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DESIGN AND CHARACTERIZATION OF AMLODIPINE BESYLATE TRANSDERMAL PATCHES USING HYDROXY PROPYL METHYL CELLULOSE AND ETHYL CELLULOSE COMBINATION

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ABSTRACT: Amlodipine besylate, an antihypertensive medication, used to bring down circulatory strain in hypertension. There are various conventional dosage forms of amlodipine besylate available, which have a few impediments, for example, first pass metabolism, persistent comfort and antagonistic impacts like cerebral pain, edema. Transdermal drug delivery systems have various advantages over conventional dosage forms such as decreased local and systemic side effects, optimized therapy, improved patient compliance, less frequent dosing, economical to the health care providers and the patients. In the present work we have studied the feasibility of transdermal drug delivery system for amlodipine besylate. Preformulation parameters of the drug have been studied and different transdermal patches were prepared by solvent casting method by using polymers like HydroxyPropyl Methyl Cellulose (HPMC) and Ethyl Cellulose (EC) in different ratios. *In vitro* release study was performed for all formulations across cellophane membrane. Skin permeation study was performed for all formulations across rat skin using buffer PBS 7.4 as receptor medium. The drug discharge was found to increment on expanding the convergence of hydrophilic polymer in the polymer lattice. This is because of the way that dissolution of soluble fraction of polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of molecules to release into the diffusion medium and hence, to cause higher release rate. The highest cumulative drug permeated was found in formulation AML3 containing HPMC and EC in the proportion 7:3.

Key Words: Amlodipine besylate, transdermal patch, HPMC, EC.

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I. INTRODUCTION

Hypertension (HTN) is emerging as a public health problems in developing countries like India. High blood pressure (BP) is one of the most important modifiable risk factors for cardiovascular diseases, which accounts for one in every eight deaths worldwide. Total deaths due to cardiovascular diseases were 9.1 million in developing countries and 1.5 million in India. It has been predicted that by 2020, there would be 111 percent increase in cardiovascular deaths in India. HTN is directly responsible for 57 per cent of all stroke deaths and 24 per cent of all coronary heart diseases (CHD) in India[1]. Hypertension or high blood pressure is a condition in which the blood pressure in the arteries is chronically elevated so sometimes it's called arterial hypertension which depends on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). With every heartbeat, the heart pumps blood through the arteries to the rest of the body. Blood pressure is the force of blood that is pushing up against the walls of the blood vessels. The heart has to work harder to pump, if the pressure is too high, and this could lead to organ damage such as heart attack, stroke, heart failure, aneurysm, or renal failure. This equals the maximum and minimum pressure, respectively. Normal blood pressure at rest is within the range of 100-140 mmHg systolic and 60-90 mmHg diastolic. Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as primary hypertension which means high blood pressure with no obvious underlying medical cause[2].

Amlodipine besylate is a peripheral arterial vasodilator that serves directly on vascular smooth muscle to cause a decrease in peripheral vascular resistance and lowering of blood pressure. Amlodipine besylate may be used in hypertensive patients with concomitant heart failure.Similarly, the incidence of other serious events, stroke, cancer, gastrointestinal bleeding and death was low, and none was attributed to Amlodipine besylate. So, it is a valuable agent for treating hypertension. Results of clinical trials support the use of Amlodipine besylate in the hypertensive patients. In accordance with the various treatment guidelines for hypertension, Amlodipine besylate should be initiated at the usual adult dosage 5 mg-10 mg in hypertensive patients[3]. In present study, transdermal drug delivery system of Amlodipine besylate was developed and evaluated.

II. MATERIAL AND METHODS

Amlodipine besylate was obtained as kind gift sample from K Pharma, Ambala. Ethyl cellulose and HPMC was obtained from Avarice Laboratories, Ghaziabad. Glycerinewas obtained fron S D Fine Chemicals Pvt. Ltd., Ambala. All other chemicals and reagents used were of analytical or pharmaceutical grade.

A. Preformulation Studies

Amlodipine besylate was identified and its purity was checked through FTIR study, melting point determination and Solubility of Amlodipine besylate was determined in water, methanol and P.B.S 7.4. Partition coefficient of AML was determined by using n- octanol as oily phase and water as aqueous phase.

B. Determination of $\lambda_{max.}$ of Amlodipine Besylate

The ultraviolet absorption maxima of Amlodipine besylate were determined spectrophotometrically with UV/VIS

spectrophotometer and it was found to be 360nm in methanol.

C. Calibration curve of drug in different solvents

The absorbance was measured in a U.V. spectrophotometer at 360nm in different solvents such as phosphate buffer 7.4 and methanol.

D. Drug excipient compatibility study

The infrared (IR) spectra were recorded using an FTIR spectrophotometer.The spectra of AML individually and in a mixture with other polymers (HPMC and EC) were obtained to check their compatibility. The FTIR spectra of HPMC and EC were also done individually to check their purity.

E. Fabrication of Amlodipine besylate transdermal patches

Amlodipine besylate transdermal patches were prepared by solvent casting technique, using different ratiosof HPMC E-15 and EC.The polymers were weighed in requisiteratios by keeping the total polymer weight 10mg in solvent mixture (1:1 ratio of chloroform: methanol). Glycerin wasincorporated as plasticizer. The drug was added tothe polymeric solution, and then they werestirred for 1hr then 3mL solution was withdrawn by using a syringe and slowly poured in a glass ring placed over a glass plate covered with aluminium foil. The glass plate was placed in a tray dryer carefully. After 24hr the dried patches were taken out andstored in a dessicator[4]. **Table 1** show transdermal patches prepared with HPMC and EC.

Table 1: Formulation of patches containing HPMC and EC with different ratios

S. No.	Formulation code	Amount of drug (mg)	HPMC:EC	Glycerin (mL)
1.	AML1	10	9:1	2
2.	AML2	10	8:2	2
3.	AML3	10	7:3	2
4.	AML4	10	6:4	2
5.	AML5	10	5:5	2
6.	AML6	10	4:6	2
7.	AML7	10	3:7	2

F. Physicochemical characterization of AML transdermal patches

Various batches of transdermal patch formulations were prepared and characterized for different parameters as below:

1. Weight variation

For each formulation, three randomly selected patches were selected. For weight variation test, three patches from each batch were weighed individually and the average weight was calculated[5].

2. Thickness

The thickness of the formulated patches was measured at three different points using a digital caliper and average thickness of three reading was calculated.

3. Folding endurance

The folding endurance wasmeasured manually for the prepared patches. A strip of film wascut and repeatedly folded at the same place till it broke. The numberof times the film could be folded at the same place without breaking/cracking gave the value offolding endurance.

4. Moisture absorption

Moisture uptake determination is also an important parameter. If a formulation absorbs moisture from environment at a high rate, it may cause microbial contamination as well as formation of pores in formulation, which may increase drug release from patch. The prepared patches were marked, then weighed individually and kept in a vacuum desiccators containing saturated Potassium chloride solution at room temperature for 3 days. After 3 days the patches were weighed again individually. The percentages of moisture content were calculated as a difference between final and initial weight with respect to initial weight.

% Moisture uptake = (Final weight – Initial weight)/Initial weight x100

5. Moisture loss

The prepared patches are weighedindividually and kept in a desiccators containing calcium chloride at room temperature. The films were weighed again after a specified interval until they show a constant weight. The percent moisture content was calculated using following formula[4].

% Moisture loss = (Initial weight – Final weight)/ Final weight x 100

6. Tensile strength

The instrument used to evaluate the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of chemical balance. One pan of the balance was replaced with one metallic plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the patch can be fixed up between two hooks of horizontal beams to hold the test film. A strip of transdermal patch of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan. The weights are added to the other side pan of the balance.

Thus, tensile strength

$$T = \frac{m \times g}{b \times t} \quad \text{Dynes/cm}^2$$

T= force at break/ initial cross-sectional area of sample.

Where,

m = mass in grams

g = acceleration due to gravity 980 cm/sec²

b = breadth of the specimen in cm

t = thickness of sample in cm.

7. Water vapour transmission rate (WVTR)

WVTR is defined as the quantity of moisture transmitted through unit area of the film in unit time. Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 gm of fused calcium chloride was taken in the vials & the polymer films were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber at 85% RH. The vials were removed and weighed at various time intervals like 3, 6, 12, 18 and 24hr to note down the weight gain[6].

8. Drug content

The patches were cut and added to a beaker containing 100mL of phosphate buffered saline of pH7.4. The medium was stirred with magnetic bead. The contents were filtered using whatman filter paper and the filtrate was examined for the drug content against the reference solution consisting of placebo films (contains no drug) at 360nm spectrophotometrically[4].

***9. In vitro* drug release studies**

The *in vitro* permeation was carried out across cellophane membrane having molecular weight cut-off 12,000-14,000. The transdermal patch was applied on cellophane membrane which was placed between donor and receptor compartment. The diffusion medium was phosphate buffer pH 7.4. The temperature of the receptor compartment was maintained by 37°C± 2°C. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously as a control. Sample (5mL) was withdrawn at suitable time intervals and replaced with equal amount of fresh media. The samples were analyzed for drug content using UV spectrophotometer.

10. Skin permeation studies

Abdominal skin of rats was used for permeation studies. Rats were sacrificed by spinal dislocation method. Hair was carefully trimmed short with a pair of scissors and the abdominal skin was removed from the rat body. Then the fat adhering to the dermal side was removed by using scalpel and isopropyl alcohol. The skin thus prepared was washed with 0.9% sodium chloride solution and sectioned to pieces of required size and used directly without further treatment.

The rat abdominal skin was mounted in such a way that stratum corneum side of the skin continuously remained in an intimate contact with the transdermal film in the donor compartment and the dermis side was in constant contact with the receptor solution. The receptor chamber was filled with saline phosphate buffer 7.4 as elution medium, at 37± 2°C, being stirred magnetically. Sample (5mL) was withdrawn at suitable time intervals and replaced with equal amounts of fresh media. The samples were analyzed for drug content using UV spectrophotometer. The permeation study was carried out for 24hr.

11. Scanning Electron Microscopy

Scanning electron microscopy has been extensively employed to study the morphology and surface topography of the film. The morphology and surface topography of the film were examined by scanning electron microscopy. The optimized patch was mounted on the SEM sample stab using a double

sided sticking tape. The samples mounted were coated with gold under reduced pressure for 5 min. to improve the conductivity using an ion sputtering device. The gold-coated samples were observed under the SEM and photomicrographs of suitable magnifications obtained[7].

12. Skin irritation study

The skin irritation studies of optimized formulation in rabbits were performed by using Draize test[8]. The hairs of rabbits were trimmed short 24hr before starting the experiment. The three squares were drawn at the each side of back of rabbit. Then squares were divided for different groups. In first group, no formulation was applied and thus it was considered as sham control group. In second group, phosphate buffer was applied as topical solution and this was referred to as control group. In third group, 20% SLS solution was applied to make it a positive control group. On 4th group, optimized formulation of transdermal patch was applied with the help of adhesive tape. Then the skin of rabbit was observed at different time intervals of 0, 12, 24, 48, 72hr after application and accordingly the area was scored for erythema and edema on grade of 0-4.

13. Effect of aging

The effect of aging on physical appearance, physicochemical properties and drug content of optimized transdermal patch formulation of Amlodipine besylate was studied by packing the polymeric films in properly sealed aluminum foil and then storing them in dessicator at ambient conditions of temperature for 60 days. Physical appearance, folding endurance and drug content studies of patches were carried out at starting of experiment as well as different time intervals during experiment.

G. RESULTS AND DISCUSSION

1. Preformulation studies

A suitable UV spectroscopic method for the analysis of amlodipine besylate was developed. The solubility study of Amlodipine besylate was found to be 0.052mg/ml, 35mg/ml and 20mg/ml in water, PBS 7.4 and methanol respectively. It was found to be freely soluble in methanol. The logarithmic value of partition (log P) was experimentally found to be 2.5. The preformulation studies involving melting point, solubility, partition coefficient of drug were found to be comparable with standard. Based upon all the above studies, drug was found to be suitable for developing the transdermal formulation.

2. Determination of $\lambda_{max.}$ of Amlodipine Besylate

The ultraviolet absorption maxima of Amlodipine besylate were determined spectrophotometrically with UV/VIS spectrophotometer and it was found to be 360nm in methanol. Fig. 1 shows the U.V. spectrum of drug in methanol.

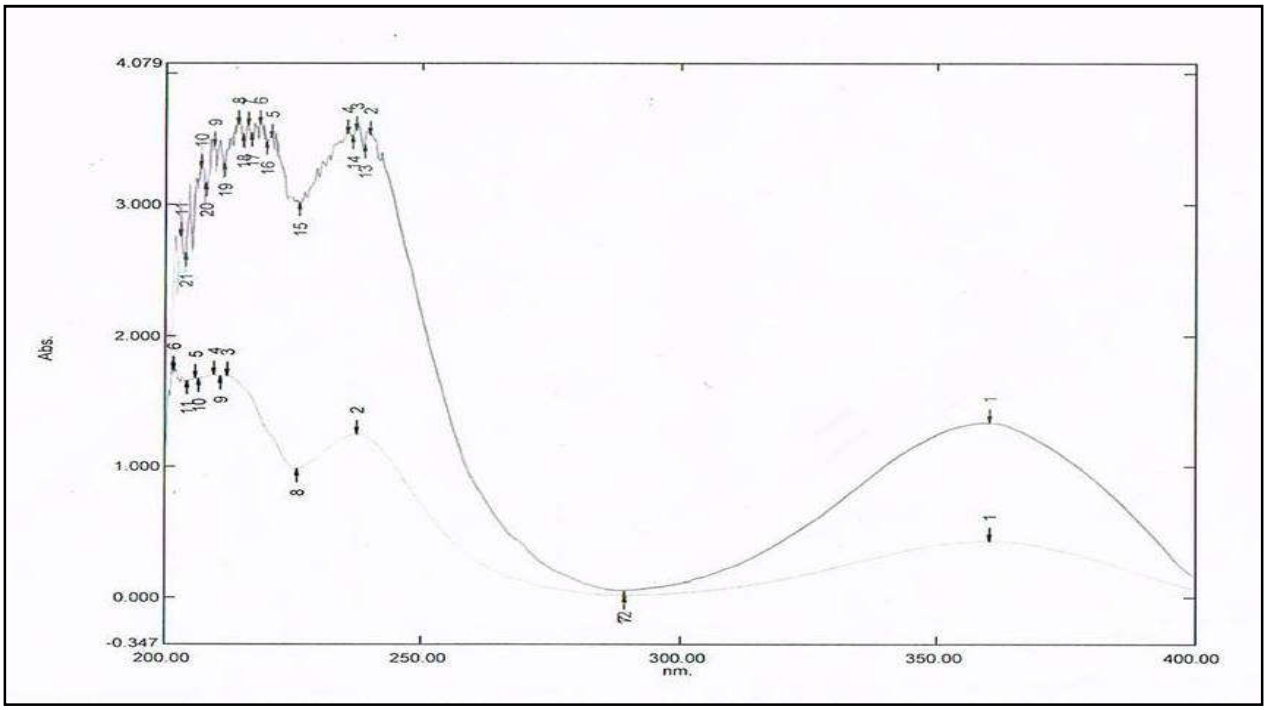

Fig. 1 U.V. spectrum of drug in methanol

3. Calibration curve of drug in different solvents

The absorbance was measured in a U.V. spectrophotometer at 360nm in phosphate buffer 7.4 and methanol.

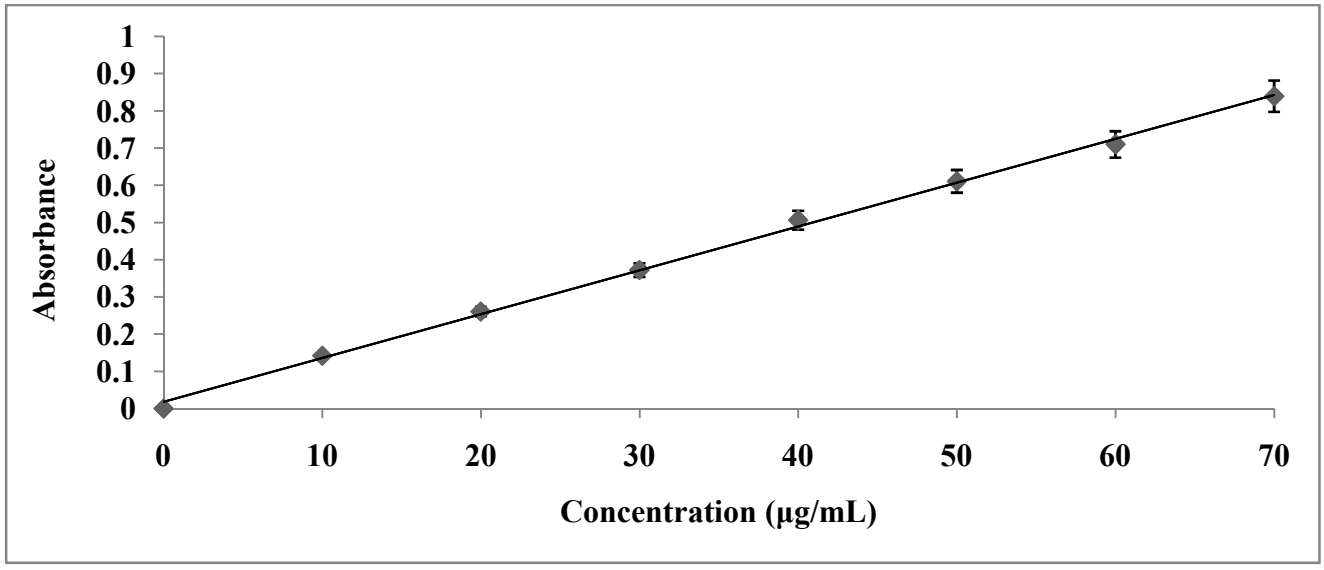

Fig. 2 Calibration curve of Amlodipine besylate in phosphate buffer pH 7.4

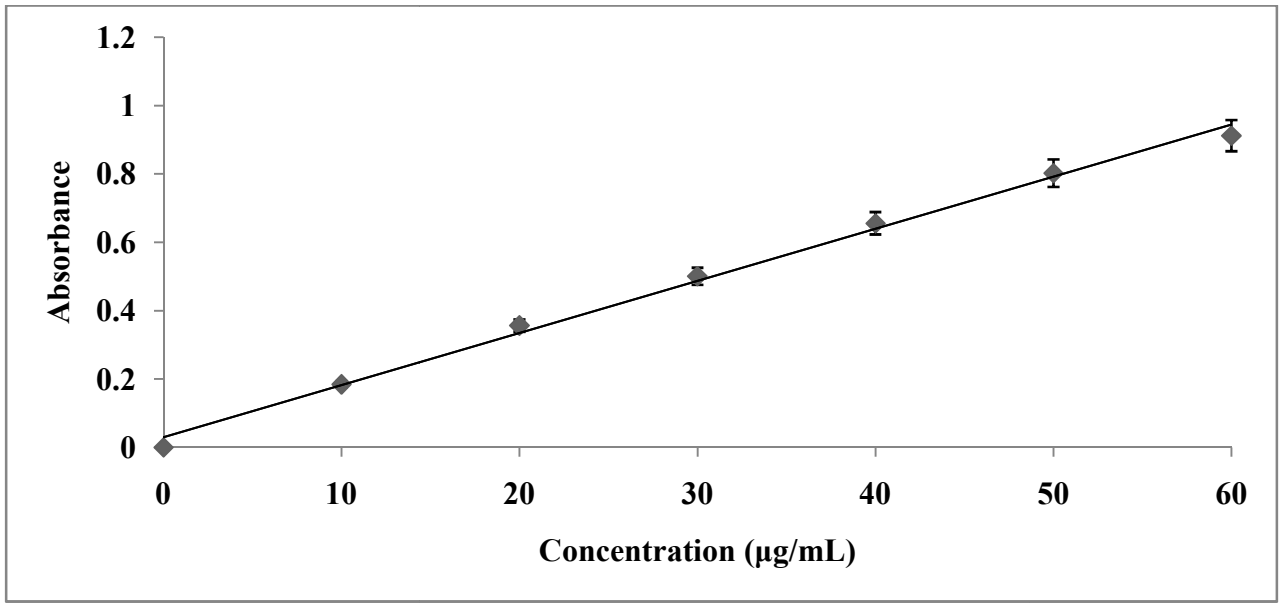

Fig. 3 Calibration curve of Amlodipine besylate in Methanol

4. Drug excipient compatibility study

Fourier transform infrared spectroscopy studies were carried out for pure drug and polymers individually as well as the mixture of pure drug and polymers. The results are summarized as follows. IR spectra of Drug and polymers are shown. The peaks can be considered as characteristic peaks of Amlodipine besylate, HPMC and EC confirming the purity of the drug. The spectra of HPMC and EC also confirm their purity. The FTIR peaks of mixture of drug and polymers showed that there was no interaction between drug and polymers.

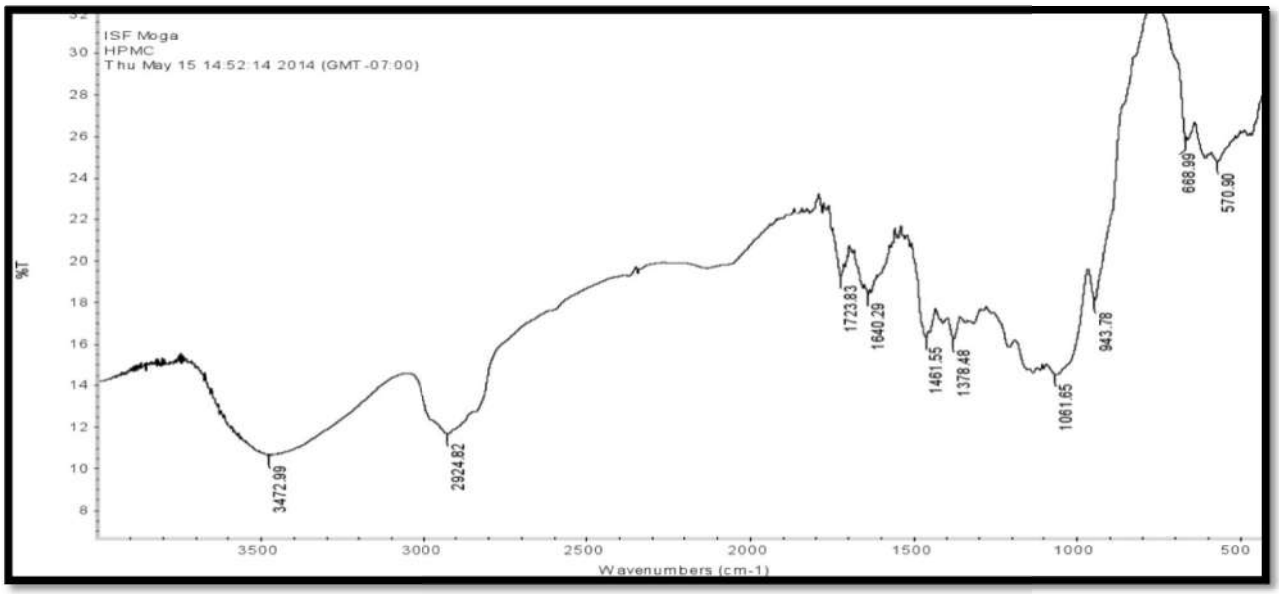

Fig. 4 FTIR spectrum of HPMC

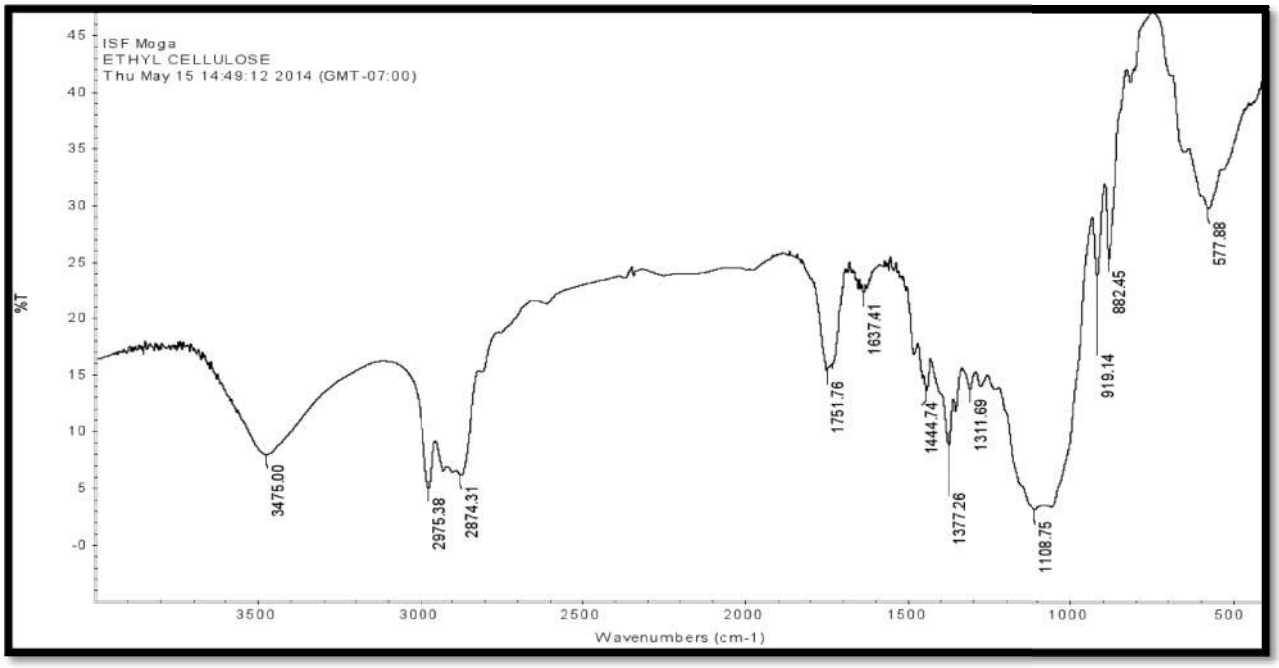

Fig. 5 FTIR spectra of EC

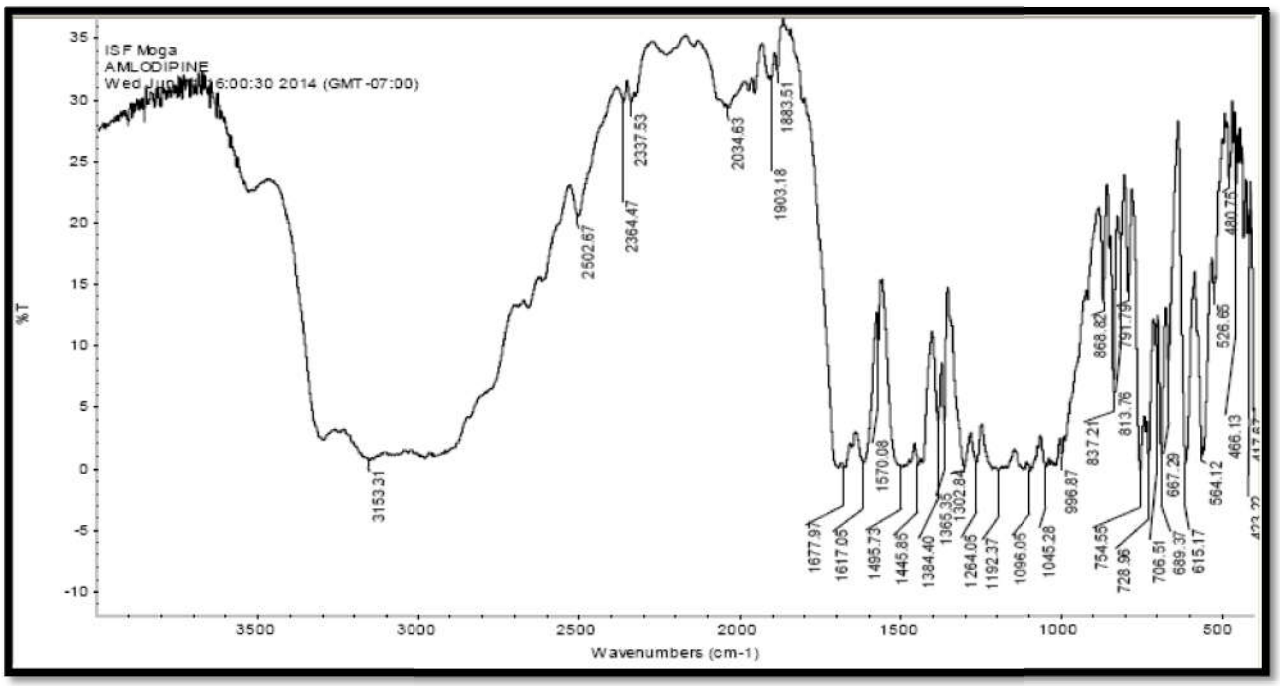

Fig. 6 FTIR of Amlodipine Besylate

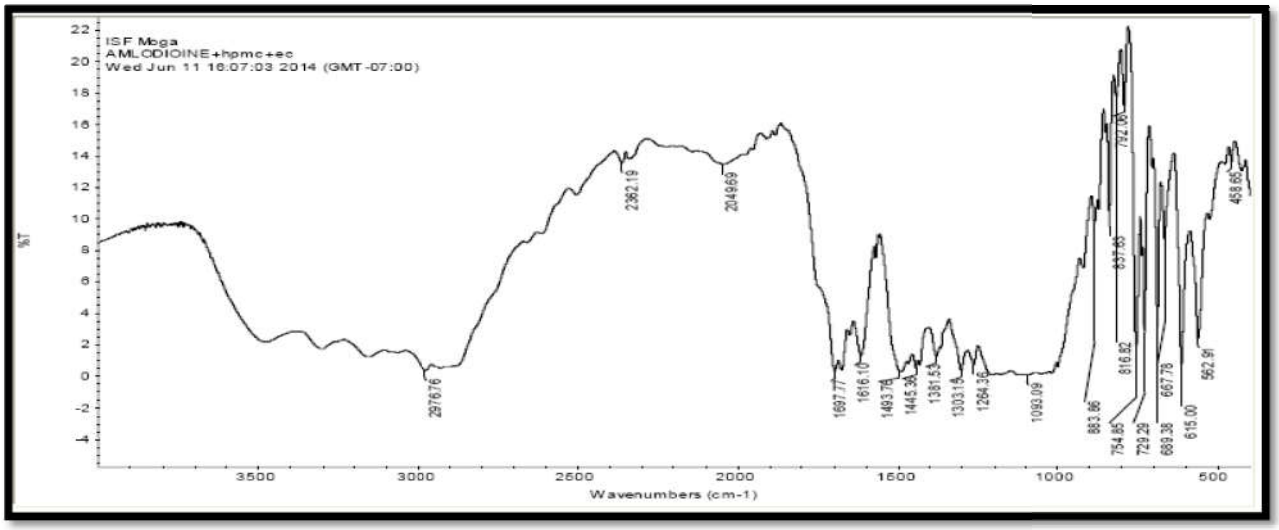

Fig. 7 FTIR of Amlodipine besylate+HPMC+EC

Table 2: FTIR analysis of Amlidipine besylate, HPMC and EC

S. No.	IR Spectra	Groups	Peak (cm^{-1})	Stretching/ Vibration/ Deformation
1.	Amlodipine besylate	C−H	2502	Stretching
		C=O	1677	Stretching
		C−C	1495	Stretching
		C−H(Aromatic)	754.5	Stretching
		N−H	3153	Stretching
2.	HPMC	O−H	3472	Stretching
		C−O	1378	Stretching
		C−H	2924	Stretching
3.	EC	C−O	1108	Stretching
		C−H	2975	Stretching

5. Physicochemical characterization of transdermal patches

Amlodipine besylate transdermal patches were prepared by solvent casting technique, using

different ratios of HPMC E-15 and EC. Prepared patches were evaluated for different physicochemical parameters as well as other release properties such as weight variation, uniformity of thickness, folding endurance, %moisture content, % moisture uptake, WVTR, drug content, diffusion studies, skin permeation studies. The variation of weight was found to be due to variation in polymer concentration in patches. Value of standard deviations was found to be low, which indicates physical uniformity of patches. The thickness of transdermal patches was measured with the help of digital caliper in our lab. The results indicated that there was no much difference in thickness within the formulations as depicted by low values of standard deviations. This indicated physical uniformity of patches.

The folding endurance values of patches increase with the increase in HPMC content. All patches showed folding endurance values above 50 which indicate that would be less brittle on application to skin. The folding endurance was found to be in the range of 85-197 as reported in Nanda S *et al*., 2012 folding endurance of patches using polymers HPMC & Eudragit was 190 &105 respectively[4] and John L *et al*., 2014 showed the value of folding endurance between 70-80[9]. The moisture absorption results indicated that moisture absorption increase with the increase in HPMC concentration and it decrease with increase in EC concentration. The moisture absorption of patches was low which prevent in microbial contamination and decrease bulkiness of patches. The result of moisture content was directly proportional to HPMC concentration due to hydrophilic nature of HPMC.

Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength.The value of tensile strength increases with increase in HPMC concentration and decreases with increase in EC concentration. The water vapor transmission data through transdermal patches are important in knowing the permeation characteristics. The value of water vapour transmission rate increases with increase in HPMC concentration due to its hydrophilic nature and decreases with increase in EC concentration due to its hydrophobic nature.

Table 3: Physicochemical evaluation of transdermal patch formulations

S. No.	Formulation Code	Average weight (mg) ± S.D.	Thickness (mm) ± S.D.	(%) Moisture absorption
1	AML1	897±0.02	0.156±0.02	9.45±0.37
2	AML 2	872±0.01	0.139±0.002	9.03±0.24
3	AML 3	725±0.02	0.121±0.03	8.71±0.22
4	AML 4	634±0.01	0.114±0.04	5.18±0.15
5	AML 5	632±0.01	0.101±0.01	4.28±0.25
6	AML 6	645±0.04	0.094±0.02	3.23±0.20
7	AML 7	501±0.01	0.090±0.03	2.46±0.33

Values are represented as mean ± SD (n=3)

Table 4: Physicochemical evaluation of transdermal patch formulations

Sr. No.	Formulation Code	Folding endurance	WVTR(gm/cm^2/h)	% Drug content
1	AML1	197±9.64	0.0054±0.006	80.5
2	AML 2	186±9.07	0.0051±0.007	82.6
3	AML 3	171.6±8.50	0.0048±0.010	87.8
4	AML 4	154±7.54	0.0045±0.005	75.6
5	AML 5	140.3±10.01	0.0043±0.008	69.7
6	AML 6	93.3±5.50	0.0040±0.011	72
7	AML 7	85.6±5.13	0.0038±0.010	70.2

Values are represented as mean ± SD (n=3)

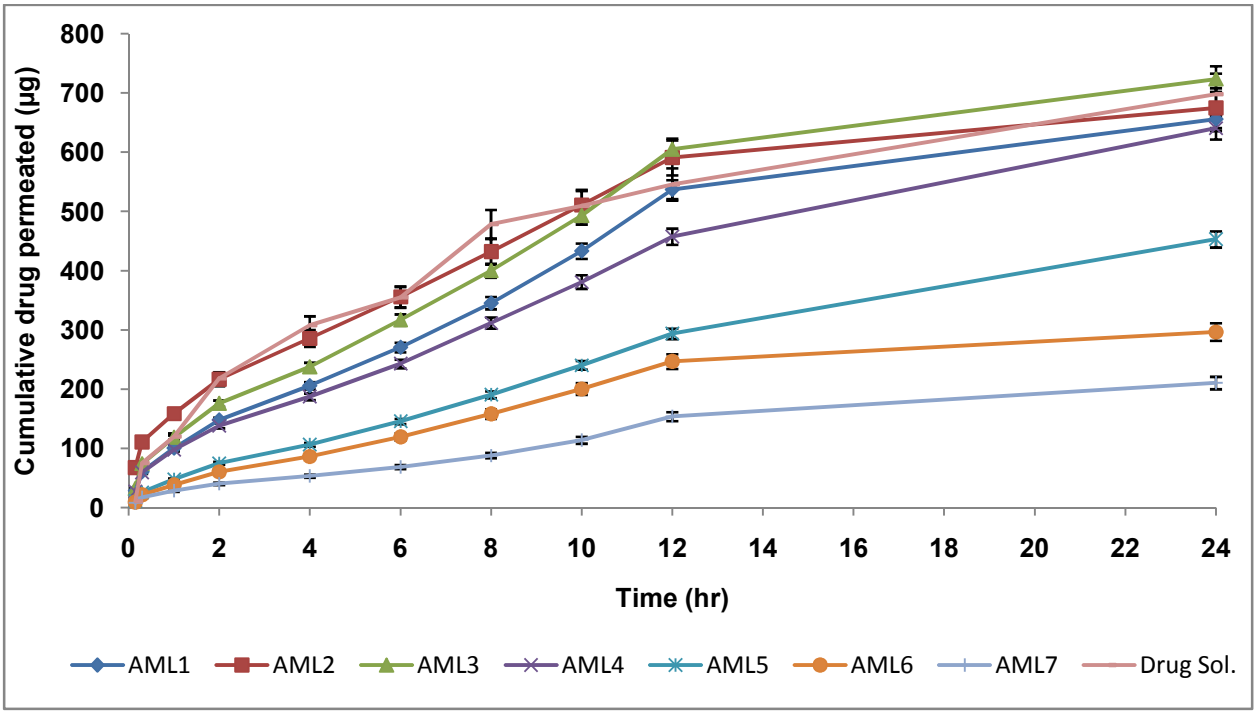

Fig. 8 Comparison of cumulative drug permeated across cellophane membrane from different transdermal formulation after 24 hr

6. *In vitro* drug release across cellophane membrane

In vitro drug release studies of patch formulations were performed using method described in methodology section. Release study required for predicting the reproducibility of drug release. Release of a drug from patches is controlled by physicochemical properties of the drug and excipient in the formulation. The *in vitro* release study predicts the *in vivo* performance of the drug. Thus these studies help in improving the formulation characteristics. *In vitro* release study was performed for all formulations across cellophane membrane using phosphate buffer P.B.S. 7.4. It was observed that as the concentrations of hydrophilic polymer HPMC increased in the formulations, the drug release rate increased substantially as compared to hydrophobic polymers EC as reported in the Nanda S *et al*., 2012 reported that as the concentrations of HPMC increased the drug released rate also increased as compared to hydrophobic polymer[4]. Formulation AML7 showed poor release.

7. *In vitro* Skin permeation studies

Skin permeation study was performed for all formulations across rat skin using phosphate buffer PBS 7.4. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of soluble fraction of polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of molecules to release into the diffusion medium and hence, to cause higher release rate[10]. The highest cumulative drug permeated was found in formulation AML3 containing HPMC and EC in the ratio 7:3.

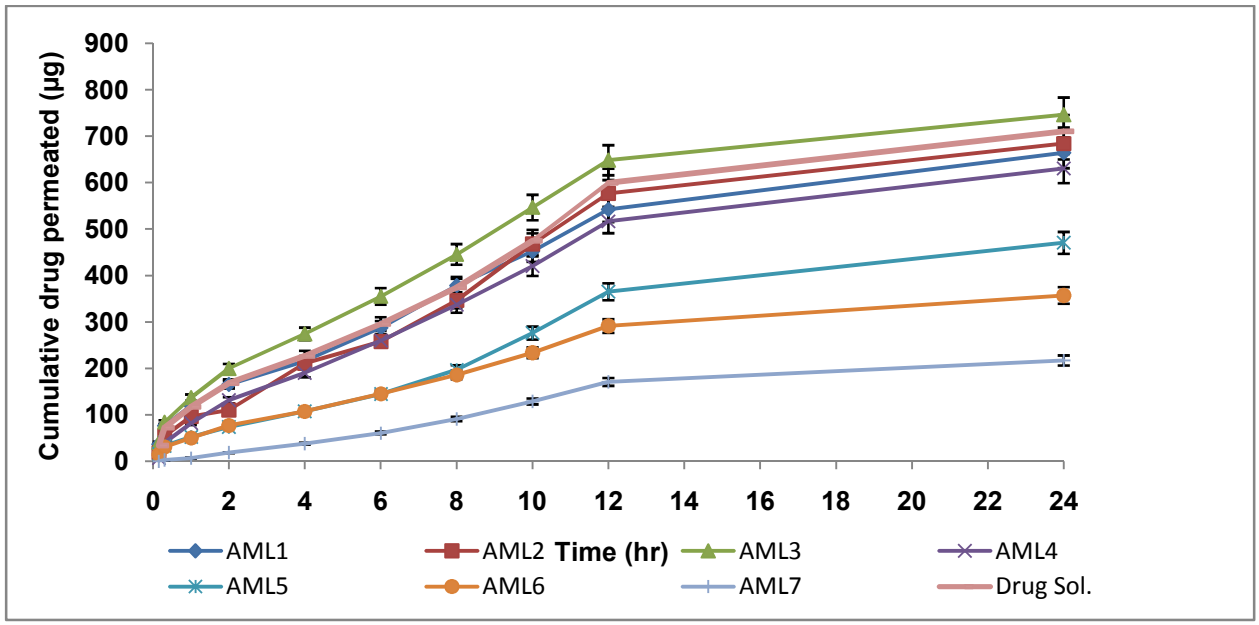

Fig. 9 Comparison of cumulative drug permeated across rat skin from different transdermal formulation after 24 hr

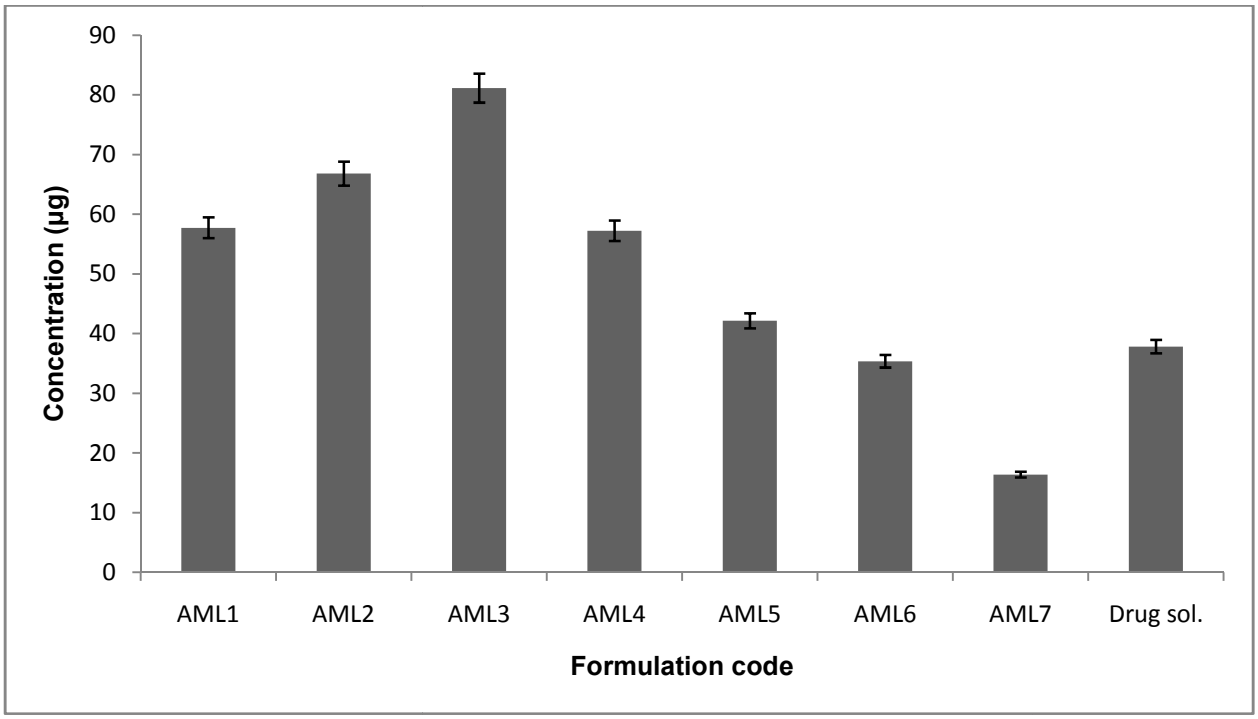

Fig: 10 Comparison drug deposition through rat skin from different transdermal formulation after 24 hr.

8. Scanning electron microscopy

SEM was performed on optimized transdermal patch formulation AML3 to detect the surface morphology of the transdermal patch. Transdermal patch was gold coated to render it electro conductive for Scanning electron microscopy. The SEM photograph of transdermal formulation is displayed below.

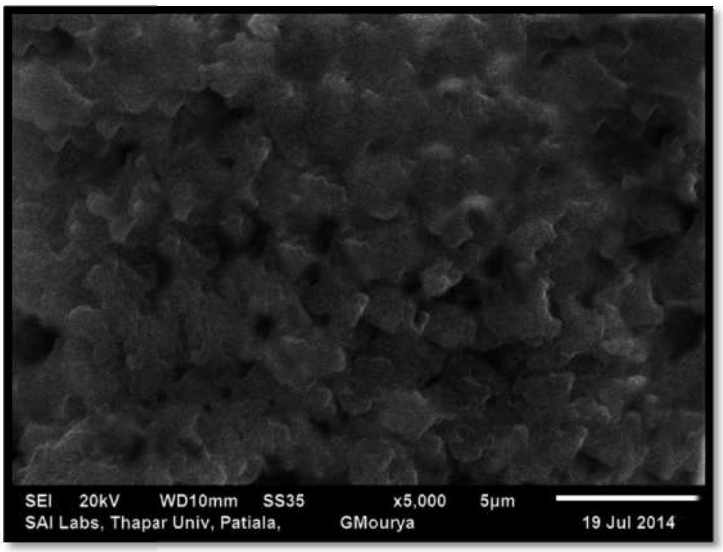

Fig. 11 SEM of formulation AML7

9. Skin irritation studies

AML3 patch formulation was chosen on the premise of physicochemical properties as well as other release properties. Thus it was selected for the skin irritation study. It was carried out using Draize's test. The results indicated that no adverse reactions were seen with the formulation. The main reason behind this is the composition of patch formulation and sustained release of drug. Results of draize test are summarized in **Table 5**.

Table 5: Skin irritation score as per draize method after application of different formulations

Formulation	Erythema				Oedema			
	1 hr	24 hr	48 hr	72 hr	1 hr	24 hr	48 hr	72 hr
Sham control	0	0	0	0	0	0	0	0
Control (PBS)	0	0	0	0	0	0	0	0
SLS (20%)	1.2	3.4	3.2	3.0	0	1.2	2.5	1.9
Drug solution	1.4	3.5	3.1	3.0	0	1.1	2.4	1.9
AML3	0	0.1	0.2	0.4	0	0	0	0

Values Represented as Mean (n = 3).

Score are define as 0 = no erythema, 1 = very slight erythema (light pink), 2 = well defined erythema (dark pink), 3 = moderate to severe erythema (light red), 4 = severe erythema (extreme redness)

Similarly defined for odema

10. Effect of ageing

Effect of ageing was studied on selected formulation AML3. It was done by packing the different films of this formulation in properly sealed aluminium foil and then stored in desiccator at ambient temperature for 60 days. The samples were evaluated for physical appearance, folding endurance and drug content. Physical appearance of patches was found to be unchanged with time. The values of folding endurance and drug content were measured at different intervals. The results are described in **Table 6**.

Table 6: Effect of ageing on formulation AML3

S. No.	Parameters	Value at 0 day	Value after 15 days	Value after 30 days	Value after 60 days
1	Folding Endurance	174±1.52	172±1.90	169±0.88	165±1.19
2	% Drug Content	89.55±0.45	87.25±1.51	86.54±1.45	85.57±0.85

Values are represented as mean ± SD (n=3)

11. CONCLUSION

Controlled release transdermal patches of AML can be prepared using solvent casting technique using HPMC and EC. The prepared patches indicated good physicochemical properties. The patches showed ideal medication content and sustained drug release. Release study of AML patches demonstrated that the drug release from the formulation varies with the different ratios of polymers such as HPMC and EC. Among all prepared formulations the formulation containing HPMC and EC (7:3) indicated better drug release of at 24 hr. By exploring the results obtained, on the premise of the *in vitro* characterization it was presumed that Amlodipine besylate can be controlled transdermally through patches developed in our lab. Transdermal patches comprising of the polymers HPMC and EC demonstrated sustained release of the drug for 24 hr.

12. ACKNOWLEDGMENTS

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CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED