

Original Research Article

Formulation and *In vitro* Evaluation of Carvedilol Transdermal Delivery System

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Abstract

Purpose: To develop and optimize carvedilol transdermal delivery system.

Methods: Solvent casting method was used to prepare patches using polymethyl methacrylate (PMMA) and Eudragit E100 (EE100) polymers, dimethylsulfoxide (DMSO) penetration enhancer, dibutylphthalate (DBP) plasticizer and Tween 80 surfactant. A 2³ factorial design was used based on three variables (PMMA, EE100, DMSO) at two levels. Second order polynomial equations indicating interplay of ingredients were obtained by factorial design using SigmaTech software for 1, 4, 8 and 20 h release data. so the design was extended to central composite design (CCD). The target formulation was obtained from contour plots and evaluated for various physicochemical parameters. including in-vitro dissolution studies.

Results: Curvature effect was observed in F1 to F8 formulations, highlighting the interplay of ingredients. The interaction term (X₂X₃) exhibited highest Sum of Squares SS ratio at 1, 4, and 8 h data with positive coefficients indicating interaction; and so extended to CCD. From contour plots target formulation, F19, was identified and evaluated. The release data, were subjected to kinetic analysis, which followed Higuchi (diffusion) model (R² = 0.9886).

Conclusion: F19 yielded release profile nearer to the theoretical predictions with R² of 0.9888 and followed Higuchi kinetics. Thus, a diffusion-mediated carvedilol matrix patch was successfully developed.

Keywords: Carvedilol, Central composite design, Drug release, Transdermal patch.

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INTRODUCTION

Continuous intravenous infusion is recognized as a superior mode of drug delivery not only to bypass first-pass elimination, but also to maintain a constant, prolonged, and therapeutically-effective drug level in the body. Such mode of drug delivery necessitates hospitalization of patients and close medical supervision of the medication. There has been an increasing awareness that the benefits of intravenous drug infusion can be closely duplicated (without its

potential hazards) by transdermal administration [1]. Several transdermal drug delivery systems (TDDS) aiming to achieve systemic delivery have recently been developed.

Few drugs are already available as transdermal patches in the market for the treatment of angina, hypertension, menopausal syndrome, hypogonadism, motion induced nausea etc [2]. Carvedilol, a non selective β -adrenergic blocker with α_1 blocking activity, is one of the most widely

Table I: Optimization designs for the development of carvedilol transdermal drug delivery system (TDDS)

Formulation code	Treatment	Level of PMMA, X ₁ (mg)	Level of Eudragit E 100, X ₂ (mg)	Level of DMSO, X ₃ (mg)
F1	1	-1 (200)	-1 (40)	-1 (60)
F2	X ₁	+1 (300)	-1 (40)	-1 (60)
F3	X ₂	-1 (200)	+1 (120)	-1 (60)
F4	X ₁ X ₂	+1 (300)	+1 (120)	-1 (60)
F5	X ₃	-1 (200)	-1 (40)	+1 (100)
F6	X ₁ X ₃	+1 (300)	-1 (40)	+1 (100)
F7	X ₂ X ₃	-1 (200)	+1 (120)	+1 (100)
F8	X ₁ X ₂ X ₃	+1 (300)	+1 (120)	+1 (100)
F9-F12	Midpoint	0 (250)	0 (80)	0 (80)
F13	+2X ₁	+2 (350)	0 (80)	0 (80)
F14	-2X ₁	-2 (150)	0 (80)	0 (80)
F15	+2X ₂	0 (250)	+2 (160)	0 (80)
F16	-2X ₂	0 (250)	-2 (0)	0 (80)
F17	+2X ₃	0 (250)	0 (80)	+2 (120)
F18	-2X ₃	0 (250)	0 (80)	-2 (40)

Key: Formulations F1 - F 8 are factorial design, 2³; formulations F9 - F12 (midpoints) are for statistical analysis; formulations F13 - F18 are star points of central composite design; Other ingredients are: dibutyl phthalate (80 mg), Tween 80 (16 mg) and carvedilol (80 mg).

prescribed drugs in the management of hypertension [3]. Low oral bioavailability (25 %) due to extensive first pass metabolism, a short plasma half-life (6 h) and the long term usage made carvedilol an ideal drug for transdermal route of administration [3-5]. Furthermore, the low molecular weight (406.5), log P (4.19), log pK_a (7.9), low dose 25-50 mg and low melting point 114 °C confers on the drug ability for it to be easily absorbed through the skin.

Polymers selected include polymethyl methacrylate, for its rate controlling attribute and Eudragit E100 for its swelling [6]. Reports are available on the use of polymethyl methacrylate and Eudragit E100 for the preparation of transdermal (TD) patches individually, but not in a combination till date [7,8].

The aim of the present study was to develop and optimize a suitable TDDS of carvedilol using 2 x 3 factorial central composite design.

EXPERIMENTAL

Materials

Carvedilol was a gift from Aurobindo Pharmaceuticals, Hyderabad. Eudragit E100 was a gift from Strides Arco Labs Pvt Limited, Bangalore. Polymethylmethacrylate (PMMA) was purchased from Himedia laboratories, Mumbai,

India. All the other chemicals were obtained from SD Fine Chemicals.

Drug/excipient compatibility studies

To ascertain the compatibility between carvedilol and excipients, differential scanning calorimetry DSC studies were carried out on carvedilol, PMMA, EE100 and a physical mixture of these three components (1:1:1) using a dynamic DSC (Shimadzu DSC-50 Thermal Analyzer) in nitrogen atmosphere at the heating rate of 5 °C/min. Fourier transform – infrared (FT-IR) studies (Shimadzu, Japan) were also carried out on carvedilol, PMMA, EE100 and their physical mixture.

Preparation of TDDS

Transdermal patches were prepared by casting method on a petriplate by solvent evaporation [9]. All the ingredients were dissolved in chloroform individually, mixed with the polymers dispersion and poured in petriplates. Then the plasticizer, surfactant and penetration enhancer were added and mixed. Prepared polymeric dispersion was poured on a petriplate of 71 cm² area and was covered with inverted funnel (to control evaporation of solvent and avoiding cracking and breaking of patch) and allowed to dry overnight. The dried patches were removed and stored in a dessicator. Concentrations of

PMMA, EE100 and DMSO were varied as per the design, and patches were observed for flexibility and other properties.

Formulation design of carvedilol TDDS

Preliminary investigation based on trial and error, experiments yielded an empirical formulation. Design of experiments (DOE) was attempted using 2^3 factorial design [10]. Three variables at two levels and with actual values were represented in Table I. The levels of all other ingredients in the formulation were fixed and the basic plan was identified. Other ingredients (fixed) were; carvedilol (80 mg), dibutylphthalate (80 mg), Tween-80 (16 mg) and chloroform (15 ml). Midpoints (code 0) were also considered, so that errors can be estimated and statistical analysis was attempted and the analysis yielded a curvature effect. Thus, a composite design with additional 6 formulations was conducted.

Central composite design

As per the principles of central composite design, six formulations were added, by extending to five levels (-2, -1, 0, +1 and +2) [11]. The variables and levels along with detailed design with actual values are reported in Table I.

Evaluation of transdermal patches

The transdermal patches were evaluated for the following physicochemical parameters [12, 13].

Thickness

The thickness of the transdermal patches was measured using a screw gauge at different points on the patch and average thickness was calculated.

Weight variation

Ten patches of 1 cm^2 were weighed using digital balance (Schimadzu, Japan) and the average weight was calculated.

Folding endurance

Folding endurance was determined by folding and opening the patch at the same place repeatedly until it breaks. The result was expressed as a number.

Moisture content determination

Patches ($n = 10$) were weighed individually and kept in a desiccator (calcium chloride) at room temperature for 24 h and the weight at various intervals during the period was noted, until there was no further loss in weight. The moisture content was calculated as % weight loss.

Moisture uptake test

The films ($n = 3$) were weighed accurately and placed in a desiccator of 75 %RH maintained using saturated solution of sodium chloride. After three days, the films were weighed and the moisture uptake was calculated as the % difference between the final and initial weights with respect to initial weight.

Drug content determination

Transdermal patches were cut into pieces of $1 \times 1 \text{ cm}^2$ and carvedilol content was determined ($n = 3$). A patch of 1 cm^2 was taken into a 50 ml beaker and 10 ml of methanol was added and shaken for 5 min. One ml was taken and diluted to 5 ml with phosphate buffer (pH 7.4) and carvedilol content determined spectrophotometrically at 285 nm in the concentration range of 5 - 30 $\mu\text{g/ml}$.

In vitro release studies

Carvedilol release from the transdermal system was evaluated using the USP paddle over disc dissolution apparatus prescribed for TDDS [14, 15a]. The dissolution test apparatus was thermostated at $32 \pm 0.5 \text{ }^\circ\text{C}$ and stirred at 50 rpm. The film was fixed on inverted glass petriplate using cyanoacrylate adhesive allowing drug to release only from upper surface and was placed at the bottom of the vessel containing 500 ml of phosphate buffer, pH 7.4. Aliquots of 5 ml of sample were withdrawn at every half an hour up to 2 h, and thereafter periodically upto 24 h, replacing with equal volume of buffer. The samples were analyzed spectrophotometrically at 285 nm. Cumulative carvedilol released was calculated. Triplicate determinations were carried out.

Data analysis

The analysis of factorial design and central composite design was attempted using Sigmatech software (Swarooptech, Hyderabad, India). The software has built in statistical analysis, standard error of the estimate, error of variance, standard deviation, F distribution test, and orthogonal functions evaluation. The analysis output gave a print out of a table containing sum of squares and coefficients. A second order equation was written from the coefficients. Further contour plots were generated based on second order equations for analysis.

RESULTS

Physical properties of carvedilol TDDS

The texture and tackiness of the patches were satisfactory. The thickness of the patches ranged

from 33 to 50 μm and varied with the composition of patches. The average weight of films of 1 cm^2 ranged from 60 – 87 mg and was proportional to the dry weight of the ingredients. Folding endurance varied from 32 - 70, and inversely proportional to PMMA concentration. Moisture content and uptake were related to the concentration of EE100 to a large extent. Carvedilol drug loading varied from 95 to 98 %.

In vitro drug release

Carvedilol release over a 24 h period is shown in Fig 1.

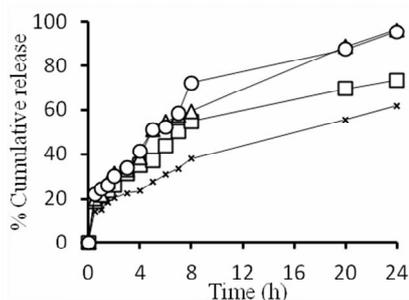


Figure 1: *In vitro* carvedilol release profile from different TDDS systems. **Key:** X = Fmid; \square = F14; Δ = Ftarget; o = F7

The concentrations of EE100 and DMSO were highest while that of PMMA was lowest for F7 and so reported higher release of 95%. The release of carvedilol at the midpoints (62%) was repeated four times (F9 – F12) for the purpose of statistical evaluation. F14 has shown a release of 73%. The carvedilol release in F19 (Target) (88%) was achieved nearest to the predicted value (24 h), and is presented in Fig 1 (Ftarget). The dissolution data of 24 h was suitably divided into four parts 1, 4, 8 and 24 h and analysis was

attempted with the polynomial equations obtained given in the Table 2. This approach was similar to oral controlled drug delivery of metoprolol succinate of USP [15b]. Though the present formulation was TDDS, this analysis adopted the same time frame.

Cumulative carvedilol release was abstracted from all 12 formulations and the responses were analyzed as per the factorial design using SigmaTech software. The central composite design was planned by including two more levels, +2 and -2 for all the three variables [11]. Thus six more formulations were developed (Table I, F13 to F18) formulated and evaluated for physical parameters and for *in vitro* carvedilol release (F13 to F18).

Central composite design - contour plot analysis

For all 18 formulations, carvedilol release data were compiled and analyzed for 1, 4, 8 and 20 h time points through contour plots [11]. Since the central composite design had three variables, it was necessary to keep one variable as constant and correlate other two variables. After extensive analysis of contour plots, it was decided to keep X_3 (DMSO) at 80 mg, and X_1 (PMMA) and X_2 (EE100) plots were analyzed. For finalizing the composition, formulation criteria (*in vitro* carvedilol release) was fixed as follows: 1 h-23%, 4 h - 30-40%, 8 h - 55-60% and 20 h -80%. For 1 h data analysis, contour plot (X_1 vs X_2) was recorded in Fig 2a. For the given criteria, polymers were identified as (150 mg (PMMA), 40 mg (Eudragit E100) of X_1 (PMMA) and X_2 (Eudragit E100) (Fig 2a). From 4 h data, contour

Table 2: Polynomial equations as per factorial design (2^3)

In-vitro release time (h)	Polynomial equation	Equation no.	Contribution of interaction terms, %	Curvature effect*
1	$y=23.4905 - 0.4177X_1 + 0.09X_2 + 0.1722X_1X_2 - 0.0322X_3 - 0.6735X_1X_3 + 0.7478X_2X_3 + 0.522X_1X_2X_3$	1	87.75%	-11.5458 to -3.0783 Significant
4	$y=31.6375-0.9485X_1 + 1.6125X_2 - 1.6345X_1X_2 + 1.2992X_3 - 1.0777X_1X_3 + 2.8003X_2X_3 - 0.2468 X_1X_2X_3$	2	69.34%	-8.4037 to -7.8203, Significant
8	$y=48.2442 - 4.3632X_1+1.7823X_2 - 3.5422X_1X_2 + 3.9195X_3 - 2.184X_1X_3 + 4.224X_2X_3 - 3.7045X_1X_2X_3$	3	56.53%	-12.3617 to -8.0838, Significant
20	$y= 59.9973 - 6.6635X_1 + 3.255X_2 - 5.6662X_1X_2 + 4.0088X_3 - 1.581X_1X_3 + 2.5115X_2X_3 - 3.5838X_1X_2X_3$	4	43.95%	-5.741 to -2.8465, Moderately significant

*Curvature effect (non-linear effect) was obtained from the software, at 95 % confidence level. If the curvature values are positive as well as negative (based on F1 to F12), then the curvature effect was predominant. Due to curvature effect, a minimum of three levels for each variable is necessary and experimentation was essential. Thus, second order equations were obtained, which are presented as contour plots.

Table 3: Carvedilol release from TDDS target formulation (F19)

Time (h)	Theoretical, (% Cumulative carvedilol release from contour plot)	Experimental, (% Cumulative carvedilol release)	Error (%)
1.0	24	21.503 ± 0.360	10.404
4.0	32	38.476 ± 0.573	-20.237
8.0	55	59.229 ± 0.458	-7.27
20.0	88	88.460 ± 2.759	-0.5227

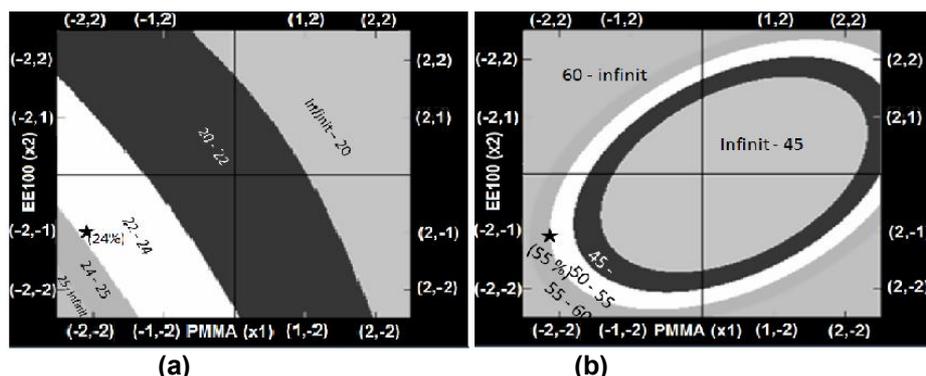


Figure 2: X_1 vs X_2 contour plot from central composite design. (a) 1 h release and (b) 8 h release. X_3 (DMSO) was constant. Target formulation, PMMA-150 mg (code -2), Eudragit E100 – 40 mg (code -1) and DMSO – 80 mg (code -0).

plot (X_1 Vs X_2) indicated the point (150 mg (PMMA), 40 mg (Eudragit E100)). These conclusions were agreeing with 1 h data analysis. For 8 h data analysis, contour plot (X_1 Vs X_2) was recorded in Fig 2b. The plots are peak and mounds. The optimal point must be at the top or round. A small change in the variables produced a drastic change in the response. In such a case, the optimized parameters must be critical. For the expected release of carvedilol, the point (-2, -2) i.e., 150 mg PMMA and 40 mg of Eudragit E100 respectively, were selected. X_1 and X_2 are codes and -2 and -1 are levels of X_1 and X_2 respectively. Equations contained codes. These can be levels such as -2, -1, 0, +1, +2 etc., of X_1 and X_2 (Fig 2b) were selected. For 20 h data, contour plot (X_1 Vs X_2) indicated curvilinear or nearly straight line. For the expected release of carvedilol (80 to 90%), point (150 mg (PMMA), 40 mg (Eudragit E100)) was chosen. Any desired level can be an input for obtaining the desired response (dissolution). After obtaining the codes for target, these were translated into absolute values (Table 3).

DISCUSSION

The swelling and permeability of EE100 and penetration enhancer might be responsible for the release of carvedilol. The release of carvedilol was almost uniform in the initial 30 min in all the formulations, approximately 20%

release and no burst effect observed. Evaluation of release pattern was suitably divided on hourly basis and was evaluated as following.

The first hour release data was analyzed and represented as a polynomial equation. The contribution of variables independently has no influence on the carvedilol release. The interaction of X_2X_3 was highest with SS ratio (37.3 %) and a positive sign of the coefficient (0.7478). It indicated that the higher the amount of X_2 and X_3 , the greater the carvedilol release. This was reasonable, because EE100 control the release and DMSO promote the carvedilol release. Interaction terms (%SS ratio X_1X_2 , X_2X_3 , X_1X_3 and $X_1X_2X_3$) contributed approximately 88 % and thus curvature effect was found significant.

The fourth hour release data was analyzed and represented in polynomial equation 2 (Table II). The interaction term X_2X_3 was the highest SS ratio (46.479 %) with a positive sign of the coefficient (2.8003) indicated direct relation between components and carvedilol release. The contribution of interaction terms was approximately 70%. Finally, it was concluded that curvature effect was predominant. The results were nearly same as that of 1 h analysis.

The eight hour release data was analyzed and represented as a polynomial equation. The interaction term of X_2X_3 was the highest with SS

ratio (20.63 %) with positive sign of the coefficient (4.2238). The contribution of interaction terms was to the tune of 57 % and curvature effect was predominant. The results were nearly same as that of 1 h and 4 h data analysis.

The 20 h release data was analyzed and also represented as a polynomial equation. PMMA (X_1) had the highest SS ratio (35.80%) with a coefficient of negative sign (-6.6635), because PMMA was the release retardant. The contribution of interaction terms was approximately 44%. Finally it was concluded that curvature effect was moderate and hence factorial design is inadequate. The time phased analysis indicated consistently curvature effect. Hence, factorial design was not sufficient and so central composite design was attempted for obtaining the target formulation.

Evaluation of the physical characteristics of the patches were satisfactory. *In vitro* carvedilol release of F14 was nearest to the expected 24 h release with PMMA content was at the lowest (-2 level) in F14.

Contour plots permitted the composition PMMA as 150 mg (-2), EE100 as 40 mg (-1) and DMSO as 80 mg; all the other ingredients in the formulation remained the same. Then transdermal patches were casted successfully and observed for thickness, weight, folding endurance, moisture content and moisture uptake and were found satisfactory. Carvedilol content was found to be 98.61%. A transdermal patch of size 3.80 cm² containing 4.14 mg carvedilol was utilized for *in vitro* carvedilol release studies and the data of F19 was reported in Fig. 1. The release of carvedilol was 20% in the initial 30 min and was considered to be necessary, so as to improve the initial carvedilol absorption through skin. Then, the release must be linear, so as to maintain the levels of carvedilol. The theoretical and observed release of carvedilol target patch was reported in Table 3 together with the error.

Thus the target formulation (F19) showed predicted carvedilol release which fitted first order release kinetics. However, the release profile of the prepared patches followed Higuchi's equation indicating that permeation of drug from the patches was governed by diffusion mechanism. As many release processes can be represented by a coupling of Fickian and non-Fickian mechanism. Ritger and Peppas introduced the power law equation $M_t/M_\infty = Kt^n$ to characterize the controlled release behavior of a drug from polymer matrices [16]. The n value (n

= 0.4376) obtained on the present study indicates that the amount of drug released by Fickian diffusion predominated. So it can be concluded that the release of drug was a diffusion-dominated mechanism.

CONCLUSION

A matrix type TDDS of carvedilol was successfully developed using casting method. PMMA and EE100 were compatible with carvedilol. The factorial design (12 formulations) exhibited curvature effect. The transdermal patches exhibited good physical properties as well as suitable release. Second order equations represented contour plots and were analyzed for obtaining the target formulation. The target formulation gave satisfactory *in vitro* carvedilol release over a 24 h period

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