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Research Article

STUDY OF THE HYDROXY PROPYL METHYL CELLULOSE (HPMC) COMBINATIONS IN THE DEVELOPMENT OF TRANSDERMAL FILM FOR AMITRIPTYLINE HCl AND THEIR *INVITRO* CHARACTERIZATION

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ABSTRACT

The present study aimed to investigate the effect of different viscosity grade hydroxy propyl methyl cellulose polymers (HPMC K4M, HPMC K15M and HPMC K100M) in different combinations in the design of amitriptyline hydrochloride transdermal film. The films were prepared (F1 to F15) by solvent evaporation method and subjected to in vitro evaluation such as physicochemical properties of thickness, folding endurance, % moisture loss, % moisture absorption, drug content, in vitro drug release, release kinetic and skin permeation. The compatibility was tested by Fourier Transform Infrared Spectroscopy (FTIR). The FTIR spectra revealed the compatibility among the drug and the polymers. The films were found to possess suitable physicochemical properties having uniform thickness and drug content. The film F14 (combination of HPMC K4M and HPMC K100M at a ratio of 3:4) showed significantly ($P<0.5$) highest percentage of amitriptyline HCl release. Maximum release of 97.23±2.11% and a skin permeation of 85.50±3.11% were obtained for the formulation F14 over a period of 24h. It can be concluded that the drug release could be modulated using different combinations of HPMC polymers. The HPMC K4M and HPMC K100M combination at a ratio of 3:4 was suitable in the transdermal delivery of amitriptyline HCl.

Keywords: Amitriptyline hydrochloride, Hydroxy propyl methyl cellulose, Transdermal film.

INTRODUCTION

The transdermal delivery offers controlled release of drug & maintain steady plasma level over a period of time, thus results in dose reduction, less frequent administration and improved patient compliance. In the development of transdermal films, hydrophilic polymer HPMC (Hydroxy propyl methyl cellulose) has been extensively employed to modulate the release kinetics of drugs. The in vitro release performance of HPMC films was found to depend on their molecular weight (viscosity grades). The low, medium and high viscosity grade HPMC has been used separately as matrix forming polymer in the development of transdermal films (Jamakandi *et al*., 2009; Pravin Gavali *et al*., 2010; Soma Ghosh *et al*., 2010**)**. However the combined use of HPMC in modulating the drug release has not yet been analysed. HPMC is regulatory approved, versatile, can hold variety of drugs and stable at all pH. They could able to produce a light, non-greasy uniform film with sufficient texture and do not interact greatly with other ingredients. Being surface active, they adsorb water providing easy dispersion, lubricity and comfort feel in occlusive condition during application on skin. HPMC based transdermal film of amitriptyline HCl reported in our earlier study showed promising results (Vijaya *et al*., 2011). Here an attempt has been made to develop transdermal films via

combinations of HPMC grades such as HPMC K4M, HPMC K15M and HPMC K100M in different ratios to achieve more controlled release characterisitics. The films were evaluated in vitro for physico chemical properties and modulation of drug release characteristics. Dibutyl phthalate (DBP) was used as a plasticizer at a concentration of 30%w/w of total dry polymer weight. The tricyclic antidepressant amitriptyline HCl was utilized as a model drug as it possesses suitable properties of low molecular weight (313.86), low therapeutic dose and melting point (196-197°C) for transdermal delivery. Moreover, the suitability of psycotrophic drugs for transdermal route have been reviewed (Aggarwal *et al*., 2009) and their oral administration results in suboptimal concentration in local tissues.

MATERIALS AND METHODS

Materials

Amitriptyline HCl was obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad. HPMC K4M, HPMC K15M and HPMC K100M were purchased from Forts India Ltd., Chennai. Ethanol was bought from Changshu vangyuvan chemical, China. Dichloromethane was purchased from Fisher Scientific, Mumbai. Dibutyl phthalate was obtained from loba chemie, Mumbai. All other solvents and reagents used were of analytical grade.

Preparation of transdermal film

Matrix type transdermal film of amitriptyline HCl was prepared using different viscosity grade HPMC as matrix forming polymer in combinations (HPMC K4M& HPMC K15M, HPMC K15M& HPMC K100M and HPMC K4M& HPMC K100M) as shown in **table 1** by solvent evaporation technique. Total polymer weight was kept at 200mg and was dissolved in dichloromethane (5ml) and ethanol (2ml) as solvents. The solution was added with dibutylphthalate (30%w/w of dry polymer) as plasticizer with constant stirring at 25°C in a closed system. 10mg of drug was homogenously dispersed and the mixture (7ml) was poured over the previously lubricated glass petridish having an area of 6cm². The solvent was then allowed to evaporate in a controlled manner by inverting a funnel over the petridish at room temperature for 24h. The dried films were collected and stored in desiccators for further evaluation.

Compatibility

The compatibility between the drug and polymers were analysed using FTIR (Fourier Transform Infrared) spectra using FTIR spectrophotometer (Perkin-Elmer, Japan) at a moderate scanning rate of 400 to 4000cm^{-1}. The spectra were observed for the existence of any physical and/or chemical interaction between the drug and polymers.

Film thickness

The thickness of the film was measured at 3 different points using a screw gauge (Syracuse, Newyork) (Jitendra Banweer *et al*., 2008).

Folding endurance

The folding endurance (FE) could be defined as the number of folds required to break the polymeric film when the folds made at the same point, till the film breaks. The FE was done manually taking a strip of films having uniform size. The number of folds a film can sustain dictated its folding endurance (Shankar *et al*., 2010).

Moisture absorption

The film was weighed accurately and placed in a desiccator containing 100ml of saturated solution of sodium chloride, which maintains 63% RH. After 72h the film was taken out of the desiccator and weighed. The moisture absorption was calculated as percentage using the formula (Shaila Lewis *et al*., 2006).

$$\text{Percentage moisture absorption} = \frac{W2 - W1}{W1} \times 100$$

Where, W_1– weight of the film after moisture absorption study.

W_2– weight of the film before moisture absorption study.

Moisture loss

The film was weighed accurately and kept in a desiccator containing 10gm of calcium chloride. After 72h the films were taken out of the desiccators and weighed. The percentage moisture loss was calculated using the formula (Shaila Lewis *et al*., 2006).

$$\text{Percentage moisture loss} = \frac{W1 - W2}{W1} \times 100$$

Where, W_1– Initial weight of the film.

W_2– Weight of the film after moisture loss study.

Flatness
Longitudinal strips were cut from the prepared film. The length of each strip was measured and the variation in length was noted. Flatness was calculated by measuring constriction of strips because of non-uniformity in flatness and 0% constriction was considered to be 100% flatness (Li *et al*., 2006).

Drug content
The amount of Amitriptyline HCl in the film was estimated using UV spectrophotometer (UV-1700-Shimadzu, Japan) at λ_{max} of 239nm (Gendy *et al*., 1993). The film was cut into small pieces (2cm²) and added to a beaker containing 100ml of phosphate buffer pH 7.4. The solution was stirred with a teflon coated magnetic bead for 24h and filtered using whatman filter paper. The filtrate was examined for Amitriptyline HCl content against the reference solution after suitable dilution.

***Invitro* release**
USP dissolution apparatus V (DS 8000 Labindia, Mumbai) of paddle over disc assembly was used for the assessment of *in vitro* drug release from the films. The transdermal film was mounted on the disc and the disc was placed at the bottom of the dissolution vessel. Phosphate buffer pH 7.4 of 900ml was used as a dissolution medium and was equilibrated to 32±0.5°C. The apparatus was operated at 100rpm and 5ml sample was withdrawn at appropriate time intervals up to 24h and analyzed for the released drug at 239nm spectrophotometrically. Cumulative percentage released drug was calculated and plotted against time (Li *et al*., 2006).

Release kinetics
To understand the mechanism and kinetics of drug release, the data from the *in vitro* release studies were analyzed using the kinetics models of zero order, first order, higuchi, kosermeyer peppas, hixson crowell and the co-efficient of correlation (R^2) values were calculated (Chandak *et al*., 2008).

***Invitro* skin permeation**
Permeation studies were performed using fresh rat abdominal skin and keshary chein type diffusion cell. The hair on the abdomen skin was removed and the animal was anaesthetized and euthanized by cervical dislocation. The skin was cut using a scissor, the fatty tissue that adheres to the skin was peeled off with a help of a scalpel and the residual fat was washed with isopropyl alcohol. The full thickness skin was tied between the donor and the receptor compartment of the diffusion cell in such a way that the stratum corneum faced the donor compartment. The film of defined area (4.9062 cm²) with drug releasing surface in close contact with the stratum corneum was placed over the skin. The receptor compartment contained phosphate buffer pH 7.4 and maintained at 37°C±0.5°C. The buffer was kept under mild agitation using a magnetic stirrer (Remi, India). The samples were withdrawn from the receptor compartment at various time intervals up to 90% of drug release. An equal volume of fresh phosphate buffer was replaced at every withdrawal of sample. The absorbance of the sample was measured at 239nm using UV spectrophotometer (Chandak *et al*., 2008).

RESULTS AND DISCUSSION

Compatibility study
The FTIR spectra for the drug and physical mixture of polymer and drug are given in **Figure 1**. In the spectra of drug, two bands at 1472cm^{-1} and 1344cm^{-1} were obtained due to the N-CH_3 stretching whereas the bands at 1600cm^{-1}, 1580cm^{-1}, 1500cm^{-1}, 1450cm^{-1} were due to the aromatic groups. These principal peaks of the drug were seemed to be unaffected in all the physical mixtures of drug & HPMC K4M, drug & HPMC K15M, drug & HPMC K100M. The peaks of respective polymers were also appeared in their respective spectra. No new peaks were found in addition to the drug and polymer. The FTIR study revealed no interaction between the drug and polymers confirms their compatibility.

Physicochemical characterization of films
The results of physicochemical evaluation are tabulated in table 2. The films were found to be flexible, smooth, opaque, non-sticky and homogeneous. A marginal difference in thickness was observed among each formulation. The folding endurance values greater than 280 no's, indicates good strength and elasticity of film. Moisture absorption study revealed the strong water absorbing capacity of film which is an inherent property of the hydrophilic polymer HPMC. The results of moisture loss have indicated the presence of considerable amount of moisture in the films.

Drug content determination
The quantity of drug present in 2cm² area was found to lie in the range of 2.52±0.162mg to

2.86±0.082mg as shown in the **table 2**. It could be said that the process employed in the preparation of film was capable of dispersing the drug uniformly throughout the film with minimum batch variability.

Invitro release

The *invitro* release behavior of amitriptyline HCl loaded transdermal films F1 to F15 is shown in **figure 2 to 4**. An initial burst release was observed for all the formulations which might be due to the direct exposure of the hydrophilic matrix film to the dissolution medium. It was observed that the drug release gets increased with increase in the ratio of HPMC K15M whereas the release gets decreased with increase in the ratio of HPMC K100M. The maximum cumulative percentage drug release of 97.23±2.11% was observed for F14 (HPMC K4M & HPMC K100M) at the end of 24h and had exhibited suitable controlled release of amitriptyline HCl compared with other formulations. Steady state release was attained rapidly and maintained up to 24h by F14 formulation. This is exactly due to the low viscous polymer HPMC K4M that provides less resistance to the movement of the drug and allows consistent erosion of the matrix. The controlled release might be due to the slow diffusion of the drug through the strong gel layer that has been formed by the high viscosity polymer HPMC K 100M. Usually the polymer forms a gel layer upon contact with the dissolution medium and the gel layer grows with time as more water permeates into the core of the matrix. This increases the thickness of the gel layer offering additional barrier for the diffusion of the drug. Hence it is the diffusional gel barrier that determines the drug release (Ali *et al*., 2008). The combination of various viscosity grades of HPMC effected an intermediate viscosity and provided the optimal controlled release. The release depends upon the polymer viscosity and the viscosity is inversely proportional to drug release. The viscosity of currently used polymers is in the order of HPMC K4M<HPMC K15M < HPMC K100M. The number indicates the viscosity in m.Pa.s, "K" denotes the hydroxyl propyl content and the letter "M" indicates 1000 times. The effect of viscosity, concentration, on drug release was predictable at high concentration of these polymers below which the effects were not clearly observed.

The drug release kinetics followed first order and the mechanism was found to be fickian diffusion mediated since the value of n was <0.5 for the kosermeyer peppas model. It could be said that the drug release process depends on drug concentration, diffusion across the polymeric network and polymer erosion. The R^2 and "n" value obtained for the kinetic models of the formulations are given in **table 3**.

Invitro skin permeation

The formulation F14 was subjected to skin permeation study based on its highest in vitro release of amitriptyline HCl. The cumulative percentage of drug permeated was found to be 85.50%±3.11% over a period of 24 h. The graph is given in **figure 5**.

Table 1: Formulation composition of amitriptyline HCl transdermal films of hydroxyl propyl methyl cellulose

Formulation code	Polymer Ratio		
	HPMC K4M	HPMC K15M	HPMC K100M
F1	4	3	-
F2	2	1	-
F3	1	2	-
F4	3	4	-
F5	4	1	-
F6	-	1	4
F7	-	1	3
F8	-	3	1
F9	-	4	3
F10	-	2	1
F11	4	-	1
F12	3	-	1
F13	2	-	1
F14	3	-	4
F15	4	-	3

Table 2: Physicochemical properties of amitriptyline HCl films of hydroxyl propyl methyl cellulose

Formulation Code	Thickness (mm)	Folding Endurance	% Moisture Absorption	% Moisture Loss	% Drug Content (mg per 2cm²)
F1	0.10±0.007	288	3.7651±0.565	6.4126±1.576	2.56±0.565
F2	0.09±0.001	281	4.5647±0.390	8.6421±1.451	2.64±0.162
F3	0.11±0.004	289	5.1167±0.405	10.6954±0.728	2.77±0.190
F4	0.08±0.012	290	4.5435±0.488	9.6654±5.955	2.60±0.106
F5	0.10±0.006	298	5.2341±0.659	1.2436±0.974	2.75±0.084
F6	0.14±0.007	295	6.1672±0.684	2.6222±0.880	2.63±0.063
F7	0.13±0.013	287	5.1987±0.230	1.3651±0.090	2.72±0.014
F8	0.12±0.008	290	4.8730±0.910	1.2371±1.094	2.74±0.155
F9	0.11±0.002	296	5.5681±0.654	2.1298±1.506	2.78±0.133
F10	0.16±0.003	287	6.1600±0.216	2.7853±5.916	2.52±0.162
F11	0.17±0.008	298	5.9813±0.718	10.6931±1.117	2.75±0.098
F12	0.08±0.013	286	4.8754±0.781	9.1134±0.6213	2.79±0.098
F13	0.10±0.005	291	5.1634±0.203	8.2357±2.390	2.75±0.007
F14	0.12±0.010	283	5.6492±0.406	9.8639±1.140	2.86±0.082
F15	0.09±0.011	289	6.2235±0.749	11.6211±1.242	2.76±0.070

values are mean ± SD, n=6

Table 3: The R² and "n" value (Kosermeyer Peppas) of kinetic models for the formulations

Formulation code	R² Value of Kinetic models				Korsmeyer Peppas model	
	Zero order	First order	Higuchi	Hixson-Crowell	R²	n
F1	0.9694	0.9909	0.9837	0.9853	0.9589	0.208
F2	0.9882	0.9906	0.9925	0.9949	0.9851	0.322
F3	0.9440	0.9858	0.9811	0.9762	0.9890	0.252
F4	0.9567	0.9843	0.9855	0.9791	0.9889	0.288
F5	0.9242	0.9378	0.9376	0.9949	0.9357	0.388
F6	0.9746	0.9803	0.9824	0.9826	0.9762	0.312
F7	0.9649	0.9766	0.9794	0.9802	0.9731	0.281
F8	0.9355	0.9730	0.9747	0.9629	0.9838	0.295
F9	0.9849	0.9923	0.9892	0.9916	0.9775	0.297
F10	0.9416	0.9656	0.9629	0.9594	0.9604	0.317
F11	0.9705	0.9869	0.9806	0.9836	0.9672	0.319
F12	0.9054	0.9732	0.9496	0.9585	0.9601	0.420
F13	0.9660	0.9955	0.9931	0.9898	0.9954	0.310
F14	0.8917	0.9911	0.9448	0.9779	0.9621	0.333
F15	0.9651	0.9491	0.9678	0.9689	0.9526	0.408

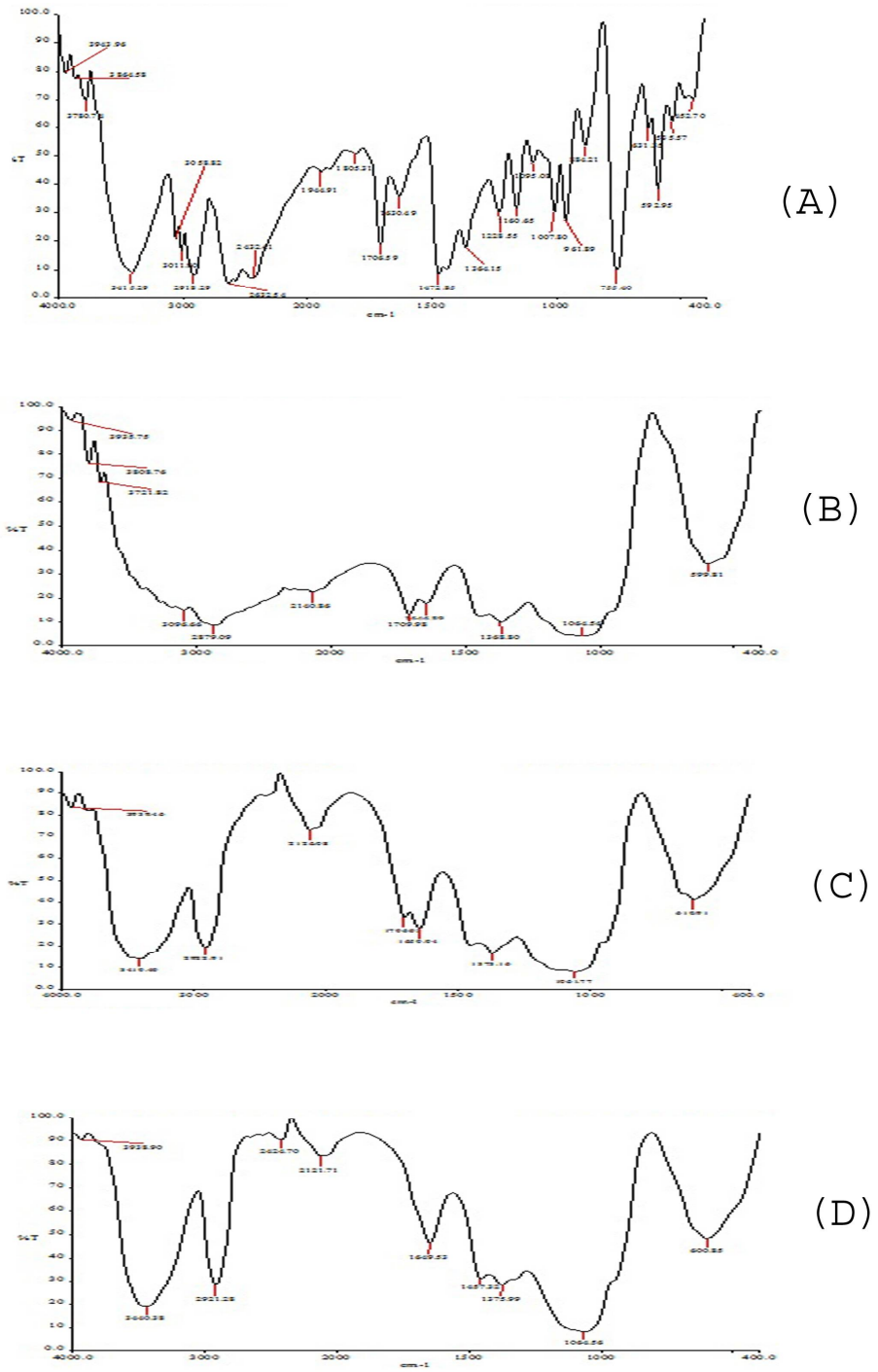

Fig. 1: FTIR spectra of drug (A), drug & HPMC K4M (B), drug & HPMC K15M (C) and drug & HPMC K100M (D)

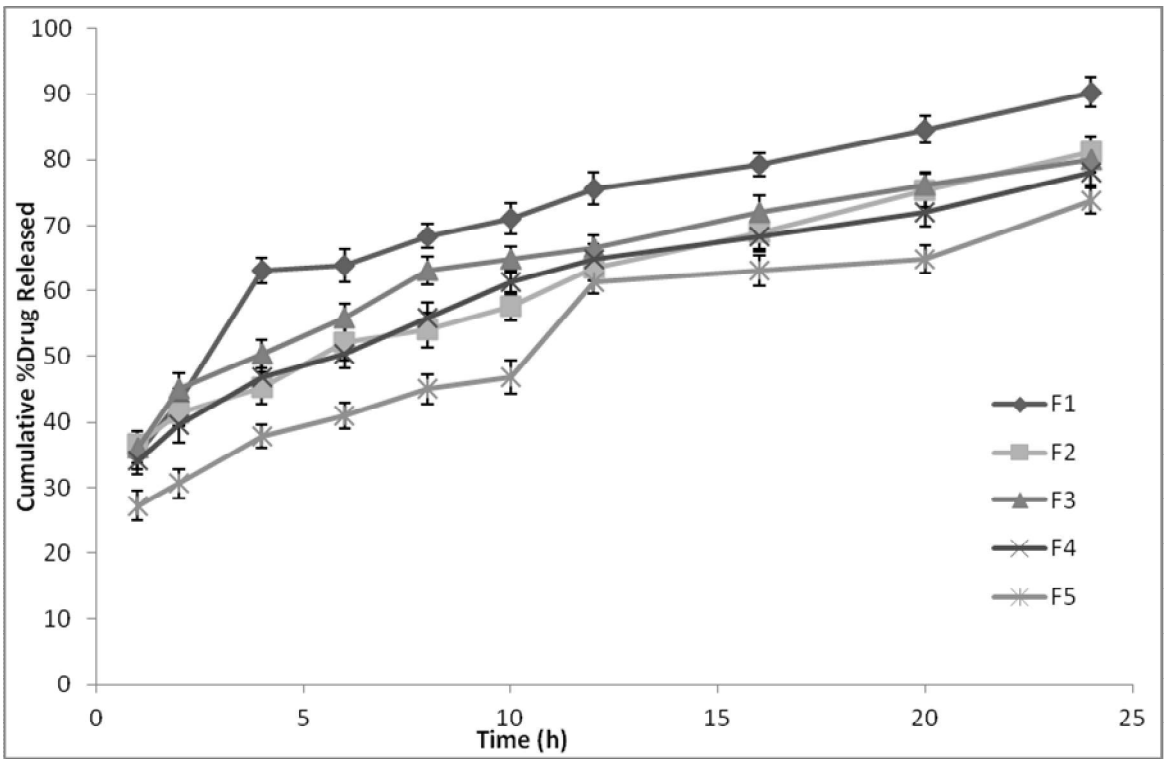

Fig. 2: Invitro amitriptyline HCl release of F1 to F5 (HPMC K4M & K15M) formulations

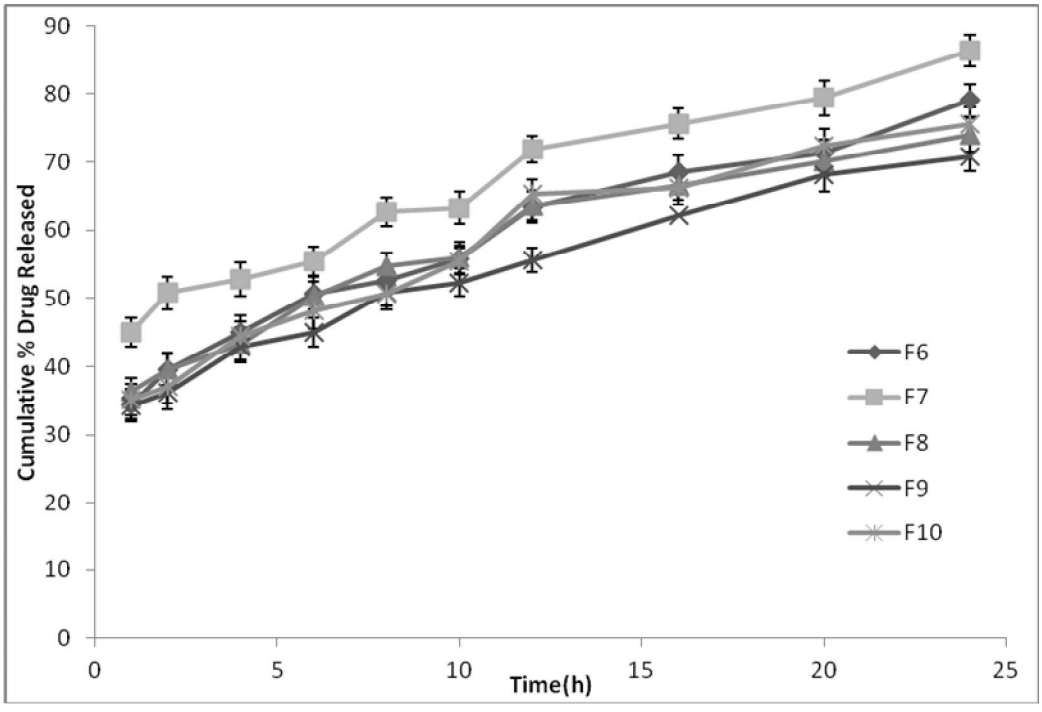

Fig. 3: *Invitro* amitriptyline HCl release of F6 to F10 (HPMC K15M & K100M) formulations

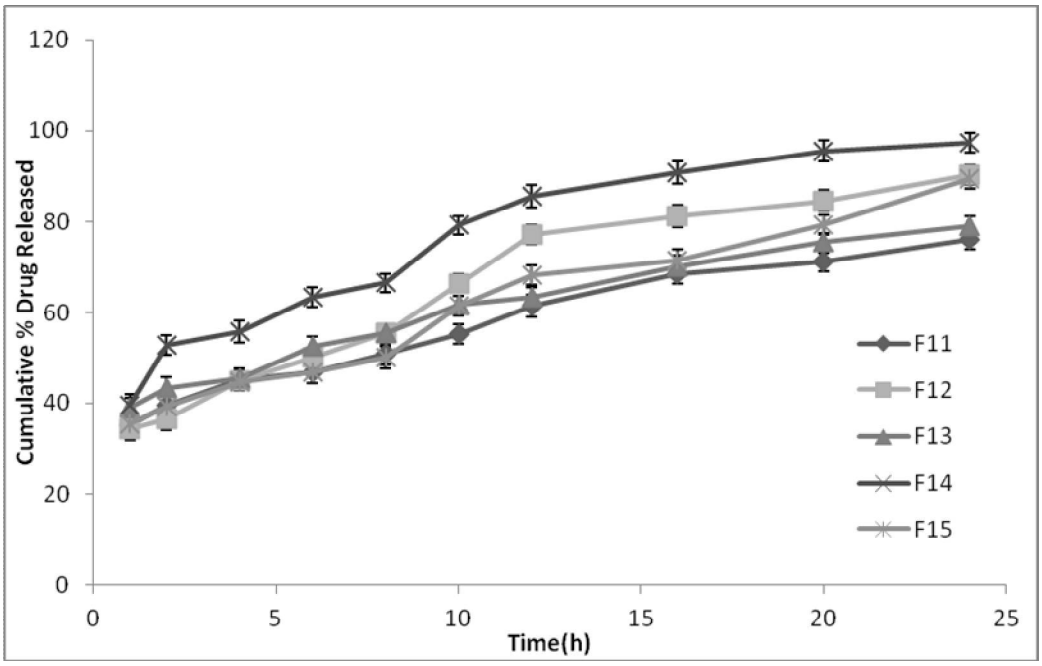

Fig. 4: *Invitro* amitriptyline HCl release of F11 to F15 (HPMC K4M & K100M) formulations

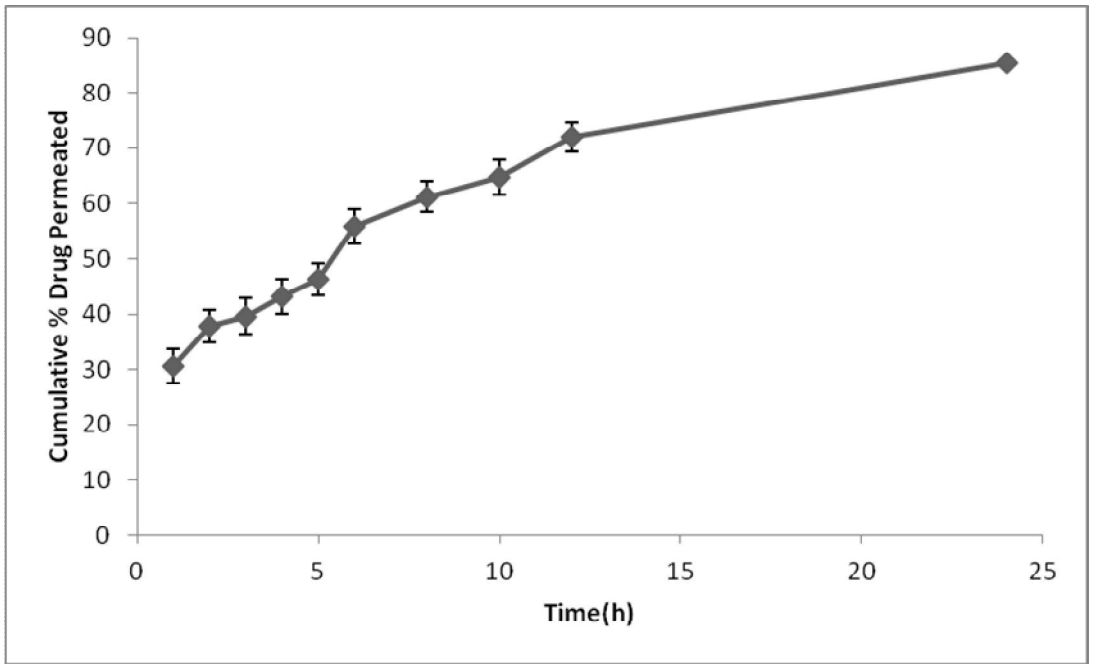

Fig. 5: *Invitro* skin permeation of formulation F14

CONCLUSIONS

The polymeric matrix prepared with a combination of HPMC not only modulated and optimized the release of amitriptyline HCl, but also produced a robust matrix film with suitable physico chemical performance. The drug release was found to be linear and followed zero order kinetics. The polymer combination of HPMC K4M & HPMC K100M in a ratio of 3:4 was selected as an optimized film formulation based on its controlled release and permeation of the chosen drug. Thus it can be concluded that the drug release increases with decrease in viscosity of HPMC polymer and the combinations of higher (HPMC K4M) and lower viscosity (HPMC K100M) grades in preparation of transdermal films would help in attaining the optimized drug release from the film.

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