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REVIEW ARTICLE: A STUDY ON NANOSTRUCTURED LIPID CARRIER SYSTEMS FOR OPTIMIZED FUROSEMIDE DELIVERY: FORMULATION AND IN VITRO EVALUATION

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ABSTRACT

Designing and evaluating nanostructured lipid carriers (NLCs) to administer furosemide effectively, a strong loop diuretic with low oral bioavailability because of its substantial first-pass metabolism and low solubility, is the main focus of this study. NLCs were created to increase medication solubility, stability, and simplify controlled release. They are made up of a mixture of liquid and solid lipids stabilized by surfactants. NLCs loaded with furosemide were made via ultrasonography and thermal homogenization. The criteria employed to optimize various formulations included drug entrapment efficiency, zeta potential, particle size, polydispersity index (PDI), and in vitro drug release. A mean particle size of less than 200 nm was observed in the enhanced NLC formulation, which also had a narrow PDI and a zeta potential that suggested high physical stability. In order to confirm effective drug loading, the entrapment efficiency was noticeably high. The quick release from the pure medication was contrasted with a continuous release profile over a 24-hour period in in vitro release tests. Based on the data, NLCs may be a promising delivery method to increase furosemide's bioavailability and therapeutic effectiveness. It is necessary to conduct additional in vivo research to prove pharmacokinetic benefits.

1. INTRODUCTION

Nanotechnology is used in a wide range of disciplines, such as environmental science, health, cosmetics, and nutraceutical research.[1] The limitations of conventional pharmaceutical delivery systems can now be mitigated by nanotechnology, which has accelerated in recent years.[2] Colloidal systems with an average diameter of less than one micron are known as nanocarriers.[3] Nanoparticles are suited for use in medical applications due to their special properties, which include their high surface-to-volume ratio and nanoscale size.[4] They can be combined with a range of support elements and pharmaceutically active substances because they are smaller than biological macromolecular medications or conventional chemotherapeutic drugs.[5]

Imaging, targeting, degradation resistance, and stimulus-based activation are made possible by these elements. But the way the body reacts to nanoparticles differs from how it reacts to traditional drugs.[6] Nanoparticles exhibit unique hydrodynamic properties and biodistribution profiles. Notably, interactions that take place at the nanobiological level may be used to improve drug dispersion.[7] Nanocarriers' encapsulating moieties can be changed to enhance their pharmacokinetic and biodistribution properties, reduce toxicity, control release, increase solubility and stability, and deliver their payload to specific locations.[8] The physiochemical properties of nanocarriers, including their surface, composition, and shape, can be changed to enhance their functionality and reduce adverse consequences.

Although nanostructured lipid carriers (NLCs) are a potential development in drug delivery systems, a number of issues prevent their use in clinical settings. These difficulties include biological barriers, stability problems, and formulation complexity.[9]

Nanocarriers include polymeric, lipidic, inorganic nanoparticles, liposomes, nanotubes, nanocomplexes, niosomes, and a variety of other forms (figure 1).[10] The surface properties of nanocarriers have a significant influence on their stability, biodistribution, bioavailability, and cellular absorption.[11] In addition to revealing possible electrostatic interactions between the nanocarrier units, the zeta potential, which stands for the

surface charge, affects the units' propensity to aggregate and makes it easier to select appropriate coating materials.[12] The half-life, toxicity, and targeting efficiency of nanocarriers are biological factors that are impacted by their form and aggregation behavior.[13] These biological processes are greatly impacted by a variety of non-spherical shapes, including cylinders, cubes, cones, hemispheres, and other complicated shapes.[14]

Furosemide, a widely used loop diuretic, is FDA-approved for managing conditions marked by fluid overload and edema like congestive heart failure, liver cirrhosis, and renal dysfunction. This review examines furosemide comprehensively, focusing on its mechanisms, indications, administration, safety, and recent updates to ensure optimal patient care.

Indications Furosemide is approved for treating volume overload in congestive heart failure, liver cirrhosis, renal failure, and nephrotic syndrome. It is particularly valuable in acute decompensated heart failure (ADHF) and as a second-line agent for hypertension in advanced kidney disease.

Mechanism of Action

Furosemide inhibits sodium and chloride reabsorption in renal tubules, leading to significant diuresis and natriuresis, thus reducing fluid overload and edema.

Pharmacokinetics

Furosemide is rapidly absorbed orally with peak effects in 1-2 hours. Its bioavailability is around 51%, with a terminal half-life of 2 hours and prolonged effects in renal impairment.

These sections provide a concise overview of furosemide's essential aspects, setting the stage for a detailed examination in your comprehensive review.

Administration Furosemide is available in both oral and intravenous forms, with intravenous furosemide being twice as potent as the oral version. Oral options include tablets (20 mg, 40 mg, and 80 mg strengths) and an oral solution (10 mg/ml or 8 mg/ml). Intravenous administration is preferred for situations requiring rapid diuresis.

Pharmacodynamics

Furosemide induces significant sodium excretion and diuresis, peaking within 3 to 6 hours. Chronic use may lead to "post-diuretic sodium retention," requiring repeated doses to maintain diuresis. The "breaking phenomenon" may reduce efficacy over time, necessitating thiazide diuretics' addition.

Use in Specific Populations Patients with Hepatic Impairment: Start furosemide cautiously in hospitalized cirrhotic patients to prevent electrolyte imbalances and hepatic coma. Patients with Renal Impairment: Adjust dosing based on glomerular filtration rate; discontinue if azotemia worsens. Pregnancy and Breastfeeding: Use furosemide cautiously in pregnancy and consider alternatives during breastfeeding due to potential fetal and lactational effects.

Adverse Effects

Furosemide's adverse effects are diverse and categorized by organ systems: Gastrointestinal: Hepatic encephalopathy, pancreatitis, jaundice, liver enzyme elevation, anorexia, oral and gastric irritation, cramping, diarrhea, constipation, nausea, and vomiting. Systemic Hypersensitivity: Severe anaphylactic reactions, systemic vasculitis, interstitial nephritis, and necrotizing angiitis. Central Nervous System: Ototoxicity, paresthesias, vertigo, dizziness, headaches, blurred vision, and xanthopsia. Hematologic: Aplastic anemia, thrombocytopenia, agranulocytosis, hemolytic anemia, leukopenia, anemia, and eosinophilia. Dermatologic: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, DRESS, acute generalized exanthematous pustulosis, exfoliative dermatitis, bullous pemphigoid, purpura, photosensitivity, rash, pruritus, and urticaria. Cardiovascular: Orthostatic hypotension, increased cholesterol and triglyceride levels. Renal: Acute kidney injury. Metabolic: Hyperglycemia, hyperuricemia, hypokalemia, and hypomagnesemia.

While furosemide is effective, its diverse adverse effects necessitate careful monitoring and individualized management to optimize patient safety and outcomes.

Preparation Methods

There are numerous techniques for the preparation of SLNs and NLCs described in the scientific literature. Selecting the most appropriate method requires careful consideration of the physicochemical properties of active ingredients, lipid matrices, and surfactants to ensure the production of stable nanostructures. The preparation methods are broadly categorized into two types, which are high-energy methods and low-energy methods.

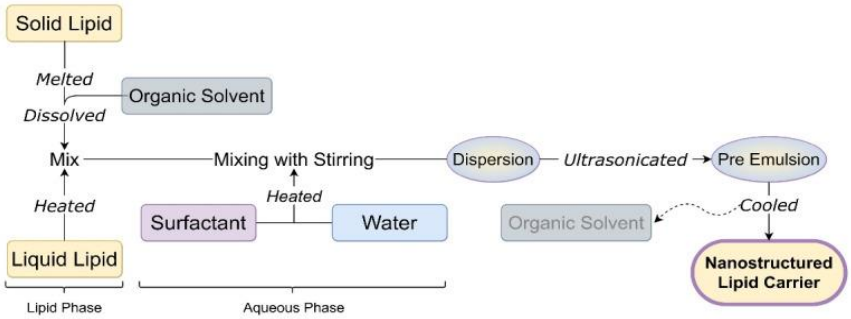

Figure: Preparation of SLNs and NLCs.

Low-energy methods involve the formation of nanodroplets without the use of devices that actively transfer energy into the system. Instead, these methods rely on physicochemical processes that generate energy through alternating heating and cooling cycles or by simply mixing the components. In these cases, the intrinsic properties of the surfactants and solvents are adequate for nanoparticle formation.[64] Examples of low-energy methods include emulsification, micro emulsification, and the phase inversion temperature (PIT) methods.

High-energy methods, in contrast, require specialized equipment capable of imparting significant energy into the system to form nanoparticles. The equipment generates high shear forces or induces high-pressure variations that provide energy greater than the interfacial tension between water and oil. Techniques such as high-pressure homogenization, solvent injection, and ultrasonification fall into this category. Shear stress refers to the force per unit area resulting from lateral interactions between fluid layers, causing material deformation due to friction among fluid particles moving at different velocities within the system. The particle size reduction achieved with high-energy methods depends on the type of equipment used and its operational parameters, including energy input, processing time, number of cycles, formulation specifics, and system properties. While high-energy methods are highly effective for large-scale production, they tend to increase production costs due to the sophisticated machinery required and may inactivate thermolabile drugs.[65]

The primary methods for producing SLNs and NLCs are illustrated in **Figure 2** and elaborated upon below, and **Table 3** shows examples of SLNs and NLCs prepared by different methods, with lipid compositions and surfactants used.

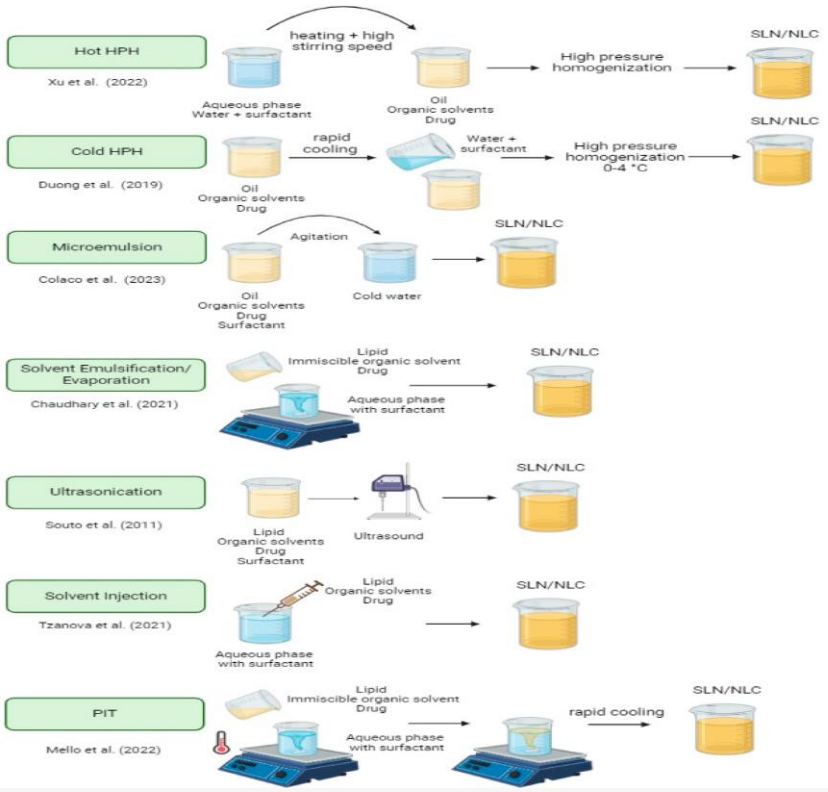

Figure 2: Main preparation methods of solid lipid nanoparticles (SLNs) and nanostructure lipid carriers (NLCs). Hot HPH (hot high-pressure homogenization), Cold HPH (cold high-pressure homogenization),

microemulsion, solvent emulsification/evaporation, ultrasonication, solvent injection and PIT (phase inversion temperature).

2. REVIEW OF LITERATURE

Gul, *et al.*, 2024
Particularly for lipophilic medications, lipids are frequently the most effective method of delivering medications at the nanoscale level. The issues with polymeric nanoparticles that were previously mentioned are resolved by this technique.

Gupta, *et al.*, 2023; Poovi, *et al.*, 2018
This enhances control over drug release, increases the capacity to load medications, and prevents pharmaceuticals from seeping out. Examining whether NLCs could be utilized as a novel method of delivering furosemide to the stomach was a key objective of this research. This was accomplished by creating furosemide-loaded nanostructured lipid carriers using the liquid diffusion technique. The synthesis method was improved by the use of a comprehensive factorial design, and the resulting NLCs were thoroughly explained.

Fathi, et al., 2023; Thombre, *et al.*, 2022
In order to increase solubility and, consequently, bioavailability, polymeric nanoparticles were the first nanotechnology initiative. They are composed of a non-toxic polymer that decomposes spontaneously and does not damage living organisms. Even though many goods had good attributes, they were unable to be commercialized because the polymers were poisonous to cells, there were solvent remnants from manufacture, there were no affordable solutions, and there were few efficient techniques to make huge volumes of nanoparticles.

Zewail, et al., 2022
The shortcomings of SLN, such as its limited drug capacity, the potential for gel formation, and drug leakage during storage because of lipid polymorphism, are addressed by the next generation of lipid nanoparticles, known as NLC. Lipids, both liquid and solid, make up NLCs.

Dalal, *et al.*, 2021
Numerous critical characteristics should be present in the ideal nano drug carrier, including the capacity to contain a sufficient amount of medication, stability in various conditions, selective release of medication at the appropriate moment, safety, effectiveness, and the potential to be rapidly and affordably scaled up. Because polymeric nanoparticles are costly and there aren't many authorized polymers that regulators believe to be safe, they haven't been employed much in clinical treatment.

Natarajan, *et al.*, 2019; Duong, *et al.*, 2020
They are made by carefully combining liquid lipids that don't mix well with solid lipids, which results in a unique nanostructure. The structure of the crystals is significantly altered when solid and liquid lipids are combined. This is in contrast to the process used to create solid lipid nanoparticles, which are often better ordered and formed when generated from a combination of solid lipids or from solid lipids alone. There is plenty of space for drug molecules in the resultant matrix, which also features obvious crystal structural defects.

Alam, *et al.*, 2018
One method for delivering the therapeutic chemical to the appropriate cell, tissue, or organ at the appropriate time and in the appropriate amount is through the use of nanotechnology in pharmaceuticals.

Ahire, *et al.*, 2018
Pharmaceutical professionals are closely examining solid lipid nanoparticles, the type of lipid nanoparticles under discussion, as a novel and clever method of administering nanomedicines.

Vital et al.,
the intravenous administration of NLCs containing paclitaxel resulted in reduced pain and reduced toxicity in patients with bone metastasis. Patients with advanced-stage cancer may be too debilitated to withstand the toxicity of other chemotherapy regimens. Thus, the association of drugs with nanostructures would reduce toxicity. Additionally, the intravenous administration of drugs has a rapid onset of action and high elimination rates from the body, necessitating frequent dosing. NLCs enable controlled drug release, maintaining drug concentration within the therapeutic window and reducing the frequency of administration.

Rudhrabatla et al.,
SLNs with melphalan, tristearin, soy lecithin, and poloxamer-188 were developed for intravenous administration using the hot homogenization technique to overcome the side effects of the chemotherapeutic agent and improve systemic circulation time. Pharmacokinetic studies were conducted in rats, and the circulation half-life increased by approximately four times with SLNs compared to the melphalan solution, in addition to having an encapsulation efficiency.

Akel et al.,
the efficiency of SLNs and polymeric nanoparticles for the nasal administration of meloxicam was compared. The findings demonstrated that SLNs had smaller particle sizes, better drug release profiles, and superior mucoadhesive properties compared to polymeric nanoparticles. This underscores the superior application potential of lipid nanostructures over other nanostructures in drug delivery systems.

Chen et al.'s study,
the plasma concentration of curcumin was increased by 6.4 times compared to isolated curcumin when it was

associated with NLCs made of tripalmitin and oleic acid (50/50%) in mice via intraperitoneal administration for brain cancer treatment. This association also enhanced the targeting of curcumin to the brain and tumor, increasing the drug's inhibition efficiency from 19.5% to 82.3%.

Dudhipala et al.,
the performances of SLNs and NLCs loaded with nisoldipine for oral administration were evaluated, as nisoldipine has low oral bioavailability, around 5%, due to first-pass metabolism. The NLCs were produced using oleic acid and trimyristin as the liquid and solid lipids, respectively, and poloxamer-188 and egg lecithin as surfactants.

3. DRUG PROFILE

Drug name: furosemide
IUPAC name: 4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid.
Molecular formula: $C_{12}H_{11}ClN_2O_5S$
Molecular weight: 330.745 g/mol
Structure:

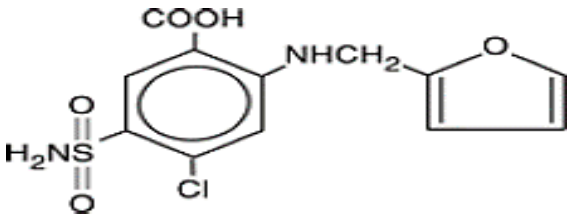

Fig-1: Chemical structural of Furosemide.

The diuretic furosemide, sometimes referred to as a water pill, is frequently used to treat edema, or fluid retention, brought on by the following illnesses.

- Congestive heart failure, a disorder in which the heart does not pump blood as efficiently as it should
- Cirrhosis and other liver diseases can cause ascites, or an accumulation of fluid in the abdomen.
- Nephrotic syndrome, a kidney illness that manifests as protein in the urine
- Hypertension, or elevated blood pressure, can also be treated with furosemide.

Your healthcare professional may also prescribe furosemide for other conditions.It accomplishes this by assisting the kidneys in eliminating water and electrolytes from the body, including sodium (salt).

4. METHODOLOGY

Furosemide was bought in Mumbai, India, from Yarrow Chem Products. The company Gattefosse in Mumbai, India, gave away free samples of Labrafil and Capryol PGMC. Indian company Central Drug House (P) Ltd provided soy lecithin and stearic acid. The cholesterol came from Specrochem Pvt. Ltd in Mumbai, India. Tween 80 came from the Chemdyes Corporation in Mumbai, India. Otto Chemika biochemika-reagents in Mumbai, India, is where we got Tween 20 and Tween 2130. DMSO came from Merck Specialties Pvt. Ltd., which is based in Mumbai, India. The rest of the drugs and reagents were all analytical grade came Somics lifesciences Pvt. Ltd. Bareilly Uttar Pradesh.

Preformulation

As part of preformulation studies, the drug's physical qualities, solubility, melting point, and compatibility with its excipients were looked into. We tested the drug's solubility by seeing how well it dissolved in three different buffer solutions: a pH 1.2 acid buffer, a pH 5.8 phosphate buffer, and a pH 6.8 phosphate buffer. It was also tested to see how well the medicine dissolved in various solvents, including water, acetone, alkali hydroxides, ethanol, methanol, DMSO, chloroform, and ether. The melting point of furosemide was found using both the open capillary tube method and DSC (Nkansah, *et al.*, 2013).

UV spectrometric assay of Furosemide

Two Furosemide standard solutions (10µg/ml) namely: a) Furosemide ethanolic solution, b)Furosemide in DMSO diluted with P^H 6.8 phosphate buffer were scanned UV spectrophotometrically over a range of 200-400 nm to determine the wavelength of maximum absorption (λmax).

The calibration curves were constructed over a concentration range of 2-10µg/ml, for standard solutions (a&b). The absorbance was recorded at their respective wavelengths and graph was plotted with concentration against absorbance.

Selection of Excipients

To choose the solid lipid, scientists looked at how well the drug dissolved in melted solid lipid. This could be done with the naked eye in normal lighting. Labrafil, cholesterol, and stearic acid were the fats used in this study. A carefully measured amount of medicine containing different lipids was cooked above the melting point of those lipids in a water bath. Test tubes were used to keep the temperature stable. We checked how well furosemide dissolved in each lipid by looking at them with normal lighting after the lipids had been melted (Saisri, *et al.*, 2021).

Analysing the Dissolvability of Different Liquid Surfactants and Lipids

Castor oil, oleic acid, and capryolpgmc were used as liquid lipids in this work. Tefen 20 and tefen 80 were used as surfactants. To test how well the drug mixed, too much of it was put into small tubes that already had two milliliters of certain oils and surfactants in them. A glass stick was used to mix the drug by hand with the right oil and surfactant. The jars were tightly closed and put in a rotary shaker where they were rotated continuously for 24 hours. For thirty minutes, the liquid lipids were spun at 3000 revolutions per minute. After the right amount of ethanol was added, the liquid that was left over after centrifugation was mixed with it. A UV

Spectrophotometer with a 274 nm range was used to test the substance's ability to dissolve (Poovi, *et al.,* 2018).

Compatibility Study

How well the drug and excipients work together is the most important factor in determining how stable a mixture is. Because of this, it is very important to find any possible chemical or physical reactions, since they can change how stable and bioavailable the drug is. FTIR was used to find out how Furosemide and the other ingredients in the mixture interacted during the compatibility tests, which were done at room temperature. The drug's FTIR spectrum was recorded in two situations: when it was given by itself and when it was mixed with labrafil m 2130 and capryol pgmc (Ahirrao, *et al.,* 2022).

Design of Experiment

A full-factorial method was used in this study to find the best way to make NLCs. The concentration of surfactant as a percentage, the ratio of solid to liquid lipids, and the ratio of total lipids to drugs were picked as the independent variables for optimization. There was a high level and a low level given to each part. For each variable, Table 1 shows both the real numbers and the encoded values. Using the factorial method, six different forms of furosemide NLCs (B1–B6) were created. The response measures measured the amount of drug released in a controlled lab setting after 7 hours and how well the drug was trapped. The trial version of Design expert statistical software was used to do the statistical study of the answers (Kim, *et al.,* 2022).

Preparation of furosemide loaded nanostructured lipid carrier (NLC)

NLCs were prepared by the solvent diffusion method. The lipid dispersion was composed of 355.4mg labrafil m 2130 cs and 82.7mg capryol pgmc, where lipids were melted at a temperature 5-10^0 above its melting point. Furosemide (200g) and liquid soya lecithin (0.5g) were dissolved in 5mL of DMSO and added to the lipid dispersion with heating at the temperature of 45-50^{0}C to form the lipid phase. Aqueous phase was prepared by dissolving tween 80 in 100mL of water. This aqueous solution was then stirred and heated to 45-50^{0}C. The lipid phase was slowly added dropwise into the aqueous phase at room temperature and mixed using high speed homogenizer at 8000 rpm for 5 minutes. The volume was made to 100ml and further treated using a probe sonicator for 20 minutes. The resultant suspensions were cooled and stored in room temperature. The same method was used to make both the NLC dispersion with drugs and the NLC dispersion without drugs (Ahire, *et al.,* 2023).

Characterization & comparison of optimized furosemide loaded NLC

Drug Content

In a 10 ml standard jar, 1 ml of a suspension of furosemide nanostructured lipid carriers was added. A little DMSO was added, and the mixture was mixed well. Then, pH 6.8 phosphate buffer was added until the right volume was reached. We took one milliliter of this solution and mixed it with fifty milliliters of pH 6.8 phosphate buffer by diluting them. A UV spectrophotometer was used to test the solution's absorbance at 279 nm. Then, the absorption of the similar blank solution was compared to it to find out how much drug was in it (Ahirrao, *et al.,* 2022).

Entrapment efficiency (E) and Drug loading (L_C)

Entrapment and how well drugs are loaded The NLC suspension was taken out by centrifugingthe Furosemide-loaded NLCs at 3000 rpm for 1.5 hours. This made 5ml of the suspension. One milliliter of the liquid that was left over after spinning was taken out and mixed with DMSO after it was diluted with pH 6.8 phosphate buffer. A UV spectrophotometer was then used to measure the drug content at a wavelength of 279 nm (Ali, *et al.,* 2018).

Entrapment efficiency was calculated using following equation.

$$E_e = [\frac{W_i - W_s}{W_i}] \times 100$$

$$L_c = [\frac{W_i - W_s}{(W_i - W_s) + W_l}] \times 100$$

Where,

W_i = weight of drug added initially
W_s = weight of drug in supernatant
W_l = weight of lipid mixture added

***In-Vitro* Drug Release**

In a lab setting, experiments were done to look into drug delivery using the dialysis method. One end of a dialysis membrane that had been soaked overnight was connected to a custom- made glass cylinder. This made sure that the preparation filled the whole inside circle of the tube. Each sample had 1 milliliter of blood put into the dialysis bag. It was 37 ± 5 ºC, and 100 ml of receptor media was used to mix the cylinder. Attached to the cylinder was a frame that made sure the membrane didn't touch the

media surface very much. An electric mixer set to 100 rpm was used to mix the receptor medium. The cellophane membrane breaks up the NLC and receptor media. When the time was right, 1 ml of the sample was taken out of the receiver section and replaced with fresh medium. The samples were weakened with phosphate buffer with a pH of 6.8. The amount of furosemide released was measured with a UV-visible spectrophotometer at a range of 279 nm.

Kinetics of drug release

In order to understand the mechanism of drug release, in vitro drug release data were treated to kinetic models such as Zero order, First order, Higuchi model and Korsmeyer- Peppa's model. Criteria for selecting the most appropriate model was based on best goodness of fit.

Stability of Furosemide loaded nanostructured lipid carrier

To investigate storage stability, the NLC formulations were stored in room temperature in the dark over a period of 60 days. Stability of the formulations was periodically monitored & evaluated the appearance, drug content, entrapment efficiency, drug loading capacity, in-vitro drug release during storage and compared with the initial formulations depicted.

Particle size and Polydispersity index (PDI)

Mean particle size (Z-average) and polydispersity index (PDI) of the prepared Furosemide loaded NLC sample and SLN sample were measured using Malvern Zetasizer version 7.01. The mean particle size was measured based on photon correlation spectroscopy technique that analyses the fluctuations in dynamic light scattering due to Brownian motion of the particles. The samples were diluted suitably with double distilled water to produce a suitable scattering intensity. All the measurements were done in triplicate, at a fixed scattering angle of 90˚ to the incident laser beam and at a temperature of 25ºC. Disposable polystyrene cuvette was used for placing the sample inside the instrument. Before putting the fresh sample, cuvette was rinsed using the sample to be measured for each experiment.

Zeta potential

Zeta potential, reflecting the electric charge on the particle surface, is a very useful way of evaluating the physical stability of any colloidal system. It was determined based on an electrophoretic light scattering technique. Zeta potential of the formulations were measured by using Malvern Zetasizer version 7.01. Zeta potential measurements were carried out using zeta dip cell, by applying a field strength of 20V/cm at 25 °C after appropriate dilution of samples with double distilled water. All the measurements were done in triplicate.

Scanning Electron Microscopy (SEM)

The SEM analysis of the samples were performed to investigate the surface morphology and homogeneity of the particles in the formulations. The samples were examined morphologically by scanning electron microscope (JSM- 6490LV, JEOL) with 15kV accelerating voltage. Samples were prepared by placing a small drop of dispersion onto an aluminium specimen stub using double-sided adhesive tape , dried and sputter coated with gold prior to imaging.

A Nanostructured Lipid Carrier Loaded with Furosemide: Stability and Performance

The best NLC mixtures were kept at room temperature and out of the light for 60 days to see how stable they were during storage. The study looked at the materials' physical features, drug content, how well they trapped drugs, how much they could hold, and how the drugs released in vitro over time. The original formulations and the changed formulations were both tested forstability.

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