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Formulation and *In-Vitro* Evaluation of Effervescent Floating Tablets of Voriconazole

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A B S T R A C T

The aim of the present study was to develop effervescent floating tablets of Voriconazole to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of polymethacrylate polymers and ethyl cellulose were employed as polymers. Voriconazole dose was fixed as 4 mg. Total weight of the tablet was considered as 250 mg. Polymers were used in the concentration of 25, 50 and 75 mg concentration. All the nine formulation containing sodium CMC, Chitosan & Guar gum in different concentration are prepared floating tablets. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. The weight variation ranges from 248.3 to 259.4. The hardness of a effervescent floating tablets of voriconazole ranges form 4.1 kg/cm^2 to 4.5 kg/cm^2. The friability its loss their weight upto 0.45 % to 0.56%. The thickness of floating tablet ranges form 4.5 mm to 4.9 mm. The Drug content of a voriconazole ranges from 98.42% to 99.87%. The buoyancy time of floating tablet ranges form 4.0 min to 4.7. Whereas from the dissolution studies it was evident that the formulation F6 showed better and desired drug release pattern i.e., 96.33 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Voriconazole, Eudragit RL 100, Eudragit RS 100, Ethyl cellulose, Sustained release tablets.

A R T I C L E I N F O

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1. Introduction

The Effervescent Systems have been used in buoyant systems utilized matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric

acid or chambers containing a liquid that gasifies at body temperature [1]. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating which is insoluble but permeable, allows permeation of water. Thus carbondioxide is released causing the beads to float in the stomach. The main mechanism involved in Floating System there are various attempts have been made to retain the dosage form in the stomach as away of increasing there tent ion time. These attempts include introducing floating dosage forms and swelling or expanding systems, muco adhesive systems, high density systems, modified shape systems, gastric-emptying delaying devices and co administration of gastric emptying delaying drugs. Among these, the floating dosage forms have been most commonly used [2].

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system [3]. After release of drug, the residual System is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also required to keep the dosage form reliably buoyant on the surface of the meal.

Advantaged of FDDS [4]

1. The gastro retentive systems are advantageous for drugs absorbed through the stomach, e.g. ferrous salts, antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence, HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. The gastro retentive systems are advantageous for drugs meant for local action in the stomach. e.g. antacids.
4. FDDS improves patient compliance by decreasing dosing frequency.
5. The better therapeutic effect of short half-life drugs can be achieved.
6. The gastric retention time is increased because of buoyancy.
7. The enhanced absorption of drugs which solubilize only in stomach.
8. The avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.

Application of FDDS:

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastro intestinal tract [5]. It retains the dosage format the site of absorption and thus enhances the bioavailability. These are summarized as follows:

1. Sustained Drug Delivery: The HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems.

2. Site-Specific Drug Delivery:

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

3. Absorption Enhancement:

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential can did a test obe formulated as floating drug delivery systems, there by maximizing their absorption. Voriconazole is a triazole antifungal medication used to treat serious fungal infections. It is used to treat invasive fungal infections that are generally seen in patients who are immuno compromised [6]. These include invasive candidiasis, invasive aspergillosis, and emerging fungal infections. The mechanism of action of voriconazole binds and inhibits ergosterol synthesis by inhibiting CYP450-dependent 14-alpha sterol demethylase. The inhibition of 14-alpha sterol demethylase results in a depletion of ergosterol in fungal cell membrane.

2. Materials and Methods

Voriconazole (Natco Labs), Chitosan, Sodium CMC & Talc (SD fine chemical, Mumbai, India), Guar Gum, Sodium bicarbonate & Magnesium stearate (Merck Specialities Pvt Ltd, Mumbai, India), Micro crystalline cellulose (Heligent pharma, Mumbai, India). All other reagents used were of analytical grade.

Methodology:

Preformulation parameters:

The quality of tablet, once formulated by rule is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane [8]. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk

volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together [9]. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where,
M = weight of sample
V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until [9] difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where,
Tap = Tapped Density
M = Weight of sample
V = Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions [9]. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b= Bulk Density
Tap = Tapped Density

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compression of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Voriconazole. Total weight of the tablet was considered as 500mg. The Voriconazole and all other ingredients were individually passed through sieve no ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method [9].

Optimization of Sodium bicarbonate concentration: Sodium bicarbonate was employed as effervescent gas generating agent [10]. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on that the concentration of sodium bicarbonate was finalized and preceded for further formulations.

Evaluation of post compression parameters for prepared Tablets: The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight [11]. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined.

The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness [12]. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance [12]. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets [12]. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2) / W] \times 100$$

Where,
W1 = Initial weight of three tablets
W2 = Weight of the three tablets after testing

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Voriconazole were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug [13]. The mixture was made up to volume with water. The solution was suitably

diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In-vitro* Buoyancy studies:** The in vitro buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl [14]. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

***In vitro* Dissolution Parameters:**

The 900ml 0f 0.1 HCl was placed in vessel and the USP apparatus II was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was continued from 0 to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced [15]. The suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 266 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

The Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model [16].

Zero order release rate kinetics: To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release

Higuchi release model: [17]

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation [18]. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100-Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant. Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion.

3. Results and discussion

The present study was aimed to developing effervescent floating tablets of Voriconazole using various polymers. All the formulations were evaluated for physicochemical properties and in-vitro drug release studies.

Preformulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Optimization of sodium bicarbonate concentration:

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 50mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

***In-Vitro* Dissolution Release Studies**

From the dissolution data it was evident that the formulations prepared with Sodium CMC as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with Chitosan retarded the drug release in the concentration of 75 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.33 % in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time. The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

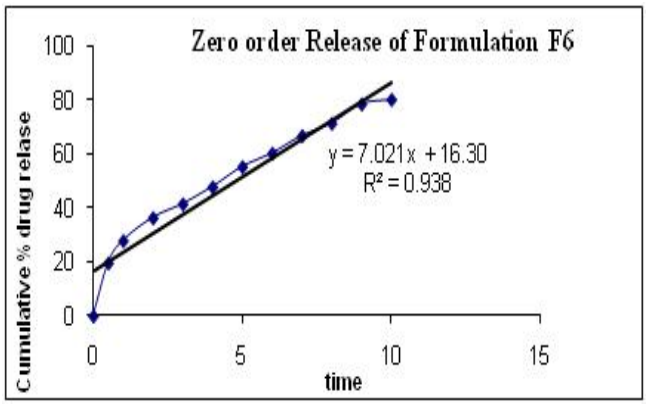

Figure 8: Zero order release kinetics graph

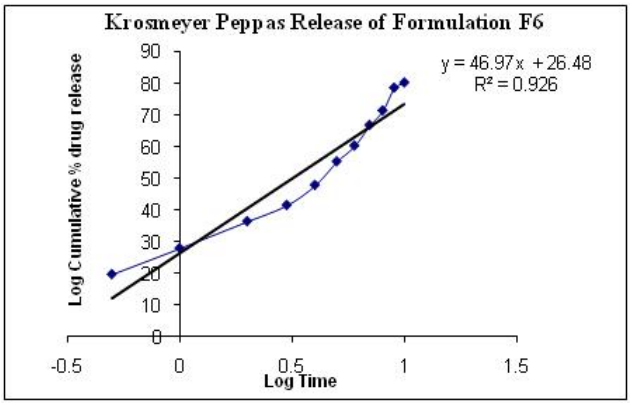

Figure 10: Krossmayer peppas graph

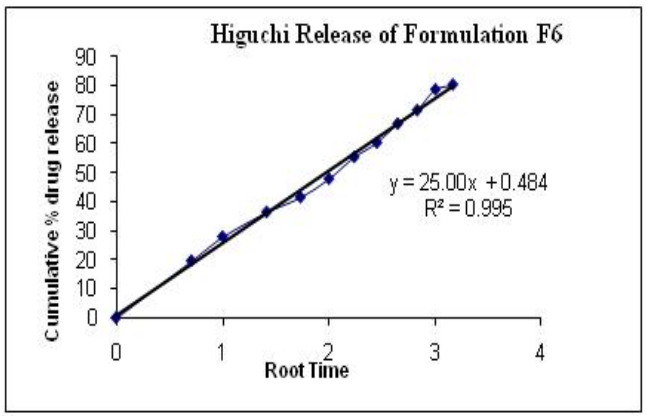

Figure 9: Higuchi release kinetics graph

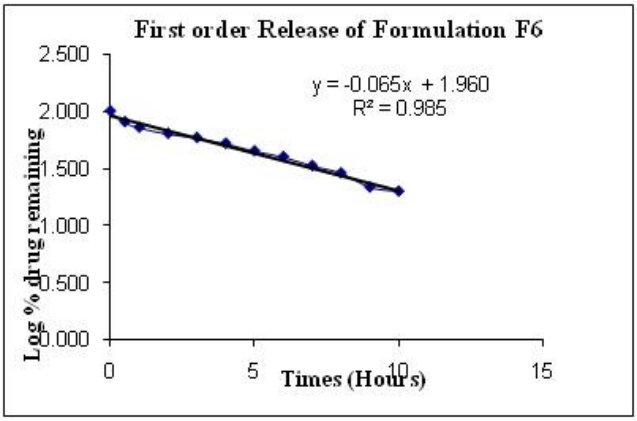

Figure11: First order release kinetics graph

Table: 1 Optimization sodium bicarbonate concentration

S.No	Excipient Name	EF1 (mg)	EF2 (mg)	EF3 (mg)
1	Voriconazole	50	50	50
2	Guar gum	50	50	50
4	$NaHCO_3$	25	50	75
5	Mg.Stearate	5	5	5
5	Talc	5	5	5
7	MCC pH 102	Q.S	Q.S	Q.S
	Total weight	250	250	250

Table: 2 Formulation compositions for floating tablets

Formulation No.	Voriconazole	Sodium CMC	Chitosan	Guar gum	$NaHCO_3$	Mag. Stearate	Talc	MCC pH 102
F1	50	25	-----	-----	50	5	5	QS
F2	50	50	-----	-----	50	5	5	QS
F3	50	75	-----	-----	50	5	5	QS
F4	50	-----	25	-----	50	5	5	QS
F5	50	-----	50	-----	50	5	5	QS
F6	50	-----	75	-----	50	5	5	QS
F7	50	-----	-----	25	50	5	5	QS
F8	50	-----	-----	50	50	5	5	QS
F9	50	-----	-----	75	50	5	5	QS

All the quantities were in mg, Total weight is 250 mg.

Table: 3 Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06

F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Table 4: *In vitro* quality control parameters for tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	252.5	4.5	0.52	4.8	99.76	4.0
F2	255.4	4.2	0.54	4.9	99.45	4.2
F3	248.6	4.4	0.51	4.9	99.34	4.5
F4	250.6	4.5	0.55	4.9	99.87	4.1
F5	259.4	4.4	0.56	4.7	99.14	4.0
F6	250.7	4.2	0.45	4.5	98.56	4.4
F7	252.3	4.1	0.51	4.4	98.42	4.5
F8	251.2	4.3	0.49	4.7	99.65	4.6
F9	248.3	4.5	0.55	4.6	99.12	4.7

Table 5A: Release kinetics data for optimized formulation (F6)

Cumulative (%) release	Time (t)	Log (%) release	log (t)	log (%) remaining
0	0			2.000
19.62	0.5	1.293	0.301	1.905
27.86	1	1.445	0.000	1.858
36.35	2	1.561	0.301	1.804
41.45	3	1.618	0.477	1.768
47.8	4	1.679	0.602	1.718
55.25	5	1.742	0.699	1.651
60.24	6	1.780	0.778	1.599
66.73	7	1.824	0.845	1.522
71.34	8	1.853	0.903	1.457
78.52	9	1.895	0.954	1.332
80.17	10	1.904	1.000	1.297
88.75	11	1.948	1.041	1.051
96.33	12	1.984	1.079	0.565

Table 5B: Release kinetics data for optimized formulation (F6)

Release rate (cumulative % release / t)	1/cum% release	Peppas log q/100	% drug remaining
			100
39.240	0.0510	-0.707	80.38
27.860	0.0359	-0.555	72.14
18.175	0.0275	-0.439	63.65
13.817	0.0241	-0.382	58.55
11.950	0.0209	-0.321	52.2
11.050	0.0181	-0.258	44.75
10.040	0.0166	-0.220	39.76
9.533	0.0150	-0.176	33.27
8.918	0.0140	-0.147	28.66
8.724	0.0127	-0.105	21.48
8.017	0.0125	-0.096	19.83
8.068	0.0113	-0.052	11.25
8.028	0.0104	-0.016	3.67

Table 6: Dissolution Data of Voriconazole Tablets Prepared with Sodium CMC, Chitosan & Guar gum in Different Concentrations

	Cumulative percent drug dissolved (n=3±SD)								
	With Sodium CMC Different Concentrations			**With Chitosan Different Concentrations**			**With Guar Gum Different concetrations**		
	F1	F2	F3	F 4	F 5	F 6	F 7	F 8	F 9
0.5	21.73	18.52	19.53	18.45	18.42	19.62	18.81	19.89	14.21
1	59.23	37.47	28.97	36.26	27.73	27.86	29.02	28.04	18.87
2	84.9	59.93	35.89	52.16	35.63	36.35	35.70	35.43	27.19
3	94.87	65.85	45.7	70.01	42.04	41.45	43.32	41.65	35.66
4	94.87	77.54	54.38	87.26	57.25	47.80	49.25	47.18	43.32
5	--	89.55	61.2	93.10	64.33	55.25	55.28	53.81	51.06
6	--	96.6	67.06	--	75.41	60.24	60.92	58.89	57.13
7	--	--	72.52	--	83.84	66.73	66.08	64.53	63.63
8	--	--	77.88	--	92.80	71.34	70.44	69.43	69.71
9	--	--	86.6	--	--	78.52	77.22	72.83	73.34
10	--	--	89.09	--	--	80.17	80.90	79.98	79.27
11	--	--	94.52	--	--	88.75	87.83	83.52	82.86
12	--	--	--	--	--	96.33	91.90	88.65	85.97

4. Conclusion

In the present research work Effervescent floating tablet formulation of Voriconazole by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various natural polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Sodium CMC were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Chitosan retarded the drug release up to 12 hours in the concentration of 75 mg (F6).The formulations prepared with Guar gum were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

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