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RESEARCH ARTICLE

A Study on Enhancement of Solubility and Dissolution Properties of Voriconazole by Solid Dispersion Technique

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Abstract: Voriconazole is a triazole antifungal drug used to treat fungal infections. It works by inhibiting fungal growth. However, voriconazole has low aqueous solubility of only 0.5 mg/mL at room temperature, making it a Class II drug according to the Biopharmaceutics Classification System (BCS). This limited solubility poses challenges for developing effective oral formulations. In this study, solid dispersions of voriconazole were prepared using different methods and carriers in an attempt to improve its solubility and dissolution rate. The physical mixture, solvent evaporation, and kneading methods were used to prepare solid dispersions with polyethylene glycol 6000 (PEG 6000) or hydroxypropyl methylcellulose (HPMC) at 1:1 or 1:3 drug to carrier ratios. The formulations were characterized based on drug content, saturation solubility, Fourier transform infrared spectroscopy (FTIR), and in vitro dissolution testing. FTIR analysis indicated minor or no molecular interaction between voriconazole and the polymers, suggesting compatibility. In vitro dissolution studies showed the solid dispersion with PEG 6000 at a 1:3 ratio achieved the highest release of 97.26% of voriconazole after 30 minutes. This represents over a three-fold increase in dissolution rate compared to voriconazole alone, demonstrating the ability of these systems to enhance voriconazole's solubility and dissolution properties.

Keywords: Voriconazole; Polyethylene Glycol; Solid dispersion; Hydroxypropyl Methyl Cellulose; Dissolution.

1. Introduction

The number of poorly soluble drug candidates has risen dramatically in recent years, challenging formulation scientists to develop oral dosage forms. A drug's solubility is a primary factor influencing its oral bioavailability. When solubility is poor, absorption may be limited by the rate of dissolution in the gastrointestinal (GI) tract. Due to its high permeability but poor aqueous solubility (0.5 mg/mL), voriconazole is classified as a Biopharmaceutical Classification System Class II drug. Inadequate permeability and solubility are common causes of low oral bioavailability. For oral administration, a drug must first dissolve in GI fluids before it can permeate the membranes and enter systemic circulation. Therefore, a drug's water solubility greatly impacts absorption via dissolution and permeation pathways.

Solid dispersions are composite solid materials consisting of at least two distinct components, typically a hydrophilic matrix and hydrophobic drug. Solid dispersion technology involves dispersing one or more active ingredients in an inert carrier matrix during the solid state to improve solubility, stability, and dissolution rate. Processes like melting, solvent evaporation, and kneading promote drug solubilization by reducing particle size. Voriconazole is a triazole antifungal used to treat fungal infections via oral or intravenous routes. In this study, solid dispersions of voriconazole were prepared with polymers like hydroxypropyl methylcellulose (HPMC) and polyethylene glycol 6000 (PEG 6000) to accelerate the dissolution rate. Solid dispersions improve absorption by presenting the insoluble drug in a finely divided state for rapid dissolution within the soluble carrier matrix. [22-24]

2. Methodology

2.1. Materials

Voriconazole was gifted by Pfizer chemicals, methanol from Hi Media laboratories. Hydrochloric acid used in dissolution media obtained from Thermo fischer scientific India pvt.limited. Hydroxy propyl methyl cellulose E5 LV (HPMC) obtained from Yarrow chem products. Poly ethylene glycol 6000(PEG 6000) from Qualigen and Distilled water was obtained from the distilled water plant.

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Upon binding to cationic liposomes, mRNA becomes embedded within the lipid bilayer, resulting in the formation of lipoplexes (LPX). This molecular complex serves to protect mRNA from nuclease hydrolysis and facilitates efficient cellular uptake. Researchers have observed that during the transfection of murine bone marrow-derived dendritic cells (BMDCs), lipoplexes composed of DOTAP/cholesterol in a 1:1 molar ratio exhibit superior performance compared to those composed of DOTAP/DOPE in a 2:3 molar ratio. [28-30]

2.2. Determination of absorption maxima

A stock solution of voriconazole (1 mg/mL) was prepared by dissolving 10 mg of drug in 10 mL of 0.1 N HCl. From this, a second stock solution (100 µg/mL) was obtained by diluting 1 mL of the first stock solution to 10 mL with 0.1 N HCl. Then, 0.4 mL of the second stock solution was further diluted to 10 mL with 0.1 N HCl. This solution was scanned on a UV-Vis spectrophotometer (Hitachi-U2000) across the wavelength range of 200-400 nm. The λmax was determined. [39-43]

2.3. Calibration curve preparation

A series of standard solutions containing 2, 4, 6, 8 and 10 µg/mL voriconazole were prepared by diluting 0.2, 0.4, 0.6, 0.8 and 1 mL of the second stock solution to 10 mL with 0.1 N HCl. Absorbance of each solution was measured at 254 nm and the calibration curve was constructed by plotting concentration versus absorbance. [45, 46]

2.4. Preparation of physical mixtures

Voriconazole was physically combined with HPMC or PEG 6000 in 1:1 and 1:3 drug:polymer weight ratios using a mortar and pestle. The mixtures were stored in a desiccator until further use [48]

2.5. Preparation of solid dispersion by kneading method

Voriconazole was dissolved in methanol, to which the polymer (HPMC or PEG 6000) was added. The solvent was evaporated under vacuum to obtain a solid mass, which was powdered and dried. [50]

2.6. Preparation of solid dispersion by solvent evaporation method

Voriconazole and polymer (HPMC or PEG 6000) were accurately weighed and triturated in a glass mortar with a small amount of methanol for 1 h to form homogeneous moist mass. The mass was dried and powdered for further analysis. [50]

2.7. Evaluation of solid dispersion system

2.7.1. Saturation solubility studies

Voriconazole pure drug, physical mixtures and solid dispersions equivalent to 20 mg of drug were weighed and added to 20 ml of 0.1N HCl in sealed vials. The vials were equilibrated at room temperature for 48 hours. An aliquot was filtered through Whatman filter paper and suitably diluted with 0.1N HCl. The concentration of voriconazole was determined by measuring absorbance at 254 nm using a pre-validated calibration curve

2.7.2. Drug content analysis

An equivalent of 20 mg voriconazole from physical mixtures and solid dispersions was weighed and extracted in 100 ml of 0.1N HCl by stirring. The solution was filtered and diluted appropriately. The drug content was quantified by measuring absorbance at 254 nm and referring to the calibration curve

2.7.3. Drug excipient incompatibility study by using FTIR

FTIR spectra of voriconazole, PEG 6000 and the solid dispersion containing voriconazole:PEG 6000 (1:3) were recorded using KBr disc method on a FTIR spectrophotometer between 450-4000 cm^{-1} with a resolution of 1 cm^{-1}

2.7.4. In vitro dissolution studies

Dissolution tests were conducted in 900 ml of 0.1N HCl at 37°C and 50 rpm using USP apparatus II. Samples equivalent to 20 mg voriconazole were subjected to dissolution at different time points. Aliquots were filtered, diluted and analyzed for drug release by measuring absorbance at 254 nm. Mean dissolution profiles were computed using PCP Disso V3.0 software from three replicate experiments

3. Results

3.1. Saturation solubility studies

The saturation solubility of Voriconazole from physical mixture and its solid dispersion systems were carried out in 0.1N HCl. The solubility of Voriconazole in 0.1N HCl was found to be 1.534±0.0025M * 10^{-3}. The results are shown in Table 1.

Table 1. Saturation solubility of voriconazole in physical mixture and its solid dispersion system prepared with HPMC and PEG 6000

Code	Drug	Polymer	Ratio	Method	Concentration (M×10^{-3} ± SD)
VP-1	Voriconazole	HPMC	1:1	PM	1.648 ± 0.0036
VP-2	Voriconazole	HPMC	1:1	SE	2.068 ± 0.0026
VP-3	Voriconazole	HPMC	1:1	KNE	3.454 ± 0.0018
VP-4	Voriconazole	HPMC	1:3	PM	1.776 ± 0.0040
VP-5	Voriconazole	HPMC	1:3	SE	3.032 ± 0.0030
VP-6	Voriconazole	HPMC	1:3	KNE	4.134 ± 0.0031
VH-1	Voriconazole	PEG 6000	1:1	PM	1.82 ± 0.0023
VH-2	Voriconazole	PEG 6000	1:1	SE	2.996 ± 0.0035
VH-3	Voriconazole	PEG 6000	1:1	KNE	3.502 ± 0.0026
VH-4	Voriconazole	PEG 6000	1:3	PM	1.874 ± 0.0021
VH-5	Voriconazole	PEG 6000	1:3	SE	.036 ± 0.0035
VH-6	Voriconazole	PEG 6000	1:3	KNE	4.546 ± 0.0045

3.2. Drug content

For each created physical mixture and each of its solid dispersion systems, the % drug content was computed. The results are shown in Table 2.

Table 2. Drug content of voriconazole in physical mixtures and solid dispersions made with HPMC and PEG 6000:

Code	Drug: Polymer	Amount of drug taken	% Drug content
VP-1	1:1	20mg	32.98
VP-2	1:1	20mg	41.25
VP-3	1:1	20mg	59.04
VP-4	1:3	20mg	67.51
VP-5	1:3	20mg	68.63
VP-6	1:3	20mg	**80.97**
VH-1	1:1	20mg	30.19
VH-2	1:1	20mg	38.02
VH-3	1:1	20mg	48.12
VH-4	1:3	20mg	52.51
VH-5	1:3	20mg	59.98
VH-6	1:3	20mg	72.86

3.3. Drug excipient compatibility studies by FTIR

Drug excipient compatibility by FTIR revealed that there is no interaction between drug and excipients as shown by neither appearance of new peak or disappearance of parent peaks in the finger print region as shown in Figure 1.

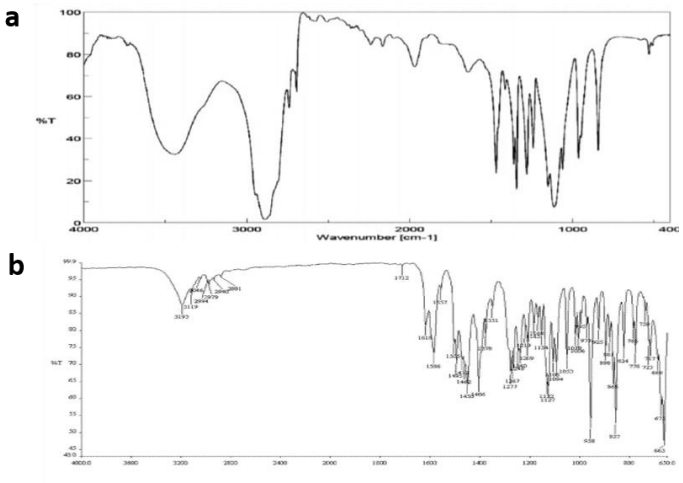

Figure 1. FTIR spectrum of a. Pure drug b. Drug excipient mixture

3.4. Dissolution studies

PCP Disso V3.0, a dissolution software, was used to analyse the dissolution profile and data. Present were the dissolution data, profiles, and model fitting data. The results are shown in Table 3 and 4.

Table 3. In vitro dissolution data of voriconazole in its pure form, in physical mixture form, and in solid dispersion systems made with 1:1 and 1:3 using HPMC

Time (min)	Pure Drug	Physical mixture Cumulative percentag drug released		Solvent evaporation Cumulative percentage drug released		Kneading Cumulative percentage drug released	
		1:1	1:3	1:1	1:3	1:1	1:3
5	0	0	0	0	0	0	0
10	4.12	6.96	7.64	6.09	8.16	10.94	12.53
20	7.24	10.47	10.92	18.55	18.21	19.21	19.62
30	13.61	17.13	13.96	29.94	22.73	25.45	29.26
45	17.66	26.29	28.59	30.89	39.45	39.84	40.76
60	21.34	32.58	30.93	41.93	54.84	55.77	55.81
90	28.01	36.23	37.12	52.34	64.03	70.34	71.55
120	30.58	41.58	52.08	68.86	73.19	86.94	90.36

Table 3. In vitro dissolution data of voriconazole in its pure form, in physical mixture form, and in solid dispersion systems made with 1:1 and 1:3 using PEG 6000

Time	Pure drug	Physical mixture Cumulative percentage drug released		Solvent evaporation Cumulative percentage drug released		Kneading Cumulative percentage drug released	
		1:1	1:3	1:1	1:3	1:1	1:3
0	0	0	0	0	0	0	0
10	4.12	5.91	8.36	5.94	7.14	12.49	14.03
20	7.24	8.24	9.27	7.51	10.28	21.45	26.62
30	13.61	12.52	14.43	11.55	21.49	40.84	42.88
45	17.66	18.61	28.58	19.72	27.86	52.77	61.93
60	21.34	29.73	40.97	32.93	44.58	72.48	75.25
90	28.01	39.29	52.34	52.51	67.77	85.04	86.52
120	30.58	42.58	63.94	69.8	84.04	92.8	97.26

3.5. Drug release kinetics

Drug release kinetic plots are shown in Figure 2.

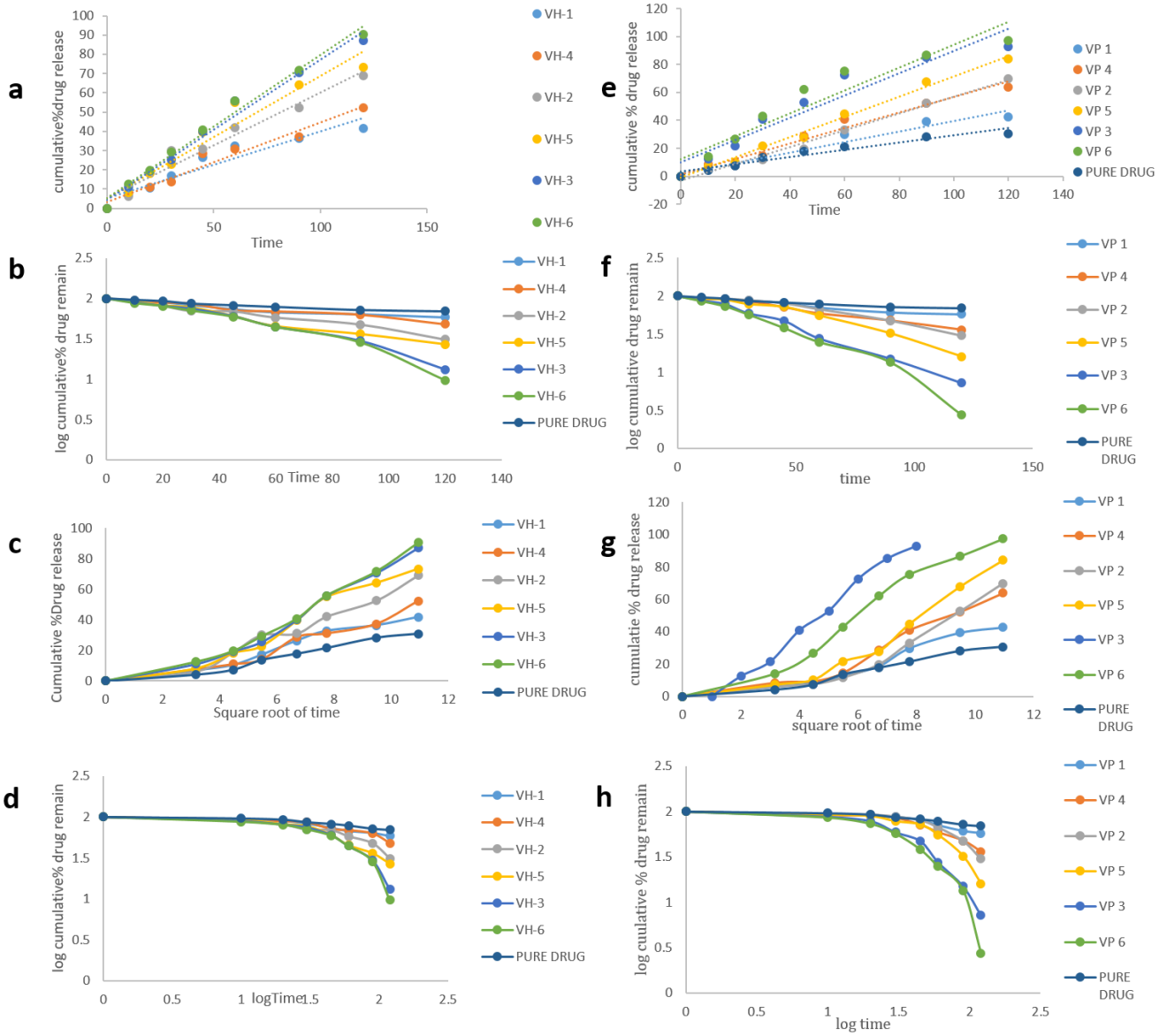

Figure 2. Drug release kinetics a. Zero order plot b. First order plot c. Higuchi plot d. Korsemeyer plot of formulations with HPMC e. Zero order plot f. First order plot g. Higuchi plot h. Korsemeyer plot of formulations with PEG 6000

4. Discussion

Solid dispersions of voriconazole were successfully prepared using polyethylene glycol 6000 (PEG 6000) and hydroxypropyl methylcellulose (HPMC) at 1:1 and 1:3 drug:carrier ratios via solvent evaporation and kneading methods. The solubility studies showed voriconazole had low aqueous solubility of 1.534±0.0025 x 10-3 mg/mL in 0.1N HCl. Incorporating PEG 6000 or HPMC increased voriconazole's solubility proportionally with carrier concentration. Among the formulations, the 1:3 KNE systems displayed the highest saturation solubility for both polymers, followed by the 1:1 KNE and SE batches. This suggests the method and carrier amount influenced voriconazole's solubilization.

Drug content analysis verified 31.19-80.97% of the theoretical amount in the solid dispersions. FTIR demonstrated no or minor interaction between voriconazole and the polymers, indicating compatibility. Dissolution tests revealed significantly enhanced voriconazole release from the solid dispersions compared to the pure drug and physical mixtures. The 1:3 PEG 6000 KNE formulation achieved over 97% dissolution within 30 minutes, representing a 3-fold increase versus voriconazole alone. This suggests the hydrophilic polymer at higher level improved wettability and solubilization dynamics. Kinetic modeling using regression coefficients affirmed the dissolution process best fitted the first order model for all formulations. Collectively, these results demonstrate solid dispersion with PEG 6000 effectively overcame voriconazole's poor aqueous solubility, validating this approach for improving its oral bioavailability. Overall drug-polymer compatibility and enhanced dissolution kinetics were achieved.

5. Conclusion

In conclusion, this study successfully developed solid dispersions of voriconazole using polyethylene glycol 6000 and hydroxypropyl methylcellulose via solvent evaporation and kneading methods. Solubility and dissolution testing demonstrated the solid dispersions significantly improved voriconazole's aqueous solubility and dissolution rate compared to the raw drug alone. Among the formulations, the 1:3 kneaded solid dispersion with PEG 6000 achieved the highest solubility and over 97% dissolution within 30 minutes, representing a three-fold enhancement. Compatibility between voriconazole and the polymers was confirmed by FTIR and drug content was within acceptable limits. The results indicate solid dispersion is a promising strategy for enhancing the oral absorption of poorly soluble drugs like voriconazole. Overall, the study highlights the utility of polymer selection and preparation technique in producing formulations with optimal solubilization effects

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Author's short biography

Kalyani Kondapalli

Kalyani Kondapalli is an academician with six years of experience in her field. She has contributed significantly to her field, with her research culminating in the publication of an article in a prestigious national journal. Her work reflects her dedication to advancing knowledge and her commitment to scholarly excellence.

Lakshmi Usha

Lakshmi Usha is an esteemed academician with over 11 years of experience in her field. Throughout her career, she has made substantial contributions to the academic community, publishing a remarkable 35 research and review articles in prestigious national and international journals. Her scholarly impact is evidenced by her impressive h-index of 6, underscoring her significant influence in her area of expertise. Her dedication to research and dissemination of knowledge underscores her commitment to advancing her field.

Shravya D

Shravya D is currently a diligent student in her fourth year pursuing a Bachelor's degree in Pharmacy. With a keen interest in pharmaceutical sciences, she is dedicated to expanding her knowledge and skills in the field. Shravya's academic journey is marked by her passion for learning and her commitment to excellence. As she progresses in her studies, she aims to contribute meaningfully to the field of pharmacy and make a positive impact in the healthcare industry.

Naga Kalyani K

Naga Kalyani is currently a dedicated fourth-year student pursuing a Bachelor's degree in Pharmacy. With a profound interest in pharmaceutical sciences, she is committed to expanding her knowledge and skills in the field. Kalyani's academic journey is marked by her passion for learning and her drive for excellence. As she progresses in her studies, she aims to contribute significantly to the pharmaceutical industry, leveraging her expertise to address healthcare challenges and improve patient outcomes**.**

Madhu Latha K

Madhu Latha is an ambitious fourth-year student enrolled in a Bachelor's program in Pharmacy. Driven by a deep-seated fascination for the pharmaceutical realm, she tirelessly endeavors to broaden her understanding and proficiency in the field. Latha's academic pursuit is characterized by her unwavering commitment to academic rigor and her aspiration for excellence. With each step forward in her educational journey, she aims to cultivate the necessary skills and knowledge to become a proficient pharmacist, dedicated to serving the community and advancing the field of pharmacy for the betterment of society