FORMULATION AND EVALUATION OF EFFERVECENT FLOATING TABLET OF VORICANAZOLE

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ABSTRACT

The objective of the present study is formulate and evaluate of floating tablet of Voriconazole, which would remain in stomach and upper part of GIT for prolonged period of time. The floating tablets of Voriconazole were prepared by direct compression using Carbopol 971P, Ethyl cellulose and Sodium carboxy methylcellulose polymers as a swelling agent. Sodium bicarbonate was used as a floating effervescent agent. FT-IR spectral studies revealed that the drug and polymer used were compatible. The tablets were formulated by taking various concentrations of polymers as a release retarding agents. The formulations were evaluated for various physical parameters, floating lag time and In-vitro drug release etc. From the results obtained, Formulation V3 gives desirable sustained effect for 12 hours having 99.36% drug release at the end of the 12 hours. Formulation V3 contain Carbopol 971P on response parameters. All Nine formulations showed satisfactory results for Floating lag time, Total floating time.

Key words: *Voriconazole, Carbopol 971P, Ethyl cellulose, Sodium carboxy methylcellulose and Floating tablets.*

INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT). Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach , low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach,superporous hydrogel systems magnetic systems etc. The current review deals with floating type gastro retentive drugdelivery system.

Need for Gastro retention: Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).Drugs that are less soluble or that degrade at the alkaline

pH. Drugs that are absorbed due to variable gastric emptying time. Local or sustained drug delivery to the stomach and proximal small intestine to treat certain conditions. Particularly useful for the treatment of peptic ulcers caused by H.Pylori infections.

Floating Drug Delivery Systems:

A floating dosage form is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble (or) unstable in intestinal fluids. The floating properties of these systems help to retain in the stomach for a long time. Various attempts have been made to develop floating systems, which float on the gastric contents and release drug molecules for the desired time period. After the release of a drug, the remnants of the system are emptied from the stomach. Based on the mechanism of buoyancy, two different technologies have been used in development of floating drug delivery systems.

These include: 1) Effervescent system 2) Non- Effervescent system.

Materials: Voriconazole from Ranbaxy, Sodium Carboxy Methyl Cellulose, Ethyl Cellulose, Carbopol, Citric acid, Sodium bicarbonate, Microcrystalline cellulose, Magnesium stearate, Talc.

METHODOLOGY: Analytical method development:

Determination of absorption maxima:

A solution containing the concentration 10 µg/ mL drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

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 angle of repose was calculated using the following formula:

Tan θ = h / r Tan θ = 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 powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula: Bulk Density = M / Vo

Where, M = weight of sample, Vo = 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 The tapped density was calculated, in gm per L, using the formula: 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.

Carr's Index = [(tap - b) / tap] × 100 , Where, b = Bulk Density Tap = Tapped Density

Procedure for direct compression method:

Drug 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 by using 9mm punch.

Formulation composition for Floating tablets

INGREDIENTS (MG)	FORMULATION CODE								
	V1	V2	V3	V4	V5	V6	V7	V8	V9
Voriconazole	50	50	50	50	50	50	50	50	50
Carbopol 971P	25	50	75	-	-	-	-	-	-
Ethyl cellulose	-	-	-	25	50	75	-	-	-
Sodium carboxy methyl cellulose	-	-	-	-	-	-	25	50	75
Citric acid	10	10	10	10	10	10	10	10	10
Sodium bicarbonate	15	15	15	15	15	15	15	15	15
Micro crystalline cellulose	141	116	91	141	116	91	141	116	91
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	4	4	4	4	4	4	4	4	4
Total Weight	250	250	250	250	250	250	250	250	250

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.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. 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. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure.

% Friability = [(W1-W2) / W1] × 100, Where, W1 = Initial weight of tablets

W2 = Weight of the 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. 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. 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* drug release studies**

Dissolution parameters:

Apparatus:		USP-II, Paddle Method,
Dissolution Medium		0.1 N HCL
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:
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. Suitable dilutions were done with media and analyzed by spectrophotometrically at 315nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:
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.

Zero order release rate kinetics:
To study the zero–order release kinetics the release rate data are 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: To study the Higuchi release kinetics, the release rate data were fitted tothe 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. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$Mt/ M\infty = K t^n$

Where, Mt/ 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 (Mt/ M∞) versus log (time) is linear.

Drug – Excipient Compatibility studies Fourier Transform Infrared (FTIR) spectroscopy: The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 550 cm^{-}

RESULTS : Analytical Method

Determination of absorption maxima

The standard curve is based on the spectrophotometer. The maximum absorption was observed at315nm.

Calibration curve: Graphs of Voriconazole was taken in 0.1N HCL. The standard graph of Voriconazole showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Pre-formulation parameters: 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 0.47 ± 0.11to 0.51 ± 0.08 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.56 ± 0.05 to 0.64 ± 0.03 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 21.4 which shows that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.14 to 1.26 indicating the powder has good flow properties

Post Compression Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, Drug content and drug release studies were performed for floating tablets.All the parameters for SR layer such as weight variation, friability, hardness, thickness, drug content were found to be within limits.

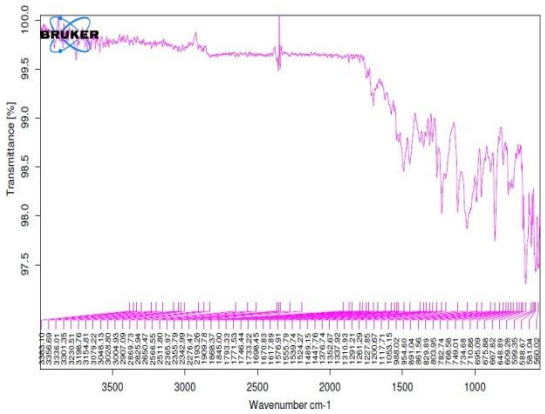
Dissolution data of Voriconazole Floating tablets containing Carbopol 971P

From the dissolution data it was evident that the formulations prepared with Carbopol 971P as polymer were retarded the drug release 12 hours. In low concentration of the polymer the drug release was unable to retarded up to 12 hours.

Whereas the formulations prepared with higher concentration of Ethyl cellulose retarded the drug release up to 12 hours in the concentration 75 mg. In lower concentrations the polymer was unable to retard the drug release up to 12 hours.

Whereas the formulations prepared with Sodium carboxy methylcellulose were retarded the drug release in the concentration of 25 mg (V7 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 92.54 % in 12 hours with good retardation.

Hence from the above dissolution data it was concluded that V3 formulation was considered as optimised formulation because good drug release (99.36%) in 12 hours.



FTIR Spectrum of optimized formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Voriconazole are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION:

Gastro retentive dosage form using Carbopol 971P, Ethyl cellulose and Sodium carboxy methylcellulose was prepared to develop a controlled release tablets that could retain in the stomach for longer periods of time delivering the drug to the site of action, i.e., stomach. Systematic studies were conducted using different concentration of rate releasing different polymers for extending the drug release in upper GIT. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies to find out the micromeritic properties to assess flowability, compressibility properties studies and all the formulations gave good results for above preformulation studies. Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet hardness, friability, weight variation, buoyancy, content uniformity, all the formulations were found within the permissible range. Finally it was concluded that Among all the formulations (V1toV9), it was observed that formulation V3 has shown better buoyancy and dissolution profile. So Formulation V3 was found to be the best formulation among others.

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