Formulation Design and Characterization of Transdermal Films of Amlodipine Besylate for Enhancing Therapeutic Efficacy

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ABSTRACT

This study is designed to develop Hydroxypropyl Methylcellulose (HPMC) based polymeric films of amlodipine besylate to explore HPMC as a rate retardant polymer in transdermal drug delivery system. Films were formulated by the solvent casting method. Physicochemical parameters of the films were evaluated (film permeability, elongation, pH, drug content uniformity and release kinetics). Results found that the elongation of formulated films were about 3.33-13.33%, whereas surface pH varies from 6.82 to 6.97. Maximum permeability flux was found 0.384 gm cm^{-2}/day for ABF7; whereas minimum for ABF3 (0.338 gm cm^{-2}/day). After 8 hours, the highest release (95.77%) was for ABF6; whereas 83.67% (least) release was for ABF3 and ABF5. For dissolution patterns, among different kinetic models, the Higuchi model was fitted nicely for release kinetic of the formulated films. It revealed that the drug release pattern and kinetics were affected due to the change in the polymer-drug ratio and solvents. It showed that HPMC plays a significant role in dissolution rate. In conclusion: we found that ABF7 is the best fit formulation for preparing HPMC based transdermal film of amlodipine besylate. Further investigation is warranted to correlate *in-vitro* and *in-vivo* findings for the potential therapeutic use.

Keywords Amlodipine besylate, Transdermal film, HPMC, Dissolution, Release Kinetics.

1. INTRODUCTION

Transdermal drug delivery (TDD) is an acceptable mode of drug delivery for administering the drug into the body across the skin. TDD is not a new concept; for thousands of years, people use medication on the skin for healing local injuries.[1] However, it takes more focus recent era as a useful mode of drug delivery. It is becoming popular in medical practice day by day due to its potentiality of using the alternative of oral and injectable dosage forms. Several advantages are noticed for TDD preparations, such as- avoidance of first-pass metabolism, delivery of steady infusion of the drug for a prolonged time, reduction of side effects, easy application and removal of TDD films/patches, patient acceptance, etc.[2,3] Moreover, it is possible to minimize the potential

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hazards (side effects) of the drug by infusing TDD drug through skin rather than intravenous infusion (a superior mode of drug delivery).[4]

Hydroxypropyl methylcellulose (HPMC) is a semi-synthetic polymer that is inert in nature, and used to prepare controlled, sustained released, and other dosage forms (tablets, films, etc).[5,6] On the other hand, amlodipine besylate belongs to the group of medication 'dihydropyridine type Ca^{2+} blockers' used to lower blood pressure and chest pain. $t_{1/2}$ of this drug is 35-50 hours and bioavailability of almost 60-65%.[7]

There are few studies have been done on amlodipine besylate for preparing TDD films[8-10]; however, more information is demanding before using it clinically. To confirm the characteristics of an ideal TDD film of amlodipine besylate, we have formulated and later investigated the different parameters of the films like-permeability profile, release pattern, pH, elongation profile, content uniformity, etc. In fact, our goal is to prepare a suitable, easier, cost-effective, controlled release amlodipine-loaded transdermal film using HPMC polymer. The retarding effects of different formulations using HPMC and solvents of different ratios have also been compared in this study.

MATERIALS AND METHODS

Materials

Amlodipine besylate (Cadila Healthcare Ltd., India) was received from Glove Pharmaceuticals Ltd., Bangladesh. Methanol, ethanol, and chloroform are from (Merck, Germany); potassium dihydrogen phosphate (BDH, UK) was collected from the analytical laboratory of Dept. of Pharmacy, NSTU, Bangladesh. All other reagents employed were analytical grades.

Formulation of the films

The transdermal films of amlodipine besylate were formed by solvent casting technique according to Rita et al. with slight modification.[11] Films were prepared by different amounts of HPMC, drug, and solvent which are presented in Table 1. Precise weight of drug and HPMC were mixed properly; and then different solvents- methanol, ethanol, chloroform were poured at prerequisite amount into the mixtures in a 25 ml volumetric flask. The homogeneous mix was poured onto petridish (D-75mm) and then kept in dry place at room temperature for evaporating the solvents. The petridishes were lubricated using paraffin oil for easy removal of the films. Films were discharged from the incubated dish after 24 hours; and then kept in the desiccator for next use.

Table 1. Formulation of amlodipine besylate loaded films containing HPMC

Formulations	Amlodipine (mg)	HPMC (mg)	Solvent (ml)
ABF1	100	100	15 (methanol)
ABF2	100	200	15 (methanol)
ABF3	100	100	15 (chloroform)
ABF4	100	200	15 (chloroform)
ABF5	100	100	15 (ethanol)
ABF6	100	200	15 (ethanol)
ABF7	100	200	5 (methanol) + 5 (ethanol) + 5 (chloroform)

AB = Amlodipine besylate

Film permeability test

4 cm^2 (2x2 cm) areas of the film were cut down from different parts of the patch. Calcium chloride solution in water was taken on a glass bottle and the film was attached to the opening of the bottle. The weight of the $CaCl_2$ filled bottles were taken again. By subtracting the bottle weight, the weight of the $CaCl_2$ solution was determined. Daily weight losses due to permeability of the films were recorded for 10 days period.[12]

Percentage elongation test

Small strips were cut down from the center, left, and right side positions of each film. At first, the primal length was measured. Then, the sliced strips were pulled on both sides until breaking point. The percentage of the increment of length was measured by using the following equation.[11]

Percentage of elongation = $(l_2-l_1)/l_1$ x 100; (l_1= Initial length of strip; l_2 = Final length of strip)

Surface pH test

The pH of the formulated films was studied in this experiment. In this aspect, 4 cm^2 (2x2 cm) pieces from different locations of tested films were cut down and allowed to swell up by keeping in distilled water (in glass tube) for 1 hour. Surface pH was measured by using a glass electrode, which was allowed to bring nearer to the film surface for a 1 minute period (during this time, pH meter can equilibrate with the surface of the films).[13]

Uniformity of drug content study

Drug content was determined for all prepared films. 4 cm^2 strips of the films were cut and weigh accurately. Then these strips were chopped up and taken into a measuring flask. The dissolving solvents (5 ml) by which the film was formed was poured in it. Strips were solvated completely through handshaking. Distilled water was added slowly for adjusting the volume up to 10ml. The solution was filtered after mixing. The filtrate was diluted using distilled water, and the dilution factor was noted for calculation. Finally, the samples were measured spectrophotometrically at 360 nm[11] (λ_{max} of amlodipine besylate) by Shimadzu UV spectrophotometer for drug content.[14]

***In-vitro* dissolution study**

In-vitro dissolution studies of our prepared films were done according to Rita et al. with slight modification.[11] For preparing buffer (pH 7.4), 0.68 gm potassium dihydrogen phosphate was weighed properly and then dissolved in 1L distilled water. NaOH was added for adjusting the pH. We have used USP XXII dissolution apparatus II (paddle) for studying drug release pattern from films. 4 cm^2 (2x2 cm) slices of the dry transdermal films were cut down and fixed over the glass plates. As a result, the drug can only release from one side of the film. The glass plate was placed at the bottom of the dissolution tester, which contained 500 ml dissolution medium at 37°C ± 0.5°C. The distance between the paddle and glass plate was 2.5 cm. We also fixed the rotation at 50 rpm. Five ml aliquot was withdrawn at regular intervals for analysis, which was replaced by the fresh phosphate buffer of same amount. Collected samples were filtered and later analyzed by UV spectrophotometer at 360 nm for getting the amount of dissolved drug released from the films.[14,15]

Drug release kinetics

After taking the data of 8 hours dissolution study of the formulated films, we have used different kinetic models for finding the best fit model of each formulation. The kinetic models were listed below-

Zero-order release model[16]: $Q_t = Q_0 + K_0t$;(Q_t= Amount of drug release/dissolved, Q_0 = Amount of drug at initial time in solution, K= Zero-order rate constant)

First order release model[17]: $LnC = LnC_0 + K_1t$; (C_t = Concentration release/dissolved drug, C_0 = Concentration of drug at initial time, K_1= First order rate constant)

Higuchi model[18-20]: $M_t = M_0 + K_Ht^{1/2}$; (M_t = Amount of released drug (cumulative), M_0 = Amount of drug at initial time, K_H = Higuchi release constant)

Korsmeyer-Peppas model[20-23]: $M_t/M_\infty = Kt^n$; (M_t/M_∞ = Drug release fraction at time t, K= Release rate constant). Here, 'n' is the release exponent, and this value is used to characterize different releases from the cylindrical shaped matrix. During drug release from a cylinder-shaped matrix, the release exponent value $n \leq 0.45$ demonstrates the Fickian diffusion mechanism. That means the drug may release from the matrix due to erosion of the polymeric chain.

On the other hand, the value of 'n' in the Korsmeyer-Peppas equation ($0.45<n<0.89$) refers to a non-Fickian (anomalous) transport mechanism. It refers that drug release is the combination of both diffusion and erosion controlled.[21]

Statistical analysis of data

Descriptive statistical analysis was done in this study by applying MS Excel 2007; and values are presented as (mean ± SD).

RESULTS AND DISCUSSION

Evaluation of film permeability studies

Permeation of $CaCl_2$ solution from the container (glass bottle) through the films was studied for 10 days. Gradual weight loss of the $CaCl_2$ solution confirmed the permeability of formulated films (Table 2). In Table 3, we found that the permeation flux value was maximum for ABF6 and ABF7, which was 0.384gmcm^{-2}/day. This indicated better permeation of films than others. Permeation coefficient indicates the rate of permeation (weight loss of solution) through the films. Maximum permeability coefficient (K_p) was found for ABF5, whereas least was observed for ABF6. Permeability co-efficient for ABF1, ABF2, ABF3, ABF4, ABF5, ABF6 and ABF7 were found as 0.081, 0.078, 0.043, 0.075, 0.124, 0.018 and 0.048 respectively.

Table 2. Comparison of film permeability among the prepared transdermal films

Formulation	Weight of container (gm)	Weight of container + $CaCl_2$ solutions (gm)	Net weight of $CaCl_2$ solution (gm)	Weight loss due to permeability of film (gm)					Weight loss of $CaCl_2$ solution (%)
				1 day later	2 days later	3 days later	7 days later	10 days later	
ABF1	69.375	124.732	55.375	54.305	53.532	52.650	51.732	47.352	14.48
ABF2	61.234	117.543	56.309	55.549	54.501	53.751	52.425	48.459	13.94
ABF3	67.572	122.356	54.784	53.652	52.702	51.549	50.135	47.356	13.50
ABF4	61.675	121.572	59.897	58.325	57.634	56.754	55.576	51.269	14.40
ABF5	65.432	116.378	50.946	50.240	49.576	50.575	47.765	43.256	15.09
ABF6	60.354	112.276	51.922	50.546	49.254	48.203	45.305	43.958	15.35
ABF7	54.935	105.461	50.526	49.725	48.375	47.298	45.509	42.759	15.37

Table 3. Permeation flux and permeability co-efficient study of transdermal films

Formulation	Permeation flux (gmcm^{-2}/day)	Permeability co-efficient (Kp)
ABF1	0.362	0.081
ABF2	0.349	0.078
ABF3	0.336	0.043
ABF4	0.360	0.075
ABF5	0.377	0.124
ABF6	0.384	0.018
ABF7	0.384	0.048

Evaluation of percentage elongation, surface pH, and content uniformity of the films

Elongation of the films can be defined as the increment of sample's gauge length just before the break point divided by the sample's original length. The greater the elongation, the higher the ductility or elasticity of the

materials. On the other hand, surface pH gave us information for predicting the formulated films are either safe or irritating for the skin. Content uniformity tests were performed to confirm the homogenous distribution of the drug (amlodipine besylate) throughout the whole film.

Comparisons of these three parameters of different films are shown in Table 4. The elongation percentage of the films varied from (3.33 ± 0.36) to (13.33 ± 0.35) %. ABF3 showed the highest percentage of elongation than other formulations, which means this film has good ductility and elasticity. Due to This value is satisfactory also for the other formulations also. Surface pH was measured for each formulation, and it was noticed that the pH of all formulations was very near to the neutral pH (□7). The overall pH of the human body is neutral (pH = 7). Although the skin's pH is slightly acidic in some cases, human skin can be easily exposed to neutral pH. The pH range of our formulated film is (6.82-6.97), which confirms the safety and non-irritation profile of the formulations. The content uniformity test confirmed that the distribution of the drug among the films was homogenous. We took strips from the different portions of the films, and then drug content was measured. It was found that the drug content (in 4 cm^2 strip) of the films of different formulations is (1.24 ± 0.008) mg/ml (mean ± STD). The deviation of content uniformity among the films is very little; hence it can be said that the results are satisfactory.

Table 4. Physicochemical evaluation of transdermal films

Formulation	Elongation (%) (mm)	Surface pH	Content uniformity/4 cm^2 film (mg/ml)
ABF1	6.67 ± 0.45	6.94 ± 0.12	1.24 ± 0.19
ABF2	10.0 ± 0.33	6.85 ± 0.15	1.38 ± 0.09
ABF3	13.33 ± 0.35	6.82 ± 0.13	1.25 ± 0.14
ABF4	10.0 ± 0.45	6.97 ± 0.16	1.13 ± 0.06
ABF5	3.33 ± 0.36	6.87 ± 0.20	1.23 ± 0.12
ABF6	6.67 ± 0.42	6.93 ± 0.23	1.18 ± 0.09
ABF7	6.67 ± 0.25	6.89 ± 0.14	1.25 ± 0.10

Value = Mean ± SD, n=3

Evaluation of *in-vitro* dissolution pattern from the films

The dissolution studies of the formulated films ABF1, ABF2, ABF3, ABF4, ABF5, ABF6, and ABF7 were carried out as USP paddle method. We have recorded the release profile of the drug for 8 hours period. (Figure 1) and (Figure 2) display Zero-order and Higuchi plots of release rate of amlodipine besylate from the films, respectively. After 8 hours, the overall drug release from the formulated films- ABF1, ABF2, ABF3, ABF4, ABF5, ABF6, ABF7 were 89.7%, 91.2%, 87%, 89.3%, 87.0%, 95.77%, and 93.1%, respectively. It was noticed that our formulated films could retard the drug release from the films for up to 8 hours. Drug release was gradual in most of the cases, and the release range from the films was (87-95.77)% after 8 hours of the study.

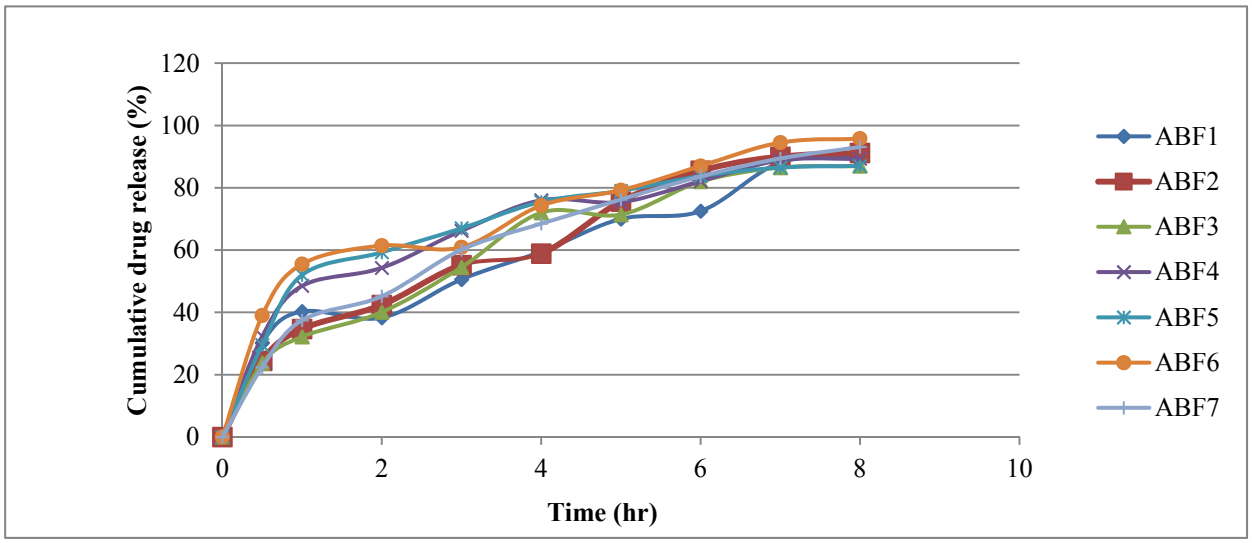

Figure (1): Zero order release kinetics of amlodipine besylate from films

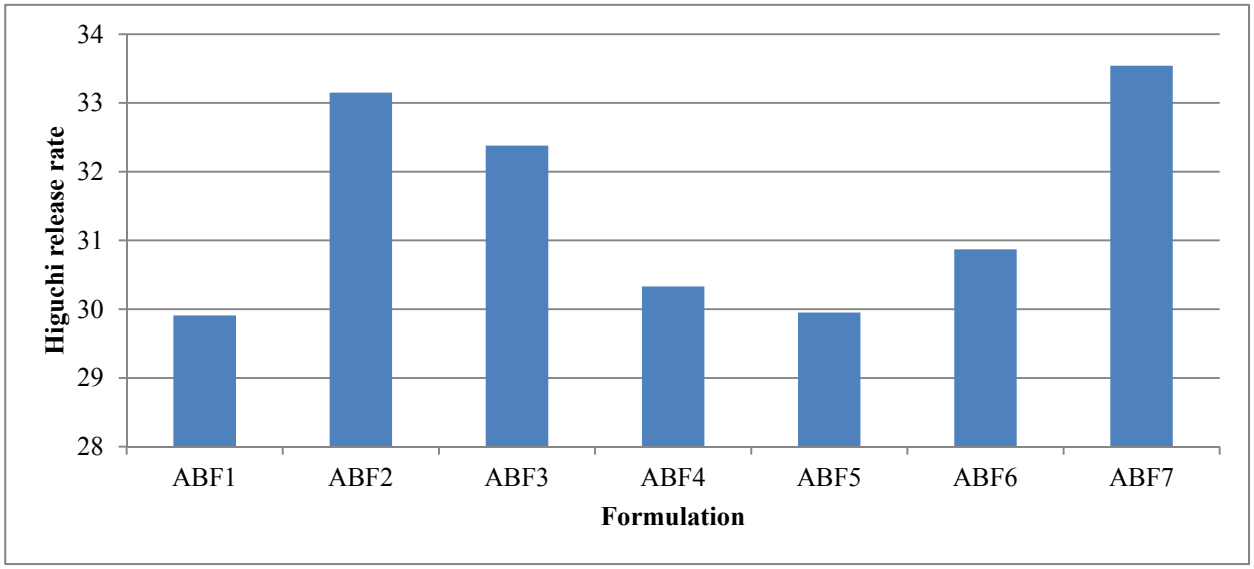

Figure (2): Higuchi release rate of amlodipine besylate from films

Table 5 represents the kinetics data of the formulated transdermal films. ABF1 best fit with Higuchi (R^2 = 0.967) kinetic model. Similarly ABF2, ABF3, ABF6, and ABF7 followed Higuchi kinetic model where R^2 values are 0.986, 0.985, 0.947, and 0.996, respectively. The rates of Higuchi release from films are shown in (Figure 2). ABF4 and ABF5 displayed Korsmeyer kinetic model with R^2 values of 0.971 and 0.988, respectively.

Release exponent value (n) of Korsmeyer release model for the formulations of ABF1, ABF2, ABF3, ABF4, ABF5, ABF6, ABF7 were 0.440, 0.509, 0.524, 0.314, 0.266, 0.281, and 0.465, respectively.

Table 5. Release kinetics of amlodipine besylate from different films

Formulation	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n
ABF1	0.911	9.475	0.931	-0.111	0.967	29.91	0.885	0.440
ABF2	0.932	10.510	0.969	-0.132	0.986	33.15	0.968	0.509
ABF3	0.909	10.150	0.980	-0.113	0.985	32.38	0.968	0.524
ABF4	0.809	9.072	0.967	-0.113	0.963	30.33	0.971	0.314
ABF5	0.766	8.813	0.950	-0.105	0.942	29.95	0.988	0.266
ABF6	0.805	9.288	0.941	-0.152	0.947	30.87	0.932	0.281
ABF7	0.913	10.480	0.986	-0.135	0.996	33.54	0.985	0.465

To confirm the drug release pattern, 'n' value was determined from Korsmeyer-Peppas equation. It was found that release exponent 'n' was ≤0.45 for the formulations ABF1, ABF4, ABF5, and ABF6. That means drug release from the matrix of these films was Fickian diffusion mediated. On the other hand, formulations ABF2, ABF3, and ABF7 follow anomalous diffusion/non- Fickian as the value of n was ($0.45 < n < 0.89$). This indicates that drug releases from these films were done through both diffusion and erosion controlled mechanism.[19-21] It was observed that Korsmeyer-Peppas kinetic represents good linearity for the formulations ABF5 and ABF7 (R^2 value is very much nearer to 1). However, in the Higuchi model R^2 value is the closest to 1 for the formulation ABF7. Hence, it can be said that ABF7 is the best fit model among our studied formulations.

CONCLUSION

The present study reveals that all the physical parameters for ideal film formation were satisfactory for the manufacturing process. We found that our formulated films can retard drug release up to 8 hours, and in most cases, the drug release patterns follow the anomalous/non-Fickian transport process. Among the experimental formulations of our study, ABF7 is the best fit formulation for preparing transdermal films. It is also possible to modulate the rate and extent of drug release from prepared films, which might be useful for preparing the desired formulation by the judicious addition of drug and polymer (HPMC). Further studies are recommended to correlate the *in-vivo* and *in-vitro* experimental findings to confirm the accurate pattern of drug release before using the films therapeutically.

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تصميم وتوصيف الأغشية عبر الجلد لأملوديبين بيزيلات لتعزيز الفعالية العلاجية

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ملخص

صممت هذه الدراسة لتطوير أغشية بوليمرية أساسها هيدروكسي بروبيل ميثيل سلولوز (HPMC) من أملوديبين بيسيلات لاستكشاف HPMC كبوليمر مثبط للمعدل في نظام توصيل الأدوية عبر الجلد. تمت صياغة الأغشية بطريقة الصب بالمذيبات.تم تقييم المعلمات الفيزيائية والكيميائية للأغشية (نفاذية الفيلم ، الاستطالة ، الأس الهيدروجيني ، توحيد محتوى الدواء وحركية الإطلاق).ووجدت النتائج أن استطالة الأغشية المركبة كانت حوالي 3.33−13.33٪ ، بينما تراوح الأس الهيدروجيني السطحي من 6.82 إلى 6.97. تم العثور على أقصى تدفق للنفاذية 0.384 جم / سم 2 / يوم لـ ABF7 ؛ بينما الحد الأدنى لـ 0.338) ABF3 جم سم −2 / يوم). بعد 8 ساعات ، كان أعلى إطلاق (95.77٪) لـ ABF6 ؛ بينما كان الإصدار 83.67٪ (الأقل) من أجل ABF3 و ABF5. بالنسبة لنمط الذوبان ، من بين النماذج الحركية المختلفة ، تم تركيب نموذج Higuchi بشكل جيد للإفراج عن الحركة الحركية للأغشية المركبة. وكشفت أن نمط إطلاق الدواء والحركية قد تأثروا بسبب التغير في نسبة البوليمر إلى الدواء والمذيبات. أظهر أن HPMC يلعب دورًا مهمًا في معدل الذوبان. في الختام ، وجدنا أن ABF7 هي أفضل صيغة مناسبة لإعداد فيلم عبر الجلد يعتمد على HPMC من أملوديبين بيسيلات. هناك ما يبرر إجراء مزيد من التحقيق لربط النتائج في المختبر وداخل الجسم من أجل الاستخدام العلاجي المحتمل.

الكلمات الدالة: أملوديبين بيسيلات ، فيلم عبر الجلد ، HPMC ، الذوبان ، الخواص الحركية.

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