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Formulation and Evaluation of Floating Matrix Tablets of Drotaverine Hydrochloride

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ABSTRACT

Drotaverine Hydrochloride is effectively used in the treatment of management of spasticity, indicated in muscle pain as muscle relaxant. Drotaverine Hydrochloride approximately 95% bounds to plasma proteins and is metabolized by liver. In the present investigation, efforts were put to develop a sustained release floating matrix tablets of Drotaverine Hydrochloride. Gastro retentative dosage form will also greatly improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which are sustained over a long period of time. Floating matrix tablets were prepared by direct compression method using sodium bicarbonate and citric acid as gas forming agents. HPMC K100M and Ethyl cellulose were used in the formula to retard drug release. Floating matrix tablets were evaluated for different quality attributes. In vitro drug release showed that polymer percentage is enough to extend the release of the drug for at least 12 hr. The dissolution curve shows that formulation FT-6 shows maximum drug release 79.37% at the end of 12 hours while FT-7 shows least 46.33 %.

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INTRODUCTION

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. These problems were overcome by sustained release systems. Gastro retentative drug delivery is one of the promising approch to retard the drug release and to retain the dosage form in stomach region. It also improve drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site. Absorption of the Drotaverine Hydrochloride is limited to upper part of the GI tract (stomach and upper part of small intestine) and bioavailability is 25-91%. Drotaverine Hydrochloride has a rapid and direct action on the smooth muscle. It acts to correct cyclic AMP and Ca imbalance at the spastic site, thereby relieving smooth muscle spasm and pain. Drotaverine Hydrochloride has a biological half-life of 7 to 12 hours so it requires three-times a day dosing. Hence attempt was made to develop Drotaverine Hydrochloride floating matrix tablets to improve all characteristics. [7,8]

MATERIAL AND METHODS

Drotaerine Hydrochloride was purchased from Swapnroop Drugs and Pharmaceuticals, Aurangabad, India. HPMC K100M, EC was procured from Molychem, Mumbai. All other reagent and materials were of analytical grade.

Formulation of Drotaverine hydrochloride Floating Matrix Tablets.[1]

The direct compression technique was followed to manufacture the Drotaverine hydrochloride tablets for all batches containing Drotaverine hydrochloride. Sodium bicarbonate was passed through # 36 sieves. Magnesium stearate and Citric acid were passed through # 60 sieves. Weighed amounts of drug as well all other ingredients were transferred into polythene bag and blended for 10 minutes. The blend was compressed using 10-station rotary press using Round shaped punches. Punches measuring 11.2 mm diameter were used for compression of the tablets. Formula for preparation of floating matrix tablets shown in table no-1

Table1: Formulation of Drotaverine hydrochloride floating Matrix tablets.

Ingredients	FT-1 mg	FT-2 mg	FT-3 mg	FT-4 mg	FT-5 mg	FT-6 mg	FT-7 mg	FT-8 mg	FT-9 mg
Drotaverine HCL	160	160	160	160	160	160	160	160	160
HPMCK100M	60	50	50	40	60	40	60	40	50
Ethyl cellulose	60	60	50	60	40	40	50	50	40
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Citric acid	25	25	25	25	25	25	25	25	25
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total weight	360	350	340	340	340	320	350	330	330

Organoleptic Properties

The prepared tablets were evaluated visually for cracks, depressions, pinholes, colour and polish.

Dimensions[1]

Thickness of the tablets was measured using vernier calipers.

Hardness test[1]

The hardness was tested using Monsanto tester. "Hardness factor", the average of the six determinations, was determined and reported.

Uniformity of weight[1]

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability test[1]

Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. It was rotated at a rate of 25 rpm. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where, W_1 = weight of the tablets before test

W_2 = weight of the tablets after test

Content uniformity[2]

Twenty tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately average weighed amount of tablets triturate was taken for analysis. Samples were transferred to different volumetric flasks and were diluted up to the mark using 0.1N hydrochloric acid. The content was shaken well and kept for 30 minutes for dissolving the drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at λ_{max} 240 nm against blank as reference.

In vitro buoyancy studies[3]

The tablets were placed in a 100 ml beaker containing 0.1 N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

Water uptake study (determination of swelling index) [3]

The swelling index of the tablets was determined in distilled water at room temperature. The water uptake study of the tablet was done using USP II dissolution apparatus. The medium used was distilled water, 900 ml, rotated at 100 rpm. The medium was maintained at 37 ± 0.5^0 C throughout the study. After every hour up to 12 hours, the tablets were withdrawn, blotted to remove excess water, and weighted. The swelling characteristics of the tablets were expressed in terms of water uptake (WU) as,

$$\% \text{ WU} = \frac{\text{Weight of the swollen tablet- Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

FT-IR Spectroscopy

The FT-IR spectrum of formulation FT-6 was recorded using FTIR spectrophotometer (Shimadzu 84005) using Potassium Bromide pellet technique. Physical mixture of Drotaverine Hydrochloride and each polymer were scanned and recorded in the range of 4000-400 cm-1.

Differential Scanning Calorimetry (DSC)

DSC analysis of formulation FT-6 was performed using Shimadzu-Thermal Analyzer DSC 60 on 2-5mg samples. Samples were heated in an open aluminium pan at a rate of 10°C/min conducted over a temperature range of 30 to 300°C under a nitrogen flow of 2 bar pressure.

In vitro dissolution study[1]

In vitro drug release study of the samples was carried out using USP – type I dissolution apparatus (Basket type). The dissolution medium, 900 ml of simulated gastric fluid (without enzyme), was placed into the dissolution flask maintaining the temperature of 37 ± 0.5 ^{0}C and rpm of 100. One Drotaverine hydrochloride matrix tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 12 hours. Samples measuring 5 ml were withdrawn after every 1 hour up to 12 hours manually. During sampling, samples were filtered. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were analyzed at 240 nm using 0.1 N Hydrochloric Acid as blank. The cumulative percentage drug release was calculated using PCP Disso v3 software.

Kinetics of in-vitro drug release

To study the in-vitro drug release kinetics, data was applied to kinetic models such as zero order, first order, Higuchi, Hixson Crowell and Korsmeyer- Pappas.

RESULT AND DISSCUSSION

Organoleptic Properties:

All the prepared matrix tablets were yellowish in color having smooth surface. The thickness of all the formulations was varies with drug: polymer ratio it ranges from 5.0-5.5 mm. The weight variation test was carried out as per official method and the average percentage deviation of all the formulation was found to be less than 5 %. It was found that all batches shows percent drug content more than 95 %.The tablet hardness of all the formulations was determined and it was found in the range 6.9-7.1 kg/cm^2. Another measure of tablet hardness was the friability. Compressed tablets that lose less than 1 % of their weight are generally considered acceptable. For all formulation tried here the weight loss was less than 1 % hence acceptable shown in table no 2. All the formulations FT-1 to FT-9 floats within one minute but FT-6 takes minimum time as it contains minimum amount of polymers.All the formulations FT-1 to FT-9 remain buoyant for more than20 hours shown in table no 4. Swelling index was performed for optimized formulation (FT-6) shown in fig. 1complete swelling of tablet takes place at the end of 8 hours after that the weight of tablet decreases. The FTIR spectrum of FT-6 exhibited characteristic signals as shown in Table. The absorption bands shown by FT-6 are characteristic of the groups present in the molecular structure of Drotaverin Hydrochloride .The presence of absorption bands corresponding to the functional groups present in the structure of Drotaverin Hydrochloride and the absence of any well-defined unaccountable peaks is a confirmation of the purity of the formulation shown in table no.5 The DSC curve of Drotaverin Hydrochloride profiles a sharp endothermic peak at 216.77°C corresponding to its melting, and indicating its crystalline nature shown in fig 3. The DSC curve of FT-6 profiles a sharp endothermic peak at 186.15°C corresponding to its melting, and indicating its crystalline nature. The shift in melting point was observed due to entrapment of drug within polymers. Drug release studies were made to determine whether the release of the drug is slow enough for at least 12 hr. The dissolution curve shows that formulation FT-6 shows maximum drug release 79.37% at the end of 12 hours while FT-7 shows least 46.33 % shown in table no.6 In order to determine the release model which best describes the pattern of drug release, the in-vitro release data were fitted to zero order, first order ,Hixson crowell , krosmeyer peppas and diffusion controlled release mechanism according to simplified Higuchi model. The preference of a certain mechanism was based on the correlation coefficient r for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release. The highest r value was obtained for krosmeyer peppas model, so swelling followed by diffusion and erosion was the predominant release mechanism for floating matrix tablets. The value of release exponent n, obtained from Krosmeyer equation was greater than 0.5 for all nine formulations FT 1-0.8473, FT2-0.8011, FT3-0.6763, FT4-0.7820, FT5-0.9046, FT6-0.8552, FT7-0.8162, FT8-0.6851 and FT9-0.8515 indicate non -fickian transport.

Table 2: Evaluation of tablets parameters

Formul-ation Code	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation			Friability (%)	Drug Content (%)
			Avg Wt (mg)	Maximum % deviation			
				(+Ve)	(-Ve)		
FT1	5.3±0.10	6.9±0.15	360	+0.26	-0.38	0.21±0.08	99.75±0.29
FT2	5.1±0.21	7.2±0.10	350	+0.85	-0.19	0.43±0.09	99.67±0.19
FT3	5.2±0.35	6.6±0.25	340	+1.02	-0.67	0.28±0.05	99.45±0.40
FT4	5.5±0.42	6.8±0.10	340	+0.89	-0.98	0.30±0.02	99.23±0.46
FT5	5.2±0.21	7.2±0.20	340	+0.21	-1.68	0.47±0.05	99.70±0.26
FT6	5.1±0.25	7.1±0.15	320	+1.32	-0.41	0.49±0.07	98.90±0.43
FT7	5.0±0.32	7.3±0.08	350	+0.40	-0.62	0.51±0.05	99.63±0.21
FT8	5.2±0.15	7.3±0.19	330	+0.83	-1.68	0.16±0.06	99.74±0.13
FT9	5.3±0.20	7.1±0.07	330	+0.91	-1.56	0.21±0.02	99.44±0.36

Table 3: Determination of buoyancy lag time

Formulation code	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
Time (second)	34	50	30	38	32	25	37	36	33

Table 4: Determination of duration of buoyancy:

Formulation code	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9
Time (Hours)	**24**	**23**	**23**	**20**	**24**	**22**	**20**	**24**	**20**

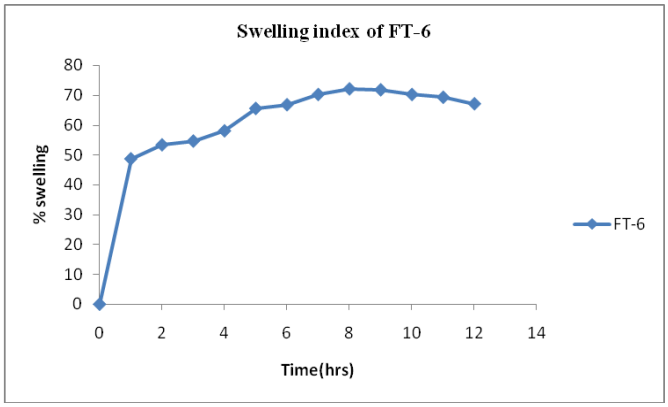

Figure 1: Swelling index of formulation (FT-6)

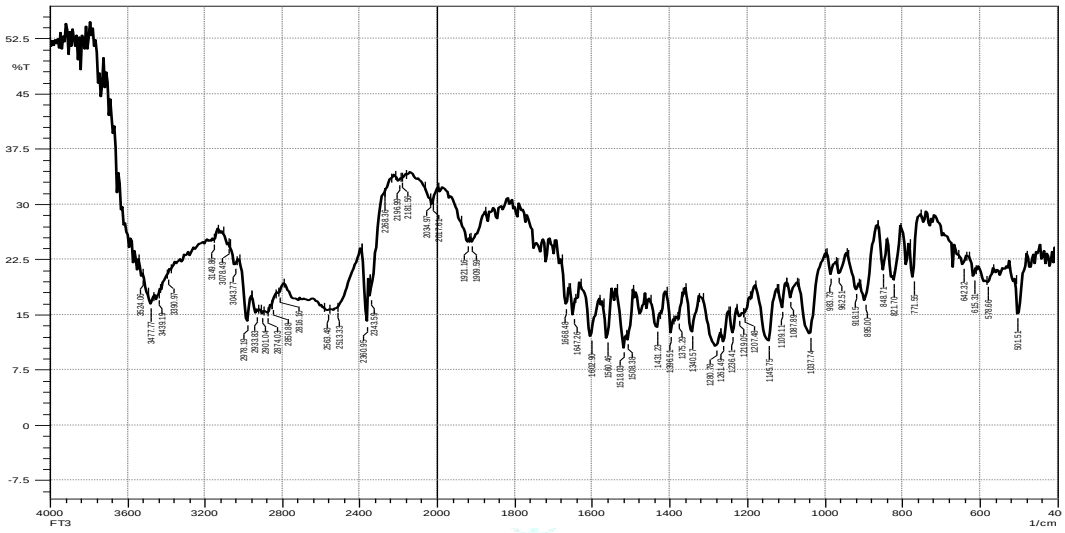

Figure 2: FT-IR of floating matrix tablet (FT-6)

Table 5: Interpretation of FTIR spectrum of FT-6

Peak observed (cm^{-1})	Interpretation
2816.16,2874.03,2850.88	C-H stretching(aliphatic)
3043.77	C-H stretching(aromatic)
1602.90	C=C stretching
1668.48	C=N stretching
1037.74	C-O stretching

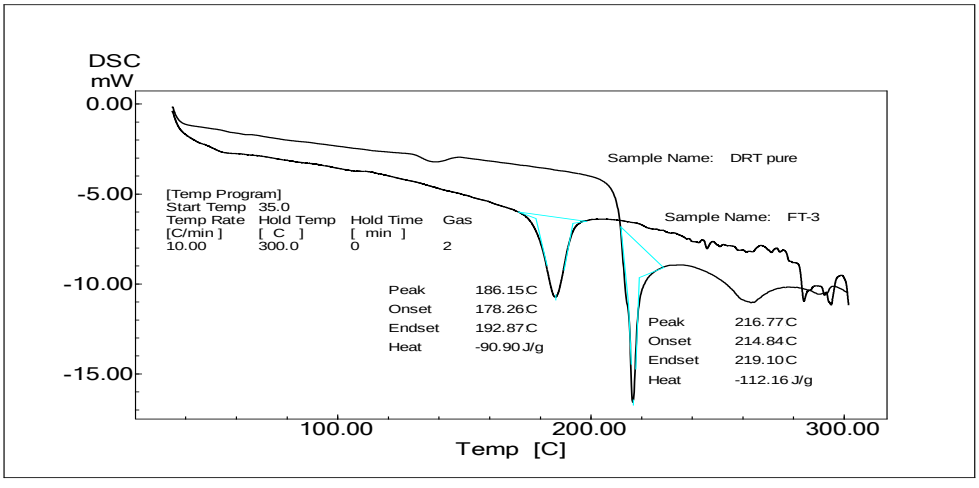

Figure 3: DSC Overlay of FT-6 and Drotaverine Hydrochloride

Table 6: Cumulative % drug released profile of Dvcl floating matrix tablets.

Time (Hours)	Cumulative % release (mean ± S.D.)								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	7.47 ± 0.69	7.99 ±0.32	11.68 ±0.36	10.54 ±0.80	5.25 ±0.52	9.82 ±0.20	6.25 ±0.32	14.03 ±0.49	8.36 ±2.83
2	13.55 ±0.85	13.72 ±0.51	16.50 ±0.34	16.69 ±1.02	10.47 ±0.59	16.93 ±3.20	10.11 ±0.34	17.57 ±0.28	13.82 ±2.31
3	18.72 ±0.75	19.65 ±0.87	17.25 ±0.34	23.75 ±1.07	12.42 ±0.89	24.67 ±0.51	13.97 ±0.37	25.36 ±0.52	21.03 ±1.49
4	25.86 ±0.97	25.22 ±0.49	20.41 ±0.30	29.49 ±2.70	18.17 ±1.48	32.81 ±0.22	21.01 ±0.23	33.25 ±0.56	26.72 ±1.63
5	28.70 ±1.47	29.79 ±0.22	26.15 ±0.41	36.90 ±2.08	20.99 ±2.61	39.54 ±0.53	21.76 ±0.56	38.41 ±1.12	31.99 ±1.17
6	35.47 ±3.96	34.31 ±0.60	31.82 ±0.51	42.09 ±1.20	25.39 ±4.33	45.89 ±0.48	26.42 ±0.67	43.54 ±1.06	37.64 ±1.43
7	39.70 ±0.49	37.57 ±0.39	35.84 ±0.53	46.09 ±0.92	29.15 ±0.69	52.50 ±1.17	29.94 ±0.39	47.67 ±0.99	42.51 ±0.63
8	44.81 ±1.14	39.32 ±0.37	38.25 ±0.51	52.81 ±1.07	34.41 ±0.93	58.28 ±0.54	33.34 ±0.59	50.65 ±0.41	47.96 ±1.94
9	48.20 ±0.68	46.73 ±0.34	43.71 ±1.20	56.74 ±1.11	38.50 ±0.43	63.69 ±0.42	36.35 ±0.39	58.20 ±2.20	52.75 ±1.04
10	52.64 ±0.36	49.59 ±0.40	50.31 ±1.03	61.99 ±0.87	41.47 ±1.36	68.58 ±0.58	39.11 ±0.41	61.09 ±1.80	57.42 ±0.44
11	56.57 ±0.68	57.70 ±0.26	52.54 ±0.63	66.20 ±0.69	46.78 ±0.48	75.74 ±2.01	42.45 ±0.26	66.38 ±3.13	62.39 ±0.36
12	61.14 ± 0.69	59.03 ±0.32	60.18 ±0.36	70.34 ±0.80	49.20 ±0.52	79.37 ±0.20	46.33 ±0.32	69.31 ±0.49	67.82 ±2.83

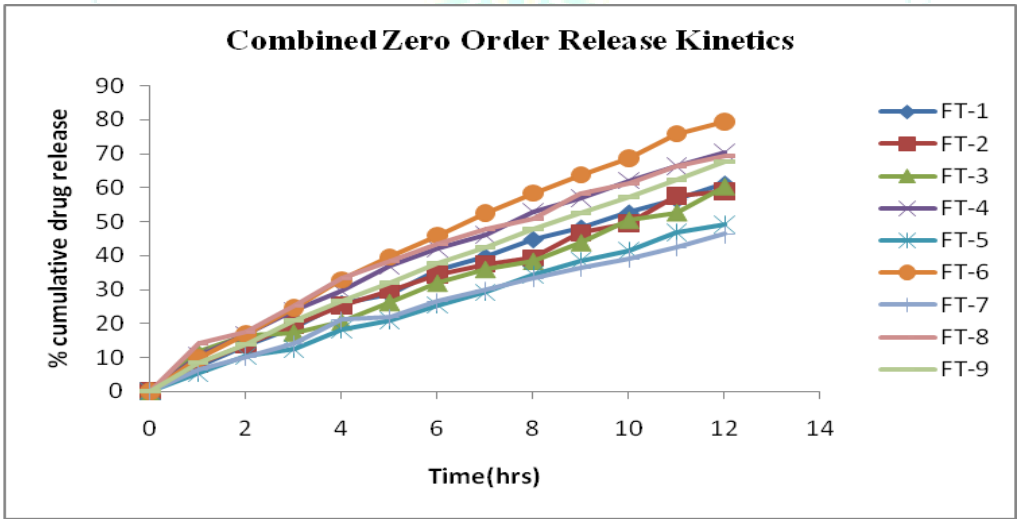

Figure 4: Comparative Dissolution profile of floating matrix tablets

Table 7: Kinetic treatment of prepared Drotaverine HCL floating matrix tablets.

Formulation Code	Coefficient of determination (r^2)					Korsmeyer plot n (release exponent)
	Zero order	First order	Higuchi square root	Hixson Crowell Cube Root	Korsmeyer plot	
FT1	0.9914	0.9914	0.9585	0.9914	0.9993	0.8473
FT2	0.9875	0.9927	0.9603	0.9949	0.9985	0.8011
FT3	0.9856	0.9848	0.9509	0.9892	0.9751	0.6763
FT4	0.9855	0.9855	0.9671	0.9855	0.9992	0.7820
FT5	0.9983	0.9983	0.9369	0.9983	0.9974	0.9046
FT6	0.9919	0.9919	0.9579	0.9919	0.9994	0.8552
FT7	0.9887	0.9887	0.9608	0.9887	0.9974	0.8162
FT8	0.9694	0.9695	0.9786	0.9694	0.9937	0.6851
FT9	0.9944	0.9944	0.9545	0.9944	0.9995	0.8515

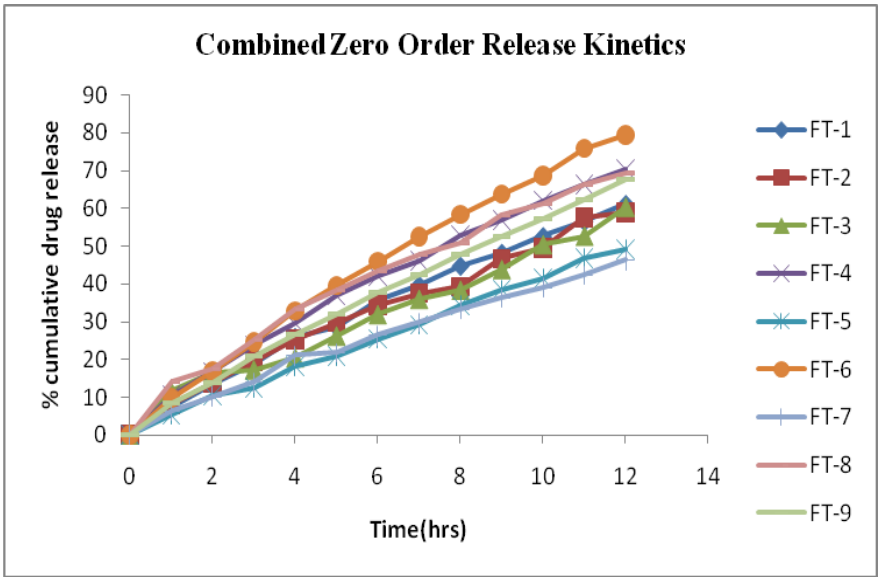

Figure 5: Combined zero order graphs of Floating Matrix Tablets

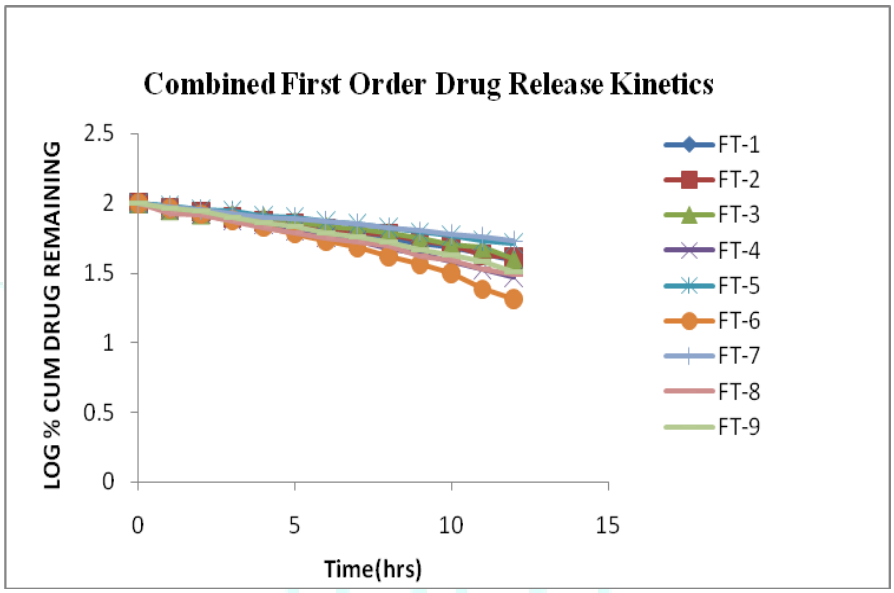

Figure 6: Combined first order graphs of Floating Matrix Tablets

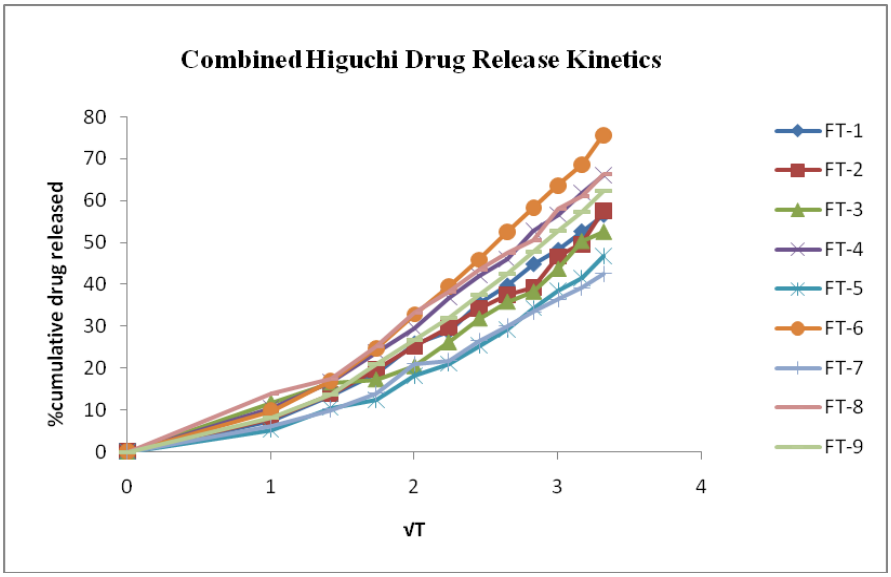

Figure 7: Combined Higuchi graph of Floating Matrix Tablets

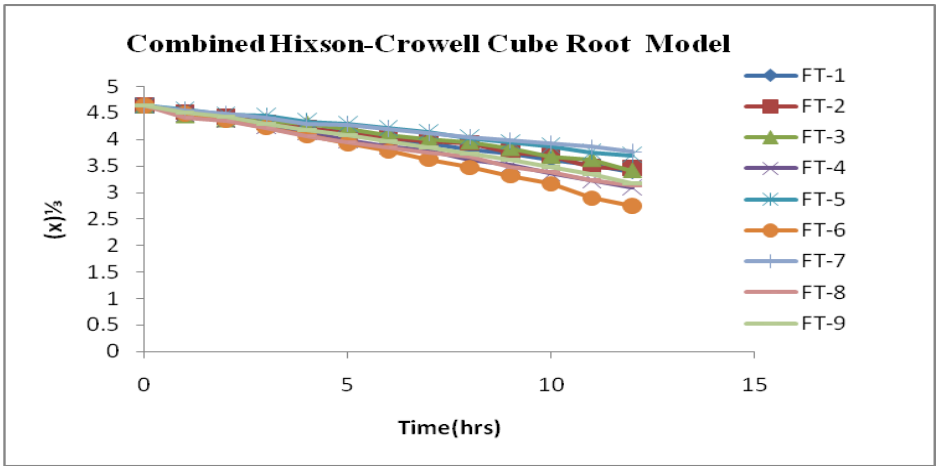

Figure 8: Combined Hixson Crowell graph of Floating Matrix Tablets

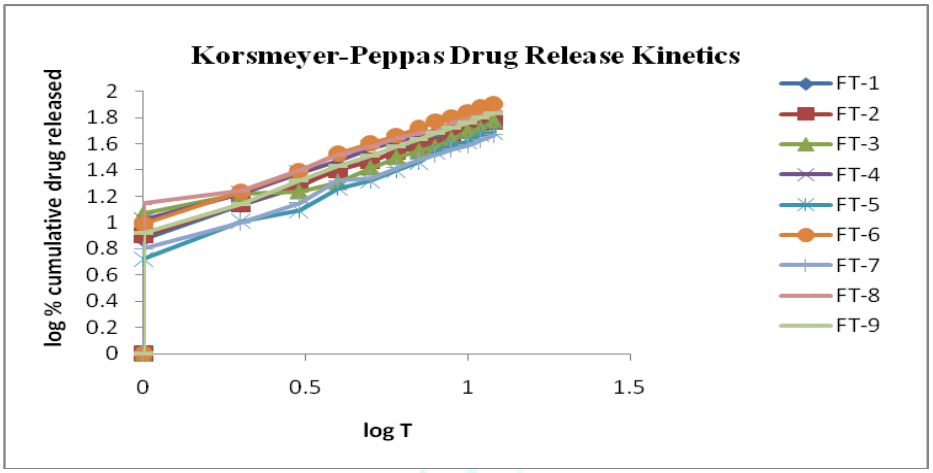

Figure 9: Combined Korsmeyer Peppas graph of Floating Matrix Tablets

CONCLUSION

Floating lag time was within 1 minute and total floating time was more than 20 hours for all the developed formulations. For floating matrix tablets, the formulation FT-6 shows highest drug release as containing minimum amount of polymers and FT-7 shows lowest drug release. For floating matrix tablets, according to 'r' value, Korsmeyer-Peppas model was the best suited for drug release i.e. diffusion phenomenon but n value obtained from Korsmeyer-Peppas equation was within 0.5 <n> 1.0 which indicates anamolous releases. So the actual mechanism of drug release was swelling or rearrangement of polymers followed by diffusion and erosion.

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