International Journal of Pharmacy and Analytical Research (IJPAR)

IJPAR |Vol.12 | Issue 2 | Apr - Jun -2023
www.ijpar.com

Research article ***Analytical research***

Formulation Development And Characterization Of Voriconazole Nanoparticles

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Published on: 13.05.2023

ABSTRACT

Nanoparticles represent a promising drug delivery system of controlled and targeted drug release. They are specially designed to release the drug in the vicinity of target tissue. The aim of this study was to prepare and evaluate Carbopol p934 nanoparticles containing Voriconazole in different drug to polymer ratio. SEM indicated that nanoparticles have a discrete spherical structure. FT-IR studies indicated that there was no chemical interaction between drug and polymer and stability of drug. The *in vitro* release behavior from all the drug loaded batches was found to be first order release and provided sustained release over a period of 12 h. The developed formulation overcome and alleviates the drawbacks and limitations of Voriconazole sustained release formulations and could possibility be advantageous in terms of increased bioavailability of Voriconazole.

Keywords: Nanoparticles, PLGA, Carbopol p934, Eudragit RL and Voriconazole.

INTRODUCTION

Nanotechnology has gained huge attention over time. The fundamental component of nanotechnology is the nanoparticles. Nanoparticles are particles between 1 and 100 nanometres in size and are made up of carbon, metal, metal oxides or organic matter[1]. The nanoparticles exhibit a unique physical, chemical and biological properties at nanoscale compared to their respective particles at higher scales. This phenomena is due to a relatively larger surface area to the volume, increased reactivity or stability in a chemical process, enhanced mechanical strength, etc.[2]. These properties of nanoparticles has led to its use various applications. The nanoparticlesdiffers from various dimensions, to shapes and sizes apart from their material[3]. A nanoparticle can be either a zero dimensional where the length, breadth and height is fixed at a single point for example nano dots, one dimensional where it can possess only one parameter for example graphene, two dimensional where it has length and breadth for example carbon nanotubes or three dimensional where it has all the parameters such as length, breadth and height for example gold nanoparticles.The nanoparticles are of different shape, size and structure. It be spherical, cylindrical, tubular, conical, hollow core, spiral, flat, etc. or irregular and differ from 1 nm to 100 nm in size. The surface can be a uniform or irregular with surface variations. Some nanoparticles are crystalline or amorphous with single or multi crystal solids either loose or agglomerated. Numerous synthesis methods are either being developed or improved to enhance the properties and reduce the production costs. Some methods are modified to achieve process specific nanoparticles to increase their optical, mechanical, physical and chemical properties. A vast development in the instrumentation has led to an improved nanoparticle characterisation and subsequent application. The nanoparticles are now used in every objects like from cooking vessel, electronics to renewable energy and aerospace industry. Nanotechnology is the key for a clean and sustainable future.[4]

Advantages of nanoparticles

Nanoparticles offer numerous advantages in drug delivery system. These advantages include, but are not limited:

- Nanoparticles have many significant advantage over conventional and traditional drug delivery system.
- Nanoparticles are control and sustain release form at the site of localization, they alter organ distribution of drug compound. They enhance drug circulation in blood, bioavailability, therapeutic efficacy and reduce

- Nanoparticles can be administer by various routes including oral, nasal, parenteral, intra-ocular etc.
- In the tiny areas of body nanoparticles shows better drug delivery as compare to other dosage form and target to a particular cell type or receptor.
- Due to small particle size nanoparticles overcome resistance by physiological barriers in the body and easily penetrates to cell walls, blood vessels, stomach epithelium and blood–brain barrier.
- Nanoparticle enhance the aqueous solubility of poorly soluble drug, which improves bioavailability of drug.
- As a targeted drug carrier nanoparticles reduce drug toxicity and enhance efficient drug distribution.
- By using polymers drug release form nanoparticles can be modified which makes polymeric nanoparticle an ideal drug delivery system for cancer therapy, vaccines, contraceptives and antibiotics.
- Useful to diagnose various diseases
- Enhanced stability of ingredients
- Prolonged shelf life
- Used in dental surgery also as filling the tiny holes in teeth.
- Change the method of drug delivery to improve customer acceptance or reduce manufacturing costs.[5-8]

Limitations of Nanoparticles

- Small size and large surface area can lead to particleparticle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms.
- In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available.[9,10]

Classification Of Nanoparticles

The nanoparticles are generally classified into the organic, inorganic and carbon based.

Nanoprecipitation method

This is another method which is widely used for nanoparticle preparation which is also called solvent displacement method. This method precipitation of polymer and drug obtained from organic solvent and the organic solvent diffused in to the aqueous medium with or without presence of surfactant. Tamizhrasi at al prepared Lumivudine loaded nanoparticles. Firstly drug was dissolved in water, and then cosolvent (acetone used for make inner phase more homogeneous) was added into this solution. Then another solution of polymer(ethyl cellulose, eudragit) and propylene glycol with chloroform prepared, and this solution was dispersed to the drug solution. This dispersion was slowly added to 10 ml of 70% aqueous ethanol solution. After 5 minutes of mixing, the organic solvents were removed by evaporation at 35° under normal pressure, nanoparticles were separated by using cooling centrifuge (10000 rpm for 20 min), supernatant were removed and nanoparticles washed with water and dried at room temperature in a desicator.

MATERIALS

Voriconazole Sura Labs, Dilsukhnagar, Hyderabad, PLGALactel,Durect corporation, Birmingham Division, Carbopol p934Eastman company, UK, Eudragit RLSRL, Span 60 (mL), Himedia, Distilled water (ml)Rankem, Dichloromethane (ml) Rankem, MethanolRankem.

METHODOLOGY

Analytical Method Development

Determination of absorption maxima

Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

For the preparation of calibration curve stock solution was prepared by dissolving 100 mg of accurately weighed drug in 100ml of Methanol(1mg/ml). Further 1ml of the stock solution was pipette out into a 100 ml volumetric flask and volume was made up with phosphate buffer (5.5pH). From this stock solution pipette out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200-400 nm using double beam UV spectrophotometer. The absorption maxima were obtained at 252 nm with a characteristic peak.

Preparation of calibration curve

It is soluble in Methanol; hence Methanol was used for solubilizing the drug. Stock solution (1 mg/mL) of Voriconazole was prepared in Methanoland subsequent working standards (2, 4, 6, 8 and 10 µg/mL) were prepared by dilution with phosphate buffer of pH-5.5. These solutions were used for the estimation Voriconazole by UV method. The whole procedure was repeated three times and average peak area was calculated. Calibration plot was drawn between concentrations and peak area. Calibration equation and R^2 value are reported.

Preparation of nanoparticles

Preparation of Voriconazole loaded nanoparticles

Voriconazole loaded Nanoparticle was prepared by previously reported emulsification sonication method. Voriconazole was dissolved in organic solvent (20 ml, methanol and DCM 30ml). Polymers in different concentrations were dissolved in water. The organic phase was added drop wise into the polymeric solution for emulsification. Then the dispersion was sonicated (20 min) with the application of ultra-probe sonication (60 W/cm^3, Hielscher, Ultra-sonics, Germany). The formulation was stirred at 1500 rpm for 6 h using a magnetic stirrer to evaporate the organic solvent. The prepared NPs were centrifuged at 15,000 rpm for 20 min at 25 °C (Remi, Mumbai, India). NPs were separated and lyophilized using cryoprotectant (Mannitol 0.2%) and stored for further evaluation.

Table 1: Composition of nanoparticles formulations (F1 to F9)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Voriconazole	200	200	200	200	200	200	200	200	200
PLGA	100	200	300	-	-	-	-	-	-
Carbopol p934	-	-	-	100	200	300	-	-	-
Eudragit RL	-	-	-	-	-	-	100	200	300
Span 60 (mL)	2	4	6	2	4	6	2	4	6
Distilled water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Dichloromethane (ml)	30	30	30	30	30	30	30	30	30
Methanol	20	20	20	20	20	20	20	20	20

RESULTS AND DISCUSSION

Preparation of Standard Graph

Determination of absorption maxima

The standard curve is based on the spectrophotometry. The maximum absorption was observed at 252nm.

Calibration curve

Graphs ofVoriconazole was taken in 7.4 Phosphate buffer

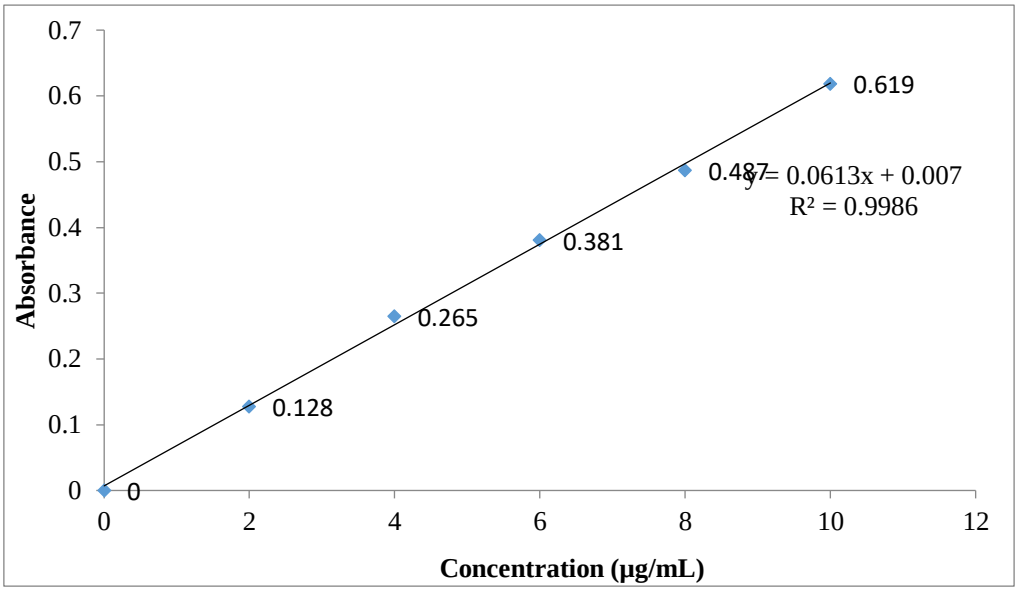

Fig 1: Standard graph of Voriconazole in 7.4 Phosphate buffer

Standard graph of Voriconazole was plotted as per the procedure in experimental method and its linearity is shown in Table 1 and Fig 1. The standard graph of Voriconazole showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Evaluation Ofvoriconazole Loaded Nanoparticles

Table 2: Evaluation of Nanoparticles

Batch No	Mean Particle size (nm)	% Yield	Drug Content	Drug encapsulation efficiency	PDI	Zeta Potential(mV)
F1	286.12 ± 18	68.14	93.51	63.92	0.668	-26.12 ± 1.8
F2	292.22 ± 19	71.54	95.81	72.29	1.268	-28.22 ± 1.9
F3	305.19 ± 16	75.92	97.65	80.41	1.153	-30.19 ± 1.6
F4	267.22 ± 20	75.20	91.54	76.91	0.868	-27.22 ± 2.0
F5	278.56± 18	79.81	94.82	82.83	0.577	-28.56± 1.8
F6	281.72± 23	86.34	98.84	87.92	0.309	-32.61± 2.3
F7	351.72± 23	73.92	95.14	62.79	0.498	-25.72± 2.3
F8	368.32± 42	77.69	97.14	70.30	0.385	-26.32± 2.2

F9	371.52± 32	83.44	97.82	76.98	0.325	-27.52± 2.4

Percentage yield of formulations F1 to F9 by varying drug was determined and is presented in Table. Highest drug content, Highest Entrapment efficiency observed for F6 formulation.
PDI observed in the F6 formulation i.e., 0.309 respectively. The Zeta potential range from -25.72 mV to -32.61 mV to all the formulations.

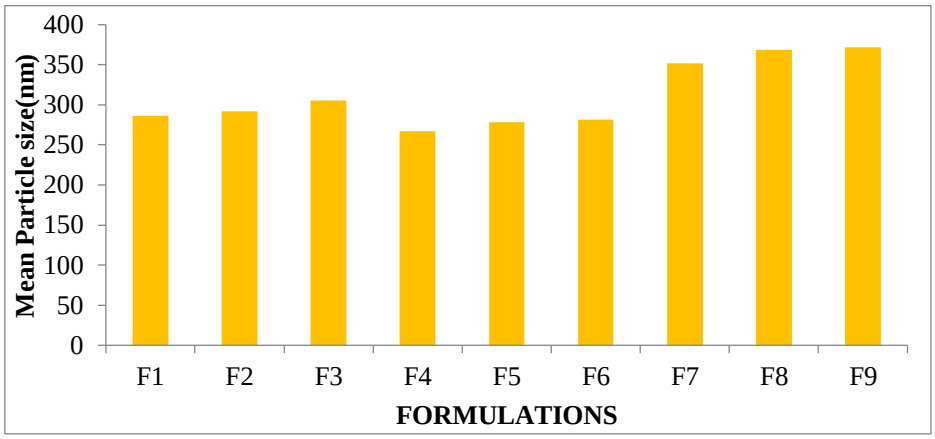

Fig 2:Mean Particle size(nm)

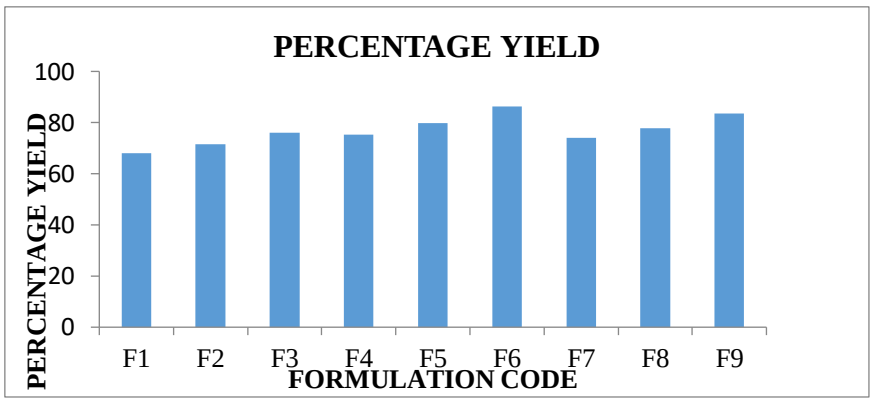

Fig3:%Yield

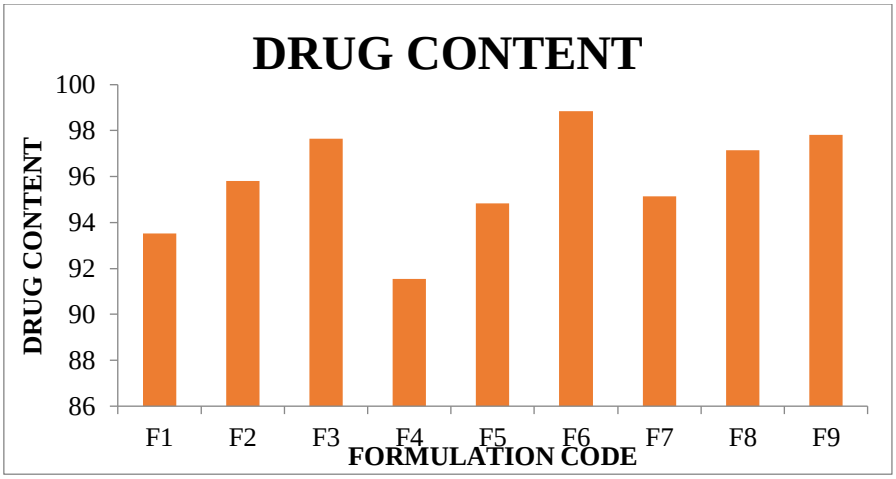

Fig4:Drug content

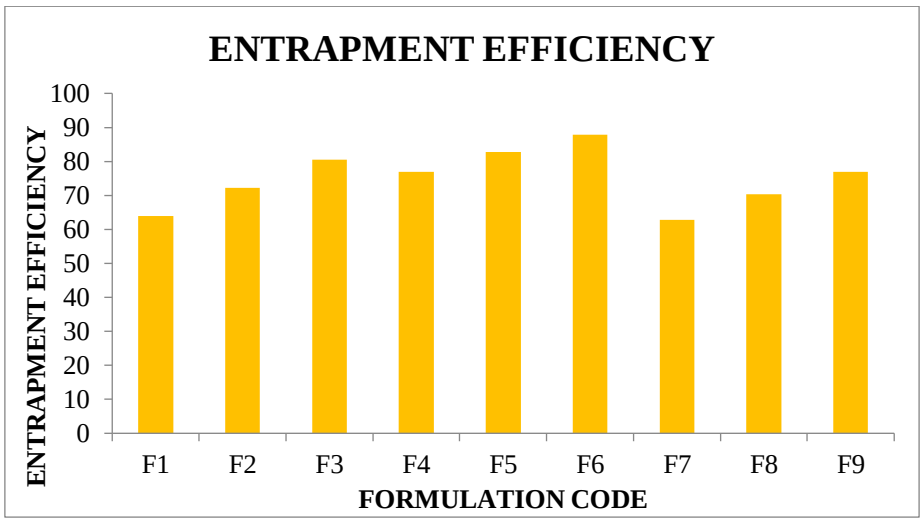

Fig5:Drug encapsulation efficiency

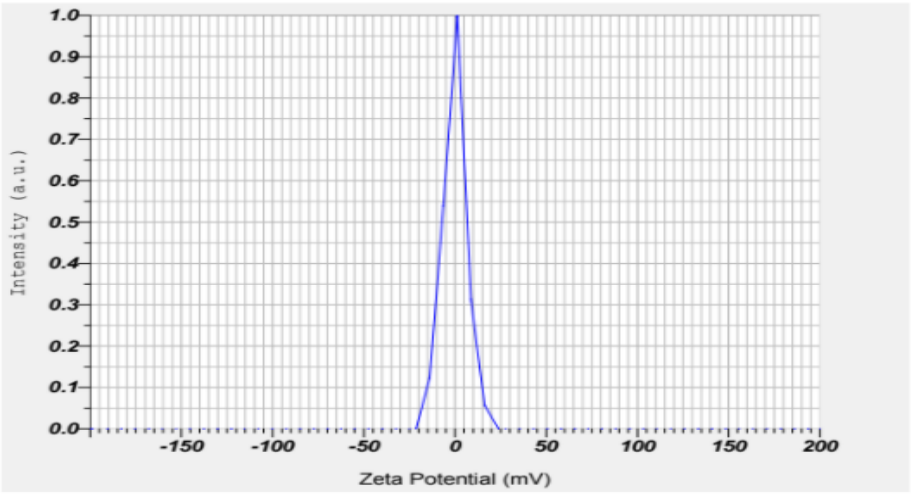

Fig 6: Zeta Potential of F6 Formulation

In vitro Drug release studies

Table3:*In vitro* Drug release studies of Voriconazole

TIME (hr)	CUMULATIVE PERCENT OF DRUG RELEASED								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	27.42	29.69	32.41	27.93	16.85	22.26	20.92	17.92	14.01
2	34.39	40.09	47.69	41.62	22.76	28.78	34.36	22.65	20.08
3	47.60	46.16	58.34	48.02	30.50	35.36	42.61	33.89	31.51
4	56.51	57.65	64.61	60.47	49.11	57.23	54.53	44.32	43.98
5	67.62	65.19	70.08	66.85	61.78	66.98	61.88	52.87	50.31
6	78.37	78.67	78.39	78.68	76.89	77.46	72.46	65.90	62.57
7	85.26	81.76	84.56	87.39	83.43	85.68	81.87	73.36	67.04
8	96.78	89.54	87.98	98.77	97.14	93.14	89.29	79.77	75.91
10	99.82	95.34	93.18			98.13	98.14	90.53	83.09
12		97.54	97.14			99.37		96.91	94.91

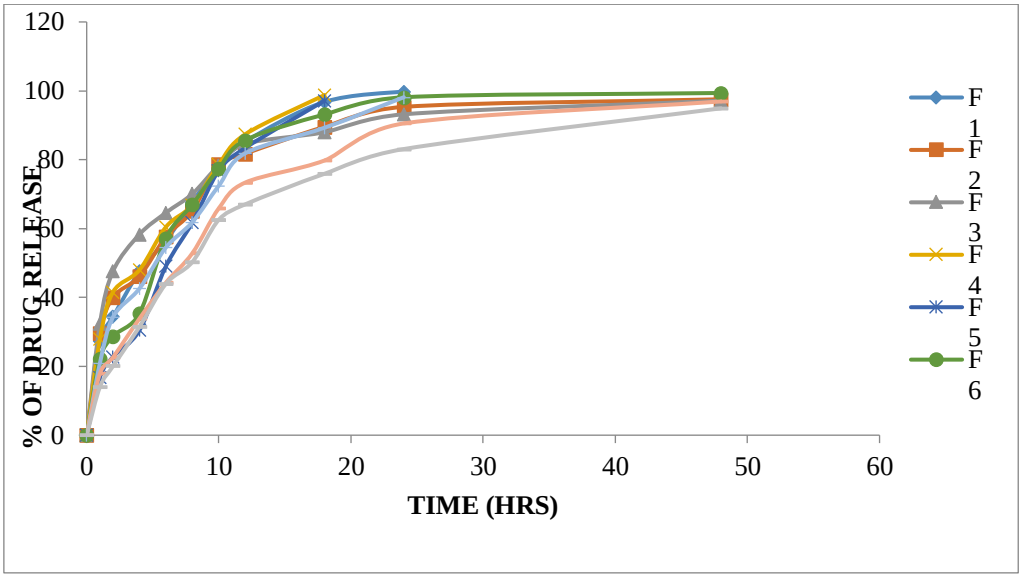

Fig 7: Dissolution study of Voriconazole Nanoparticles

Hence based on dissolution data of 9 formulations, F6Carbopol p934 (1:3)(300mg) formulation showed better release (99.37%) up to 12 hours. So F6 formulation is optimised formulation.

Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of drug release from Nanoparticles. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyerpeppas mechanisms and the results were shown in below table it follows the zero order kinetics.

Table 4: Release kinetics data for optimized formulation (F6)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
22.26	1	1.000	1.348	0.000	1.891	22.260	0.0449	-0.652	77.74	4.642	4.268	0.374
28.78	2	1.414	1.459	0.301	1.853	14.390	0.0347	-0.541	71.22	4.642	4.145	0.496
35.36	4	2.000	1.549	0.602	1.811	8.840	0.0283	-0.451	64.64	4.642	4.013	0.628
57.23	6	2.449	1.758	0.778	1.631	9.538	0.0175	-0.242	42.77	4.642	3.497	1.144
66.98	8	2.828	1.826	0.903	1.519	8.373	0.0149	-0.174	33.02	4.642	3.208	1.433
77.46	10	3.162	1.889	1.000	1.353	7.746	0.0129	-0.111	22.54	4.642	2.825	1.817
85.68	12	3.464	1.933	1.079	1.156	7.140	0.0117	-0.067	14.32	4.642	2.428	2.213
93.14	18	4.243	1.969	1.255	0.836	5.174	0.0107	-0.031	6.86	4.642	1.900	2.741
98.13	24	4.899	1.992	1.380	0.272	4.089	0.0102	-0.008	1.87	4.642	1.232	3.410
99.37	48	6.928	1.997	1.681	-0.201	2.070	0.0101	-0.003	0.63	4.642	0.857	3.784

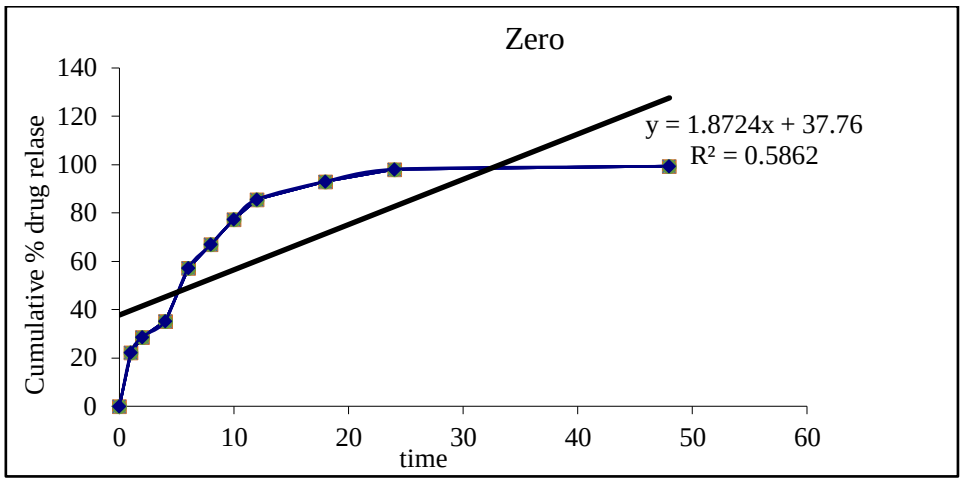

Fig 8: Graph of zero order kinetics

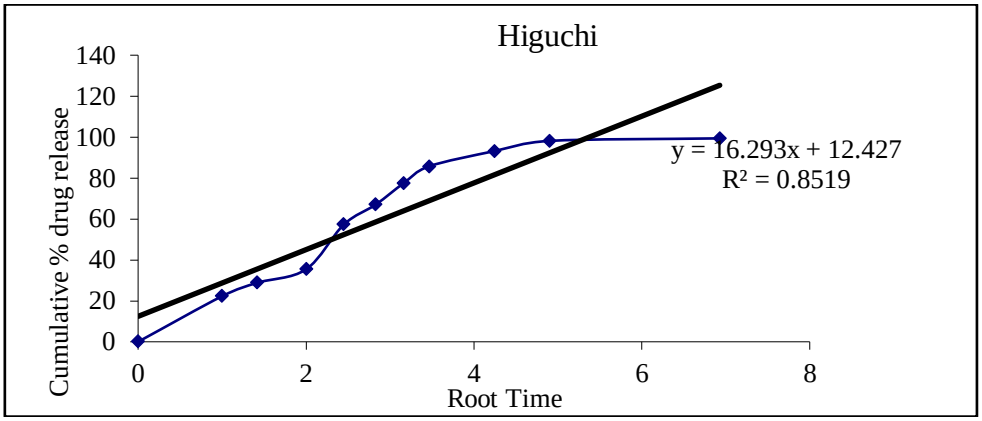

Fig9: Graph of higuchi release kinetics

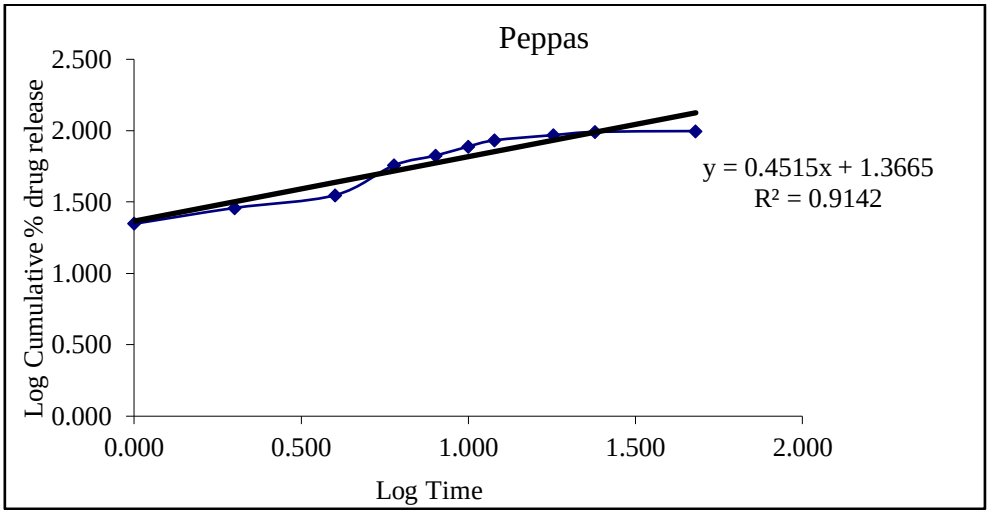

Fig 10: Graph of peppas release kinetics

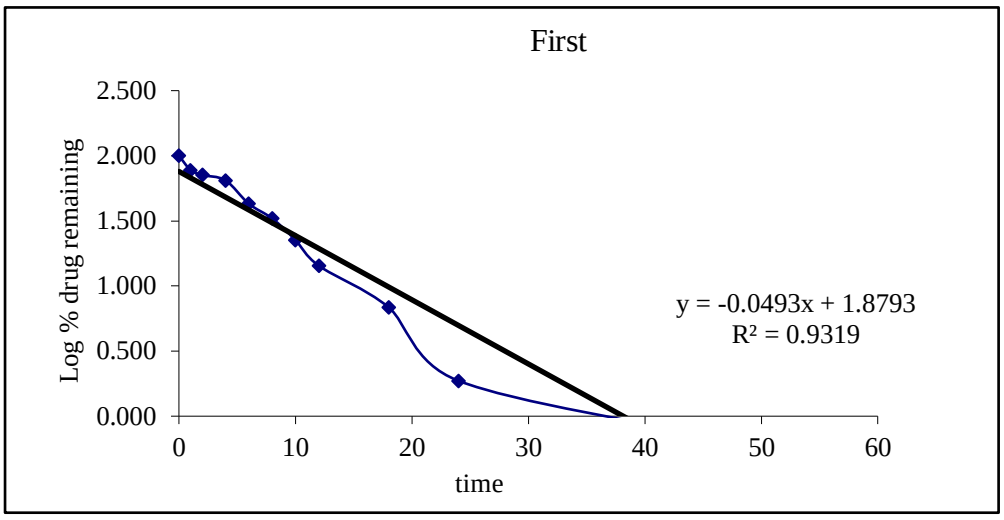

Fig11: Graph of first order release kinetics

Based on the data above results the optimized formulation followed first order release kinetics.

Drug – Excipient compatibility studies

Fourier Transform-Infrared Spectroscopy

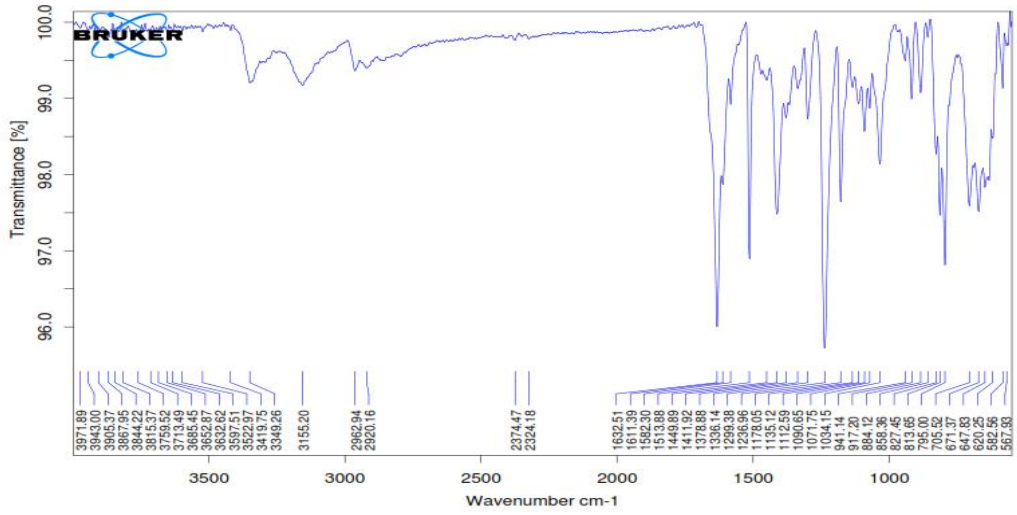

Fig12: FT-TR Spectrum of Voriconazole pure drug

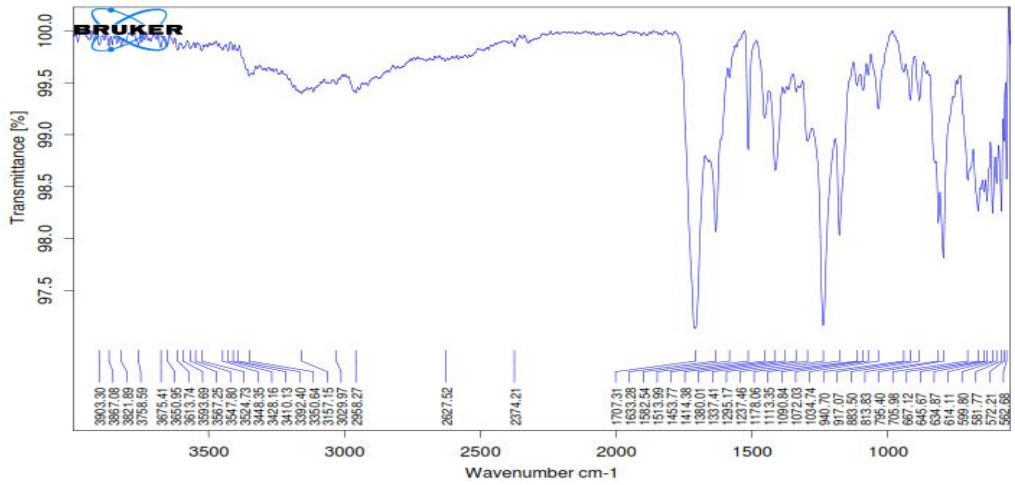

Fig 13:FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearance of peaks of pure drug and in optimised formulation.

SEM

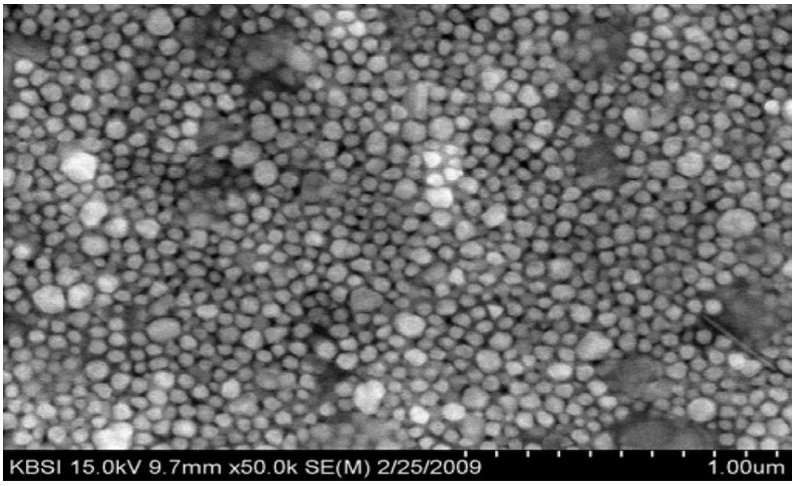

Fig 14:SEM graph of optimized formulation

SEM studies showed that the Voriconazole - loaded nanoparticles had a spherical shape with a smooth surface as shown in Figure.

XRD

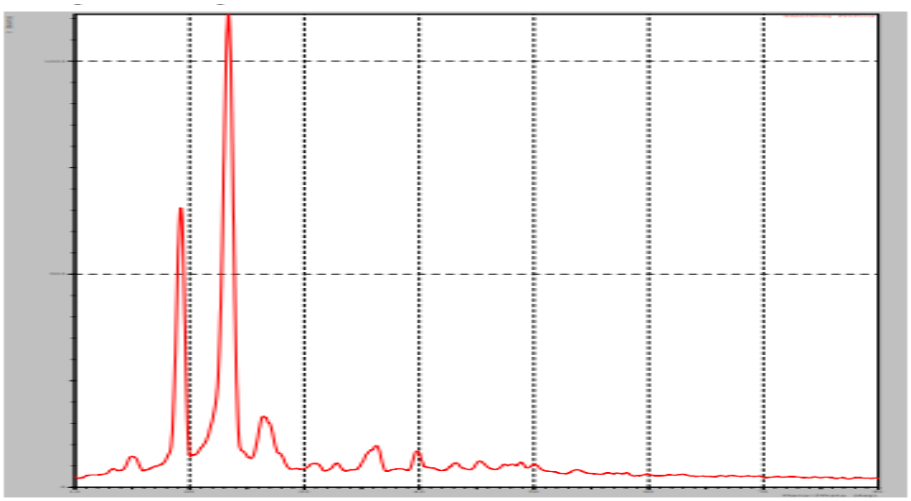

Fig 15: Voriconazole F6 optimised formulation

CONCLUSION

Nanoparticles have a special place in nanoscience and nanotechnology, not only because of their particular properties resulting from their reduced dimensions, but also because they are promising building blocks for more complex nanostructures.In our current work, we have prepared Voriconazole nanoparticles.emulsification sonication method is a simple, fast and reproducible method which is widely used for the preparation of both nanospheres and nanocapsules and its superior advantage is obtaining small particles size and narrow size distribution. The optimized Voriconazole loaded Carbopol p934 nanoparticles formulations (F6) were in nano size range (281.72±23nm) with high drug release (99.37%) adequate encapsulating efficiency exhibiting a homogenous, stable and effective.

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