

Novel Citric Acid Dendritic Hydrogels for the Delivery of Econazole Nitrate and its Antifungal Activity

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ABSTRACT

Econazole is an imidazole derivative antifungal drug with distinguished antifungal properties. But the bioavailability of conventional econazole preparations is poor because of poor solubility and lipophilicity or lipophilic nature. Thus frequent application of the preparation is required to maintain therapeutic levels at the site of action. Such repeated doses may produce toxic affects thereby limiting the clinical use of the drug. Citric acid dendrimers give an opportunity to overcome the above limitations by improving its solubilization and drug permeation properties. Thus, the aim of current study is to design citric acid dendrimer hydrogels and study its influence on the drug release and anti-fungal activity of loaded drug. Dendritic architecture and size strongly influences the invitro release and antifungal activity of drug. Antifungal activity of designed Econazole hydrogel was measured by Agar plate diffusion method. Zone of inhibition values showed that citric acid dendrimers considerably enhanced the antifungal activity of Econazole to a greater extent and the effect was more with lower generation hydrogels. The operative mechanism is probably the smaller size (G2) that penetrates the fungal cell membrane more efficiently than higher generation (G3 and G4) hydrogels.

INTRODUCTION

Econazole is an imidazole antifungal derivative, used primarily for the treatment of both systemic and topical fungal infections (Albertini *et al.*, 2009). It is believed that econazole interacts with a cytochrome P-450 enzyme, 14- α demethylase that converts lanosterol to ergosterol. Ergosterol is an important constituent of fungal cell membrane. As econazole inhibits its formation, then there might be increased cellular permeability followed by leakage of cellular contents (Vera-Cabrera *et al.*, 2010). In addition, econazole also inhibits endogenous respiration, transformation of yeasts to their respective mycelial forms, interaction with membrane phospholipids, purine uptake and biosynthesis of phospholipids and triglycerides. In spite of these, econazole is lipophilic in nature and practically insoluble in water (Pandey *et al.*, 2005). This property limits the use of econazole in designing pharmaceutical formulations as therapeutic efficiency of the formulation will also get decreased. Since then various efforts have been made for the development

of efficient carrier systems that overcome the limitations of Econazole and improve the therapeutic efficiency of the drug.

Citric acid dendrimers is an approach towards improving therapeutic efficiency, solubility and bioavailability of entrapped drugs. Dendrimers are a class of monodispersed polymers with definite molecular weight and host-guest entrapment properties (Tomalia, 2004). Because of their repeated branching nature and nanometer size; dendrimers are considered most suitable for targeting therapeutic agents to the target site (Svenson, 2009). Among all dendrimers, citric acid dendrimers are popular and easy to synthesize. They have been considered as vehicles for different routes of delivery such as oral, Transdermal, ocular, i.v etc (Cheng *et al.*, 2008). Considering the use of dendrimers for drug delivery, it should be noted that they are bio-compatible, non-toxic (Jain *et al.*, 2010). They offer various advantages over linear polymers when used in drug delivery design (Amaresh, 2012). Their monodispersed nature and nanometer size range allows easy passage of dendrimers across biological barriers (Kakade *et al.*, 2013). Therapeutic agents get attached either to the surface or interior of the citric acid dendrimers through covalent conjugation or electrostatic interaction (Tambe *et al.*,).

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Moreover, it is said that some dendrimers itself possess a little anti-bacterial and anti-fungal activity (Janiszewska *et al.*, 2012). Thus, in the treatment of fungal and bacterial infections, dendrimers play an additive role besides being carriers for the drug (Winnicka *et al.*, 2011). Treatment of any skin infections requires maximum concentration of drug at the target site and clinical efficacy depends on the ability of drug to penetrate skin barriers and prevent fungal growth (Alberti *et al.*, 2001). As our skin is negatively charged, cationic dendrimers are supposed to interact with the skin and increase its permeability¹³. Further, dendrimers being carriers, serve the lipophilic drug in a solubilized form to the skin from where it get transported to stratum corneum more efficiently owing to the high affinity of hydrophobic forms to skin lipids (Venuganti and Perumal, 2009,2008).

In current study, an attempt was made to design and deliver citric acid dendrimers encapsulating an antifungal agent in a semisolid i.e. hydrogel form. Further, the influence of citric acid dendrimers on the invitro drug release and anti-fungal activity of drug on pathogenic fungal strains were also studied.

MATERIALS AND METHODS

Materials

Econazole nitrate (Yarrow Chemicals, Mumbai), Polyethylene glycol 400 (Finar chemicals Pvt. Ltd., Ahmedabad), Sodium Carbonate, Potassium Permanganate, Thionyl Chloride, Dimethyl formamide, Propylene glycol, Tween 80 (Sd Fine Chemicals Ltd., Mumbai), Pyridine, Diethyl ether and Carbopol 934 were used for the synthesis of Econazole dendrimer hydrogels. All the procured chemicals were of analytical grade.

Method of Preparation

Preparation of Econazole dendrimer gel is a lengthy process and involves the following steps:

- a. Synthesis of citric acid dendrimers
- b. Drug loading in the synthesized dendrimers
- c. Preparation of hydrogels of constructed Econazole dendrimers

Synthesis of 4 generations of citric acid dendrimers:

Citric acid dendrimers can be synthesized following Divergent technique based on the established and reported procedure:

Step 1: for the synthesis of dendrimers, 35.5gms of Potassium permanganate was weighed and dissolved completely in 694ml of water in a beaker. In another beaker, 3.75gms of Sodium carbonate was dissolved in 38ml of water. Both the solutions were mixed together with the addition of 110ml of Polyethylene glycol and stirred with the help of a magnetic stirrer for about 3-4hrs followed by cooling the mixture at 4-5°C by immersing in an ice bath for 20 minutes. Obtained reaction mixture

was filtered and collected filtrate was heated and cooled continuously till a 100ml concentrated liquid was obtained. This solution was covered with a layer of ether and after sometime both aqueous and ether layers were separated using a separating funnel. The collected aqueous layer was heated in a mantle at 70°C for the complete removal of ether from the mixture leaving behind a white precipitate. The so obtained precipitate is Polyethylene glycol diacid, nothing but Generation 1 dendrimer.

Step 2: G1 dendrimer was treated with 6ml of Thionyl chloride in a round-bottomed flask equipped with condenser and magnetic stirrer for 45-60min. Mixture obtained after condensation was heated to 70°C to collect Chlorinated Polyethylene glycol, which is a G1.5 dendrimer. Obtained G1.5 was dissolved in 20ml of DMF and kept in ice bath for 24hrs. Simultaneously, in another beaker 100mg of citric acid as dissolved in 10ml of DMF and 120ml of pyridine and placed on an ice bath overnight. Next day, both the solutions were taken from ice bath, mixed and incubated at 50-60°C in an incubator for 6hrs. Product obtained was Generation 2 dendrimer, which was further purified by Column Chromatography. In order to obtain G4 dendrimer, steps of *step 2* was repeated continuously with increasing amounts of Thionyl chloride and citric acid (Reddy *et al.*, 2014) (Table 1).

Drug loading in the synthesized dendrimers

For the purpose of drug loading, synthesized dendrimer was made to dissolve in 10ml of DMF and 10mg of Econazole, dissolved in a suitable solvent (i.e methanol) was added drop wise to the dendrimer solution. Drug-dendrimer solution was stirred on a magnetic stirrer for 24hrs at 50rpm speed. Amount of drug encapsulated in the dendrimers was estimated spectrophotometrically through UV spectrophotometer at 271.5nm (Rao *et al.*, 2015).

Preparation of Dendrimer hydrogels

Econazole loaded dendrimer gels were prepared by Dispersion method. As per the method, gelling agent i.e., carbopol 934 was soaked in water 2hrs before prior to preparation. Later, it was stirred to a homogenous mixture at a temperature of 40°C. The above mixture was neutralized with the drop wise addition of 20%NaOH solution to allow gel formation. In another beaker, methyl paraben and propyl paraben were dissolved in ethanol and added to carbopol mixture and stirred well. Tween 80 and propylene glycol were added to the hydrogel base with continuous stirring.

Finally drug loaded dendrimer solution was added to the above hydrogel to give out Econazole dendrimer hydrogel (Sosnowska and Winnicka, 2013) (Table no.2).

Table 1: Formulation of Dendrimers.

Formulation	KMNO ₄	Na ₂ CO ₃	PEG400	Thionyl chloride	Citric acid	Pyridine	DMF
F1(G1)	35.5gm	3.75gm	110ml	-	-	-	-
F2(G2)	35.5gm	3.75gm	110ml	6ml	0.1g	100ml	30ml
F3(G3)	35.5gm	3.75gm	110ml	8ml	0.2gm	100ml	30ml
F4(G4)	35.5gm	3.75gm	110ml	10ml	0.4gm	100ml	30ml

Table 2: Formulation of Dendrimer Hydrogels.

S. No.	Ingredients	Quantity
1.	Econazole loaded dendrimer solution	2ml
2.	Carbopol 934	34 mg
3.	Propylene Glycol	2ml
4.	Sodium Hydroxide	q.s
5.	Tween 80	0.2ml
6.	Methyl Paraben	q.s
7.	Propyl Paraben	q.s
8.	Ethanol	2ml
9.	Water	10ml

Characterization of dendrimers

Econazole loaded dendrimers were characterized by IR spectroscopy and Differential Scanning calorimetry

FT-IR studies

FT-IR spectra of drug, plain dendrimers and drug loaded dendrimers were performed to confirm the drug loading and compatibility between drug and dendrimers. It was carried using FT-IR spectrophotometer (Bruker, Germany) in the region 4000cm⁻¹ to 400cm⁻¹. Samples were mixed with Potassium bromide in the ratio 100:1 and compressed to discs by applying pressure of 10kg in a hydraulic press. Obtained pellet was placed under light path and spectra were recorded (Reddy *et al.*, 2014).

Differential scanning calorimetry

DSC of drug and drug loaded dendrimer samples was performed to examine the thermal stability of drug and drug loaded samples over a range of temperatures. DSC studies were performed using DSC module (DSC Q20 V24.11 Build 124, USA). Known quantity of drug and drug loaded samples was placed in an aluminium pan and lid was tucked onto pan. Pan was then kept on a sample holder whose temperature was equilibrated at 35°C. Later, temperature was raised at a rate of 10°C/min under nitrogen gas pressure till the sample gets deteriorated. In the resulting curve, temperatures for each curve were obtained. The curves provided information regarding stability and phase transitions for studied samples (Vijayakumar *et al.*, 2012).

Zeta potential

Zeta potential is an indicator of stability of the synthesized dendrimers and measured using Zeta Sizer. It is the measure of extent of electrostatic attractive or repulsive forces between the particles (Zaman *et al.*, 2014). Smaller particles possess a high zeta potential value offering stability to the preparation. Such particles resist agglomeration or flocculation and

remain dispersed throughout dispersion. When zeta potential value is small, particles experience attractive forces leading to flocculation or aggregation of particles.

Evaluation of Econazole dendrimer hydrogels

Percentage drug entrapment studies

Percentage drug entrapment studies were carried using UV spectroscopic method. These studies determine the efficiency of a preparation method to incorporate drug into the dendrimer gels. To determine the amount of drug encapsulated in gels, known amount of dendrimer gel equivalent to 10mg was dissolved in 10ml of methanol and the solution was centrifuged for 10min at 100rpm. The resultant filtrate was diluted suitably and observed under UV at 271.5nm to determine the drug inside the dendrimer gel complex (Reddy *et al.*, 2014).

Anti-fungal activity of Econazole and drug loaded dendrimer hydrogels

Anti-fungal activity of synthesized dendrimer hydrogels were investigated using Agar plate Diffusion method. Two human pathogenic fungal strains i.e. *Candida krusei* and *Candida albicans* were used for estimating anti-fungal activity of prepared formulations. Petridishes with Sabouraud's agar media were prepared and inoculated 100µL of candidal strains. Later the plates were dried and with the help of a sterile cork borer of diameter 6mm, wells were made in the agar plates. Simultaneously, known amount of different formulations of dendrimer hydrogels (G2, G3 and G4) equivalent to 10mg were diluted with 10ml of methanol and 10µL was transferred to the wells. Hydrogel without econazole and dendrimer (placebo), hydrogel with econazole and hydrogel with citric acid dendrimer were used as controls and were introduced simultaneously onto agar plates along with G2, G3 and G4 hydrogels.

Plates were then incubated at 37 °C ± 0.1 °C for 24 h. Antifungal activity was expressed as mean of inhibition zones (mm) around each well (Winnicka *et al.*, 2012).

Invitro drug release of Econazole from Dendrimer hydrogels

Diffusion studies of prepared dendrimer hydrogels was carried using Franz diffusion cell and drug release through cellophane membrane was determined by UV spectroscopic method. Gel sample (0.5g) was placed on a cellophane membrane in donor compartment with 100ml of phosphate buffer of pH 5.5 as dissolution medium in receptor compartment¹⁸. This assembly was maintained on a magnetic stirrer at 37°C. As the diffusion studies proceed, 1ml of sample was withdrawn periodically at 0.5, 1, 2, 4, 6, 8, 12, 24 and 48hrs from receptor medium and simultaneously replaced with equal amounts of fresh buffer. Collected samples were diluted appropriately and analyzed using UV spectrophotometer at 271.5nm with methanol as blank (Rao *et al.*, 2015).

RESULTS AND DISCUSSION

FT-IR studies

FT-IR studies were performed both for the drug and drug loaded formulations using FT-IR spectrophotometer. Results of the study showed IR spectrum of pure drug was almost equal to the standard drug, Econazole. In case of drug loaded formulations,

characteristic peaks of both drug and dendrimers were at their wavelengths. Results clearly indicated that drug has interacted and there was compatibility between the drug and polymers of dendrimers. Thus there was no change in the chemical integrity of Econazole. (Table no.3, Fig no. 1-4)

Zeta potential

Zeta potential of drug loaded Dendrimers was determined using Zetasizer. Technique adapted for performing Zeta Potential was Dynamic Light Scattering Technique. The values of Zeta potential for Econazole loaded dendrimers ranged from -37 to -48, indicating good stability of the formulations (Ciolkowski *et al.*, 2011).

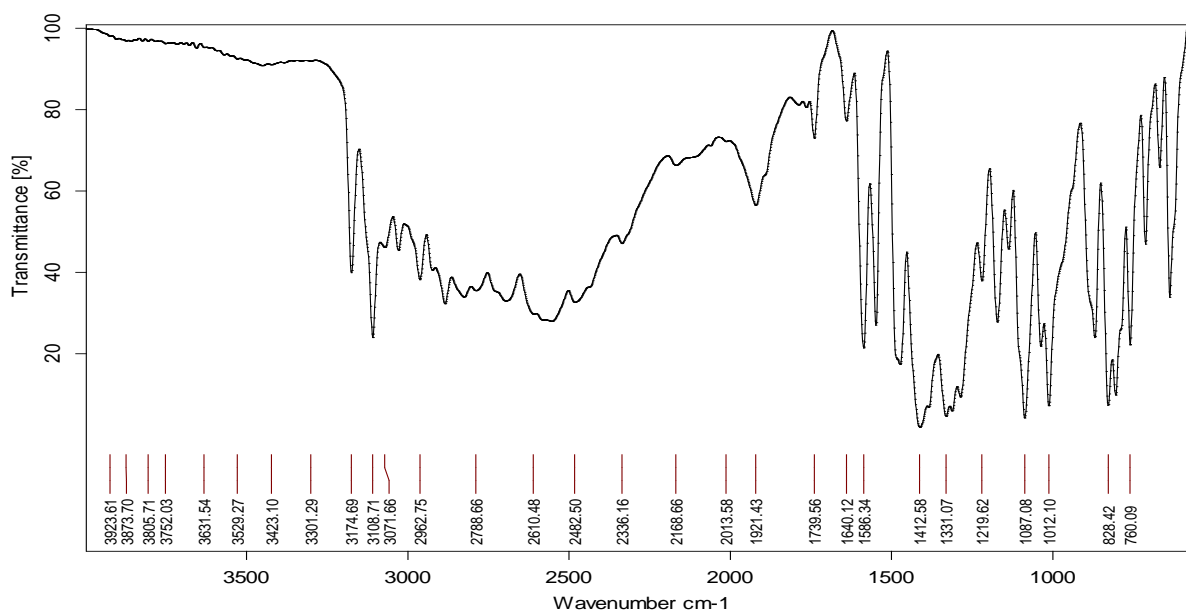
Table 4: Zeta Potential of different Dendrimer Generations.

Formulation Code	Zeta Potential
G2	-48
G3	-41
G4	-37

Stability of the formulations is contributed to the smaller dendritic size and repulsive electrostatic forces of dendrimers (Table no.4).

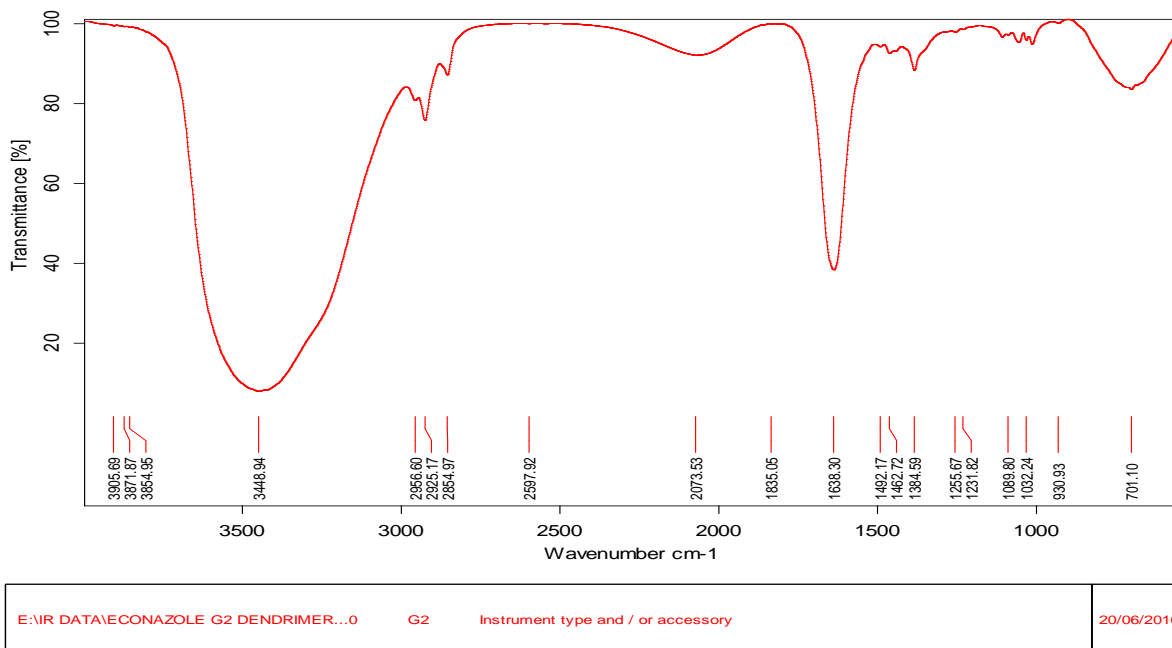
Table 3: Functional Groups of Infra Red Spectroscopy.

Polymers	Groups assigned				
	O-H stretch cm ⁻¹	C-H stretch cm ⁻¹	C=C stretch cm ⁻¹	C-C stretch cm ⁻¹	C-O-C stretch cm ⁻¹
Drug (Econazole)	3423.20	2962.75	1640.12	1472.58	1219.62
Econazole+G2dendrimer	3448.94	2966.06	1638.30	1492.78	1231.82
Econazole+G3dendrimer	3451.48	2968.09	1638.77	1462.05	1255.14
Econazole+G4dendrimer	3441.47	2964.84	1638.28	1465.33	1232.46

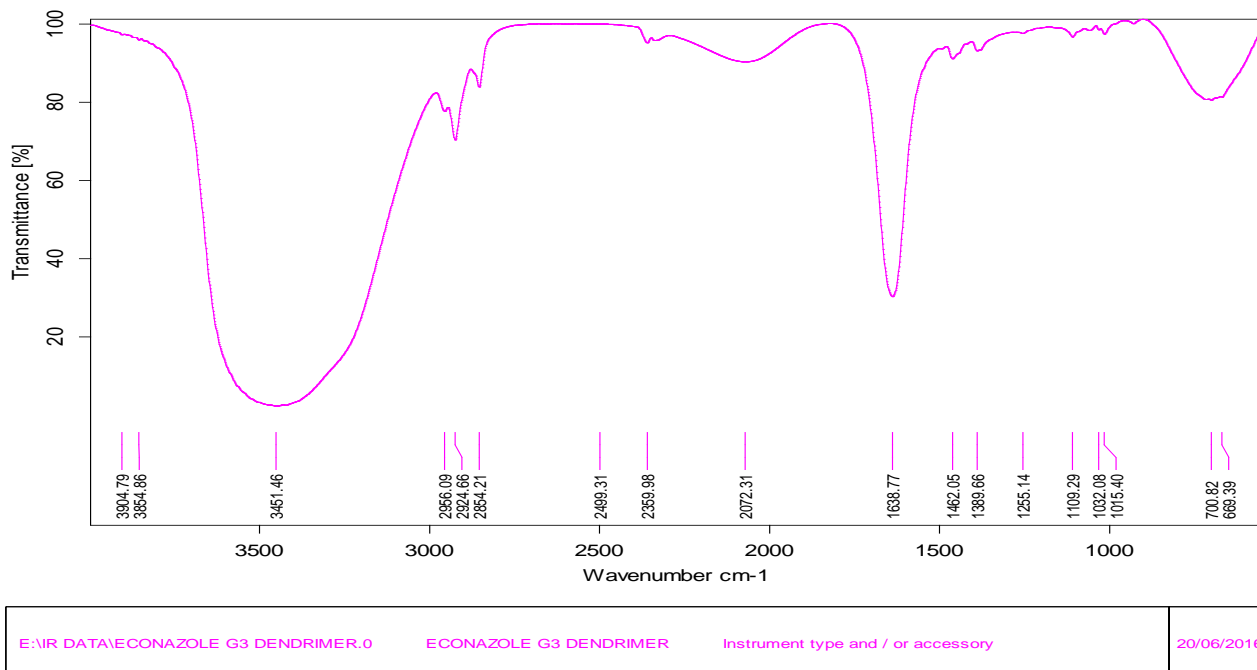


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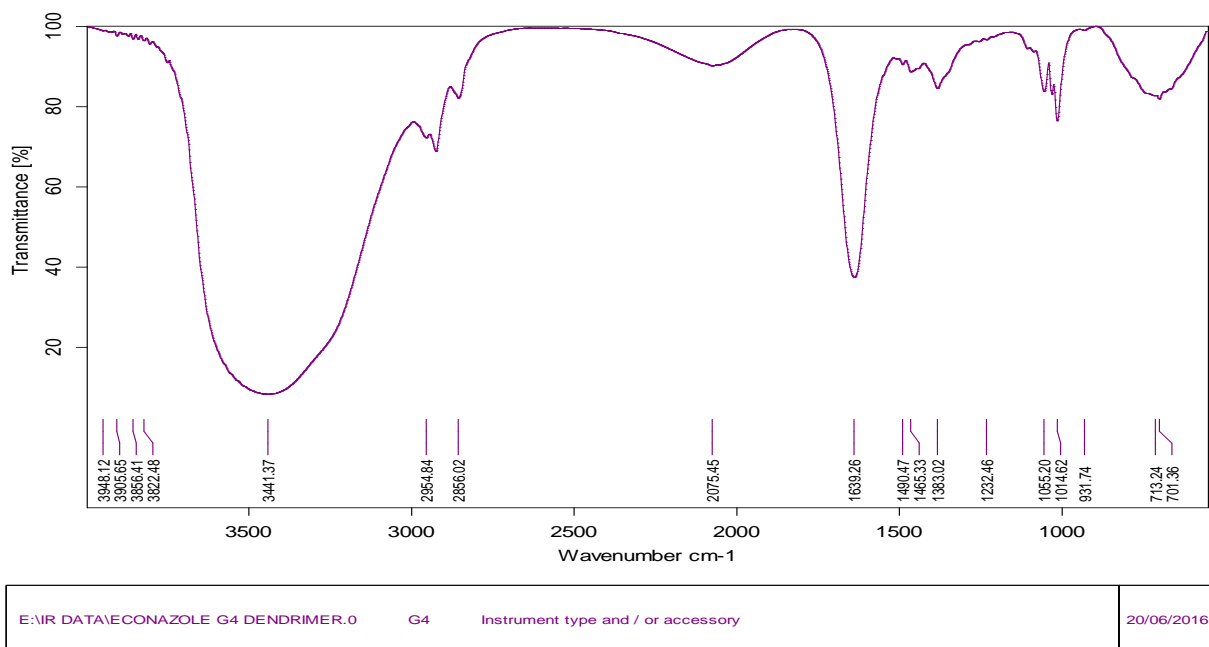
Page 1/1
Fig 1: FT-IR spectrum of Econazole



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Fig. 2: FT-IR Spectrum of 2nd generation Econazole loaded Dendrimer



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Fig. 3: FT-IR Spectrum of 3rd generation Econazole loaded Dendrimer



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Fig 4: FT-IR Spectrum of 4th generation Econazole loaded Dendrimer

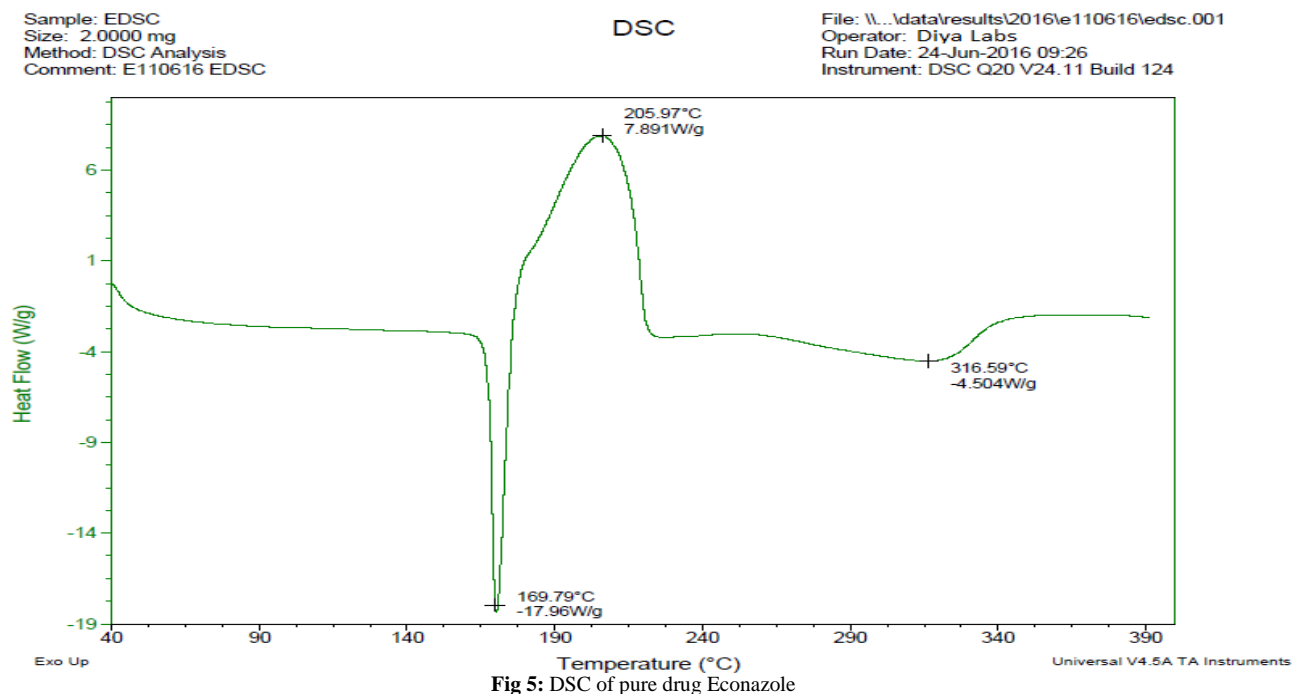


Fig 5: DSC of pure drug Econazole

DSC analysis

Differential scanning calorimetry curves suggested that 4th generation Econazole loaded citric acid dendrimer was not a physical mixture. Upon heating to 90°C, drug Econazole experienced an endothermic transition which was previously

referred as melting point of the compound. Further, broad endothermic peaks were observed between 96.05°C and 156.52°C for 4th generation Econazole loaded dendrimer. Characteristic peaks of Econazole were almost disappeared in the drug loaded 4th generation dendrimer (Fig no. 5,6).

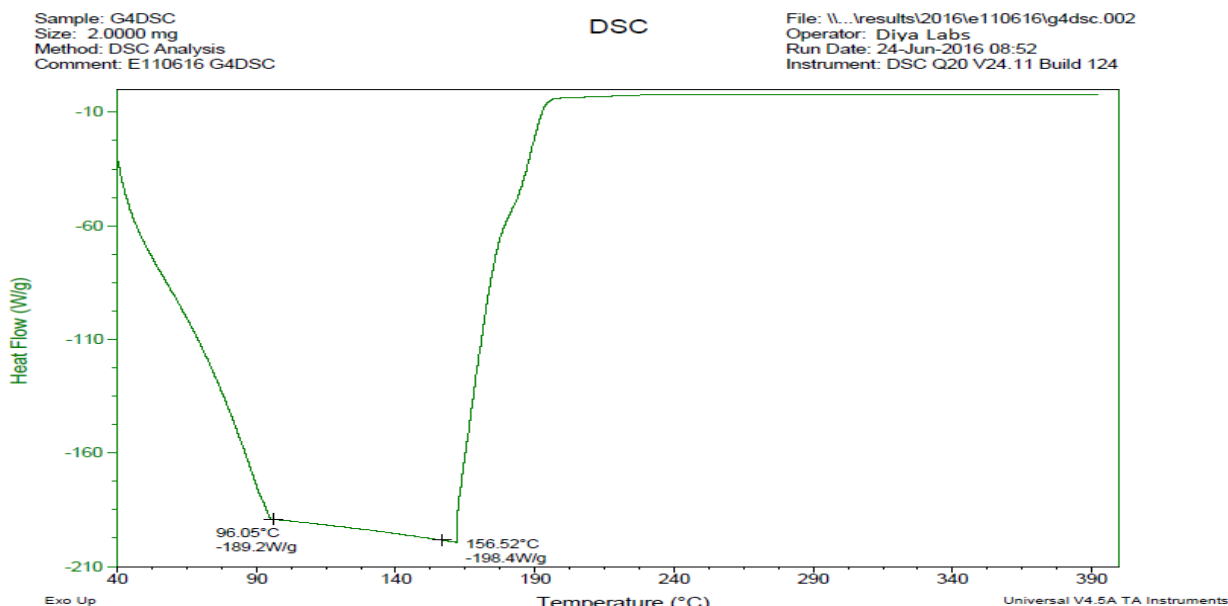


Fig 6: DSC of 4th generation Econazole loaded Dendrimer

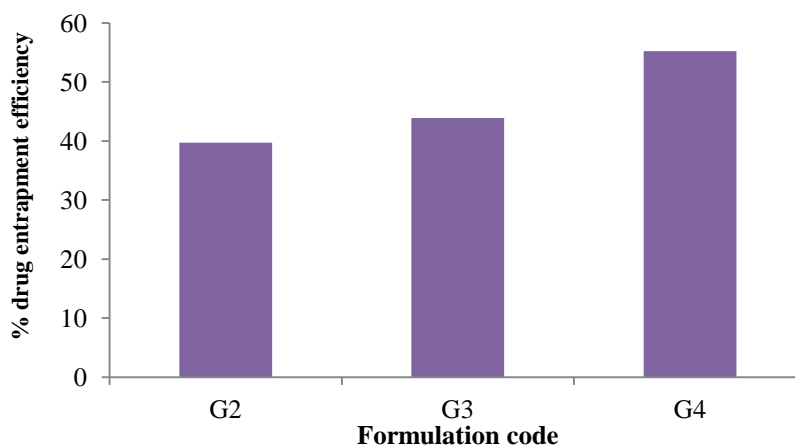


Fig 7: Entrapment efficiencies for Econazole loaded Dendrimer Hydrogels

Percentage drug entrapment studies

Results of percentage drug entrapment studies for dendrimer hydrogels carried through UV spectroscopic method were in the range 39.7-55.25%. Drug entrapment was found high for G4 hydrogel i.e., 55.25% as compared to G2 and G3. Thus from the results it was evident that drug entrapment increases with higher generations (Fig no.7).

Anti-fungal activity of Econazole loaded dendrimer hydrogels

Influence of dendrimers on the antifungal activity of econazole was clearly seen from the results. Anti-fungal activity of dendrimer hydrogels against Candidal strains increased to a larger extent as compared to the pure drug, Econazole. Among G2, G3 and G4 hydrogels, zone of inhibition was comparatively more for G2 generation. From the results it was believed that, size of the dendrimer molecule affects the penetration ability and anti-fungal activity of encapsulated drugs. Thus, G2 being smaller in size

could have penetrated the fungal cells efficiently and cut the growth of fungal strains as compared to G3 and G4 molecules (Table no.5, Fig no. 8).

Invitro drug release studies

Invitro drug release studies were carried for G2, G3 and G4 Econazole loaded dendrimer hydrogels using phosphate buffer of pH 5.5. Results of the study clearly demonstrated that dendrimer hydrogels of higher generations i.e., 4th generation was able to sustain the drug release more efficiently as compared to lower generations (2nd and 3rd generations). From the above result, it is clear that as the generations increase complexity of dendrimers also increase that leads to sustained effect. Release kinetic studies of the formulations showed that they followed Zero order release mechanism. Higuchi matrix equation confirmed that the release followed Diffusion controlled mechanism (Fig no.9). justification has been provided in the e-mail.



Fig. 8(a): Anti-fungal activity of Econazole on *C. krusei* Fig. 8(b) Antifungal activity of Econazole on *C. albicans*.

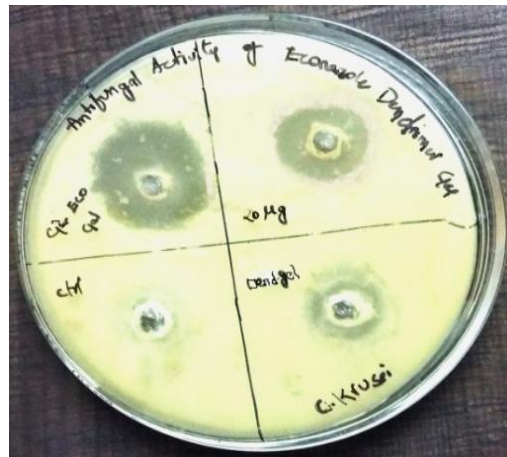


Fig. 8(c) Antifungal activity of placebo, Dendrimer gel, pure drug and drug loaded Dendrimer gel

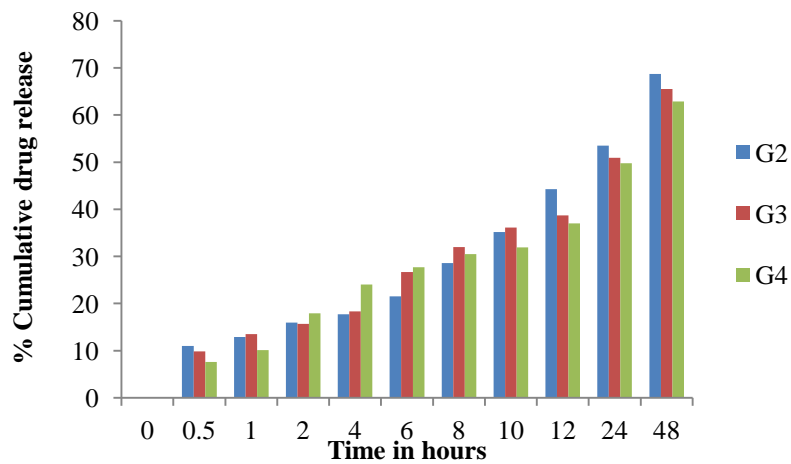


Fig 9: Cumulative drug release of Econazole loaded dendrimer hydrogels.

Table No. 5 Zone of Inhibition for Dendrimer Hydrogels

Formulation Code	Zone of Inhibition (Mm)	
	<i>C. krusei</i>	<i>C. albicans</i>
G2	24	14
G3	19	12
G4	17	10
Pure drug	11	-
Dendrimer gel	3	-
Placebo	0	-

CONCLUSION

In current study, we have designed citric acid dendrimer hydrogels as carriers for the delivery of antifungal drug, Econazole. Synthesized hydrogels were evaluated for various parameters such as entrapment efficiency, DSC analysis, in-vitro drug release, antifungal activity etc. Size and architecture of citric acid dendrimers strongly influences the anti-fungal activity, invitro drug release, entrapment efficiency parameters of drug, econazole. Thus they are considered novel carriers for the delivery of antifungal agent to the resistant producing strains of *Candida krusei* and *Candida albicans* for treating topical fungal infections.

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Conflict of Interests: There are no conflicts of interest.

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