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Carboxymethyl Tamarind Gum-Based Amorphous Solid Dispersion of Voriconazole: Formulation, Characterization, Dissolution and Pharmacokinetic Evaluation

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Abstract: *Background: Voriconazole (VRZ) is a triazole antifungal agent with limited aqueous solubility, making dissolution an important formulation consideration. Solid dispersion (SD) technology can improve wetting, dispersion and the apparent dissolution of poorly water-soluble drugs. The present study investigated carboxymethyl tamarind gum (CMTG), a chemically modified natural polysaccharide, as a hydrophilic carrier for VRZ. Methods: CMTG was prepared from tamarind gum and characterized. VRZ-loaded SDs were prepared by the kneading method at drug:carrier ratios of 1:1, 1:2 and 1:3 using both native tamarind gum (TG) and CMTG. The SDs were evaluated for drug content, saturation solubility, dissolution, FTIR, DSC, PXRD, SEM and EDS. Antifungal activity against Candida albicans and an oral pharmacokinetic study in Wistar rats were also performed. The optimized SD was incorporated into immediate-release tablets by direct compression. Results: CMTG showed improved aqueous solubility compared with native TG and exhibited characteristic FTIR bands associated with carboxymethyl groups at approximately 1745.58 and 1402 cm−1. The optimized VRZ:CMTG SD5 (1:2) increased VRZ saturation solubility from 0.016±0.001 to 1.19±0.06 mg/mL, corresponding to a 74.37-fold enhancement. Pure VRZ showed 39% dissolution, whereas SD5 achieved complete release within 120 min. The SD produced a 24±1.2 mm zone of inhibition against C. albicans compared with 18±1.5 mm for pure VRZ. In rats, the SD produced a higher Cmax (0.964±0.01 µg/mL) than pure VRZ suspension (0.456±0.05 µg/mL), and Tmax was reduced from approximately 3 to 2 h. Conclusion: CMTG functioned as an effective natural-polymer carrier for VRZ SD, improving apparent solubility, dissolution and selected pharmacokinetic parameters. The findings support further development of CMTG-based amorphous SDs for poorly water-soluble antifungal agents.*

Keywords: Voriconazole; carboxymethyl tamarind gum; solid dispersion; kneading method; solubility enhancement; dissolution; Candida albicans; pharmacokinetics.

I. INTRODUCTION

Oral drug absorption depends on adequate dissolution of the active pharmaceutical ingredient in gastrointestinal fluids before membrane permeation. Poor aqueous solubility can therefore limit dissolution and contribute to variable oral performance. The uploaded thesis identifies solid dispersion technology as a practical approach for BCS class II drugs because a hydrophobic drug can be dispersed within a hydrophilic matrix, increasing wettability, accessible surface area and dissolution rate.

Tamarind gum (TG), a galactoxyloglucan obtained from Tamarindus indica seeds, is a nonionic, branching natural polysaccharide with hydrophilic, swelling, adhesive and gel-forming characteristics. Chemical modification is used to overcome some limitations of native gums. Carboxymethylation introduces carboxymethyl groups and increases

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hydrophilicity and water interaction. In the thesis, CMTG showed higher cold-water solubility than TG and was therefore investigated as a carrier for VRZ solid dispersion.

The objective of this work was to develop and characterize VRZ-loaded CMTG solid dispersions, compare them with TG-based dispersions, identify the optimum drug:carrier ratio, and evaluate the optimized dispersion in terms of dissolution, antifungal activity, pharmacokinetics and immediate-release tablet performance.

II. MATERIALS AND METHODS

2.1 Materials

Voriconazole and tamarind gum were used as the model drug and natural polymer, respectively. CMTG was synthesized from TG. Methanol, sodium hydroxide and monochloroacetic acid were used during polymer modification and formulation work. Other tablet excipients included microcrystalline cellulose, Fujicalin, crosscarmellose sodium (CCS), talc and magnesium stearate, according to the thesis formulation plan.

2.2 Preparation and characterization of CMTG

Tamarind gum was converted to its alkoxide in a sodium-hydroxide-containing methanolic medium. Carboxymethylation was carried out by reaction with monochloroacetic acid through nucleophilic substitution. The thesis reports a 50 g batch with a carboxymethylated product yield of 50.6±4.17% and a degree of substitution of approximately 0.16–0.20. CMTG was characterized by organoleptic examination, solubility, pH, swelling, viscosity, microscopy, ATR-FTIR, thermal analysis, solid-state 13C NMR and PXRD.

2.3 Preparation of VRZ solid dispersions

VRZ was dissolved in an appropriate quantity of methanol and the carrier was incorporated. The mixture was continuously kneaded in a mortar for 30 min. The solvent was allowed to evaporate, after which the hardened mass was dried, triturated and passed through sieve No. 80. The resulting SDs were stored in sealed containers at 30±1°C. Six batches were prepared: SD1–SD3 using TG at 1:1, 1:2 and 1:3 drug:carrier ratios, and SD4–SD6 using CMTG at the same ratios.

Batch	Drug:Carrier	Carrier	Aqueous solubility (mg/mL)	Fold enhancement
Pure VRZ	—	—	0.016±0.001	—
SD1	1:1	TG	0.09±0.003	5.62
SD2	1:2	TG	0.94±0.01	58.75
SD3	1:3	TG	1.00±0.02	62.50
SD4	1:1	CMTG	1.09±0.04	68.12
SD5	1:2	CMTG	1.19±0.06	74.37
SD6	1:3	CMTG	1.17±0.07	73.12

Table 1. Saturation solubility of pure VRZ and TG/CMTG-based SDs. Values are reported as mean ± SD of three determinations.

2.4 Characterization of SDs

Drug content and percentage yield were determined after preparation. Saturation solubility was evaluated by the shake-flask method using distilled water, with samples equilibrated for 24 h at 37°C and 100 rpm and quantified spectrophotometrically at 238 nm. In vitro dissolution was performed in pH 6.8 phosphate buffer. FTIR was used to assess drug–carrier interactions, DSC to examine thermal behavior, PXRD to assess crystallinity, SEM to examine morphology and EDS to confirm elemental composition.

2.5 Antifungal activity

The agar/cup-plate method was used against Candida albicans. The thesis compared optimized VRZ:CMTG SD, pure VRZ and CMTG, with a negative control.

2.6 In vivo pharmacokinetic study

Adult male Wistar rats weighing 150–200 g were used under the animal protocol reported in the thesis (IAEC No. YSPM/YTC/PHARMA-IAEC/2021-22/14). Two groups of six rats received either pure VRZ suspension or SD5 at a

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VRZ-equivalent oral dose of 50 mg/kg. Blood samples were collected over 24 h and plasma VRZ was quantified by HPLC using a C18 column, with acetonitrile/water/acetic acid as mobile phase and UV detection at 256 nm. Pharmacokinetic parameters included Cmax, Tmax, t1/2, AUC0-t and AUC0-∞.

2.7 Immediate-release tablet formulation and stability

The optimized SD was incorporated into 50 mg VRZ-equivalent immediate-release tablets by direct compression using Fujicalin and microcrystalline cellulose with CCS as superdisintegrant. Powder blends and tablets were evaluated for flow properties, thickness, diameter, hardness, friability, weight variation, content uniformity, disintegration, water absorption and dissolution. The optimized formulation was subjected to accelerated stability testing at 40°C/75% RH for three months.

III. RESULTS AND DISCUSSION

3.1 CMTG characteristics

CMTG was obtained as an irregular, faint-brown powder. Its cold-water solubility was 10.53±1.28 mg/mL, compared with 1.59±0.16 mg/mL for native TG. A 1% CMTG dispersion had a pH of 5.94, a swelling index of approximately two times the dry volume and a viscosity of 167.66±2.5 cP. ATR-FTIR showed bands at approximately 1745.56 cm−1 (C=O), 1639 cm−1 and 1402 cm−1 associated with carboxyl-containing groups, supporting successful carboxymethylation. The thesis also reports an amorphous PXRD pattern for CMTG.

3.2 Solubility enhancement

The results demonstrate a clear carrier-dependent improvement. TG-based dispersions produced 5.62–62.50-fold enhancement, whereas CMTG-based dispersions produced 68.12–74.37-fold enhancement. SD5 (VRZ:CMTG 1:2) showed the highest measured solubility (1.19±0.06 mg/mL) and was selected as the optimized SD. The improved performance is consistent with the higher hydrophilicity and dispersion capacity of the chemically modified polymer described in the thesis.

3.3 Dissolution behavior and solid-state characterization

Pure VRZ showed approximately 39% dissolution in pH 6.8 phosphate buffer, whereas SD5 achieved complete release within 120 min. FTIR, DSC and PXRD findings were interpreted in the thesis as evidence of successful SD formation and reduced crystallinity/amorphization of VRZ. SEM showed drug distributed within the polymeric matrix, while EDS demonstrated the expected elemental composition. These findings collectively support improved wetting, dispersion and dissolution of VRZ in the CMTG matrix.

3.4 Antifungal activity

Sample	Zone of inhibition (mm)
VRZ:CMTG SD	24±1.2
Pure VRZ control	18±1.5
CMTG	11±1.0
Negative control	NA

The optimized SD produced a larger inhibition zone than pure VRZ in the thesis assay. The increased apparent antifungal activity may be associated with improved dissolution and dispersion of the drug; however, the study design does not establish a direct mechanistic causal relationship.

3.5 Pharmacokinetic performance

Parameter	Pure VRZ suspension	VRZ:CMTG SD5
Cmax (µg/mL)	0.456±0.05	0.964±0.01
Tmax (h)	3.00±0.07	2.00±0.05
AUC0-∞ (µg·h/mL)	4.77±0.06*	10.26±0.08*

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SD produced a significantly higher AUC0-t and a Cmax of 0.964±0.01 µg/mL versus 0.456±0.05 µg/mL for pure VRZ ($p<0.05$).

The higher Cmax and earlier Tmax suggest faster systemic appearance of VRZ following administration of SD5. The thesis interprets these findings as improved oral exposure associated with enhanced dissolution. Because the study used a small animal sample, the pharmacokinetic findings should be considered preliminary.

3.6 Immediate-release tablets

Parameter	F5 result
Thickness (mm)	2.17±0.15
Diameter (mm)	10.02±0.02
Hardness (kg/cm²)	5.12±0.37
Friability (%)	0.23±0.03
Weight (mg)	358.65±0.50
Content uniformity (%)	100.76±0.80
Disintegration time (s)	57.27±1.0
Water absorption (%)	94.42±0.48

Among the tablet batches, F5 showed the most promising rapid-release behavior, reaching approximately 100% dissolution at 40 min. At higher CCS concentrations, the thesis reports reduced release, which was attributed to increased viscosity/gel formation, higher hardness and reduced water penetration.

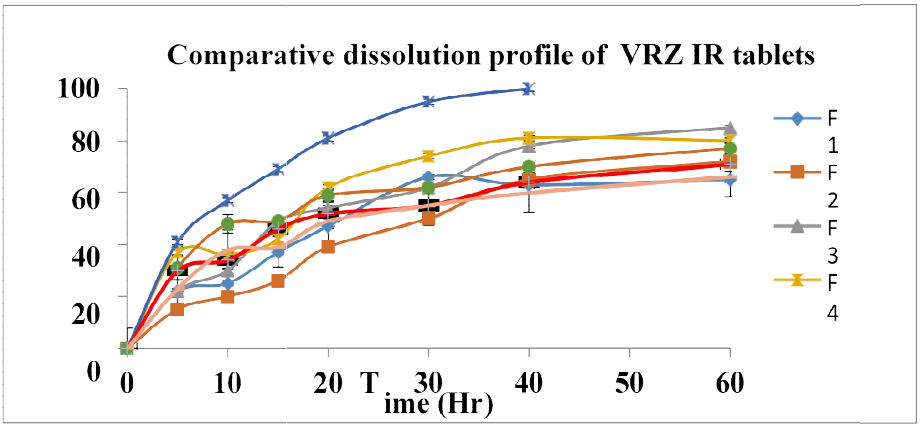

Figure 2. Dissolution profile of the optimized VRZ tablet formulation F5

IV. CONCLUSION

Carboxymethylation substantially improved the aqueous behavior of tamarind gum and provided a hydrophilic carrier suitable for VRZ solid dispersion. Among the investigated batches, SD5 containing VRZ:CMTG at 1:2 showed the highest aqueous solubility and complete dissolution within 120 min. The optimized SD also produced a larger C. albicans inhibition zone and improved selected pharmacokinetic parameters in Wistar rats. Incorporation of the optimized SD into immediate-release tablets produced rapid drug release, with F5 reaching complete release within 40 min. Overall, the thesis data support CMTG as a promising natural-polymer carrier for VRZ solid dispersions, while further confirmatory pharmacokinetic, stability and scale-up studies are warranted.

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