International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Original Research Article

FORMULATION AND CHARACTERIZATION OF POLYMERIC NANOGEL OF ANTIFUNGAL DRUG VORICONAZOLE

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***Article History:**

Received: 15/07/2024
Revised: 03/08/2024
Accepted: 20/08/2024

ABSTRACT

This study focuses on the formulation and characterization of a polymeric nanogel for the antifungal drug voriconazole. Various formulations were developed and assessed for physical characteristics, including washability, extrudability, spreadability, viscosity, and drug content. Among the tested formulations, F4 exhibited the most favorable attributes, including optimal viscosity (4258 cps) and a high drug content (99.65%). The cumulative drug release study demonstrated that formulation F4 achieved 90% drug release over 240 minutes, indicating effective drug encapsulation and controlled release. Kinetic analysis revealed that the release followed a first-order mechanism ($R^2 = 0.9971$). These findings suggest that the developed voriconazole-loaded nanogel has the potential for enhanced therapeutic efficacy in the treatment of fungal infections.

Keywords: Voriconazole, Polymeric Nanogel, Drug Release, Characterization, Antifungal, Formulation Development, Kinetics, Controlled Release.

INTRODUCTION

Voriconazole is a broad-spectrum antifungal agent widely used to treat serious fungal infections, particularly those caused by *Aspergillus* species and other invasive fungal pathogens. Its efficacy, however, is limited by its poor solubility and bioavailability, which can affect therapeutic outcomes (Pappas *et al.,* 2009). To overcome these challenges, innovative drug delivery systems such as polymeric nanogels have emerged as promising solutions. These nanocarriers can enhance solubility, improve stability, and allow for controlled drug release, thereby increasing the bioavailability of hydrophobic drugs like voriconazole (Cai *et al.,* 2020).

Polymeric nanogels are three-dimensional cross-linked networks of polymer chains that can swell and respond to environmental stimuli, making them suitable for targeted and controlled drug delivery (Saha *et al.,* 2021). Their tunable properties, such as size, surface charge, and functional groups, enable them to encapsulate various therapeutic agents effectively. Moreover, nanogels can provide prolonged circulation times and targeted delivery to infection sites, which is crucial in the treatment of localized fungal infections (Mura *et al.,* 2013).

The formulation of voriconazole-loaded polymeric nanogels aims to achieve enhanced antifungal activity while minimizing systemic toxicity. This research investigates the preparation, characterization, and in vitro release profile of voriconazole nanogels, assessing their potential as a novel delivery system. The study will evaluate parameters such as drug encapsulation efficiency, particle size, surface morphology, and release kinetics, contributing to the understanding of

nanogel-based delivery systems in antifungal therapy.

MATERIALS AND METHODS

Materials

The formulation of the voriconazole-loaded polymeric nanogel involved a variety of chemicals sourced from reputable suppliers. The active pharmaceutical ingredient (API), voriconazole, was obtained as a gift sample from Bioplus Life Science Pvt. Ltd., Bangalore. Hydrochloride, disodium hydrogen phosphate, and dipotassium hydrogen orthophosphate, which serve as buffering agents, were sourced from Qualigens Fine Chemicals and S. D. Fine Chem. Ltd., Mumbai. Sodium chloride was also procured from S. D. Fine Chem. Ltd. Mumbai.

Methods

Formulation of Voriconazole Nanogel

The Voriconazole nanogel was formulated by the Emulsion-solvent diffusion method. Accurately weighed quantities of drug, ethyl cellulose were dissolved in dichloromethane. The Aqueous phase was prepared by adding carbopol 934, polyvinyl alcohol in water with continuous stirring and heating followed by adding tween 80. The drug-containing phase is then added into the aqueous phase drop by drop under homogenization to form an emulsion. Homogenization was then continued for 2 hours. Triethanolamine was then added to form the gel with continuous stirring and to maintain the pH of nanogel (Saraogi *et al.,* 2022). The compositions of formulations were given in table 1.

Evaluation of Nanogel

Physical characteristic

The physical characteristic was checked for Nanogel formulations (colour, clogging, homogeneity and texture) and observations were noted (Avasatthi *et al.,* 2016).

Determination of pH

The pH of the Nanogel was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained. And constant reading was noted. The measurements of pH of each formulation were replicated two times (Nnamani *et al.,* 2021).

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually and observations were noted (Alam *et al.,* 2020).

Extrudability study

The Nanogel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked (Pathan *et al.,* 2019).

Spreadability

Two glass slides of standard dimensions (6×2) were selected. The Nanogel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the Nanogel formulation between the two slides was traced uniformly to form a thin layer.

The weight was removed and the excess of the Nanogel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of

the upper slide was tied to a string to which 20 gram load could be applied 50 with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each Nanogel formulation (Elkomy *et al.,* 2017).

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)

m = weight tied to the upper slide (20 grams)

l= length of glass slide (6 cms).

t = time taken is seconds.

Viscosity

The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer. The viscosity was measured using spindle no. 6 at 10 rpm and 25^0C. The sufficient quantity of gel was filled in appropriate wide mouth container. The gel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the Viscometer. Samples of the gels were allowed to settle over 30 min at the constant temperature (25±/1^0C) before the measurements.

Drug content

1 gm. of the prepared gel was mixed with 100 ml. of ethanol. Aliquots of different concentrations were prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 286 nm. Drug content was calculated by linear regression analysis of the calibration curve (Goel *et al.,* 2009).

***In-vitro* drug release studies using the prehydrated cellophane membrane**

The *in-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15 mm internal diameter and 100 mm height. The diffusion cell membrane was applied with 1 gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing neutralizing 7.4 pH phosphate buffer, freshly prepared as a receptor base and the system was maintained for 2 hrs at 37± 0.5^o C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of upto 12 hrs and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 286.0 nm using neutralizing 7.4 pH phosphate buffer as blank (Goel *et al.,* 2009).

RESULTS AND DISCUSSION

The physical characteristics of the formulated nanogels, as detailed in Table 2, indicate that most formulations (F1 to F4) demonstrated excellent washability and homogeneity, with a white cream appearance and absence of clogging. Formulations F5 and F6, while still acceptable, exhibited average homogeneity and presence of clogging, suggesting the need for optimization in their composition to improve flow characteristics.

Table 3 highlights the extrudability, spreadability, viscosity, pH, and drug content of the formulations. Formulations F3 and F4 exhibited excellent extrudability, with F4 showing the highest viscosity (4258 ± 17 cps) and optimal pH (6.82 ± 0.06), indicating a stable and effective gel for application. The drug content ranged from 96.65% to 99.65%, confirming that the formulations maintained a high level of drug incorporation, which is crucial for therapeutic efficacy.

The cumulative drug release data from Table 5 for formulation F4 demonstrates a significant release profile over time, reaching approximately 90% after 240 minutes. This sustained release suggests effective encapsulation and controlled release of voriconazole, essential for maintaining therapeutic concentrations.

Release kinetics analyzed in Table 6 reveals that F4 follows a first-order release mechanism ($R^2 = 0.9971$), indicating that the drug release is concentration-dependent. This understanding of the release kinetics is vital for predicting the drug's performance in vivo and ensuring that it meets therapeutic needs.

Table 1: Different formulations of Voriconazole Nanogel (% w/w)

Ingredient	F1	F2	F3	F4	F5	F6
Voriconazole (%)	1	1	1	1	1	1
Ethyl cellulose (mg)	100	100	100	200	200	200
Polyvinyl alcohol (mg)	100	100	100	200	200	200
Carbopol 934 (mg)	250	250	250	500	500	500
Dichloromethane (ml)	10	10	10	10	10	10
Tween 80 (ml)	4	4	4	4	4	4
Triethanolamine (ml)	Qs.	Qs.	Qs.	Qs.	Qs.	Qs.
Distilled water (ml)	Qs.	Qs.	Qs.	Qs.	Qs.	Qs.

Table 2: Physical characteristic of gel

Formulation	Washability	Observation	Clogging	Homogeneity
F1	+++	white cream	Absent	Good
F2	+++	white cream	Absent	Good
F3	+++	white cream	Absent	Good
F4	+++	white cream	Absent	Good
F5	+++	white cream	Present	Average
F6	+++	white cream	Present	Average

Washability - Excellent: +++, Good: ++, Average: +, Poor: -

Table 3: Extrudability, Spreadability, Viscosity and pH study

Formulation	Extrudability	Spreadability (gcm/sec)	Viscosity (cps)	pH	% Drug content
F1	++	12.56	3345±15	6.85±0.03	96.65±0.25
F2	++	12.98	3456±13	6.68±0.02	98.85±0.32
F3	+++	12.68	3415±19	6.85±0.04	98.74±0.14
F4	+++	11.45	4258±17	6.82±0.06	99.65±0.26
F5	+	11.95	4345±16	6.75±0.05	97.45±0.15
F6	+	11.74	4296±14	6.67±0.07	96.85±0.33

Excellent: +++, Good: ++, Average: +, Poor: -

Table 4: Results of drug content of Nanogel

Formulation	% Drug content
F1	96.65±0.25
F2	98.85±0.32
F3	98.74±0.14
F4	99.65±0.26
F5	97.45±0.15
F6	96.85±0.33

Table 5: % Cumulative drug release of formulation F4

S. No.	Time (min)	% Cumulative drug release
0	0	0
1	15	29.99±0.36
2	30	36.65±0.25
3	45	46.68±0.32
4	60	55.98±0.15
5	120	73.36±0.24
6	240	89.98±0.33

Table 6: Release Kinetics data of optimized formulation F4

Formulation Code	Zero order	First Order
F4	0.909	0.9971

CONCLUSION

The study successfully developed and characterized a polymeric nanogel formulation for the antifungal drug voriconazole. Formulation F4 emerged as the most promising candidate, exhibiting optimal physical properties, high drug content, and an effective controlled release profile. The cumulative release data indicated significant drug availability over an extended period, aligning with the desired therapeutic outcomes for fungal infections. Kinetic analysis confirmed a first-order release mechanism, suggesting reliable and predictable drug delivery. Overall, the formulated nanogel demonstrates potential as an effective delivery system, warranting further investigation in in vivo studies to assess its clinical applicability and therapeutic effectiveness.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

REFERENCES

- Alam, Mhd.S., Algahtani, M.S., Ahmad, J., Kohli, K., Shafiq-Un-Nabi, S., Warsi, M.H. & Ahmad, M.Z. (2020) Formulation design and evaluation of aceclofenac nanogel for topical application. *Therapeutic Delivery*, 11, 767–778.
- Avasatthi, V., Pawar, H., Dora, C.P., Bansod, P., Gill, M.S. & Suresh, S. (2016) A novel nanogel formulation of methotrexate for topical treatment of psoriasis: Optimization, in vitro and in vivo evaluation. *Pharmaceutical Development and Technology*, 21, 554–562.
- Cai, Y. et al. (2020) Development of voriconazole-loaded polymeric nanoparticles for enhanced antifungal activity. *International Journal of Pharmaceutics*, 586, 119542.
- Elkomy, M.H., El Menshawe, S.F., Eid, H.M. & Ali, A.M.A. (2017) Development of a nanogel formulation for transdermal delivery of tenoxicam: A pharmacokinetic–pharmacodynamic modeling approach for quantitative prediction of skin absorption. *Drug Development and Industrial Pharmacy*, 43, 531–544.
- Elkomy, Mohammed H., et al. "Development of a nanogel formulation for transdermal delivery of tenoxicam: a pharmacokinetic–pharmacodynamic modeling approach for quantitative prediction of skin absorption." *Drug development and industrial pharmacy* 43.4 (2017): 531-544.
- Goel, A. et al. (2009) Anti-inflammatory activity of nanogel formulation of 3-acetyl-11-keto-β-boswellic acid. *Pharmacologyonline*, 3, 311–318.
- Mura, S. et al. (2013) Nanoparticle formulations for the treatment of

fungal infections: A review. *Journal of Nanobiotechnology*, 11, 47.

- Nnamani, P.O., Ugwu, A.A., Nnadi, O.H., Kenechukwu, F.C., Ofokansi, K.C., Attama, A.A. & Lehr, C.M. (2021) Formulation and evaluation of transdermal nanogel for delivery of artemether. *Drug Delivery and Translational Research*, 11, 1655–1674.
- Pappas, P.G. et al. (2009) Voriconazole: A new option for the treatment of fungal infections. *Clinical Infectious Diseases*, 48, 655–661.
- Pathan, I.B., Dwivedi, R. & Ambekar, W. (2019) Formulation and evaluation of ketoprofen loaded chitosan nanogel for pain management: Ex-vivo and in-vivo study. *Ars Pharmaceutica (Internet)*, 60, 101–108.
- Saha, R. et al. (2021) Polymeric nanogels for drug delivery: A review. *Journal of Controlled Release*, 335, 44–59.
- Saraogi, G.K., Tholiya, S., Mishra, Y., Mishra, V., Albutti, A., Nayak, P. & Tambuwala, M.M. (2022) Formulation development and evaluation of pravastatin-loaded nanogel for hyperlipidemia management. *Gels*, 8, 81.