

Available online on 15.07.2022 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Research Article

Preparation of Luliconazole loaded silver nanoparticles Topical gel

Ajay Kumar^{1*}, Abhishek Soni², Ashish Kumar¹, Yashpal¹, Jyoti Devi³¹ Assistant Professor, Arni School of Pharmacy, Arni University, (Kathgarh), Tehsil Indora, Distt. Kangra, Himachal Pradesh² Department of Pharmaceutics, School Pharmacy, Abhilashi University, Chail Chowk, Mandi, Himachal Pradesh³ Research Scholar of Pharmaceutics, Himalyan Institute of Pharmacy Kala Amb, Himachal Pradesh

Article Info:

Abstract



Article History:

Received 16 May 2022
Reviewed 19 June 2022
Accepted 24 June 2022
Published 15 July 2022

Cite this article as:

Kumar A, Soni A, Kumar A, Yashpal, Devi J, Preparation of Luliconazole loaded silver nanoparticles Topical gel, Journal of Drug Delivery and Therapeutics. 2022; 12(4):31-35

DOI: <http://dx.doi.org/10.22270/jddt.v12i4.5424>

*Address for Correspondence:

Ajay Kumar, Assistant Professor, Department of Pharmaceutics, Arni School of Pharmacy, Arni University, Kathgarh, Tehsil Indora, Distt. Kangra, Himachal Pradesh PIN 176401

After optimization of the luliconazole loaded silver nanoparticles formulation it was given a gel base for topical delivery the silver nanoparticles have a very low viscosity. The gel was formed by varying the concentration of carbopol 940 as 0.75%, 1. %, 2%. The optimized luliconazole loaded silver nanoparticles formulation LSN14 was incorporated into different concentration carbopol gel base of different concentrations of carbopol and evaluated for various in vitro characterization parameters homogeneity, grittiness, measurement of pH, drug content, viscosity study, Spreadability, in - vitro drug release studies and drug release kinetics. All prepared gel formulation having different concentration of carbopol was homogenous and uniform in appearance and free from grittiness except the formulation LSN14G1Have not sufficient thickness and thus it was not used further evaluation. On the basis of result of above parameters LSN14G3 was selected for further in-vitro drug release study. Comparison of In vitro Percentage drug release study of Control gel of Luliconazole and luliconazole loaded silver nanoparticle gel formulations LSN14G3 and in - vitro drug release profile the Percentage drug release of prepared silver nanoparticle gel was found to be higher in sustained manner 93.36±0.56 after 24 hr as compare to control gel 38.50±1.21.

Keywords: optimization, silver-nanoparticles, carbopol, kinetics, luliconazole

INTRODUCTION

In previous research the luliconazole loaded silver nanoparticles preparation and evaluation is done. All prepared formulation dispersion was uniform and homogenous in physical appearance on visual observation. No phase separation and precipitation of luliconazole drug. The percentage drug entrapment of all prepared formulation was found to be in the range of 28.69±0.88 to 86.25±0.32. Percentage drug entrapment of Luliconazole in optimized formulation LSN14 was found to be 80.48±0.31. Particle size and value of PDI was found to be 34.8nm and 0.104. In addition of the zeta potential demonstrated the stability of prepared nanoparticles was found to be -12.4mv . TEM images

demonstrated spherical shape of silver nanoparticle with size less then 30nm.

After optimization of the luliconazole loaded silver nanoparticles formulation it was given a gel base for topical delivery the silver nanoparticles have a very low viscosity. The gel was formed by varying the concentration of carbopol 940 as 0.75%, 1. %, 2%, for the preparation of the gel the required amount of carbopol was dipped in a sufficient amount of water for 24 hrs and the luliconazole loaded silver nanoparticles formulation was added after neutralizing the pH of carbopol.

METHODS

The following parameters were evaluated for optimization of Luliconazole loaded silver nanoparticles Topical gel. ¹

Table 1: Composition of different Luliconazole loaded silver nanoparticles Topical gel

S.no.	Formulation code	Silver nanoparticles containing luliconazole equivalent to (%w/w)	The concentration of Carbopol 980 (%w/w)
1	LSN14G1	1	0.75
2	LSN14G1	1	1
3	LSN14G1	1	2

Evaluation of Luliconazole loaded silver nanoparticles Topical gel

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and the presence of any aggregates.

Grittiness

All the formulations were evaluated microscopically for the presence of particles if any. No appreciable particulate matter was seen under a light microscope. Hence obviously the gel preparation fulfills the requirement of freedom from particulate matter and from grittiness as desired for any topical preparation.¹

Measurement of pH

The pH of various formulations was determined by using a digital pH meter. 1 g of gel was dissolved in 100 ml of distilled water and stored for two hours. The measurements of pH of each formulation were done in triplicate and average values are calculated. The pH of the topical gel formulation should be between 3–9 to treat the skin infections.

Drug content

Weighed 1 gm of each gel formulation were transferred in 50 ml of the volumetric flask containing 50 ml of water and stirred for 30 min. The volume was made up to 50 ml and filtered. 1 ml of the above solution was further diluted to 10 ml with alcohol and again 1 ml of the above solution was further diluted to 10 ml with alcohol. The absorbance of the solution was measured spectrophotometrically.¹

Viscosity study

The viscosity of gel was determined by using a Brookfield viscometer DVII model with a T-Bar spindle in combination with a helipath stand.

a) Selection of spindle: Spindle T 95 was used for the measurement of viscosity of all the gels.

b) Sample container size: The viscosity was measured using 50 gm of gel filled in a 100 ml beaker.

c) Spindle immersion: The T-bar spindle (T95) was lowered perpendicular in the centre taking care that spindle does not touch the bottom of the jar.

d) Measurement of viscosity: The T-bar spindle (T95) was used for determining the viscosity of the gels. The factors like temperature, pressure and sample size etc. Which affect the viscosity was maintained during the process. The helipath T-bar spindle was moved up and down giving viscosities at a number of points along the path. The torque reading was always greater than 10%. The average of three readings taken in one minute was noted as the viscosity of gels.¹

Spreadability

Spreadability was determined by apparatus which was suitably modified in the laboratory and used for the study. It consists of a wooden block, which was provided by a pulley at one end. By this method, Spreadability was measured on the basis of 'Slip' and 'Drag' characteristics of gels. A ground glass slide was fixed on this block.³ An excess of gel (about 2 gm) was placed on this ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the gel

between the slides. Excess of the gel was scrapped off from the edges.

Spreadability was then calculated using the following formula:

$$S = M \times L / T$$

Where, S = is the Spreadability, M = is the weight in the pan (tied to the upper slide), L = is the length moved by the glass slide and T = represents the time taken to separate the slide completely from each other.

In vitro drug release studies

The release of Luliconazole loaded silver nanoparticles Topical gel was determined using the Franz diffusion apparatus. The membrane was dipped in the medium for 24hrs before use the membrane was mounted between the donor and receiver compartment of the Franz diffusion cell; on which the gel was spread completely to cover most of the area. An accurately measured amount of control gel and silver nanoparticle gel was transferred to donor chamber of franz diffusion apparatus. The receiver chamber of the apparatus contains the 35ml of phosphate buffer pH 7.4. The study was carried out at a constant speed of 50 rpm and at 37°C. At predetermined time intervals, aliquots were withdrawn, filtered through a sterile Millipore filter and the drug content was determined spectrophotometrically. The results were the mean values of three runs.¹

Drug release kinetics

The quantitative analysis of the values obtained in dissolution /release test is easier when mathematical formulae that express the dissolution results as function of some of the dosage forms characteristics are used.

Zero order kinetics

Dissolution of drug from a dosage form that do not disaggregate and release the drug slowly that is where drug release rate is independent of its concentration can be represented as

$$A_0 - A_t = k_t \text{----- (I)}$$

Where A_0 is initial amount of drug in the dosage form; A_t is the amount of drug in the dosage form at time 't' and 'k' is the proportionality constant. Dividing this equation by A_0 ;

$$1 - (A_t / A_0) = k_t / A_0$$

$$\text{or } 1 - A_t / A_0 = k_0 t \text{----- (II)}$$

Where $1 - (A_t / A_0)$ represents the fraction of drug dissolved in time 't' and k_0 the zero order release constant. Graphical representation of fraction of drug dissolved verses time will be linear. This relation can be used to determine the drug dissolution of various types of modified release dosage forms e.g. some transdermal systems, matrix tablets with low soluble drugs coated forms, and osmotic systems etc. The dosage forms following this profile, release the same amount of drug by unit time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

First order kinetics

The first order kinetics was first applied for drug dissolution studies by Gibaldi and Feldman in 1967 (Gibaldi and Feldman, 1970) and later by Wagner in 1969 (Wagner, 1967). In this case the drug release rate is concentration dependent; that can be depicted in decimal logarithm as

$\log A_t = \log A_0 + K_1 t / 2.303 \text{----- (III)}$ Where A_t is the amount of drug released in time 't', A_0 is the initial amount of the drug in the solution and k_1 is the first order release constant. Here the graphical representation of the decimal

logarithm of drug released verses time will be linear. Example: The dosage form follows this profile such as those containing water soluble drug in a porous matrices release the drug that is proportional to the amount of drug released by unit time diminish.

Higuchi model

Higuchi in 1961 and in 1963 developed models to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices. To study the dissolution from a planer system having a homogeneous matrix the relation obtained was;

$$A = [D (2C - C_s) C_s t]^{1/2} \text{----- (V)}$$

Where A is the amount of drug released in time 't' per unit area, C is the initial drug concentration, C_s is the drug solubility in the matrix media and D is the diffusivity of drug molecules in the matrix substance. Example: Dissolution of drug in suspension from ointment bases can be depicted by using this relation. ⁴ To study the dissolution from a planer a spherical heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the relation obtained:

$$A = D\varepsilon/\tau (2C - \varepsilon C_s) C_s t \text{----- (VI)}$$

Where A, D, C, C_s and t has the same meaning as in equation (V), ε is the matrix porosity, τ is the tortuosity factor of the capillary system.

In general way Higuchi model can be simplified (generally known as the simplified Higuchi model) as,

$$A = K_H t^{1/2} \text{----- (VII)}$$

Where K_H is the Higuchi dissolution constant. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent.

Korsmeyer peppas model

In 1983 Korsmeyer et al. (Korsmeyer et al, 1983) developed a simple, semi-empiric model, when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t).

$$A_t/A_\infty = at^n \text{----- (VIII)}$$

Where 'a' is the constant incorporating structural and geometrical characteristic of the dosage form, n is the release exponent, indicative of the drug release mechanism and the function of 't' is A_t/A_∞ (fractional release of drug).

In 1985 Peppas (Peppas, 1985) used this n value in order to characterize different release mechanism concluding for values for a slab, of $n = 0.5$ for Fickian Diffusion, between 0.5 and 1.0 or $n = 1.0$, for mass transfer following a non-fickian model. $0.5 < n < 1.0$, for anomalous transport. To determine the exponent 'n' the position of the release curve where $A_t/A_\infty < 0.6$ should only be used. This model is generally used to analyze the release of polymeric dosage form, where the release mechanism is not well known or when more than one type of release phenomenon could be involved.⁵

RESULT AND DISCUSSION

Incorporation of luliconazole loaded silver nanoparticles into carbopol gel

The optimized luliconazole loaded silver nanoparticles formulation LSN14 was incorporated into different concentration carbopol gel base of different concentrations of carbopol and evaluated for various in vitro characterization

parameters like pH, drug content, viscosity and in vitro drug release study etc.

Evaluation of luliconazole loaded silver nanoparticles into carbopol gel

Physical Appearance, Grittiness of gel

Table 2: Physical appearance and grittiness of all luliconazole loaded silver nanoparticles into carbopol gel

S. No.	Formulation code	Appearance	pH
1	LSN14G1	Non-Homogenous gel, less thick, free from Grittiness	7.0±0.37
2	LSN14G2	Homogenous gel, thick, free from Grittiness	7.1±0.55
3	LSN14G3	Homogenous gel, thick, free from Grittiness	6.98±0.17

All prepared gel formulation having different concentration of carbopol was homogenous and uniform in appearance and free from grittiness except the formulation LSN14G1 have not sufficient thickness and thus it was not used further evaluation. pH of all gel formulations were in a range of 6.98±0.17 to 7.1±0.55.

Percentage drug content

Percentage drug content of two luliconazole loaded silver nanoparticle gel formulation LSN14G2 and LSN14G3 was shown in table no 18

Table 3: Value and states of percentage drug content of all gel formulations

Formulation code	Percentage drug content
LSN14G2	95.910±0.449
LSN14G3	97.281±0.124

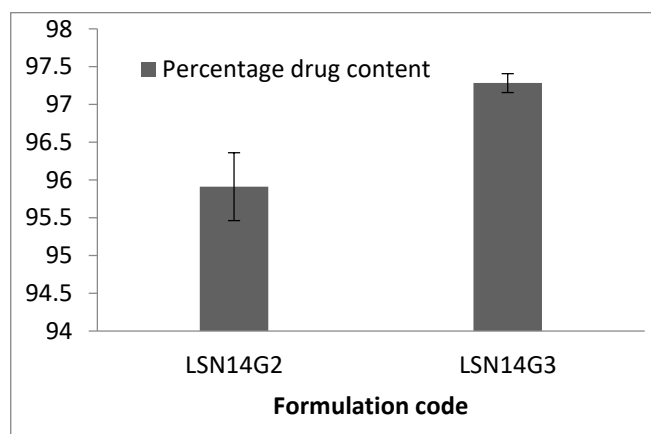


Figure 1: Bar Graph of Percentage drug content of all luliconazole loaded silver nanoparticle gel formulations

Percentage drug content of all prepared formulation were found in a range of 95.910±0.449 to 97.281±0.124 (Figure 1). Different concentration did not affect the percentage drug content significantly but it slightly increases on increasing the concentration of carbopol.

Viscosity of gel

Table 4: Value and states of Viscosity of luliconazole loaded silver nanoparticle gel formulations

S.No.	RPM	Viscosity (CPs) of LSN14G2	Viscosity (CPs) of LSN14G3
1	10	5289±7.63	6893±3.51
2	50	3155±3.05	4854±2.64
3	100	2691±8.88	3693±4.16

Viscosity of both formulation LSN14G2 and LSN14G3 was found to be within a range. Determination of Viscosity at

different rpm indicated the flow property as well as mechanical strength of gel. In viscosity study, gel was remaining homogenous means there was no breakdown of gel observed. From figure no. indicated viscosity of gel increased in simultaneous proportion on increasing concentration of gelling agent. The reason being that as concentration increase polymeric chains were come very close with each other that will increase denseness of gel.

Spreadability

Spreadability of the prepared formulation LSN14G2 and LSN14G3 was found to be 13.69 ± 0.98 & 16.02 ± 0.058 g.cm/s.

On the basis of result of above parameters LSN14G3 was selected for further in-vitro drug release study.

Comparison of In vitro Percentage drug release study of Control gel of Luliconazole and luliconazole loaded silver nanoparticle gel formulations LSN14G3

Table 5: Value and states of Percentage drug study of Control gel of Luliconazole and luliconazole loaded silver nanoparticle gel formulations LSN14G3

Time(min.)	Percentage drug release of Control gel	Percentage drug release of LSN14G3
0	0±0	0±0
0.5	3.85±0.120	6.84±0.056
1	6.33±0.0.121	13.53±0.028
2	8.97±0.077	18.12±0.065
4	12.14±0.070	28.15±0.38
6	16.68±0.028	40.93±0.75
8	22.29±0.56	61.63±0.57
10	33.51±0.57	79.58±0.65
12	35.38±0.52	91.43±0.66
24	38.50±1.21	93.36±0.56

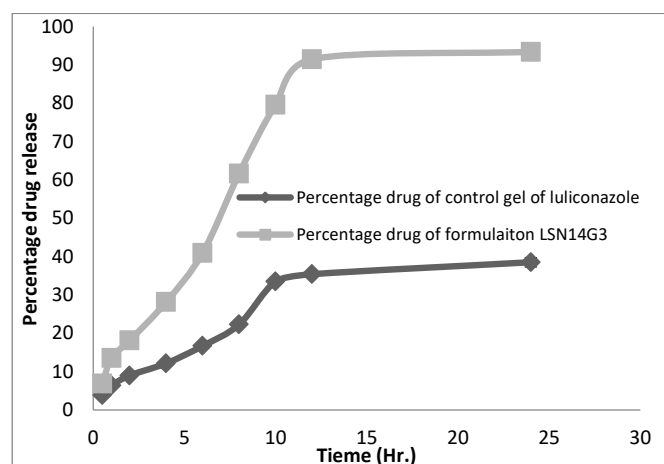


Figure 2: Comparison Graph of In-vitro drug release of control gel of luliconazole and luliconazole loaded silver nanoparticle gel formulations LSN14G3

On Comparison of In vitro drug release profile the Percentage drug release of prepared silver nanoparticle gel was found to be higher in sustained manner 93.36 ± 0.56 after 24 hr as compare to control gel 38.50 ± 1.21 as shown in figure no. 2. In vitro drug release profile of silver nanoparticle gel of luliconazole demonstrated that luliconazole slowly diffuse out from the silver nanoparticle and release for longer period of time.

In-vitro drug release kinetic Study

In-vitro drug release kinetic data of formulation LSN14G3 submicron emulsion gel was as given below.

Zero order

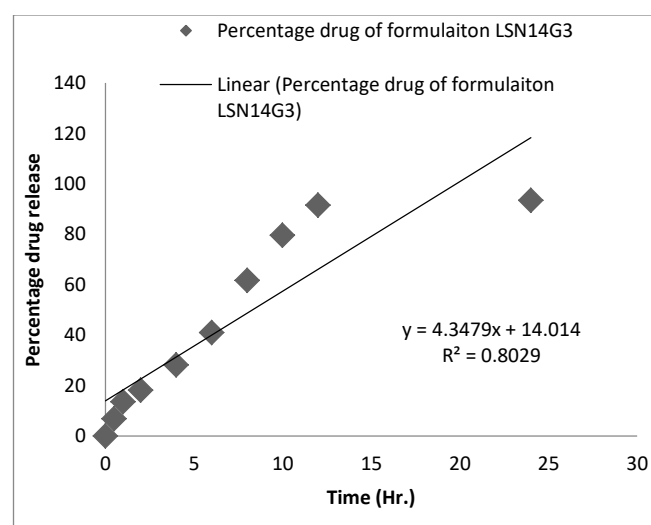


Figure 3: Graph of Zero order kinetics for silver nanoparticle gel formulation LSN14G3

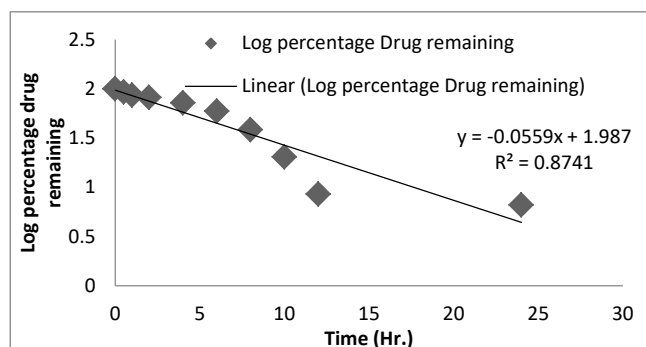
First order

Figure 4: Graph of First order kinetic for silver nanoparticle gel formulation LSN14G3

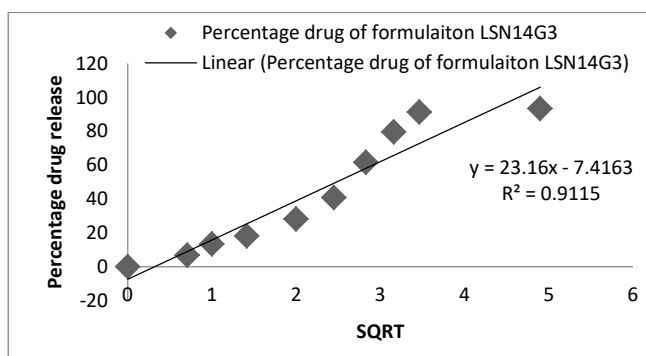
Higuchi Model

Figure 5: Graph of Higuchi model kinetic for silver nanoparticle gel formulation LSN14G3

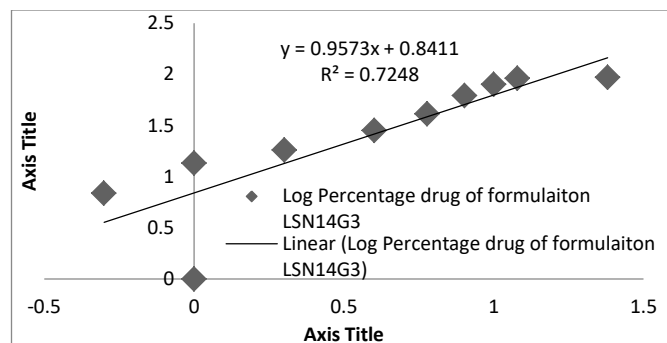
Korsmeyer –Peppas model

Figure 6: Graph of Korsmeyer–Peppas model kinetic for silver nanoparticle gel formulation LSN14G3

The calculated regression coefficients for zero order, first order and Higuchi models and Korsmeyer were shown in figure no 21-24. The release of luliconazole from formulation LSN14G3 gel formulation follows Higuchi model because it has a higher value of regression coefficient 0.911 than other models of drug release.

CONCLUSION

Optimized formulation was embedded into carbapol gel and different formulation was prepared by changing concentration of carbapol. All formulations of gel were evaluated for physicochemical properties, and were found to be homogeneous with no grittiness & pH of all formulation was found to be neutral. All prepared gel formulation having different concentration of carbapol was homogeneous and uniform in appearance and free from grittiness except the formulation LSN14G1. It has not sufficient thickness and thus it was not used for further evaluation. pH of all gel formulations were in a range of 6.98 ± 0.17 to 7.1 ± 0.55 . The value of viscosity varies with addition of carbapol in different amount. Percentage drug content of all prepared formulation were found in a range of 95.910 ± 0.449 to 97.281 ± 0.124 . Viscosity of both formulation LSN14G2 and LSN14G3 was found to be within a range. On comparison of in vitro drug release profile the percentage drug release of prepared silver nanoparticle gel was found to be higher in sustained manner 93.36 ± 0.56 after 24 hr as compared to control gel 38.50 ± 1.21 . The release of luliconazole from formulation LSN14G3 gel formulation follows Higuchi model because it has a higher value of regression coefficient 0.911 than other models of drug release.

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