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Review Article

Antibacterial - Sulphamethoxazole Nanoemulsion: A Systematic Review

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Abstract

Nanoemulsion is submicron-sized colloidal particulate phase that is thermodynamically and kinetically stable isotropic dispersions which is made up of two immiscible liquids- water and oil. It is stabilized by an interfacial film made by efficient surfactant and co-surfactant to form a homogenous phase. Sulfamethoxazole is a 1, 2-oxazole moiety with a methyl group at the position 5 and a 4-aminobenzenesulfonamido group at the 3rd position. It functions as an antibacterial, anti-microbial etc. This systematic review emphasizes on nanoemulsion's preparation methods, merits and demerits and uses as incorporated anti-bacterial agent Sulfamethoxazole. Sulfamethoxazole relates to sulfonamide category that blocks the folate synthesis in microbial organisms i.e., bacteria. Sulfamethoxazole accomplishes this by blocking the action of enzyme dihydropteroate synthase which antagonizes p-aminobenzoic acid (PABA) during the formation of dihydrofolate. It includes various methods to prepare nanoemulsion i.e., microfludization, solvent evaporation etc. Nanoemulsion has multiples of advantages in terms of better skin penetration power, non-irritant to mouth etc over other dosage forms. It is suitable for topical, oral and parenteral use. This study concludes, anyone method can be chosen from different techniques to formulate sulfamethoxazole nanoemulsion and can be used in numerous treatments. It has better skin permeability power that makes it excellent.

Keywords: Nanoemulsion; Sulfamethoxazole; Antibacterial; Plasticizer; Review

Introduction

Nanoemulsion is submicron-sized colloidal particulate phase that is thermodynamically and kinetically stable isotropic dispersions which is made up of two immiscible liquids-water and oil. It is stabilized by an interfacial film made by efficient surfactant and co-surfactant to form a homogenous phase. Surfactants with different properties (ionic or non-ionic) have been utilized in these nanoemulsions. Nonionic surfactants, anionic surfactants, cationic surfactants and zwitterions surfactants were the most extensively utilized among. Oil-in-water (O/W) emulsions with typical droplet diameters ranges 50-1000 nm were the first nanoemulsions used [1].

Sulfamethoxazole is a 1, 2-oxazole moiety with a methyl group at the position 5 and a 4-aminobenzenesulfonamido group at the 3rd position. It functions as an antibacterial, anti-microbial etc. It is a sulfonamide antibiotic- a member of isoxazole family and a substituted aniline. It is made of a sulfanilamide.

IUPAC name: 4-Amino-N-(5-methyl-1,2-oxazol-3-yl) benzenesulfonamide

M. f.- $C_{10}H_{11}N_3O_3S$

M. w.- 253.28g/mol.

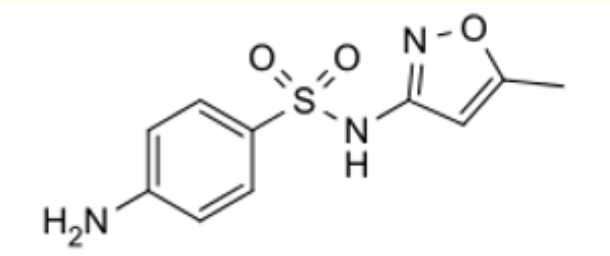

Figure 1: Structure of Sulfamethoxazole.

MOA of sulfamethoxazole

Sulfamethoxazole relates to sulfonamide category that blocks the folate synthesis in microbial organisms i.e., bacteria. Sulfamethoxazole accomplishes this by blocking the action of enzyme dihydropteroate synthase which antagonizes p-aminobenzoic acid (PABA) during the formation of dihydrofolate [2]. Sulfamethoxazole is a CYP2C9 inhibitor that is metabolised by the CYP450 system in the liver. It has a half-life of 6-12h which increases up to 20-50 hours with kidney failure.

Methods of preparation

It includes various methods to prepare nanoemulsion i.e., micro-fludization, solvent evaporation etc. [3-6].

Solvent evaporation method

Drug solution is developed and emulsified into another liquid after which the solvent is evaporated and thus drug precipitation occurs. In order to control crystal formation and particle aggregation a high-speed stirrer is used. Solvent evaporation approach is very similar to hydrogel-A method. The main difference b/w hydrogel-A method and solvent evaporation is that the drug mixture is miscible with drug anti-solvent.

Ultrasonication

A premixed dispersion is agitated at a 20hz in this approach, which reduces the size of the particles to nanodroplets. The emulsion is subsequently driven through a high shear area, resulting in droplets of uniform size. A water jacket is used to regulate the temperature in this technology. This method is utilised when a droplet size of less than 0.2 is desired [7].

Microfluidization

A microfluidizer was utilised in this method, which uses large positive displacement pump (500-20000psi) to force the material through an interaction chamber containing stainless steel micro-channels on the impingement region, resulting in the formation of very small sub-micron particles. The mixture is cycled in the microfluidizer until the required particle size is achieved. The final product is filtered to separate the smaller from the larger droplets, resulting in a homogeneous nanoemulsion. Uluata., *et al*. used a microfluidizer to make octadecane O/W nanoemulsions and found that when the number of runs and homogenization pressure increased, the droplet size shrank [8].

Spontaneous emulsification

Three steps of nanoemulsion preparation were required for this procedure. The first step entailed making an organic solution with oil and a lipid soluble surfactant in a water miscible solvent with a hydrophilic surfactant, then magnetically swirling this organic layer into the aqueous phase. In the third stage, the organic solvent was removed by evaporation. Sugumar., *et al*. used spontaneous emulsification to create a stable eucalyptus oil nanoemulsion, with mean droplet sizes ranging from 50 to 100 nm [9].

Brute force method

For dispersing the oil droplets into the micro range, this method involves using physical force. High pressure homogenizers, high speed mixers, small pore membranes, and high frequency ultrasonic devices have all been used in the creation of nanomeulsions. Nanoemulsion features like as small size, optical transparency, and high kinetic stability are influenced by processing variables such as emulsification time, amount of mixing, energy input, and emulsifying path, among others [10].

Persuasion method

The persuasive method of nanoemulsion preparation does not use any external force; instead, fine dispersions are formed when phase transitions occur by changing temperature or composition while keeping other parameters stable [11].

Persuasion methods can be broadly classified as-

- Phase-I transition from near-optimal state by single variable change, which entails changing one formulation variable i.e., temperature or salinity to near-optimal value.
- Phase transition through near-optimal state by multiple variable changes i.e. changing various variables.

- Catastrophic inversion refers inversion of low internal phase emulsion into an exterior phase.
- Liquid crystal formation stabilized phase transition which involves nanodroplets stabilization.

Estimation parameters

Stability studies

Stability studies are done to determine drug stability in the presence of various environmental conditions i.e., temperature, humidity and light. Nanoemulsion stability tests are performed after storing the formulation in a dispersed and freeze-dried state up to 2 years according to ICH Guidelines. Storage conditions were used as: ambient (252°/605% RH), refrigerated (53°), and freeze (–205°). The required amount of nanoemulsion is kept in glass vials that are firmly sealed. Samples are taken at predetermined intervals and analysed for particle size, loading, and EE, as well as the *in vitro* drug release profile [9].

Percent transmittance

Using a UV spectrophotometer set to a specific wavelength and distilled water as blank, the % transmittance of a fomulated nanoemulsion is determined. When the % transmittance of a nanoemulsion is greater than 99% it is kept in as transparent nature [31]. Harika., *et al*. observed a % transmittance for a nanoemulsion containing amphotericin-B more than 97% [12].

Viscosity measurements

The physicochemical characterisation of nanoemulsions relies heavily on the determination of viscosity. Viscosity is measured with a variety of instruments, including an Ostwald viscometer, Hoeppler falling ball viscometer, Stormer viscometer, Brookfield viscometer and Ferranti-Shirley viscometer. Brookfield is the preferably used viscometer for measuring nanoemulsion viscosity among all other viscometers. The viscosities determine whether the system is O/W or W/O type emulsion. Low viscosity indicates O/W while high viscosity indicates water in oil emulsion [13].

Interfacial tension

Interfacial tension can be used to investigate the formation and properties of nanoemulsions. The presence of a surfactant layer or middle-phase nanoemulsion with balanced aqueous and oil phases results in extremely low interfacial tension. To determine ultralow interfacial tension, the spinning-drop apparatus is utilised. Interfacial tensions are determined by spinning a low-density phase drop inside a cylindrical capillary filled with high-density component and analysing the drop's shape (Bhosale., *et al.* 2014).

Estimation of pH and osmolarity

The pH of a nanoemulsion is measured with a pH metre, and the osmolarity of the emulsion is determined with a microosmometer using the freezing point method. This is done by transferring 100 l of nanoemulsion into a microtube and taking measurements [14].

In-vitro drug release study

In vitro drug release studies aid in predicting medication formulation effectiveness *in vivo*. A USP dissolving equipment is used to determine a drug's *in vitro* release rate. The medication equivalent to 10 mg was disseminated in nanoemulsion or dried nanoparticles, which were then put into dialysis layer and kept in a flask containing buffer. This experiment is conducted at 370.5°F at a stirring speed of 50rpm. At regular intervals, the eq. volume of sample is removed and replaced with fresh dissolving medium. The absorbance of the sample is measured by spectrophotometer at a certain wavelength after the samples have been diluted appropriately. The percent drug release at various time intervals is calculated using the absorbance of the collected sample [12].

Particle size and polydispersity index determination

These factors are investigated using Malvern Zetasizer and Photon Correlation Spectroscopy (PCS) which measures the variation in light scattering caused by Brownian motion of particles over-time. PCS is based on the idea that particles with a smaller size travel faster than particles with a larger size. The laser beam is diffracted in solution by sub-micron particles. The estimated photoelectron time correlation function produces a histogram of the line width distribution, which can be linked to particle size. To measure particle size, a weighed amount of formulation is dispersed in double-distilled water to provide a homogeneous dispersion which must be utilised immediately for particle size and PDI measurements (Baboota., *et al*. 2007).

Zeta potential estimation

The zeta potential is being used to determine the surface charge of particles while they are submerged in liquid. The physicochemical parameters of the drug, polymer, vehicle, the presence of electrolytes and their adsorption determine the zeta

potential. It is measured with Malvern Zetasizer equipment. The zeta potential of nanoemulsion is determined by diluting it and calculating it based on the electrophoretic mobility of oil droplets [15].

Advantages

Nanoemulsions have several advantages over other dosage forms (Bhosale., *et al*. 2014) that includes as below -

- Nanoemulsion has a greater surface area and free energy that make them more efficient to transport.
- They don't show creaming, flocculation, coalescence and sedimentation that are inherent in the process.
- It comes in a variety of forms, including foams, creams, liquids, and sprays.
- They are non-poisonous and non-irritant.
- If it contains biocompatible surfactants then it can be taken by mouth.
- It is better for human and veterinary uses.
- It improves the uptake of hydrophilic substances in cell cultures.
- It can be used to replace liposomes, vesicles and lamellar liquid crystalline phases.
- Nanoemulsions can penetrate the rough skin surface due to their small size- improves active penetration.
- It is the first step in the production of nanocapsules and nanospheres facilitating nanoprecipitation and interfacial poly-condensation.

Demerits [16]

- Stabilization necessitates a high concentration of surfactants/ cosurfactants.
- Temperature and pH have an impact on its stability.
- The Oswald ripening effect can induce instability.

Applications

Nanoemulsions are frequently used for following mentioned delivery routes (Eyler and Shvets, 2019) -

- Parenteral delivery
- Oral
- Topical

Conclusion

Nanoemulsions have enormous promise as a medicine delivery method that might be fully realised if they are properly utilised. With such a precise delivery system, quality assurance and quality control are critical, so the evaluation tests must be carried out thoroughly.

This study concludes, anyone method can be chosen from different techniques to formulate sulfamethoxazole nanoemulsion and can be used in numerous treatments. It has better skin permeability power that makes it excellent [17].

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Nil.

Conflict of Interest

None.

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