REPUBLIC OF SOUTH AFRICA

REPUBLIEK VAN SUID AFRIKA

PATENTS ACT, 1978

CERTIFICATE

In accordance with section 44 (1) of the Patents Act, No. 57 of 1978, it is hereby certified that:

Dr. Kumaraswamy Gandla; Dr. Anna Balaji; Dr. Neerugatti Dora babu; Lalitha Repudi; Dr. Archana S. Patil; Imad Raouf Zahreddine; Dr.Qutaiba Abdulkareem Qasim

Has been granted a patent in respect of an invention described and claimed in complete specification deposited at the Patent Office under the number

2023/01633

A copy of the complete specification is annexed, together with the relevant Form P2.

In testimony thereof, the seal of the Patent Office has been affixed at Pretoria with effect from the **31st** day of **May 2023**

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Registrar of Patents

REPUBLIC OF SOUTH AFRICA FORM P2
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REGISTER OF PATENTS

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54	Title of invention
SOLID LIPID NANOPARTICLES FOR TARGETTED DRUG DELIVERY	

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COMPLETE SPECIFICATION

[Section 30(1) – Regulation 28]

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TITLE OF INVENTION

54	SOLID LIPID NANOPARTICLES FOR TARGETTED DRUG DELIVERY

SOLID LIPID NANOPARTICLES FOR TARGETTED DRUG DELIVERY

TECHNICAL FIELD

[0001] The present disclosure relates to nanoparticle applications, in particular, it relates to solid lipid nanoparticles for targeted drug delivery.

BACKGROUND

[0002] Background description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0003] Nanoparticles are polymeric particles with size in a range from 10-1000 nm. These nanoparticles can be effectively employed to carry drugs through adsorption or incorporation along with a drug. During the past few years, solid lipid nanoparticles has been introduced as an alternative carrier system to conventional carrier system for drug delivery. These conventional carrier systems such as emulsions, liposomes, polymeric nanoparticles are used for pharmaceutical drugs and active ingredients.

[0004] Solid lipid nanoparticles as a carrier system have been used for delivery of several drugs including prednicarbate and imidazole and was reported to have a targeted drug delivery potential. Loaded by solid lipid nanoparticles, drugs will be released at right rate and dose at specific sites in body during a certain time to realize the accurate delivery, which can enhance the therapeutic efficacy as well as reduce the toxicity and the side effect of drugs.

[0005] Müller *et al.* presented a study on the Solid lipid nanoparticles (SLN) as a carrier system for the controlled release of drugs. (Müller, R.H., Lippacher, A., Gohla, S.,

2000a. In: Wise, D. (Ed.), Handbook of Pharmaceutical Controlled Release Technology. Marcel Dekker, New York, USA, pp. 377–392). Jenning *et al.* presented a scientific paper on encapsulation of retinoids in solid lipid nanoparticles (SLN). (V. Jenning, S. Gohla, J. Microencapsul. 18 (2001) 149 – 158). The Solid lipid nanoparticles possess a number of advantageous characteristics for the topical route of application for a drug. Clotrimazole is a topical broad-spectrum antifungal agent used for the treatment of a wide variety of dermatophyte infections and candidiasis. To increase its systemic absorption, it is necessary to improve the epidermal uptake and reduce systemic absorption via a topical route.

[0006] Therefore, there is a need for solid lipid nanoparticles-based system with safe and targeted drug delivery. To facilitate enhanced bioavailability of drugs, a solid lipid nanoparticle for targeted drug delivery is disclosed. The present disclosure overcomes the above-mentioned limitations associated with the traditionally available method, any of the above-mentioned invention can be used with the presented disclosed technique with or without modification.

[0007] The present invention utilizes hot homogenization method for formulating solid lipid nanoparticle for targeted drug delivery, which improves the solubility and bioavailability of the drugs. The percentage of incorporated drug in the lipid matrix i.e. the entrapment efficiency was evaluated. Incorporation of clotrimazole as drug led to high entrapment efficiency. This can be attributed to its lipophilic character. The results of the in vitro release studies to evaluate controlled release of the drug indicated that release rate decreases for solid lipid nanoparticle with a higher lipid concentration.

[0008] All publications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided

herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

OBJECTS OF THE INVENTION

[0009] It is an object of the present disclosure which provides solid lipid nanoparticles for targeted drug delivery.

[0010] It is an object of the present disclosure to provide a method to prepare solid lipid nanoparticles for targeted drug delivery.

SUMMARY

[0011] The present disclosure relates to a solid lipid nanoparticle for targeted drug delivery comprising of a drug; glyceryl tripalmitate; and tyloxapol.

[0012] In an aspect of the present disclosure, the drug is clotrimazole.

[0013] The present disclosure also relates to a method of preparation of solid lipid nanoparticle for targeted drug delivery, the method comprising of heating glyceryl tripalmitate at a temperature of 90°C; adding a drug to form a hot lipid phase; dispersing the hot lipid phase in a hot surfactant solution by a dispersing equipment to obtain a pre-emulsion; and homogenizing the pre-emulsion at 90°C by high pressure homogenization.

[0014] In an aspect of the present disclosure, the adding a drug includes adding 5-7% clotrimazole.

[0015] In an aspect of the present disclosure, the dispersing in a hot surfactant solution is dispersing in hot 3-5% tyloxapol solution.

[0016] In an aspect of the present disclosure, the dispersing the hot lipid phase is at a speed of 7500-8000 rpm for 1 min.

[0017] In an aspect of the present disclosure, the homogenizing the pre-emulsion is by applying three homogenization cycles at a pressure of 500 bar.

[0018] One should appreciate that although the present disclosure has been explained with respect to a defined set of functional modules, any other module or set of modules can be added/deleted/modified/combined, and any such changes in architecture/construction of the proposed system are completely within the scope of the present disclosure. Each module can also be fragmented into one or more functional sub-modules, all of which also completely within the scope of the present disclosure.

[0019] Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawing figures in which like numerals represent like components.

BRIEF DESCRIPTION OF THE DRAWING

[0020] The accompanying drawing is included to provide a further understanding of the present disclosure, and are incorporated in and constitute a part of this specification. The drawing illustrates exemplary embodiments of the present disclosure and, together with the description, serve to explain the principles of the present disclosure.

[0021] FIG. 1 illustrates a flowchart of method of preparation of solid lipid nanoparticle for targeted drug delivery.

[0022] It should be noted that the figure is not drawn to scale, and the elements of similar structure and functions are generally represented for illustrative purposes throughout the figure. It should be noted that the figure does not illustrate every aspect of the described embodiments and do not limit the scope of the present disclosure.

DETAILED DESCRIPTION

[0023] Aspects of the present disclosure relate to solid lipid nanoparticles for targeted drug delivery and method of preparation.

[0024] In the following description, numerous specific details are set forth in order to provide a thorough understanding of the embodiments of the present invention. The embodiments will be apparent to one skilled in the art.

[0025] Embodiments of the present invention include various steps, which will be described below. The steps may be performed by hardware components or may be embodied in machine-executable instructions, which may be used to cause a general-purpose or special-purpose processor programmed with the instructions to perform the steps. Alternatively, steps may be performed by a combination of hardware, software, and firmware and/or by human operators.

[0026] In an embodiment of the present disclosure, solid lipid nanoparticle for targeted drug delivery is disclosed. The invention discloses solid lipid nanoparticle for targeted drug delivery and method of preparation. The solid lipid nanoparticle comprises of a drug; glyceryl tripalmitate; and tyloxapol. The drug is clotrimazole.

[0027] The drug clotrimazole is taken in an amount of 5-7%. The lipid glyceryl tripalmitate is taken in an amount of 10-19%. Tyloxapol is taken as a surfactant for preparing solid lipid nanoparticle. Tyloxapol is taken as a solution with 3-5% tyloxapol.

[0028] The solid lipid nanoparticles were prepared by hot homogenization. Hot homogenization is carried out at temperatures above the melting point of the lipid and can therefore be regarded as the homogenization of an emulsion. A pre-emulsion of the drug loaded lipid melt and the aqueous emulsifier phase is obtained by high-shear mixing device.

[0029] In an embodiment of the present disclosure, the method of preparation of solid lipid nanoparticle for targeted drug delivery is disclosed. The lipid glyceryl

tripalmitate was taken. The glyceryl tripalmitate was heated glyceryl tripalmitate at a temperature of 90℃. A drug was added in the heated glyceryl tripalmitate to form a hot lipid phase. The drug added was clotrimazole in an amount of 5-7%. The obtained hot lipid phase was dispersed in a hot surfactant solution by a dispersing equipment to obtain a pre-emulsion.

[0030] The hot surfactant solution taken for dispersion was hot 3-5% tyloxapol solution. The dispersing of the hot lipid phase was done at a speed of 7500-8000 rpm for 1 min. Thereafter, homogenizing of the pre-emulsion at a temperature of 90℃ by high pressure homogenization was done. The homogenizing of the pre-emulsion was done by applying three homogenization cycles at a pressure of 500 bar.

[0031] The morphology of solid lipid nanoparticles was observed by using photon correlation spectroscopy. The mean particle size and the polydispersity index (PI) as a measure of the width of the distribution were measured. It could be observed that the nanoparticles were well-formed and had optimum lipid coating.

[0032] The percentage of incorporated drug i.e. the entrapment efficiency was determined by spectrophotometric determination at 243 nm. The amount of free drug was detected in the supernatant after centrifugation. The amount of incorporated drug was determined as a result of the initial drug minus the free drug. The entrapment efficiency was calculated as per the standard formula.

[0033] The in vitro release studies were performed with static Franz diffusion cells to evaluate controlled release of the drug. The diffusion of the drug from the lipid particles was analyzed for a period of twenty-four hours.

[0034] The results show that the obtained nanoparticles were solid and nearly spherical particles. The solid-lipid nanoparticle has high loading ratio. It could also be observed that the particle size increased with the increase of lipid concentration. The effective diameter of the nanoparticles was 0.76 μm with a narrow polydispersity index of

0.28 on Day one. The effective diameter of the nanoparticles was 0.72 µm with a narrow polydispersity index of 0.23 on Day ninety. After three months of storage at different temperatures the mean diameters of solid lipid nanoparticles remain same i.e. below (<) 1 µm, which highlights the physical stability of these solid lipid nanoparticles.

[0035] The percentage of incorporated drug in the lipid matrix i.e. the entrapment efficiency was evaluated. The entrapment efficiency of the solid lipid nanoparticles was calculated to be 69%. Incorporation of clotrimazole as drug led to high entrapment efficiency. This can be attributed to its lipophilic character.

[0036] The results of the in vitro release studies to evaluate controlled release of the drug indicated that release rate decreases for solid lipid nanoparticle with a higher lipid concentration. If the lipid glyceryl tripalmitate is taken in an amount of 19% then the release rate decreases as compared to 10% of lipid glyceryl tripalmitate. After twenty-four hours, the release rate for 10% of lipid glyceryl tripalmitate was 24% and the release rate of 19% of lipid glyceryl tripalmitate was 18%.

[0037] The present disclosure presents an optimal solid lipid nanoparticle for targeted drug delivery and its method of preparation.

[0038] The solid lipid nanoparticle prepared by the given method have following advantages-

- The solid lipid nanoparticle has high loading ratio.
- The solid lipid nanoparticle has high entrapment efficiency.
- The solid lipid nanoparticle has demonstrated to have optimum release profile.
- The solid lipid nanoparticle has demonstrated to have high bioavailability due to targeted drug delivery.

[0039] While the foregoing describes various embodiments of the invention, other and further embodiments of the invention may be devised without departing from the basic

scope thereof. The scope of the invention is determined by the claims that follow. The invention is not limited to the described embodiments, versions or examples, which are included to enable a person having ordinary skill in the art to make and use the invention when combined with information and knowledge available to the person having ordinary skill in the art.

Claims:

1. A solid lipid nanoparticle for targeted drug delivery comprising of:

   a drug;
   glyceryl tripalmitate; and
   tyloxapol.

2. The solid lipid nanoparticle for targeted drug delivery as claimed in claim 1, wherein the drug is clotrimazole.

3. A method of preparation of solid lipid nanoparticle for targeted drug delivery comprising of:

   heating glyceryl tripalmitate at a temperature of 90°C;
   adding a drug to form a hot lipid phase;
   dispersing the hot lipid phase in a hot surfactant solution by a dispersing equipment to obtain a pre-emulsion; and
   homogenizing the pre-emulsion at 90°C by high pressure homogenization.

4. The method of preparation of solid lipid nanoparticle for targeted drug delivery as claimed in claim 3, wherein the adding a drug includes adding 5-7% clotrimazole.

5. The method of preparation of solid lipid nanoparticle for targeted drug delivery as claimed in claim 3, wherein the dispersing in a hot surfactant solution is dispersing in hot 3-5% tyloxapol solution.

6. The method of preparation of solid lipid nanoparticle for targeted drug delivery as claimed in claim 3, wherein the dispersing the hot lipid phase is at a speed of 7500-8000 rpm for 1 min.

7. The method of preparation of solid lipid nanoparticle for targeted drug delivery as claimed in claim 3, wherein the homogenizing the pre-emulsion is by applying three homogenization cycles at a pressure of 500 bar.

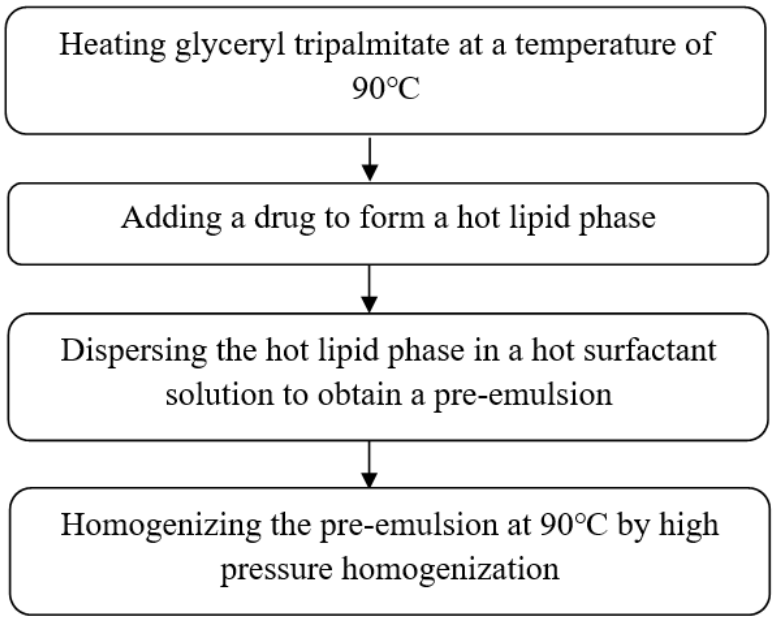

Figure 1: Flowchart of method of preparation of solid lipid nanoparticles for targeted drug delivery

ABSTRACT

SOLID LIPID NANOPARTICLES FOR TARGETTED DRUG DELIVERY

The invention discloses solid lipid nanoparticles for targeted drug delivery and method of preparation. The solid lipid nanoparticle comprises of a drug; glyceryl tripalmitate; and tyloxapol. The drug is clotrimazole. The present invention utilizes hot homogenization method for formulating solid lipid nanoparticle for targeted drug delivery, which improves the solubility and bioavailability of the drugs. The percentage of incorporated drug in the lipid matrix i.e. the entrapment efficiency was evaluated. Incorporation of clotrimazole as drug led to high entrapment efficiency. This can be attributed to its lipophilic character. The results of the in vitro release studies to evaluate controlled release of the drug indicated that release rate decreases for solid lipid nanoparticle with a higher lipid concentration.

Figure 1 shall be reference figure.