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Research Article

FORMULATION AND EVALUATION OF VORICONAZOLE FLOATING TABLETS

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ABSTRACT

The present study involves in the preparation and evaluation of floating tablets of Voriconazole by wet granulation method by using the hydrophilic polymer such as hydroxy propyl methyl cellulose (HPMC K4M) and Carbopol 934 P. Sodium bicarbonate and citric acid were incorporated as gas generating agent. The study aims to achieve extended retention in the stomach which may result in prolonged absorption in proximal part of the small intestine. The prepared tablets were evaluated in terms of thickness, average weight, hardness, friability, drug content uniformity, swelling index, *in- vitro* buoyancy study and *in-vitro* dissolution study. The formulated tablet Hardness was found to being the range of 5.5 ±0.42 to 7.0±0.35 kg/cm^2, the % friability was in the range of 0.72± 0.26 to 0.96± 0.14. *In-vitro* release studies were carried out using USP XXII dissolution test apparatus. The tablet containing Voriconazole was released from batch F1-F5 found to be 75.12 to 97.2 %. The release of drug from tablets sufficiently sustained for 12 hours by *in vitro* release study. The lower polymer to drug ratio there was a significant increase in drug release, F2 found to be the best formulation.

Keywords: Gastro retentive dosage form, floating tablet, Voriconazole, absorption window, HPMC K4M.

INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits and one of the most prominent oral drug delivery is floating drug delivery system for sustained release and controlled release .Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are: A. Effervescent System, and B. Non-Effervescent System. Floating drug delivery systems are designed to provide the following advantages (1) increased and more effective absorption for drugs which have specific absorption sites (2) increased contact time for local activity in the stomach where such is required and (3) the ability to decrease dosing frequency.

Voriconazole is an Antifungal Agent; it binds and inhibits ergosterol synthesis by inhibiting cyp450-dependent 14-alpha sterol demethylase. Voriconazole is incompletely absorbed from GI tract, within absorption window confined to upper part of GI tract. It also has half-life about 1.7 hours and its absolute bioavailability is reported to be about 45-50% of the administered oral dose. An obstacle to the more successful use of Voriconazole therapy is high incidence of GI symptoms seen in about 30% patients, especially during initial weeks of treatment. Patient compliance decreases with frequent dosing regimen and side effects associated with the same. In order to optimize the therapy research efforts have been focused on the development of oral sustained release (SR) preparations as well as controlled release gastro retentive dosage forms. A conventional oral SR formulation releases most of the drug content at colon, thus requiring that the drug will be absorbed from colon. The above drawbacks provide a rationale for developing Voriconazole as a gastro retentive dosage form, which is retained in the stomach and produces a constant input of drug to the absorption site. This improves bioavailability of the drug, reduces frequency of dosing, thus minimizes side effects and enhances patient compliance. The present study outlines a systematic approach for the development of Intragastric Buoyant Tablets of Voriconazole with a view to enhance its oral bioavailability and efficacy.

MATERIALS AND METHODS

Voriconazole was received as a gift sample from Glen mark generic Ltd in Mumbai. HPMC K4M is received as a gift sample from Molychem. Mumbai, Carbopol 934 P is received as a gift sample from Colorcon Asia Pvt. Ltd., Citric Acid is received as a gift sample from Rolex.

Mumbai. All other materials were used of Pharma grade.

Formulation of hydrodyamically balanced tablets of Voriconazole [1, 2, and 3]

Floating matrix tablets containing Voriconazole were prepared by wet granulation technique using variable concentrations of HPMC K15M, Carbopol 934P with sodium bicarbonate. All the ingredients except magnesium stearate and talc were blended in glass mortar uniformly. Mixed all the ingredients and passed through sieve no#60. Granulation was done with sufficient solution of PVP K30 and Isopropyl Alcohol. Wet mass was passed through sieve no #12 and dried at 45-55oC for 2 h. dried granules were sized by sieve no # 18 and mixed with magnesium stearate and talc. Granules obtained were compressed with 13mm punch. The weights of the tablets were kept constant for formulations F1 to F5.

Physicochemical evaluation of intragastric buoyant tablets

i) Pre-compression parameters:

a) Angle of repose *(θ):* [4]

The frictional forces in a loose powder or granules can be measured by angle of repose. "This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane". The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

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

Where θ = angle of repose
h = height
r = radius

b) Compressibility index[5, 6]

The flow ability of powder were evaluated by comparing the bulk density (d_0) and taped density (d_f) of powder and the rate at which it packed down. Compressibility index is calculated by,

Compressibility index (%) = $\frac{d_f - do}{d_f} \times 100$

Where do = bulk density
df = tapped density

II) Post-compression parameters: [7, 8]

a) Shape of tablets

The compressed tablets were examined under the magnifying lens for the shape of the tablet.

b) Tablet dimensions

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness was measured individually.

c) Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

d) Friability test

The friability of tablets was determined using roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w final). The % friability was then calculated by,

Percentage of friability = 100 ($1-w_0/w$)

Percentage friability of tablets less than 1% is considered acceptable.

e) Tablet density[6]

Tablet density is an important parameter for floating tablets. The tablet will float when its density is less than that of gastric fluid (1.004g/cc). The density was determined using following formula.

$V = \pi r^2 h$

$d = m/v$

Where v = volume of tablet (cc)
r = radius of tablet (cm)
h = crown thickness of tablet (mm)
m = mass of tablet

f) Weight variation test[6]

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. The following percentage deviation in weight variation is allowed.

g) Buoyancy / floating test [9, 10, 18]

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

h) Swelling study [11, 12]

The swelling behaviour of a dosage form is measured by studying its weight gain or water uptake. The dimensional changes measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake is measured in terms of percent by using following formula.

$w_u = \frac{w_t - w_0}{w_0} \times 100$

w_t = weight of dosage form at time t.
w_0 = initial weight of dosage form

i) Test for content uniformity [13]

Weigh and powder 20 tablets, weigh accurately a quantity of powder equivalent to 200mg of Voriconazole, shake with 70 ml of water and diluted to 100 ml with water. Dilute 10 ml of the stock and diluted to 100ml with water. Further dilute 10 ml to 100ml and measure the absorbance at 255nm by taking 798 as the (1%, 1cm) at the maximum about 255nm.

j) In-vitro drug release study[14, 15]

In-vitro release studies were carried out using USP XXIII, paddle dissolution test apparatus. 900ml of simulated gastric fluid (pH 1.2) was taken in dissolution vessel and the temperature of the medium was maintained at 37^{0}C±0.5^{0}C. The speed was 100 rpm. 1ml of sample was withdrawn at predetermined time intervals for 12 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1N HCl as a blank at λmax 255 nm using U.V. Spectrophotometer.

Peppas-Korsmeyer equation was given as [16, 17]

$\% R = ktn$

Where R= drug release
K=constant
n=slope

RESULTS AND DISCUSSION

Hydrodynamically balanced tablets of Voriconazole (Intragastric Buoyant Tablets) were prepared and evaluated to increase its local action and bioavailability. In the present study 5 formulations with variable concentration of polymer were prepared and evaluated for Physico-chemical, *invitro* drug release studies.

Preformulation studies

a) Melting point determination

Melting point of Voriconazole was found to be in the range 127-130C, which complied with IP standards, indicating purity of the drug sample.

b) Solubility

Voriconazole is low soluble in water. It is soluble to the degree of one part in two parts of water and one part in 100 parts of ethanol. It is insoluble in chloroform, acetone, Methylene chloride and ether.

c) Compatibility study

Compatibility studies were performed using FTIR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Voriconazole were obtained at 1473cm-1 and 1028cm-1.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. The spectra for all formulations were shown in Fig. 1 to 2.

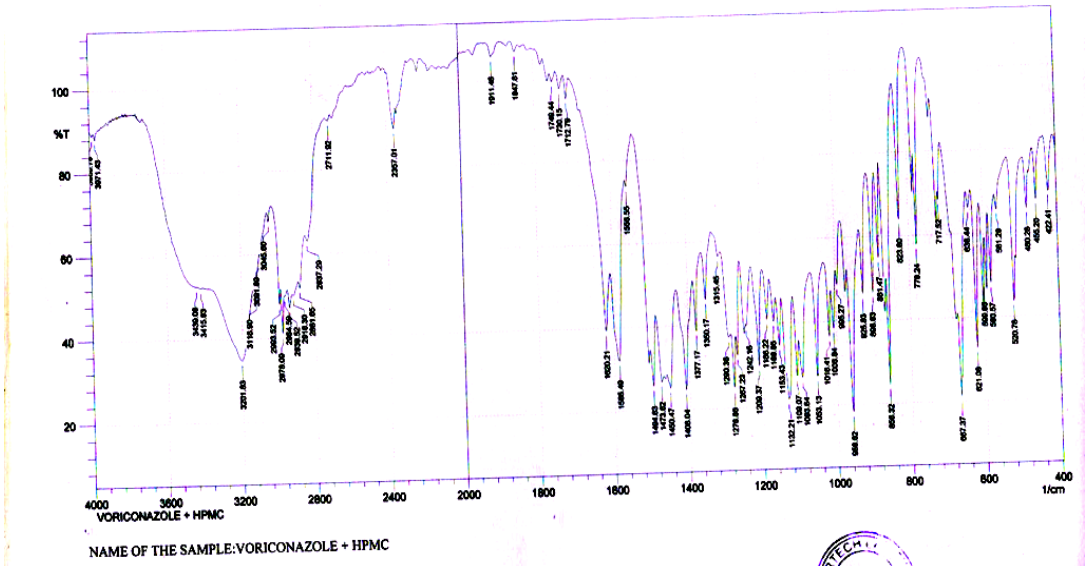

Fig: 1 FTIR (kbr) spectrum of voriconazole and HPMC K4M

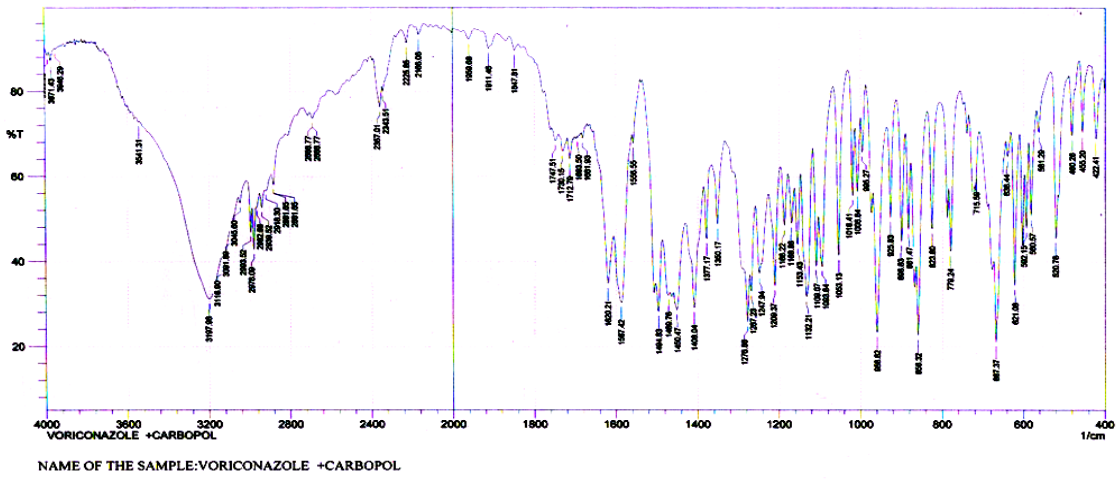

Fig: 2 FTIR (kbr) spectrums of voriconazole and carbopol 934 P

Standard calibration curve of voriconazole

Standard calibration curve of Voriconazole was determined by plotting absorbance Vs concentration at 255nm and it follows the Beer's law. The results were show in Table 1 and Fig 3 .the regression value is 0.9965 and slope is 0.0287.

Table 1: Calibration curve of Voriconazole at 255nm by UV spectrophotometer

S. No.	Concentration (µg/ml)	Absorbance (255 nm)
1	2	0.132
2	4	0.224
3	6	0.326
4	8	0.426
5	10	0.524
6	12	0.627
7	14	0.731
8	16	0.796
9	18	0.892
		0.0257
		0.9976

Slope; Regression Value

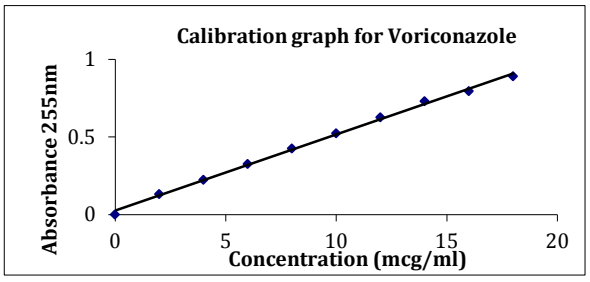

Fig: 3 standard graphs for voriconazole by uv spectrophotometer

Evaluation of intragastric buoyant tablet formulations

Pre-compression parameters

Angle of repose and compressibility index was given in table 2.

ii. Post-compression parameters

Shape of the tablet, Tablet dimensions, Hardness, Friability, Weight variation , Drug content uniformity of the tablets are listed in table 3, and Tablet density, buoyancy lag time, total floating time are given in table 4.

Table 2: Angle of Repose, Compressibility Index

Batch	Angle of repose	Bulk density g/cc	Tapped density g/cc	Compressibility index (%)
F1	$25^0.30' \pm 0.11$	0.4952	0.5742	13.94
F2	$26^0.41' \pm 0.51$	0.4785	0.5654	15.87
F3	$25^0.28' \pm 0.42$	0.4865	0.5857	17.39
F4	$28^0.56' \pm 0.47$	0.4586	0.5236	12.84
F5	$29^0.52' \pm 0.32$	0.4726	0.5621	16.22

Table 3: Physical properties of tablets of batch F1 to F5

Batches	*Diameter (mm)	*Thickness (mm)	*Hardness (kg/cm^2)	*Friability (%)	*weight variation (mg)	*drug content uniformity (mg)
F1	13.09 ±0.040	5.16 ±0.010	5.5 ±0.47	0.96± 0.14	800.65 ±1.29	98.9± 0.56
F2	13.08 ±0.006	5.14 ±0.012	6.0 ±0.32	0.72± 0.26	801.50 ±1.74	96.1± 0.41
F3	13.09 ±0.067	5.12 ±0.06	6.0 ±0.54	0.91±0.11	799.55 ±1.18	95.8± 0.72
F4	13.08 ±0.070	5.16 ±0.011	5.5 ±0.42	0.86±0.19	800.05 ±1.37	95.2± 0.19
F5	13.08 ±0.056	5.16 ±0.012	7.0 ±0.35	0.79±0.21	801.65 ±1.49	96.7± 0.35

***- average of three values ; ± - standard deviation.**

Table 4: Tablet Density, Buoyancy Lag Time, Total Floating Time

Batch	Tablet density (g/cc)	Buoyancy lag time (sec)	Total floating time (hrs)
F1	0.97	62	>8
F2	0.92	46	>8
F3	0.94	55	>12
F4	0.90	40	> 12
F5	0.99	71	>12

a) Swelling study

Swelling study was performed on all batches (F1 to F5) for 5 hrs. The results of swelling index were shown in Table 5.

Table 5: Swelling Index of Tablets of Batch F1 to F5

Time	Swelling Index (%)				
	F1	**F2**	**F3**	**F4**	**F5**
1 hr	38	36	35	32	30
2 hrs	51	46	42	39	41
3 hrs	60	56	49	41	46
4 hrs	77	64	57	49	54
5 hrs	86	77	68	56	60

b) In-vitro drug release studies

All the five formulations of prepared floating tablets of Voriconazole were subjected to invitro release studies were carried out using dissolution apparatus, 0.1N HCl (pH 1.2). The invitro release of all five batches of floating tablets showed the release with an initial effect. In the first hour drug released was 25.2%, 21.6%, 22.10%, 19.36%, and 17.32% for F1, F2, F3, F4 and F5 are shown in Table 6 and fig 6.

Fig 4: Buoyancy / Floating Test

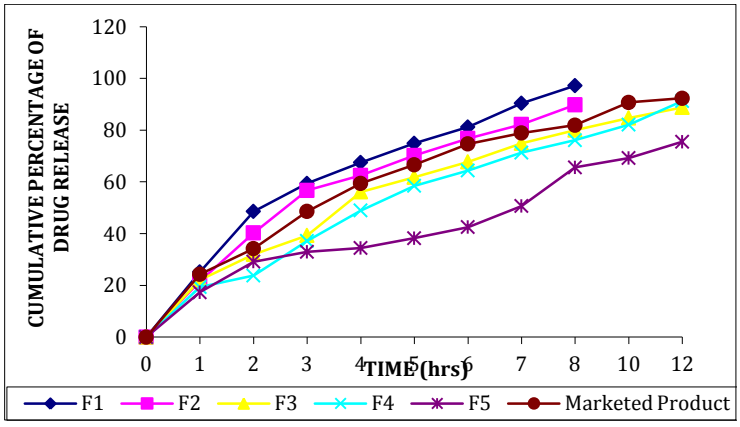

Fig 5: I*n* Vitro Drug Release Profile for Tablets of Batches F1 to F5

CONCLUSION

It was concluded that preformulation study and drug excipients compatibility study was done initially and results directed the further course of formulation. IR spectra studies revealed that the drug and the polymers used were compatible. The tablets were formulated using various concentrations of polymers such as HPMC K4M and Carbopol 934P and effervescing agent (sodium bicarbonate). Results of *invitro* drug release studies using USPXXIII dissolution apparatus indicated that the F4 (Carbopol 934 P-150 mg, Sodium bicarbonate-50 mg) had good sustained release. From the in-vitro dissolution data it was found that formulation F1 and F2 containing HPMC K4M released 97.2% and 95.8% of drug within 8 hr of the study indicating that the polymer amount is not sufficient to control the drug release. F4 containing Carbopol 934 P (150 mg) alone released 91.23% of drug with in 12 hrs. It concludes F4 had better-sustained release than the other formulation (F1, F2, and F3& F5). The optimized formulation F4 had better control over release rate when compared with the marketed product **(**Rextro 200mg) release rate.

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