RESEARCH ARTICLE

Design, Development and Characterization of Econazole loaded Nanoparticles for Topical Application

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ABSTRACT

Background and Objectives: Econazole nitrate (ECN) loaded nanoparticles with topical administration were the focus of the current study, which aimed to improve the topical efficacy of the medicine in treating fungal infections while also mitigating the drug's gastrointestinal (GI) side effects. Further colloidal carrier methodology was employed as a method for the topical administration of medications with precision.

Method: The emulsification-diffusion (E-D) method is an alternate approach for preparing nanogels that avoids the toxicity-solvent issues associated with the emulsification-evaporation technique. Its ease of use, enhanced stability, and adaptability have all been verified by a variety of research groups. ECN loaded with dichloromethane in stabilizer solution, formulated by high-speed homogenization at elevated pressure. The addition of aqueous phase with repeated homogenization cycles causes drug diffusion into nanogels. Further addition of mannitol as cryoprotectant and Carbapol 940 as gelling agent stabiles the formulation.

Results: The typical size of the particles, polydispersity index (PDI), and zeta potential were all measured with the use of the Malvern zetasizer. Of the five NFs, the lyophilized batch of NF3 exhibited the lowest zeta potential (-11.6 mV) and the PDI (0.208), indicating that the composition was stable. DSC and XRD analysis revealed an amorphous transformation of ECN. The scanning electron micrograph demonstrated discrete, roundish particles. The existence, viscosity, and spreading ability of a gelled dispersion of the selected NLCs were evaluated. Total od 77% of the medication was released *in-vitro* from a chosen formulation of ECN-loaded nanogels. As a result, it is reasonable to assume that ECN-loaded nanogels are an effective drug delivery system for treating fungal infections since they prolong the duration of drug release.

Conclusion: Under degraded conditions, there are not any peaks that conflict with one another. As a result, a technique was developed that is highly applicable due to its sensitivity, strength, accuracy, and demonstration of stability.

Keywords: Econazole nitrate, Nanoparticles, Emulsification-diffusion (E-D) method, Drug delivery, Scanning electron microscopy.

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INTRODUCTION

Targeted medication delivery involves administering the medicine to a specific area where it will have the desired effect while limiting the drug's distribution to other, less important areas. Improved medication efficacy is the result[1,2] The carrier plays a crucial role in transporting the medicine to its destination. Because of the rapid development of the colloidal drug delivery system, the field of regulated and targeted drug administration has made significant strides. Using colloidal carriers is one method for regulating transdermal medication delivery to target the skin's deeper layers with active ingredients. In the near future, we will need nanodisperse systems like liposomes, nanoemulsion, and nanoparticles. Nanoparticles are gaining popularity as potential novel carriers for topically applied colloidal medicines.

This approach provides substantial safeguards against chemical degradation of the medication. The optimal method for creating nanoparticles relies on the chemical and physical characteristics of the medication and polymer being employed. Because of its superior biodegradability, biocompatibility, and scalability, SLN was preferred over polymeric nanoparticles. Yet, they suffered from issues like insufficient drug loading and release. In response to these issues, scientists developed a novel type of lipid carrier they termed nanostructured lipid carriers (NLC).[3,4]

NLC is produced by combining lipids of varying solid and liquid forms. The dissimilarity in structure causes the formation of an incomplete, amorphous cluster that serves as a trap for the drug. SLN is able to work around its inherent issues thanks to its faulty alignment and amorphous nature.[5,6] The imidazole chemical econazole nitrate (ECN) has antifungal activity towards numerous fungus species. Most commonly, it is used to treat infections brought on by the yeast *Candida albicans*.[7] Econazole nitrate blocks the enzyme cytochrome P-450, which stops the body from making ergosterol. This makes cells more permeable, which lets their contents leak out and kills the cells.[8-10] About 98% of the drug binds to plasma proteins, and very little of it is absorbed when applied to the skin.[11] In this research, we sought to develop econazole-loaded nanoparticles for topical administration and characterize their size, shape, and composition. The optimized formulation was evaluated.

MATERIALS AND METHODS

Materials

Econazole nitrate was gift model from FDC (Aurangabad, India). Analytical-grade chemicals are used for work.

Methods

To create nanoparticles, researchers turned to the solvent diffusion technique. To a volume of 66 mL of 0.2% surfactant solution, we added 150 mg of medication dissolved in 9 mL of dichloromethane. The result was a main emulsion. A high-pressure homogenizer (Turrax T25 at 8000 rpm) was used to process the emulsion into nanoemulsion after diluting it with 75 mL of clean water for 5 minutes. To prevent drug degradation during the lyophilization cycle mannitol (3% w/v) was added to the nanoemulsion, then stored in the deep freezer for 24 hours before freeze-drying. The lab freeze drier was set to -70°C, and the drying process took 48 hours. Various stabilizers were used to keep the freeze-dried nanogels from falling apart. When treated with NF2, these batches can be used to create a stable emulsion. Freeze-drying was required to obtain the solid particles.[12-15]

Evaluation of Nanoparticles

Fourier Transform Infrared Spectroscopy Study

Drug (ECN) and excipients physical combination FTIR spectra were recorded in the solid state using potassium bromide as solvent in the 400 to 4000 cm^{-1} range. Drug excipients study was also done for any chemical and physical changes via FTIR spectroscopy for functional group changes.[16]

Differential scanning calorimetric analysis

The amorphous nature of the medication in the adjuvants was determined using differential scanning calorimetric analyses. Mettler Toledo, Switzerland's DSC 822c was utilised to study ECN, the drug/excipient physical combination, and the ECN nanogels. A metal baking dish was used to weigh the samples. At a pace of 10°C per minute, the temperature was varied between 0 and 800°C. The atmosphere was kept inert by purging it of nitrogen.[17]

X-ray diffraction analysis

XRD examination was on several samples by Brucker Axs, 08 Advance, Germany using Cu as the radiation source. The X-ray diffractometer was used to look at the pure medication (ECN) and the optimised batch (NF2). The XRD pattern was scanned between 10 and 89° at an angle of 2.40 mA of current and 45 kV of voltage for both medications.[18]

Zeta potential determination

Nano ZS90, Malvern, UK, was used to determine the zeta potential of synthesized NLCs. Three separate analyses were performed after enough dilutions with deionized water were ensured. The experiment was conducted at an accelerated voltage & a pressure of 18 kV and 0.8 mmHg, respectively.[19]

In-vitro drug release studies

Drug release of both unloaded NLCs nanogel and NLCs nanogel loaded with ECN was tested at Electrolab, India. The appropriate number of samples was located on donor section of diffusion cell, and samples were stored in the appropriate sections. The receptor's environment is a phosphate buffer (pH 7.4). Medium in receptor chamber constantly stirred at 500 rpm to maintain a temperature of 37 ± 1°C. Phosphate buffer containing 2 mL aliquots was removed and reintroduced at regular intervals (pH 7.4). Aliquots were collected and run through a UV-visible spectrophotometer to determine how much medication was released.[20,21]

RESULTS AND DISCUSSION

FTIR Study

The IR spectrum of the optimized batch (NF2) was obtained after scanning at IR spectrophotometer and obtained

peaks were interpreted (Figure 1). The drug was loaded in nanoparticles successfully because there was no presence of drug peak in spectrum of NF2. The peak was observed at 2939 cm^{-1} indicating aliphatic C-H (stretch). IR peaks for C-O and C-N chemical bonding at 1381, 1319, 1261 and 1197 cm^{-1}, respectively. For C-Cl aromatic, the peaks were observed at 1084, 1020 and 929 cm^{-1}. The peaks 875, 717, 624, 412 cm^{-1} peaks were also present in the spectrum which shows the chemical bonding of C-H (bend).

DSC Analysis

We obtained the DSC thermogram, the formulation, and the physical mixing of ECN with the excipients. DSC thermograph showed sharp endothermic peak. These peaks denoted the melting point of sample (Figure 2). The reported melting point was 166.2°C. The onset of melting endotherm was found to be at 167.5°C. It was nearly similar to the reported melting point. It confirms that sample was econazole. The percent crystallinity of the pure econazole was 6.99%. Therefore, it showed that, drug was crystalline.

XRD Studies

The pure medication (ITZ) and the optimized batch (NF2) were analyzed using an XRD. The 2Θ values were recorded for together samples. In the diffractogram of ITZ (Figure 3), 2Θ values presents as 12.32, 13.45, 14.42, 4.76, 8.79, 10.95, 16.54, 17.84, 17.50, 19.25, 23.40, 25.30, 27.03, 27.98, 20.32, 21.15, 22.40, and 28.76°. These record 2Θ value of sample similar with previous values of econazole. It means sample was econazole and drug was nearby in crystalline nature. The 2Θ values of econazole 4.76, 8.79, 12.32, 14.42, 16.54, 17.84, 17.50, 19.25, 22.40, 23.40, 25.30, 27.98 and 28.76° were not present in diffractogram of the optimized batch sample (NF2) (Figure 3). These explain that, the econazole may convert from its basic crystalline nature to another crystalline form.

Surface tonography compared between batches that were optimized (NF2) and those that were not (NF3). Pictures were taken at X30, X500, X1000, and X3000 magnification of NF2 and NF3 tissue samples, respectively. Nanoparticles

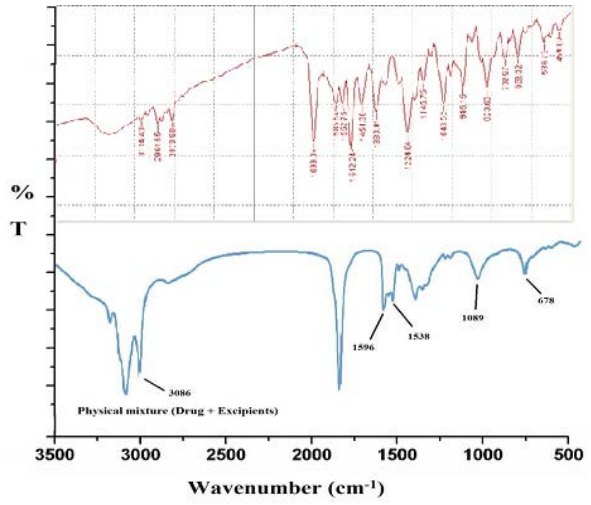

Figure 1: Econazole nitrate and physical mixture FTIR spectra

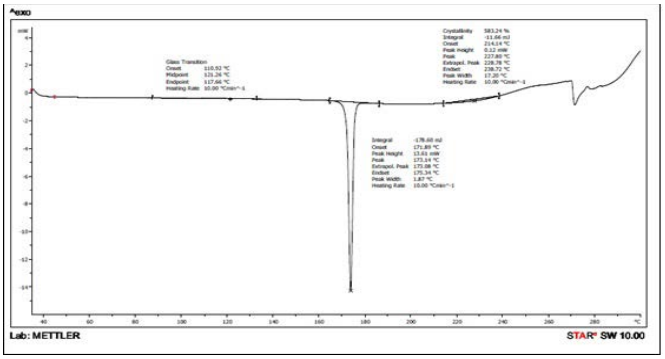

Figure 2: DSC Thermograph of Econazole

created in both the optimized and non-optimized batches did not have a spherical form. The characterization of econazole nanoparticles shows in Table 1.

Optimization of nanoparticles

Each batch's composition was determined using a variety of techniques, including infrared spectroscopy, XRD, scanning electron microscopy, particle size, PDI, zeta potential, percent drug, and *in-vitro* drug release studies. The lyophilized NF2 batch had the smallest particle size of the six batches, measuring in at 162.2 nm. The PDI for the NF2 batch was 0.208, which is much closer to zero than previous batches. Their zeta potential can measure nanoparticles' stability. The zeta potential (-17.8) of NF2 demonstrates the stability and lack of aggregation of the produced nanoparticles. The total of drug present in nanoparticles was resolute by drug content and the maximum amount of drug was present in NF2 batch (94.8%). The NF2 batch was also good and maximum drug release. By studying the IR spectroscopy of NF2 batch it was found that drug was successfully loaded and there was not any interaction between drug and excipients. The XRD

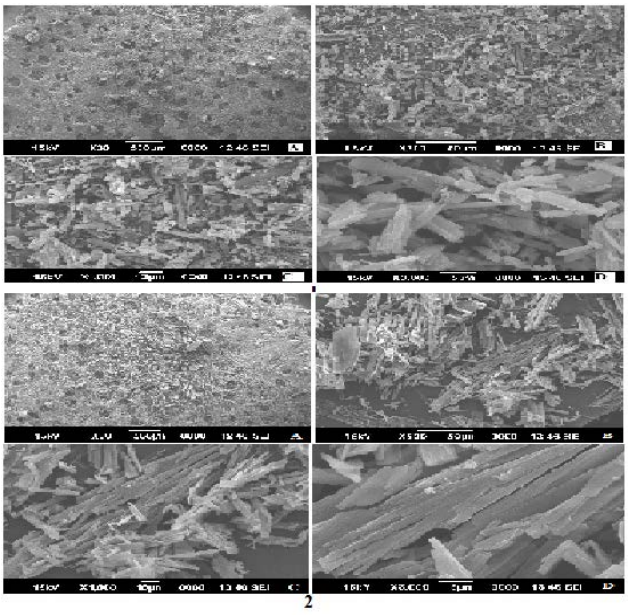

Figure 3: SEM images of NF2 (1) and NF3 (2) at X30 (A), X500 (B), X1000 (C), X3000 (D) magnifications

Table 1: Characterization of econazole nanoparticles

Formulation code	Before lyophilization			After lyophilization				
	Particle size (nm)	PDI	Zeta potential (mV)	Particle size (nm)	PDI	Zeta potential (mV)	Drug content (%)	Cumulative drug release (%)
NF 1	205.3	0.4	-15.9	193	0.5	-12.6	67.6	55.69 (± 0.5)
NF 2	93.93	0.4	-8.72	167.2	0.2	-17.8	94.8	86.15 (± 0.5)
NF 3	183.5	0.1	-21.6	501.4	0.9	-11.6	18.9	81.2 ((± 0.4)
NF 4	197.3	0.1	-45	435.4	0.7	-27.6	67.2	62.06 (± 0.3)
NF 5	53.75	0.5	-24.5	1090	1	-14	44.2	81.58 (± 0.7)

Table 2: Viscosity of topical nanogel formulations

Formulation code	Evaluation parameter					
	pH	Homogeneity	Spreadability (Diameter (cm))	Viscosity (Poise)	Drug content (%)	%Cumulative drug release
NG1	6.5	Good	3.0	107.4	59.60	79.33 (± 0.2%)
NG2	6.8	Good	2.2	160.2	77.00	85.24 (± 0.9%)
NG3	6.8	Good	2.0	1434.5	70.47	34.38 (± 0.5%)

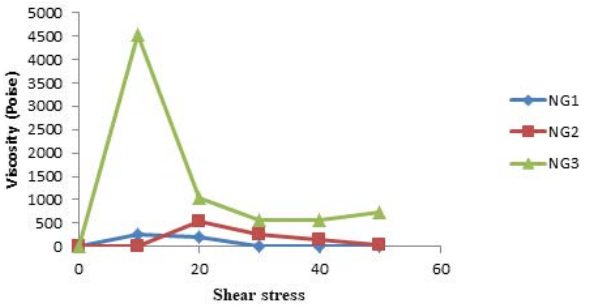

Figure 4: Viscosity of topical nanogel formulations

demonstrates both proper drug loading and a transformation in the drug's fundamental crystalline structure. Nanoparticles in the NF2 batch were non-spherical, of uniform size and surface finish, as revealed by scanning electron microscopy. Thus, the NF2 batch was selected as the optimal one to use for fabricating the topical nanogel in light of the desired outcomes seen for metrics.

Viscosity

Rheological behavior of topical nanogel formulations were considered by using Brookfield rheometer. The results were depicted in Table 2.

Three different nanogel formulations (NG1, NG2, and NG3) were tested for their topical viscosity and found to range from 107.4 to 1434.5 poise. As the concentration of the Carbopol 940 increased, the viscosity also increased (Table 2). The graph was plotted as shear stress vs. viscosity (Figure 4). It indicated that, as shear stress increased, viscosity was reduced. From these batches the NG2 batch was desired consistency.

CONCLUSION

The solvent diffusion approach successfully included econazole nanoparticles into the topical gel. Based on results NF 2 batch was selected as the optimal one. The most effective batch of nanoparticles was employed to create a topical nanogel. Because it possessed the desired physicochemical qualities, the NG2 batch of topical nanogel was chosen. The topical nanogel from the NG2 batch had its antifungal activity measured in a test tube. In conclusion, econazole-containing nanogels may be useful for treating fungal skin infections.

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