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Formulation and evaluation of voriconazole nanocapsules

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Abstract

The current study's goal was to create as well as assess voriconazole nanocapsules using the diffusion of emulsion solvent technology. Voriconazole was made using the emulsion solvent diffusion method and is loaded with ethyl cellulose and HPMC Nanocapsules. The FTIR data showed that there was no drug-polymer interaction and that voriconazole nanocapsules filled with ethyl cellulose were stable. The absence of incompatibility in the formulation was investigated using compatability investigations such as FTIR and DSC. SEM is used to determine the morphological particle size of the voriconazole nanocapsules. F1 through F8 are the complete formulation codes for which the nanocapsules were tested. A percentage yield of 83.32% to 88.61% was discovered. There was 65.8 to 98.5% drug content. The nanocapsules' particle size ranged from 78 µm to 33 µm, while their drug entrapment effectiveness ranged from 54.4% to 91.4% and their drug loading capacity from 56.8% to 97.7%. The study period for swellability was 0.8 to 1.5 seconds. The optimal formulation, F8, showed an in vitro dissolving rate of 61.89%. Numerous mathematical models, including zero order, first order, Higuchi matrix, and Korsmeyer Peppas model, were fitted to the available data on drug dissolution in vitro. The R2 value and m value of the Voriconazole Nanocapsules model were 0.937, 0.399, 0.899, 0.785, and 2.560, respectively. Up to 45 mints of medication were released from the nanocapsules. The HPMC and ethyl cellulose-loaded Voriconazole nanocapsules were made under ideal circumstances and have good release properties.

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INTRODUCTION

The oil-filled core of nanocapsules, surrounded by polymeric membranes, contains medications that, given the right circumstances, can release their contents through a reaction to biological, chemical, thermal, or environmental stimuli. Colloidal

nanocapsules are produced by depositing premade polymers (PLA, PLGA, PCL, and PEG) between surfaces. It works well for administering medications that are hydrophobic. Lipid nanocapsules have been applied to rat tumour cases that are resistant to many drugs [1].

Interactions like electrostatics, covalent bonds, hydrogen bonds, etc., can be utilised as the driving force for the assembly of the multilayer shell. The hollow capsules are created as a result of the sacrificial template dissolving. Nanocapsules resemble vesicles in that they have a polymeric membrane enclosing a liquid core or polymer matrix that holds the medicine within. The active ingredients are contained within the cavity as a molecular dispersion, either liquid or solid. These hollow nanocapsules can contain a wide range of materials, including biopolymers like proteins and nucleic acids as well as chemicals, catalysts, even dyes [2].

Intravenous administration of submicron-sized nanocapsules releases the medicine within upon reaching the target. One way to help route nanocapsules—which are one thousandth of a millimetre in size—from the bloodstream to a generated tumour is to coat their surface with an antibody.

The capsules burst open and release their medicinal contents as soon as they make contact with the tumour due to an immediate blast. Approximately 6 nm, or one millionth of a millimetre, of gold particles attach to the polymer surface. These particles are particular to the laser light and help the capsules position their drug load capacity at the correct time [3].

Synthetic or natural polymer-based polymeric nanoparticles are generally stable and easily modifiable on the surface. Better bioavailability and regulated medication release in particular areas can be attained by adjusting their properties. The development of drug release control systems, which may stabilise labile materials like proteins, peptides, or DNA and also target specific sites with drugs, has made extensive use of biodegradable polymers [4]. Also pursued is the creation of biodegradable polymeric nanoparticles for use in tissue engineering. They can stay for days or even weeks and deliver the medication into the target since they are biodegradable. Intracellular medicines have demonstrated the effectiveness of PLA and PLGA. PLGA and PEG are typically coupled because PEGylation lessens immunogenicity, minimises intramolecular aggregation, increases solubility and stability in water, and extends the drug's duration in the systemic circulation [5].

MATERIALS AND METHODS

The gift sample is a Voriconazole from Hetero drugs Limited, Ethylcellulose (Rohm Gmbh & CoKG, Germany), HPMC (SD Fine Chemical Limited), Ethanol (Ruchi Global limited, Madhya Pradesh).

METHODS:

Compatibility studies:

IR studies: Drug preformulation research pertaining to the drug as well as polymer interaction become unstable when the drug and polymer interact during production.In the proper polymer, they are quite important [6]. FTIR Spectroscopy was utilised to determine whether Variconazole and the cellulose polymer were compatible. (Japan; Perkin Elmer Jasco FTIR-401).

Differential scanning calorimetry

A plot of heat flux (rate) versus temperature at a given temperature rate is the result of a DSC. It offers details about the sample's physical characteristics. It might be amorphous or crystalline in nature. Thermogravipics indicate that in certain formulations, there may be a drug-polymer interaction [7].

Morphology of the Particles:

The size distribution, shape, as well as particle size of the nanocapsules are ascertained using the following techniques.

Scanning Electron Microscopy:

SEM stands for scanning electron microscopy. When assessing the general morphology and shape of the nanocapsules, it is quite helpful. SEM (scanning electron microscopy) was used to determine the morphology and surface appearance of coated and ethyl cellulose nanocapsules [8]. After the particles were freeze-dried, they were coated with gold palladium using a sputter coater (Balzers SCD 004, Liechtenstein) to produce a 20 nm thick coating, and they were

Table 1 Formulations of Voriconazole Nanocapsules

SI.No	Ingredients	F1	F 2	F 3	F 4	F 5	F6	F 7	F 8
1	Voriconazole	2.0	3.0	2.0	3.0	2.0	3.0	2.0	3.0
2	Ethyl Cellulose	1.0	1.5	2.0	2.5	1.0	1.5	2.0	2.5
3	HPMC	1.5	2.0	1.5	2.0	1.5	2.0	1.5	2.0
4	Ethanol in ml	10	10	10	10	10	10	10	10
5	Distilled water in ml	100	100	100	100	100	100	100	100

examined under a microscope (JSM-6400, Tokyo, Japan).

Procedure of Voriconazole Nanocapsules

Distilled water was used as the external phase in the Emulsion solvent Diffusion method to create the Voriconazole Nanocapsules. The internal phase is composed of a concentration of polymers such as HPMC and ethyl cellulose and a good solvent, ethanol, which includes voriconazole. In an organic solvent mixture including polymers in varying ratios, the drug and polymers were co-dissolved. Under agitation, the medication solution was gradually administered using a syringe into the exterior water phase. For almost one hour, the system was continuously agitated at 800 rpm [9]. In addition to the poor solvent absorbing into the excellent solvent. The droplets created nanocapsules as they steadily solidified. To isolate the Nanocapsules from the preparation system, the system was filtered. The finished object was dried after being cleaned with distilled water. The procedure was done at room temperature the entire time. The medication to polymer ratio was displayed.

Evaluation of Nanocapsules

Percentage production yield (PY)

Practical mass of Nanocapsules

$$PY\ (\%) = \frac{Practical\ mass\ of\ Nanocapsules}{Theoretical\ mass} \times 100$$

Every formulation was tested three times, therefore the PY (%) were determined.

Entrapment efficiency: The Emulsion Solvent Diffusion process was used to prepare the nanocapsules.It underwent a 40-minute, 14,000 rpm centrifugation at 10°C. The HPMC and ethyl cellulose contain the prescribed dose of voriconazole. The amount that was discovered in the supernatant differed from the total amounts used to create the Nanocapsules. A UV spectrophotometer set at 262 nm was used to measure the amount of free voriconazole in the supernatant. The following formula is used to calculate it [10].

$$\%EE = \frac{M_{Initial\ drug} - M_{Free\ drug}}{M_{Initial\ drug}} \times 100$$

Drug loading efficiency:

After the drug loading efficiency was eliminated, distilled water was used to wash away any leftover sediments or precipitations. It is distributed in a 10 mL volumetric flask containing a chloroform:acetone (2.5:2.5, v/v) combination. It is used to make sure the medication is completely extracted from the nanocapsules, and it is sonicated for thirty minutes. Chloroform was added to make the volume up to 10 ml. The final mixture was centrifuged for 30 minutes at 14,000 rpm as well as 10°C. The supernatants were then collected, and the loaded drug was measured in triplicate using a UV spectrophotometer set at 262 nm [11].

Particle size determination [12]:

Optical microscopy was used to measure the nanocapsules' particle size. For particle size, about 100 Nanocapsules were identified. By suspending in water, the distribution of particle size has been measured.

Equilibrium swelling studies of Nanocapsules: The phosphate buffer (pH 7.4) was filled with a preweighed quantity of nanocapsules. It can swell as long as its weight stays the same. Following their removal and blotting using filter paper, the weight variations of the Nanocapsules were recorded [13]. Using the following formula, the degree of swelling (a) was determined.

α=wg-wo/wo

Drug content determination: To remove the medication, 50 mg of Voriconazole Nanocapsules were broken up and suspended in water. The

filtrate was tested spectrophotometrically for drug concentration at 262 nm after 24 hours, using water as the blank [14].

***In-vitro* drug release studies:**

In-vitro drug release studies were carried out utilising the USP XXIV dissolution apparatus type II using a 500 ml dissolve media [15]. For forty-five minutes at fifty revolutions per minute, the dissolving medium is held at pH 7.4 ± 0.2 and the temperature at 37 ± 0.5 °C. Using the findings of the in-vitro release profiles acquired for every formulation, the following data treatment modes were plotted:

1. First order kinetic model: log cumulative proportion of medication remaining vs time

2. The Higuchi model's cumulative percent drug release versus the square root of time

3. Cumulative drug residual percentage over time (using a zero order kinetic model)

4. The Korsmeyer-Peppas model shows the log cumulative percent of drugs released vs log time.

Data Analysis: The data was acquired and then it was fitted in to the Zero order, First order, Higuchi matrix, and Korsmeyer and Peppas model in order to assess the mechanism for the release and release rate kinetics of the dosage form. After comparing the r-values, the best-fit model had been chosen.

1. **Zero order kinetics:** In the event that the region remains unchanged and no equilibrium circumstances are reached, medication will be released gradually upon dissolution from pharmaceutical dosage forms that do not disintegrate. The following equation can be used to express it.

$$Q_t = Q_o + K_o t$$

2. First order kinetics: The release rate data were fitted to the following equation in order to investigate the first order release rate kinetics.

$$\text{Log } Q_t = \log Q_o + K_1 t / 2.303$$

3. Higuchi model: This model is developed by several theoretical models. To study the release of water-soluble and low soluble drugs.They are incorporated in to semisolids and or solid matrices, the equation is

$$Q_t = K_H . t^{1/2}$$

4. Korsmeyer Peppas release model

The release rate data are fitted to the following equation in order to study this model.

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

RESULTS AND DISCUSSION:

Compatability studies

IR studies

FTIR is used to record the infrared spectrum of the pure itraconazole sample. Table 1 compares this with the typical functional group frequencies of voriconazole. Figures 1 through 5 display the formulation's FTIR spectrum.

Comparison of FT-IR Spectra of Voriconazole and Formulae

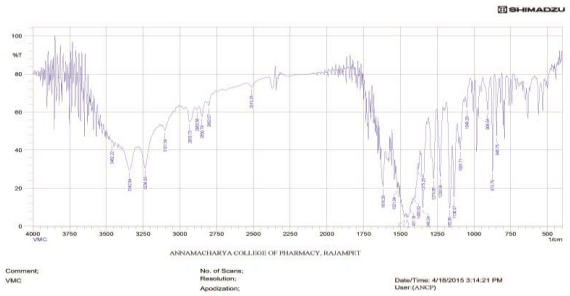


Figure 1: The pure drug's FTIR spectrum (Voriconazole)

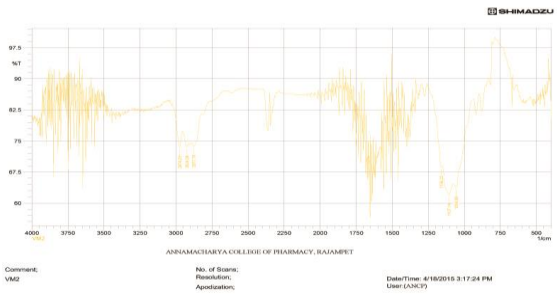


Figure 2**: FTIR Ethyl Cellulose Spectrum**

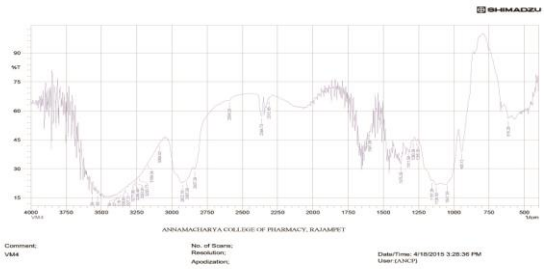


Figure 3**: HPMC FTIR Spectrum**

Table 2 Interpretations of FTIR

Functional Groups	Voriconazole	Ethyl Cellulose	HPMC	Drug + Ethyl Cellulose	Drug + Ethyl Cellulose + Hpmc
C-H Stretch (Aromatics)	3236.55	2924.09	2922.16	2974.23	3358.07
-O-H- (Hydrogen bonded alcohols and phenols)	2513.25	1056.99	2594.26	3346.50	3415.93
C-O Stretch (Alcohols)	1521.84	1107.14	1157.29	1049.28	1165.00
C-H Rocking (Alkanes)	873.75	2924.09	615.29	1274.95	1230.58
O-H Bending (Carboxylic acids)	348.24	3327.21	3277.06	3170.97	1274.95

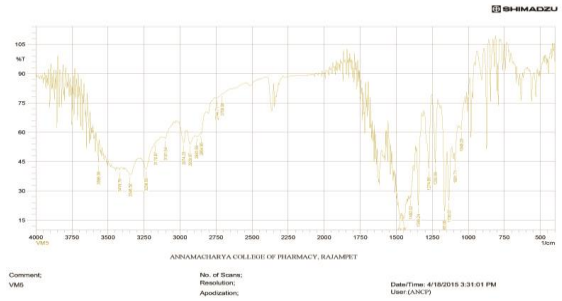


Figure 4: The drug's FTIR spectrum with ethyl cellulose

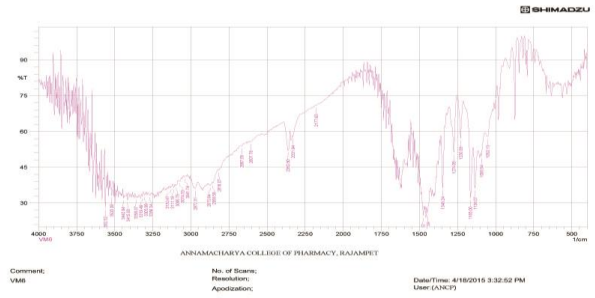


Figure 5: FTIR Spectrum of Drug + EC + HPMC

Differential scanning calorimetry:

The exothermic peak of the DSC sample spectra for the pure medication is 122.50 c and -10.65 mw. The mixed sample includes HPMC, ethyl cellulose, and drug (vonicoconazole). The mixture's endothermic peak measures 286.2 oC and -7.50 mw, while the exothermic peak measures 121.9 oC and -9.29 mw. The drug and excipient compatibility indicates that there is no compatibility in the formulation. as indicated by Table 3. It works well for completing the nanocapsule formulation process. The DSC spectrum displayed in Figures 6 and 7.

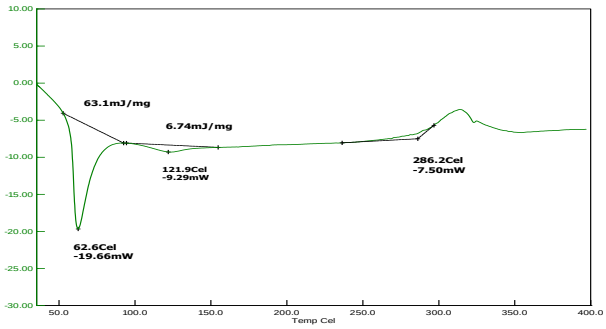


Figure 6: DSC spectrum of pure drug Voriconazole

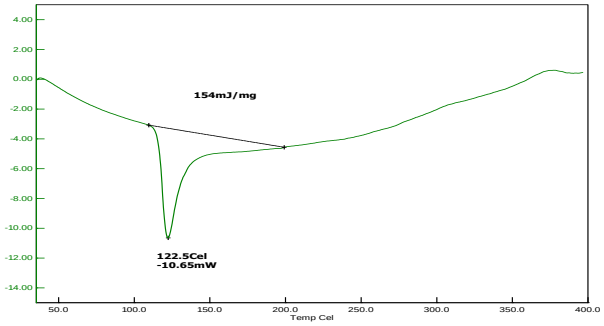


Figure 7: DSC spectrum of Mixtures (Drug + EC + HPMC)

MORPHOLOGY OF THE PARTICLES:

The shape, size distribution, as well as particle size of voriconazole nanocapsules are ascertained by the following techniques.

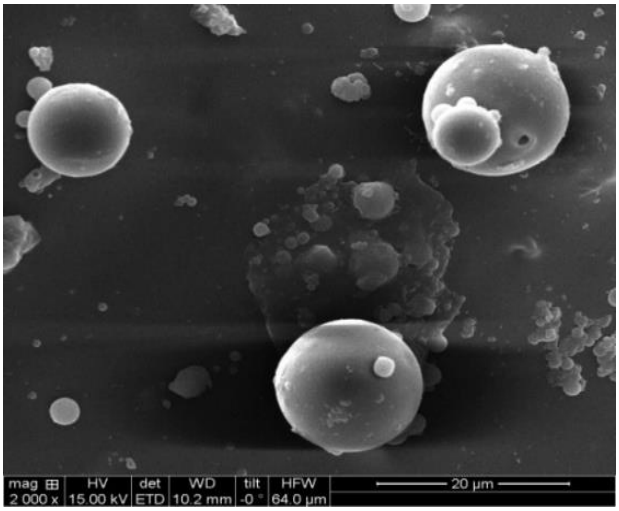
SEM

Photomicrographs were acquired at the appropriate magnifications, as well as scanning electron microscopy (SEM) was used to determine the morphology and structure of the nanocapsules. Figure 8 displays the photos of the optimised formulation captured using scanning electron microscopy.

Table 3 Evaluation parameters of Voriconazole Nanocapsules

Formulation code	Percentage yield (%)	Entrapment efficiency	Entrapment Loading Efficiency	Particle size (μm)	Swelling Index (Sec)	% Drug Content Determination
F1	83.32	54.4	56.8	78	0.8	65.8
F2	92	87.3	87.7	63	0.2	69.4
F3	73.14	71	84.3	89	0.5	90.5
F4	78.76	60	71.9	51	0.7	89.9
F5	88.82	63.8	70.4	94	0.2	75.6
F6	81.51	60.8	68.4	96	0.6	85.6
F7	81	58.8	64.4	82	0.3	88.7
F8	86.61	91.4	97.7	33	1.5	98.5

Shape and Surface Morphology



Figures 8: Samples of SEM for the Best Formulations of F8

Evaluation of Voriconazole Nanocapsules

Percentage Yield

The yield of production for Voriconazole nanocapsules made using ethyl cellulose and HPMC is displayed in Table 4.

Encapsulation efficiency

Drug entrapment efficiency (%EE)

F 1-54.4%, F2-87.3%, F3-71%, F 4-60%, F5-63.8%, F6-60.8%, F7-58.8, F 8-91.4, and so on are the percentage entrapment efficiency. Good formulation and excellent efficiency are demonstrated by the F 8. Results are displayed in Table 3.

Entrapment Loading (%EL)

F1–56.8%, F2–87.7%, F3–84.3%, F4–71.9%, F5–70.4%, F6–68.4%, F7–64.4%, and F8–97.7% are the percentages of entrapment loading. Good formulation and excellent efficiency are demonstrated by the F 8. Results are displayed in Table 3.

Particle size

F 1 (78 μm), F 2 (63 μm), F3 (89 μm), F4 (51 μm), F 5 (94 μm), F 6 (96 μm), F 7 (82 μm), as well as F 8 (33 μm) indicate the particle size distribution of Nanocapsules. formula as displayed in Table 3.

Equilibrium swelling studies of Nanocapsules

Nanocapsules, weighed out to the nearest hundred milligramme, were submerged in phosphate buffer (pH7.4) and allowed to expand to a steady weight. Following the removal of the nanocapsules and blotting with filter paper, Table 3 displays the weight changes that were measured.

Percentage drug content Determination:

The distribution of drug content in Nanocapsules has been demonstrated with the following drug contents: F 1 (65.8%), F 2 (69.4%), F3 (90.5%), F4 (89.9%), F 5 (75.6%), F 6 (85.6%), F 7 (88.7%), and F 8 (98.5%). formula as displayed in Table 3.

***In vitro* dissolution Studies:**

The drug release rate kinetics mechanism from dosage forms was deciphered by fitting the observed in vitro drug dissolution data to multiple mathematical models, including zero order, first order, Higuchi matrix, and Korsmeyer Peppas model. Table 4 shows compliance with the values. Figure 9 shows the percentage drug release together with data to several kinetic models for various formulations of Nanocapsules.

Table 4 In Vitro dissolution Studies

S.No	Time	% of Drug release							
		F1	F2	F3	F4	F5	F6	F7	F8
1	5	2.58	2.06	5.82	6.71	12.63	14.22	15.60	16.40
2	10	3.61	5.90	8.33	13.42	16.54	17.90	20.30	30.08
3	15	5.69	7.48	12.62	15.59	20.26	24.18	24.18	35.80
4	20	8.61	12.59	15.59	20.31	24.23	24.99	28.90	40.72
5	25	22.58	16.49	18.29	19.23	28.08	40.08	40.80	47.42
6	30	20.42	31.09	31.9	38.39	38.10	41.56	44.52	51.34
7	35	31.06	42.8	33.8	41.62	40.41	42.98	46.73	61.23
8	40	28.09	39.40	52.2	57.07	63.74	72.04	70.60	59.91
9	45	40.61	49.44	56.12	62.89	71.28	74.72	81.28	90.78

Table 5 Release Order Kinetics data of Variconazole Nanocapsules

Time	% cumulative drug release	Log cumulative % drug release	Log cumulative % drug release	% cumulative drug release
0	0	0	0	0
5	15420	4.188	4.188	15420
10	27060	4.432	4.432	27060
15	34800	4.541	4.541	34800
20	38640	4.587	4.587	38640
25	46380	4.666	4.666	46380
30	50220	4.7	4.7	50220
35	54210	4.733	4.733	54120
40	61860	4.791	4.791	61860
45	88920	4.948	4.948	88920

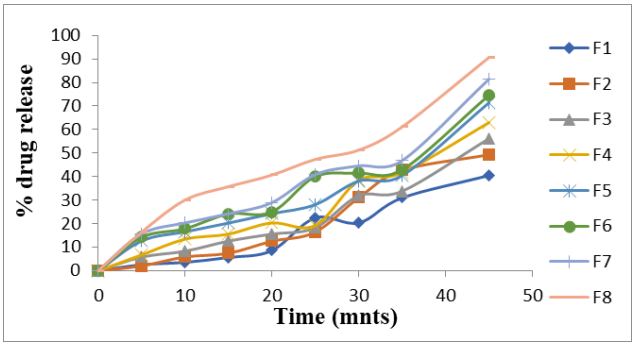


Figure 9: *In vitro* dissolution studies of Voriconazole Nanocapsules

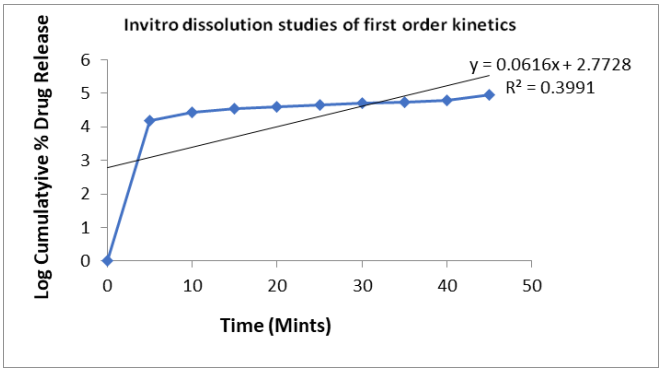


Figure 11: F 8 of First-order kinetics *in vitro* dissolution experiments

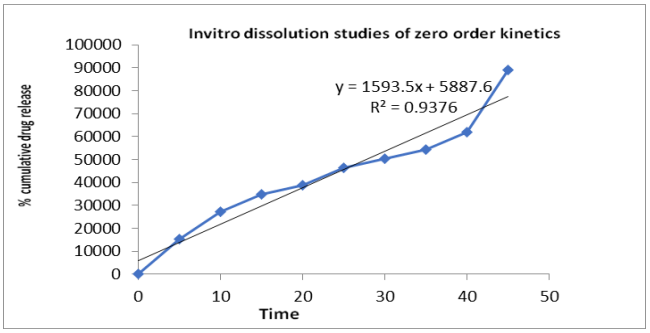


Figure 10: F 8 of Zero Order Kinetics *In vitro* Dissolution Studies

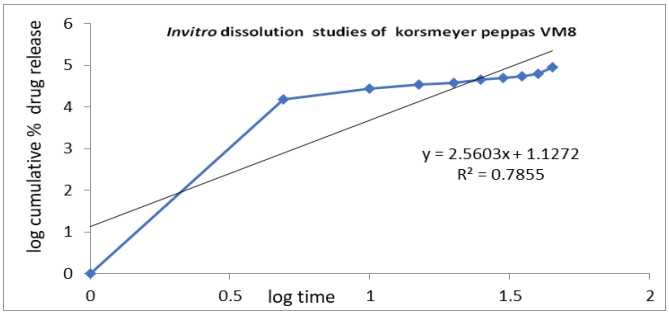


Figure 12: F 8 of the Korsmeyer Peppas in vitro dissolution experiments

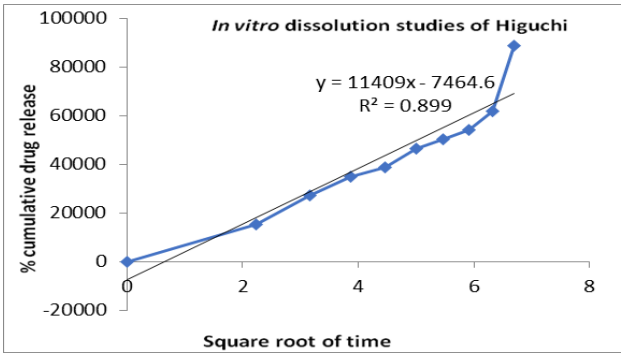


Figure 13: F8 of the Higuchi *in vitro* dissolution studies

Table 7: Release kinetics of Voriconazole Nanocapsules (F8)

Model	Equation	F 8	
		R^2	M
Zero order	Mo-Mt=kt	0.937	1593
First order	InM=InMo	0.399	0.061
Higuchi's Matrix	$M_0-M_t = kt1/2$	0.899	11409
Korsmeyer-Peppar	log (M_0-M_t)= log k + n log$t$	0.785	2.560

CONCLUSION

In this work, voriconazole nanocapsules for a sustained drug delivery method were developed. According to the results, formulation F8 appears to have excellent morphological properties. The best formulation's yield of microspheres was found to be F8 (86.61%), its entrapment efficiency was determined to be (91.4%), its drug loading efficiency to be (96.7%), its swelling index to be (1.5 sec), its particle size to be (33 µm), its drug content determined to be (98.5%), and its in vitro drug release was fitted with many Release kinetic studies of a sustained manner with constant fashion over an extended period of time for 45 minutes. It was found that the ethyl cellulose content had a substantial impact on every evaluation parameter. Therefore, voriconazole nanocapsules may show to be a viable option for safe and efficient long-term medication delivery.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Adriana RP, Letıcia SF, Rodrigo PS, Alberto MD, Edilson VB, Tania MHC, et al. Nanocapsule @ xerogel microparticles containing sodium diclofenac: A new strategy to control the release of drugs. International Journal of Pharmaceutics. 2008;358(1-2): 292-95.

[2] Adriana RP, Leticia C, Graziela M, Leonardo US, Nadya PD, Silvia SG, et al. Structural model of polymeric nanospheres containing indomethacin ethyl ester and in vivo antiedematogenic activity. International Journal of Nanotechnology. 2007;4(5):454-467.

[3] Aiyer HN, Seshadri R, Raina G, Sen R, Rahul R, et al. Study of Carbon Nanocapsules (Onions) and Spherulitic Graphite by Stm and Other Techniques. In: Fullerene Science Tech, 1995;3(6):765-777.

[4] Andrieu V, Fessi H, Dubrasquet M, Devissaguet JP, Puisieux F, Benita S, et al. Pharmacokinetic evaluation of indomethacin nanocapsules. Drug Design and Delivery. 1989;4(4):295-302.

[5] Arenas LT, Dias SLP, Moro CC, Costa TMH, Benvenutti EV, Lucho AMS, et al. Structure and property studies of hybrid xerogels containing bridged positively charged 1 4-diazoniabi cycle [2 . 2 . 2] octane dichloride. Journal of Colloidal Interface and Science. 2006;297(1):244-250.

[6] Beduneau A, Saulnier P, Anton N, Hindre F, Passirani C, Rajerison H, et al. Pegylated nanocapsules produced by an organic solvent free method: Evaluation of their stealth properties . Pharmaceutical Research. 2006;23(9):2190-99.

[7] Benita. S. Microparticulate drug delivery systems: release kinetic models. Microspheres, Microcapsules and Liposomes (the MML Series). R. Arshady (Ed.), Citrus Books, London. 1998;255- 278.

[8] Benvenutti EV, Pavan FA, Gobbi SA, Costa TMH, et al. FTIR thermal analysis on anilinepropylsilica xerogel. Journal of Thermal Analysis and Calorimetry. 2002;68(1):199-206.
[9] Bernardi A, Zilberstein AC, Jager E, Campos MM, Morrone FB, Calixto JB, et al. Effects of indomethacin loaded nanocapsules in experimental models of inflammation in rats. British Journal of Pharmacology. 2009;158(4):1104-11.
[10] Bingyun S and Daniel TC, et al. Spatially and temporally resolved delivery of stimuli to single cells. Journal of the Amarican Chemical Society. 2003;125(13):3702-3703.
[11] Boal AK, Ilhan F, Derouchey JE, Thurn AT, Russell TP, Rotello VM, et al. Self-assembly of nanoparticles into structured spherical and network aggregates. Nature. 2000;404(6779):746-748.
[12] Bouchemal K, Briancon S, Perrier E, Fessi H, Bonnet I, Zydowicz N, et al. Synthesis and characterization of polyurethane and poly (ether urethane) nanocapsules using a new technique of interfacial polycondensation combined to spontaneous emulsification. International Journal of Pharmaceutics. 2004;269(1):89-100.
[13] Boudad H, Legrand P, Lebas G, Cheron M, Duchene D, Ponchel G, et al. Combined hydroxypropyl-[beta] - cyclodextrin and poly (alkylcyanoacrylate) nanoparticles intended for oral administration of saquinavir. International Journal of Pharmaceutics. 2001;218(1-2):113-24.
[14] Bruce MN. Hybrid nanocomposite materials between inorganic glasses and organic polymers. Advanced Materials. 1993;5(6):422-33.
[15] Burger KN, Staffhorst RW, de Vijlder HC, Velinova MJ, Bomans PH, Frederik PM, et al. Nanocapsules: lipid-coated aggregates of cisplatin with high cytotoxicity. Nature Medicine. 2002;8(1):81-84.