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DEVELOPMENT AND EVALUATION OF FLOATING SUSTAINED RELEASE BILAYER TABLETS CONTAINING TRIMETHOPRIM

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ABSTRACT

Trimethoprim is a class of antibacterial drug. It has been used in the treatment of bladder infections. Other uses include for middle ear infections and traveler's diarrhea. Bilayer floating tablets of Trimethoprim were developed by direct compression method. Immediate release layer contains 50mg of drug and super disintegrant sodium starch glycolate, serves the purpose of loading dose. Sustained release layer contained HPMC K100, natural polymers like xanthan gum, guar gum, locust bean gum, karaya gum release the drug for 12 hrs time. Sodium bicarbonate and citric acid are used to produce effervescence. Floating lag time of optimized tablet is 92 sec, whereas floating duration is more than 12 hrs. FTIR results revealed that there was no interaction between drug and HPMC K100 / xanthan gum. The post compression parameters of developed tablet are satisfactory. In this study it was confirmed that the formulations containing HPMC K100, have shown better floating properties and finally the formulation containing a combination of HPMC K100 and Xanthan Gum in 3:1 ratio, has shown slower *in-vitro* drug release properties. The release kinetics of optimized formulation prepared with the combination of HPMC K100 and xanthan gum followed zero order kinetics.

KEYWORDS: Floating Bilayer Tablet, Trimethoprim, HPMC K4M, Xanthan Gum, FTIR.

INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages.[1] Sustained release tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs.[2] Oral drug delivery continues to rise in popularity as formulation scientists look for ways to control drug release and improve patient convenience. However, developing oral sustained release tablets for water soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these water-soluble drugs if not formulated properly. may readily release the drug at a faster rate and produce a toxic concentration of drug on oral administration.[3]

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets allows for designing and modulating the dissolution and release characteristics.[4] The term bilayer tablets containing subunits that may be either the same (homogeneous: one layer of drug for immediate release while second layer for sustained release) or different (heterogeneous: sequential release of two drugs in combination or separate two incompatible substances).[5] The important advantages of bilayer tablets are ability to combine different release rate IR and SR in the same tablet for chronic condition requiring repeated dosing; retain potency and ensure dose accuracy; blood level of a drug can be held at consistent therapeutic level for improved drug delivery, accuracy and safety; reduction of adverse effects.[6,7]

Trimethoprim binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). THF is an essential precursor in the thymidine synthesis pathway and interference with this pathway inhibits bacterial DNA

synthesis. Trimethoprim's inhibitory activity for bacterial dihydrofolate reductase is sixty thousand times greater than for human dihydrofolate reductase. Sulfamethoxazole inhibits dihydropteroate synthase, an enzyme involved further upstream in the same pathway. Trimethoprim and sulfamethoxazole are commonly used in combination due to possible synergistic effects, and reduced development of resistance. This benefit has been questioned.

MATERIALS AND METHOD

The chemicals used in this study were pure drug like Trimethoprim (Yarrow chemicals) and polymers like HPMC K4M, Xanthan gum, Guar gum, Karaya gum, Locust bean gum and other excipients like micro crystalline cellulose, magnesium stearate, talc, sodium bicarbonate, citric acid (Yarrow chemicals)

Pre-formulation study: Pre-formulation studies were conducted to confirm the compatibility of drug with polymers used. These studies were conducted by using FTIR spectrophotometer. In this method, the IR spectra of pure drug, physical mixtures containing drug and polymers (1:1) and tablet triturate were analyzed.

Evaluation of flow properties: Prepared powder blend of the different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index.

Preparation of floating bilayer tablets

The drug and excipients mentioned in Table 1 were passed through a 60 # size mesh prior to the preparation of the dosage form. All the ingredients sufficient to produce 20 tablets are weighed separately and mixed thoroughly for 10mi the mixture of first layer was subjected to slight compression to using ten station rotary tablet machines

The drug and excipients mentioned in Table 2 were passed through a 60 # size mesh prior to the preparation of the dosage form. All the ingredients were weighed separately and mixed thoroughly for 10 min. This mixture is placed over the first layer and subjected for final compression to produce tablet with 6±0.5 Kg/cm^2 hardness. Bilayer tablet containing immediate release layer (IR) and sustained release layer (SR) is termed as formulations F1, F2 and so on.

Table 1: Formulation of sustained (SR) and immediate (IR) drug release layers of Dothiepin HCL bilayer tablet. Formulation for immediate release layer.

Ingredients	Weight in (mg)
Trimethoprim	50
Sodium starch glycolate	10
Micro crystalline cellulose	64
PVP	15
Magnesium stearate	5
Talc	5
Sunset yellow	1
Total	150

Table 2: Formulation of Sustained Release Layer of Trimethoprim (Maintenance Dose).

Ingredients	Weight in (mg)									
	1	2	3	4	5	6	7	8	9	10
Trimethoprim	150	150	150	150	150	150	150	150	150	150
HPMC K100	100	-	-	-	75	-	75	75	50	50
Xanthan gum	-	100	-	-	25	-	-	-	25	-
Guar gum	-	-	100	-	-	75	25	-	25	25
Karaya gum	-	-	-	100	-	25	-	25		25
Citric acid	15	15	15	15	15	15	15	15	15	15
Sodium bicarbonate	35	35	35	35	35	35	35	35	35	35
MCC	20	20	20	20	20	20	20	20	20	20
Mg. Stearate	5	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3	3

Evaluation

Hardness test: The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2.

Friability test: Tablet strength was tested by Roche friabilator. Pre-weighed tablets were allowed for 100 revolutions (4 min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The % friability was then calculated by,

$$F = \frac{(W\ initial) - (W\ final)}{(W\ initial)} \times 100$$

Uniformity of weight: 20 tablets from each of the formulation were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, and JAPAN). The average weights for each brand as well as the percentage deviation from the mean value were calculated.

Drug content uniformity

Accurately weighed quantity of the powder tablet equivalent to 20mg of the drug and 80mg of tablet powder was transferred to 100ml volumetric flask separately. 50ml of buffer solution of pH 1.2 was added. And then the volume was made up to 100ml with the same buffer solution, mixed solution was filtered through the membrane filtered. 5ml of the filtrate was diluted to 50 ml with same buffer solution and examined under U.V Spectrophotometry at 288nm.

***In vitro* drug release**

The release of Trimethoprim from floating tablets was determined by using dissolution type-II test apparatus. The dissolution test was performed using 900 ml 0.1N HCl solution at 37 ± 0.5ºC temperature and at 50 rpm. At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbance of the diluted samples was measured at 288 nm for Trimethoprim by using UV spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from standard curve. Dissolution test was continued for 12 hours using pH 6.8 phosphate buffer.

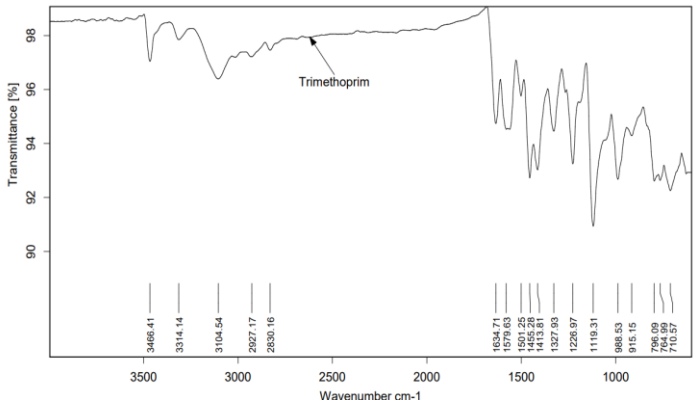
RESULTS AND DISCUSSION

The standard graph of Trimethoprim has shown good linearity with r2 value 0.997 in pH 6.8 buffer solution which suggests that it obeys the “Beer-Lambert’s law”

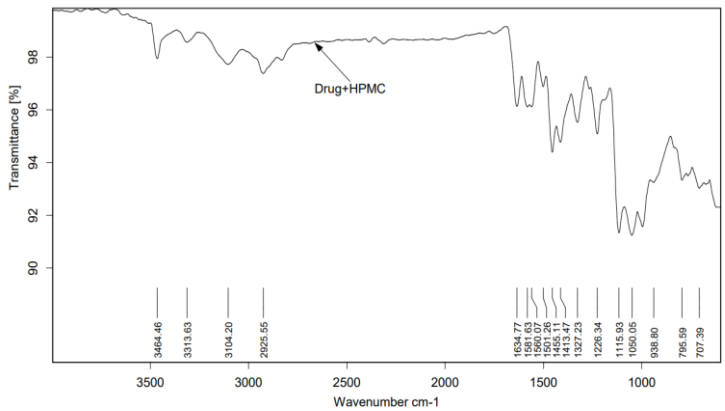
FTIR

Drug polymer interaction was checked by comparing the IR spectra of the formulations with the IR spectra of the pure drug. There was no significant change in the functional groups between the IR spectra of the pure drug and also no additional peaks were seen in the selected formulations. This confirms that no interaction between drug and excipients.

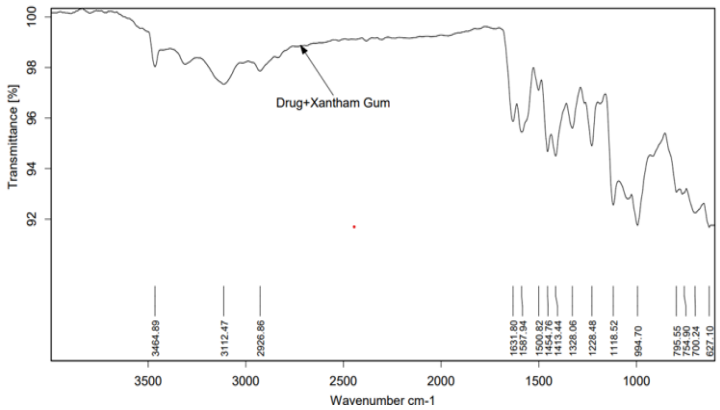
Ftir of Drug and Polymer interaction



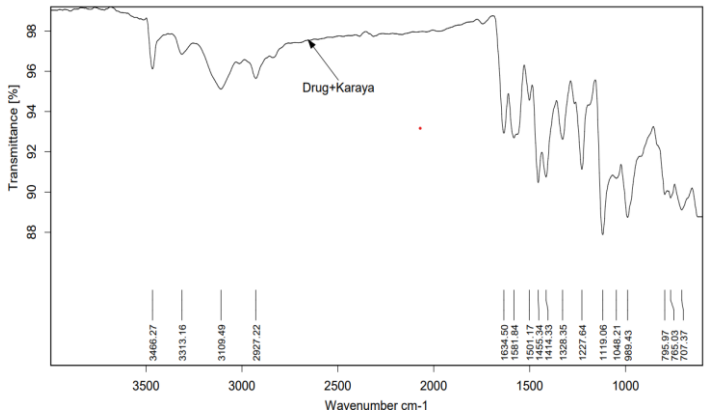
FT-IR of Trimethoprim.



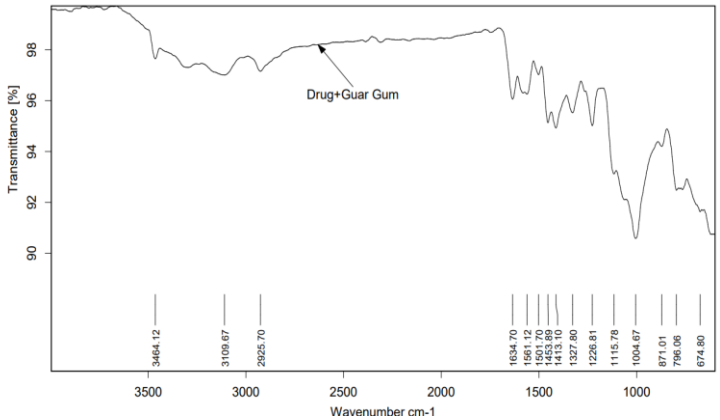
FT-IR of Trimethoprim+HPMC K100.



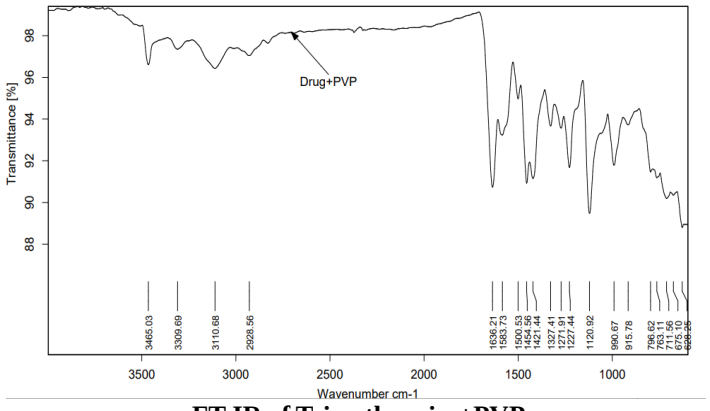
FT-IR of Trimethoprim +XANTHAN GUM.



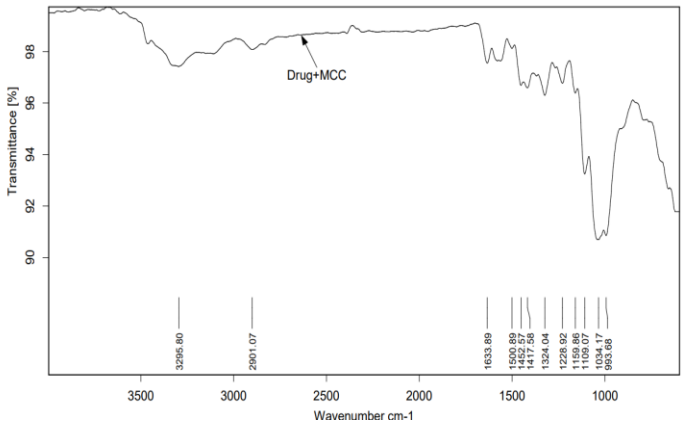
FT-IR of Trimethoprim+GUAR GUM.



FT-IR of Trimethoprim+KARAYA GUM.



FT-IR of Trimethoprim+PVP.



FT-IR of Trimethoprim+MCC.

Evaluation of bilayer tablet

The Trimethoprim tablet was evaluated for hardness, thickness, friability, weight variation and drug content uniformity. The hardness was in the range of 6.1 to 6.7 kg/cm^2, which was in accordance with the bi-layer tablet. The thickness was from 3.54 to 3.83mm suggested uniformity in thickness for bi-layer tablet. The friability was less than 1% indicated good handling of the layer. The weight variation results suggested uniformity in weight of layers.

Table 3: Pre-compression parameters for Trimethoprim immediate Release and Sustained release layers.

Batchcode	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index	Hausnr Ratio	Angle of Repose(ɵ)
SR1	0.476±0.05	0.545± 0.02	12.45±0.06	1.12±0.05	25.20±0.01
SR2	0.568±0.04	0.651±0.02	14.33±0.04	1.18±0.06	22.56±0.02
SR3	0.502±0.04	0.571±0.02	11.82±0.03	1.13±0.04	23.42±0.02
SR4	0.515±0.07	0.595±0.03	13.95±0.04	1.15±0.04	24.40±0.02
SR5	0.519±0.04	0.591±0.02	12.86±0.03	1.13±0.05	24.40±0.02
SR6	0.499±0.02	0.582±0.04	12.08±0.02	1.15±0.08	23.10±0.03
SR7	0.531±0.04	0.610±0.03	13.76±0.02	1.15±0.07	23.51±0.04
SR8	0.532±0.03	0.591±0.03	14.25±0.03	1.13±0.05	24.42±0.02
SR9	0.488±0.03	0.553±0.03	11.43±0.03	1.12±0.07	22.90±0.01
SR10	0.568±0.04	0.651±0.02	14.33±0.04	1.18±0.06	22.56±0.02

Post compressional parameters

Table 4: Post compressional parameters of trimethoprim bilayer tablets.

Batchcode	Hardness (kg/cm^2)	Thickness(mm)	Friability %	Weight Variation (mg)	Drug content %
F1	6.5±0.4	3.60±0.043	0.291±0.05	499.3±9.15	98.73±0.31
F2	6.2±0.2	3.54±0.055	0.308±0.02	498.9±9.98	98.53±0.58
F3	6.1±0.2	3.72±0.085	0.415±0.07	497.9±9.78	98.57±0.33
F4	6.6±0.1	3.70±0.067	0.152±0.04	499.5±9.91	97.58±0.51
F5	6.4±0.6	3.64±0.054	0.419±0.02	499.5±9.91	98.57±0.68
F6	6.6±0.3	3.76±0.048	0.244±0.08	499.2±9.85	99.65±0.01
F7	6.2±0.2	3.78±0.028	0.298±0.08	499.1±9.19	97.12±0.78
F8	6.7±0.3	3.83±0.039	0.205±0.03	497.9±9.99	98.58±0.91
F9	6.3±0.4	3.58±0.026	0.393±0.02	498.5±9.83	98.57±0.32
F10	6.5±0.2	3.66±0.016	0.355±0.07	499.8±8.97	98.57±0.30

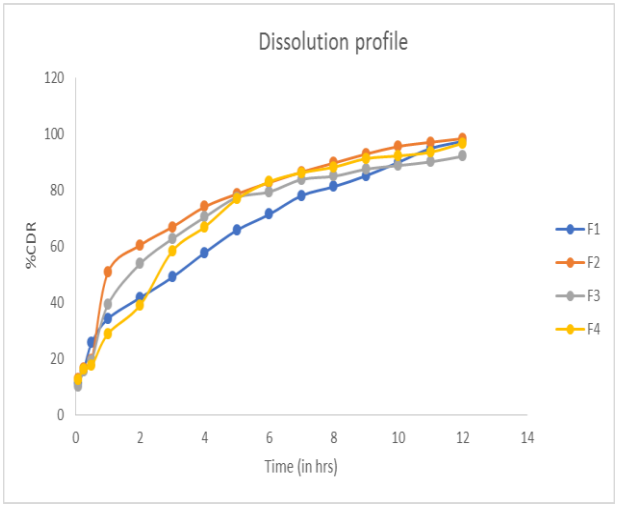
***In vitro* drug release studies**

The floating sustained release layer of Trimethoprim tablet were designed using individual HPMC K100, xanthan gum, guar gum, and karaya gum alone and also in combination of two polymers (3:1 HPMC K100: Natural polymer) and three polymers (3:0.5:0.5 HPMC K100: Natural polymer: Natural polymer). The total weight of the polymers used in the formulation was 33.33% of total weight of SR layer. All the batches of formulated layers were produced under similar condition to avoid processing variables. The *in vitro* release study of Trimethoprim study was conducted in 0.1N HCl for 12 hours. The *in vitro* release data of Trimethoprim is shown in Table- 03. The *in vitro* release is depending upon nature of drug, nature of polymer, drug to polymer conc. and the medium used. In the present work HPMC

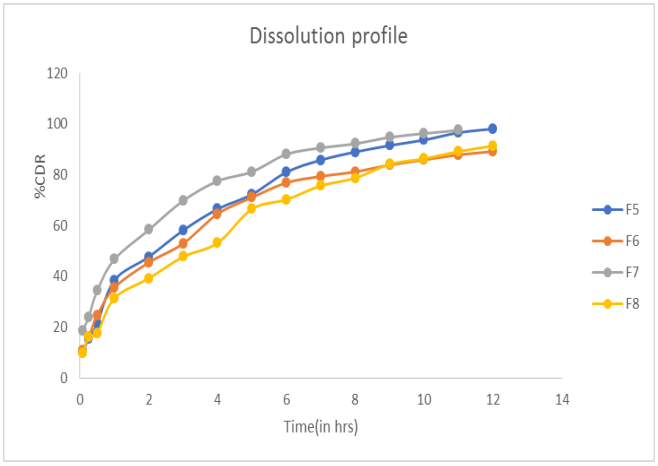
K100, Xanthan gum, guar gum, and karaya gum were used as hydrophilic polymers in the preparation of sustained release layer. The highest release for 12 hrs was observed with HPMC K100 which is commonly used hydrophilic matrix, gets swelled and forming viscous gel thereby rapidly releasing the drug. Among all the formulation, formulation F6 contained 15% of total weight of tablet of HPMC K100 and 5% of total weight oftablet of Xanthan gum releases 99.65% of drug up to 12 hrs.

Table 5: Percentage cumulative drug released of formulations F1-F10.

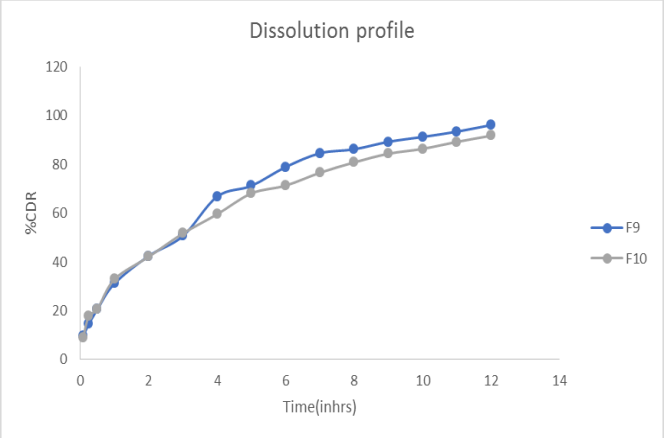
Time	Percentage of drug release (%CDR)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
5min.	11.23	12.62	10.19	12.27	10.71	10.02	12.27	9.67	9.67	9.16
15min.	15.92	16.62	15.40	16.27	15.92	15.40	18.69	15.92	14.53	17.82
30min.	25.64	19.40	19.23	17.50	24.60	21.30	23.91	17.50	20.61	20.79
1hr.	34.15	50.59	39.16	28.77	35.53	38.47	34.32	31.37	31.20	32.93
2hr.	41.63	60.35	53.75	39.02	45.44	47.69	46.66	39.19	42.49	42.15
3hr.	48.95	66.82	62.64	58.29	52.94	58.13	58.31	47.72	50.67	51.72
4hr.	57.66	74.00	70.33	66.84	64.60	66.51	69.80	53.14	66.83	59.57
5hr.	65.69	78.58	77.33	76.78	71.08	72.30	77.50	66.54	71.24	68.12
6hr.	71.31	82.65	79.32	82.93	76.87	81.04	81.22	70.25	78.93	71.31
7hr	77.97	86.38	83.74	86.13	79.38	85.80	88.07	75.69	84.56	76.58
8hr	81.17	89.59	84.87	88.13	81.20	89.01	90.59	78.72	86.21	80.82
9hr	85.07	92.80	87.39	91.17	83.89	91.54	92.25	84.17	89.25	84.37
10hr	89.84	95.50	88.70	92.14	85.88	93.71	94.77	86.34	91.26	86.37
11hr	94.78	96.99	90.01	93.45	87.88	96.59	96.26	89.21	93.43	89.24
12hr	97.31	98.01	92.01	96.67	89.19	98.08	97.56	91.39	96.13	91.76



***In -Vitro* release Profile of F-1 to F-4 Formulations.**



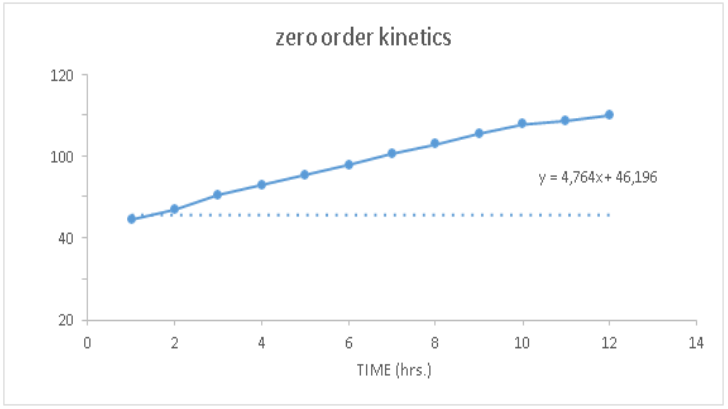
***In -Vitro* release Profile of F-5 to F-8 Formulations.**



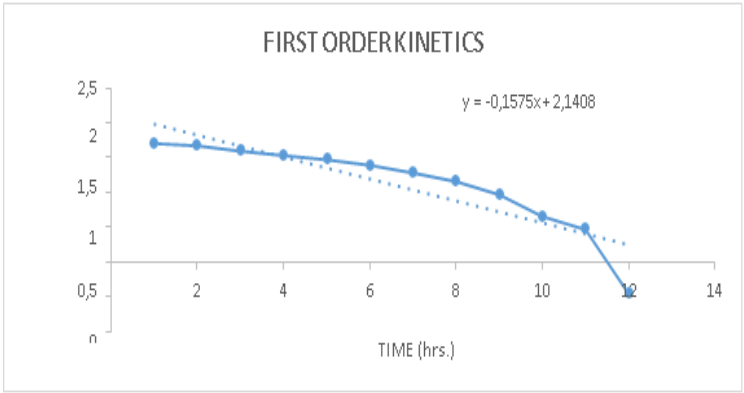
***In -Vitro* release Profile of F-9 and F-10 Formulations.**

Release kinetics

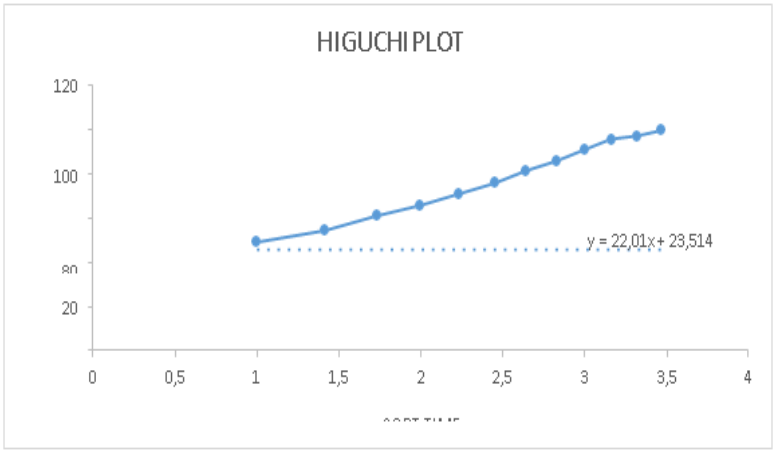
The *in vitro* release data from Trimethoprim was processed to plot different kinetics approaches and the values are mentioned in Table 6. The obtained kinetics data is plotted as follows zero order (Percent of drug release vs. time), first order (logarithm of the percent drug remained vs. time), Higuchi (Percentage CDR vs. square root of time), Korsmeyer-Peppas (Log percent drug release vs. log time) in order to establish drug release mechanism and kinetics of drug released. The goodness of best fit was evaluated by regressional analysis of the said models. The kinetics of *in vitro* drug release from the entire formulated bilayer layer tablet obeyed zero order with the high regression r^2 value of 0.999 as compared to first order which showed less r^2 values. As the polymers used were matrix material hence Higuchi model was applied which showed good linearity with high regression 0.995 to 0.843 suggested that the release mechanism was diffusion controlled. The *in vitro* release data was subjected to Korsmeyer-Peppas model, which shows good linearity with high r^2 value of 0.997 to 0.961. Values of n between 0.45 and 0.89 can be regarded as an indicator for both the phenomena (Anomalous transport). The n value of optimized formulation F6 is 0.309 and it is clear that all formulae have n values below 0.45. This indicates that the drug release majorly depends on diffusion-controlled phenomenon.



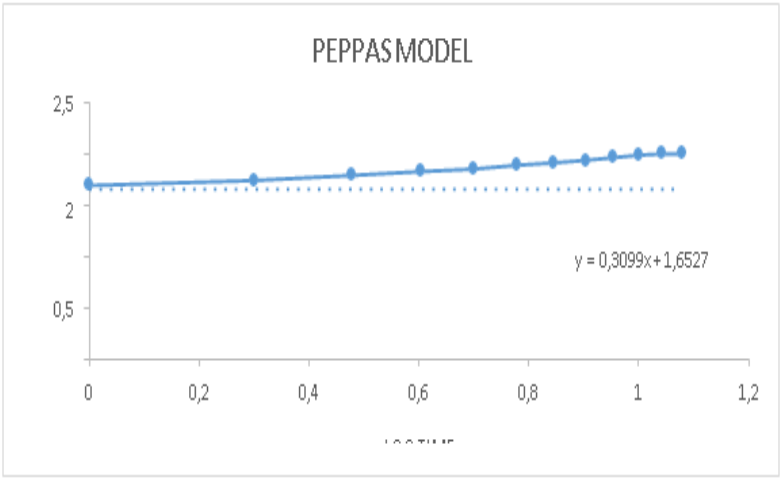
Zero order kinetic of *in vitro* release data of formulation F -5 bilayer tablet.



First order kinetic of *in vitro* release data of formulation F -5 bilayer tablet.



Higuchi plot of *in vitro* release data of formulation F -5 bilayer tablet.



Peppas model of *in vitro* release data of formulation F -5 bilayer tablet.

CONCLUSION

Trimethoprim floating tablets were developed using one synthetic polymer and four natural polymers in order to achieve sustained release of drug. To develop sustained release layer the polymers were used individually and also in combination. Among all formulation F5 containing HPMC K4M, xanthan gum and guar gum (3:0.5:0.5) released almost all amount of incorporated drug during the period of 12 hrs. This optimized formulation was observed to float in the dissolution media more than 12 hrs. Hence, combination of HPMC K4M with natural polymers Xanthan gum and guar gum can be successfully used to develop floating sustained release tablets.

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