Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 01 Year 2024 Page 588:596

Formulation And Development Of Transdermal Patch Of Amlodipine Besylate Using Novel Polymers As Rate Controlling Membrane

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Article History

Received:
Revised:
Accepted:

Abstract:

This research study aims to formulate, prepare and evaluate transdermal drug delivery system for the purpose of controlled release of Amlodipine Bebesylate as a model drug using different polymers as a rate controlling membraneamlodipine undergoes first pass metabolism and also has easy permeability through skin therefore transdermal system of Amlodipine Bebesylate can be developed. The transdermal patches for the delivery were prepared by evaporation method i.e., solvent evaporation method. A matrix-type amlodipine besylate transdermal drug delivery system was prepared using novel polymers such as hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (SCMC) and Carbopol P 934 as a rate controlling or rate limiting membrane which delivers the drug or releases the therapeutic drugin controlled and a predetermined manner and rate. The formula for the transdermal patch was optimized using the experimental design. On the basis of the Data from drug release studies and the drug content the optimized batch was found to be F14 showing 80.1% of drug release and 95.62% of drug content. The patches were also evaluated forvarious evaluation parameters such as thickness uniformity,weight variation, moisture content determination, hygroscopicity &tensile strength.

Keywords: Amlodipine Besylate, Hydroxy propyl methylcellulose, Carbopol P934, Sodium carboxy methylcellulose.

INTRODUCTION

Transdermal drug delivery defines the topical or via topical route of application of active ingredients to healthy, skin is the site of application for this specific route ,which is for the local treatment of subcutaneous tissues or systemic treatment.[(1)]TDDS Flow through the skin to the systemic circulation is increased, thereby reducing drug metabolism and retention in the skin [(2,3)] Transdermal therapeutic systems release drugs when applied to intact skin, defined as a self-contained, self-contained dosage form. It enters the systemic circulation in a controlled manner. [(2, 3)]

The advantages of transdermal drug delivery system: Improve patient compliance in therapy that lasts for longer, which eliminates first-pass metabolism, control drug dosing, maintain constant plasma drug levels over time, and minimize intra- and intra-individual variability to deliver therapy. You can suspend or cancel it. as needed. [4, 5, 6]They are non-invasive and avoid the inconvenience of treatment by parentals. It may be an alternative to oral drug administration in the following cases: B. Effective in treating vomiting and diarrhea, eliminating multiple dosing intervals, improving treatment efficiency and patient compliance [7,8]

Transdermal drug delivery system has certain disadvantages: In the case of TDDS, effective drugs may be suitable candidates. Some patients may experience contact dermatitis when using the patch due to the ingredients in the patch. This system is not cheap and therefore uneconomical. Transdermal drug delivery (TDDS) is preferably not suitable for all category of drugs [9,10]) The pores and skin acts as a barrier to the penetration of medication and different chemicals. In transdermal drug transport systems, the drug enters the systemic flow from the pores and skin floor thru the pores and skin layers.[11]

Hypertension is a persistent disease in which blood pressure increases and give rise to affect the blood carrying artries. Around the world, a large proportion of the population suffers from hypertension, making it the most common fatal disease. As it is a chronic disease associated with disorders, treatment for longer term is required and advised. In such cases, transdermal drug delivery systems can definitely be used for long-term treatment. [12]

Amlodipine is a dihydropyridine derived calcium channel blocker that prevents transmembrane (within the cell) entry of calcium ions into cardiac (heart) smooth muscle.The elevated blood pressure is reduced by the relaxation of the vascular smooth muscles[9]. It undergoes hepatic first pass metabolism therefore to avoid this, the transdermal therapeutic system of Amlodipine besylate can be developed.[13,14]

MATERIALS USED AND METHODS WHICH HAS BEEN FOLLOWED

Amlodipine besylate wasreceived from PBS Healthcare Private limited as a gift sample and HPMC was purchased from S.D. It is based on. [5] Fine Chem Ltd (SCMC, Mumbai) and Carbopol P934 were purchased from CDH Pvt Ltd, glycerin and methanol were purchased from Rankem Lab and were of analytical grade.

Preparation of Matrix patches

Using solvent evaporation method,the polymers were taken in different ratios i.e. HPMC: Carbopol, HPMC: SCMC, HPMC: Carbopol: SCMC and Carbopol: SCMC. These polymers were soaked in the distilled water and then were kept overnight for swelling. The magnetic stirrer was used for the mixing of the polymeric solution.Amlodipine was then dissolved in the above polymeric solution and was mixed well. Then glycerol was added in sufficient quantity in the above solution. Finally, preparation was poured into the petridish and allowed for evaporation at a controlled rate by covering the Petri dishes with the funnel.Then the dried films were removed and kept in dessicator and were further evaluated. [15,16,17]

Table No.1. Formula for Transdermal Patches

S.No	Ingredient	Formulation													
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
1	Amlodipine bebesylate (mg)	10	10	10	10	10	10	10	10	10	10	10	10	10	10
2	HPMC(gm)	0.1	0.2	0.3	0.4	0.5	0	0	0	0.1	0.2	0.3	0.2	0.3	0.4
3	Carbopol P 934(gm)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0	0	0	0.3	0.3	0.3
4	SCMC(gm)	0	0	0	0	0	0.1	0.2	0.3	0.1	0.2	0.3	0.3	0.4	0.5
5	Glycerol (%)	10	10	10	10	10	10	10	10	10	10	10	10	10	10
6	water(ml) (distilled water)	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml	50 ml

Physical appearance

Transdermal patches which was formulated were visually observed for clarity, colour, softness, and smooth purpose.

Determination of drug content

A 1 cm 2 area was cut from the film and dipped and later dissolved completely in a sufficient quantity of methanol. The capacity was set to 10ml. Then, 0.1 ml of this solution was taken out and diluted to 10 ml. Absorbance was measured at 359nm. The active ingredient content in the film was calculated from the absorption rate and dilution rate.[18,19]Results obtained are shown in Table 1.1

Table No. 1.1 Determination of Drug content in the formulation

S.No.	Formulation	Drug Content
1	F_1	92.3%
2	F_2	92.43%
3	F_3	93.90%
4	F_4	90%
5	F_5	91.1%
6	F_6	90.53%
7	F_7	93.2%
8	F_8	91.7%
9	F_9	92.34%
10	F_{10}	93.01%
11	F_{11}	94.3%
12	F_{12}	93.9%
13	F_{13}	94.89%
14	F_{14}	95.62%

***In vitro* determination of drug release by Diffusion cell**

The transdermal film which was formulated was placed on a semipermeable membrane and that film wasattached to a modified diffusion cell in such a manner that the drug releasesthesurface of the cell faced the receptor compartment which was filled with phosphate buffer at 37±10°C and pH 7.4. The solution was stirred continuously. Sampling was done in 60 minutes. A 5 ml sample was removed and an equal volume replaced with pH 7.4 phosphate buffer. All the samples were analyzed for the content determination of active ingredient using a Ultraviolet visible spectrophotometer at 359 nm.

The observations are shown in table No. 1.2

Table No. 1.2 *In-vitro* drug release

Formulation code	Cumulative % of drug release	Time of drug release(hrs)
F1	61.4	24 hrs
F2	56.4	24 hrs
F3	51.6	24 hrs
F4	45.9	24 hrs
F5	49.2	24 hrs
F6	59.3	24 hrs
F7	54.3	24 hrs
F8	59.3	24 hrs
F9	46.7	24 hrs
F10	49.9	24 hrs
F11	60.7	24 hrs
F12	67.9	24 hrs
F13	69.7	24 hrs
F14	80.1	24 hrs

Graph of Cumulative% Drug Release of formulation from F1 to F14

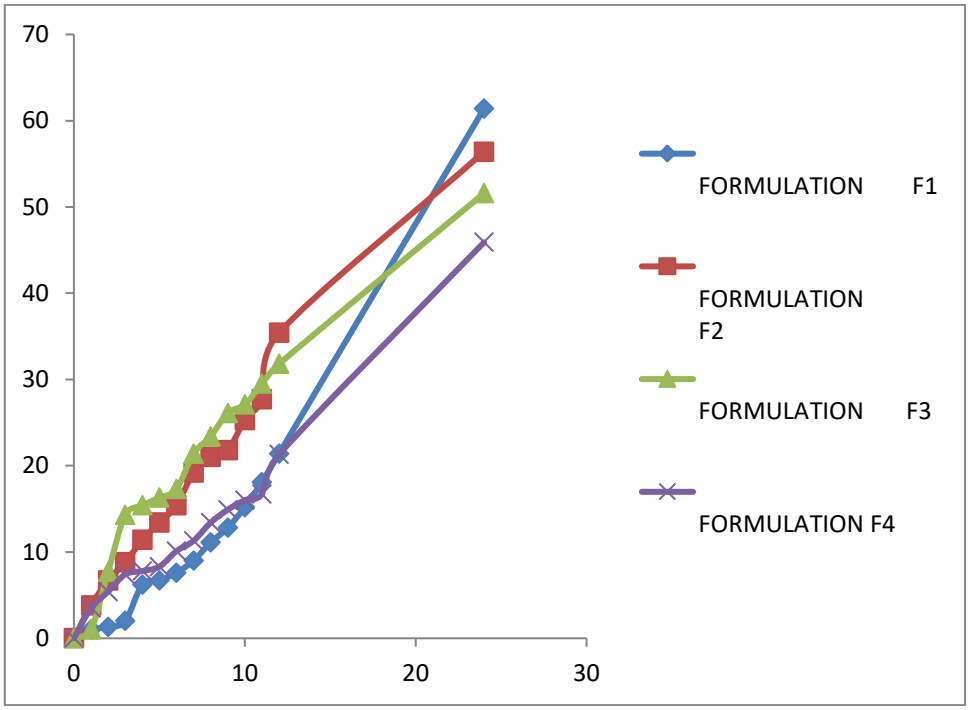

Figure No. 1.1 Cumulative% Drug Release of Formulation from F1 to F4

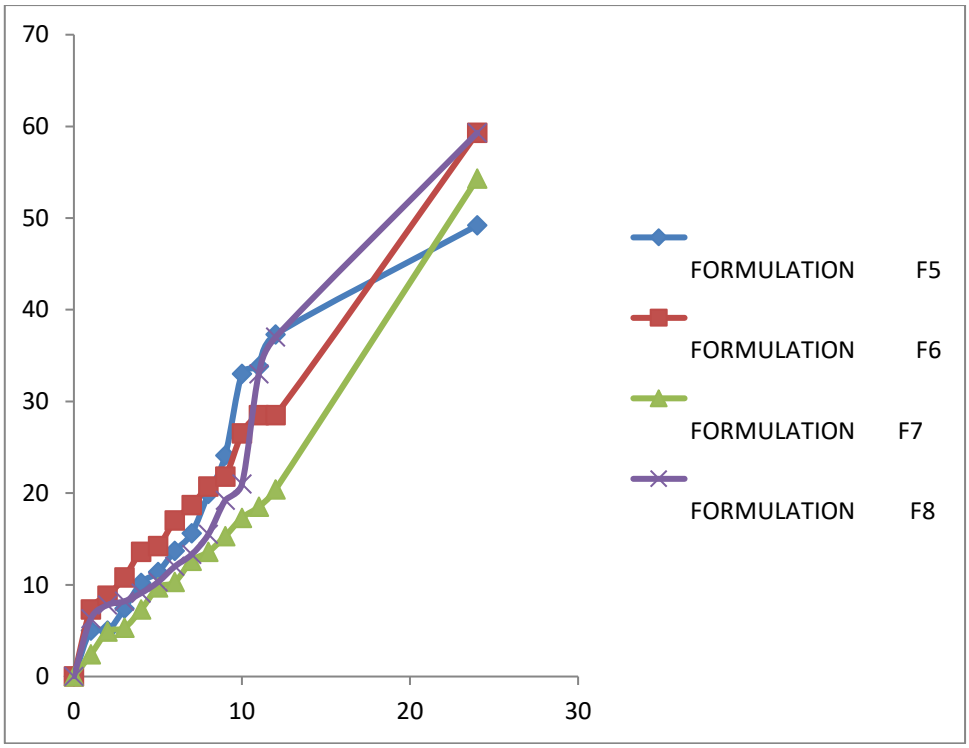

Figure No. 1.2Cumulativepercentagedrug Release of Formulations F_5 to F_8

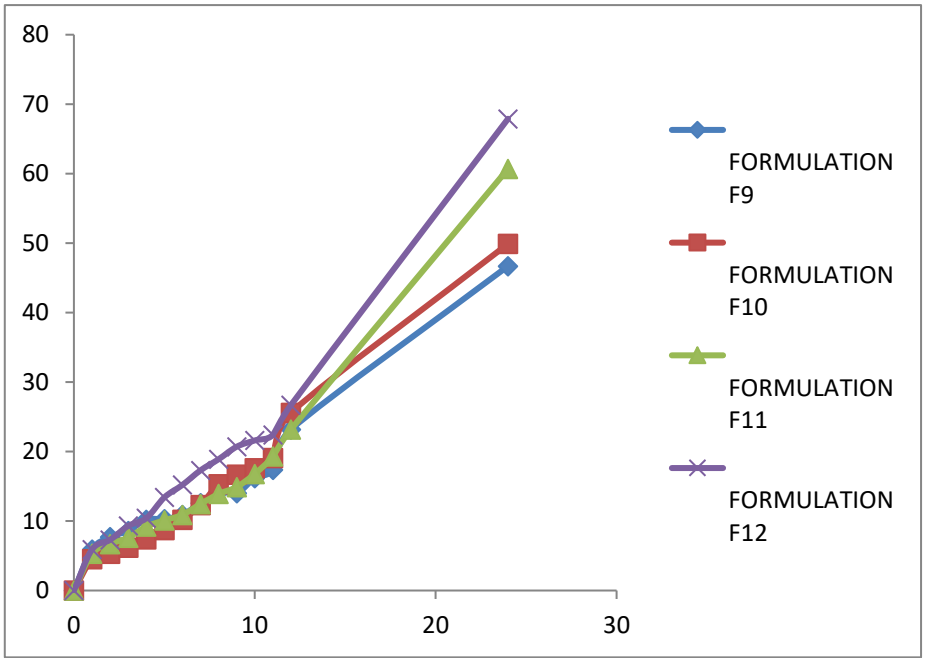

Figure No. 1.3Cumulative% Drug Release of Formulation from F9 to F12

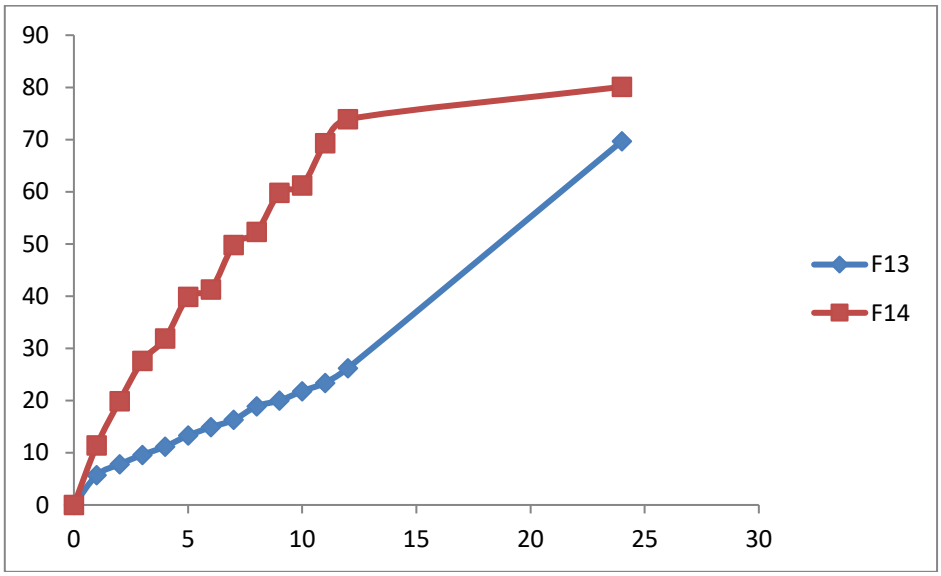

Figure No. 1.4Cumulative% Drug Release of Formulation from F13 to F14

Thickness

Film thickness was measured using a digital caliper and the minimum thickness of the film was 0.001 mm. Thickness was mainly measured at five+ different points on the pavement, and the five measurements were averaged with standard deviation.[20,21]Observations are shown in table No.1.4

Weight Variation

The weight fluctuation test was carried out by cutting out the film into a 2×2 cm 2 area and weighing it with an electronic scale. By performing a weight variation test, you can check weight uniformity and batch-to-batch variation. [22]Observations are shown in table No.1.4

Moisture Content

Transdermal patches after their preparation were individually weighed and then placed in a calcium chloride desiccator at 37°C for 24 hours. If the weight of an individual patch did not change, the final weight was

recorded. The moisture content was measured and the percentage was determined as the difference between the initial and final weights divided by the final weight.[23]Observations are shown in Table No.1.4

Moisture Uptake

Determination of the physical stability and the film integrity the absorption test could be carried out in the humid conditions. Themoisture absorption capacity could be determined as follows. The films were placed in desiccator at 79.5 % R.H. The films were removed out from the desiccator after processing of 3 days and were weighed.[24]Finally, the moisture uptake or absorption of the films was determined.Observations are shown in Table No.1.4

Tensile Strength

Tensile strength testing of the films was carried out using laboratory-developed equipment. The crushing device was modified into a tensile strength measuring device.The tensile strength was then measured.[25] Observation are shown in table No.1.3

Table No 1.3 Thickness,weight variation, moisture content, moisture uptake and tensile strength

Formulation	Thickness(mm)	Weight Variation(mg)	%Moisture Content	%Moisture Uptake	Tensile Strength(Kg/cm^2)
F14	0.24±0.01	401±0.3	0.38±0.05	4.01±0.06	398±1.51

***In vitro* permeation study: Flux**

Permeability coefficient can be defined as the speed of a drug across a cell membrane is measured in cm/h. thepermeabilitycoefficient(P)canbecalculatedfromtheslopeofthegraphofpercentageofdrugtransportedversusti measfollows:

P = slope * Vd / S

Where, Vd = Volume of donor solution

S = Surface area of tissue.

Flux- defines the amount of drug substance that passes through a barrier of uniform cross section in a unit time.It can be calculated as:

Flux (J) = P * CD

Where, CD = concentration of the donor solution.[26] The flux calculated is shown below in the table no.1.4

Table No.1.4 Permeability coefficient and flux of formulationF14

S.No.	Time(hrs)	Permeability coefficient(cm/hr)	Flux (%)
1	24hrs	21.05	39.9%

Kinetics of drug release:

Table No.1.5 Analysis of release kinetics

S.No.	Time (hours)	CDR(Q) Mg	√t	Log t	%Q	Log Q	%Drug remain (Qr)	Log Qr
1	0	0.00	0.000	0	0	0	100	2
2	1	1.14	1.000	0.000	11.4	1.04	88.6	1.94
3	2	1.99	1.414	0.301	19.9	1.29	80.1	1.90
4	3	2.76	1.732	0.477	27.6	1.44	72.4	1.85
5	4	3.19	2.000	0.602	31.9	1.50	68.1	1.83
6	5	3.99	2.236	0.698	39.9	1.60	60.1	1.77
7	6	4.13	2.449	0.778	41.3	1.61	58.7	1.76
8	7	4.98	2.646	0.846	49.8	1.69	50.2	1.70
9	8	5.23	2.828	0.903	52.3	1.71	47.7	1.67
10	9	5.98	3.000	0.964	59.8	1.77	40.2	1.60

11	10	6.12	3.162	1.000	61.2	1.78	38.8	1.58
12	11	6.93	3.317	1.041	69.3	1.84	30.7	1.48
13	12	7.39	3.464	1.079	73.9	1.86	26.1	1.41
14	24	8.01	4.899	1.380	80.1	1.90	19.9	1.29

Where CDR (Q) = Cumulative drug release; % CDR (%Q) = % Cumulative drug release; % Qr = percent drug remained.

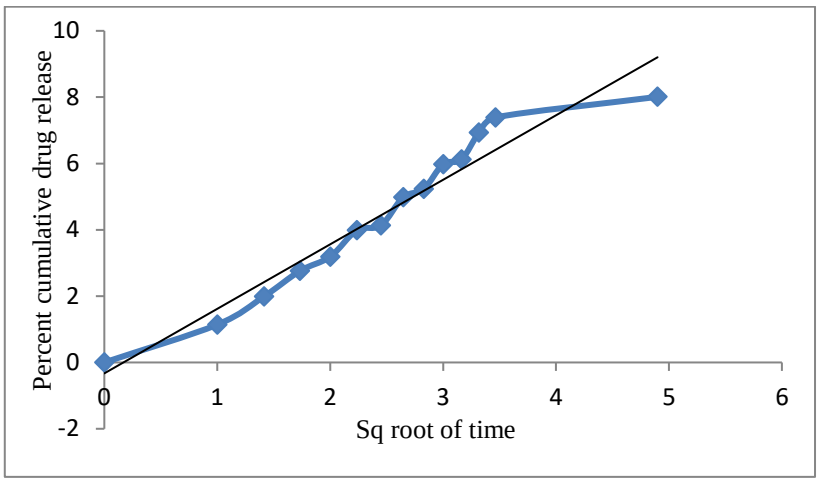

Figure No. 1.5: Higuchi model for formulation F14

S.No.	Model	R^2
1.	Higuchi	0.964

RESULTS AND DISCUSSION

The manufactured transdermal patch was smooth, flexible, and uniform. A total of 14 formulations were formulated with different ratios of HPMC, Carbopol P-934, and SCMC. The composition or the concentration of all the formulations is shown in above mentioned Table 1. The optimized batches were selected based on drug content or concentration and in vitro drug release from diffusion studies. Batch F14 shows the highest release of active ingredients. Therefore, the optimized batch was found to be F14. Higher concentrations of SCMC and HPMC polymers were used in this patch. Higher drug release and drug content were observed as the concentration of polymers such as HPMC and SCMC increased. It is known how important the diffusion of polymers is to release drugs from matrix systems to ensure sustained release performance. The results showed that drug release from the patch increased with increasing concentration of HPMC containing SCMC. Higher drug release and drug content were observed as the concentration of polymers such as HPMC and SCMC increased. The results showed that drug release from the patch increased with increasing concentration of HPMC containing SCMC. The uniform weight of the patch was 401 ± 0.3 mg.The moisture content and moisture absorption rate of the film were 0.38±0.05 and 4.01±0.06.The permeability coefficient was 21.05 and the flow rate was 39.9%.

The physical parameters of weight variation, thickness, folding strength, water content and hygroscopicity of the optimized batch were determined. The uniform weight of the patch was 401 ± 0.3 mg and the thickness was 0.24 ± 0.01 mm, which met the requirements of the pharmacopeia. Uniformity in weight and thickness represent that the polymer solution is properly distributed throughout the patch. The tensile strength was 398±1.51 kg/cm2. The moisture content and hygroscopicity were 0.38 ± 0.05 and 4.01 ± 0.06, meeting the requirements of the pharmacopoeia.

CONCLUSION

Transdermal therapeutic the system is a self-contained dosage form that, when applied to intact skin, releases the active ingredient into the systemic circulation in a controlled manner.In this project, we are developing a transdermal patch for the antihypertensive drug amlodipine using a novel polymer. Hypertension is a chronic illness in which blood pressure increases in the arteries. Around the world, a large proportion of the

population suffers from hypertension, making it the most common fatal disease. As it is a chronic disease, long-term treatment is required. In such cases, transdermal drug delivery systems can definitely be used for long-term treatment.

Amlodipine is a dihydropyridine derived calcium channel blocker that prevents transmembrane (within the cell) entry of calcium ions into cardiac (heart) smooth muscle. The elevated blood pressure is reduced by the relaxation of the vascular smooth muscles.

In vitro drug release and permeation studies of patches with cellophane membrane barriers were performed using a modified diffusion cell. The prepared film was placed on a semipermeable membrane and attached to a modified diffusion cell such that the drug release surface of the cell faced the receptor compartment filled with phosphate buffer at 37 ± 10 °C and pH 7.4.The Samples was analyzed for drug release using a Ultraviolet Visible spectrophotometer at 359 nm. We found that 80.1% of the drug permeated the membrane.The permeability coefficient and transmittance were 63 and 39.9%, respectively. Data obtained from in vitro release were fitted to model fitting analysis (zero-order model, Higuchi model, first-order model, and Korsmeyer-Pepas model). Interpretation of the data was based on the determined values of the regression coefficients. The best fitting model was the Higuchi model with the highest correlation coefficient of 0.964, indicating that the release of amlodipine from the transdermal patch was sustained release.

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