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DESIGN AND CHARACTERIZATION OF VORICONAZOLE MICROSPHERES

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Abstract:

The objective of the presentreserach work was to formulate bioadhesive microspheres of Voriconazole using different polymers Eudragit RS 100, Ethyl Celulose, Sodium alginate were formulated to deliver Voriconazole via oral route.Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size. The invitro drug release decreased with increase in the polymer.Analysis of drug release mechanism showed that the drug release from the formulations followed diffusion and the best fit model was found to be Korsmeyer-Peppas.FT-IR studies were carried out to find out the possible interaction between the selected drugs and polymer. FT-IR studies revealed that there was no interaction between the selected drugs and polymer. Among the different batches, Formulation F6 was selected as the ideal formulations, after considering their mean particle size, free flowing nature, better drug loading capacity, and in vitro drug release. The % drug release microspheres was found to be 97.65%.

Keywords: *Voriconozole,Microspheres*

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INTRODUCTION:

For many decades, medication of an acute disease or a chronic disease has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems [1-3]. An appropriately designed sustained or controlled release drug delivery system can be major advance toward solving the problem associated with the existing drug delivery system [4,5].

The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug.

- Spatial placement relates to targeting a drug to a specific organ or tissue, while
- Temporal delivery refers to controlling the rate of drug delivery to the target tissue [6].

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be filled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable motility and relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e.,

stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [7].

The objective in designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain a constant drug blood level. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time, i.e release from the dosage form should follow zero order kinetics [8].

Definition and General Description:

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats, and waxes. The natural polymers include albumin and gelatin [9,10] the synthetic polymers include polylactic acid and polyglycolic acid. Fig. 1 shows two types of microspheres: Microcapsules, where the entrapped substance is completely surrounded by a distinct capsule wall, and micromatrices, where the entrapped substance is dispersed throughout the microsphere matrix.

Microspheres are small and have large surface to volume ratios. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often dictating their activity.

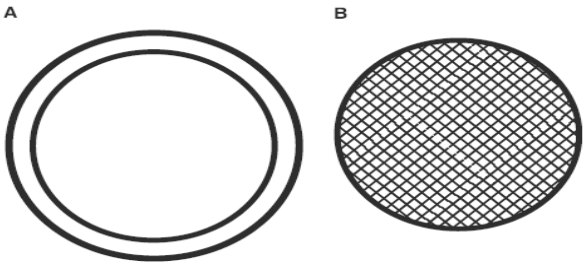

Fig 1:Schematic diagram illustrating microspheres. (A) Microcapsule consisting of an encapsulated core particle and (B) micromatrix consisting of homogeneous dispersion of active ingredient in particle.

Materials:

Table 1: List of Materials:

Voriconazole	Natco LABS
Ethyl Cellulose	Merck Specialities Pvt Ltd, Mumbai, India
Eudragit RS 100	SD fine chemical, Mumbai, India
Sodium Alginate	SD fine chemical, Mumbai, India
Calcium Chloride	Merck Specialities Pvt Ltd, Mumbai, India
Sodium Hydroxide Pellets	Merck Specialities Pvt Ltd, Mumbai, India
Potassium di hydrogen phosphate	Heligent pharma, Mumbai, India
Methanol	SD fine chemical, Mumbai, India

METHODOLOGY:

Determination of λmax:

Stock solution (1000µg/ml) of Vorniconazole was prepared in 0.1N HCl. This solution was appropriately diluted with 0.1N HCl (pH 1.2) to obtain a concentration of 10µg/ ml. The resultant solution was scanned in the range of 200nm to 400nm on UV-Visible spectrophotometer. The drug exhibited a λmax at 256nm.

Preparation of Standard Calibration Curve of Vorniconazole: [11]

- 10 mg of Vorniconazole was accurately weighed and dissolved in 10ml of 0.1N HCl (Stock Solution – I) to get a concentration of 1000 µg/ml.
- From the stock solution- I, 1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
- From the stock solution- II,aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 5 to 35µg/ml. The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 256nm against reference solution 0.1N HCl (pH 1.2).

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Method of Preparation Ionotropic Gelation Method:

Batches of microspheres were prepared which involved reaction by using Ethyl Cellulose and Eudragit RS 100 as polymers. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Voriconazole (100 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The Microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of Microspheres and then air-dried.

Table 2: Prepared formulation of Microspheres

S. no	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug	100	100	100	100	100	100	100	100	100
2	Eudragit RS 100	100	200	300						
3	Ethyl Cellulose				100	200	300			
4	Sodium Alginate	20	20	20	20	20	20	100	200	300
5	Methanol(ml)	5	5	5	5	5	5	5	5	5
6	Water(ml)	10	10	10	10	10	10	10	10	10
7	Calcium chloride(5%)	QS	QS	QS	QS	QS	QS	QS	QS	QS

Characterization of Microspheres:

Percentage yield

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Microspheres)}}{\text{Theoretical mass (Polymer + Drug)}} \times 100$$

Drug entrapment efficiency:

Microspheres equivalent to 100 mg of the drug Voriconazole were taken for evaluation. The amount of drug entrapped was estimated by crushing the Microspheres. The powder was transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using simulated gastric fluid pH 6.8 . After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 242 nm. The amount of drug entrapped in the Microspheres was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental DrugContent}}{\text{Theoretical Drug Content}} \times 100$$

In vitro drug release study:

The diffusion studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^{0}C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 6.8 (900ml). A quantity of accurately weighed Microspheres equivalent to 100mg Voriconazole each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 242nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric fluid pH 6.8 maintaining sink conditions throughout the experiment.

In-Vitro Drug Release Kinetics

The release data obtained was fitted into various mathematical models.The parameters 'n' and time component 'k',the release rate constant and 'R', the regression coefficient were determined by Korsmeyer-Peppas equation to understand the release mechanism.

To examine the release mechanism of Voriconazole from the Microspheres, the release data was fitted into Peppa's equation,

$$Mt / M\infty = Kt^n$$

Where, **Mt / M∞** is the fractional release of drug, 't' denotes the release time, 'K' repr-esents a constant incorporating structural and geometrical characteristics of the device, 'n' is the diffusional exponent and characterize the type of release mechanism during the release process.

RESULTS AND DISCUSSIONS:

Determination Of λmax:

Stock solution (1000µg/ml) of Vorniconazole was prepared in 0.1N HCl. This solution was appropriately diluted with 0.1N HCl (pH 1.2) to obtain a concentration of 10µg/ ml. The resultant solution was scanned in the range of 200nm to 400nm on UV-Visible spectrophotometer. The drug exhibited a λmax at 256nm.

A solution of 10µg/ml of Voriconazole was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 256nm in 0.1N HCl and had good reproducibility. Correlation between the concentration and absorbance was found to be near to 0.9999, with a slope of 0.0244.

Table 3: Standard Calibration curve of Voriconazole

Concentration (µg/ml)	Absorbance
5	0.121
10	0.244
15	0.367
20	0.484
25	0.610
30	0.734
35	0.852

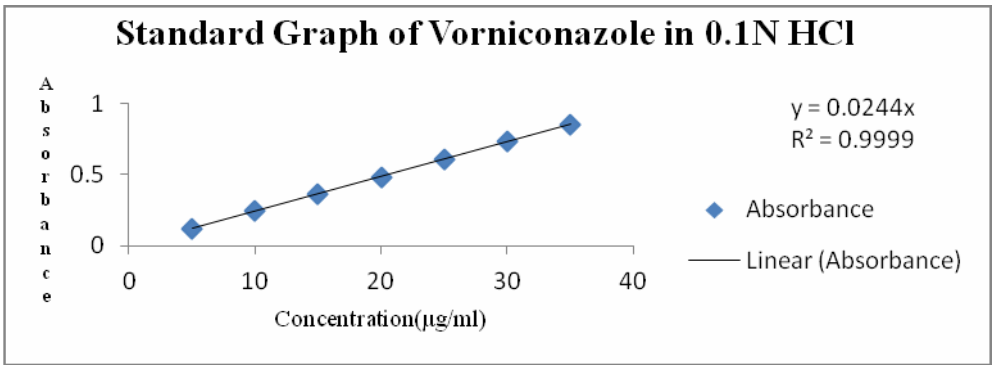

Fig 2: Standard graph of Voriconazole

Evaluation and Characterisation of Microspheres

Percentage Yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug- polymer solution, adhesion of polymer solution to the magnetic bead and Microspheres lost during the washing process. The percentage yield was found to be in the range of 76 to 92% for Microspheres containing HPMC polymer.

Table 4 : % yield of the formulations

Formulation	% yield
F1	87.61
F2	76.45
F3	87.24
F4	91.65
F5	84.54
F6	87.43
F7	89.76
F8	75.86
F9	79.22

DRUG AND EXCIPIENT COMPATABILITY STUDIES

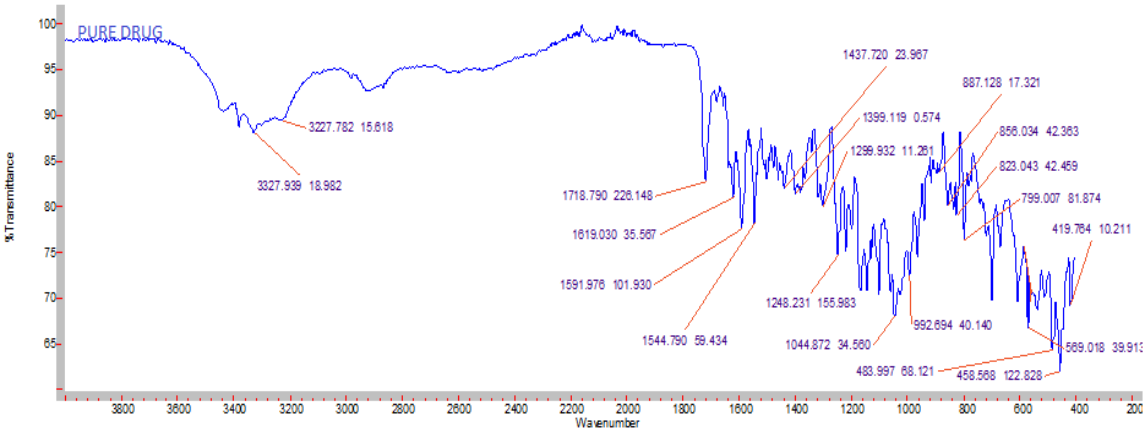

Fig 3:FTIR spectrum of pure drug

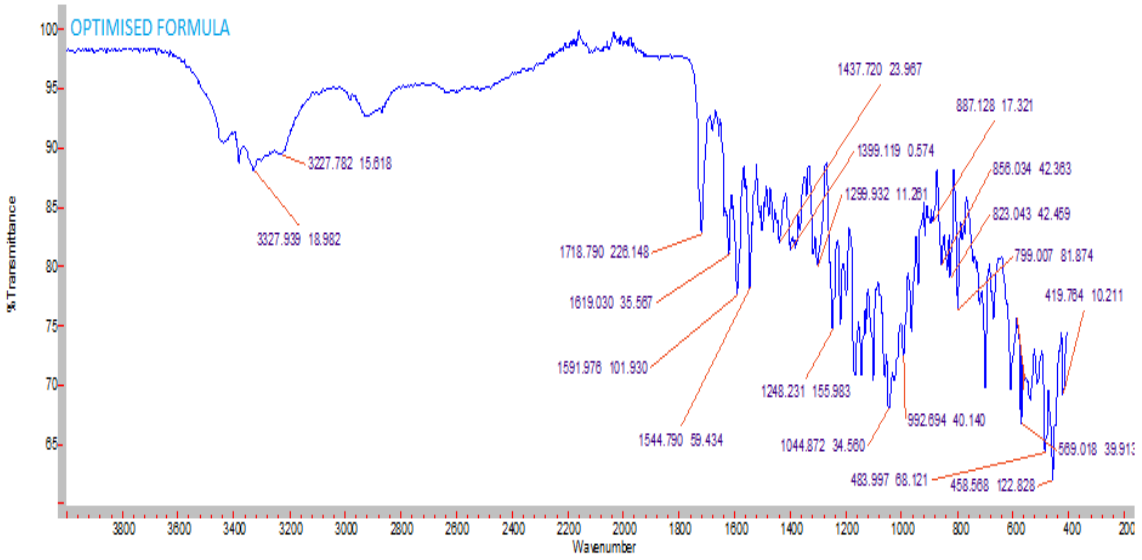

Fig 4:FTIR spectrum of optimised formulation:

Table 5: pre formulation parameters

s.no	Formulation Code	Mean particle size (µm)	Bulk density Gm/cm^3	Tapped density	Hausner's Ratio	Carr's index	Angle of repose
1	F1	650	0.49±0.04	0.54±0.	16.21±0.06	0.86±0.06	25.11
2	F2	670	0.52±0.09	0.52±0.	16.87±0.05	0.98±0.05	25.67
3	F3	720	0.50±0.05	0.58±0.	17.11±0.01	0.64±0.03	25.54
4	F4	690	0.51±0.06	0.54±0.	17.67±0.08	1.12±0.04	25.43
5	F5	780	0.52±0.03	0.57±0.	16.92±0.04	6.8±0.08	27.34
6	F6	770	0.53±0.04	0.56±0.	17.65±0.09	1.06±0.09	26.22
7	F7	760	0.43±0.04	0.53±0.	16.24±0.06	0.84±0.06	27.11
8	F8	690	0.51±0.09	0.54±0.	16.67±0.05	0.87±0.05	26.67
9	F9	700	0.53±0.05	0.55±0. 05	17.73±0.01	0.67±0.03	28.54

Discussion on results:

The bulk density and tapped density of the microsperes were found to be 43 gm/cm^3-53 gm/cm^3 and 53 gm/cm^3 - 58 gm/cm^3 respectively. The obtained lies within the range.this results help in calculating the % compressibility of the Microspheres.

The % compressibility of Microspheres was determined by carrs compressibility index. The results obtained for % compressibility for all the formulation within the range.

The results obtained for hausners ratio for all the formulation within the range of index 16.24-17.73. This indicates the Microspheres have good flow character.

The angle of repose values obtained for the formulations ranged from 25.11- 28.54. This indicates the Microspheres have good flow character.

Table 6: Percentage of the prepared Microspheres

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESIO
		INITIAL	FINAL	
1	F_1	20	13	65
2	F2	20	14	70
3	F3	20	15	75
4	F4	20	17	85
5	F5	20	12	60
6	F6	20	13	65
7	F7	20	16	23
8	F8	20	14	20
9	F9	20	17	30

***In-Vitro* Drug Release Studies:**

Diffusion studies of all the formulations were carried out using franz diffusion apparatus. The diffusion studies were conducted by using diffusion media, pH 6.8.

This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The release of the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

Table 7: *In-Vitro* drug release data of Voriconazole Microspheres

TIME (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	23.56	19.35	17.72	14.45	26.36	21.32	19.81	17.19	16.1
2	30.45	29.72	24.28	23.23	35.62	31.18	23.73	36.45	29.74
3	41.39	37.43	34.72	31.93	42.34	39.78	35.23	47.65	30.56
4	52.49	45.64	39.83	38.51	53.81	47.34	44.32	54.65	48.29
5	61.25	54.83	51.92	46.82	63.21	56.78	50.43	68.45	57.1
6	71.56	62.34	64.67	76.23	71.43	64.47	56.45	70.23	65.25
7	84.34	69.25	71.54	84.41	73.52	70.76	61.32	76.87	70.32
8	79.34	83.56	79.81	89.72	88.64	84.81	67.54	80.34	76.25
9	77.81	79.48	88.29	91.42	93.89	97.65	70.43	85.43	79.23

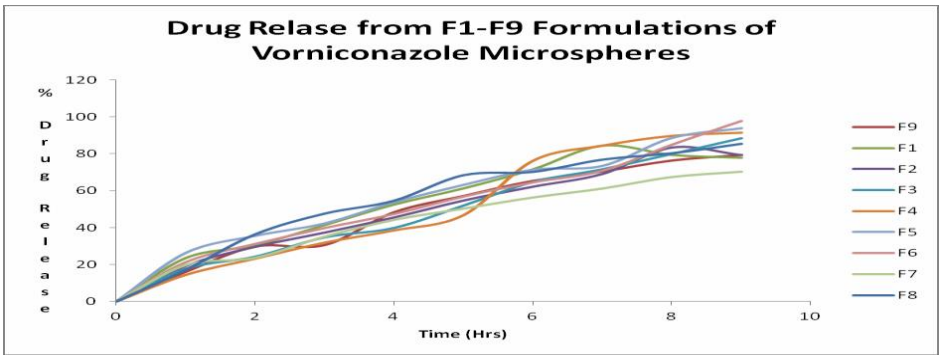

Fig 5:Drug release from F1to F9 Vorniconazole

From this diffusion values it was evident that the formulations prepared with Ethyl Cellulose as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the microspheres. As the concentration of polymer increases the retarding nature was also increased. Ethyl Cellulose in the concentration of 300 mg showed good % drug release i.e., 97.65 in 9 hours. Where as in the concentration of 200 mg it showed less drug release due to increased retarding nature of polymer.

From the above results it was evident that the formulation F6 is best formulation with desired drug release pattern extended up to 9 hours.

In-Vitro Drug Release Kinetics

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in-vitro drug diffusion data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher

coefficient of determination with the Korsmeyer-Peppas model (R^2 = 0.914 to 0.996) whereas release exponent value (n) ranged from 0.498 to 0.743. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

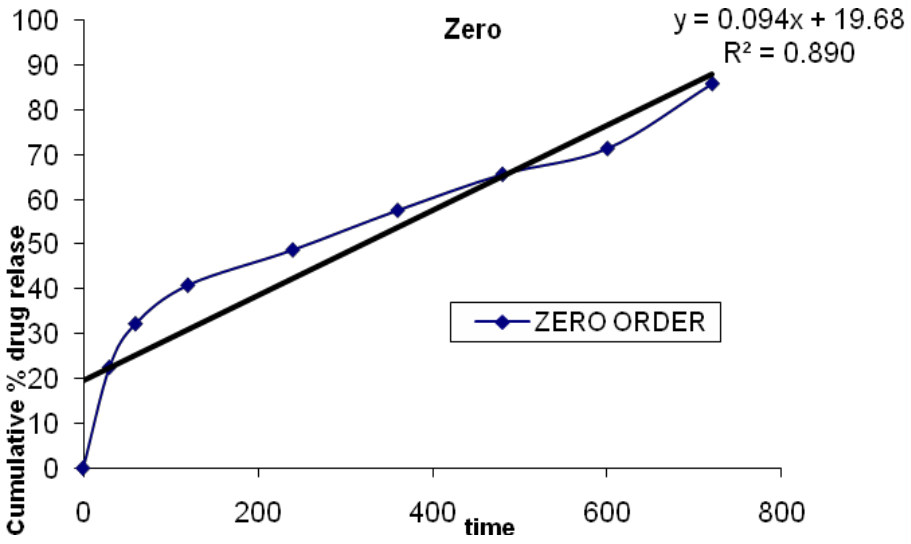

Fig 6: zero order- kinetic model

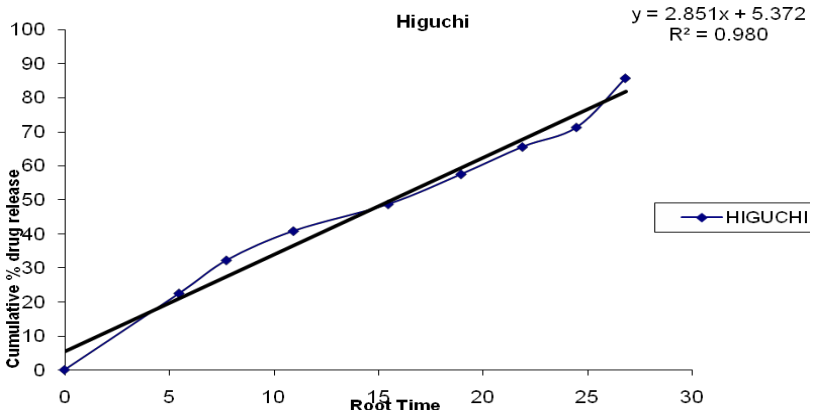

Fig 7: higuchi model-kinetic model

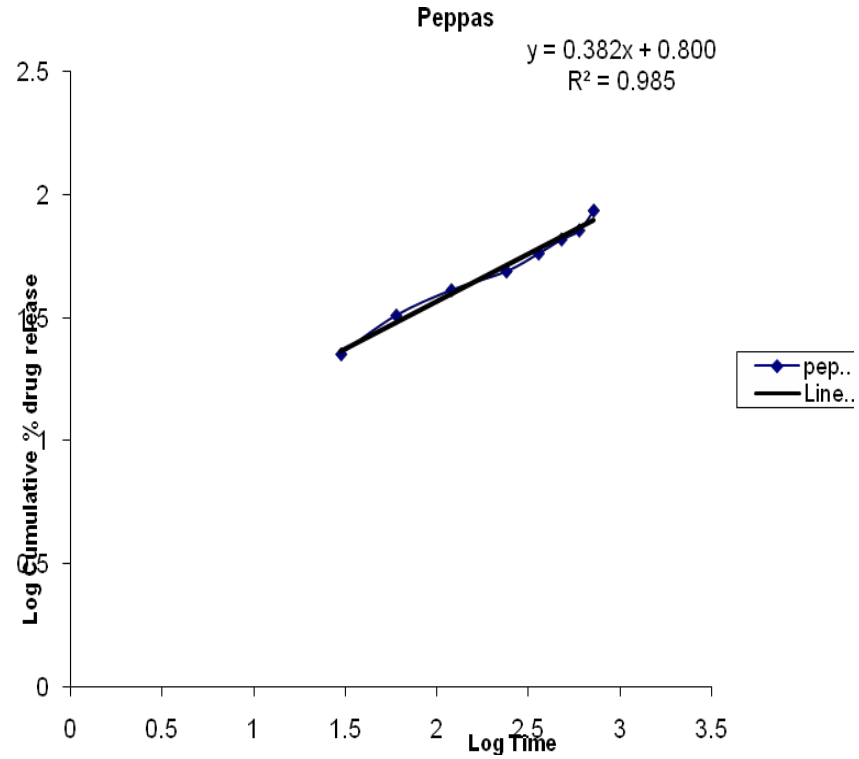

Fig 8: Peppas- kinetic model

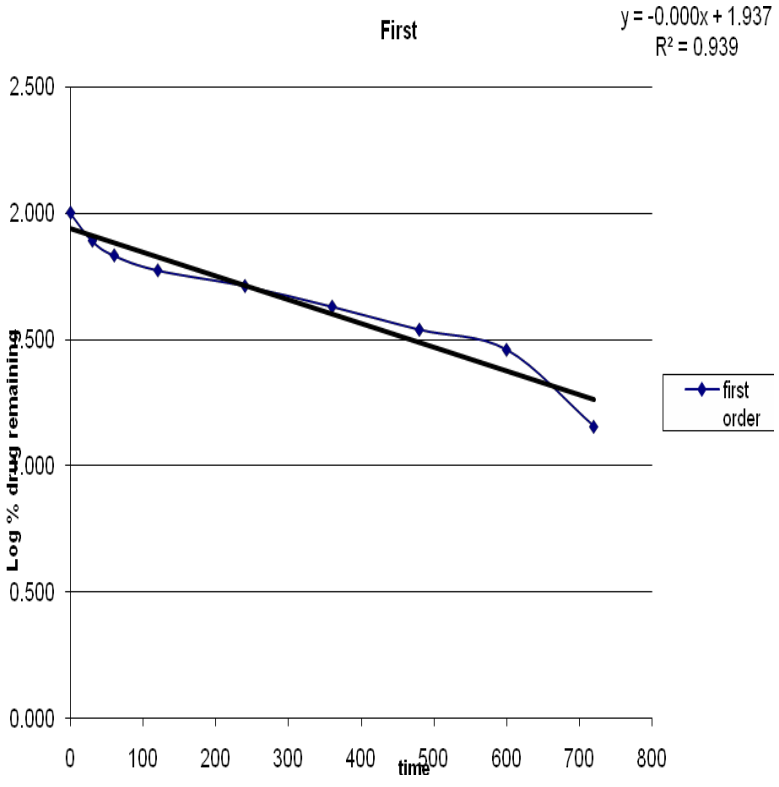

Fig 9: First order- kinetic model

CONCLUSION:

In the present work, bioadhesive microspheres of Voriconazole using different polymers Eudragit RS 100, Ethyl Celulose, Sodium alginate were formulated to deliver Voriconazole via oral route.Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size. The invitro drug release decreased with increase in the polymer.Analysis of drug release mechanism showed that the drug release from the formulations followed diffusion and the best fit model was found to be Korsmeyer-Peppas.FT-IR studies were carried out to find out the possible interaction between the selected drugs and polymer. FT-IR studies revealed that there was no interaction between the selected drugs and polymer. Among the different batches, Formulation F6 was selected as the ideal formulations, after considering their mean particle size, free flowing nature, better drug loading capacity, and in vitro drug release. The % drug release microspheres was found to be 97.65%.

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