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Research Article

EFFECT OF POLYMERS AS MATRIX SYSTEM IN FORMULATION OF SUSTAINED RELEASE THEOPHYLLINE MATRIX TABLET

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ABSTRACT

The aim of present study was to develop sustained release matrix tablets of Theophylline, a bronchodilator used in the treatment of asthma. To study the effect of type, viscosity and concentration of polymer on drug release; the matrix tablets were formulated by wet granulation method using hydrophilic polymer hydroxypropylmethylcellulose (HPMC K4M, HPMC K15M and HPMC K100M), hydrophobic polymer (Cetostearyl alcohol and Bees wax) and combination of both the polymers (HPMC K100M and Cetostearyl alcohol) as the matrix material in different proportions. PVP K25 in IPA and water (9:1) was used as granulating fluid. Formulations were subjected for pre-compressional and post-compressional parameters. The granules showed good flow properties and compressibility index. Drug release studies indicated that viscosity of HPMC was inversely proportional to the drug release from tablet. Matrix tablet when prepared using combination of polymers (FC1 and FC2) sustained the release of drug. In case of formulation containing combination of HPMC K100M and Cetostearyl alcohol (FC2), the drug release was found to be dependent on the relative proportions of HPMC K100M used in the matrix system. The results of the *in vitro* dissolution study indicated that combined formulations showed sustained drug release. Drug release followed Higuchi model indicating drug release by combination of diffusion of drug as well as erosion of tablet surface.

Keywords*:* Theophylline, Sustained release matrix tablet, *In- Vitro,* Higuchi model, Hydrophilic polymer, Hydrophobic polymer.

INTRODUCTION

Tablets are widely prescribed and accepted oral dosage form which offers advantages such as taste masking, accuracy of dose, ease of administration, protection of drug against temperature, humidity, oxygen, light and stress during transportation.[1] Sustained release drug delivery systems maintain therapeutic blood levels uniform for extended period of time. The effectiveness of delivery system is increased due to reduced frequency of dosing, minimizing dose and side effects of drug. The drug release from matrix tablets is sustained by dispersing the drug in polymeric system.[2]

Theophylline is used in treatment of COPD (Chronic Obstructive Pulmonary Diseases) mainly in bronchial asthma. It is administered as conventional tablets in a dose of 400 mg to 800 mg daily in divided doses. It is quickly absorbed and eliminated with a plasma half life of 6 to 8 h and t_{max} of 1 to 2 h. Due to rapid absorption and elimination of drug the plasma concentration-time profile of its conventional system results in a typical peak-valley curve phenomenon making it difficult to maintain a steady state plasma level. Hence, repeated dosing is required to maintain uniform concentration of drug in body to produce its therapeutic effect.[3, 4] In the present study, the effect of hydrophilic, hydrophobic polymer alone and in combination was investigated in formulation of sustained release matrix tablet of Theophylline.

MATERIAL AND METHODS

Material

Theophylline was generously gifted by Cipla Pvt. Ltd. Goa, India. Hydroxypropylmethyl cellulose (HPMC) K4M, HPMC K15M and HPMC K100M were provided by Colorcon Asia Pvt. Ltd, Verna, Goa, India. Cetostearyl alcohol (CSA), Bees wax (BW), starch and talc were provided by S. D. Fine Chem. Ltd., Mumbai, India. Lactose, Magnesium Stearate and Poly vinyl pyrrolidone K25 were obtained from Loba chemical Pvt. Ltd., Mumbai, India. Isopropyl alcohol was obtained from Spectrochem Pvt. Ltd., Mumbai. All other chemicals were of analytical grade used as received.

Table 1: Composition of matrix tablets of Theophylline

Ingredients	F1	F2	F3	F4	F5	FC1	FC2
Theophylline (mg)	400	400	400	400	400	400	400
HPMC K4M (mg)	200	-	-	-	-	-	-
HPMC K15M (mg)	-	200	-	-	-	-	-
HPMC K100M (mg)	-	-	200	-	-	100	150
Cetostearyl alcohol (mg)	-	-	-	200	-	100	50
Bees Wax (mg)	-	-	-	-	200	-	-
Lactose (mg)	25	25	25	25	25	25	25
Starch (mg)	15	15	15	15	15	15	15
Talc (mg)	5	5	5	5	5	5	5
Magnesium stearate (mg)	5	5	5	5	5	5	5
PVP K25 (%)	10	10	10	10	10	10	10
IPA:Water (9:1)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	650	650	650	650	650	650	650

* Quantity in mg for one tablet

Methods

Preparation of matrix tablet

Matrix tablets were prepared by wet granulation method using polymer and other excipients given in Table 1. All ingredients were weighed accurately and mixed thoroughly for 5 minutes to obtain a uniform mixture of powder and blended homogeneously for 15 minutes by triturating in a glass mortar and pestle. Granulating fluid prepared by mixing PVP K25 in IPA and water in the ratio of 9:1 was added into the mixture of powder till a coherent mass was formed. Then it was passed through sieve # no. 10 to form granules. The collected granules were dried at 40 °C ± 2 °C for 1 h, and finally passed through sieve # no. 12. Granules were lubricated by blending with magnesium stearate and talc. Prepared granules were

evaluated for pre-compressional parameter. Above granules were compressed in Tablet Compression Machine (Rimek tablet press, Ahmadabad) using 12 mm punch size, by adjusting average weight to 650 mg and tablets obtained were evaluated for post-compressional parameter.

Evaluation of granules[5]

Both loose bulk density (LBD) and tapped bulk density (TPD) were determined by using bulk density apparatus (Konark instruments Ind. Mumbai). After 100 taps, the tapped volume of packing was noted. LBD and TPD were calculated by using formulae:

LBD = weight of the powder / volume of packing

TBD = weight of the powder / tapped volume of packing

The compressibility index was determined by

Carr's index (%) = [(TBD-LBD)] / TBD

The Hausner's ratio was determined by

Hausner's ratio = TBD / LBD

The angle of repose of granules was determined by funnel method. Angle of repose was calculated using the equation

$$\theta = \tan^{-1}(h/r)$$

Where, θ is angle of repose, h is height of powder cone in cm and r is radius of powder cone base in cm.

Evaluation of matrix tablets

The formulated matrix tablets were evaluated for hardness, weight variation, thickness, diameter, friability and drug content. Tablet hardness was determined for six tablets using a Monsanto hardness tester (Campbell electronics, Mumbai)[5]. The weight variation was evaluated on 20 tablets using an electronic balance and the test was performed according to the official method.[6] The thickness and diameter was determined for three tablets with the help of a calibrated dial Vernier caliper. Friability was determined as per IP guidelines, tablets corresponding to about 6.5 g were taken and placed in a Roche Friabilator (Electro lab, Mumbai) and rotated at 25 rpm for a period of 4 min. The percentage weight loss was determined using formula:

$$F = \left[\frac{Wt_{Initial} - Wt_{Final}}{Wt_{Initial}}\right] \times 100$$

Drug content of the matrix tablets was determined by weighing and finely grinding 10 tablets of each batch. Weight of powder equivalent to 10 mg of Theophylline was accurately weighed, suspended in 100 ml of phosphate buffer pH 7.4 and shaken for 15 min. The solution was filtered and 5 ml of filtrate was diluted to 50 ml with same medium and analyzed at 272 nm using UV/VIS spectrophotometer (Shimadzu, Japan) against a reagent blank and the content was compared from a calibration curve prepared with standard Theophylline in the same medium.[6]

Scanning electron microscopy

The dried samples were coated with gold using JOEL JFC 110E Ion sputter coater for about 2 min to obtain a coating thickness of about 200 A°. Surface morphology of tablets was determined by taking micrographs at an accelerating voltage of 15 KV with Joel JSM-6360 (SEM), Germany.

Swelling characteristics

Matrix tablets were introduced into vessel of dissolution apparatus having 500 ml of dissolution media (pH 7.4). The tablets were removed at interval of 0.5 h for 3 h, allowed to drain and thickness, radius and swollen weight of each tablet was determined.

Infrared spectroscopic studies

Fourier-transformed infrared (FT-IR) spectroscopic studies were performed to check the compatibility between drug and polymer in formulations. The FT-IR spectra of drug alone and with formulation polymers were obtained by KBr disk method and compared with the standard FT-IR spectrum of the pure drug.

***In vitro* release studies**

In vitro release studies were carried for matrix tablet using USP XXIII dissolution test apparatus (Basket Type). Initially tablets were placed in 900 ml of 0.1 N HCl for 2 h maintained at 37±0.5 °C and then in phosphate buffer pH 7.4 for up to 24 h. The basket was rotated at 50 rpm. 5 ml sample was withdrawn manually after initial 0.5 h in 0.1 N HCl and after 1 h interval in phosphate buffer pH 7.4 up to 24 h with replacement of fresh buffer to maintain sink condition and analyzed for drug content after diluting with the 100 ml of respective medium, using a UV-visible spectrophotometer at 272 nm. The actual content in samples was obtained from a calibration curve prepared with standard Theophylline. Dissolution studies were carried out in triplicate.

Release Kinetics[7, 8, 9]

The rate and mechanism of drug release from prepared matrix tablets was analyzed by fitting dissolution data into Zero-order, First order, Higuchi and Korsemeyer Peppas model. The best formulation was compared with marketed product formulation for drug release study.

RESULT AND DISCUSSION

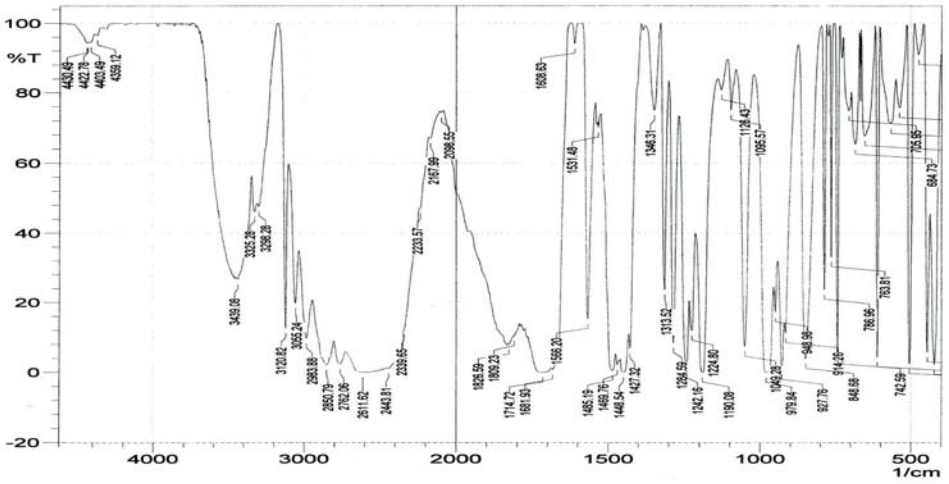
A successful attempt has been made to formulate sustained release matrix tablets of Theophylline using hydrophilic, hydrophobic and combination of both polymers. The influence of polymer used on drug release from the formulations was investigated. Total seven formulations were prepared. F1 to F3 were prepared using different grades of hydrophilic polymers HPMC K4M, HPMC K15M and HPMC K100M respectively. F4 to F5 were prepared using different hydrophobic polymers Cetostearyl alcohol and Bees wax respectively. FC1 and FC2 were prepared by combination of hydrophilic polymer HPMC K100M and hydrophobic polymer CSA.

Compatibility study of drug and polymer were conducted by employing I.R. Spectral studies [Figure 1]. Following characteristic peaks were observed with pure Theophylline as well as the formulations containing Theophylline: C=O - (stretching) 1714.72 and 1681.93 cm^{-1}, C-H - (stretching) 3055.24 cm^{-1}, 1^0 N-CH_3 (Stretching) in range of 3250-3550 cm-1 and 2^0 N-CH_3 (Stretching) in range of 3300-3400 cm^{-1}, which confirmed drug-polymer compatibility.

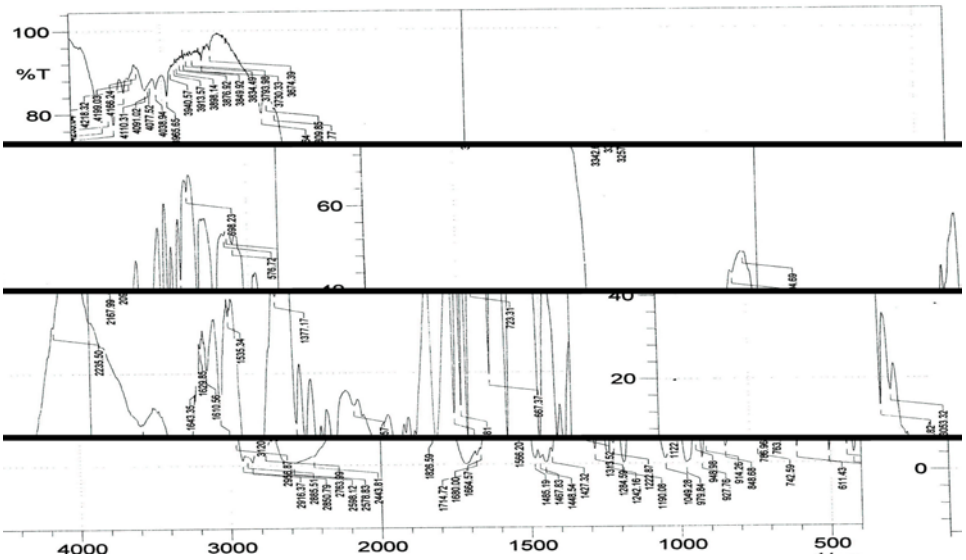
Table 2: Pre-Compression evaluation of granules and powder blends

Formulation	F1	F2	F3	F4	F5	FC1	FC2
Bulk Density (g/ml)	0.443±0.03	0.417±0.01	0.449±0.03	0.444±0.03	0.423±0.01	0.464±0.04	0.462±0.06
Tapped density (g/ml)	0.511±0.04	0.486±0.03	0.494±0.03	0.527±0.02	0.495±0.05	0.569±0.05	0.540±0.05
Angle of Repose (°.')	26.78±0.90	28.40±0.65	29.76±0.71	28.85±1.01	26.39±0.86	27.99±0.97	29.06±0.68
Carr's Index	11.71±0.96	11.63 0.78	13.53±0.67	12.52±0.69	13.57±0.87	13.01±0.42	12.51±0.38
Hausner's Ratio	1.166±0.06	1.165±0.05	1.190±0.06	1.176±0.05	1.190±0.04	1.183±0.06	1.172±0.04

All values are Mean±S.D. of triplicate



a) FT-IR spectra of pure Theophylline



b) FT-IR Spectra of Formulation FC3

Fig. 1: FT-IR Spectra of pure drug and with Formulations a) Pure drug Theophylline b) Formulation FC3

Pre compressional parameters are the key factors in tablet production. Thus granules and powder blends were evaluated for LBD, TBD, compressibility index, angle of repose and Hausner's Ratio (Table 2). The LBD and TBD of granules ranged from 0.417±0.01 g/ml to 0.464±0.04 g/ml and 0.486±0.03 g/ml to 0.569±0.05 g/ml respectively. The LBD and TBD were found to be increased when combination of hydrophilic and hydrophobic polymers was used (FC1-FC2). The angle of repose for all formulated granules was < 30 ° indicating good flow properties. This was further supported by lower compressibility index and Hausner's ratio values.

The hardness and friability of the formulated matrix tablets were ranged from 4.8±0.30 kg/cm² to 6.2±0.3 kg/cm² and 0.11±0.03 % to 0.25±0.02 % respectively (Table 3). The drug content of all the formulations was ranging from 96.21±0.56 % to 99.73±0.77 % (Table 3). The thickness of tablets was ranged from 4.10±0.1 mm to 4.27±0.2 mm (Table 3).

Swelling characteristics were observed by measuring the initial surface area and weight of all the formulations and the change in surface area and weight observed after hydrating for 3 h (Table 4).

Table 3: Post-Compression evaluation of matrix tablets

Formulation	F1	F2	F3	F4	F5	FC1	FC2
Thickness (mm)*	4.17±0.29	4.10±0.10	4.23±0.21	4.03±0.06	4.13±0.23	4.25±0.15	4.27±0.25
Weight (mg)**	652.7±4.33	655.3±4.92	649.7±4.83	652.3±4.90	650.4±6.20	654±4.09	653±4.97
Hardness (kg/cm²)*	5.16±0.28	4.80±0.30	5.20± 0.80	5.50±0.50	5.70±0.60	5.80±0.30	6.20±0.30
Friability (%) ***	0.12±0.01	0.154±0.06	0.145±0.04	0.256±0.20	0.111±0.03	0.129±0.04	0.136±0.05
Drug Content (%)*	96.21±0.56	98.77±0.77	98.13±0.47	98.06±0.43	97.10 ±0.34	99.73±0.77	99.03±0.30

*Mean±S.D. (n=3), ** Mean±S.D. (n=10), *** Mean±S.D. (n=6)

Swelling characteristics of formulations indicated that tablet surface area and weight after hydration for 3 h were more in formulations containing hydrophilic polymer than those containing hydrophobic polymer and were found to be increased with increase in viscosity of hydrophilic polymer HPMC (F1 to F3). In formulations containing combination of both the

polymers swelling surface area was greater and was found maximum in FC2 containing more amount of hydrophilic polymer. This may be due to increase in gel strength and dissolution media holding capacity of the tablet.[10] It was observed that swelling in axial direction was faster than radial direction [Figure 2]. More increase in axial swelling might be due to compression force and gravitational force acting in axial direction of tablets.[11] Figure 3 shows the SEM images of formulation FC2 of matrix tablet surface at 500X, 1000X and 2000X resolutions. Tablets thickness and diameter indicated that die fill was uniform and compression force was constant. On visual inspection tablets appear smooth without any fracture.

Table 4: Swelling index of Formulated Matrix Tablets

Formulation	Surface Area (mm^2)		Weight (mg)	
	Before Swelling	After Swelling	Before Swelling	After Swelling
F1	312.15 ± 2.05	484.71± 1.99	652.67 ± 2.53	1151.00 ± 2.52
F2	305.50 ± 2.78	494.86 ± 2.18	654.00 ± 2.05	1164.00 ± 1.53
F3	316.17 ± 2.29	500.50 ± 2.21	655.33 ± 2.42	1189.00 ± 2.52
F4	301.38 ± 2.61	411.88 ± 2.94	653.33 ± 2.89	968.00 ± 2.08
F5	310.91 ± 2.51	405.96 ± 2.65	653.00 ± 2.65	848.00 ± 1.53
FC1	320.05 ± 1.11	507.42 ± 2.18	654.05 ± 1.73	1140.00 ± 1.53
FC2	320.97 ± 2.42	567.47 ± 2.18	655.33 ± 1.53	1298.00 ± 2.53

Values are Mean±S.D. of triplicate

The *in vitro* dissolution studies showed the effect of different viscosity grades of HPMC (K4M, K15M and K100M) on the dissolution is shown in [Figure 4]. Release rate varied among HPMC viscosity grades as the viscosity of HPMC was increased the release rate extended for more than 12 h. *In vitro* release data showed 97.78 % , 86.39 % and 78.27 % cumulative drug release at the end of 12 h from low (F1), medium (F2) and high (F3) viscosity grade of formulations containing HPMC respectively. Thus, viscosity of HPMC is inversely proportional to the rate of drug release from formulation; increase in viscosity of HPMC showed sustained drug release.[12]

Formulation F4 and F5 showed 76.74% and 83.36 % cumulative drug release respectively at the end of 12 h indicating reduced rate and extent of drug release due to reduced porosity of the matrix [Figure 4]. It was observed that the drug release was sustained from formulations containing hydrophobic polymer CSA as compared to hydrophilic HPMC polymer. This may be due to hydrophobic nature of CSA, which restrict the penetration of the medium inside the matrix and restricts the formation of gel layer around the matrix as present in hydrophilic HPMC.[13] % cumulative drug release from FC1 and FC2 was showed 91.75 % at the end of 20 h and 98.29 % at the end of 24 h respectively with initial burst release of 20-35 % [Figure 5]. Thus incorporation of hydrophobic polymer along with hydrophilic polymer have better drug release retarding ability as compared to tablets formulated using hydrophilic and hydrophobic polymer alone.

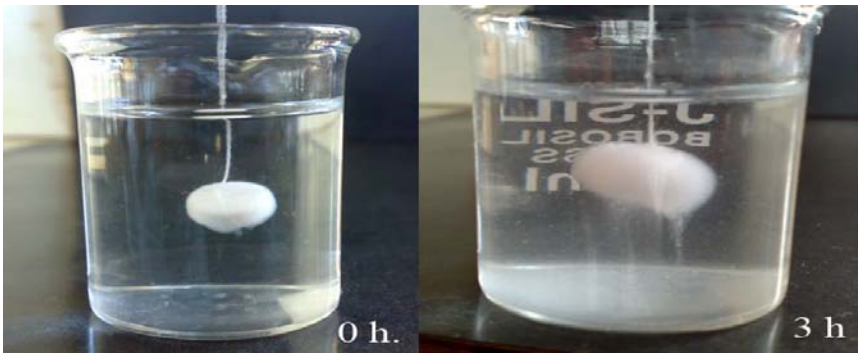
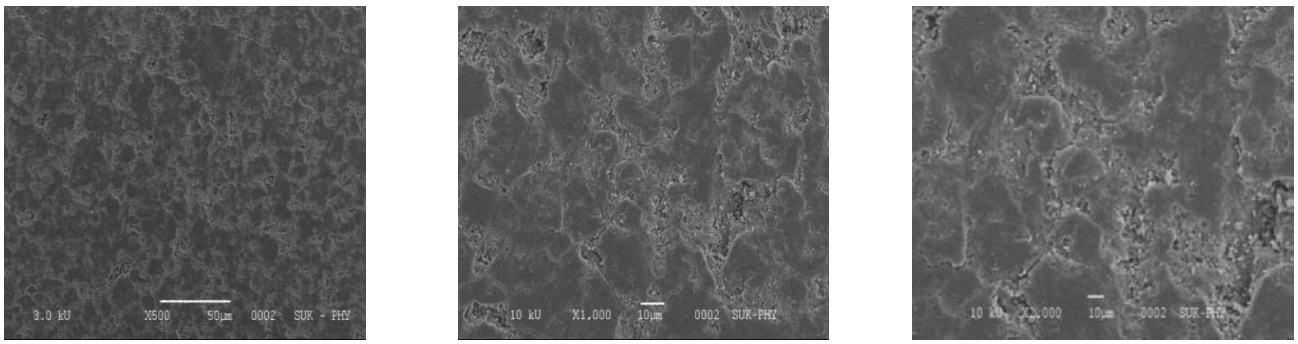


Fig. 2: Swelling characteristics of Formulation FC3



I: 500X **II: 1000X** **III: 2000X**

Fig. 3: SEM images of Formulation FC2 at 500X, 1000X & 2000X

Formulation FC2 containing HPMC K100M and CSA in concentration of 1:0.375:0:125 (Drug : HPMC K100M : CSA) was selected as best formulation and compared for drug release with marketed formulation. Marketed formulation showed 96.14% drug release at the end of 16 h. Formulation FC2 showed better sustained drug release than marketed formulation, shown in [Figure 6].

In order to describe the drug release kinetics of drug from formulations as well as in the marketed preparation, various equations were used. Data was analyzed for kinetic models and results tabulated in Table 5.

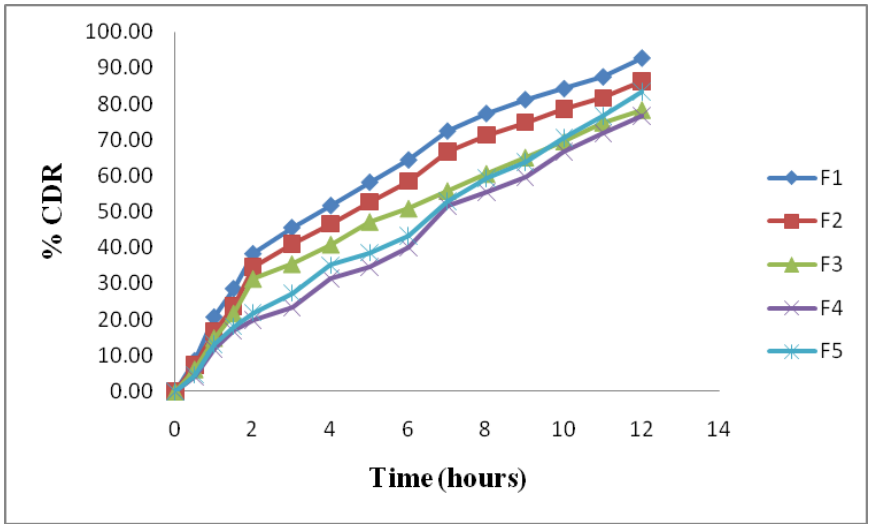


Fig. 4: Effect of hydrophilic and hydrophobic polymer on *in vitro* drug release

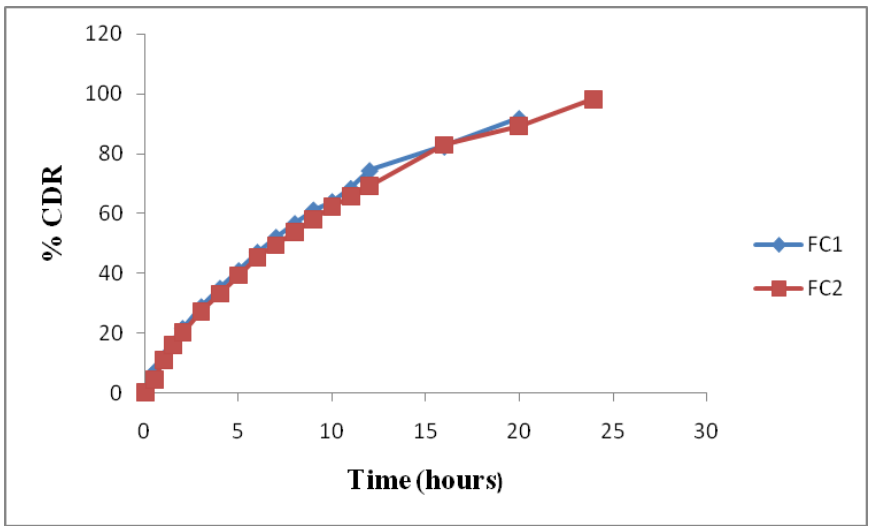


Fig. 5: Effect of combined polymrs on *in vitro* drug release

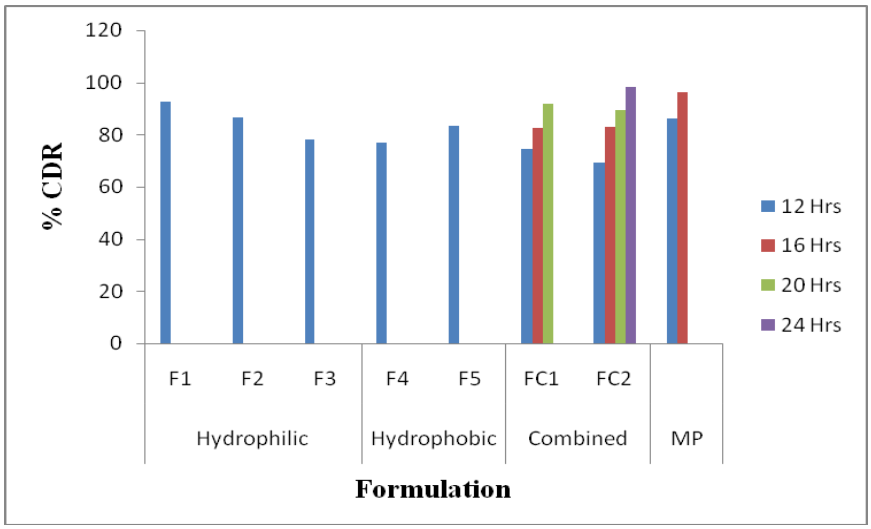


Fig. 6: Comparative *in vitro* drug release of Formulatd Matrix Tablets and Marketed product

The dissolution data of all combined formulations when fitted in accordance with first order equation, a linear relationship was obtained with 'r' (correlation coefficient) value close to unity, showing that the release was an apparent first-order process.[14] To find out exact mechanism, dissolution data of all formulations were fitted in Higuchi square root equation and Korsmeyer-Peppas equation. The formulations in this study were best expressed by Higuchi's classical diffusion equation, as the plots of Higuchi model showed high linearity (r: 0.9783 to 0.9994). The linearity of the plot indicated that drug release from the matrix occurred by combination of two mechanisms, diffusion of drug from tablet matrix and erosion of tablet surface. Thus amount of drug released was dependent on the matrix drug load[15]. To confirm the diffusion mechanism, the data was fitted to Korsmeyer-Peppas model. The formulations showed good linearity (r: 0.9607 to 0.9958). In Korsmeyer-Peppas model, 'n' is the diffusional exponent indicative of mechanism of drug release.[16] The n values for all formulations ranged from 0.6715 to 0.8339, indicating that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.89$). Based on the n values, it was observed that drug release from the matrix occurred by combination of two mechanisms, diffusion of drug from tablet matrix and erosion of tablet surface. [17, 18]

Table 5: Model Fitting of Release Profile of Formulated Matrix Tablets

Formulations		F1	F2	F3	F4	F5	FC1	FC2	MP
Zero order r		0.9431	0.9491	0.9600	0.9923	0.9932	0.9611	0.9684	0.9837
First order r		0.9794	0.9927	0.9886	0.9744	0.9551	0.9963	0.9901	0.8595
Higuchi's r		0.9930	0.9940	0.9937	0.9783	0.9809	0.9971	0.9994	0.9651
Korsmeyer-	R	0.9607	0.9665	0.9614	0.9774	0.9788	0.9958	0.9809	0.9934
Peppas	N	0.6715	0.7108	0.7137	0.8339	0.8141	0.7284	0.8014	0.6968

CONCLUSION

Matrix system using hydrophilic, hydrophobic and combination of polymers successfully provided sustained release of drug from matrix tablets of Theophylline. Increase in the viscosity of polymer showed sustained drug release from the formulation. Combination of hydrophilic polymer hydroxypropylmethylcellulose (HPMC K100M) and hydrophobic polymer Cetostearyl alcohol (CSA) in concentration of 1:0.375:0:125 (Drug: HPMC K100M: CSA) were effective in providing sustained release of Theophylline for up to 24 hours. Hence sustained release matrix system could be favorable to maintain drug concentration for longer duration of time.

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