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## Design and optimization of reservoir type transdermal patches of carvedilol

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### Abstract

The objective of present research work was to design and optimize reservoir type transdermal patches of carvedilol. These patches were prepared by solvent casting technique using hydrophilic polymers and polyvinyl pyrrolidone K30 (rate controlling membrane). The patches were characterized for physico-chemical properties and were found within acceptable limits. The *in-vitro* drug release was performed using Franz diffusion cell for the selection of optimized formulation from all prepared formulations. Formulation R7 was selected as optimized formulation since it shows highest flux for 24 hr and the drug release from all formulations follows zero order release kinetics. Formulation R7 shows excellent relationship between *in-vitro* diffusion profile and *ex-vivo* permeation profile with regression coefficient ( $r^2 = 0.999$ ). Formulation R7 was found to be stable for short term stability studies as per International Council of Harmonization (ICH) guidelines. The study demonstrated that the present system has a potential of delivering active across skin in controlled manner with desired systemic activity.

**Keywords:** Carvedilol, flux, reservoir, *in-vitro* diffusion, *ex-vivo* permeation, zero order

### 1. Introduction

With the increasing demand for patient compliance, therapies has led in development of transdermal drug delivery systems (TDDS) that has numerous virtues over traditional drug delivery systems. The TDDS facilitates controlled release of actives, and encourages patients' compliance and ease with its non-invasiveness and painlessness. [1] The TDDS has added merits like improved systemic bioavailability resulting by avoiding the first pass metabolism. Intersubject variability because oral administration, like pH, the presence of enzymes, food and gastrointestinal transit times can all be eliminated. [2]

The intention in designing of novel transdermal drug delivery system is to obtain a controlled, predictable, and reproducible release of the active pharmaceutical ingredient into the systemic circulation after topical application. These systems act as a drug reservoir and control the drug transfer rate. When the transdermal flux of is controlled by the device instead of by the skin, delivery of the drug is more reproducible, leading to smaller inter- and intra- subject variations because the drug release from the device can be controlled accurately than the permeability of the skin. [3, 4]

Carvedilol is competitive  $\alpha_1$ -,  $\beta_1$ - and  $\beta_2$ -adrenergic blocker activity with number of ancillary activities like antioxidant, calcium antagonist blocking and smooth muscle proliferation action. Ratio of  $\alpha_1$ - and  $\beta$ - receptor potency (antagonistic) of carvedilol is 1: 10. For carvedilol 1:10 ratio of  $\alpha_1$  to  $\beta$ - receptor shows antagonist potency. It is approved in treatment for hypertension for twice a day administration by US Food and Drug Administration (FDA) either alone or in combination other therapeutic agents used in the treatment of primary hypertension, heart failure or myocardial infarction. Mostly carvedilol is used with the diuretics in combination. [5]

Carvedilol is Biopharmaceutical Classification System (BCS) Class II drug which is practically insoluble in dilute acids and water. It is having high lipophilicity, protein binding ability and under goes rapid stereo-specific first pass metabolism results in lower oral bioavailability. Poor water solubility is also imperative issue in declining the bioavailability of drug since absorption of drug is dissolution rate limiting step which is responsible for delayed absorption. It is having biological half-life between 2-6 hr. It is mainly metabolized in liver by hepatic CYP2D6 and CYP2C9 enzymes results in the formation of seven inactive metabolites. [6] In the present research work seven formulations of Carvedilol were designed using sodium alginate and xanthan gum in various proportions by solvent evaporation method using

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aluminium foil as backing membrane. Dibutyl phthalate, turpentine oil and polyvinyl pyrrolidone K-30 were used as plasticizer, penetration enhancers and rate controlling membrane respectively. The prepared patches were evaluated for the parameters like thickness, tensile strength, folding endurance, % elongation, % moisture content, % moisture uptake, % drug content, *in vitro* drug release, *in-vitro* permeation and stability study. The objective of present research work was to design and optimize a reservoir type transdermal delivery system for carvedilol. The transdermal patches of carvedilol were prepared by solvent casting method using hydrophilic polymers namely sodium alginate and xanthan gum in variable ratio and polyvinyl pyrrolidone K30 as a rate controlling membrane.

## 2 Materials and Methods

### Materials

Carvedilol was obtained as a gift sample from Dr Reddy's laboratory Ltd., (Hyderabad, India), Sodium alginate and xanthan gum were procured from Sisco Research Laboratories, (Mumbai, India). Dibutyl phthalate, turpentine oil and polyvinyl pyrrolidone K-30 were purchased from Sigma Chemicals Ltd., (Mumbai, India), Sigma Aldrich (Mumbai, India) and S.D. Fine Chemicals (Mumbai, India) respectively. All other chemicals and solvents used were of analytical grade.

### Methods

#### 2.1 Evaluation of backing membrane

Backing membrane acts as flexible film which provides low vapor transmission rate and greater oxygen transmission rate. Aluminium foil was used in design of transdermal drug system as backing membrane. Primary study was performed to test the influence of thickness of aluminium foil on moisture vapor transmission rate through aluminium foil. The MVT is the moisture transmitted per unit area of transdermal patch per unit time. Transmission cells of glass were consists of 2 g of anhydrous calcium chloride and film of particular area was fixed on to cell brim. Assembly was weighed and put in humidity chamber ( $80 \pm 5\%$  RH) at  $27 \pm 2^\circ\text{C}$  for one day. Then reweighed the sample cell for the determination of moisture vapor transmission by using Eq. (1)

$$\text{Moisture vapor transmission} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \quad (1)$$

**Table 1:** Formulation of transdermal patches of Carvedilol

Formulation	Polymer (%)		Dibutyl phthalate (%)	Turpentine oil (%)
	Sodium alginate	Xanthan gum		
R1	1	7	2.0	3.0
R2	2	6	2.0	3.0
R3	3	5	2.0	3.0
R4	4	4	2.0	3.0
R5	5	3	2.0	3.0
R6	6	2	2.0	3.0
R7	7	1	2.0	3.0

#### 2.5 Evaluation of carvedilol TDDS

The selection of optimized formulation was done considering the physicochemical properties and cumulative percent drug release at 20 hr ( $Q_{20}$ ) and diffusion coefficient (n) after applying the kinetic model to the data obtained. The optimized formulations were further evaluated for the skin irritation studies, stress stability studies and ex- vivo studies.

#### 2.2 Primary screening of permeation enhancer

Drug reservoir prepared by using various ratios of sodium alginate and xanthan gum. Drug solution was poured into uniform dispersion by slight stirring using magnetic stirrer. The homogeneous dispersion dried at  $45^\circ\text{C}$  for 6 hr. Rate controlling membrane casted on drug reservoir using 0.10% (w/v) of polyvinyl pyrrolidone K30 (PVP K30) in dichloromethane and dibutyl phthalate and added turpentine oil as permeation enhancer about (0.5 to 3 %). In- vitro release drug study performed using Franz diffusion cell with receptor compartment having capacity 25 ml. Cellophane membranes was used for drug diffusion studies. Receptor compartment of diffusion cell was filled with phosphate buffer pH 7.4 containing 20% of PEG. The samples were taken at predetermined time intervals up to 24 hrs and analysis for drug content at wavelength of 242 nm. The graph was plotted between cumulative amount of drug permeated per unit area and time using permeation parameters like steady state flux that is  $J_{SS}$  were determined.

#### 2.3 Screening of rate controlling membrane

Polymeric rate controlling membrane study was carried out for checking the effect of different polymeric combinations by keeping constant rate controlling membrane 0.10% (w/v) of polyvinyl pyrrolidone K30 (PVP K30) in dichloromethane on the drug release from various transdermal drug delivery systems. The composition of primary trial batches R1 to R7 were presented in Table 1.

#### 2.4 Preparation of transdermal patches

Transdermal drug delivery systems were prepared by solvent evaporation method. The molds bottom wrapped with aluminum foil as a backing membrane. Drug reservoir formulated by using 8% w/v polymer solution used in combination in various ratios of polymers namely sodium alginate and xanthan gum. The solution of drug was added into uniform dispersion by slow stirring with cyclomixer (Remi Laboratory Instruments, Mumbai, India). Dibutyl phthalate was used as plasticizer. Rate controlling membrane was casted on drug reservoir using 0.10% w/v of PVP K30 in dichloromethane and dibutyl phthalate (2%). The turpentine oil 3% v/v was used as penetration enhancer (Table 1). Transdermal formulations were cut into small patches of 3.14  $\text{cm}^2$  and placed into desiccators until study was completed.

##### 2.5.1 Physical appearance

All the transdermal patches were visually inspected for color, clarity, flexibility, smoothness and uniformity.

##### 2.5.2 Uniformity of weight

Six transdermal patches of each formulation were cut into 3.14  $\text{cm}^2$  and weighed using digital balance (Dolphin Pharmacy Instruments Pvt. Ltd., India) individually and

average weight was determined standard deviation was calculated. [8]

### 2.5.3 Uniformity of thickness

Thickness of each patch was determined at six different positions on the same patch using micrometer screw gauge (Mitutoyo, Japan). The average thickness and standard deviation for all the formulations were determined. [9]

### 2.5.4 Tensile strength

The tensile strength of patches was evaluated using advanced force gauge (Ultra-Test, Macmecin, UK) which consist of (two load) cell grip. The upper one was movable and lower one was fixed. The transdermal patch strips were fixed within cell grips and force applied continuously at 2 mm/ sec until patch broken. From dial reading ( $\text{kg}/\text{cm}^2$ ), the readings of tensile strength of film were recorded. [10]

### 2.5.5 Percentage elongation break test

Percentage elongation break test was determined by measuring length before break point of patch. Following Eq. (2) was used for determination of percentage elongation.

$$\text{Elongation percentage} = [(L_1 - L_2)/L_2] \times 100 \quad (2)$$

Where,

$L_1$  - final length of strip, cm

$L_2$  - initial length of strip, cm

Thickness of patch was measured by using digital micrometer screw gauge (Mitutoyo, Japan) at different three places. Then mean thickness value for each patch was calculated. [11]

### 2.5.6 Drug content

Finally the transdermal patches were evaluated for drug content. About 5  $\text{cm}^2$  film was cut into small pieces put into 100 ml phosphate buffer pH 7.4 for 24 hr and followed by ultra-sonication for 15 min. After filtration drug content was determined UV-Visible spectrophotometric ally (UV-1700 Shimadzu, Japan) at an absorption maxima 242 nm. [12]

### 2.5.7 Folding endurance

Patch with area (1  $\text{cm}^2$ ) was accurately cut and folded repeatedly at same place till patch was broken. Total number of times, patches folded at one place without breaking that was value of folding endurance. [13]

### 2.5.8 Flatness test

Three strips were cut from each patch at different points that from center, right side and left side. Each strip was measured in terms of length. Difference in length was observed due to non-uniformity in flatness. It was measured by percent constriction. [14]

### 2.5.9 Moisture content

The three patches of each formulation were weighed and kept in a desiccators containing calcium chloride at 40°C for 24 hrs. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to the final weight using Eq. (3) [15].

$$\text{Moisture content (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (3)$$

### 2.5.10 Percent moisture uptake

In this method patches weighed then kept in desiccators at room temperature for one day. In desiccators saturated

solution of potassium chloride placed for maintaining relative humidity of 84%. After 24 hr the patches were reweighed. [16] And the percent moisture uptake was calculated using Eq. (4)

$$\text{Percent moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (4)$$

### 2.5.11 Percent moisture loss

First individually patches were weighed and placed in desiccators which contain calcium chloride and temperature maintains 40°C. After 24 hr the patches were reweighed. [17] Percent moisture loss was calculated by using Eq. (5).

$$\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \quad (5)$$

### 2.5.12 Water vapor transmission rate

Glass vials of uniform diameter were used as transmission cells in this study. The transmission cells were washed and dried at temperature 100°C in hot air oven (LabHosp, Mumbai, India). The patch was attached over brim placed in cell containing 1 g of anhydrous calcium chloride and respective transdermal patch was fixed over the brim. Then each cell was accurately weighed and kept in desiccators containing a saturated solution of potassium chloride for maintaining 84% relative humidity. Then cells were taken out and reweighed. [18] The water vapor transmission rate was calculated using Eq. (6).

$$\text{Water vapor permeability} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Time} \times \text{Area}} \quad (6)$$

### 2.5.13 In-vitro release studies of carvedilol TDDS

Franz diffusion cell ((Dolphin Pharmacy Instruments Pvt. Ltd., India) with a surface area of 3.14  $\text{cm}^2$  was used for in-vitro release studies. The transdermal patch was kept in the donor compartment and it was separated from the receptor compartment by dialysis membrane (Hi media molecular weight cut off 5000). The donor and receptor compartment held together using clamp. The receiver compartment contained 25 ml of phosphate buffer solution of pH 7.4 containing 20% v/v of PEG-400, stirred at 500 rpm and temperature was maintained at  $37 \pm 0.5^\circ\text{C}$ . Samples of 1 ml were withdrawn at pre-determined time intervals and replenished with an equal volume of fresh medium. The drug content in the samples was determined by UV-visible spectrophotometer (UV1700 Shimadzu, Japan) at 242 nm. Cumulative percentage of the drug released were calculated and plotted against time. [19, 20]

### 2.5.14 Kinetic data analysis

In order to ascertain exact mechanism of drug release from modified release drug pellets, the drug release data obtained with all eight formulations were analyzed using kinetic models like zero order rate kinetics (cumulative percent drug release Vs time), first order rate kinetics (Log cumulative percent drug release Vs time), Higuchi model (cumulative percent drug release Vs square root of time), Korsmeyer-Peppas model (Log cumulative percent drug release Vs Log time) and Hixon-Crowell model [(percent drug retained)<sup>1/3</sup> Vs time]

The Korsmeyer-Peppas model is widely used when the release mechanism is not well known or when more than one release phenomenon could be involved. The 'n' value could be used to characterize different mechanisms. [21] Korsmeyer-Peppas Eq. (7) is given as;

Cumulative % drug release (% R) = k. t<sup>n</sup> or

$$\text{Log } (\% R) = n \text{ Log } k + \text{Log } t \text{ (8)}$$

Where,

- R = drug release,
- k = release rate constant,
- n = slope of straight line and
- t = time in hr.

Fitting of the drug release data into kinetic models was shown in Table 2.

**Table 2:** Interpretation of diffusional release mechanisms

S. No.	Slope (n)	Mechanism
1.	0.5	Fickian diffusion
2.	0.5 – 1.0	Non-Fickian diffusion (anomalous transport)
3.	1.0	Case II transport
4.	> 1.0	Super case II transport

### 2.5.15 Ex-vivo permeability studies

Franz diffusion cell (Dolphin Pharmacy Instruments Pvt. Ltd., India) was used for ex- vivo permeation studies and the skin was mounted between the two compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the release surface of the TDDS under test. A dialysis membrane (Hi Media, molecular weight cutoff 5000) was placed over the patch, in order to secure it tightly in the way that will not get dislodged from the skin. The receiver phase contained 12 ml phosphate buffer solution of pH 7.4 containing 20% v/v PEG 400 which was stirred at 500 rpm on a magnetic stirrer and the whole assembly was kept at 37 ± 0.5 °C. Samples of 1 ml were withdrawn at pre-determined time intervals up to 24 hrs, the volume was replenished with an equal volume of fresh medium and analyzed by UV-Visible spectrophotometric ally (UV1700 Shimadzu, Japan).

### 2.5.16 Skin irritation studies

Wister rats were divided into four groups (n = 3 per group) were treated once daily over a period up to 7 days as following groups: Group I normal, Group II 0.8% v/v aqueous formalin solution, Group III drug control without turpentine

oil, Group IV transdermal patch with turpentine oil. After 8 day the site of application was observed visually for erythema and oedema [23].

### 2.5.17 Stress stability studies

The optimized formulation was wrapped into the aluminium foil and stored at 40± 2.0°C and 75% RH for time of 3 months in stability chamber (Remi Laboratory Instruments, Mumbai, India). After 3 months, patches were tested for drug content and in- vitro release studies. Similarly the optimized formulation was wrapped in the aluminium foil and stored at 25± 0.5°C and 60% RH for time of 3 months in stability chamber (Remi Laboratory Instruments, Mumbai, India). [24] Dissolution profile of product compared with the drug release on the day of preparation of patches using similarity factor (f<sub>2</sub>) that is calculated using Eq. (9)

$$f_2 = 50. \text{Log } \{ [1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100 \}$$

Where, n = number of sample points,

R<sub>t</sub> = percent of marketed product observed and

T<sub>t</sub> = percent of test formulations release observed.

FDA has set a published standard for similarity factor (f<sub>2</sub>) value (50-100) for indication of similarity between two dissolution profiles. To use mean data, for extended release products, the coefficients of variation for mean dissolution profile of a single batch should be less than 10%. The average difference at any dissolution sampling point should not be greater than 15% between test and reference products. [25, 26]

## 3 Results and Discussions

The reservoir type of carvedilol transdermal patches were prepared using sodium alginate and xanthan gum. Preliminary batches were prepared and evaluated. The TDDS was designed using sodium alginate and xanthan gum as polymers and which can modulate the cumulative drug release at 20 hrs (Q<sub>20</sub>) and diffusion coefficient (n).

### 3.1 Screening of backing membrane

Preliminary trial of the backing membrane of transdermal patch of B6, B7 and B8 shows low WVT and maximum tensile strength, so 0.6 mm aluminium foil was used as a backing membrane for the study (Table 3).

**Table 3:** Composition and evaluation of primary trial of backing membrane

Batch	Aluminum foil (mm)	WVT (g/ cm <sup>2</sup> / 24 hr)	Tensile strength (kg/ cm <sup>2</sup> )
B1	0.25	8.12 ± 0.07	2.71 ± 0.07
B2	0.3	7.93 ± 0.05	2.96 ± 0.04
B3	0.35	7.33 ± 0.03	3.15 ± 0.06
B4	0.4	7.12 ± 0.06	3.37 ± 0.05
B5	0.45	6.73 ± 0.04	3.53 ± 0.03
B6	0.5	6.94 ± 0.05	3.74 ± 0.02
B7	0.55	5.88 ± 0.01	3.98 ± 0.04
B8	0.6	5.09 ± 0.02	4.17 ± 0.03

Where, the data was expressed in (Mean ± SD) for sample size (= 3 n).

### 3.2 Screening of permeation enhancer

Among the enhancer examined, exhibited had the highest

enhancing effect on the permeation of carvedilol through 3.0 % v/v turpentine oil concentration (Table 4).

**Table 4:** Composition and evaluation of primary trial of permeation enhancer

Batch	Turpentine oil (%)	Drug in donor compartment ( $\mu\text{g}$ )	Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )
PE1	0.5	1565	23.31
PE2	1.0	1565	27.78
PE3	1.5	1565	30.87
PE 4	2.0	1565	33.44
PE 5	2.5	1565	37.07
PE 6	3.0	1565	41.65

Where, the data was expressed in (Mean  $\pm$  SD) for sample size (n = 3).

### 3.3 Preparation of reservoir type Carvedilol patches

The patches were successfully prepared using solvent casting techniques as shown in Table 1 and were characterized for various evaluation parameters.

### 3.4 Evaluation of Carvedilol TDDS

#### 3.4.1 Physical appearance

All the prepared films were clear, flexible, uniform and smooth.

#### 3.4.2 Uniformity of weight

The average weight of the prepared patches ranges between  $27.67 \pm 0.32$  to  $30.73 \pm 0.75$  mg. As the concentration of sodium alginate in formulation increases the average weight of patch also increases (Table 5).

#### 3.4.3 Uniformity of thickness

The average thickness of the prepared patches ranges between  $0.53 \pm 0.02$  to  $0.57 \pm 0.02$  mm which were observed in significant limit (Table 5).

#### 3.4.4 Tensile strength

As the concentration of xanthan gum in the patch increases the tensile strength also increases from  $2.27 \pm 0.15$  to  $2.70 \pm 0.17$  g/cm<sup>2</sup> (Table 5).

#### 3.4.5 Percent elongation

The values of % elongation were found between  $14.93 \pm 0.08$  to  $17.00 \pm 0.21\%$  which were found within acceptable limits. As the concentration of sodium alginate in formulation increases the % elongation of patch also increases (Table 5).

#### 3.4.6 Drug content

The drug content values were acceptable within the range of  $97.07 \pm 0.47$ – $98.60 \pm 0.10\%$  (Table 5).

### 3.4.7 Folding endurance

Folding endurance of prepared patch formulations was found to be between 61–66 which were within satisfactory limits (Table 5).

### 3.4.8 Flatness test

The uniformity in flatness of the patches indicates that the formulation by solvent evaporation technique was reproducible and the formulation maintains acceptable surface smoothness.

### 3.4.9 Moisture content

All the formulations forms flexibility and non-sticky patches where moisture content was within significant limit. The moisture content of formulations was found in the range of  $1.88 \pm 0.01$  to  $2.03 \pm 0.02\%$  (Table 6).

### 3.4.10 Percent moisture uptake

The % moisture uptake of the patches formulated with sodium alginate and xanthan gum in various ratios were found lies in between  $1.113 \pm 0.008$  to  $1.229 \pm 0.007\%$ . Which could protect formulations from microbial contamination thus reduces bulkiness of the formulations and increases the stability (Table 6).

### 3.4.11 Percent moisture loss

The % moisture loss was found to be  $2.01 \pm 0.246$  to  $4.61 \pm 0.106$  and it increases with increasing in concentration of sodium alginate polymer in the combination (Table 6).

### 3.4.12 Water vapor transmission rate

The water vapor transmission values were found to be in the range of  $2.52 \pm 0.01$  and  $4.29 \pm 0.02$  mg/cm<sup>2</sup>sec. As the concentration of sodium alginate increases the water vapor transmission values also increases (Table 6).

**Table 5:** Physicochemical characterization of transdermal patches

Formulation	Average weight <sup>a</sup> (mg)	Thickness <sup>a</sup> (mm)	Tensile strength <sup>b</sup> (g/cm <sup>2</sup> )	% Elongation <sup>b</sup>	Drug content <sup>b</sup> (%)	Folding endurance <sup>b</sup>
R1	$27.67 \pm 0.32$	$0.55 \pm 0.03$	$2.27 \pm 0.15$	$14.93 \pm 0.08$	$98.33 \pm 0.12$	$62.67 \pm 2.08$
R2	$28.47 \pm 0.49$	$0.57 \pm 0.02$	$2.30 \pm 0.10$	$15.22 \pm 0.31$	$98.57 \pm 0.06$	$65.67 \pm 3.06$
R3	$29.57 \pm 0.78$	$0.55 \pm 0.01$	$2.33 \pm 0.25$	$16.14 \pm 0.14$	$97.97 \pm 0.25$	$63.67 \pm 2.08$
R4	$28.77 \pm 1.34$	$0.57 \pm 0.02$	$2.37 \pm 0.06$	$15.93 \pm 0.52$	$98.47 \pm 0.15$	$65.33 \pm 1.53$
R5	$29.90 \pm 0.35$	$0.54 \pm 0.02$	$2.50 \pm 0.10$	$15.94 \pm 0.05$	$97.07 \pm 0.47$	$61.33 \pm 2.08$
R6	$30.73 \pm 0.75$	$0.56 \pm 0.02$	$2.70 \pm 0.17$	$17.00 \pm 0.21$	$98.17 \pm 0.12$	$64.00 \pm 3.00$
R7	$30.33 \pm 0.45$	$0.53 \pm 0.02$	$2.67 \pm 0.12$	$16.91 \pm 0.32$	$98.60 \pm 0.10$	$66.33 \pm 3.21$
R7S1	$30.29 \pm 0.39$	$0.53 \pm 0.01$	$2.64 \pm 0.13$	$16.89 \pm 0.32$	$98.11 \pm 0.08$	$64.34 \pm 1.83$
R7S2	$30.38 \pm 0.89$	$0.54 \pm 0.02$	$2.56 \pm 0.09$	$16.36 \pm 0.17$	$97.38 \pm 0.34$	$62.62 \pm 2.25$

Where, <sup>a</sup> and <sup>b</sup> indicates the values as mean  $\pm$  SD (n = 6) and (n = 3) respectively.

**Table 6:** Moisture content, % moisture uptake, % moisture loss and water vapor transmission rate of transdermal patches

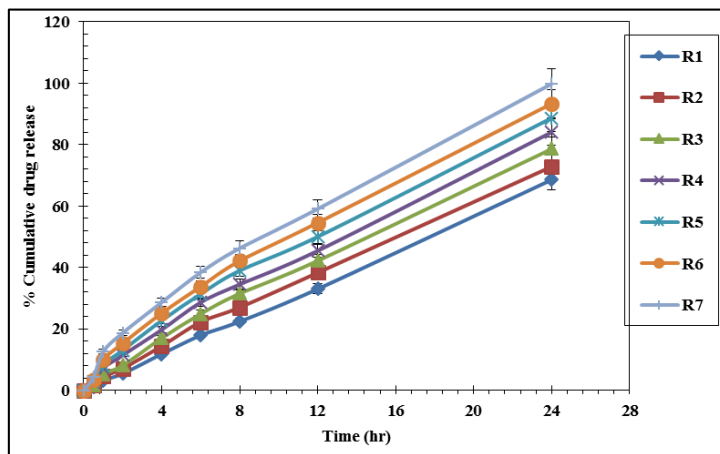
Formulation	Moisture content (%)	% Moisture uptake	% Moisture loss	Water vapour transmission (mg/cm <sup>2</sup> .sec)
R1	1.88±0.01	1.113±0.008	3.34±0.143	2.52±0.01
R2	1.88±0.01	1.141±0.004	3.69±0.134	3.89±0.02
R3	1.96±0.02	1.189±0.007	4.61±0.106	4.29±0.02
R4	1.94±0.02	1.197±0.003	2.01±0.246	2.87±0.01
R5	1.93±0.01	1.206±0.005	3.67±0.318	3.06±0.03
R6	2.03±0.02	1.215±0.009	3.69 ±0.049	3.13±0.02
R7	1.87±0.02	1.229±0.007	3.38±0.119	3.25±0.02
R7S1	1.85±0.01	1.227±0.015	3.26 ±0.114	3.17±0.01
R7S2	1.87±0.02	1.218±0.03	3.23 ±0.115	3.19±0.03

Where, <sup>a</sup> indicates the values as mean ± SD (n = 3).

**3.4.13 In-vitro release studies of carvedilol reservoir type TDDS**

The cumulative amount of drug release was found to be affected by concentration of sodium alginate and xanthan gum polymer in the reservoir system. At the 2% concentration of penetration enhancer and release controlled membrane shows the excellent control over cumulative amount of drug release from the transdermal patch (Fig.1). As the concentration of

xanthan gum decreased in the formulation the drug release rate increases significantly. Formulation R7 releases almost all the quantity of drug (Q<sub>24</sub>) from the formulation at the end of 24 hr and hence was selected as the optimized formulation. As the concentration of xanthan gum decreased in the formulation the release rate from the formulation was increased significantly. The formulation R7 releases almost all the quantity of drug (Q<sub>24</sub>) at the end of 24 hr and hence was selected as the optimized formulation.



**Fig 1:** In-vitro release profile for Carvedilol reservoir type TDDS

**3.4.14 Kinetic analysis of data**

In-vitro release data was fitted using different kinetic models formulation R7 release profile shows rapid flux as it contains higher concentration of sodium alginate polymer. All the formulation release fits into zero order kinetics. The

Korsmeyer-Peppas model ‘n’ values for all the formulation were about 0.5 indicates drug release mechanism by Fickian diffusion as hydrophilic polymers were used in the formulation (Table 7).

**Table 7:** Kinetic analysis of data

Formulation	Zero order	First order	Hixon-Crowell	Higuchi	Korsmeyer- Peppas	
	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	R <sup>2</sup>	n
R1	0.999 <sup>a</sup>	0.725	0.831	0.903	0.750	0.497
R2	0.996 <sup>a</sup>	0.690	0.827	0.931	0.815	0.519
R3	0.992 <sup>a</sup>	0.664	0.816	0.942	0.863	0.541
R4	0.989 <sup>a</sup>	0.628	0.804	0.831	0.821	0.506
R5	0.982 <sup>a</sup>	0.604	0.795	0.963	0.843	0.512
R6	0.987 <sup>a</sup>	0.581	0.779	0.969	0.752	0.511
R7	0.980 <sup>a</sup>	0.548	0.763	0.876	0.863	0.505

Where <sup>a</sup> Indicates best fitted kinetic model for the formulation.

**3.4.15 Calculation of targeted release rate (in- vivo release) to achieve steady state plasma concentration of drug**

Cumulative amounts of drug permeated in µg/cm<sup>2</sup> were plotted against time and drug flux (µg/cm<sup>2</sup>/hr) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed skin surface (3.14 cm<sup>2</sup>) and the permeability coefficient was deduced by dividing the

flux by initial drug load. The target flux was calculated using the following Eq. (10).

$$J_{\text{Target}} = \frac{C_{\text{ss}} \text{Cl}_t \text{BW}}{A}$$

Where, A represents the surface area of the transdermal patch (i.e., 3.14 cm<sup>2</sup>); BW, the standard human body weight of 70 kg; C<sub>ss</sub>, the Carvedilol concentration at the therapeutic level

(0.534  $\mu\text{g/ml}$ ) and the *clt*, the total body clearance 0.52 L/hr/kg (8.5 ml/min/kg); the calculated target flux value for Carvedilol was 10.11  $\mu\text{g/cm}^2\text{hr}$ .<sup>[22]</sup>

**3.4.16 Ex-vivo permeability studies**

From Eq. (10) the calculated target flux value for carvedilol

from optimized formulation should be 10.11  $\mu\text{g/cm}^2\text{hr}$ . Fig. 2 reveals that the formulation R7 has similar drug permeability and flux value up to 24 hr. Finally the *in-vitro* release data was correlated with ex-vivo permeability data for R7 formulation shows 0.999 coefficient of correlation indicates excellent *in-vitro-ex-vivo* co-relationship.

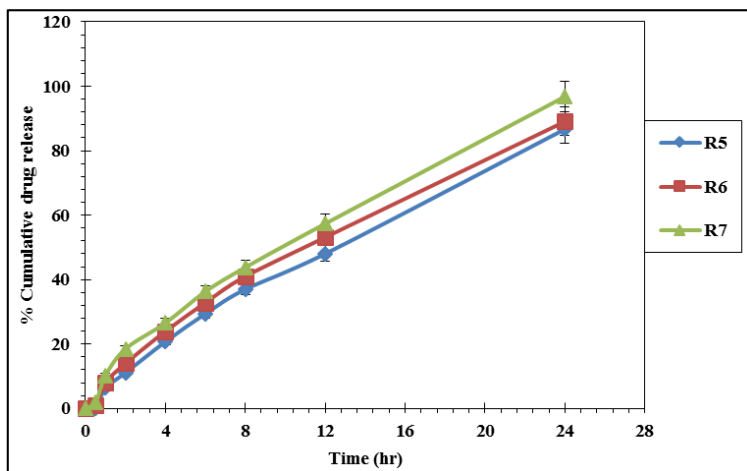


Fig 2: Ex-vivo permeability studies of reservoir type carvedilol TDDS

The similarity factor ( $f_2$ ) and difference factor ( $f_1$ ) values when the *in-vitro* release profile from patch was compared with ex-vivo permeation profile of R7 formulation were 81.26

and 5.03 respectively. This confirms excellent *in-vitro-ex-vivo* co-relationship for the R7 formulation.

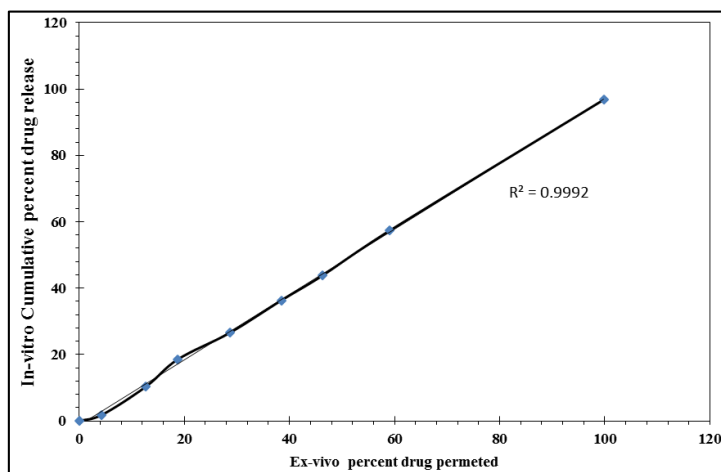


Fig 3: In-vitro diffusion- ex-vivo permeation correlation ship for carvedilol TDDS

**3.4.17 Skin irritation studies**

To evaluate effect of excipient on the skin irritation on Wister rats after daily application of optimized patch formulation R7 up to 7 days and test group was compared with controlled

group visually on 8<sup>th</sup> day. No signs of erythema, oedema or any other skin reaction were observed shows that the prepared patches were bio-compatible with skin (Table 8).

Table 8: Skin irritation test

Group	Condition	WR1	WR2	WR3
I	Normal	-	-	-
II	Formalin solution 0.8%	++	++	++
III	Drug control	-	-	-
IV	TDDS	-	-	-

Where - indicates no erythema and ++, well defined erythema

**3.4.18 Stress stability study**

The optimized formulation R7 was stored for short term stability according to ICH guideline was evaluated for their physicochemical characteristics as showed in Table 5 and Table 6. The formulation stored for stability study was found

to be clear, flexible, smooth and uniform. It shows all the physical characteristics in significant limits and *in-vitro* drug release was shown in Fig. 4. The *in-vitro* drug release from the R7 formulation on the day of preparation was compared with stored at 25°C and 60% relative humidity condition as



per ICH guideline shows similarity factor and difference factor values 92.57 and 2.41 respectively indicates that no significant change in the *in-vitro* release profile after 3 months. Similarly the *in-vitro* drug release from the R7 formulation on the day of preparation was compared with stored at 40°C and 75% relative humidity condition as per

ICH guideline shows similarity factor and difference factor values 78.39 and 7.14 respectively indicates that no significant change in the *in-vitro* release profile after 3 months. This indicates the stability of optimized formulation as per short term stability study.

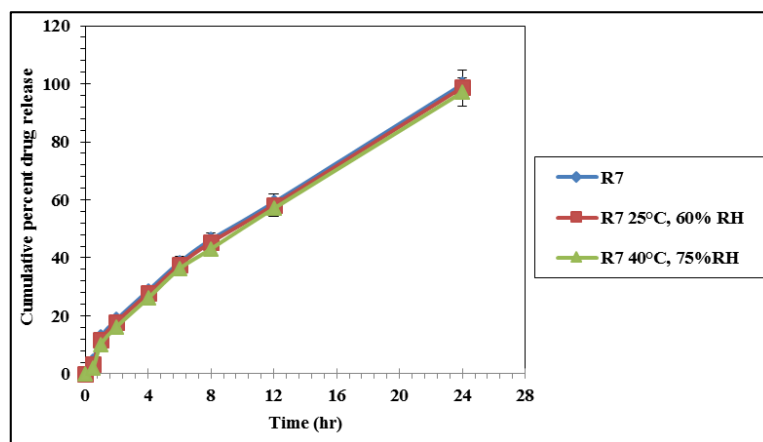


Fig 4: *In-vitro* release profile from stability batch

#### 4. Conclusions

A transdermal drug delivery system offers the advantage over the conventional drug delivery system who has difficulty in swallowing liquids or solids. Also few unwanted effects of Carvedilol may overcome by administration through this drug delivery due to fluctuation in plasma concentration of drug can be greatly reduced, first pass effect can be avoided and frequent dosing could be avoided. The present study shows that the Carvedilol patch containing polymer ratio of 7:1 (sodium alginate: xanthan gum) and turpentine oil (3%) as penetration enhancer was selected as best formulation. The R7 formulation shows good *in-vitro* release and ex-vivo permeation correlations which demonstrates the validity of conduct of test. The transdermal patches of required flux were prepared with suitable physico-chemical characteristics. Further studies are recommended to find therapeutic usefulness in human by conducting pharmacodynamics and pharmacokinetics studies.

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#### 6. References

1. Prausnitz MR, Langer R. Transdermal drug delivery. *Nature Biotechnology*. 2008; 26:1261-1268.
2. Lee H, Song C, Baik S, Kim D, Hyeon T, Kim DH. Device assisted drug delivery. *Advanced Drug Delivery Review*. 2018; 127:35-45.
3. Rawat S, Vengurlekar S, Rakesh B, Jain S, Srikarti G. Transdermal delivery by iontophoresis. *Indian Journal of Pharmaceutical Sciences*. 2008; 70(1):5-10.
4. Mohamed A, Yasmin S, Asgar A. Matrix type transdermal drug delivery systems of metoprolol tartrate. *in vitro* characterization. *Acta Pharmaceutica*. 2003; 53(2):119-125.
5. Michael AW, Domenic AS, Elizabeth AT, Malini I, Richard F, George LB. Controlled release Carvedilol in the treatment of essential hypertension. *American Journal of Cardiology*. 2006; 98:32-38.
6. Odon P, Borut K, Franc V. Carvedilol dissolution improvement by preparation of solid dispersions with porous silica. *International Journal of Pharmaceutics* 2011; 406(1-2):41-48.
7. Dezfuli AR, Aravindram AS, Manjunath M, Ganesh NS, Shailesh T. Development and evaluation of transdermal films loaded with antihypertensive drug. *International Journal of Pharma Bio Sciences*. 2012; 3(3):559-569.
8. Kulkarni R. Comparative evaluation of polymeric films for transdermal application. *Eastern Pharmacist* 2002; 516(43):109-111.
9. Madishetti SK, Palem CR, Gannu R, Thatipamula RP, Panakanti PK, Yamsani MR. Development of domperidone bilayered matrix type transdermal patches: Physicochemical, *in vitro* and ex vivo characterization. *DARU Journal of Pharmaceutical Sciences*. 2010; 18(3):221-229.
10. Ramesh G, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y. Development of carvedilol transdermal patches: Evaluation of physicochemical, ex vivo and mechanical properties. *PDA Journal of Pharmaceutical Science and Technology*. 2008; 62(6):391-401.
11. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of Repaglinide. *International Scholarly Research Notices Pharmaceutics* 2011; 9:24-32.
12. Ubaidulla U, Reddy MVS, Kumaresan R, Farhan JA, Khar RK. Transdermal Therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on *in-vitro* and in-vivo characteristics. *American Association of Pharmaceutical Scientists Pharmaceutical Science Technology*. 2007; 8(1):1-8.
13. Arora P, Mukherjee B. Design, development, physicochemical, and in- vitro and in- vivo evaluation of transdermal patches containing diclofenac diethyl ammonium salt. *International Journal of Pharmaceutical Technology Research*. 2009; 1:12-21.
14. Pawar PM, Solanki KP, Mandali VA. Recent Advancements in Transdermal Drug Delivery System. *International Journal of Pharmaceutical and Clinical Research*. 2018; 10(3):65-73.



15. Gupta R, Mukharjee B. Development and *in-vitro* evaluation of diltiazem hydrochloride transdermal patches based on povidone-ethyl cellulose matrices. Drug Development Industrial Pharmacy. 2008; 29(1):1-7.
16. Devi K, Saisivum S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Development Industrial Pharmacy. 2003; 29(5):495-503.
17. Shinde AJ, Garala KC, More HN. Development and characterization of transdermal therapeutics system of tramadol hydrochloride. Asian Journal of Pharmaceutics. 2008; 2(4):265-269.
18. Suddala S, Joshi G, Sahoo SK, Rao YM. Preparation and evaluation of matrix type transdermal patches of domperidone maleate: *in vitro* and *ex vivo* Characterization. Indian Journal of Pharmaceutical Education and Research. 2017; 51(4):217-221.
19. Friend DR. *In-vitro* skin permeation techniques. Journal of Controlled Release. 1992; 18(3):235-248.
20. Franz TJ. Percutaneous absorption: On the relevance of *in vitro* data. Journal of Investigational Dermatology. 1975; 64(3):190-196.
21. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences. 2001; 13(2):123-133.
22. Bhanja S, Ellaiah P, Chaudhari R. Design and evaluation of methotrexate buckle Mucoadhesive patches. International Journal Pharmaceutical Biomedical Sciences. 2010; 1(2):31-36.
23. Draize JH, Woodward G. Methods for the Study of irritation and toxicity of substances applied topically to the skin and mucous membranes. Journal of Pharmacology Experimental Therapeutics. 1944; 82(3):377-379.
24. Sakarkar DM, Dorle AK, Mahajan NM, Sudke SG. Design of sustained release pellets of ferrous fumarate using cow ghee as hot-melt coating agent. International Journal of Pharmaceutical Investigation. 2013; 3(3):3151-3156.
25. FDA. Guidance for dissolution testing of immediate release solid oral products, 1997.
26. FDA. Guidance for the Development, evaluation and application of *in vitro/in vivo* correlations for extended release solid oral dosage forms, 1997.