AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Development and Evaluation of Floating Sustained Release Bilayer Tablets Containing Drotaverine HCl

Naveen Kumar HR, Ashok Kumar P*, Suresh V. Kulkarni, Manjunath K

Department of Pharmaceutics, Sree Siddaganga college of pharmacy,B. H. Road, Tumkur-572102 Karnataka, India.

ABSTRACT

Bilayer floating tablets of Drotaverine HCL were developed by direct compression method. Immediate release layer contains 20 mg 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, karaya gum release the drug for 12 hours' 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 hours. FTIR results revealed that there was no interaction between drug and HPMC K100 / xanthan gum. The post compression parameters of developed tablets were found to be 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 exhibited decent sustained 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, Drotaverine HCL, HPMC K100, Xanthan Gum, FTIR.

*Corresponding Author Email: ashokkumarscp@gmail.com

Received 10 October 2022, Accepted 09 November 2022

Please cite this article as: Kumar A *et al*., Development and Evaluation of Floating Sustained Release Bilayer Tablets Containing Drotaverine HCl. American Journal of PharmTech Research 2022.

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, a conventional formulation is required to be administered in multiple doses, and therefore lacks patient compliance [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].

DROTAVERINE HCl is an antispasmodic drug that works by inhibiting phosphodiesterase-4 (PDE4).5 It is a benzylisoquinoline derivative that is structurally related to papaverine, although it displays more potent antispasmodic activities than papaverine. Drotaverine has been used in the symptomatic treatment of various spastic conditions, such as gastrointestinal diseases, biliary dyskinesia, and vasomotor diseases associated with smooth muscle spasms [8]

MATERIALS AND METHOD

The chemicals used in this study were pure drug like Drotaverine HCL (Yarrow chemicals) and polymers like HPMC K100, Xanthan gum, Guar gum, Karaya 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 for immediate release layer 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 10 min the mixture of first layer was subjected to slight compression to using ten station rotary tablet machines.

Drug and excipients for sustained release layer mentioned in Table-2 were passed through a 60 # size mesh prior to the preparation of the dosage form. All the ingredients where weighed separately and mixed thoroughly for 10 min. These mixtures is placed over the first layer and subjected for final compression to produce tablet with 6 ± 0.5 Kg/cm2 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 Drotaverine HCL bilayer tablet.

Formulation for immediate release layer.

Ingredients	Weight in (mg)
Drotaverine HCL	20
Sodium starch glycolate	40
MCC	123
Polyvinyl pyrrolidone	5
Magnesium stearate	2

Table 2: Formulation for sustained release layer:

Ingredients	Weight in (mg)									
	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9	SR10
Drotaverine HCL	60	60	60	60	60	60	60	60	60	60
HPMC K100	100	-	-	-	-	75	75	75	50	50
Xanthan gum	-	100	-	-	-	25	-	-	25	25
Guar gum	-	-	100	-	-	-	25	-	25	25
Karaya gum	-	-	-	100	100	-	-	25		

Citric acid	9	9	9	9	9	9	9	9	9	9
Sodium bicarbonate	21	21	21	21	21	21	21	21	21	21
MCC	44	44	44	44	44	44	44	44	44	44
Mg. Stearate	3	3	3	3	3	3	3	3	3	3
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/cm^2.

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,

$$F = (W_{initial}) - (W_{final}) / (W_{initial}) \times 100$$

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 60mg 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 filter. 5ml of the filtrate was diluted to 50 ml with same buffer solution and examined under U.V. Spectrophotometry at 221 nm.

In Vitro Drug Release:

The release of Drotaverine HCL 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 221 nm for Drotaverine HCL 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 1.2 buffer.

RESULTS AND DISCUSSION:

The standard graph of Drotaverine HCL has shown good linearity with r^2 value 0.999 in pH 1.2 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:

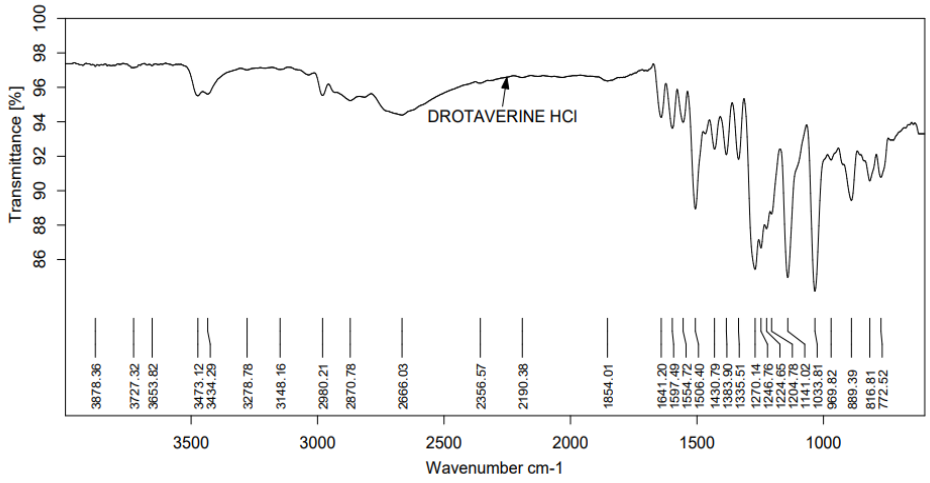


Figure 1: FTIR of Drotaverine HCl

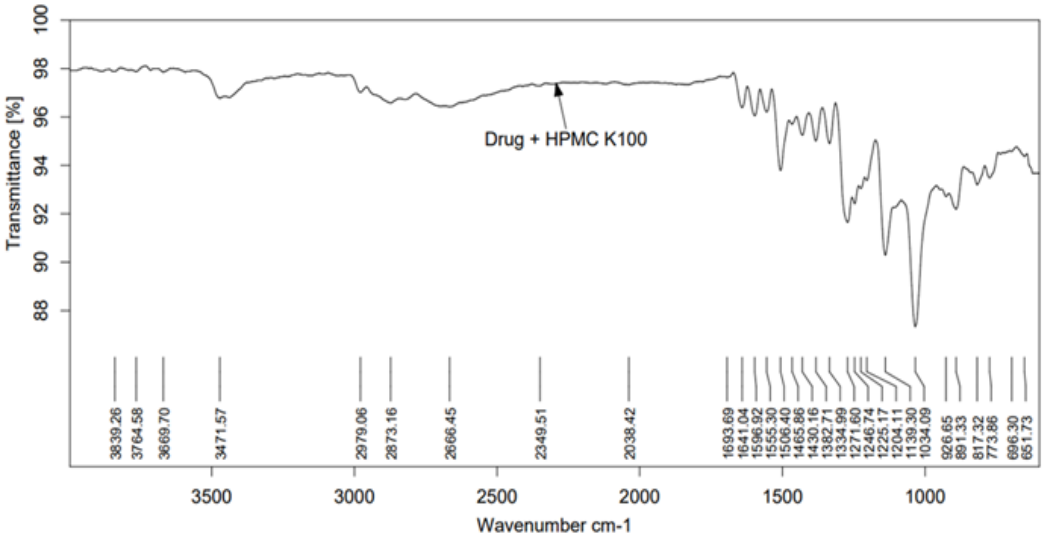


Figure 2: FT-IR of Drotaverine HCl+HPMC K100

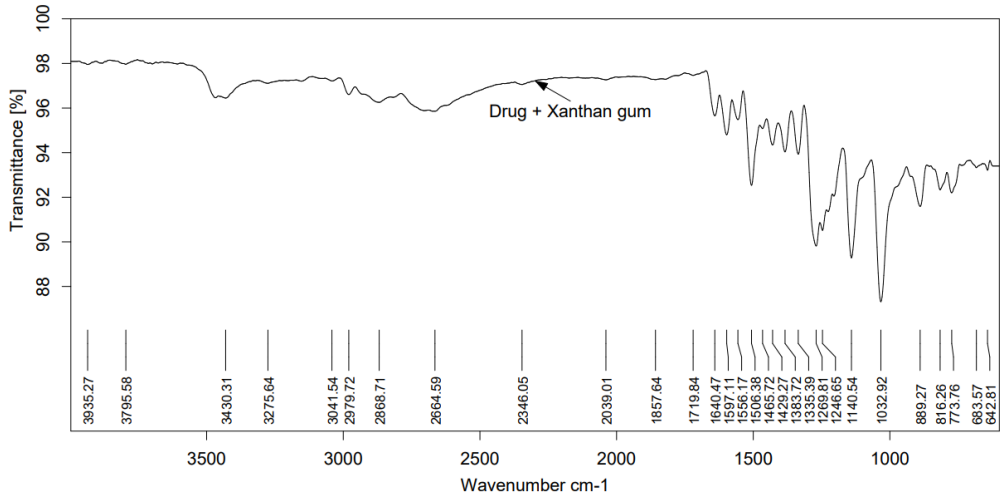


Figure 3: FT-IR of Drotaverine HCl+Xanthan Gum

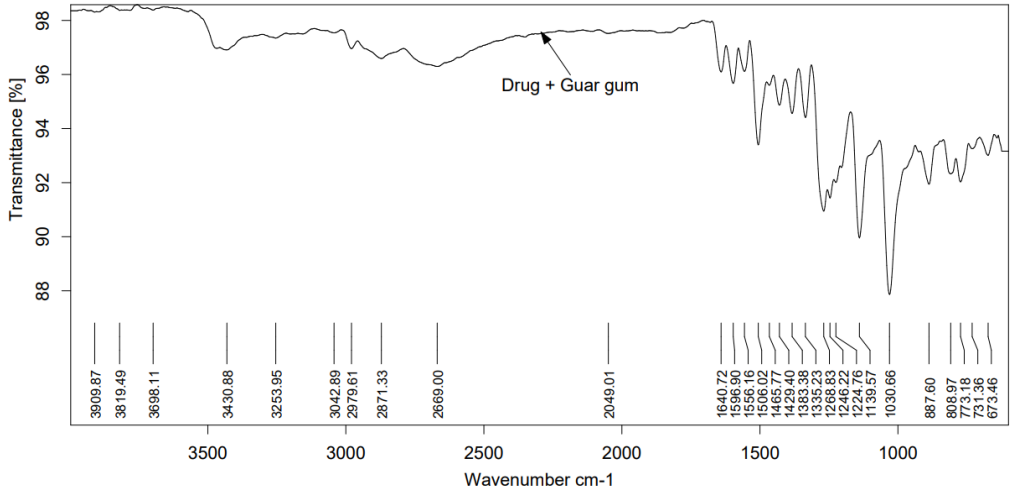


Figure 4: FT-IR of Drotaverine HCl+Guar Gum

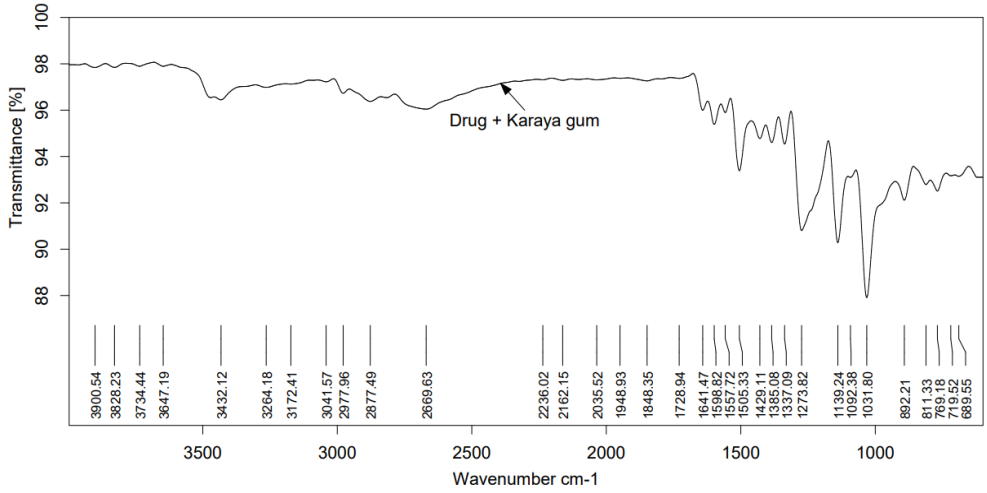


Figure 5: FT-IR of Drotaverine HCl+Karaya Gum

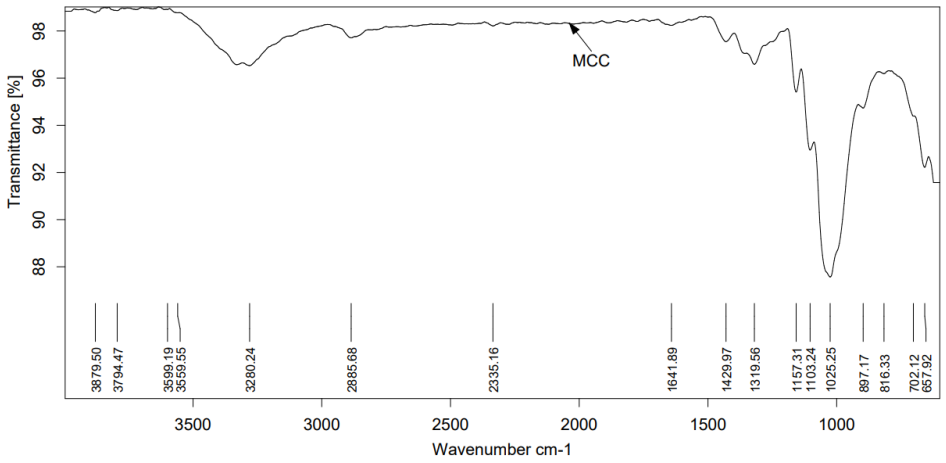


Figure 6: FT-IR of Drotaverine HCL+ MCC

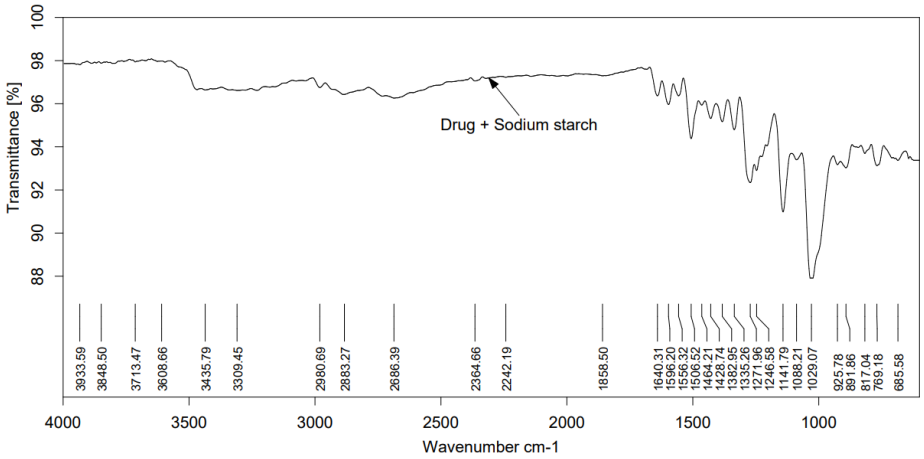


Figure 7: FT-IR of Drotaverine HCL+PVP

Evaluation of Bilayer Tablet:

The Drotaverine HCL 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 3.40 to 3.62 mm suggested uniformity in thickness for bi-layer tablet. The friability was less than 1% indicated good handling of the layers. The weight variation results suggested uniformity in weight of layers

Table 3: Pre-compression parameters for Drotaverine HCL immediate release and sustained release layers.

Batch Code	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's index	Hausner 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 Drotaverine HCL Bilayer tablets.

Batch code	Hardness (kg/cm^2)	Thickness (mm)	Friability %	Weight Variation (mg)	Drug content %
F1	6.5±0.02	3.41±0.06	0.10±0.05	499.3±9.15	98.73±0.31
F2	6.2±0.04	3.40±0.06	0.19±0.02	498.9±9.98	98.53±0.58
F3	6.1±0.02	3.41±0.08	0.18±0.07	497.9±9.78	98.57±0.33
F4	6.6±0.02	3.41±0.07	0.23±0.04	499.5±9.91	98.58±0.51
F5	6.4±0.03	3.40±0.07	0.26±0.02	499.5±9.91	98.57±0.68
F6	6.6±0.05	3.50±0.03	0.10±0.08	499.2±9.85	99.65±0.01
F7	6.2±0.04	3.61±0.08	0.11±0.08	499.1±9.19	98.57±0.78
F8	6.7±0.02	3.58±0.09	0.15±0.03	497.9±9.99	98.58±0.91
F9	6.3±0.05	3.60±0.06	0.13±0.02	498.5±9.83	98.57±0.32
F10	6.5±0.06	3.59±0.08	0.15±0.07	499.8±8.97	98.57±0.30

In vitro Drug Release Studies:

The floating sustained release layer of Drotaverine HCL tablet were designed using individual HPMC K100, xanthan gum, guar gum, locust bean 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 1: Natural polymer 2). The total weight of the polymers in the formulation used 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 Drotaverine HCL study was conducted in 0.1N HCl for 12 hours. The *in vitro* release data of Drotaverine HCL is shown in Table 5 and illustrated in Figure 9, 10 and 11. The in vitro release is depending upon nature of drug, nature of polymer, drug to polymer ratio and the medium used. In the present work, HPMC K100, xanthan gum, guar gum, locust bean 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 formulation F6 which contains HPMC K100 which is commonly used hydrophilic matrix, gets swelled and forming viscous gel thereby rapidly releasing the drug. Among all the formulations, formulation F6 contained 25% HPMC K100 and 4.16% of xanthan gum and guar gum each released 98.65% 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

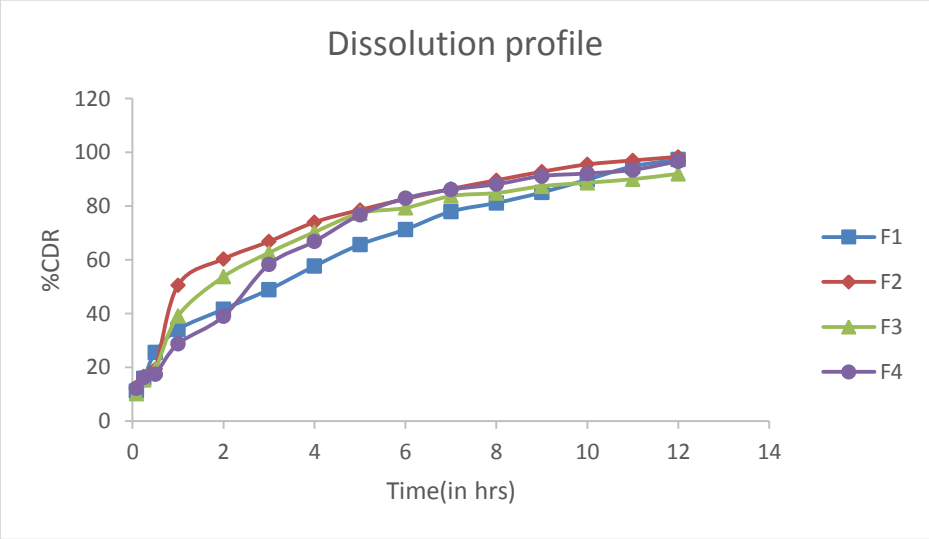


Figure 9: *In -Vitro* release Profile of F-1 to F-4 Formulations prepared with individual polymers.

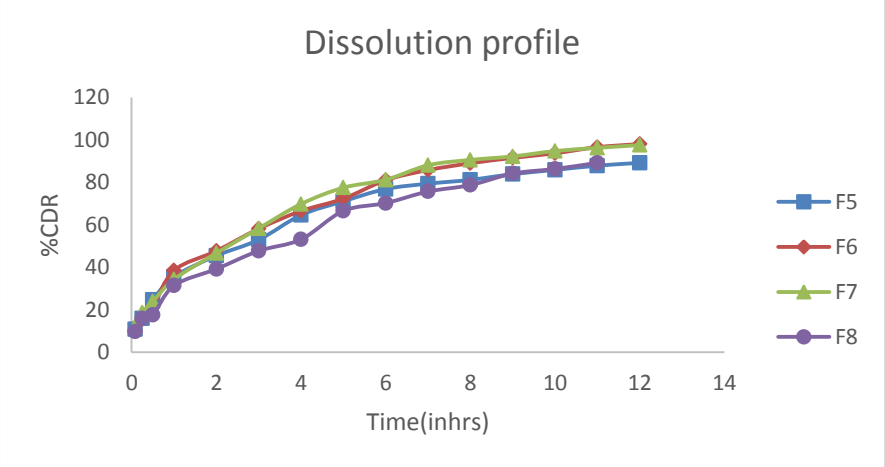


Figure 10: In-Vitro release Profile of F-5 to F-8 Formulations prepared with combination oftwo polymers.

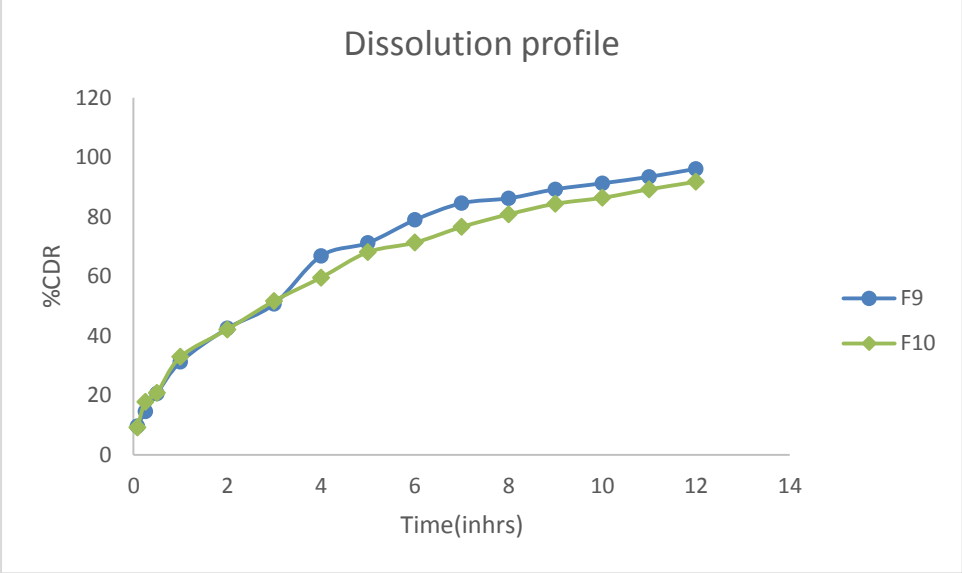
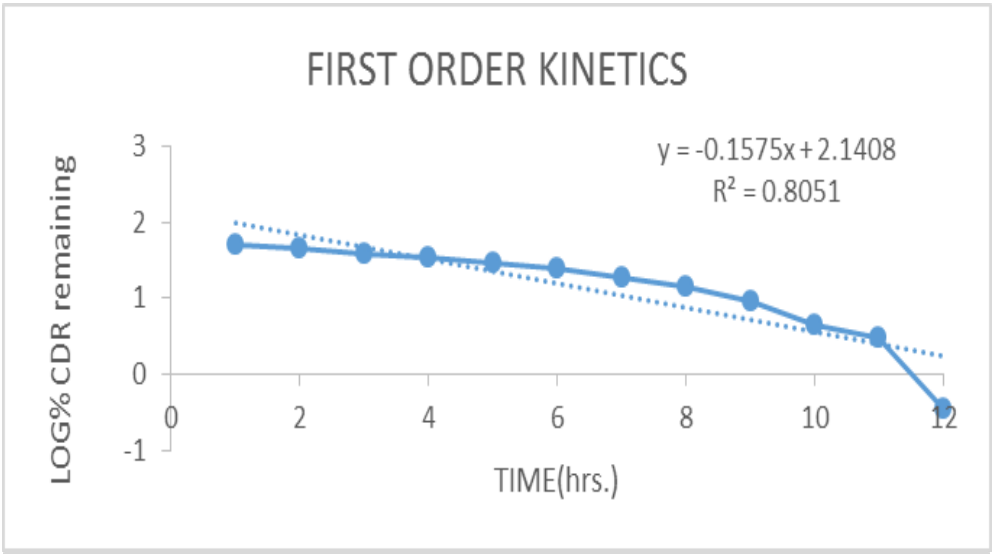
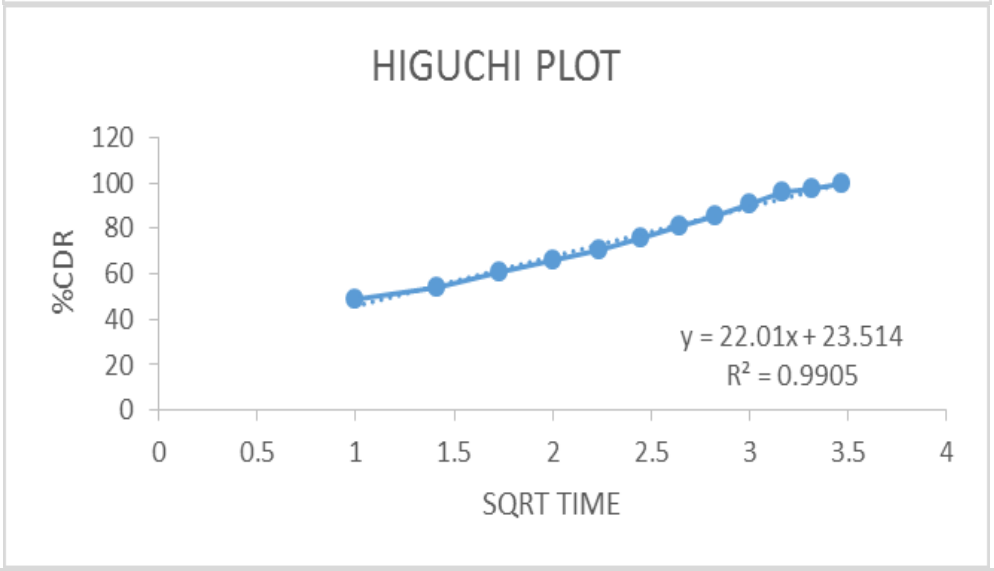


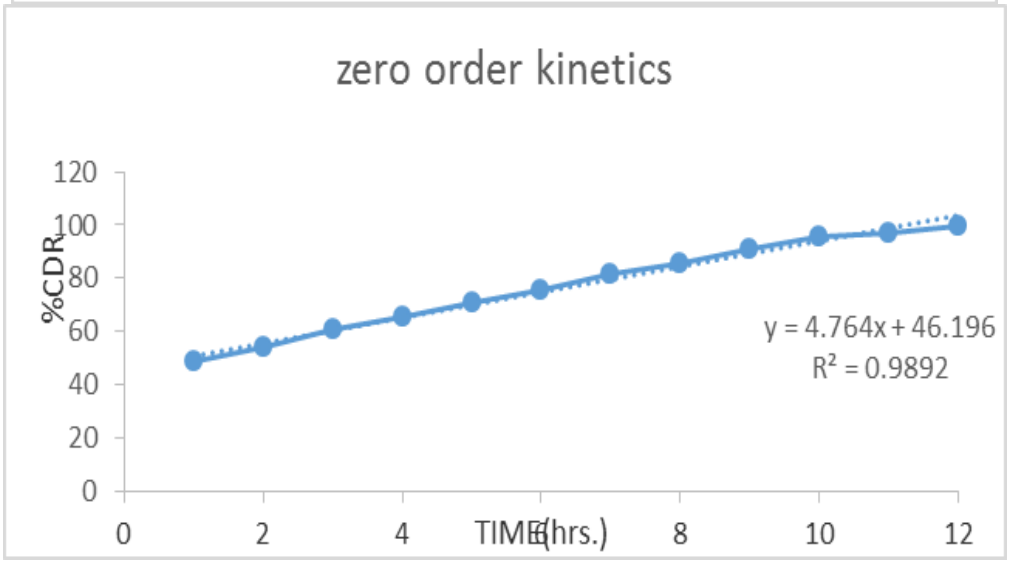
Figure 11: In-Vitro release Profile of F-9 to F-10 Formulations prepared with combination three polymers.

Release Kinetics:

The in vitro release data from Drotaverine HCL was processed to plot different kinetics approaches. The kinetics of *in vitro* drug release from the entire formulated bilayer layer tablet obeyed Higuchi release with the high regression r^2 value of 0.99 as compared to others. As the polymers used were matrix material hence Higuchi model was applied which showed good linearity with high regression 0.99 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 0.999 to 0.961. Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fick's diffusion, and a case-II transport, for the description of drug release from a swelling polymer. For a matrix tablet, when n takes the value of 0.45 it indicates diffusion-controlled drug release and for the value 0.89, it indicates swelling-controlled drug release. 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 formulation have n values below 0.45. This indicates that the drug release majorly depends on diffusion-controlled phenomenon (Figure 12).


FIRST ORDER KINETICS
y = -0.1575x + 2.1408
R² = 0.8051
LOG% CDR remaining
TIME(hrs.)
3
2
1
0
-1
0
2
4
6
8
10
12


HIGUCHI PLOT
y = 22.01x + 23.514
R² = 0.9905
%CDR
SQRT TIME
120
100
80
60
40
20
0
0
0.5
1
1.5
2
2.5
3
3.5
4


zero order kinetics
y = 4.764x + 46.196
R² = 0.9892
%CDR
TIME(hrs.)
120
100
80
60
40
20
0
0
2
4
6
8
10
12

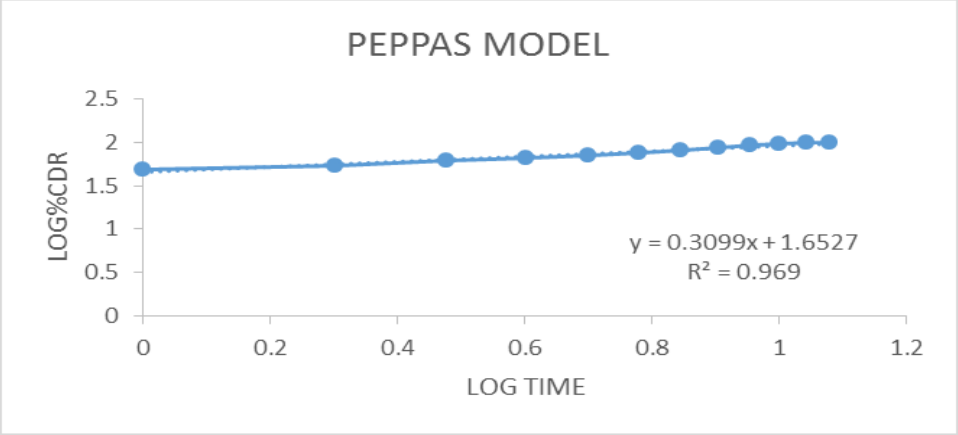


Figure 12: Kinetics of *in vitro* release data of formulation F6 bilayer tablet.

CONCLUSION:

Drotaverine HCL 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 F10 containing HPMC K100, 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 K100 with natural polymers Xanthan gum and guar gum can be successfully used to develop floating sustained release tablets.

ACKNOWLEDGMENT:

The authors are thankful to me management, Sree Siddaganga college of pharmacy, for providing necessary facilities to carry out this work.

REFERENCES:

1. Chien YW. Novel Drug Delivery System. ed., New York, USA: Marcel Dekke; 1992; 139-96.
2. Vyas SP, Khar R K. Controlled Drug Delivery: Concepts and Advances. Delhi: Vallabh Prakashan;2002; 155-95.
3. Saleh MA, Yellela SR, Srinivas SP, Satyanaryana V. *In vitro* and *in vivo* evaluation of guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. AAPS PharmSciTech 2005; 6(1): E14-E21.
4. Remya PN, Damodharan N, Sulakshan Kumar CV. Formulation and evaluation of bilayered tablets of ibuprofen and methocarbamol. Int. J. Pharm. Tech. Res 2010; 2(2): 1250-1255.
5. Moiz, Prathima Srinivas M, Sadanandam M. Formulation and evaluation of bilayer

tabletsof montelukast and levocetirizine dihydrochloride using natural and synthetic polymers. International Journal of Drug Delivery 2011; 3(4): 597-618.

6. Mohamed Halith S, Jayaprakash S, Kulathuran Pillai K. Formulation and evaluation of bilayer tablets of amlodipine besilate and metoprolol succinate. Der Pharmacia Lettre. Scholars Research Library 2011; 3(4): 143-145.
7. Jadhav RT, Payal H, Patil, Pratibha R, Patil. Formulation and evaluation of bilayer tablet of piracetam and vinpocetine. J. Chem. Pharm. Res 2011; 3(3): 423-431.
8. Available from : https://www.drugoffice.gov.hk/eps/do/en/consumer/home.html