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FORMULATION AND EVALUATION OF NANOSPONGE LOADED ISOCONAZOLE NITRATE TOPICAL GEL

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ABSTRACT: Nanosponges are a new class of materials and made of microscopic particle with few nanometers wide cavities, in which a large variety of substances can be encapsulated. Isoconazole nitrate is an azole antifungal drug. It has broad spectrum activity against dermatophytes, Pathogenic yeast, pathogenic filamentous fungi. This medication is used to treat skin infections such as jock itch, ringworm infection and vaginal candidiasis. The present study intends to carry out formulation and evaluation of Isoconazole nitrate loaded nanosponges. In this work the nanosponges were prepared by emulsion solvent diffusion method. The optimized nanosponge formulation characterized by using different parameters such as UV-vis spectral analysis, FTIR, SEM, DSC, Entrapment efficiency, Particle size, zeta potential and *in-vitro* drug release study. The antifungal activity of the Isoconazole nitrate nanosponge (ISN – NS) was evaluated for 8 different formulations which all showed good results. Further by using the formulation 4 (F4) of ISN nanosponge loaded gel and plain gel was also formulated. Then it was evaluated for appearance, viscosity, pH, drug content, Spreadability, *in-vitro* release, kinetic modelling and its antifungal activity. The formulated ISN loaded nanosponge gel showed good zone of inhibition when compared with plain gel and marketed formulation, which confirms better antifungal activity and sustained drug release.

Keywords: Isoconazole nitrate, Ethyl cellulose, Emulsion solvent diffusion method, Anti-fungal gel Candida albicans.

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INTRODUCTION

Targeted drug delivery system is a special form of drug delivery system where the pharmacologically active moiety or medicament is selectively targeted to its site of action and not to the non- target organs or tissues. Targeted drug delivery implies for selective and effective localization of pharmacologically moiety at preidentified target in therapeutic concentration, thus minimizing the toxic or side effects and provides better therapeutic index [1]. Nanosponges are tiny mesh like structures in which large variety of substances can be encapsulated and size of about a virus less than 1 µm. The penetrable nature and small size they can bind poorly water-soluble drugs and improve their bioavailability by modifying the pharmacokinetic parameters. They are tiny sponges with a size of about a virus filled with a wide variety of drug particles, the tiny sponges can circulate around the body until they reach a specific target site and stick on the surface and release the drug in a controlled manner [2]. Anti-fungal drugs represent a pharmacologically diverse category of drugs that are crucial components in the modern medical management of fungal infections like mycoses. Isoconazole nitrate (ISN) belongs to the azole class of antifungal agents, It has been mainly used for superficial fungal diseases like cutaneous candidiasis, Jock itch (Tinea curis), Tinea corporis and Tinea pedis. Isoconazole nitrate exhibits fungistatic activity that arrests fungal growth by targeting the biosynthesis of some integral components of the fungal cell membrane. Isoconazole nitrate is BCS class II drug having poor solubility and low bioavailability which limits its antifungal efficiency. Conventional dosage forms such as cream, lotion do not offer a prolonged duration of action which improves the efficiency of isoconazole and also reported the side effects like skin rash, burning, blistering, itching, swelling, redness, dryness, irritation. Hence it important to formulate Isoconazole nitrate loaded nanosponges which may improve the solubility and dissolution rate of drug as well as providing controlled release profile. Nanosponge system having desirable features for the relief of local symptoms with low dose there by reducing the side effect [3].

Nanosponges can be effectively incorporated int o topical gel for increased drug release and increased retention of dosage form on the skin by reducing the local side effect of drug. Hence it can reduce the fluctuations in the concentration of drug and improves the patient compliance [4]. Hence the present work is focused on formulation and evaluation nanosponge loaded Isoconazole nitrate topical gel [5].

MATERIALS AND METHODS

Isoconazole nitrate was obtained from Yarrow chem products, Mumbai. All other chemicals and solvents like ethyl cellulose, Polyvinyl alcohol, Carbapol 934, Dichloromethane, Methyl paraben, Propyl paraben, Triethanolamine were of analytical grade.

METHODS

Drug- Excipient Compatibility Studies (FTIR)

The FTIR analysis of Isoconazole nitrate (drug), and Ethyl cellulose (polymer) was carried to evaluate the functional groups that might be involved in its formulations.

Preparation of standard calibration curve

Different concentrations of drug solutions were prepared by diluting weighed quantity of ISN with methanol. The absorption maximum (λmax) was found to be 273nm.

Preparation of Isoconazole nitrate nanosponge

Isoconazole nitrate nanosponge (ISN NS) were prepared by emulsion solvent diffusion method. In this preparation it mainly consists of two phases i.e., organic phase and aqueous phase. The organic phase consists of accurately weighed amount of ISN and ethyl cellulose dissolved in dichloromethane. The aqueous phase which consists of polyvinyl alcohol (PVA) dissolved in warm water. The organic phase was gradually added into an aqueous phase and stirred using magnetic stirrer (1200 rpm) for 2 hours at room temperature. Nanosponges formed were filtered using Whatman filter paper and dried at room temperature [14]. Different formulations were prepared as shown in table 1.

Table 1: Composition of ISN nanosponge

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Isoconazole nitrate (mg)	100	100	100	100	100	100	100	100
Ethyl cellulose (g)	0.15	0.2	0.25	0.3	0.15	0.2	0.25	0.3
Dichloromethane (ml)	20	20	20	20	20	20	20	20
Polyvinyl alcohol (% w/v)	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3

Evaluation of nanosponges

Entrapment efficiency

The entrapment efficiency of prepared ISN nanosponge was mainly used to measure the concentration of free drug in dispersion medium and it was carried out by using ultracentrifugation method. To calculate the entrapment efficiency, by the addition of 1ml of nanosuspension into 4ml of water and centrifuged it for 90 minutes (15000rpm). Then the supernatant was examined by spectrophotometer at 273nm and it can be calculated by using following formula:[13]

% Entrapment efficiency= W(t) - W (0) / W(t) ×100

Determination of Particle size and Zeta potential

The size distribution and surface charge of the optimized ISN-NS were determined by using Malvaren zetasizer. The zeta sizer having zeta cells, polycarbonate cell with gold plated electrodes and using a suitable medium (water) for sample preparation. It is essential for the characterisation of stability of nanosponges[15].

Scanning electron microscopy

SEM analysis was performed to determine their microscopic characters (shape & morphology) of prepared ISN nanosponges. Dried ISN Ns was sonicated with distilled water, small drop of this sample was placed on a glass slide allowed to dry. A thin layer of gold was coated to make the sample conductive. Joel JSM-6480 LV SEM machine was operated at a vacuum of the order of 10-5 Torr. The accelerating voltage of the microscope was kept in the range 12-20 KV [14].

Thermal analysis (DSC)

Thermal analysis of Isoconazole nitrate (ISN), mixture of Ethyl cellulose and Polyvinyl alcohol (PVA), Nanosponge physical mixture and ISN loaded nanosponge(F4) was carried out using differential scanning Calorimetry (DSC, Mettler Toledo, Database: STARe Default DB V16.10: METTLER). The calibration was done by using an aluminium standard. Samples (Mixture of ethyl cellulose and PVA-6mg, ISN-6mg, Physical mixture-7mg, ISN nanosponge-9mg) were accurately weighed into DSC aluminium pans having capacity of 40 µL and then sealed with aluminium lid. Empty pan used as a reference. Thermograms were obtained at a scanning rate of 10 K/min conducted over a temperature range of 30-200°C in the environment of liquid nitrogen [20].

***In-vitro* drug release of ISN nanosponges**

The *in-vitro* release of ISN nanosponges were determined using a dialysis bag diffusion technique. 6ml of the nano suspension was placed inside the dialysis bag, tied at both ends and dipped in the dissolution media of pH 7.4 phosphate buffer at a temperature of 37±0.5°C. 2 ml of aliquot was withdrawn at particular intervals and replaced by an equal volume of a fresh dissolution medium. After suitable dilution, the samples were determined spectrophotometrically at 273 nm and absorbance were noted. The concentration of test samples was calculated by using the regression equation of the calibration curve and the equation is depicted below:

% Drug release = (Amount of drug released/ Total drug) ×100

Evaluation of antifungal activity of ISN NS against *candida albicans*

Well diffusion method

The SDA media was autoclaved, cooled and poured into the petri plates and kept for 15

minutes to solidify. Sterile cotton swab was dipped in to prepared inoculums (broth) and seeded all over the SDA plate by rotating through an angle of 60^0. Then with the help of sterile well puncture (5 mm diameter), wells were made in the inoculated plate and labelled.100µL of each prepared formulation of NS suspension F1, F2, F3 F4, F 5, F6, F7, F8 were transferred in to the well with the help of micropipette. Then the plates were incubated at 37℃ for 48 hours and observed for the zone of inhibition, which is suggested by the clear area around the well.

Preparation of ISN nanosponge loaded topical gel

The gelling agent carbapol 934 was initially soaked in water for 24 hrs for complete swelling of the polymer. To the weighed amount of carbapol (1%w/v) gel base, ISN nanosponge formulation (F4) equivalent to 1%w/w were uniformly dispersed. 0.01g of methyl paraben and propyl paraben was added and finally triethanolamine was added dropwise with gentle stirring using a homogenizer for adjusting the pH. The pure drug loaded plain gel was also prepared in the same way using the drug instead of nanosponge formulation [19].

Evaluation studies of prepared nanosponge topical gel

Physical examination, determination of pH and rheological evaluation

The prepared formulations evaluated for their colour, homogeneity and consistency. The pH of prepared formulation was determined by direct immersion of electrode in a pH meter. The measurement of viscosity of prepared gel was done with a Brookfield viscometer. The gels were allowed to rotate at 10rpm using spindle no: 64 and the readings were noted.

Drug content

1 gm of the gel was taken and dissolved in 100 mL of phosphate buffer pH 7.4. The volumetric flasks were kept for 2 hrs and shaken well properly. Then the solution was passed through the filter paper and filtered. From 1 mL of above solution was taken and diluted to 10 mL and this solution was measured spectrophotometrically at 273 nm.

Drug content = Concentration × Dilution factor

Spreadability testing

0.5g of the formulation was placed within a circle of 2cm pre-marked on a ground glass slide. Then gel formulation sandwiched between this slide and the second slide having equal dimension. A weight of 500g was placed to rest on upper slide for 5min.The increase in the diameter due to gel spreading is noted.

***In- vitro* drug release study of antifungal gel**

Studies were performed for ISN loaded nanosponge gel, plain ISN gel and marketed formulation. In vitro release studies were carried out using bi-chambered donor receiver compartment model (Franz diffusion cell) and this was placed on magnetic stirrer and temperature maintained at 37±0.5℃. One end of the chamber was covered with dialysis membrane, which is previously dipped in phosphate buffer (pH 7.4) and buffer was placed in the receptor cell. Accurately measured 2.5ml of the formulation poured on a dialysis membrane, which was in contact with receptor medium. Samples were withdrawn at specified time intervals and the medium was replaced with equal volume of phosphate buffer pH 7.4. The samples were determined spectrophotometrically by measuring the absorbance at 273nm [22].

Mathematical modelling for drug release kinetics [23]

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the following equation:

$$Q0 - Qt = K_o t$$

First-order model

The release of drugs which followed first-order kinetics can be expressed by the equation:

$$dc/dt = - Kc$$

Higuchi model

This model is to describe the drug release from a matrix system and the model expression is given by the equation:

$$Ft= Q= AD (2C- CS) Cst$$

Korsemeyer-Peppas model

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsemeyer-Peppas model and the equation is depicted below:

$$Mt/M\alpha = Ktn$$

Comparison of antifungal activity of prepared formulation with marketed formulation

The comparison was carried out by Kirby- Baurer disc diffusion method and the fungus *candida albicans* was used for the study. Microbial suspension of C. *albicans* was spreaded onto the solidified SDA agar media by using sterile cotton swab and was allowed to dry for 10 mins. Formulated gel containing drug loaded nanosponge impregnated discs were aseptically transferred onto the inoculated agar plates and left to be incubated for 2 days and same as for marketed formulation. The zone of inhibition obtained was calculated.

RESULTS AND DISCUSSION

Drug excipient compatibility studies (FTIR)

The spectrums were recorded for the pure drug and physical mixture of drug and polymer. The FTIR spectra of ISN shows characteristic peaks at 1338 cm^{-1} indicated the presence of an aromatic amine, a peak at 829.42 cm^{-1} which indicated the presence of C-Cl stretching, a peak at 1586cm^{-1} indicated the presence of C=C (aromatic stretching), a peak at 1468.84 cm^{-1} indicated the presence of N=C. The result of FTIR analysis for Ethyl cellulose is depicted below. Spectra showed transmission peaks at 3565.53cm^{-1} indicates the presence of O-H stretching. The spectra show transmission at 2901.04 cm^{-1}, which indicates the presence of C-H stretching. The peak at 1428.34 cm^{-1} indicates the presence of carboxylate group. The peak at 1372.40 cm^{-1} indicates the presence of C-O stretching.

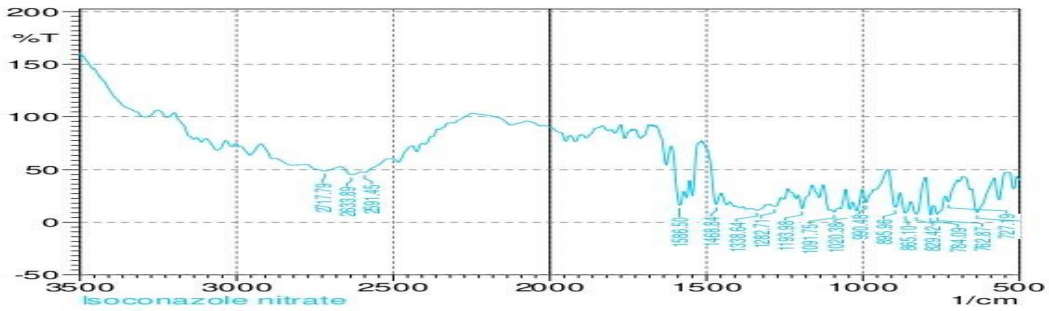

Fig. 1: FTIR spectra of ISN

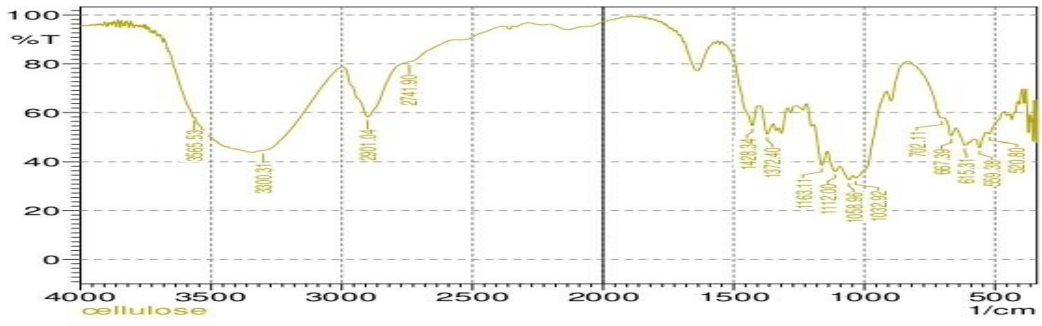

Fig.2: FTIR spectra of Ethyl cellulose

The formulation after visual examination, colour of the drug was found to be white, odourless and solid powder in state. The formation of ISN was followed by measuring the corresponding UV-visible absorption spectrum of ISN over a range of 200 to 400nm. The spectra of ISN showed maximum absorption at 273nm.

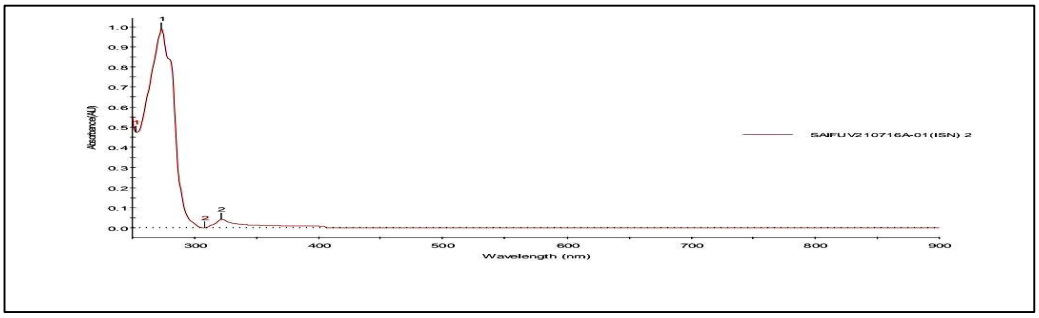

Fig. 3: UV-visible spectroscopy of ISN

Entrapment efficiency

From this study the %EE of Isoconazole nitrate (ISN) within the formulated ISN-nanosponges. Eight batches of samples were evaluated, and the entrapment efficiency of samples was found to be 89.50%, 87.68%, 82.76%, 77.68%,71.50%,69.80%, 64.70%,61.60%. Out of which, F4 batch showed optimum %EE compared to other batches. Hence from these results the optimized %EE of the nanosponges was found to be 89.50%.

Determination of particle size and zeta potential

The particle size of ISN- NS was found to be 128.0 nm with polydispersity index (PDI) value 0.242 and zeta potential was found to be -2.56 mV. The formulation stability was found to be good.

Scanning Electron Microscopy (SEM)

SEM analysis of the formulated Isoconazole nitrate nanosponges were performed to evaluate the surface morphology of nanosponges. SEM images showed the nanosponge was porous with a smooth surface morphology and spherical in shape. The SEM image showing ISN NS confirmed for the development of nanostructures.

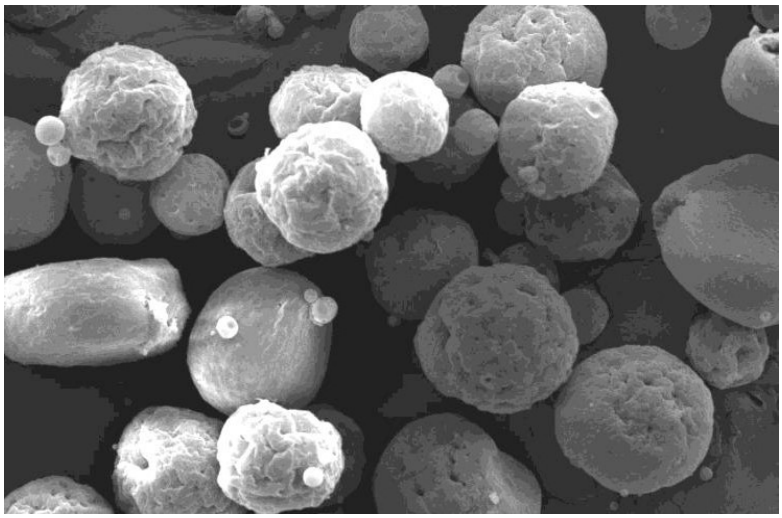

Fig.4: SEM image of Isoconazole nitrate nanosponge

Thermal analysis study (DSC)

The DSC studies were carried out for ISN, physical mixture of ethyl cellulose and polyvinyl alcohol and ISN nanosponge. The thermogram of pure drug has shown a sharp endothermic peak at 185.09° C, which corresponds to its melting point. DSC thermogram of physical mixture showed characteristic peak corresponding to the drug which indicates that no interaction occurred between the components. The DSC thermogram of nanosponge formulation has shown an endothermic peak at 153.74°C, which corresponds to the melting transition temperature of drug and polymers. It was found that there was no interaction between the drug and polymer.

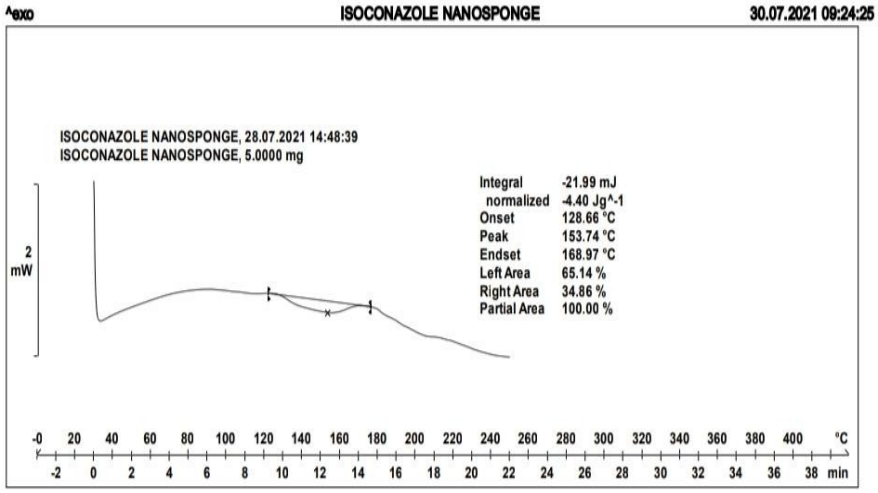

Fig. 5: DSC Thermogram of ISN nanosponge

***In- vitro* drug release study**

The in vitro drug release study of all eight ISN nanosponge formulation was done and the results were found that 84.6%, 85.3%, 87%, 88.6%, 83.1%, 81.6%, 86.4%, and 79.0%. Out of which, the fourth batch (F4) shows optimum % invitro release compared to other batches. Hence from these studies, the ISN NS (F4) % drug release was found to be 88.6%.

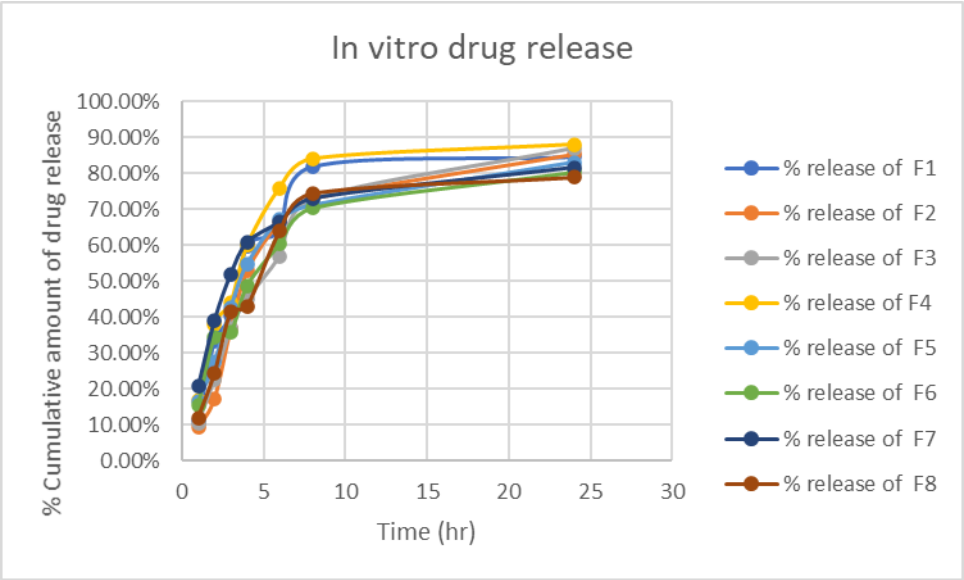

Fig. 6: In vitro drug release study of formulation (F1-F8)

Evaluation of antifungal activity of ISN NS against *Candida albicans*

The study of antifungal activity of ISN NS against *candida albicans* was performed and the results are depicted in the table below:

Table2: Antifungal activity of F1-F8

Sl.No	FORMULATION CODE	ZONE OF INHIBITION (mm)
1	F1	21 mm
2	F2	23 mm
3	F3	28 mm
4	F4	32 mm
5	F5	12 mm
6	F6	8 mm
7	F7	7mm
8	F8	7mm

Evaluation of prepared gel

Physical examination, determination of pH and viscosity

The gels obtained were colourless, clear and jelly in nature. The obtained pH of prepared ISN NS loaded gel(S1) was found to be 5.17 and for plain gel (S2) is 5.34. The viscosities of prepared formulations (S1 and S2) were determined by using a Brookfield viscometer. The spindle was rotated at 10rpm and the viscosity was found to be 5234cps for S1 and 4982 for S2.

Drug content

The percentage drug content of 2 formulations i.e., drug loaded plain gel and nanosponge loaded gel was found to be 90.54% and 92.25% respectively.

Spreadability test

Spreadability studies were carried out for both the formulations (S1and S2) and it was found to be 12.2g cm/sec and 8.9g cm/sec respectively.

***In- vitro* drug release study**

In vitro drug release study of the prepared formulations (S1 and S2) was carried out using dialysis bag diffusion method and the amount of drug released in different time intervals were observed. From the in vitro release data, it was found that the formulation S2 has been released higher rate than S1. The drug loaded plain gel (S2) released its 92.3% of drug at 8hrs itself, while S1 takes 24 hrs to release its 86% drug. This indicates the formulation S1 follows the sustained drug release than S2.

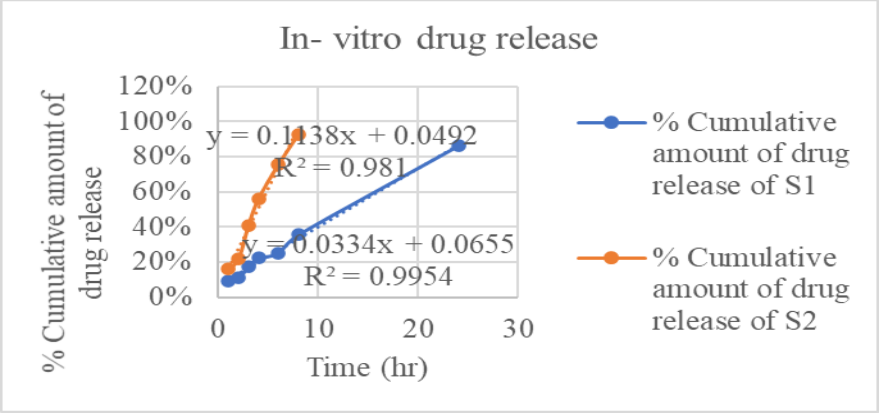

Fig.7: *In-vitro* drug release of S1 and S2

Mathematical modelling for drug release kinetics

From the interpretation of data, the study data was subjected to goodness of fit test by linear regression analysis to zero-order, first-order, Higuchi model and Korsemeyer-Peppas model to ascertain the mechanism of drug release. The correlation coefficient (R_2) values of nanosponge gel in various models is given along with the figures. From the data it was found that R2 values of zero order release was higher than that of first order release. S1 and S2 follows zero order kinetics with regression coefficient value 0.995 and 0.9475 respectively. From Korsemeyer - peppas plot helps to find out the drug release transport system. S1 and S2 follows non fickian transport.

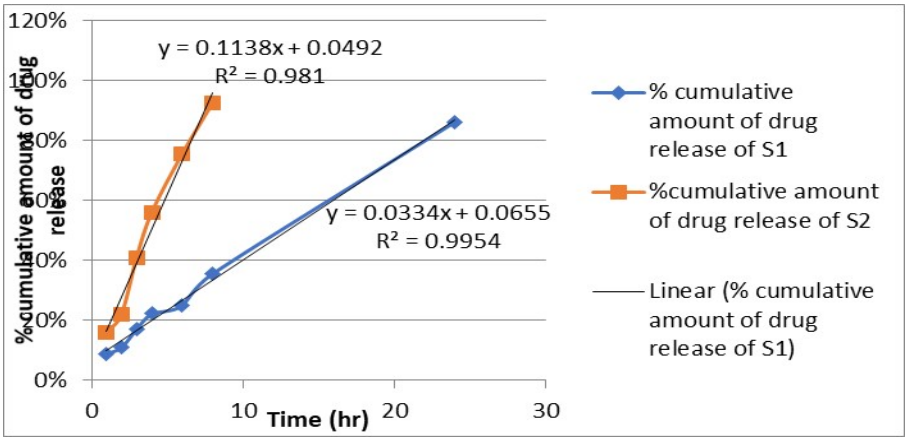

Fig.8: Zero- order plot for S1 and S2

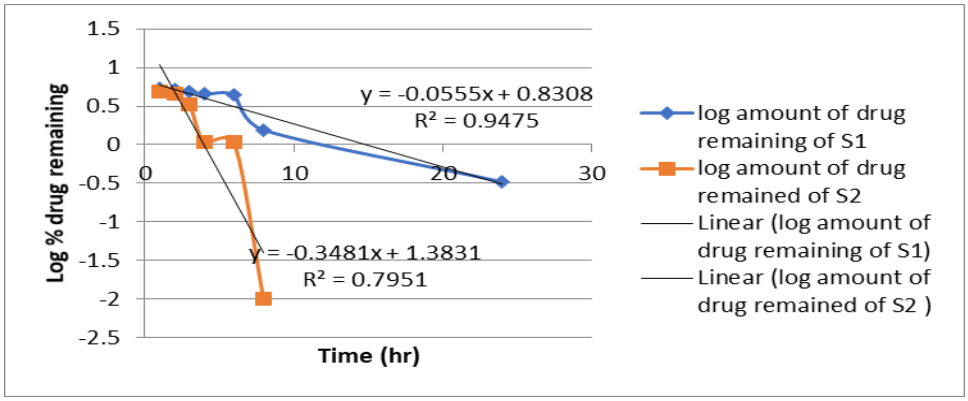

Fig. 9: First- order plot for S1 and S2

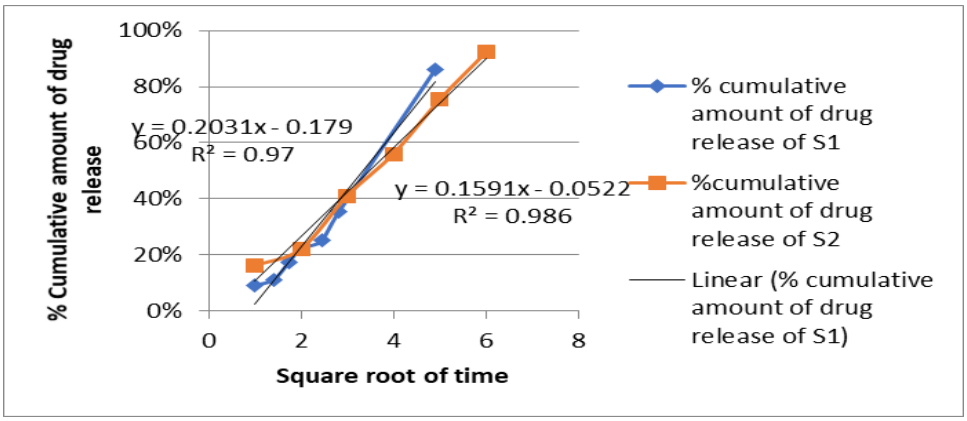

Fig. 10: Higuchi plot for S1 and S2

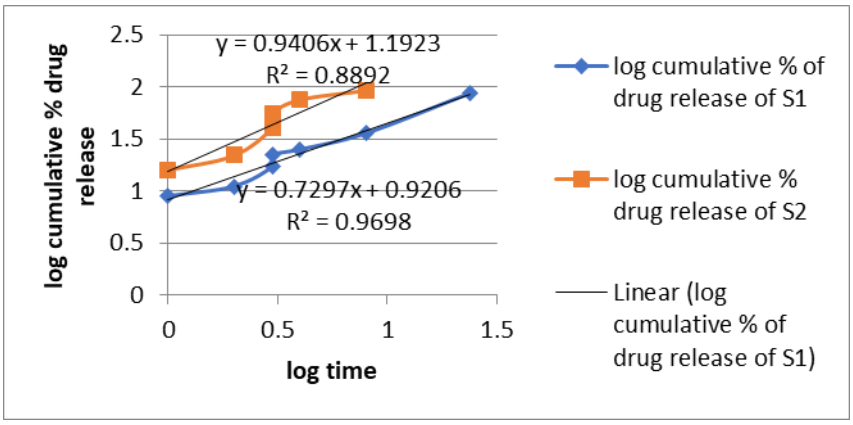

Fig.11: Korsemeyer-Peppas plot for S1 and S2

Comparison of antifungal activity of prepared formulation with plain gel and marketed formulation

The comparison was done by Kirby-Baurer disc diffusion method and the fungus used was *candida albicans*. From the study the prepared formulation (S1) was found to have more zone of inhibition when compared with the marketed gel (standard) and plain drug loaded gel (S2) showed lesser zone of inhibition.

SL.NO	FORMULATION CODE	ZONE OF INHIBITION
1.	ISN- loaded nanosponge gel (S1)	32 mm
2.	Marketed formulation (Standard)	30mm
3.	ISN loaded plain gel (S2)	19 mm

Table3: Comparison of zone of inhibition of formulated topical gel with marketed product

CONCLUSION

Nanosponge loaded gel were found to be an efficient drug delivery system for topical drug delivery due to their smaller size, controlled drug release and better stability. Characterization of the drug and excipients was carried out by FTIR, DSC, UV spectroscopy, melting point and solubility studies. The drug-excipient compatibility was studied by FTIR and DSC and it was found that there is no interaction between the drug and excipients. All the prepared Isoconazole nanosponges were white in color and had a rigid structure. The mean particle size of all nanosponge formulations was found in nanometer range. Surface morphology of optimized nanosponges was evaluated by scanning electron microscopy and was concluded that nanosponges were spherical in shape and uniform in size and its surface was porous in nature. The nanosponge based gel formulation prepared using Carbopol 934 was estimated for pH, viscosity, drug content, spreadability, *in -vitro* drug release, drug release kinetics and antifungal activity. Based on the observations, the optimized formulation was effective for topical use as Isoconazole nanosponge loaded topical gel and shows a controlled release effect.

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