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Research Article

PREPARATION AND IN VITRO EVALUATION OF HYDROXY PROPYL METHYLCELLULOSE FILMS FOR TRANSDERMAL DELIVERY OF SERTRALINE HYDROCHLORIDE

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ABSTRACT

The study was aimed to develop hydroxy propyl methylcellulose (HPMC) based matrix type transdermal film for the antidepressant sertraline hydrochloride(SH) to avoid systemic side effects and gastric disorders after oral administration Polymeric grades HPMC K4M, HPMC K15M, HPMC K100M and solvents such as acetone, ethanol and isopropyl alcohol were used in the preparation of film (S1 to S9) by solvent evaporation method. Polyethylene glycol 400 was added as a plasticizer at a concentration of 150% w/w of polymer. Permeation enhancers of propylene glycol and oleic acid were employed to enhance the skin permeation of SH. The films were evaluated in vitro for thickness, folding endurance, percentage moisture absorption, percentage moisture loss, water vapour transmission, tensile strength, drug content, in vitro release and skin permeation. Maximum SH release of 39.94%±0.543% was obtained for HPMC K15M formulation (S4) prepared using acetone and water as solvents at a ratio of 9:1. The permeation of SH across the rat abdominal skin was 20.27%±0.051% and was increased to 38.19%±0.063% in the presence of permeation enhancers oleic acid (1%) and propylene glycol (30%) at a ratio of 1:5.The optimized film S4 did not produce any noticeable skin reactions. The drug release followed higuchi kinetics with non fickian diffusion mechanism. In conclusion, the polymer grades of HPMC containing plasticizer had influenced the SH release profile and the incorporation of permeation enhancers increased the permeation of SH.

Keywords: Transdermal delivery, Sertraline hydrochloride, HPMC, PEG 400, In vitro evaluation.

INTRODUCTION

Transdermal delivery system delivers the drug into systemic circulation via skin and it offers many advantages over conventional dosage forms. It avoids hepatic first pass metabolism, reduces gastrointestinal side effects and delivers steady infusion of drug over an extended period of time. It decreases the frequency of administration and improves patient compliance1. This transdermal delivery has been approached successfully in the delivery of many therapeutic agents including the class of antidepressant drugs2. Sertraline hydrochloride (SH) is a bi-cyclic anti-depressant administered orally in the treatment of major depression. It is slightly soluble in water (3.8 mg/ml at 25°C) and sparingly soluble in ethanol, possess suitable physic chemical properties and thus has been identified for transdermal delivery by the author in earlier studies utilizing eudragit polymers3.. However the present work was aimed to study the effect of hydroxyl propyl methyl cellulose (HPMC) polymer grades such as HPMC K4M, HPMC K15M, and HPMC K100M in the development of transdermal film formulations of SH. The purpose of this study was to analyse the controlled release characteristics of the drug in HPMC films, since the polymer influences the drug release and thus alters the bioavailability of drug across the skin.

EXPERIMENTAL

Materials

Sertraline hydrochloride was obtained from Orchid Pharmaceuticals, Chennai. Hydroxy propyl methylcellulose

was received from Fourts India Laboratories Pvt. Ltd., Chennai. Polyethylene glycol 400, oleic acid and Propylene glycol were received from Qualigens fine chemicals, India. All other solvents used were of analytical grade and deionized water was used throughout the study.

Preparation of HPMC matrix film containing SH

The matrix type HPMC film was prepared by solvent evaporation method4. The polymer HPMC (K4M, K15M, and K100M) was dissolved in solvent mixtures of various proportions as given in Table 1. The solution was added with plasticizer PEG 400 and stirred at 25°C in a closed system. 10mg of SH was added, mixed and poured over a level of aluminium foil kept in a petridish (area 6cm2). The solvent was allowed to evaporate at room temperature. After 24h the films were collected, cut into 2cm^2 and stored in a desiccator for further studies.

Percentage Moisture Absorption

Films were weighed accurately (initial weight) and placed in a desiccator containing 100ml of saturated solution of sodium chloride that maintains 63% RH. After 72h, the films were taken out and weighed (final weight). The percentage moisture absorption was calculated using the formula5

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage Moisture Loss

The films were weighed accurately (initial weight) and kept in a desiccator containing 10g calcium chloride. After 72h, the films were taken out and weighed (final weight). The percentage moisture loss was calculated using the formula6

$$\text{Moisture loss (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Table 1. Formulation Composition of HPMC Films containing SH

Formulation	HPMC K4M(mg)	HPMC K15M (mg)	HPMC K100M (mg)	PEG 400	Acetone (ml)	Ethanol (ml)	Isopropyl alcohol (ml)	Water (ml)
S1	200	-	-	150% w/w of polymer mass	9	-	-	1
S2	200	-	-		-	8	-	2
S3	200	-	-		-	-	6	4
S4	-	200	-		9	-	-	1
S5	-	200	-		-	8	-	2
S6	-	200	-		-	-	6	4
S7	-	-	200		9	-	-	1
S8	-	-	200		-	8	-	2
S9	-	-	200		-	-	6	4

PHYSICOCHEMICAL EVALUATION

Film thickness

The thickness was assessed at three different points in the film using screw gauge (Mitutoyo, Japan).

Folding endurance

Folding endurance value denotes the ability of film to withstand rupture. A strip of film was cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Water Vapour Transmission (WVT)

For the determination of WVT, one gram of calcium chloride was weighed and placed in a previously dried empty vial having equal diameter. The polymer film was pasted over the vial with the help of silicon adhesive grease and the adhesive was set for 5min. Then the vials were accurately weighed and placed in a humidity chamber maintained at 68%RH. The vials were weighed again at the end of every day up to 7 consecutive days. An increase in weight was

considered as a quantitative measure of moisture transmitted through the film6

$$WVT = W/ST$$

Where, W- Increase in weight in 24h, S- Area of the film exposed (cm^2), T- Exposure time (h)

Tensile strength

Two ribbon shaped cuttings (4×3cm) from the film were prepared and fitted in a tensile strength apparatus (Instron 3369.UTM, Japan). The force and elongation were measured when the film broke. The tensile strength was calculated using the following equation7

$$\text{Tensile strength} = F/a.b\ (I+L/I)$$

Where, F- Force required to break, a- Width of the film, b- Thickness of the film, L- Length of the film, I-Elongation of film at break point.

Drug content

The films were cut into small pieces and added to a beaker containing 100ml of phosphate buffer pH 6.4. The mixture was stirred with a Teflon coated magnetic bead for 24h. The content was filtered using a Whatman filter paper. The filtrate was examined for drug content against the reference solution consisting of placebo film (containing no drug) at 239nm by UV spectrophotometer(UV – 1700, Shimadzu) after appropriate dilution.

In vitro Release of SH from HPMC matrix and its kinetics

The in vitro release was examined using a dissolution apparatus fitted with modified stainless steel disc assembly (USP Apparatus 5, paddle over disc). The HPMC film was mounted on the disc and placed at the bottom of dissolution vessel. The dissolution medium of pH 7.4 was equilibrated to 32±0.5°C, operated at 100rpm. Samples were withdrawn and replaced with equal volume of fresh buffer at appropriate time intervals up to 24h and analyzed for SH content at 239nm using UV spectrophotometer. The cumulative percentage released drug was plotted against time. To understand the kinetics and mechanism of drug release, the in-vitro release data were analyzed using kinetics models such as zero order, first order, Higuchi's, Hixson crowell and their co-efficient of regression (R2) values were calculated8. The 'n' value was obtained from Koresmeyer-peppas model to know the mechanism of drug release.

Ex vivo Permeation of HPMC matrix film containing SH

Skin preparation

A male rat was euthanized and the abdominal area was shaved and the skin was excised with a help of a scissor. The fat underneath the skin was removed using scalpel, washed with water and used immediately for permeation study.

Preparation of SH HPMC matrix film containing an enhancer

HPMC matrix along with plasticizer was prepared as stated in the preparation of matrix film. The enhancer mixture of propylene glycol (30%w/w) and oleic acid (1%) at a ratio of 1:5 was added to the matrix and stirred well for homogenous dispersion. This mixture was then poured over an aluminium foil placed in a petridish. The film was allowed to form over night. A film of defined area (4.9062cm2) was used for the study.

Permeation study

The study was performed using locally fabricated Keshary chien type diffusion cell of 50ml capacity. The skin was clamped between the donor compartment containing film and the receptor compartment containing phosphate buffer of pH 7.4 in such a way that the stratumcorneum side of skin faced the donor compartment. The samples were withdrawn from the receptor compartment at various time intervals up to 24h and same volume of fresh phosphate buffer was replaced every time9. The residual drug present in case of film was also analyzed at the end of study. The sample was analyzed at 239nm by UV spectrophotometer and the cumulative amount of SH permeated in the presence and absence of enhancer was determined and plotted against time. The permeability coefficient values were derived from the plot.

RESULTS

Physicochemical evaluation

The physicochemical properties of the SH films are given in Table 2.

In vitro Release of SH from HPMC matrix Film

The in vitro release profile of formulations is shown in fig 1-3. The formulation S4 (HPMC K15M, acetone & water) had produced a maximum SH release percentage (39.94% ± 0.543%) in a period of 24h.

The formulations yielded highest R2 value which was obtained by plotting square root of time against percentage drug released for the higuchi kinetic model. The value of n

Table 2. Physicochemical characterization of sertraline hydrochloride transdermal films

Formulation Code	Thickness (mm)	Folding Endurance (no's)	Moisture Absorption (%)	Moisture Loss (%)	Water Vapour Transmission (g/cm²)	Tensile Strength (MPa)
S1	0.12±0.05	254±1.76	2.86±0.02	3.91±0.01	1.42±0.012	7.85±0.14
S2	0.14±0.02	268±1.64	3.12±0.01	7.64±0.01	1.64±0.014	8.73±0.12
S3	0.15±0.01	274±1.43	2.54±0.02	5.71±0.03	0.53±0.017	7.92±0.21
S4	0.13±0.01	275±1.64	5.19±0.02	2.32±0.01	0.54±0.021	11.23±0.14
S5	0.13±0.03	282±2.12	2.83±0.02	4.42±0.03	3.12±0.014	10.34±0.27
S6	0.14±0.02	287±1.98	4.92±0.01	3.89±0.01	0.62±0.012	11.16±0.33
S7	0.16±0.03	289±1.64	3.89±0.02	2.64±0.02	2.43±0.011	6.45±0.52
S8	0.18±0.02	290±2.12	2.14±0.01	4.92±0.03	0.02±0.009	6.62±0.20
S9	1.19±0.03	294±1.64	3.24±0.03	6.24±0.03	0.64±0.004	6.02±0.055

Values are mean±S.D, n=6

Table 3. Release kinetics of sertraline hydrochloride films

Formulation	R^2 value of Release Kinetic models				
	Zero order	First order	Higuchi model	HixsonCrowell model	Koresmeyer peppas model - n value
S1	0.951	0.882	0.961	0.954	0.641
S2	0.843	0.907	0.944	0.850	0.678
S3	0.771	0.788	0.982	0.782	0.493
S4	0.829	0.839	0.912	0.836	0.882
S5	0.784	0.809	0.945	0.801	0.589
S6	0.931	0.940	0.943	0.937	0.883
S7	0.866	0.883	0.932	0.878	0.771
S8	0.921	0.930	0.944	0.927	0.866
S9	0.929	0.942	0.963	0.938	0.090

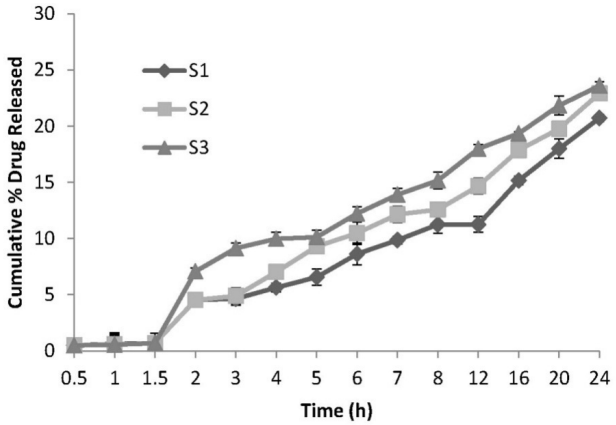

Fig 1: In vitro release of sertraline hydrochloride from HPMC matrix film S1, S2 and S3.

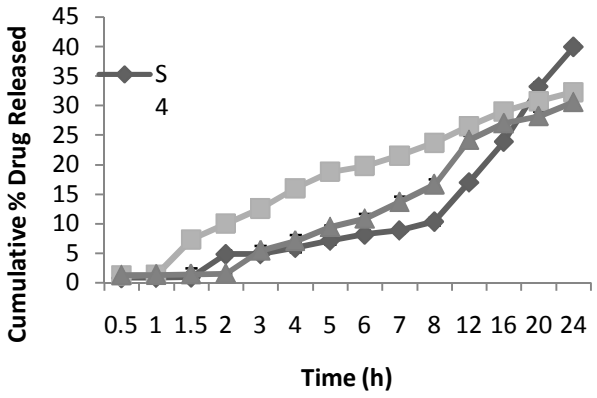

Fig 2: In vitro release of Sertraline Hydrochloride from HPMC matrix film S4, S5 and S6.

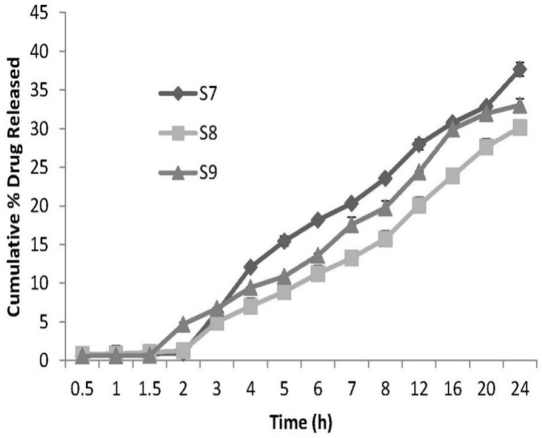

Fig 3: In vitro release of sertraline hydrochloride from HPMC matrix film S7, S8 and S9.

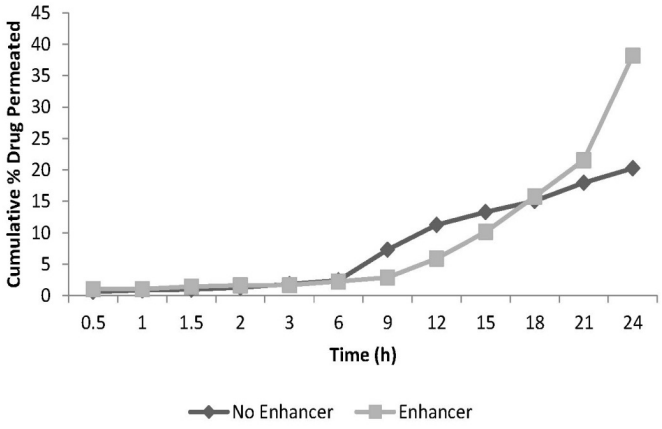

Fig 4: In vitro permeation of S4 in the presence and absence of enchancer

was >0.5 except formulation S3. The R2 and n values calculated are given in Table 3.

Ex vivo Permeation of SH from HPMC matrix film

The study was carried out for S4 which had produced a highest percentage drug release. The cumulative percentage of SH permeated through the rat skin was found to be 20.27%±0.05% in 24h. The permeation has increased to 38.19%±0.06% in the presence of enhancers in the film.

DISCUSSION

The prepared HPMC matrix films were found to be flexible, smooth and transparent with uniformity in thickness as reflected in low standard deviation. The film flexibility is reflected in tensile strength values which were found to lie between 7.02±0.12MPa to 12.23±0.16MPa. Folding endurance test results indicates the film integrity and that they would not break with general skin folding when applied on skin. Moisture absorption and moisture loss percentage of films showed the hydrophilic nature of HPMC polymer and it has been observed that this depends on the solvents employed in their preparation. This indicates uniform drug distribution in all the film formulations (S1 to S9).

No burst release had occurred and the release was slow and steady up to 24h of study. There was no much difference found in drug release when ethanol, isopropyl alcohol and water were used as solvents, whereas the use of acetone has resulted in higher drug release($P<0.5$). This might be due to the solubility characteristics of the drug in this mixture of solvents. It has been reported that the casting solvents employed in the preparation of film affect the crystallnity of drug in films[10]. A significant difference in drug release profile ($P<0.5$) was obtained for HPMC K100M, K15M and K4M polymers. These polymers possess high, medium and low viscosity respectively. The number indicates the viscosity in m.Pa.s, "K" denotes the hydroxyl propyl content of the polymer and the letter "M" indicates 1000 times. Hence, a fast release from a less viscous polymer HPMC K4M, a slow release from high viscous polymer HPMC K100M and an optimum of slow and steady release from medium viscous polymer HPMC K15M has been achieved. The process of drug release followed higuchi kinetic model. The mechanism of drug release was found to be non fickian diffusion as the value of n>0.5 except formulation S3. The permeation study clearly indicates that the addition of enhancers propylene glycol as solvent and oleic acid as fatty acid increases the cumulative percentage of SH permeation from the optimized formulation S4 by two fold ($P<0.5$), hence would helps to achieve therapeutic drug concentration in blood plasma. However, for the effect of other penetration enhancers and active penetration enhancement technologies could be adopted in future for the much enhanced permeation of SH.

CONCLUSION

The HPMC matrix film formulation S4 containing HPMC K15M, PEG as plasticizer, acetone and water as solvents in the presence of permeation enhancer had delivered SH transdermaly. The optimized film elicited sustained release characteristics. It has been suggested to utilize advanced penetration enhancing technologies for the much effective transdermal delivery of sertraline hydrochloride.

REFERENCES

1. Mamatha T, Venkateshwara rao J, Mukkanti K. Ramesh G. (2009) Current trends in biotechnology and pharmacy. 3(2): 1-16.
2. Ashvini S Kadam, Mukesh P Ratnaparkhi, Shilpa P Chaudhary. (2014) Int. J. Res. Dev. Pharm. L. Sci. 3(4): 1042-1053.
3. Vijaya R, Ruckmani K. (2011) DARU. 19(6): 424 - 432.
4. Narashima Murthy S, Shobha Rani R, Hiremath. (2002) AAPS Pharm Sci Tech. 2(1): 1-5.
5. Sanjay Dey, Annaya Malgope. (2010)Int. J. Phram. Pharmaceu. Sci. 2(1): 137-142.
6. Qing Li, Hiroyuki, Tsuji, Yukio, Kato, Yoshimichi, Sai, Yoshiyuki, Kubo, Akira, Tsuji. (2006) J. Control. Rel. 110: 542-546.
7. Ramesh Gannu, Vamshi Vishnu Y, Kishan V, Madhusudhan Rao Y. (2007) Curr. Drug Deliv. 4: 69-76.
8. Chandak AR, Priya Ranjan, Prasad Verma. (2008) Journal of the Pharmaceutical Society of Japan. 128(7): 1057-66.
9. Shaila Lewis, Pandey S, Udupa N. (2006) Ind. J.of Pharm. Sci. 68: 179-184.
10. Satyanarayan Pattnai K, Kalpana Swain, Subarata Mallick, Zhiqun Lin. (2011) Int.J.Pharm. 406: 106-110.

