International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 9(E); September 2018; Page No. 15567-15570
DOI: http://dx.doi.org/10.24327/ijcar.2018.15570.2847

Research Article

FORMULATION AND EVALUATION OF ANTI-FUNGAL DRUG LOADED SOLID LIPID NANOPARTICLES FOR TOPICAL DELIVERY

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A R T I C L E I N F O

Article History:

Received 4th June, 2018
Received in revised form 25th July, 2018
Accepted 18th August, 2018
Published online 28th September, 2018

Key words:

Solid lipid nanoparticles, Ketoconazole, Hydrogel, solvent evaporation method, *Candida albicans,* Sustained drug release.

A B S T R A C T

Purpose: To Formulate and Evaluate Ketoconazole loaded Solid Lipid Nanoparticles and further Incorporation into Hydrogel for Sustained release.
Methods: Preparation of Ketoconazole loaded Solid Lipid Nanoparticles by Solvent emulsification/Evaporation Method.
Result: Optimized formulation of Solid Lipid Nanoparticles shown less particle size 721 nm. Hydrogel formulation showed better cumulative drug release profile after 12 hrs i.e. 82.54 %.
Conclusion: Incorporation of Solid Lipid Nanoparticles into hydrogel gave rise to biocompatible system that is able to deliver the drug in a sustained manner and effective against *Candida albicans*.

INTRODUCTION

Nanotechnology is a theoretical and experimental field of applied science and technology. Solid lipid nanoparticles (SLNs) are at the forefront of the rapidly developing field of nanotechnology. SLNs are in the submicron size range of 50-1000 nm [Swathi Mutyam, Bala Prabhakar, 2013). The use of solid lipid instead of liquid lipid is beneficial as it has been shown to increase control over the release kinetics of encapsulated compounds and to improve the stability of incorporated chemically-sensitive lipophilic ingredients [Neha Yadav *et al*, 2013]. Ketoconazole (Ktz) is broad spectrum anti-fungal agent, having high melting point, poor water solubility undergoes chemical degradation such as hydrolysis and oxidation [Thiruganesh Ramasamy *et al*, 2012]. Lipid matrix is made from physiological lipids, which decreases the danger of toxicity Compared with conventional carriers such as cream, tincture and emulsion; SLNs combine their advantages such as controlled release, in vivo good toleration, and protection of active compound. The incidence of superficial fungal infections of skin, hair and nails has been increased in worldwide. It has been estimated that about 40 million people have suffered from fungal infections in developing and under developed nations [Sevgi Gungor *et al,* 2013]. The size of the lipid particle ensures close contact to the stratum corneum and can increase the bioadhesion and occlusive properties, which is desired requirement for topical application. Further, incorporation of SLNs into hydrogel gave rise a biocompatible system [Safal Jain *et al,* 2010].

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MATERIAL AND METHODS

Materials: Ketoconazole gift sample by (Sankalp healthcare and allied product, pvt. Ltd, Tasawade, Maharashtra). Glycerol monostearate, Stearic acid, Tween 80, Poloxamer 407, Ethanol, Carbopol 934, Triethaloamine, Glycerol obtained from Loba Chemie, (Mumbai, India).

Preparation of Ketoconazole-loaded Solid Lipid Nanoparticles

Ktz-loaded SLNs were prepared by solvent emulsification/evaporation method. The desired amount of lipid was dissolved in organic phase and Ketoconazole was dissolved by adding into the solution. An aqueous phase was prepared by dissolving the emulsifier in distilled water and heating to the same temperature of oil phase. Homogenization was performed using mechanical stirrer for 30 minutes. Ktz-loaded SLNs was finally obtained by allowing the hot nanoemulsion cool to room temperature [A. Pavankumar Reddv *et al.* 2010].

Table 1 Composition of Ktz-loaded various SLNs formulations

Formulation code	Drug (mg)	Stearic acid (gm)	Glycerol monostearate (gm)	Tween 80 (ml)	Poloxamer 407 (mg)	Methanol (ml)	Water (ml)
A	400	1	-	-	200	5	20
B	400	1	-	0.2	-	5	20
C	400	-	1	-	200	5	20
D	400	-	1	0.2	-	5	20

Table 2 Composition of Ktz-loaded SLNs B formulations

Formulation Code	Drug (mg)	Stearic acid (gm)	Tween 80 (ml)	Methanol (ml)	Water (ml)
B1	400	1	0.4	5	20
B2	400	1	0.6	5	20
B3	400	1	0.8	5	20

Characterization of Ketoconazole-loaded solid lipid nanoparticles

Particle size measurement

Ktz-loaded SLNs solution was suitably diluted with DI water before analyzing particle size and size distribution using Dynamic Light Scattering (Malvern 2000M, Instrument, UK) [Ambikanandan Misra *et al*, 2005].

Determination of zeta potential

Zeta potential was measured using laser Doppler electrophoretic mobility measurements on a Zetasizer 300 HSA (Malvern Instrument, UK) at a temperature 25℃ [Keerthana K *et al,* 2017].

Entrapment efficiency

The entrapment efficiency was determined by separating Ketoconazole from the SLNs by centrifugation (Remi R-8C, India) at 8,000 rpm for 30 minutes. The supernatant was assayed spectrophotometrically at 242.5 nm for entrapment efficiency [Vinod Kumar Verma *et al*, 2014]

Scanning electron microscopy (SEM)

The morphology (shape and surface characteristics) of sample was studied by SEM (model JSM 840A, JEOL, Japan). [Gajanan S Sanap *et al,*2013].

Preparation of Hydrogel containing Ktz-loaded SLNs

Hydrogel was prepared by the use of direct method; the polymer (Carbopol 934) was dispersed gently into water with constant stirring by using magnetic stirrer, and stored for overnight [Maria Antonietta Casadei *et al,* 2011].

Table 3 Composition of Hydrogel formulation

Carbapol (mg)	KTZ loaded SLNs (ml)	Glycerol (ml)	Triethaloamine (ml)	Water (ml)
200	5	q.s	q.s	q.s

q.s = quantity sufficient

Characterization of Hydrogel containing Ktz-loaded SLNs

Homogeneity

This was done by visual inspection of gel after the settlement of gel in suitable containers. Gels were analyzed for their appearance and existence of any clog. [Roohi Kesharwani *et al,* 2016]

pH evaluation

The pH of the dispersion was measured using digital pH meter, and then pH is recorded [Abita M H *et al*, 2015].

Viscosity

Brookfield viscometer was used to measure the viscosity of gel. For this purpose, spindle No. 04 was used. Viscosity was recorded by rotating spindle at 10 rpm [Laith Hamza Samein, 2014].

Spreadability

The spreadability of the hydrogel was measured by spreading the hydrogel on the circle of 2 cm diameter premarked on glass plate and then second glass plate was employed. Then, diameter of circle after spreading of the hydrogel was determined [Abita M H *et al*, 2015].

Drug Content uniformity

The drug content uniformity was determined by UV spectrophotometric method. Gel was taken and dissolved in methanol and shaken well in a shaker to mix it properly. The drug content was measured spectrophotometrically [Elisabetta Esposito *et al,* 2013].

Differential scanning calorimetry (DSC)

Thermogram of hydrogel containing Ktz-loaded SLNs, were recorded using (Mettler-Toledo DSC 1) with a computerized data station [Nagi A Alhaj *et al,* 2008].

Permeation Study

In vitro permeation study of hydrogel containing Ktz-loaded SLNs were carried out using Franz diffusion. Cellophane membrane was mounted on the receptor compartment with slide facing donor compartment. Drug permeability studies were conducted for 12 hrs. The samples were withdrawn from the receptor cell at regular time intervals of time and were analyzed spectrophotometrically [E. B. Souto *et al,* 2004].

Antifungal activity

Antifungal activity was carried out by disc technique by using Sabouraud dextrose agar. Standard concentrations of drug and hydrogel formulation were placed in the bores and incubated the Petri plates for 24 hrs at 37^0 in incubator. Then the zone of inhibition was observed and calculated the radius of the zone of inhibition against *Candida albicans* [Rohan M. Shah *et al,* 2017].

RESULTS

Characterization of Ketoconazole-loaded solid lipid nanoparticles

Particle size and Zeta potential

Particle size of all formulations shown in table no: 4. Depending on particle size formulation B selected as good. Particle size of formulation B2 shown less particle size that is 721nm due to excessive addition of tween 80. Hence, formulation B2 selected as an optimized formulation based on particle size. Formulation B2 shows -24 mV zeta potential. It provides an electric repulsion for maintaining the stability of SLNs dispersion.

Entrapment efficiency

Entrapment efficiency of formulation batches shown in table no: 4. Entrapment efficiency of formulation B2 was found to be 90.32%. A high amount of drug could be incorporated in nanoparticles dispersion as compared to other formulations.

Table No 4 Particle size, % entrapment efficiency of various formulations

Formulation Code	Particle size (nm)	%Entrapment efficiency
A	1024	86.69
B	921	80.43
C	1120	75.27
D	976	71.40
B1	836	84.91
B2	**721**	**90.32**
B3	785	89.45

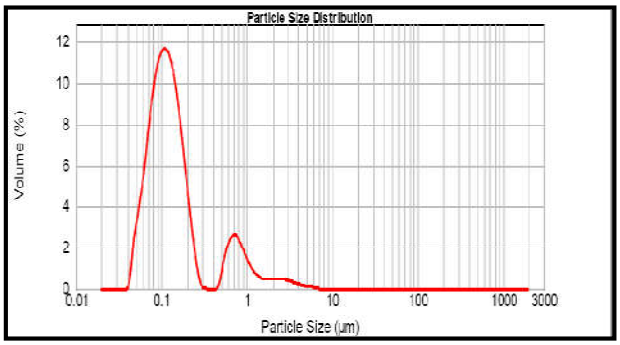

Fig No1 Particle size distribution of optimized formulation of SLN B2

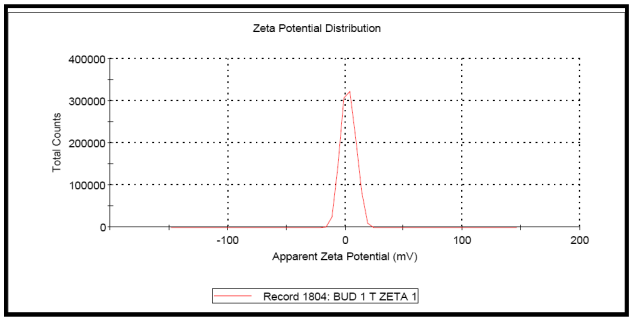

Fig No 2 Zeta potential of optimized formulation of SLN B2

Scanning Electron Microscopy (SEM)

The morphological analysis of the SLNs, studied by Scanning Electron Microscopy (SEM). SEM photomicrograph of optimized formulation B2 shown in following figure no:

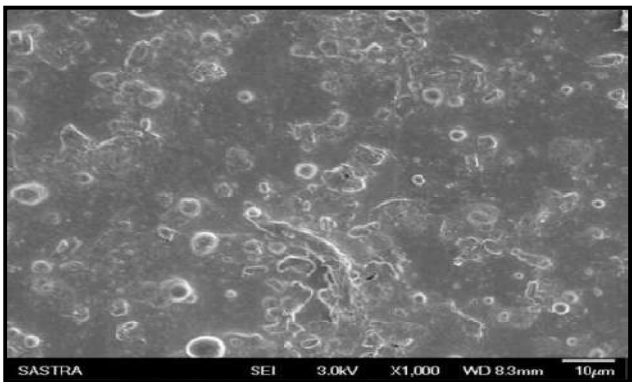

Fig 3 Scanning electron microscopy image of optimized formulation of SLN B2

Characterization of Hydrogel containing Ktz-loaded SLNs

Table 5 Characterization of hydrogel containing Ktz-loaded SLNs

pH	Viscosity (c.p)	Spreadability (cm)	% Drug content uniformity	Zone of inhibition (Cm)		% drug release
				Drug	Hydrogel	
5.7	1624	3.5	92.05	1.3	1.0	82.54

Differential scanning calorimetry (DSC)

Differential scanning calorimetry studies were carried out to examine the physical state of Ketoconazole inside the hydrogel. The thermogram of Hydrogel containing Ktz-loaded SLNs of optimized formulation shows endothermic peak starting at 109.72℃ with melting peak at 135.52℃.

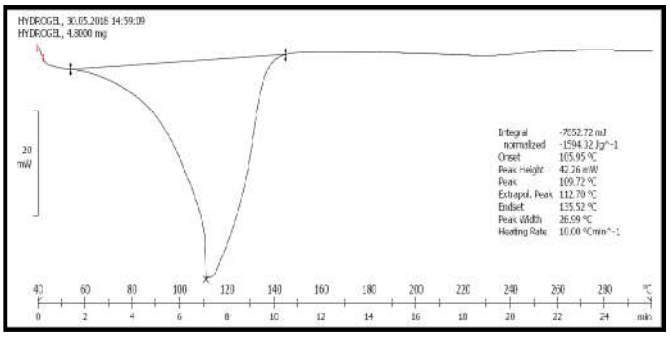

Fig No 4 DSC thermogram of hydrogel formulation (B2)

DISCUSSION

The Solid lipid nanoparticles were successfully prepared by solvent evaporation method in that process the drug is entrapped into matrix of solid lipid. The preparation process was simple, reliable, and inexpensive. Formulation B2 shown less particle size as compared to other formulations. Increase in the concentration of tween 80, decreases the particle size, this may be due to the decrease the surface tension between organic and aqueous phase, it also helps to stabilize the newly generated surfaces and particle aggregation. Further, excessive addition of tween 80 in formulation increases the polydispersity index. SLNs were smooth and spherical in shape. Ketoconazole loaded solid lipid nanoparticles were successfully incorporated into hydrogel. This hydrogel formulation was characterized for Homogeneity, pH measurement, viscosity, drug content uniformity, spreadability, drug release and antifungal activity. It shows acceptable results. It had shown better cumulative drug release profile after 12 hrs i.e. 82.54 %. It shown that hydrogel containing Ktz -loaded SLNs gives better sustained release profile for a prolonged period. The obtained results showed that, the prepared hydrogel containing Ktz-loaded SLNs has high antifungal properties as evidenced by higher inhibition zone. This could be attributed to the fact that Ktz-loaded SLNs can prevent production of the membranes that surround fungal cells.

CONCLUSION

Formulation B2 selected as an optimized formulation based on particle size. Increase in the concentration of tween 80, decreases the particle size, this may be due to the decrease the surface tension between organic and aqueous phase, it also helps to stabilize the newly generated surfaces and particle aggregation. Ketoconazole loaded solid lipid nanoparticles were successfully incorporated into hydrogel. This hydrogel formulation was characterized for Homogeneity, pH measurement, viscosity, drug content uniformity, spreadability, drug release and antifungal activity. It shows acceptable results. Hydrogel formulation was found effective against *Candida albicans*. This study was concluded that the incorporation of optimized SLNs into hydrogel gave rise to

biocompatible system that is able to deliver the drug in a sustained manner.

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How to cite this article:

Tejasvini Chavan *et al* (2018) ' Formulation and Evaluation of Anti-Fungal Drug Loaded Solid Lipid Nanoparticles For Topical Delivery ', *International Journal of Current Advanced Research,* 07(9), pp. 15567-15570.
DOI: http://dx.doi.org/10.24327/ijcar.2018.15570.2847

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