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FORMULATION AND IN VITRO EVALUATION OF CARVEDILOL MATRIX TRANSDERMAL PATCHES CONTAINING PERMEATION ENHANCERS

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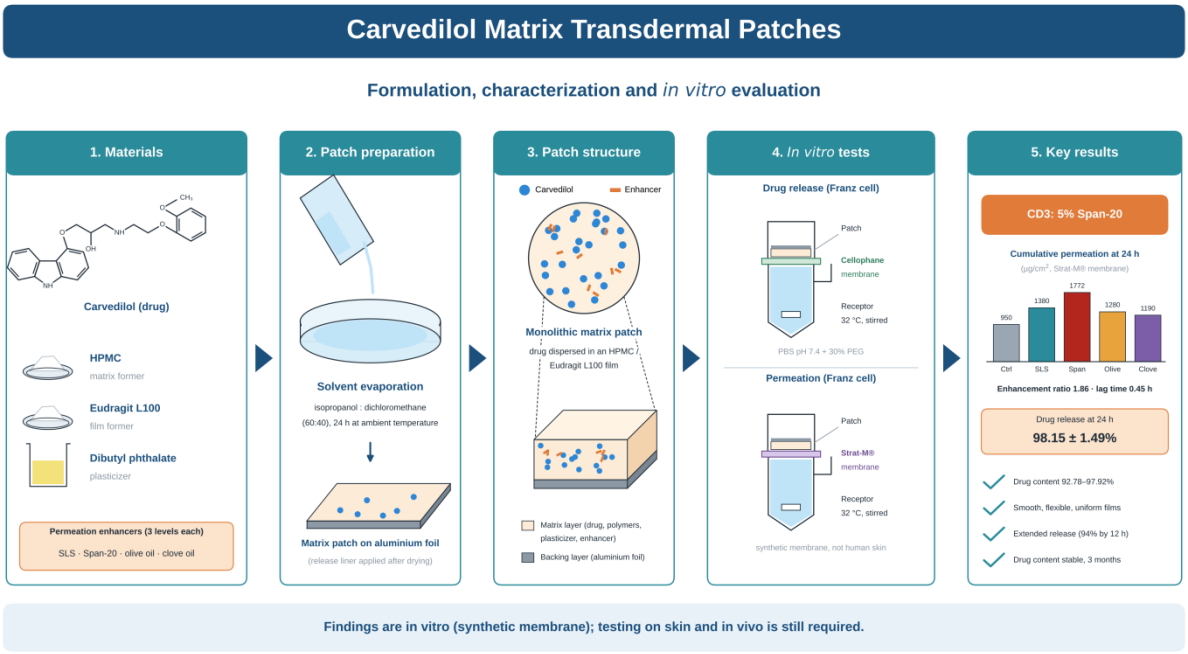
ABSTRACT

Carvedilol undergoes extensive first-pass hepatic metabolism, which limits its oral bioavailability. This study aimed to develop matrix-type transdermal patches of carvedilol and to evaluate the effect of polymer composition and chemical permeation enhancers on drug release and on permeation across a Strat-M® synthetic membrane in vitro. Patches were prepared by solvent evaporation using hydroxypropyl methylcellulose with Eudragit L100 or ethyl cellulose, dibutyl phthalate as plasticizer and aluminium foil as backing. The hydroxypropyl methylcellulose–Eudragit L100 (3:2) matrix was loaded with sodium lauryl sulfate, Span-20, olive oil or clove oil at three levels each. Patches were characterized physicochemically; drug release (cellophane membrane) and permeation (Strat-M® membrane) were studied in Franz diffusion cells; the best formulation was stored under accelerated conditions. All patches were smooth, flexible and uniform, with drug content of 92.78–97.92%. The enhancer-free matrix released 94.80% of the drug in 24 h, compared with 98.15 ± 1.49% for the matrix containing 5% w/w Span-20. Span-20 (5% w/w) gave the greatest cumulative permeation across the membrane (1771.86 ± 16.4 µg/cm² in 24 h versus 950.4 ± 18.2 µg/cm² for the control), an enhancement ratio of 1.86 and the shortest lag time

(0.45 h). After 3 months at 40 °C and 75% relative humidity, drug content fell by about 1% of its initial value. The 5% Span-20 patch is a promising candidate for further study; evaluation on mammalian skin and in vivo is required.

KEYWORDS: Carvedilol; Transdermal patch; Span-20; Permeation enhancer; Eudragit L100; Strat-M membrane.

GRAPHICAL ABSTRACT



graphical abstract: materials, patch preparation and structure, in vitro tests and key results for carvedilol matrix transdermal patches.

INTRODUCTION

Carvedilol is a non-selective β-adrenoceptor antagonist with additional α_1-adrenoceptor blocking activity and is widely used in the treatment of hypertension, ischaemic heart disease and chronic heart failure.[1,2] Although it is well absorbed after oral administration, carvedilol undergoes extensive stereoselective first-pass hepatic metabolism, so that its absolute oral bioavailability is only about 25–35% and plasma concentrations vary considerably between individuals.[2,3] Its relatively short elimination half-life means that immediate-release tablets are given twice daily in long-term therapy, which can reduce patient adherence.[2]

Transdermal drug delivery avoids gastrointestinal degradation and hepatic first-pass metabolism, can provide controlled and prolonged drug input, and allows therapy to be

stopped simply by removing the patch.[4–6] The principal limitation is the stratum corneum, which restricts the passage of most drugs; successful delivery therefore depends on the physicochemical properties of the drug, the polymer matrix and, frequently, the use of chemical permeation enhancers.[7,8] Recent reviews describe a wide range of chemical and physical strategies for overcoming this barrier.[9,10] Advanced carriers and devices have also been applied to carvedilol; for example, a microneedle patch loaded with a carvedilol nanosuspension raised relative bioavailability about 2.82-fold compared with a marketed formulation.[11] Microneedle systems for antihypertensive drugs are being widely explored,[12] and nanocarrier-based systems are also under investigation.[13] These approaches, however, require more complex manufacture, whereas matrix-type patches are simple to prepare and their release can be tuned through the polymer composition.[14]

Carvedilol (molecular weight 406.5; log $P \approx 3.97$) combines a low dose, high lipophilicity and extensive first-pass metabolism and has therefore been regarded as a suitable candidate for transdermal delivery.[14] Several carvedilol patch systems have been reported. Tanwar et al. described membrane-moderated patches with an HPMC reservoir and Eudragit RL100 or RS100 membranes, in which the non-ionic surfactants Tween 80 and Span 80 increased permeation across hairless guinea pig skin, Span 80 being the more effective;[15] Ubaidulla et al. compared hydrophilic and hydrophobic matrices *in vitro* and *in vivo*;[16] Gannu et al. prepared monolithic matrices of hydroxypropyl methylcellulose (HPMC) with Eudragit RS 100, Eudragit RL 100 or hydroxypropyl cellulose and 8% d-limonene, the best of which delivered 2987.67 µg/cm² across rat abdominal skin in 24 h together with suitable mechanical properties;[17] Aparna et al. optimized a polymethyl methacrylate–Eudragit E100 system by factorial and central composite designs;[18] and Mo et al. reported release of about 100% within 12 h from an Eudragit RS-100 patch containing Span 80, with improved bioavailability in rats.[14]

Most of these studies used Eudragit RS/RL grades or a single enhancer class. To our knowledge, the combination of HPMC with Eudragit L100 (EL100), an anionic methacrylic acid copolymer that dissolves above about pH 6 and can therefore generate pores in the matrix at physiological pH,[19] has not been compared with an ionic surfactant (sodium lauryl sulfate, SLS), a non-ionic surfactant (Span-20) and two natural oils (olive and clove oil) as enhancers for carvedilol. A related HPMC/EL100 system containing Span 20 has been described for tizanidine hydrochloride, in which 15% w/w Span 20 gave the highest

permeation enhancement through rabbit skin,[20] which supports the rationale of the present approach.

Accordingly, the objectives of this work were (i) to develop matrix transdermal patches of carvedilol using HPMC with EL100 or ethyl cellulose (EC); (ii) to select a base matrix on the basis of film properties and *in vitro* release; (iii) to compare the effect of four permeation enhancers, each at three concentrations, on drug release and on permeation across a Strat-M® synthetic membrane; and (iv) to characterize the best-performing formulation with respect to release kinetics and short-term stability.

MATERIALS AND METHODS

Materials

Carvedilol was obtained as a gift sample from BeloorBayir Biotech Ltd., Tumkur, India. Eudragit® L100 was obtained from Glenmark Pharmaceuticals Ltd., India, and aluminium foil from Gujarat Foils Ltd., Indore, India. Hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), Span-20, sodium lauryl sulfate (SLS), dibutyl phthalate (DBP), olive oil, clove oil and other excipients were procured from commercial suppliers. Isopropanol, dichloromethane, ethanol and methanol were obtained from HiMedia Laboratories Pvt. Ltd., India, and analytical-grade chemicals from Loba Chemie Pvt. Ltd. and S.D. Fine-Chem Ltd., Mumbai, India. The Strat-M® membrane used was catalogue no. SKBM02560 (25 mm discs). All materials were used as received. The overall experimental plan is shown in Fig. 1.

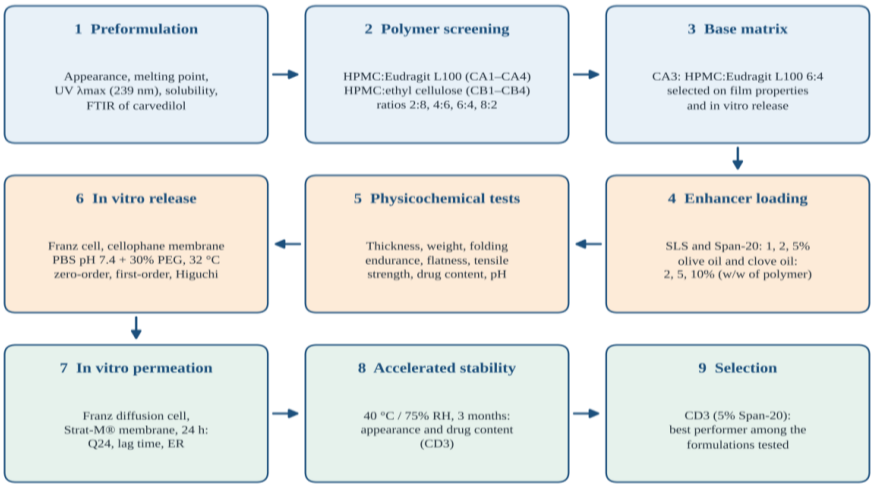


Fig. 1: overall experimental plan for the development and evaluation of carvedilol matrix transdermal patches.

Preformulation and quantitative estimation of carvedilol

The physical appearance, melting point, UV absorption maxima and solubility of carvedilol in different solvents were determined as preformulation parameters. The infrared spectrum of carvedilol was recorded over 4000–400 cm^{-1} using an FTIR spectrophotometer. Standard solutions of carvedilol (2, 4, 6, 8 and 10 µg/mL) were prepared in phosphate buffer (pH 7.4), each in triplicate, and scanned from 200 to 400 nm using a UV–Vis spectrophotometer (Shimadzu UV-1800, Kyoto, Japan). The wavelength of maximum absorption (λmax) was 239 nm. The calibration curve was linear over 2–10 µg/mL, with a coefficient of determination (R^2) of 0.9990 (absorbance versus concentration, n = 3). All subsequent spectrophotometric analyses were performed at 239 nm.

Preparation of matrix transdermal patches

Patches were prepared by the solvent evaporation method. HPMC and EL100 (or EC) were weighed in different ratios to give a total polymer weight of 2 g per batch and dissolved in isopropanol:dichloromethane (60:40, v/v) under magnetic stirring. DBP was added at 20% w/w of the total polymer weight (400 mg) as plasticizer, followed by carvedilol at 20% w/w of the polymer weight (400 mg), and the mixture was stirred for 30 min to obtain a homogeneous drug–polymer dispersion. Eight polymer-screening batches without enhancer were prepared: CA1–CA4 (HPMC:EL100 = 2:8, 4:6, 6:4 and 8:2) and CB1–CB4 (HPMC:EC in the same ratios). On the basis of film properties and *in vitro* release, HPMC:EL100 (6:4, i.e. 3:2) was selected as the base matrix (CA3). SLS and Span-20 were then incorporated at 1, 2 and 5% w/w, and olive oil and clove oil at 2, 5 and 10% w/w of the polymer weight (Table 1).

The dispersion was cast onto an aluminium-foil-backed glass Petri dish with a casting area of approximately 37 cm^2. An inverted funnel was placed over the dish to control the rate of solvent evaporation, and the films were dried at ambient temperature for 24 h. The dried films were removed, covered with wax paper as release liner and stored in airtight containers until evaluation. Circular patch specimens with an area of approximately 3.14 cm^2 were cut for the evaluations below. The structure of the matrix patch is shown schematically in Fig. 2.

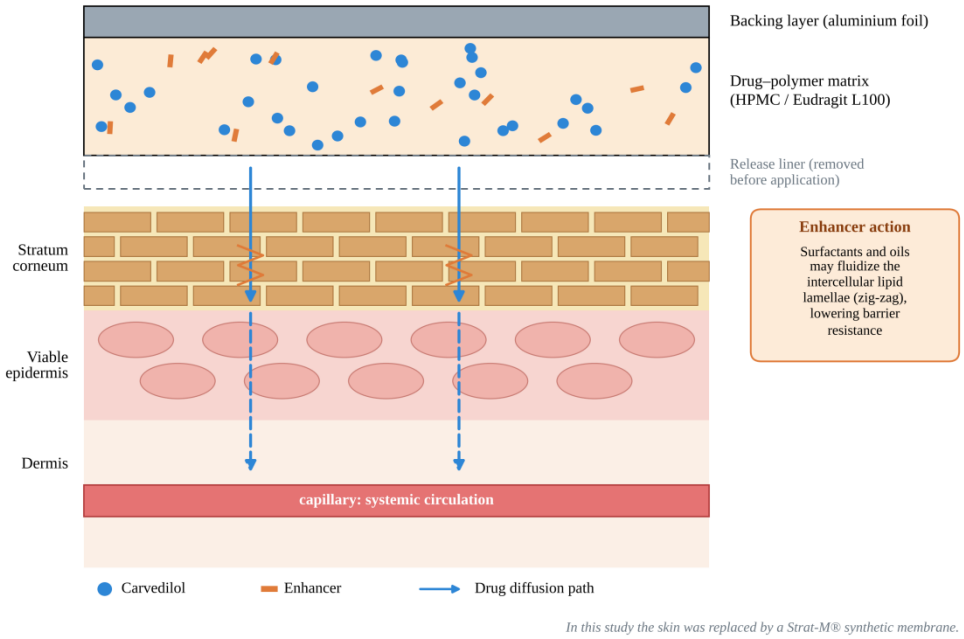


Fig. 2: schematic cross-section of the matrix transdermal patch applied to the skin and the proposed action of permeation enhancers on stratum corneum lipids (release liner removed before application; a Strat-M® membrane replaced skin in this study).

Table 1: Composition of carvedilol matrix transdermal patches.

Code	Polymer system	Ratio	HPMC (mg)	EL100 or EC (mg)	Enhancer (% w/w of polymer)	Enhancer (mg)
CA1	HPMC:EL100	2:8	400	1600	–	–
CA2	HPMC:EL100	4:6	800	1200	–	–
CA3 (base)	HPMC:EL100	6:4	1200	800	–	–
CA4	HPMC:EL100	8:2	1600	400	–	–
CB1	HPMC:EC	2:8	400	1600	–	–
CB2	HPMC:EC	4:6	800	1200	–	–
CB3	HPMC:EC	6:4	1200	800	–	–
CB4	HPMC:EC	8:2	1600	400	–	–
CE1	HPMC:EL100	6:4	1200	800	SLS 1%	20
CE2	HPMC:EL100	6:4	1200	800	SLS 2%	40
CE3	HPMC:EL100	6:4	1200	800	SLS 5%	100
CD1	HPMC:EL100	6:4	1200	800	Span-20 1%	20
CD2	HPMC:EL100	6:4	1200	800	Span-20 2%	40
CD3	HPMC:EL100	6:4	1200	800	Span-20 5%	100
CO1	HPMC:EL100	6:4	1200	800	Olive oil 2%	40
CO2	HPMC:EL100	6:4	1200	800	Olive oil 5%	100
CO3	HPMC:EL100	6:4	1200	800	Olive oil 10%	200
CC1	HPMC:EL100	6:4	1200	800	Clove oil 2%	40
CC2	HPMC:EL100	6:4	1200	800	Clove oil 5%	100
CC3	HPMC:EL100	6:4	1200	800	Clove oil 10%	200

All batches contained 400 mg carvedilol and 400 mg dibutyl phthalate (total polymer 2000 mg). HPMC, hydroxypropyl methylcellulose; EL100, Eudragit L100; EC, ethyl cellulose; SLS, sodium lauryl sulfate.

Physicochemical evaluation of patches

Appearance and thickness. Patches were examined visually for uniformity, smoothness, flexibility, colour, cracks and air bubbles. Thickness was measured at five randomly selected points with a calibrated digital micrometer and expressed as mean ± SD.

Weight variation. Ten patches of identical dimensions were weighed individually on an analytical balance, and the mean weight and percentage variation were calculated.

Folding endurance. A patch was folded repeatedly at the same place until it cracked or broke; the number of folds required was recorded as the folding endurance.

Flatness. Three longitudinal strips were cut from different regions of each patch, and their lengths were measured before and after the strips were allowed to relax. Percentage constriction was calculated as:

% Constriction = $[(L_1 - L_2) / L_1] \times 100$

where L_1 and L_2 are the initial and final lengths of the strip, respectively. Flatness (%) = 100 − % constriction.

Drug content. A patch specimen of 2 cm^2 was immersed in 100 mL of phosphate buffer (pH 7.4) and shaken vigorously for 24 h at room temperature to extract the drug. The solution was filtered through Whatman No. 42 filter paper and suitably diluted with the same medium, and the absorbance was measured at 239 nm against an appropriate blank. Drug content was calculated from the calibration curve and expressed as a percentage of the theoretical content.

Tensile strength. The mechanical strength of the patches was evaluated using a universal tensile testing machine. Rectangular strips (25.4 mm × 50 mm) were mounted between the grips, and tensile force was applied at a constant crosshead speed of 50 mm/min until the strip fractured. Tensile strength was calculated by dividing the force at break by the initial cross-sectional area of the specimen: tensile strength (kg/mm^2) = force at break (kg) / [width (mm) × thickness (mm)]. Measurements were made in triplicate.

Surface pH. The patch surface was moistened with distilled water and allowed to equilibrate, and the pH was measured with a calibrated digital pH meter.

In vitro drug release study

In vitro release was studied in a Franz diffusion cell. A cellophane membrane was mounted between the donor and receptor compartments, and the patch was placed on the membrane. The receptor compartment was filled with phosphate buffer (pH 7.4) containing 30% polyethylene glycol 400 (PEG 400), maintained at 32 ± 0.5 °C and stirred continuously. The co-solvent was used because carvedilol is practically insoluble in aqueous buffer (Table 3); this medium is not physiological, and the release data are intended for comparing formulations. Samples were withdrawn at predetermined intervals up to 24 h (the 1, 4, 12 and 24 h values are reported here) and replaced with an equal volume of fresh receptor medium to maintain a constant volume, and the drug was assayed at 239 nm. Cumulative percentage release was calculated from the measured concentrations with correction for the amount withdrawn previously, and the mean data were fitted to the zero-order ($Q = k_0t$), first-order [$\log(100 - Q) = \log 100 - k_1t/2.303$] and Higuchi ($Q = k_H\sqrt{t}$) models,[21–23] where Q is the cumulative percentage released at time t. The Korsmeyer–Peppas model was not applied because the release profile contained too few points within the first 60% of release for a reliable estimate of the release exponent.[24,25]

In vitro permeation study

In vitro permeation was studied in vertical Franz diffusion cells[26] using the Strat-M® synthetic membrane, a non-animal, multilayer polymeric membrane impregnated with a synthetic lipid blend that is used for screening of transdermal permeation. It is not human skin, and its predictive ability depends on the compound and formulation.[27,28] The receptor compartment was filled with phosphate buffer (pH 7.4) and maintained at 32 ± 0.5 °C under continuous stirring at 50 rpm. A patch was placed in the donor compartment in contact with the membrane. Samples were withdrawn at predetermined intervals up to 24 h, replaced with equal volumes of fresh receptor medium and analyzed at 239 nm using the calibration curve; the cumulative amount permeated per unit area (corrected for sampling) was plotted against time and is reported as Q_{24}. The average permeation rate was calculated as Q_{24}/24 h; this is not a steady-state flux. Lag time was obtained from the time-axis intercept of the linear portion of the plot. The enhancement ratio (ER) was calculated from Q_{24}:

ER = Q_{24} (enhancer formulation) / Q_{24} (control)

where the control is the enhancer-free base patch (CA3).

Accelerated stability study

The best-performing patch (CD3) was stored at 40 ± 2 °C and 75 ± 5% relative humidity for 3 months in accordance with the conditions of the ICH Q1A(R2) guideline for accelerated testing.[29] Samples were evaluated at 0, 30, 60 and 90 days for appearance and drug content, and the initial and 3-month values are reported. This 3-month study is shorter than the 6 months recommended by the guideline and is therefore preliminary.

Ethical statement

No human participants or live animals were used. The permeation experiments used a commercial synthetic membrane, so ethics committee approval was not required.

Statistical analysis

Results are expressed as mean ± SD of three independent samples (n = 3). Formulations were compared at a prespecified endpoint (24 h) by one-way ANOVA ($p < 0.05$ taken as significant). Where reported, differences were considered statistically significant at $p< 0.05$.

RESULTS AND DISCUSSION

Preformulation studies

Carvedilol was a white to off-white, odourless, crystalline powder with a bitter taste and a melting point of 114–115 °C (Table 2). In methanol the UV spectrum showed maxima at 242 nm and 284–285 nm, and 239 nm was used for analysis in phosphate buffer (pH 7.4). Carvedilol was practically insoluble in water and in phosphate buffer and soluble in dimethyl sulfoxide and dichloromethane (Table 3). Its low aqueous solubility explains the need for a co-solvent in the release medium and is consistent with its lipophilic character (log $P \approx 3.97$),[14] which favours partitioning into the stratum corneum.

Table 2: Physical characteristics of carvedilol.

Parameter	Observation
Physical appearance	Crystalline solid powder; white to off-white; odourless; distinctly bitter taste
Melting point	114–115 °C
UV absorption maxima (λmax)	Methanol: 242 nm and 284–285 nm; phosphate buffer (pH 7.4): 239 nm

Table 3: Solubility of carvedilol in different solvents.

S. No.	Solvent	Symbol	Descriptive term
1	Water	–	Practically insoluble
2	Ethanol	+++	Sparingly soluble
3	Phosphate buffer (PBS), pH 7.4	–	Practically insoluble
4	Ethanol:PBS pH 7.4 (20:80)	+	Very slightly soluble
5	Ethanol:PBS pH 7.4 (40:60)	++	Slightly soluble
6	Dimethyl sulfoxide	++++	Soluble
7	Dichloromethane	++++	Soluble
8	Methanol	+++	Sparingly soluble

Key: ++++, soluble (10–30 parts of solvent per part of solute); +++, sparingly soluble (30–100 parts); ++, slightly soluble (100–1000 parts); +, very slightly soluble (1000–10,000 parts); –, practically insoluble (>10,000 parts).

The FTIR spectrum of carvedilol (Fig. 3) showed a strong, sharp band at about 3340 cm^{-1} attributed to N–H/O–H stretching, aliphatic C–H stretching near 2930 cm^{-1}, aromatic C=C stretching and N–H bending bands at about 1600 and 1500 cm^{-1}, a strong aryl alkyl ether (C–O–C) band at about 1255 cm^{-1}, a C–O stretching band near 1100 cm^{-1}, and an aromatic C–H out-of-plane bending band at about 750 cm^{-1}. These bands correspond to the functional groups of the carvedilol molecule (secondary amine, secondary alcohol, aryl ether and aromatic rings) and serve as reference peaks for later drug–excipient compatibility studies.

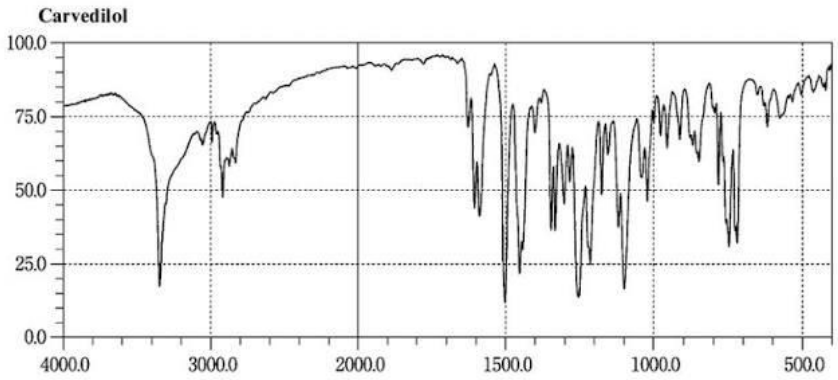


Fig. 3: FTIR spectrum of carvedilol (transmittance, %, versus wavenumber, cm^{-1}).

Formulation of patches

HPMC, EC and EL100 were chosen because of their film-forming ability and capacity to modify release. Patches prepared without plasticizer were brittle and cracked on handling. Incorporation of DBP at 20% w/w of the dry polymer weight produced smooth, uniform and flexible films, and this level was retained in all subsequent batches. All formulations contained 20% w/w drug relative to the polymer weight. Based on the screening series CA1–

CA4, in which the polymer combination with the most favourable release behaviour and film properties was sought, CA3 (HPMC:EL100, 3:2) was selected as the base matrix, to which the four enhancers were added at three levels each (Table 1).

Physicochemical characterization of the patches

All films were smooth, flexible and homogeneous, with no cracks, air bubbles or surface defects, indicating satisfactory film formation. For the characterized batches (Table 4), patch weight ranged from 231.49 ± 4.48 mg to 243.51 ± 2 mg and thickness from 0.426 ± 0.08 mm to 0.517 ± 0.06 mm, with low standard deviations that reflect uniform casting. Thickness increased with the HPMC proportion in the HPMC:EL100 series (0.426 mm for CA1 to 0.517 mm for CA4). All patches showed 100% flatness (no constriction), which indicates that they would remain smooth on the skin and give uniform contact. Folding endurance (72 ± 5.08 to 82 ± 4.63 folds) and tensile strength (0.355 ± 0.05 to 0.395 ± 0.08 kg/mm²) indicate that 20% w/w DBP provided adequate plasticization. Drug content ranged from 92.78 ± 0.21% to 97.92 ± 0.09%, indicating satisfactory drug distribution. Surface pH was 5.8–5.9 for the enhancer-free patches and 6.8 for CD3; this is slightly above the usual skin-surface range (about pH 4–6), and the higher value for CD3 should be confirmed by replicate measurement. The potential for skin irritation was not tested.

Table 4: Physicochemical properties of the base matrices (CA1–CA4) and the best-performing formulation (CD3) (mean ± SD)

Code	Thickness (mm)	Weight (mg)	Folding endurance	Tensile strength (kg/mm²)	Flatness (%)	Drug content (%)	Surface pH
CA1	0.426 ± 0.08	232.53 ± 2	72 ± 5.08	0.367 ± 0.06	100	92.78 ± 0.21	5.9
CA2	0.434 ± 0.03	231.49 ± 4.48	76 ± 5.37	0.381 ± 0.07	100	96.50 ± 0.57	5.9
CA3	0.483 ± 0.01	231.57 ± 3	79 ± 4.11	0.364 ± 0.03	100	96.39 ± 0.45	5.8
CA4	0.517 ± 0.06	234.48 ± 1	79 ± 4.15	0.355 ± 0.05	100	97.63 ± 0.36	5.8
CD3	0.482 ± 0.04	243.51 ± 2	82 ± 4.63	0.395 ± 0.08	100	97.92 ± 0.09	6.8

Flatness of 100% indicates no constriction. n = as stated under Statistical analysis.

In vitro drug release

Release studies across a cellophane membrane into phosphate buffer (pH 7.4) containing 30% polyethylene glycol showed extended release over 24 h. Cumulative release at 24 h from

the HPMC:EL100 patches CA1–CA4 ranged from 83.40 ± 2.25% to 94.80 ± 1.85% (Table 5, Fig. 4a). Release rose as the HPMC proportion increased from 20 to 60%, probably because hydration of HPMC creates aqueous channels that shorten the diffusion path, while the anionic EL100, which dissolves above about pH 6,[19] may contribute additional pores at pH 7.4. At 80% HPMC (CA4), release fell slightly (90.20 ± 2.10%), which may reflect a more viscous gel layer that lengthens the diffusion path; the film of CA4 was also the thickest (0.517 mm, Table 4), although the thickness differences among batches were small relative to their standard deviations. The EC series (CB1–CB4) was screened in parallel and was not carried forward because it gave lower release and less satisfactory films than the HPMC:EL100 series (data not shown). CA3 gave the highest release with satisfactory film properties and was therefore chosen as the base matrix.

Incorporation of Span-20 into CA3 altered the release profile in a concentration-dependent manner. At 24 h, CD1 (1%) released 89.80 ± 1.95%, CD2 (2%) 94.10 ± 1.70% and CD3 (5%) 98.15 ± 1.49%, compared with 94.80 ± 1.85% for the enhancer-free CA3 (Table 5, Fig. 4b). The 24-h values of CD2 and CD3 thus differ from the control by 3.4 percentage points or less, which is small relative to the standard deviations, and 1% Span-20 gave slightly lower release than the control. The clearer advantage of CD3 appears at the early time points (28.40 ± 1.1% at 1 h and 68.90 ± 1.6% at 4 h, versus 22.40 ± 1.15% and 58.45 ± 1.70% for CA3). This effect may be attributed to the wetting and solubilizing action of the surfactant on the lipophilic drug within the matrix. Release from CD3 was largely complete by 12 h (94.20 ± 1.3%), with only a small further increase during the next 12 h, so the system provides extended rather than constant-rate release. Release data for the SLS, olive oil and clove oil series are not included here, so Span-20 could be compared with the other enhancers only in the permeation study.

Table 5: Cumulative drug release (%) from base formulations and Span-20 formulations (mean ± SD)

Formulation	1 h	4 h	12 h	24 h
CA1 (HPMC:EL100 2:8)	14.25 ± 1.12	42.30 ± 1.80	74.15 ± 2.10	83.40 ± 2.25
CA2 (4:6)	18.60 ± 0.94	50.15 ± 1.65	81.90 ± 1.74	89.50 ± 1.98
CA3 (6:4, control)	22.40 ± 1.15	58.45 ± 1.70	89.30 ± 2.05	94.80 ± 1.85
CA4 (8:2)	20.10 ± 1.30	53.80 ± 1.45	84.60 ± 1.90	90.20 ± 2.10
CD1 (CA3 + Span-20 1%)	23.10 ± 1.05	59.20 ± 1.50	84.50 ± 1.80	89.80 ± 1.95
CD2 (CA3 + Span-20 2%)	25.60 ± 1.20	64.10 ± 1.40	89.20 ± 1.60	94.10 ± 1.70
CD3 (CA3 + Span-20 5%)	28.40 ± 1.1	68.90 ± 1.6	94.20 ± 1.3	98.15 ± 1.49

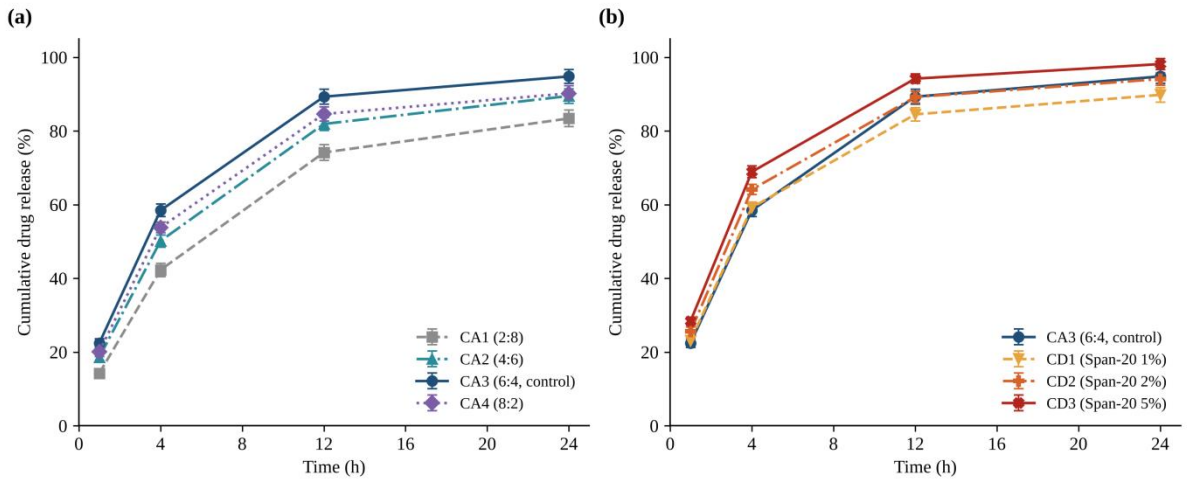


Fig. 4: in vitro release profiles of carvedilol patches: (a) base matrices ca1–ca4 (hpmc:el100 ratios in parentheses); (b) span-20 formulations cd1–cd3 compared with the enhancer-free control ca3 (mean ± sd).

In vitro permeation across the Strat-M® membrane

Cumulative permeation of carvedilol across the Strat-M® membrane over 24 h is given in Table 6 and Fig. 5. All four enhancers increased permeation relative to the enhancer-free control CA3 (950.4 ± 18.2 µg/cm²). Span-20 (5%, CD3) gave the highest cumulative permeation (1771.86 ± 16.4 µg/cm²), the highest average permeation rate (73.83 ± 0.68 µg/cm²/h), the shortest lag time (0.45 ± 0.08 h) and an enhancement ratio of 1.86, followed by SLS (5%, ER 1.45), olive oil (10%, ER 1.35) and clove oil (10%, ER 1.25). The surfactants were tested at 5% and the oils at 10%, so the enhancers were not compared at equal concentration, and only the highest level of each enhancer was examined in the permeation study. The concentration–response relationship, and therefore the true optimum, was not established: 5% is the highest Span-20 level tested, and a higher level might give still greater permeation.

Table 6: Permeation parameters across Strat-M® synthetic membrane (mean ± SD)

Formulation	Enhancer	Cumulative permeation at 24 h (µg/cm²)	Average permeation rate (µg/cm²/h)	Lag time (h)	ER
CA3	None (control)	950.4 ± 18.2	39.60 ± 0.76	0.85 ± 0.12	1.00
CE3	SLS (5%)	1380.2 ± 19.5	57.51 ± 0.81	0.65 ± 0.09	1.45
CD3	Span-20 (5%)	1771.86 ± 16.4	73.83 ± 0.68	0.45 ± 0.08	1.86
CO3	Olive oil (10%)	1280.5 ± 18.1	53.35 ± 0.75	0.72 ± 0.11	1.35
CC3	Clove oil (10%)	1190.4 ± 17.3	49.60 ± 0.72	0.78 ± 0.10	1.25

Average permeation rate = cumulative permeation at 24 h divided by 24 h; it is not a steady-state flux. ER, enhancement ratio (cumulative permeation at 24 h of the enhancer formulation divided by that of control CA3). Each enhancer is shown at its highest concentration tested.

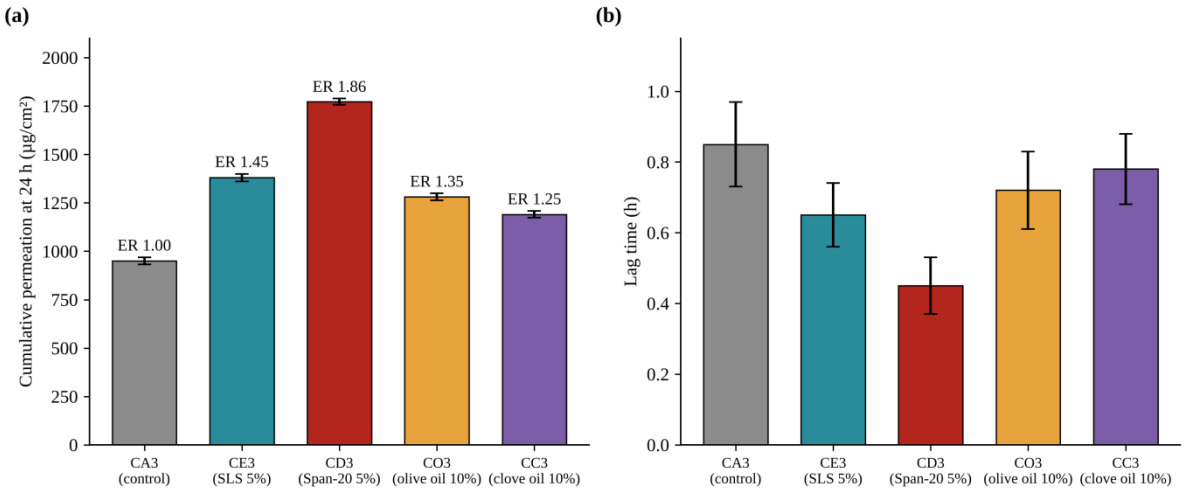


Fig. 5: effect of permeation enhancers on (a) cumulative permeation at 24 h (ER, enhancement ratio, shown above the bars) and (b) lag time of carvedilol across Strat-M® membrane (mean ± SD).

The superior effect of Span-20 is consistent with the known action of surfactants and fatty-acid-type enhancers, which can fluidize or disorder the intercellular lipid lamellae of the stratum corneum and thereby lower its diffusional resistance (Fig. 2).[7,8] Whether the same mechanism operates in the lipid-impregnated Strat-M® membrane was not examined here. Non-ionic surfactants also increased carvedilol permeation in earlier work, in which Span 80 gave greater enhancement than Tween 80,[15] and Span 20 (15% w/w) gave the highest permeation enhancement among the tizanidine hydrochloride HPMC/EL100 formulations tested.[20] SLS, although effective in the present study, is an ionic surfactant with a recognized potential to irritate skin,[8] which favours Span-20 for further development, subject to irritation testing. Olive oil and clove oil gave smaller enhancement (ER 1.35 and 1.25), in line with the general view that natural oils act mainly through lipid disruption of moderate intensity.[8]

Direct comparison of absolute permeation values with other reports is not possible because membranes, enhancers and conditions differ; for example, Gannu et al. reported 2987.67 µg/cm² in 24 h across rat abdominal skin for their best formulation containing 8% d-limonene,[17] whereas the present work used a synthetic membrane. The ER values obtained

here refer to the same membrane and are therefore the more meaningful measure of enhancement. Because the average permeation rate ($Q_{24}/24$) is not a steady-state flux, it should not be compared with published flux values.

Strat-M® is a commercially available, non-animal membrane used for permeation screening. Its performance is drug- and formulation-dependent: published comparisons support its usefulness for selected compounds but do not establish equivalence to human skin.[27,28] It contains no hair follicles or living cells and differs from human skin in lipid composition and thickness. The permeation results therefore describe carvedilol transport across this membrane under the conditions used and must not be extrapolated directly to human skin or to clinical performance.

Release kinetics

To characterize the release behaviour, the mean release profiles (1–24 h) were fitted to zero-order, first-order and Higuchi models (Table 7, Fig. 6). Zero-order kinetics gave the poorest fit for all batches ($R^2 \leq 0.82$), whereas the first-order and Higuchi (matrix diffusion) models described the data better (R^2 0.84–0.95). The first-order model was superior for the Span-20 formulations and especially for CD3 ($R^2 = 0.951$), in line with the rapid early release followed by a plateau seen in Fig. 4, whereas the two models gave similar R^2 values for CA1, CA2 and CA4. These fits are consistent with diffusion-controlled release from a hydrating matrix containing swelling HPMC and EL100, which dissolves at pH 7.4, but they do not prove the mechanism. Because only four time points were available and release exceeded 60% at the later points, the R^2 values are indicative only; the Korsmeyer–Peppas analysis, which gives the release exponent and transport mechanism, requires a denser sampling schedule and is planned.

Table 7: Coefficients of determination (R^2) for fitting of mean release data (1, 4, 12 and 24 h) to kinetic models.

Formulation	Zero-order	First-order	Higuchi
CA1	0.819	0.931	0.935
CA2	0.788	0.929	0.916
CA3	0.746	0.931	0.886
CA4	0.757	0.901	0.894
CD1	0.724	0.888	0.869
CD2	0.708	0.909	0.856
CD3	0.690	0.951	0.842

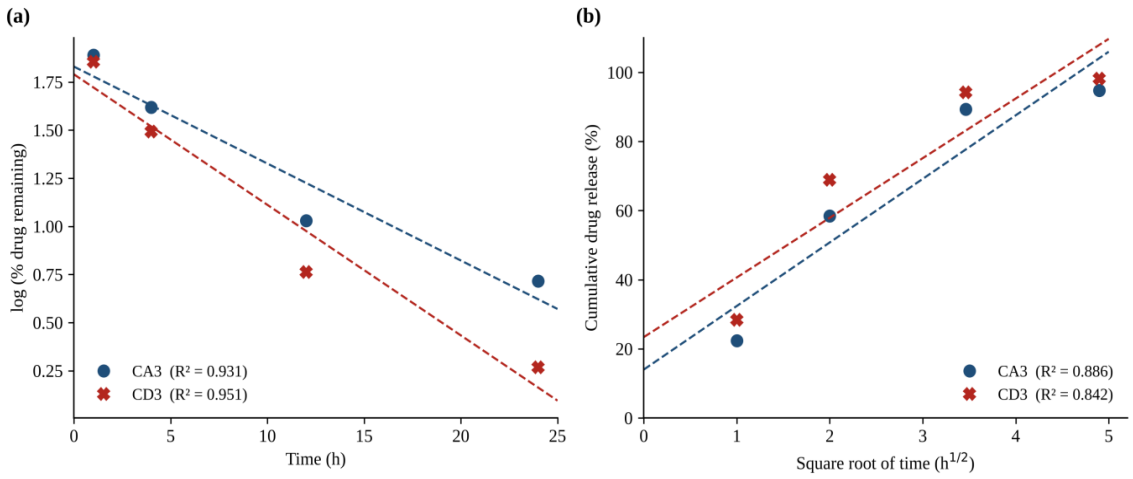


Fig. 6: kinetic plots for the control (ca3) and best-performing (cd3) patches: (a) first-order plot and (b) higuchi plot (symbols, mean data; dashed lines, linear regression).

Accelerated stability

After 3 months at 40 ± 2 °C and 75 ± 5% RH, the best-performing patch CD3 showed no change in physical appearance, and its drug content fell slightly from 97.92 ± 0.09% to 96.85 ± 0.3% (Table 8). This is an absolute decrease of 1.07 percentage points (1.1% of the initial value), below the 5% change from the initial assay that ICH Q1A(R2) defines as a significant change.[29] These results indicate short-term stability of the matrix under accelerated conditions; because the guideline accelerated study covers 6 months and no long-term data are available, no shelf life can be assigned.

Table 8: Accelerated stability of the best-performing patch CD3 (mean ± SD).

Parameter	Initial (0 days)	3 months, 40 °C / 75% RH
Appearance	Smooth, flexible, uniform	No change
Drug content (%)	97.92 ± 0.09	96.85 ± 0.3

Limitations

This study is limited to *in vitro* experiments on a synthetic membrane. Skin irritation, patch adhesion (no adhesive layer was incorporated), drug–excipient compatibility (FTIR of the physical mixture and patch, DSC), surface morphology (SEM), moisture content and uptake, residual solvent and pharmacokinetics were not part of the present dataset. DBP was used as plasticizer, but phthalates are subject to increasing regulatory and toxicological scrutiny, and alternatives such as polyethylene glycol 400 or triethyl citrate should be evaluated for a clinical product. Dichloromethane is a class 2 residual solvent under ICH Q3C(R8), and its residual level in the dried patches should be determined.[30] The release medium contained

30% polyethylene glycol and the drug had to cross a cellophane membrane, so the release data serve to rank formulations rather than to predict *in vivo* performance. The drug content of all batches (92.78–97.92%) was below the theoretical value, and the assay at 239 nm should be checked for interference by the enhancers, particularly clove oil, which contains the UV-absorbing compound eugenol. The permeation receptor contained pH 7.4 buffer, in which carvedilol is poorly soluble, so sink conditions at the highest permeation levels should be confirmed in future work, and release and permeation after storage were not re-evaluated. Future work should therefore evaluate the best-performing formulation on excised mammalian skin, assess irritation and adhesion, and establish plasma concentration–time profiles *in vivo*.

CONCLUSION

Matrix transdermal patches of carvedilol were prepared by solvent evaporation using HPMC and Eudragit L100, with dibutyl phthalate as plasticizer. The HPMC:EL100 (3:2) matrix (CA3) gave the best balance of film properties and release among the screened polymer ratios. Of the four enhancers studied, 5% w/w Span-20 (CD3) gave the greatest cumulative permeation across the Strat-M® membrane (1771.86 ± 16.4 µg/cm² in 24 h), an enhancement ratio of 1.86 and the shortest lag time (0.45 h), together with the fastest early drug release and a slightly higher 24-h release (98.15 ± 1.49%) than the control; its drug content decreased by about 1% after 3 months under accelerated conditions. CD3 is therefore the best-performing formulation among those tested and a promising candidate for further development, subject to confirmation on mammalian skin and *in vivo*.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

RR conceived and supervised the study and drafted the manuscript. SK, GK, LP and YY carried out the formulation, evaluation and data compilation. All authors reviewed and approved the final manuscript.

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