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DESIGN AND DEVELOPMENT OF ITRACONAZOLE LOADED NANOSPONGES FOR TOPICAL DRUG DELIVERY

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Abstract:

The aim of present research work isto develop a topical gel formulation of Itraconazole loaded nanosponges to increase the solubility, permeability, stability and to control the Itraconazole release for a prolonged period.Itraconazole loaded nanosponges was prepared by cross-linking different concentrations of β- Cyclodextrin withcarbonate bonds of di phenyl carbonate in different proportions, which are porous as well as nanosized.Drug was incorporated by solvent evaporation method by dissolving the drug in various solvents like ethanol, acetone and chloroform. The preparednanosponges were incorporated into carbopol gel. From the encapsulation efficiency of the drug loaded nanosponges formulations,it was observed that as the crosslinking ratio increased the encapsulation efficiency was found to be enhanced. It is also found that the encapsulation efficiency of drug loaded nanospongeswereinfluenced by the solvent used for drug loading by solvent evaporation technique. Based on the drug encapsulation efficiency , drug content and extent of sustained nature , the gel prepared with β- Cyclodextrin and crosslinking agent in 1:1 ratio, chloroform as a solvent and carbopol as agellling agent (I12 formulation) was concluded to be the best formulation. All the formulations followed zero order release kinetics and mechanism of drug release was governed by Peppas model.The diffusion exponential coefficient(n) values were found to be in between 0.9402to 1.1864indicating non ficki an diffusion mechanisam.

Keywords: *Itraconazole, β-cyclodextrin, nanosponges, diffusion rate*

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INTRODUCTION:

Nanosponges are the progressionin nano technology, which are the prominent answers for the various formulation challenges like low aqueous solubility, controlled release and targeted release. As compared to nano paricles these are less prone to bursting and releases the drug in a controlled and predictablemanner throughout the intended period of application or administration[1] . Nanosponges are beneficial for the passive targeting of drugs to skin, there by accomplishing major benefits such as reduction of total dose, retention of dosage form on the skin for prolonged period.Nanosponge loaded topical dosage forms can act as local depot for sustained drug release as well as rate- limiting membrane barrier for inflection of systemic absorption and thus overcoming the limitations of topical formulations. They are non- irritating, non-mutagenic, non- allergenic and non-toxic.Itraconazoleis an imidazole derivative and used for the treatment of local and systemic fungal infections. It is a BCS Class II drug having very low solubility and high permeability. Theoral use of Itraconazoleis not much recommended as it has many side effects.

Most of these infections spread onlyin the skin layers but upon prolonged time they may be converted to systemic infections which may be mortal. Oral administration of Itraconazoleis not convenient due to its severe side effects and its short half-lIe (3–6 h) that requires frequent dosing[2]. Itraconazoleis a BCS Class II drug that has a dissolution rate limited poor bioavailability so it needs to be incorporated into a proper vehicle to have right levels of topical absorption. The conventional topical Itraconazole formulations release the drug for a shorter period at high quantities which causes the adverse effects like stining,zerythema,edema,vesicat,edema,vesication,de squamation,pruritusand urticaria due to the toxicity on the epithelial cells of the skin . The conventional topical dosage cannot reside at the site of application for longer times anddoes not release the drug in sustained manner.

Various methods are available to sustain the release of the drug. Among them the nanosponges have some unique advantages, which are three dimensional sponges like nanostructure encapsulating the drug. The nanostructure have potential for decreased skin irritation and stabilization of sensitive activities. Moreover nanosponges have good penetration into stratum corneum by overcoming the skin barrier effect and maintaining the good physical and chemical stability[3].

MATERIALS AND METHODS:

Itraconazole was the generous gIt from Aurobindo Pharma Ltd , Hyderabad. Carbapol 934 P was procured from SD Fine chemicals Ltd, Mumbai.β-cyclodextrin and Di phenyl carbonate were purchased from SigmaAldrich (Milan, Italy). All other ingredients used were of analytical grade.

Synthesis of β- cyclodextrinnanosponges:

β- cyclodextrin based nanosponges was prepared using Di phenyl carbonate as a cross-linker. Nanosponges were prepared using different ratios of β- cyclodextrin and Di phenyl carbonate [1:0.25, 1:0.5.1:0.75 and 1:1]. Finely homogenized anhydrous β-cyclodextrinandDi phenyl carbonate were placed in a 100 ml conical flask. The system was gradually heated to 100 ^{0}C under magnetic stirring, and left to react for 5 h. During the reaction crystals of phenol appeared at the neck of the flask. The reaction mixture was left to cool and product obtained was broken up roughly. The solid was repeatedly washed with distilled water to remove unreacted β-cyclodextrinand then with acetone, to remove the unreacted Di phenyl carbonate and the phenoll present as by-product of the reaction. After purIication, nanosponges were stored at 25 ^{0}C until further use[4].

Preparation of Itraconazole loadednanosponges:

The Itraconazole loading into β-cyclodextrinnanospongeswas carried out by solvent evaporation technique. In this various solvents like chloroform, acetone and ethanol were used. In100 ml of each solvent 4000 mg of Itraconazole was dissolved separately to form solutions. To the each solution, preparednanospongeswere added and triturated until the solvent evaporated. While triturating the clumps of nanospongeswere segregated and absorbs the drug solubilised solvent. The solid dispersions were dried in an oven overnight (at 50 ^{0}C at atmospheric pressure) to remove any traces of solvents and were sieved through 60 # and used for further work[5].

Preparation of Itraconazole nanosuspension:

The dried drug encapsulated nanosponges were collected and required quantities of drug equivalent nanosponges were transferred into 250ml volumetric flask containing 100ml methanol in order to remove the free unencapsulated drug by solubilisingin the methanol. The drug encapsulated nanosponges were separated from the free drug by membrane filtration by using 0.22µ membrane filter. The residual drug loaded nanosponges were collected and dispersed in distilled water by using ultra sonication to form a nanosuspension[6].

Formulation of carbopol gel containing Itraconazole loadednanosponges:
500 mg of carbopol 934 was dispersed in 5 ml of distilled water and allowed for swelling over night. The swelled carbopol was stirred for 60 minutes at 800 rpm. The previously prepared required Itraconazoleequivalent nanosuspensions , methylparaben and propylparaben were incorporated into the polymer dispersion with stirring at 500 rpm, by a magnetic stirrer for 1 h. The P^H of above mixture was adjusted to7.4 with tri ethanolamine (0.5%). The gel was transferred in to a measuring cylinder and the volume was made up to 10ml with distilled water [7].

Evaluation studies:
Fourier Transform Infrared (FTIR) spectroscopy:
To confirm the formation of nanosponges, Fourier Transform Infrared (FTIR) spectroscopy studies was used. Potassium Bromide pellet method was used in the study. The spectra was studied for the conformational changes of optimized drug when compared with the pure drug and pure excipients spectrums[8]. The spectra were recorded in the wave number region of 4000-500cm^{-1}.

Encapsulation efficiency:
The encapsulation efficiency of nanosponges was determined spectrophotometrically (λmax = 261 nm). A sample of Itraconazolenanosponges (100 mg) was dissolved in 100 ml of methanol and kept it for overnight. 1 ml of the supernatant was taken and diluted to 10 ml with a solution containing 4.5 P^H phosphate buffer and was analysed at 255 nm using UV-visible spectrophotometer. From the absorbance the free drug content was calculated. The methanol dispersion containing Itraconazolenanosponges was then ultra sonicated to release the encapsulated drug from the nanosponges structure[9]. Then the solution was filtered by using 0.22µ filter paper and the filtrate was analysed at 255 nm using UV visible spectrophotometer for the total drug content. The encapsulation efficiency (%) of the nanosponges will be calculated according to the following equation,

$$\text{Encapsulation efficiency} = \frac{\text{Encapsulated drug content in nanosponges}}{\text{Total drug content}} \times 100$$

All measurements were performed in triplicate. The results of the best polymer and crosslinking agent ratio were analysed statistically for their significance of difference.

Determination of particle size distribution
The particle size distribution was determined by using Dynamic Light Scattering (DLS) technique. The equipment used for the particle size distribution is HORIBA particle size analyzer. In this technique the particle sizes of a batch of the nanosponges were observed and from the standard deviation and mean particle size of nanosponges, the Poly Dispersity Index (PDI) was calculated. The poly dispersity index is the indication for the nature of dispersity[10].

Determination of zeta potential
Zeta potential is a measure of surface charge of dispersed particles in relation to dispersion medium. It was determined by using HORIBA zeta sizer having the capability of determination of zeta potential. The zeta potential value is the indication of physical stability of the nanosponges[11].

Evaluation of drug loaded Nano sponges containing gels:
The drug loaded Nano sponges containing gels were evaluated for P^H,ViscositySpreadability, Extrudabilityand Mucoadhesive time[12]**.**

Drug content in the DLNS containing gel formulations:
The sample of 1 gram of gel formulation containing 10 mg of Itraconazole was dissolved in methanol, filtered and the volume will be made to 20 ml with methanol. The drug content will be determined by diluting the resulting solution for 10 times with a solution containing7.4 P^H phosphate buffer and the absorbance was measured at 255 nm using UV Visible spectrophotometer [13].

In-vitro drug diffusion study:
Modified Franz diffusion cell was used for these studies. Cellophane membrane was used as the simulation for the skin. Cellophane membrane was mounted in a modified Franz diffusion cell. The known quantity (1g of gel containing 100 mg of the drug equivalent ILNS) was spread uniformly on the cellophane membrane on donor side. The solution containing 7.4 P^H phosphate buffer solution was used as the acceptor medium, from which 3ml of samples were collected for every hour and the same amount of fresh medium was replaced to maintain sink conditions for 12 hrs. While taking the samples from

the acceptor medium, precautions were taken that no air bubbles were formed in the acceptor medium[14]. The fresh samples were analyzed at 255nm by UV-spectrophotometer and the amount of drug diffused for each hour was calculated. All the samples were analysedin triplicate.

RESULTS AND DISCUSSION:

The FTIR structure of formed nanosponges were studied by comparing with unreacted β-cyclo dextrin and diphenyl carbonate FTIRspectra.In all the ratio of nanosponges, the major peaks were observed at 940 cm^{-1}which represents the α-1,4 glycoside bond which is the indication that there was no change in the cyclodextrin linkages. The absence of peaks responsible for carbonyl group of the diphenyl carbonate at 1768 cm^{-1} in the nanospongesis the indication of the removal of C=O from diphenyl carbonate. The absence of peaks responsible for –C=C- at 1591 and 1497 cm^{-1} in the IR spectra of nanospongesis indication of absence of phenol rings which were present in the unreacted diphenyl carbonate. Similarly absence of an intense peak responsible for –C=O group at 1157 cm^{-1} inthe IR spectra of nanospongesis the indication of removal of C=O group from the diphenyl carbonate which might be attached to the primary of secondary hydroxyl groups of β- cyclodextrin by leaving phenol as by product. All these changes infers that the formation of nanosponges by reacting of primary/secondary hydroxyl groups of betacyclo dextrin with the carbonyl groups of diphenyl carbonate. From the encapsulation efficiency of the drug loaded nanosponges formulations it was inferred that , as the crosslinking ratio increased the encapsulation efficiency was found to be enhanced. The order of encapsulation efficiency in the nanospongesis 1:1>1:0.75>1:0.5>1:0.25.It is also found that the encapsulation efficiency of drug loaded nanosponges are influenced by the solvent used for drug loading by solvent evaporation technique. Chloroform >Acetone >Ethanol.

The change in the encapsulation efficiency with respect to solvent might be due to the solubility of Itraconazolein the particular solvent.The extended sustained release was observed in all the 12 formulations. But the extent of sustained nature was varied from one ratio to other. The order of sustained action was as follows 1:1>1:0.75>1:0.5>1:0.25.

Based on the drug encapsulation efficiency, drug content and extent of sustained nature formulation 12 was concluded to be the best formulation. The results of the present investigation overlay the path and provide substantial information for the utilization of Beta cyclodextrin in the development of drug delivery systems. The optimized formulation (I12) were evaluated for their particle size and zeta potential.The particle size (334 nm) and zeta potential (-26.7 mV) was found to be good enough to maintain the physical stability of the nanosponges.

Carbopol gels containingnanosponges prepared with β -cyclodextrin and Di phenyl carbonatein dIferent ratios and by using ethanol as a solvent shown drug release for a period of 7 hours, 7.5 hours, 8 hours and 9.5 hours respectively. Carbopol gels containingnanosponges prepared with β -cyclodextrin and Di phenyl carbonatein different ratios and by using acetone as a solvent shown drug release for a period of 8 hours, 8.5 hours, 9 hours and 10 hours respectively.Carbopol gels containingnanosponges prepared with β -cyclodextrin and Di phenyl carbonatein dIferent ratios and by using chloroform as a solvent shown drug release for a period of 8.5 hours, 9 hours, 9.5 hours and 11 hours respectively.Based on the drug encapsulation efficiency , drug content and extent of sustained nature , the gel prepared with polymer and crosslinking agent in 1:1 ratio, chloroform as a solvent and carbopol as agellling agent (I12formulation) was concluded to be the best formulation.The initial burst release decrease with increase in concentration of crosslinking agent. To ascertain the mechanism of drug release, the dissolution data was analyzed by zero order, first order, and Higuchi and Peppas equations. The correlation coefficient values (r) and diffusion kinetics values were shown in table 4. Amount of drug diffused versus time curves exhibited straight line for the formulations and confirmed that the diffusion rate followed zero order release kinetics.Percentage of drug release versus square root of time curves shows linearity and proves that all the formulations followed Peppas model.

The diffusion exponential coefficient(n) values were found to be in between 0.9841to 0.9968indicating non fickian diffusion mechanisam. These results indicated that the diffusion rate was found to be decrease with increase in concentration of cross linking agent.The optimized formulation has good spreadability, extrudability and mucoadhesive nature. The P^H and viscosity of the formulation were appropriate for the topical drug delivery and nanosponges technique was a better choice for sustained release .

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Table1: Composition of Itraconazoleloaded nanosponges using different solvents

S. No	Batch code	Polymer : cross linking agent (mg)	Drug (mg)	Solvent
1	ILNS1	4000:1000	4000	Ethanol
2	ILNS2	4000:2000	4000	Ethanol
3	ILNS3	4000:3000	4000	Ethanol
4	ILNS4	4000:4000	4000	Ethanol
5	ILNS5	4000:1000	4000	Acetone
6	ILNS6	4000:2000	4000	Acetone
7	ILNS7	4000:3000	4000	Acetone
8	ILNS8	4000:4000	4000	Acetone
9	ILNS9	4000:1000	4000	Chloroform
10	ILNS10	4000:2000	4000	Chloroform
11	ILNS11	4000:3000	4000	Chloroform
12	ILNS12	4000:4000	4000	Chloroform

Table 2:Encapsulation efficiency of Itraconazoleloaded nanosponges

S. No	Batch code	%Encapsulation efficiency (n=3)
1	ILNS1	71.29±1.07
2	ILNS2	74.34±1.03
3	ILNS3	78.47±2.57
4	ILNS4	81.59±1.37
5	ILNS5	76.36±1.05
6	ILNS6	80.52±1.91
7	ILNS7	84.68±2.20
8	ILNS8	88.77±2.09
9	ILNS9	78.15±2.06
10	ILNS10	82.26±2.27
11	ILNS11	86.33±2.84
12	ILNS12	90.44±2.29

Table 3:Percentage of drug content in the Itraconazoleloaded nanospongescontaining gel formulations

S. No	Batch code	% Drug content	Average Particle size(nm±S.D)	Polydispersity Index`(X±SD)	Zeta Potential (mV±SD)
1	I1	99.34±0.85	307.3±3.65	0.291±0.11	+39.8±1.6
2	I2	99.41±0.21	296.4±2.75	0.274±0.13	+48.9±1.2
3	I3	99.23±0.47	279.3±2.69	0.266±0.09	+53.7±1.1
4	I4	99.64±0.60	265.3±3.9	0.253±0.12	+58.4±1.3
5	I5	99.22±0.89	299.3±2.18	0.277±0.09	+38.6±1.1
6	I6	99.30±0.40	287.2±2.57	0.268±0.07	+41.5±1.2
7	I7	99.41±0.30	273.3±2.75	0.252±0.06	+52.6±1.4
8	I8	99.52±0.40	256.5±1.65	0.238±0.09	+55.1±1.3
9	I9	99.53±0.89	267.4±2.15	0.251±0.11	+37.4±2.1
10	I10	99.64±0.40	258.6±2.7	0.245±0.07	+42.3±1.2
11	I11	99.13±0.21	247.1±2.26	0.229±0.13	+53.4±1.5
12	I12	99.48±0.41	238.5±2.25	0.219±0.06	+66.3±1.6

Table 4: *In vitro* drug diffusion kinetic data of Itraconazole loaded nanospongescontaining gel formulations

Formulation	Correlation coefficient				Diffusion Rate Constant (mg/hr) Ko	T_{50} (hr)	T_{90} (hr)	Diffusion Exponent (n)
	Zero order	First order	Higuchi	Peppas				
I1	0.9702	0.8290	0.9741	0.9971	14.8	3.3	6.0	0.6162
I2	0.9939	0.8168	0.9496	0.9946	13.4	3.7	6.6	0.7970
I3	0.9971	0.8138	0.9427	0.9947	12.4	4.0	7.2	0.8301
I4	0.9994	0.8085	0.9271	0.9971	10.4	4.8	8.6	0.9290
I5	0.9963	0.8175	0.9457	0.9972	12.4	4.03	7.25	0.8162
I6	0.9928	0.8020	0.9236	0.9997	11.4	4.3	7.1	0.9650
I7	0.9993	0.7977	0.9136	0.9999	11	4.5	8.2	1.0618
I8	0.9991	0.7984	0.9147	0.9993	9.8	5.1	9.2	1.0840
I9	0.9976	0.7964	0.9404	0.9975	12.5	4.0	7.2	0.8418
I10	0.9998	0.8044	0.9268	0.9995	11.62	4.3	7.8	0.9427
I11	0.9994	0.8068	0.9228	0.9928	10.20	4.9	8.7	1.0301
I12	0.9998	0.7640	0.9261	0.9993	9.09	5.5	10.0	1.1035

Table 5: Physical properties of optimized gel

Formulation	Viscosity (cps)	Extrudability (N)	Spreadability (g.cm/sec.)	pH	Muco adhesive Time
I12	3985±72	92.41± 0.05	34.61±2.11	4.46±0.02	>12 hrs

Figure 1: FT-IR spectra of Itraconazole(A), β-Cyclodextrin (B), diphenyl carbonate (C)and optimized formulation(D)