdermal patches. The maximum concentration for Oral carvedilol was found to be 4.15 ± 0.34 μg/ml at maximum time period of 2 Hrs whereas for formulation F6 and F7, maximum concentration was found to be 4.65 ± 0.56 and 5.42 ± 0.12 μg/ml respectively. Elimination half life was found to be prolonged in formulation F6 and F7; it means drug was not eliminated completed in the body for extended time period. Less value of elimination rate constant indicates sustained release of action. AUC for the Formulation F6 and F7 was found to be high as compared to oral administration of carvedilol. F6 and F7 showed maximum bioavailability as compared to oral bioavailability Table 6.

Table 6
Pharmacokinetic parameters of drug after oral Carvedilol and transdermalpatch of Carvedilol.

parameters	Oral	F6	F7
Cmax (μg/ml)	4.15 ± 1.34	4.55 ± 0.56	5.42 ± 0.12
Tmax(h)	2 Hrs	12 Hrs	12 Hrs
Ke (h-1)	0.210 ± 0.004	0.033 ± 0.021	0.025 ± 0.05
T1/2 (h)	3.45 ± 1.67	15.67 ± 1.45	16.78 ± 1.09
AUC(0–24) (μg h/ml)	41.78 ± 2.67	67.89 ± 1.98	75.43 ± 2.11
AUC(0-∞) (μg h/ml)	42.09 ± 2.21	154.23 ± 1.23	165.88 ± 0.89
F%	–	162.494	180.540

C_{max}: Maximum concentration of drug in blood, T_{max}: time taken to reach maximum concentration,
K_e: elimination rate constant, $T_{1/2}$: half-life of drug, AUC: area under curve, F (%): relative bioavailability

3.12. Transdermal patches efficacy in rats against hypertension

Table 8 shows administration of Dexamethasone increased BP in Rats. The treatment, in which Carvedilol was given orally, decreases BP significantly. But maximum effect was occurred at 2 h, later on BP increased up to 24 h. It was observed that at 24 h, BP at initial and at 24 hrs was same. Both systolic and diastolic BP values are shown in Table 8. In contrast with administration of transdermal patch (formulation F6 and F7) BP decreases gradually. Maximum drop of BP was observed at 6 h. In 1st hour BP dropped significantly and result continued up to 24 h. Formulation F7 showed maximum drop of BP at 6 h. Hence, it was concluded that, transdermal patch of Carvedilol produced sustained and continued drug release than oral administration. Since Carvedilol which was given orally acted very fast but later on its effect going decreasing and increases BP again. Hence, this is clearly indicated that, formulated Carvedilol patches released the drug slowly in specific time period, and it leads to control over high BP for extended duration in 24 h. Hence, transdermal patch (Formulation F7) overcomes the problems oral administration like low bioavailability. Both systolic and diastolic BP values are shown in Table 7 **and** Table 8**.**

4. Conclusion:

In the development of transdermal patches of Carvedilol, it was concluded that transdermal patch is superior over oral administration and deliver the drug for prolonged duration and also best option for treatment and management of hypertension and thereby in Heart failure. But for their efficacy at clinical level needed to be studied further.

Research conducted on animals

The presented research conducted on the rats and all the rules followed as per the animal ethics committee guidelines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 7
Antihypertensive effect of transdermal route and oral route for Carvedilol (Reduction of systolic BP).

Group	Treatment	Systolic mean BP (mmHg)						
		Initial	1 Hr	2 Hr	4 Hr	6 Hr	10 Hr	24 Hr
I	Control	178.92	178.11	177.34	175.54	174.67	177.98	178.22
II	Oral	175.55	130.32	102.34	120.22	132.98	140.11	173.85
III	F6	177.93	125.26	118.32	110.38	103.20	107.23	110.23
IV	F7	177.21	120.34	114.97	102.21	98.44	101.32	104.45

Table 8
Antihypertensive effect of transdermal route and oral route for Carvedilol (Reduction of Diastolic BP).

Group	Treatment	Diastolic mean BP (mmHg)						
		Initial	1 Hr	2 Hr	4 Hr	6 Hr	10 Hr	24 Hr
I	Control	94.34	95.12	94.78	96.11	95.32	91.56	93.98
II	Oral	92.21	88.90	82.34	89.54	90.76	91.94	92.98
III	F6	93.93	90.12	85.44	83.45	82.87	82.76	82
IV	F7	94.22	83.67	82.66	81.9	80.45	81.23	81.87

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