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REVIEW ON COLON TARGET NANOSTRUCTURED LIPID CARRIERS'S FORMULATION

Pankaj P. Borase*, Sanjay Kshirsagar, Jaydeep Dusane, Priya Thakare, Vrushali Mogal

MET's B.K.C. College of Pharmacy, Adgaon, Nashik-422003.

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For Correspondence:

Pankaj P. Borase

MET's B.K.C. College of Pharmacy, Adgaon, Nashik-422003

E-mail:

pankajpborase10@gmail.com

ABSTRACT

Inflammatory bowel disease (IBD) ulcerative colitis (UC) & Crohn's disease (CD) if not treated leads to colon cancer. NLC's have shown potential for specific accumulation in inflamed tissue. The objective was to optimize NLC's formulation which will release drug specifically at targeted site in colon. Different analytical methods were mentioned for the formulation process of nano structured lipid carriers. Nano-sized particles range from nano-liposomes, to dendrimers, to self nano-emulsifying systems, to quantum dots, to carbon-based nanoparticles like nano-tubes and nano- fibers. The present study aimed to evaluate influences of mixed lipids and their proportions on formation and properties of nanostructured lipid carriers(NLCs).

INTRODUCTION [04, 06, 13, 23, 33]

The oral aspect is considered to be most convenient for administration of drugs to Patients. It is a serious drawback in conditions when localized delivery of drugs into the colon is required as drugs needs to be protected from the hostile environment of upper GIT. Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowel diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, and colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs. Specific drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, crohn's disease and systemic delivery of protein and peptide drugs.The colon specific drug delivery system (CSDDS) should be capable of protecting the drug en route to the colon. The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in body so that the desired drug concentration can be achieved promptly and then maintained. Targeted drug delivery implies selective and effective localization of drug into the target at therapeutic concentrations with limited access to non-target sites. A targeted drug delivery system is preferred in drugs having instability, low solubility and short half-life, large volume of distribution, poor absorption, low specificity and low therapeutic index. Targeted drug delivery may provide maximum therapeutic activity by preventing drug degradation or inactivation during transit to the target site. Solids intended for targeted drug release into the lower gastrointestinal GI tract are beneficial for the localized treatment of several colonic diseases and conditions, mainly inflammatory bowel diseases, irritable bowel syndrome and colon cancer.

COLON TARGETED DRUG DELIVERY SYSTEMS ARE MAINLY USED FOR [9, 20, 32]

(1) Drugs used for local effects in colon inflammatory bowel disease like ulcerative colitis and Cohn's disease. eg. 5-amino salicylic acid, Sulphasalazine, hydrocortisone acetate, 5- fluorouracil.

(2) Macro molecule structures peptide and proteins for systemic effects, because colonic environments are less hostile to these drugs. e.g.: calcitonin, interleukin, interferon, insulin, growth hormone, erythropotien, analgesic peptides oral vaccines, contraceptives, peptides etc. (3) Drugs which are poorly absorbed orally, as colon has longer residence time and is highly responsive to agents that enhance the absorption of poorly absorbable drugs.

(4) For the avoidance of hepatic first pass metabolism of drugs.

(5) Where the delay in systemic absorption is therapeutically desirable, especially in disease susceptible to diurnal variation.

(6) Some orally administered drugs which exhibit poor uptake in upper gastrointestinal to show enzymatic action. e.g.: Metoprolol, Nifedipine, Isosorbide, Theophylline, Diclofenac, and Ibuprofen.

ADVANTAGES OF COLON TARGETING DRUG DELIVERY SYSTEM: - [1, 6, 9]

Colon is an ideal site for the delivery of agents to cure the local diseases of the colon. Local treatment has the advantage of requiring smaller drug quantities. Reduces dosage frequency. Hence, lower cost of expensive drugs. Possibly leading to a reduced incidence of side effects and drug interactions. The colon is an attractive site where poorly absorbed drug molecules may have an improved bioavailability. Reduce gastric irritation caused by many drugs (e.g. NSAIDS). Bypass initial first pass metabolism. Extended daytime or night time activity. Improve patient compliance. Targeted drug delivery system. It has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. It has low hostile environment, less peptidase activity so peptides, oral vaccines, insulin, growth hormones, can be given through this route.

NANOSTRUCTURED LIPID CARRIERS (NLC'S):- [14, 27]

A new generation of lipid carriers (NLCs) consisting of a lipid matrix blended with oil and surfactant with a special nanostructure. Developed to overcome drug expulsion due to highly ordered crystalline lipid matrices formation over a period of time. Incorporation of liquid lipid help to increase drug loading in the formulation of NLC's. These NLCs can be produced by high-pressure homogenization and the process can be modified to yield lipid particle dispersions with solid contents from 30–80%. Carrier system. However, the NLC system minimizes or avoids some potential problems associated with SLN. These are produced from blend of solid and liquid lipids, but particles are in solid state at body temperature. Lipids are versatile molecules that may form differently structured solid matrices, such as the NLC and the lipid drug conjugate nanoparticles that have been created to improve drug loading capacity. Production of NLC is based on solidified emulsion technologies. NLC can present an insufficient loading due to drug expulsion polymorphic transition during storage, particularly if the lipid matrix consists of similar molecules. Drug release from NLC occurs by diffusion and simultaneously by lipid particle degradation in the body. They have been utilized in the delivery of anti-inflammatory compounds.

AIMS OF NANOSTRUCTURED LIPID CARRIERS:- [2,15]

1. Possibility of controlled drug release and drug targeting.

2. Increased drug stability.
3. High drug payload.
4. Incorporation of lipophilic and hydrophilic drugs.
5. No bio toxicity of the carrier.
6. Increase permeability.
7. No problems with respect to large scale production and sterilization.
8. Increased Bioavailability of entrapped bioactive compounds

ADVANTAGES OF NLC'S [10, 13]

1. Use of biodegradable physiological lipids which decreases the danger of acute and chronic toxicity and avoidance of organic solvents in production methods high drug loading capacity,
2. Improved bioavailability of poorly water soluble molecules
3. Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application
4. Possibility of scaling up.
5. Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment
6. NLC's have better stability compared to liposomes
7. Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
8. High concentration of functional compound achieved.
9. Lyophilization possible.

LIMITATIONS OF COLON TARGETING DRUG DELIVERY SYSTEM: -[7, 36]

1. Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
2. Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.
3. Drug should be in solution form before absorption and rate limiting for poor soluble drugs.
4. Incomplete release of drug.
5. The resident microflora could also affect colonic performance via metabolic degradation of the drug.
6. Multiple manufacturing steps.
7. An important limitation of the pH sensitive coating technique is the uncertainty of the location and environment in which the coating may start to dissolve.
8. Limitations of prodrug approach are that it is not very versatile approach as its formulation depends upon the functional group available on the drug moiety for chemical linkage.

METHODS OF PREPARATION OF NLC'S:- [3, 11,16, 25, 29]

1) High Shear Homogenization: [3]

High shear homogenization technique was initially used for the solid lipid nanodispersions . HSH method is used to produce NLC's by melt emulsification. Homogenization is a fluid mechanical process that involves the subdivision of droplets or particles into micro- or nanosize to create a stable emulsion or dispersion. High pressure homogenizers push a liquid with high pressure (100–2000 bar) through a narrow gap (in the range of few microns) lipids used in this study include trimyristin, tripalmitin, a mixture of mono, di and triglycerides (Witepsol W35, Witepsol H35) with glyceryl behenate and polaxomer 188 used as stearic stabilizers (0.5% w/w). HPH method involves 2 processing procedures, a. Hot homogenization, b. Cold homogenization

a. Hot Homogenization: [28]

This is applied to lipophilic and insoluble drugs. This technique does not suit for hydrophilic drugs into NLCs because of higher partition of drug in water. 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. Usually, lower particle sizes are obtained at higher processing temperatures because of lowered viscosity of the lipid phase (Lander,2000), although this might also accelerate the drug and carrier degradation. Better products are obtained after several passes through the high-pressure homogenizer (HPH), typically 3-5 passes. High pressure processing always increases the temperature of the sample (approximately 10° at 500 bars). In most cases, 3-5 homogenization cycles at 500-1500 bar are sufficient. Increasing the homogenization leads to an increase of the particlesize due to particle coalescence, this occurs because of the high kinetic energy of the particles.

b. Cold Homogenization: [39]

Cold homogenization technique is used for hydrophilic drugs. If the drugs have low aqueous solubility in the melted lipid, then surfactants can be used for solubilization of the drug. The solid particles are dispersed in an aqueous surfactant solution at a temperature below the lipid melting point, forming a 'pre-suspension'. The presuspension is then subjected to HPH below the lipid melting temperature to reduce the solid particle size. The advantage of this method is avoidance of or minimizes the melting process of lipid and hence it is suitable for thermo sensitive and thermo labile drugs relative to hot HPH, Cold HPH generally produces larger mean particle sizes and broader particle size distributions.

2) Solvent Evaporation Method:[35]

In this method, the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as the solvent for dissolving or dispersing the drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent like gelatin, poly(vinyl alcohol), polysorbate-80, poloxamer-188, sodium dodecyl sulfate etc. to form either oil in water i.e. o/w emulsion (for encapsulation of hydrophobic drugs) or water in- oil i.e. w/o nanoemulsion (for encapsulation of hydrophilic drugs). After formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature or under reduced pressure or by continuous stirring formed nanoparticles can be concentrated by filtration, centrifugation or lyophilization. Emulsification is done by high-speed homogenization or sonication to produce small particles. Particle size was found to be influenced by the type and concentrations of stabilizer, homogenizer speed and polymer concentration. Most frequently used polymers are PLA, PLGA, ethyl cellulose, cellulose acetate phthalate, poly-ε-caprolactone and poly (h-hydroxybutyrate). Drugs encapsulated were Albumin, Texanus toxoid, Loperamide, Testosterone, Prazinquante, Cyclosporin A, Nucleic acid and Indomethacin.

3) Microemulsion Based Method:[17, 24]

NLC's can be produced by micro emulsification method of molten lipids as the internal phase, and the subsequent dispersion of the microemulsion in an aqueous medium under mechanical stirring. They are made by stirring an optically transparent mixture at 65-70oc which is typically composed of a low melting fatty acid (stearic acid), an emulsifier (polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate),co-emulsifiers (Sodium mono octyl phosphate) and water. The hot microemulsion is dispersed in cold water under stirring. Typical volume ratios of the hot microemulsion to cold water are in the range of 1:25 to 1:50. Nanoparticles were produced only with solvents which distribute very rapidly into the aqueous phase (acetone), while larger particle sizes were obtained with more lipophilic solvents. The dilution process is critically determined by the composition of the microemulsion. According to the literature the droplet structure is already contained in the microemulsion and therefore, no energy is required to achieve submicron particle size. The hydrophilic co-solvents of the microemulsion might play similar role in the formation of lipid nanoparticles as the acetone for the formation of polymer nanoparticles.

4) Solvent displacement and interfacial deposition:[18, 26]

Methods based on spontaneous emulsification of the organic internal phase containing the dissolved polymer into the aqueous external phase. Solvent displacement forms nanospheres or nanocapsules, whereas interfacial deposition forms only nanocapsules. Solvent displacement involves the precipitation of a preformed polymer from an organic solution and the diffusion of the organic solvent in the aqueous medium in the presence or absence of a surfactant. The polymer is dissolved in a water-miscible solvent of intermediate polarity, leading to the precipitation of nanospheres. This phase is injected into a stirred aqueous solution containing a stabilizer as a surfactant. Polymer deposition on the interface between the water and the organic solvent, caused by fast diffusion of the solvent, leads to the instantaneous formation of a colloidal suspension. Solvent and the nonsolvent of the polymer must be mutually miscible. The progressive addition of the polymer solution to the non-solvent generally leads to the formation of nanospheres close to 200 nm in size.

5) Multiple Micro emulsification:[12, 23]

Multiple micro emulsification is also used for production of NLC's. For the preparation of hydrophilic loaded NLC's, a novel method based on solvent emulsification-evaporation has been used (Cortesi,2002). Here the drug is encapsulated with a stabilizer to prevent drug partitioning to external water phase of w/o/w double emulsion. But it has inherent instabilities due to coalescence of the internal aqueous droplets with in the oil phase, coalescence of droplets and rupture of the oil layer on the surface of the internal droplets.

6) Nano precipitation:[5, 31]

This method is also called as solvent displacement method. Nano precipitation method is based on interfacial deposition of a polymer after displacement of a semi polar solvent miscible with water from a lipophilic solution. It involves addition of drug and polymer in water-miscible organic solvent (acetone) into large amount of nonsolvent, usually water containing surfactant.Nano precipitation occurs by a rapid desolvation of the polymer when the polymer solution is added to the non-solvent. As soon as the polymer-containing solvent has diffused into the dispersing medium, the polymer precipitates, involving immediate drug entrapment. Rapid diffusion of the solvent into aqueous phase results in a decrease in the interfacial tension between the two phases, which increases the surface area and leads to formation of small droplets of organic solvent even without any mechanical stirring, extended shearing/stirring rates, sonication

or very high temperatures. A problem associated with this technology is that the formed nanoparticles need to be stabilized to avoid growth in micrometre crystals and it provides poor entrapment efficiency for water-soluble drugs. Most commonly used method for the preparation of PLGA nanoparticles.

7) Desolvation Technique:[22, 38]

In desolvation process, nanoparticles are obtained by an intermittent or continuous drop-wise addition of ethanol/acetone to an aqueous solution of albumin (pH5.5) under continuous stirring until the solution became turbid. During the addition of ethanol/acetone into the solution, albumin is phase separated due to its diminished water-solubility. The morphologically formed albumin particles being not sufficiently stabilized could consequently redissolve again after dispersion with water. Therefore, co-acervates were hardened by cross-linking with glutaraldehyde where the amino moieties in lysine residues and arginine moieties in guanidino side chains of albumin are solidified by a condensation reaction with the aldehyde group of glutaraldehyde. Fig. 4 illustrates steps of nanoparticles preparation by desolvation method.

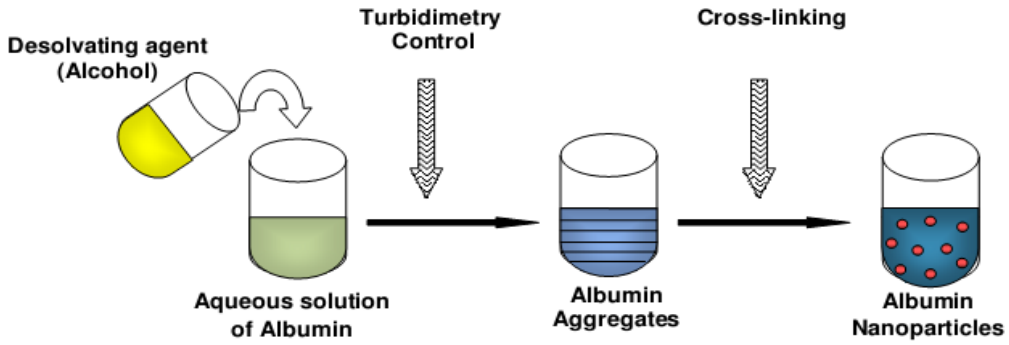

Fig.1 Preparation of albumin NPs by desolvation method

Co-Acervation Or Ionic Gelation Method: [19]

This method is commonly used for the preparation of chitosan, gelatine and sodium alginate nanoparticles. Formation of nanoparticles is based on ionic interaction between oppositely charged macromolecules. The method involves a mixture of two aqueous phases, in which one is the polymer and the other is a polyanion sodium tripolyphosphate. In this method, cationic group of polymer interacts with polyanion tripolyphosphate to form coacervates with a size in the range of nanometre. Coacervates are formed as a result of electrostatic interaction between two aqueous phases, whereas ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction conditions at room temperature.

8) Salting Out: [20, 37]

Salting-out method is based on the separation of a water miscible solvent from aqueous solution via a salting-out effect. This method involves an emulsification step by avoiding the use of surfactants and chlorinated solvents. It is based on the phenomenon in which solubility of a non-electrolyte in water is decreased upon addition of an electrolyte. The preparation method consists of an electrolyte-saturated aqueous solution (usually magnesium chloride hex hydrate, sodium chloride, magnesium acetate) containing PVA as a viscosity increasing and stabilizing agent to obtain viscous gel. The organic phase composed of the polymer and the drug dissolved in acetone under continuous mechanical stirring at room tem0perature.Most commonly acetone is used as solvent because of its solubilizing properties and easily removed from aqueous solution upon salting-out with electrolytes. After addition of viscous gel into organic phase under continuous stirring causes salting out of the organic solvent, inducing formation of nanoparticles. Finally both solvent and electrolyte are eliminated by cross-flow filtration. This method is widely used in the pharmaceutical industry because its purity, high yield, speed and simplicity of the operation. The thermal treatment does not require at any stage of sample processing and therefore it may be especially useful for the incorporation of thermo labile drugs.

9) Spray Drying Technique: [21]

This is one of the preparation method of nanoparticles and usually used for drying of solutions and suspensions. The method is based on drying of atomized droplets in a stream of hot air and can be applied for formulation of nanoparticles. In this method, polymer is first dissolved in aqueous solvent; drug is then dissolved or dispersed in the solution along with a suitable cross-linking agent. This solution or dispersion is then atomized in a stream of hot air. Atomization leads to the formation of small droplets from which solvent evaporates instantaneously leading to the formation of free flowing particles. Various process parameters like size of nozzle, spray flow rate, atomization pressure, inlet air temperature, compressed spray air flow and extent of cross linking are required to be carefully controlled in order to get the desired size of particles. Higher encapsulation efficiency for hydrophilic drugs can be achieved with the spray-drying method using aqueous solutions. When spray drying method compared with other methods, it provides a relatively rapid and convenient production technique that is easy to scale up and involves mild processing conditions.

10) Polymerization Method:[8]

In polymerization methods, monomers are polymerized with subsequent entrapment of drug particles to form nanoparticles or adsorbed on their surface in an aqueous solution. Drug is incorporated either by dissolving in the polymerization medium or by adsorption onto the nanoparticles after completion of polymerization. The nanoparticles suspension is then purified to remove traces of various free stabilizers and surfactants employed for polymerization by ultracentrifugation and re-suspending the particles in an isotonic surfactant-free medium. Nano capsules formation and their particle size depend on the concentration of the surfactants and stabilizers used.

CONCLUSION

Different studies of are demonstrated that there is higher drug deposition in colonic inflammatory area from the NLC's formulation. Thus NLC's formulation is a promising tool for releasing the drug specifically in inflammatory area for effective treatment of IBD, similar formulation with anticancer drug can be used for colonic cancer.

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