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FORMULATION AND EVALUATION OF SOLID LIPID NANOPARTICLES CONTAINING CELECOXIB

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ABSTRACT

The oral administration of Celecoxib causes gastrointestinal ulcers and bleeding in chronic use. Due to gastrointestinal bleeding it may cause anaemia. Also, use of Celecoxib is limited by its poor solubility and low bioavailability. Thus, the present study aimed at design and development of a drug delivery system which could enhance the solubility of Celecoxib. Lipid based drug delivery has attracted much attention during recent years as innovative strategy to overcome insufficient bioavailability of hydrophobic drugs. S-SLN can also offer better patient compliance. One of the most popular and commercially viable formulation approaches for solving these problems is SLN which have been shown to be reasonably successful in improving the oral bioavailability of various poorly water-soluble SLN are isotropic mixtures of drug, oil/lipid, surfactant, and/or cosurfactant, which form fine emulsion/lipid droplets, ranging in size from approximately 100 nm on dilution with physiological fluid. The drug, therefore, remains in solution in the gut, avoiding the dissolution step that frequently limits the absorption rate of hydrophobic drugs from the crystalline state SLN can be optimized with the help of phase diagram, when such a system is released in the lumen of the GIT, it disperses to form a fine emulsion with the aid of GIT fluid.

KEY WORDS: Celecoxib, Nano-Particles, Surfactant, Drug delivery, Micro sponges.

INTRODUCTION

The drug delivery technology landscape has become highly competitive and rapidly evolving. More and more developments in delivery systems are being integrated to optimize the efficacy and cost- effectiveness of the therapy. New classes of pharmaceuticals, biopharmaceuticals (peptides, proteins and DNA-based therapeutics) are fuelling the rapid evolution of drug delivery technology. These new drugs typically cannot be effectively delivered by conventional mean. Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system In the current years the development of new drugs is not sufficient for the drug treatment. But it also involves the development of suitable drug delivery system at site of action. The in-vivo fate of the drug is not only determined by the properties of the drug, but it is also determined by the carrier system, which permits a controlled and localized release of the active drug according to the specific need of the therapy. The biggest challenge up to date is to control the delivery rate of the medicaments by various modern technologies met by extensive research. However, TDS is not practical for delivery of materials whose final target is the skin itself. The controlled release of drug from the formulation into the epidermis such that the drug remains primarily localized with only a restricted amount entering the systemic circulation, is a means of controlling side-effects.

Thus, the need exists for delivery systems to maximize the period of time that an active ingredient is present, either on the skin surface or within the epidermis while minimizing its transdermal penetration into the body. Another potential problem in topical delivery of drugs relates to uncontrolled evaporation of the active ingredient, unpleasant odour, the use of unaesthetic vehicles which may be greasy, sticky and may cause discolorations, since this can result in the lack of patient compliance. Carrier technology is the potential solution to these challenges. Microparticles and nanoparticles have been increasingly researched to achieve targeted and sustained release of drugs.

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These include microspheres, liposomes, and nanoparticles etc. which alter the absorption and release characteristics of the drug. Microspheres are unable to control the release rate of drug from itself

Once the outer wall is ruptured the drug contained within microspheres will be released from it. Liposomes having demerits like lower drug entrapment, difficulty in preparing formulation, limited chemical stability and microbial stability so the preservatives are required. Solid lipid nanoparticles are having most of the benefits in the topical drug delivery. Nanomaterial can easily enter in to the systemic circulation by inhalation or ingestion, and possibly also via skin absorption, especially if the skin is damaged. Once in the blood stream, nanomaterials can be transported around the body.

The microsponge-based polymeric microspheres uniquely overcome problems associate with above technologies. Microsponges are extremely small, inert, indestructible spheres that do not pass through the skin. Rather, they collect in the tiny nooks and crannies of the skin and slowly release the entrapped drug, as the skin needs it. They are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects and modify drug release.

Microsponges are microscopic spheres capable of absorbing skin secretions, therefore reducing oiliness and shine from the skin. Spherical particles composed of clusters of even tinier spheres are capable of holding four times their weight in skin secretions. These products are typically presented to the consumer in conventional forms like creams, gels or lotions and they contain a relatively high concentration of active ingredients. Recently their use is also being investigated for oral drug delivery. This article provides concise information to the various aspects of the structure, development, applications and future of microsponges.It is to be introductory to the vast amount of research that has been done and the large number of opportunities that exist in the field of microsponges.

Defining Microsponges:

The Microsponge Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. The size of the microsponges ranges from 5-300μm in diameter and a typical 25μm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention. The surface can be varied from 20 to 500 m2/g and pore volume range from 0.1 to 0.3cm3/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent.

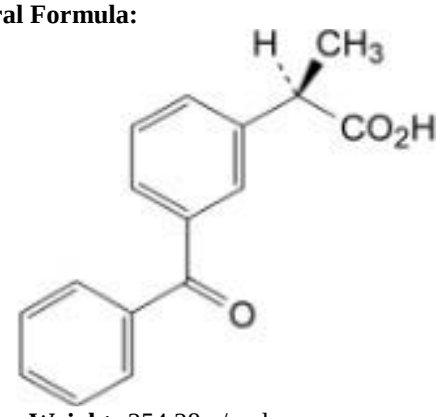
MATERIALS AND METHODS

DRUG PROFILE: CELECOXIB (IP, 2007, Sweetman, 2009)

Chemical Name: (RS)-2-(3-benzoylphenyl) propionic acid

Molecular Formula: $C_{16}H_{14}O_3$

Structural Formula:



Molecular Weight: 254.28 g/mol

Drug Category: Non-steroidal Anti-inflammatory Drug

Appearance: White or almost white, crystalline, Odourless powder.

Solubility:

Practically insoluble in water. Freely soluble in ethanol, chloroform, acetone, ether also soluble in benzene and strong alkali.

Melting Point: 92-97ºC

Dose: 100 to 200 mg in 2 to 4 divided doses

Storage:

Store in well closed containers, protect from moisture.

BCS: CELECOXIB is BCS Class-II drug (low solubility and high Permeability)

Stereochemistry:

CELECOXIB has two enantiomers (R) and (S).The (S) – enantiomer responsible for pharmacological effect, whereas the (R)- is therapeutically less active or inactive.

Therapeutic uses: Osteoarthritis, Rheumatoid arthritis, as analgesic in Soft tissue injuries, Dysmenorrhoea, Postoperative pain, acute gout, Bursitis, Tendinitis and to reduce Fever (anti- pyretic)

Dissociation constant:

pKa of CELECOXIB in water is 4.55

Side Effects:

Gastrointestinal irritation and ulcerogenic effect. It may also cause nausea, diarrhoea, abdominal pain, constipation and flatulence.

Mechanism of Action:

CELECOXIB is a non-selective COX inhibitor. It may stabilize lysosomal membranes and a powerful antagonist of bradykinin an important chemical mediator of pain and inflammation.

Preformulation Studies and Characterization Of Celecoxib

Preformulation studies are essential for the rational development of any dosage form of a drug substance. A detailed understanding of the properties of the drug along with excipients is essential to minimize formulation problems at the later stages of drug development. Preformulation studies are designed to identify those physiochemical properties of a drug that may influence the formulation design, method of manufacture and pharmacokinetics properties of the resultant product. The goals of preformulation studies include the selected or the correct form of the drug substance, evaluation of its physical properties, and a thorough understanding of its stability and compatibility profiles.

Physicochemical Characterization

(a) Appearance

CELECOXIB is a white, crystalline, odourless powder

Solubility

Solubility of drug was determined in different solvents at room temperature by adding excess of drug to 10 ml volumetric flasks with different solvents. The containers were sealed and kept it for 24 hrs at ambient temperature with appropriate shaking. After 24 hrs, the solutions were filtered through 0.45 µm millipore filter, diluted suitably and analyzed spectrophotometrically at 260 nm.

Identification of Drug

(a) Ultraviolet Spectral Analysis

CELECOXIB 50mg was dissolved in 50ml of phosphate buffer pH 7.4 and 0.1N HCl (pH 1.2) to prepared a stock solution of 1000µg/ml concentration, which was then further diluted to prepared 10µg/ml solution and was subjected to scaning in range of 200-300nm using UV-Visible Spectrophotometer (Cary5000, Varian, Australia).The wavelength at which maximum absorbance occurred was selected for the analysis of drug samples in subsequent studies.

(b) Fourier Transformation Infrared Analysis

The Fourier Transformation Infrared spectroscopy (FTIR) was performed in Fourier-Transform Infrared Spectrophotometer (FTIR Spectrophotometer Perkin-Elmer BX II) by KBr pellet method in the range of 4000-500 cm-1 to confirm the authenticity of the drug CELECOXIB.

(c) Differential Scanning Calorimetric Analysis

DSC thermogram of CELECOXIB was recorded using Differential Scanning Calorimeter (Perkin-Elmer DSC-4000, USA) to confirm authenticity of drug sample. A small amount (2-5mg) of sample was sealed in the aluminium pan and heated in a temperature range 26-300ºC at the heating rate of 10ºC per minute in the presence of nitrogen atmosphere.

Preparation of Solid Lipid Nanoparticles of Celecoxib

Solid lipid nanoparticles were prepared by solvent injection technique (Schubert and Muller-Goymann, 2003). CELECOXIB (50mg) and specified amount of glyceryl monostearate was dissolved in 5ml of isopropyl alcohol with heating at melting temperature of glyceryl monostearate. Simultaneously the aqueous solution of specified amount of Poloxamer 407 was prepared in 25 ml of distilled water at the same temperature. When both the phases reached the same temperature the organic phase was quickly injected into the aqueous phase with continuous stirring at 400 rpm for 30 min on magnetic stirrer. To this dispersion 4 ml of 0.1N HCl was added to decrease the pH to around 1.5-2.0 to cause the aggregation of SLNs for the ease of separation. Thereafter, the dispersion was centrifuged at 10,000 rpm for 60 min at 10ºC in Remi Cooling centrifuge. The sedimented soft pellet was then separated and resuspended in 25 ml of distilled water containing 4% Poloxamer 407 (by weight) as stabilizer with stirring at 1000 rpm for 10 minutes and subjected to ultrasonication for 1 min to get a desired particle size (Shah and Pathak, 2010).

Characterization of Solid Lipid Nanoparticles Particle Size And Zeta Potential Analysis

The size of solid lipid nanoparticles, polydispersity index and zeta potential were determined by particle size analyser (Malvern Zetasizer).

Entrapment Efficiency

The suspension of solid lipid nanoparticles was centrifuged at 10000 rpm for 60 min at 10ºC. The supernatant was analysed for free CELECOXIB at 260 nm spectrophotometrically.

% Entrapment Efficiency = Amount of drug added- Amount of free drug in supernatant

X 100

Amount of drug added

IN-VITRO DRUG RELEASE STUDIES

The *in-vitro* drug release studies were performed on solid lipid nanoparticles by dialysis bag diffusion technique using USP dissolution apparatus II (Paddle type) (stirring speed 100 rpm in 250 ml, phosphate buffer pH 7.4 temperature 37±0.5ºC). Solid lipid nanosuspension equivalent to 5 mg CELECOXIB was filled in dialysis membrane having pore size of 2.4 nm and molecular cut-off 12000-14000 Da and was put in a flask containing 250 ml of phosphate buffer pH 7.4. Sample aliquots of 5 ml were withdrawn at specific intervals and replaced with equal volume of fresh buffer solution to maintain the sink

conditions. The samples were analysed by UV-Visible spectrophotometer at 260 nm against the suitable blank. The absorbance was used to calculate the concentration using calibration curve.

NUMERICAL OPTIMISATION OF SLNs

A numerical optimisation tool of design expert software, using the desirability approach was employed to obtain a batch having the desired response. The combined effect of different variables on responses was studied in 3-D response surface plots, which were generated using design expert software to obtain a batch having the desired response In this study, the optimisation of independent variables was carried out with the goal of minimum particle size, in range percent entrapment efficiency and maximum percent cumulative drug release. The numerical optimisation provided an optimum batch of solid lipid nanoparticle which was prepared and characterized by DSC.

CHARACTERIZATION OF OPTIMIZED BATCH

Differential Scanning Calorimetric Analysis

The physical state of drug inside the solid lipid nanoparticles was investigated by DSC. The DSC thermogram of optimized batch was obtained using Differential Scanning Calorimeter (Perkin-Elmer, USA). The sample was sealed in aluminium pan and heated in range of 25-300ºC at a heating rate.

RESULTS AND DISCUSSION

Preformulation Studies

Physiochemical Characterization

(a) Appearance: CELECOXIB is white, crystalline, odourless powder.

(b) Solubility of Drug in different solvents

CELECOXIB is freely soluble in methanol, ethanol, isopropyl alcohol, acetone and soluble in strong alkali. It is practically insoluble in water.

(c) Melting Point

The endothermic peak with a peak maximum at 98.07ºC was observed obtained in the thermogram, indicate the melting point and crystalline anhydrous nature of the drug. The onset melting of drug was at 93.54ºC.

Identification of Drug

(a) Ultraviolet Spectral Analysis: To know the absorption maxima (λ_{max}) of CELECOXIB, spectral scan of CELECOXIB in Phosphate buffer pH 7.4 was recorded which showed the maximum absorbance at 260 nm. This λmax was further used to prepare calibration curve and estimation of Absorbance spectrum of drug in phosphate buffer pH 7.4.

Drug Entrapment Efficiency

The Entrapment Efficiency ranged from 60.55% – 92.70% which indicated that increase in amount of glyceryl monostearate also increased the entrapment efficiency of drug because of the increased concentration of mono-, di-, and triglycerides which act as solubilizing agents for highly lipophilic drug and provide a less ordered solid lipid matrix and left enough space to accommodate drug molecules.The Entrapment Efficiency was decreased with increasing concentration of surfactant in aqueous phase because of the well-known fact that the aqueous solubility of drug increases with increase in surfactant concentration.

***IN-VITRO* DRUG RELEASE STUDIES**

The release profile of CELECOXIB loaded solid lipid nanoparticle showed the cumulative drug release from 39.84% – 67.08% over a period of 12 hrs. The solid lipid nanoparticles displayed a biphasic drug release pattern with initial burst release followed by sustained release of drug. The burst release may be ascribed to the drug associated with the surface of particles. The results displayed that the release was chiefly dependent on the concentration of lipid. An increase in the lipid concentration caused a decrease in the release rate because lipid content increases the packing density of lipid molecules in given space; as a consequence of which the release is reduced. However, the percent cumulative drug release increased with corresponding increase in poloxamer 407 concentration which could be attributed to the decrease in particle size and increase in surface area available for dissolution.

CHARACTERIZATION OF OPTIMIZED BATCH

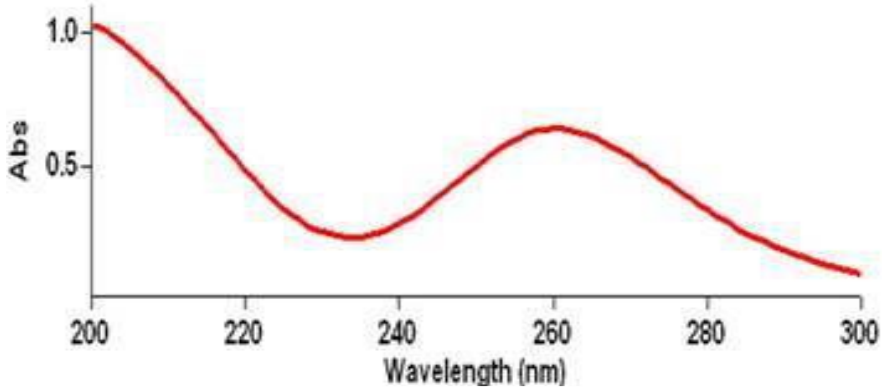
Differential Scanning Calorimetric Analysis

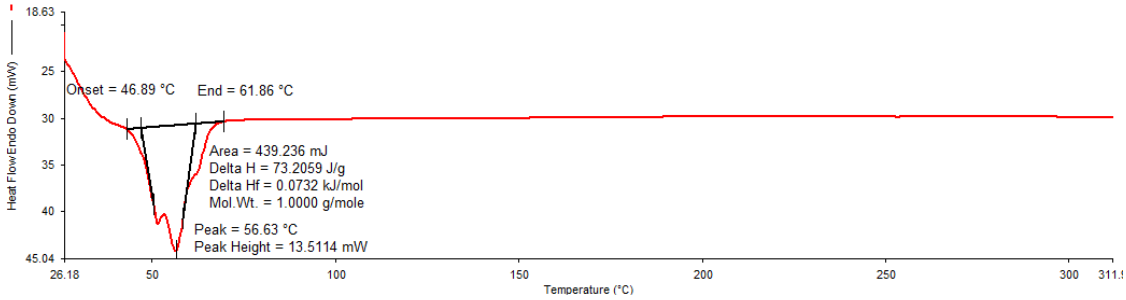
The thermograms of all investigated SLN systems did not show the melting peak of CELECOXIB around 98 ºC indicating the conversion of crystalline CELECOXIB to the amorphous form which could be attributed to complete dissolution of the drug in the molten lipid matrix. The melting point of glyceryl monostearate in SLNs was depressed showing slight shift to lower temperature side when compared to the corresponding bulk lipid. This melting point depression could be due to the small particle size (nanometer range), the high specific surface area, and the presence of surfactant - in other words, the depression can be attributed to the Kelvin effect (Jenning *et al.,* 2000b). Kelvin realized that small, isolated particles would melt at a temperature lower than the melting temperature of bulk materials.

In the same way, the melting enthalpy values of different lipids in SLN formulations showed drastic depression compared to their bulk lipids from 73.205 J/g to 510.071 J/g respectively. These lower melting enthalpy values suggested less ordered lattice arrangement of the lipid within nanoparticles compared to the bulk materials (Hou *et al.,* 2003). For the less-ordered crystal or amorphous state, the melting of the substance requires less energy than the perfect crystalline substance, which needs to overcome lattice force. Therefore this decrease in the melting point and enthalpy values is associated with numerous lattice

defects and the formation of amorphous regions in which the drug is located.

UV Spectrum scans of CELECOXIB in Phosphate Buffer (pH 7.4)





CONCLUSION

The coating capsules of containing lyophilized SLNs with cellulose acetate phthalate significantly reduced the release of drug in the simulated gastrointestinal fluid. The drug release from the prepared capsules was studied and it was found that about 4% of CELECOXIB was released after 2 hrs, while more than 57% was released after 12 hrs followed the mechanism of sustained release of drug. Hence, prevent the excessive exposure of drug to stomach mucosal lining. The *in-vitro* study data can be corroborated with further *in-vivo* studies in animal models. Thus, paving the way for the development of a promising drug delivery system for more effective therapeutic management of rheumatoid arthritis.

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