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RESEARCH ARTICLE

Solubility Enhancement of Efinaconazole using Neem Gum and Evaluation of Antifungal Activity

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Abstract

Objectives: Efinaconazole is an anti-fungal drug of BCS class II used for treating Onchomycosis. Neem gum known for its antifungal properties was purified and used as hydrophilic carrier. Solid dispersions by physical mixture and solvent evaporation method were prepared using purified Neem gum. **Methods:** The prepared solid dispersions in ratios 1:1, 1:3 and 1:6 were characterized for percentage yield, assay, solubility, and dissolution studies. The optimized solid dispersion SD6 was formulated as gel for ease of application. Gels were characterized for physico-chemical properties and *in-vitro* diffusion studies. The optimized gel was evaluated for anti-fungal activity. **Findings:** FTIR, DSC and XRD studies of optimized SD6 showed compatibility and amorphous nature respectively. G2 gel formulation containing SD6 solid dispersion showed 80.4±0.14% when compared to G1 56.76±0.34% release in 8hrs. Both the gels followed zero order and Higuchi release. Antifungal studies indicated more efficiency of G2 gel by zone of inhibition when compared with G1 containing only drug. G2 gel was found to be stable for one month. **Novelty :** In the present research work purified neem gum, which is natural carrier and neem known for its antifungal activity was used to enhance the solubility of drug and evaluate the antifungal activity of drug with purified neem gum. **Conclusion:** Hence it can be concluded, purified Neem gum can be used as hydrophilic carrier and as solubility of Efinaconazole was enhanced its antifungal activity was also increased.

Keywords: Onchomycosis; Efinaconazole; Neem gum; Solid dispersions; Antifungal

1 Introduction

Drug solubility plays an important role in its absorption by any route of drug delivery, as maximum number of drugs are absorbed by passive diffusion. In topical delivery,

drug adsorption is assumed to follow Fick's first law of diffusion. Solubility of drug in the vehicle of dosage form and partitioning of drug through skin are the challenging factors for topical delivery. Solid dispersions (SD) are one effective strategy in increasing solubility of drug. Solid dispersions are dispersions of drug in biologically inert carrier which is usually hydrophilic. The most common methods for SD are fusion and solvent evaporation, which change a substance from a crystalline to an amorphous state either entirely or partially, increasing the substance's solubility and bioavailability.[1] Carriers used in solid dispersion are of two types. Natural (eg. Neem gum, Guar gum, Karaya gum, Xantham gum etc.) and Synthetic (eg. Sodium alginate, Methyl cellulose, HPMC etc.). Natural carriers are readily available and biocompatible when compared to synthetic polymers. Natural gums such as Sodium Alginate, Guar Gum, Xanthan Gum, and Locust Bean Gum as polymers were used to enhance solubility of Carvedilol (BCS Class-II).[2]

Neem gum (NG), natural polymer, is derived from Azadirachta indica, or Neem, trees. The potential applications of Neem gum as a mucoadhesive agent and tablet binder have been studied. Because of its high swelling index, high capacity for retaining water, digestibility, binding ability, and ease of availability, Neem gum is used extensively. Purified Neem gum has been studied as solid dispersion carrier for enhancing solubility of Aceclofenac.[3]

Efinaconazole is a triazole compound with anti-fungal activity, which belongs to BCS-II, it is poorly soluble or insoluble in water.[4] Onychomycosis, a nail infection primarily caused by dermatophytes, is treated topically with this antifungal medication. There are four approved classes of anti-fungal drugs for the treatment of onychomycosis: the allylamines, azoles, morpholines, and hydroxyl pyridinones. Efinaconazole is the first azole FDA approved in the USA to be used topically in the treatment of onychomycosis. It is a common disease, with a prevalence of 10% -12% in the US. By preventing the fungus from synthesizing ergosterol in its cell membrane, the drug acts as an antifungal. It's *in-vitro* activity against dermatophytes is comparable to that of amorolfine and terbinafine, and it is more effective than other antifungals that are currently on the market, such as ciclopirox and itraconazole. Since efinaconazole has a low keratin affinity, poor water solubility, and low surface tension, it also penetrates nails more deeply than other topical antifungals.[5] Efinaconazole spanlastic nanovesicles[6], 10% alcoholic based topical solutions[7], transferosomel gel[8] have been researched. Antifungal efficiency of plant extracts & polysaccharide based nano hydrogels would minimize the toxicity of azole antifungals was recommended based on studies.[9]

In the present study, neem gum plant extract which is known to have antifungal activity and studies have shown purified neem gum acts as a hydrophilic carrier in enhancing solubility was selected as the carrier. Efinaconazole, a topical azole antifungal agent used for nail onchomycosis, having poor aqueous solubility was selected as drug. The study aim is to enhance the solubility of efinaconazole using purified neem gum by solid dispersions and formulate as gel. As gel dosage form can be easily applied to the affected area and it also has more wettability and absorbs into skin enhancing absorption. Efinaconazole gel was further evaluated for antifungal activity.

2 Methodology

2.1 Materials and Methods

Efinaconazole was procured from Hetero Drugs Pvt Ltd, Neem Gum purchased from Amazon, Carbopol 974, Tween 20, Triethanolamine, Ethanol and Distilled water were procured from SD fine-chem limited.

2.2 Drug Excipients Compatibility Studies by FTIR

The spectrum analysis of Efinaconazole and polymers which is used for preparation of gels was studied by FTIR. FTIR spectra were recorded by KBr pellet method using a Shimadzu Corporation (Kyoto, Japan) facility (model - 8400S). The IR spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1}. The resultant spectrum was compared for any spectral changes and observed for the presence of characteristic peaks for the respective functional group in the compound.[10]

2.3 Purification of Neem Gum

The gum was dried well and powdered using mortar and pestle. The powdered gum was passed through a #100 sieve after which it was solubilized in distilled water. The concentrated solution of the gum was precipitated using ethanol. The precipitate was separated and dried at 60°C. The resultant dried gum was powdered again and passed through a #100 sieve, and it was then stored in an airtight container for use.[11,12]

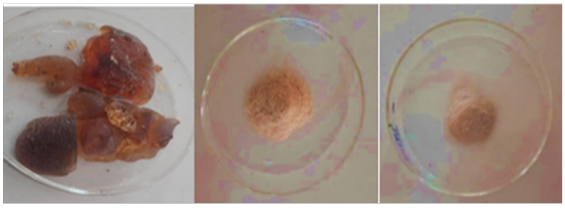

Fig 1. (a) Neem gum tears (b) Powdered Neemgum (c) Purified Neem gum

2.4 Characterization of Purified Neem Gum:[12–14]

Swelling Index: Accurately weighing 1g of NG, it was transferred to a measuring cylinder and vigorous shaking was done to disperse the gum in distilled water. After 24 hours, the volume that the NG sediment occupied was recorded. The swelling index, expressed as a percentage, was calculated according to the following equation:

$$SI = \frac{X_1 - X_0}{X_0} \times 100$$

Where X_0 is the initial height of the powder in the graduated cylinder and X_1 is the height of the swollen gum after 24 hours.

Water Retention Capacity: After the swelling index study was carried out, the contents of the measuring cylinder were filtered using a muslin cloth, and the water was allowed to drain completely into a dry 100 ml graduated cylinder. The volume of the water collected was noted. The water retained by the sample was determined as the difference between the original volume of the mucilage and the volume of the drained water. The amount of water retained per unit volume of a polysaccharide is referred to as its water retention capacity or water absorption capacity.

Viscosity Measurement: Viscosity of 1% aqueous NG solution was determined using a Brookfield LVDV+PRO viscometer in accordance with USP guidelines.

Angle of Repose: The fixed funnel method was employed to measure the angle of repose and calculated using the following equation:

$$\tan(\theta) = \frac{h}{r}$$

Where h is the height of the heap of powder and r is the radius of the heap of powder.

Hydration Capacity: 1g of powdered NG was added to a 15 ml tube. After adding 10 ml of distilled water to the powder, the mixture was centrifuged at 1000 rpm for 10 minutes. After that, the supernatant was removed by taking out and inverting the tarred centrifuge tube. The decanted tube was weighed on a digital balance, and the hydration capacity was calculated using the following equation[8]:

$$HC = \frac{Weight\ of\ hydrated\ sample}{Weight\ of\ dry\ sample}$$

Compressibility: The compressibility index (Carr's index) was determined using the following equation:

$$Carr's\ index\ (\%) = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100$$

Preparation of solid dispersion using purified neem gum as carrier[14]

Solid dispersions were made in the ratios of 1:1, 1:3, and 1:6 of drug and purified Neem as carrier by Physical mixture and Solvent evaporation in accordance with Table 1.

Table 1. Formulation table of solid dispersions

Formulation code	Drug and carrier (ratio)	Method
SD1	1:1	Physical mixture
SD2	1:3	Physical mixture
SD3	1:6	Physical mixture
SD4	1:1	Solvent evaporation
SD5	1:3	Solvent evaporation
SD6	1:6	Solvent evaporation

2.5 Characterization of Solid Dispersion:[1,15]

Percentage yield: calculated by substituting in the formula and weighing the amount of solid dispersion after preparation.

$Percentage\ yield = Practical\ yield / Theoretical\ yield\ x\ 100$

Assay: Using solvent evaporation and physical mixture methods, quantities of the physical mixtures (100 mg equivalent to drug) were dissolved in 100 ml of distilled water containing 1.5% Tween 20. After the samples were filtered, the drug content was measured at 261 nm using spectrophotometry.

Solubility Study: Fill an Effendroff tube with 2ml of distilled water and top it off with extra solid dispersion powder. After 24 hours in an orbital shaker, place it in a half-hour ultracentrifuge running at 10,000 rpm. Next, remove the supernatant and dilute it to 10ml using distilled water and 1.5% tween-20, then observe absorbance.

In Vitro **Drug Release Study**: Using 900 ml of phosphate buffer saline (pH 7.4) with 1.5% Tween 20 at 37 ± 0.5 °C and a type II USP dissolution test apparatus (EDT-08L-Electrolab, Mumbai, India) run at 100 rpm, the dissolution rates of the solid dispersions equivalent to 100 mg of drug were determined. The dissolving medium was removed in 5 ml aliquots at 5, 10, 15, 30, 45, 60, 90, 105, and 120 minutes. The samples underwent spectrophotometric analysis at 261 nm after being appropriately diluted.

Differential Scanning Calorimetry: Using a differential scanning calorimeter (DSC 1, Mettler Toledo, Switzerland) with a heating rate of 10°C/minute from 30°C to 300°C in a nitrogen atmosphere, DSC thermograms of the drug, purified Neem gum, and the optimized SD were obtained.[10]

X-Ray Diffraction Studies: Using a diffractometer (PW 1140, Mettler Toledo, Columbus, OH, USA) and Cu-Kα radiation, powder XRD patterns of the drug, purified Neem gum, and SD were recorded.[10]

Preparation of gel:[16] In a beaker, combine 5 ml of distilled water with 200mg of Carbopol 974. Thoroughly mix until a homogenous dispersion forms. Since the Efinaconazole (1g) is very insoluble in distilled water, add it to another beaker and dissolve it in 4 ml of ethanol. Add the drug and ethanol mixture to the carbopol mixture and stir until a uniform dispersion forms. Next, add the triethanolamine drop wise and stir continuously to create a homogenous gel mixture.

2.6 Evaluation of topical gels[17,18]

Clarity: Under a black and white background, the prepared gels' clarity was evaluated visually and rated as follows: turbid +, clear ++, and very clear +++.

pH determination: Digital pH meter was used to determine pH of each formulation.

Drug content: 100mg of gel was taken and dissolved in 100ml of pH 7.4 phosphate buffer saline with 1.5% Tween 20. The volumetric flasks were kept for shaking for 15min. The solution was passed through, Whatman filter paper and after appropriate dilutions the drug content was measured at 261 nm using a corresponding placebo gel.

Homogeneity: The gel's appearance was assessed visually. This was assigned a grade of Excellent +++, Good ++, and Satisfactory +.

Extrudability: [13] A Pfizer hardness tester was used and % Gel excluded is calculated and graded for 70% as +, 80% as ++ and 90% as +++.

Spreadability: The mass of the upper plate was standardized at 150g and spreadability was calculated by using

$S = m \times l/t$

Where, S = spreadability, m = weight tied to the upper glass slide, l = length of the glass slide, t = time taken in seconds.

Determination of viscosity: The Brookfield viscometer LV DV-II PRO was used to measure the viscosity of the prepared gels.

In-vitro **diffusion studies**: Franz diffusion cells were used for the diffusion studies. The cell was made locally, and the receptor compartment was kept at a 25 ml receptor volume. The donor and receptor compartments were separated by the dialysis membrane used in the diffusion experiments. The 1000 mg gel formulation was applied to the membrane uniformly, then secured with a clamp. The receptor compartment's hydrodynamics were stabilized by spinning it at 200 rpm with a magnetic stirrer after it was filled with pH 7.4 phosphate buffer saline containing 1.5% Tween 20. One milliliter sample was taken at predefined intervals and swapped out for an equivalent volume of buffer. Following dilution, the samples were examined using a UV-VIS double beam spectrophotometer set to operate at 261 nm**.**

Model dependent kinetics: The release data acquired for G1 and G2 were fitted into different kinetic models to determine release kinetics and release mechanism. Regression coefficient (r^2) was calculated for all the formulations. Release component "n" was calculated from Korsmeyer-Peppas equation. These calculations were carried out using MS-office excel.

Evaluation of Anti-fungal activity: [18,19] The antifungal activities of Efinaconazole were evaluated by disk diffusion assay. Briefly, ***Candid albicans*** *(NCIM no. 3665)* and ***Candida glabrata*** *(NCIM no. 336)* was cultured in **MGYP** (Malt Extract, Glucose,

Yeast Extract and Peptone) medium containing agar at 28 °C for 2 days. After incubation, the concentration of spores in the suspension was adjusted with 0.1 M PBS to 1×10^8 CFU/ml using a hemocytometer. Next, a 1-cm-dimaeter hole was punched in sterilized filter paper, which was then laid on the centre of each MGYP plate followed by uniform spreading of 100 μL of the prepared spore suspension on the plate. A 5 μL sample solution was then impregnated into each disk. To prepare control plates, a disk soaked in spore suspension and sterilized water was incubated. The zone of inhibition (ZOI) was determined by measuring the mean diameter of the area of growth inhibition surrounding the disk following two days of incubation at 28 °C.

Stabilitystudies: [18] After a month of room temperature storage, the optimized gel formulation G2 was tested for stability. Every week, the drug content, physical characteristics, and *in vitro* diffusion studies were evaluated.

3 Results and Discussion

3.1 Drug excipient compatibility studies by FTIR

FTIR study was done to verify if there was any interaction between the pure drug and polymers employed. The FTIR graphs of pure drug, solid dispersion (1:6) and neem gum is given in Figure 2. In efinaconazole FTIR scan, principal peaks were found at 1690-1640 cm^{-1}, 1400-1000 cm^{-1}, 1342-1266 cm^{-1}, 1200-1275 cm^{-1}, 1450 cm^{-1} representing various functional groups such as imine/oxime, fluoro compound, aromatic amine, alkyl aryl ether, methyl groups present. The peaks in IR spectra of solid dispersion SD6 (Figure 2) shows drug peaks, suggesting no interaction present in the drug and the excipients. This also implies that the drug is stable and compatible with the excipients chosen.

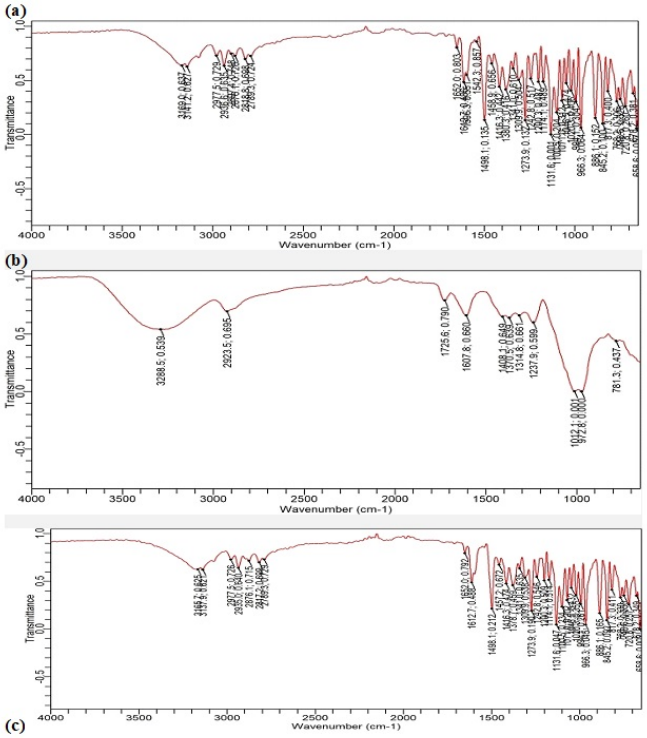

Fig 2. FTIR spectra (a) Efinaconazole (b) purified Neem gum (c) Solid Dispersion (SD6)

3.2 Result and Discussion of Characterisation of neem gum

From the results of characterization of neem gum and purified neem gum (Table 2), it is observed, swelling index of modified or purified Neem gum was less and viscosity was also less. Hydration capacity and water retention capacity were more for purified or modified Neem gum. It has also been reported by Madhuri S Rodde et al. that low viscosity property helps in enhancing solubility and bioavailability of poorly soluble drug [12]. Hence, from these observations, modified or purified Neem gum can

Table 2. Characterisation of Neem gum and purified Neem gum

S.no	Properties	Neem gum	purified Neem gum
1	**Swelling Index**	33%	21.5%
2	**Water retention capacity**	2ml	2.9ml
3	**Viscosity**	1.763±0.15cps	1.257±0.20cps
4	**Angle of repose**	24.2^0	28.36^0
5	**Hydration capacity**	0.96	1.1
6	**Density**	$0.6gm/cm^3$	$0.56gm/cm^3$
7	**Compressibility index (%)**	21	21

be used as hydrophilic carrier, and both (purified neem gum and neem gum) found to have good flow property and passable compressibility index.

Table 3. Characterisation of solid dispersions

Solid Dispersions	Percentage yield (%)	Assay (%)	Solubility (mg/ml)
SD1	100%	96.32	0.001
SD2	100%	93.01	0.016
SD3	100%	94.16	0.027
SD4	52%	89.18	0.043
SD5	91%	87.01	0.061
SD6	91.14%	94.16	0.121

3.3 Result and Discussion of Characterisation of solid dispersion

Solid dispersions prepared by physical mixture and solvent evaporation were characterized, from results given in Table 3, it is observed 1:6 ratio of drug: carrier solid dispersion prepared by solvent evaporation has the highest solubility of 0.121mg/ml when compared to pure drug aqueous solubility 0.0168mg/ml [12]. The solubility of efinaconazole drug by solvent evaporation technique was enhanced by 7.2 times. Using purified neem gum as carrier, solubility of atorvastatin by solvent evaporation method was enhanced by 4.43 times [12].

When compared with physical mixture method, the percentage yield and assay by solvent evaporation method are less as in solvent evaporation method the drug and carrier are dissolved in the solvent and carrier is complexed with the drug at molecular level. In the preparation method, the drug and carrier are completely solubilised in the solvent and later solvent is evaporated, so as drug is complexed with carrier, percentage yield varies. Whereas in physical mixture method drug and carrier are physically mixed according to the ratios so there is no loss of drug or carrier and hence 100% percentage yield is obtained. Based on solubility studies SD6, solid dispersion is optimized.

From Figure 3, Dissolution studies of 1:6 ratio solvent evaporation solid dispersion has shown 96% release in 30 min when compared to 1:6 ratio physical mixture 78.22% and pure drug 46.67%. Hence, 1:6 ratio solid dispersion prepared by solvent evaporation has been optimized. Similarly, solid dispersion by solvent evaporation method showed maximum release and was optimized with atorvastatin solid dispersion with purified neem gum as carrier [12].

3.4 Differential Scanning Calorimetry (DSC)

DSC is a very powerful technique used to evaluate material properties such as glass transition temperature, melting point, crystallization, specific heat capacity, purity, oxidation behaviour and thermal stability of a compound. From Figure 4, sharp peak indicates that the drug powder is crystalline in nature. The broad peak in the Figure 4 **b & c** indicates that it is Amorphous in nature.

3.5 X-ray diffraction (XRD)

XRD is a versatile non-destructive analytical technique used to analyze physical properties such as phase composition, crystal structure and orientation of powder, solid and liquid samples. From Figure 4, XRD of pure drug represents that the sample has more crystalline nature and XRD of Neem gum represents that the sample has more amorphous nature.

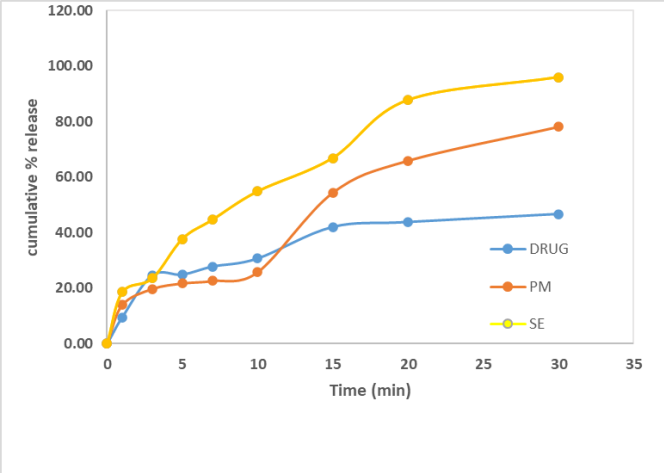

Fig 3. Graphical representation of dissolution studies

DSC and XRD studies of optimized SD6 solid dispersion prepared by solvent evaporation showed amorphous nature which is more soluble. Similar results of broad peaks and amorphous nature of drug is reported by Chennuri A et al. [10] The optimized solid dispersion was formulated as gel for ease of application.

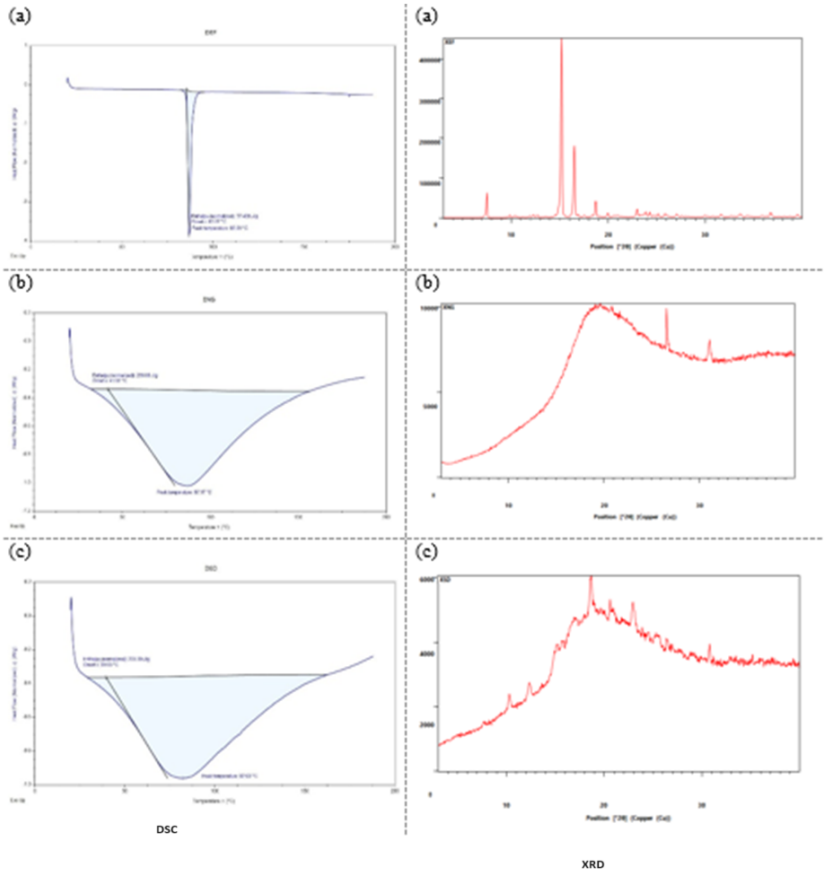

Fig 4. DSC and XRD (a) Efinaconazole (b) Neem Gum (c) Solid Dispersion (1:6)

3.6 Physical Evaluation of Gel

The clarity, Homogeneity, Extrudabilityof formulation G1 and G2 was found to be +++. The pH of formulationG1 and G2 was found to be 6.85±0.1, 6.2±0.1 respectively. Spreadabilityof formulation G1 and G2 was found to be 30gm/cm, 46gm/cm respectively. Drug content of formulation G1 and G2 was found to be 97.65±0.32, 98.27±0.11 respectively. Viscosity of formulation G1 and G2 was found to be 34325±120cps, 33200±120cps. In-vitro diffusion studies are represented in Figure 5.

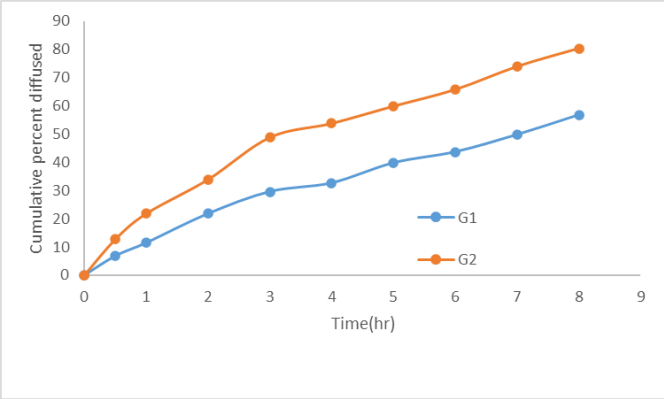

Fig 5. *In-vitro* diffusion studies of Gel

The optimised 1:6 ratio of solid dispersion by solvent evaporation was prepared as gel using Carbopol 974 (2%). The gel was evaluated, and physiochemical properties were found to be within pharmacopoeial limits. In-vitro diffusion studies showed maximum release by G2 gel formulation which contained optimised solid dispersion SD6. Similar results were obtained for econazole topical gel by Mohammad F Bayan et al.[19] Both the gel formulations followed zero order release and Higuchi release pattern, which indicates the formulation is matrix type. From Korsmeyer-peppas release both the formulations are following super case II transport which is zero order release. So, the formulations are matrix type and following zero order release.[19]

3.7 Antifungal Studies

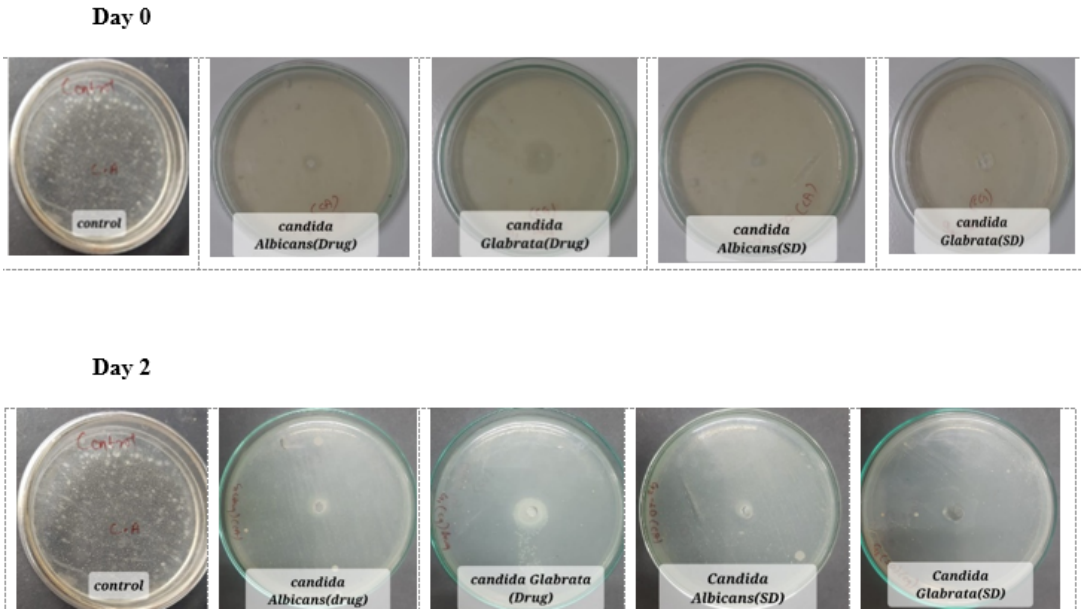

Fig 6. Antifungal studies

Table 4. Zone of inhibition

Organism	Drug (G1)	Solid Dispersion (G2)
Candida albicans	5mm	7mm
Candida glabrata	10mm	15mm

From Figure 6, antifungal studies against *Candida albicans* and *Candida Glabrata*, where the antifungal activity is evaluated by zone of inhibition. It can be seen in the pictures, in control where fungal growth is there as drug was not added and whereas in other pictures drug is added in the form of gel and the fungal growth is minimised. On comparison of pictures of Day 0 and day 2, the zone of inhibition is clearly seen. G1 is gel containing drug and G2 is gel containing drug in solid dispersion.

From, Table 4, the zone of inhibition studies it is seen the gel G2 containing SD6 solid dispersion was having more efficiency when compared to pure drug as solubility of drug was enhanced. The antigungal activity was also efficient with *Candida glabrata* when compared with *Candida albicans*. Similar zone of inhibiton studies were reported with econazole gel [19] and luliconazole niosomal gel [20] formulations and efinaconazole anti-fungal activity against onchomycosis. [21]

3.8 Stability studies

Based on evaluation results, optimized G2 gel was stored at room temperature over a period of 1 month and evaluated for physical appearance, drug content and in-vitro diffusion studies every week. The optimized G2 gel is stable for a period of one month (Table 5).

Table 5. Stability studies of G2

Evaluation parameter	Period of stability studies				
	Day 0	Day 7	Day 14	Day 21	1 month
Physical appearance	Clear gel	Clear gel	Clear gel	Clear gel	Clear gel
Drug content (%)	98.27±0.11	98.15±0.25	98.12±0.15	98.06±0.09	98.01±0.05
In-vitro diffusion (%)	80.40±0.26	80.36±0.11	80.23±0.14	80.18±0.16	80.05±0.27

4 Conclusion

Onchomysis is a nail infection causing thickened, brittle, crumbly or ragged nails. It is mainly caused due to dermatophytes. Efinaconazole anti-fungal drug against onchomycosis, is a poorly soluble drug. It is being reported that efinaconazole is soluble in organic solvents [4] and has poor aqueous solubility, but using organic solvents in the formulation would worsen the discomfort of nails affected by onchomycosis. Purified neem gum has been proven to enhance the solubility of aceclofenac [3] and atorvastatin [12]. Its solubility is enhanced by preparing solid dispersion using purified neem gum as a natural carrier. Physicochemical properties of purified neem gum such as viscosity, hydration capacity, water retention capacity and anti-fungal activity make it a suitable carrier for enhancing solubility. Drug excipient compatibility studies by FTIR proved drug and carrier were compatible. Solid dispersions by physical mixture and solvent evaporation method were prepared and characterized. SD6 formulation of solid dispersion prepared by solvent evaporation was maximum soluble and released maximum amount of drug in 30 min. Solubility of efinaconazole as solid dispersion of purified neem gum was increased by 7.2 times by solvent evaporation method. In this study purified neem gum, not only enhanced the solubility but also its antifungal property enhanced the antifungal activity of efinaconazole.

Characterisation of SD6 by DSC and XRD studies, showed amorphous nature against crystalline nature of drug, supporting the enhancement of solubility. The optimized solid dispersion was formulated as gel, to minimize the discomfort of nails due to onchomycosis and ease of application of formulation to affected part. As gel disperses well into skin and gets absorbed giving emollient effect and also is non-sticky. Gel, physicochemical properties were found to be within pharmacopoeial limits, and release pattern was zero order release and Higuchi model indicating matrix type. Solid dispersion SD6 containing gel G2 suppressed the growth of Candida Albicans and Candida Glabrata when compared with control, to which drug was not added. The gels were found to be stable. In conclusion, purified neem gum has enhanced the solubility, dissolution, and antifungal activity against onchomycosis of efinaconazole.

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