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REVIEW ON FORMULATION & EVALUATION METHODS OF INSITU SOLID LIPID NANOPARTICLES GEL DOSAGE FORMS

Erla Naga Chandrika[1]* and Chennu M. M. Prasada Rao[2]

[1]Research Scholar, School of Pharmacy, Raffles University, Neemrana- 301705.
[2]Professor, School of Pharmacy, Raffles University, Neemrana- 301705.

***Corresponding Author: Dr. Erla Naga Chandrika**

Research Scholar, School of Pharmacy, Raffles University, Neemrana- 301705.

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ABSTRACT

This review discusses contemporary research on solid lipid nanoparticles (SLNs) for encapsulation and delivery of active and antioxidant compounds, encompassing various synthesis techniques and applications across multiple fields. The development of SLNs begins with the choice of solid lipid matrices, emulsifiers/surfactants, and types of active compounds or antioxidants, alongside synthesis methods and their respective applications. The lipid type influences crystal morphology, active compound release kinetics, and encapsulation efficacy. Various fabrication methods for SLNs can encapsulate both hydrophilic and hydrophobic antioxidants, each possessing distinct advantages and drawbacks. The design of fabrication, which entails selecting lipid matrices, surfactants, and fabrication techniques, critically influences SLN characteristics. High-shear homogenization paired with ultrasonication emerges as the preferred method due to its simplicity and efficacy. A well-conceived fabrication design yields SLNs that effectively stabilize active compounds and antioxidants, rendering them suitable for diverse applications.

KEYWORD:- *Insitu* Gels, Solid Nano Particles, Solvent evaporation method, High Shier homogenisation.

INTRODUCTION

Poorly soluble drugs are common in pharmaceuticals, resulting in low bioavailability. The prevalence of low solubility drug candidates in drug discovery has risen, with 70% of new candidates exhibiting poor aqueous solubility recently. These compounds present considerable difficulties for formulation scientists in enhancing bioavailability and establishing targeted drug delivery systems. Delivering drugs to the brain is particularly challenging due to the blood-brain barrier (BBB) and brain-cerebrospinal fluid barrier (BCSFB).[1]

1.4.3.1 Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are biocompatible colloidal dispersions measuring 100–500 nm, well tolerated in vivo. These nanoparticles are advantageous due to lower toxicity, production feasibility, and scalability compared to other formulations. SLNs have garnered significant interest due to their superior qualities over alternative colloidal drug delivery systems.

Potential Advantages of SLN

Potential advantages of solid lipid nanoparticles include

- Biocompatibility with physiological lipids.
- Increased permeability and enhanced bioavailability due to small size and lipid content.
- Enhanced stability and protection for encapsulated drugs compared to liposomes or micelles.
- Capability for passive or targeted delivery, including CNS.
- High capacity for drug loading.
- Versatility for various administration routes.
- Ability for controlled drug release.
- Reduced variability in release kinetics.
- Facilitation of large-scale production and sterilization.

Formulation methods for solid lipid nano particles

Numerous techniques exist for the synthesis and fabrication of SLNs, such as high-speed homogenization, ultrasonication, high-pressure homogenization at varying temperatures, solvent evaporation, supercritical fluid extraction of emulsions (SFEE), multiple emulsions, and spray-drying.[2]

High-Shear Homogenization/ High-Speed Homogenization and Ultrasonication[3-4]

High-shear homogenization and ultrasonication are commonly utilized techniques for fabricating solid lipid nanoparticles (SLNs). Initially, high-shear

homogenization produced solid lipid nanodispersions with micro-sized particles. Increased stirring speed does not markedly reduce particle size but raises the polydispersity index slightly. Combining this method with ultrasonication utilizes cavitation energy to achieve nano-sized dispersion particles. This technique offers several advantages, including scalability, solvent-free operation, enhanced product stability, and improved drug loading. Typically, high-shear homogenization is performed at elevated temperatures, referred to as the hot homogenization technique. A schematic of the ultrasonication and high-speed homogenization methods is depicted in Figure 3.

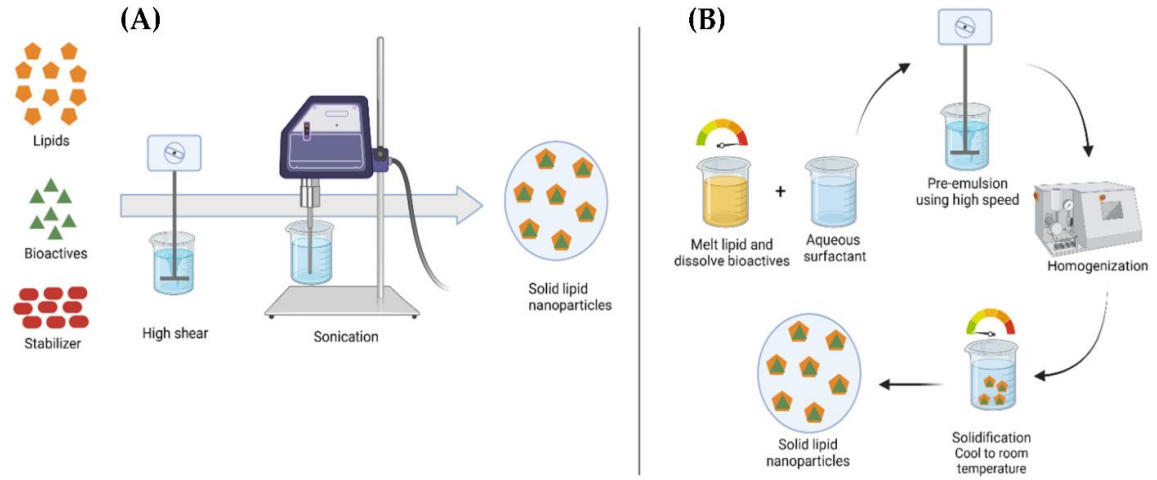

Figure 3: Schematic representation of ultrasonication method (A) and hot homogenization technique (B).[3]

The ultrasonication and high-speed homogenization methods are effective for SLN fabrication. The process begins by mixing active compounds into melted lipid. Subsequently, the heated liquid phase is added and emulsified via ultrasonication or high-speed stirring. Alternatively, the water phase can be dripped onto the lipid phase during high-speed stirring to obtain an ultrasonicated pre-emulsion. The production temperature must exceed the lipid's melting point by at least 5 °C to prevent recrystallization. The nanoemulsion is filtered through a membrane to eliminate impurities before storing the SLNs at 4 °C. Stability enhancement can be achieved through lyophilization, producing SLN powder with added cryoprotectants like trehalose or mannitol.

This fabrication method is straightforward, requiring low surfactant concentrations and accessible laboratory equipment. It is commonly utilized for SLN coatings and drug delivery systems. However, it may result in non-uniform particle size distribution, impacting storage stability, and raises the risk of metal contamination from ultrasonication. The ultrasonication method has been refined to produce stable formulations, where high-temperature combinations with homogenization yield smaller SLN particles by reducing nanoparticle surface tension. Optimal nanoparticle production occurs when ultrasonication is paired with high-shear homogenization, thus addressing its inherent weaknesses.

The lipids used in ultrasonication and high-speed homogenization comprise glyceryl behenate, tri-behenate, GMS, tristearin glyceride, and stearic acid. Concurrently, the applicable surfactants include Poloxamer 188, lecithin, and Tween. The synthesis of SLNs via ultrasonication commences with the solubilization of the active compound in melted lipid, followed by heating the mixture to 10 °C above the lipid's melting point. Subsequently, the lipid-active compound mixture is combined with preheated surfactants and cosurfactants, reheated, and stirred until a pre-emulsion is achieved.

The resultant pre-emulsion is then subjected to emulsification using an ultrasonicator at a stress efficiency of 35–40% for 3–5 minutes. Prior to ultrasonication, the methods may be combined, as indicated by Woo et al., wherein homogenization can precede ultrasonication on the lipid-surfactant mixture. The homogenization technique may involve high-shear or high-speed homogenization, with pre-emulsion treatment conducted at 13,000 rpm for 4 minutes or 10,000 rpm using a high-speed homogenizer.[4]

Post-ultrasonication, the emulsion's elevated temperature necessitates its transfer into cold water (1–4 °C) and stirring with a magnetic stirrer for 3 minutes to facilitate the crystallization of SLNs into a nanoparticle suspension. The process of isolating the SLNs involves centrifugation at 12,000 rpm for a full hour at a chilly 4 °C. Subsequently, the SLNs undergo lyophilization utilizing a freeze-dryer and are preserved in a refrigerator.

High-Pressure homogenization[5]

High-pressure homogenization (HPH) is widely used for producing solid lipid nanoparticles (SLNs). This process is applicable for large-scale industrial SLN manufacturing. The operational pressure ranges from 100

to 2000 bar, with fat content reaching up to 40%. Two fabrication approaches exist for SLNs via HPH: hot and cold processes. The hot homogenization process operates at temperatures 5–10 °C above the fat's melting point. Micronutrients are dissolved in melted lipids and mixed with an aqueous surfactant using an Ultra-Turrax mixer to create a pre-emulsion. Heat reduces viscosity, yielding smaller and uniform particles, where pre-emulsion quality is crucial for nanoparticle outcomes. Thus, temperature and pressure regulation is essential to prevent the degradation of active ingredients.

In the cold homogenization method, active compounds are mixed with melted lipids and rapidly cooled using dry ice or liquid nitrogen. The cooled lipid is then milled to form microparticles (50–100 µm), which are mixed with cold surfactants to create pre-suspensions. These pre-suspensions undergo homogenization in a high-pressure reactor under cold conditions to form a dispersion. The HPH process continues until nanoparticles are generated. This cold technique addresses issues associated with the hot method, particularly minimising active compound degradation from high temperatures.

Solvent evaporation[6]

SLN fabrication involves emulsification by incorporating fat into an o/w emulsion. Lipophilic ingredients are dissolved in water and cyclohexane. The organic solvent is removed to yield fat microparticles. These microparticles are subsequently precipitated to form nanoparticles. Sjostrom synthesized cholesterol acetate nanoparticles measuring 25 to 100 nm using lecithin/sodium glycocholate. Westesen and Siekmann confirmed these findings by producing phospholipid-stabilized solid lipid nanoparticles with effective lipid o/w emulsions.

The SLNs' characteristics are influenced by the fat-surfactant combination and fat concentration. This method is advantageous for thermosensitive active components, as it operates at low temperatures and integrates hydrophilic components with o/w/o emulsions. Nonetheless, the presence of toxic organic solvents necessitates the identification of non-toxic alternatives.

Other methods[7]

Other fabrication methodologies that have been established encompass the supercritical fluid technique, double-emulsion method, and spray-drying technique. Utilizing the supercritical fluid process in developing solid lipid nanoparticles (SLNs) offers the perk of sidestepping solvent usage, thus making the entire fabrication procedure more efficient and safer than other approaches that engage solvent use. Numerous innovations in nanoparticle fabrication exist, including SLNs, which can be swiftly synthesized utilizing supercritical carbon dioxide solutions (RESS) techniques. Using carbon dioxide (99.99%) as a solvent alternative in this approach can yield SLNs exhibiting optimal characteristics.

The synthesis of SLNs via the double-emulsion method is predicated on the evaporation of the emulsified solvent utilized to incorporate hydrophilic compounds into the SLNs. The double emulsion w/o/w can be generated through a two-step process. Initially, a w/o microemulsion is formulated by introducing a solution containing the active ingredient into a mixture composed of melted lipid and surfactant/cosurfactant at a temperature marginally exceeding the lipid's melting point to achieve a homogeneous microemulsion system. The surfactants employed to create w/o emulsions may include lecithin or monoglycerides. Subsequently, the w/o microemulsion produced is combined with a mixture of water, surfactant, and cosurfactant to establish a w/o/w double emulsion. Typically, Tween 80 is utilized to formulate w/o/w emulsions. The methodology for preparing SLNs via the double-emulsion technique is illustrated in Figure 4. Hydrophilic compounds incorporated into SLNs necessitate protection or stabilization by applying a stabilizer to avert partitioning into the aqueous phase during the solvent evaporation process. The SLNs are subsequently centrifugated at 12,000 RPM for 30 minutes at a reduced temperature (±4 °C).

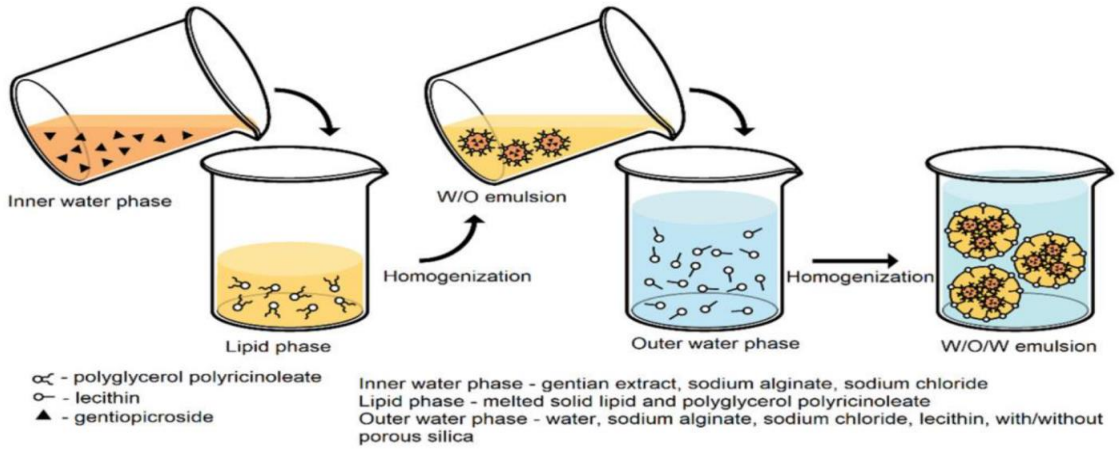

Figure 4: The preparation of SLNs by the double-emulsion method.[6]

Spray-drying methodologies are implemented as a substitute for the lyophilization process. This technique facilitates the transition of solid lipid nanoparticles (SLNs) from a liquid state to a solid (powder) state. Freitas and Müller for using lipids exhibiting a melting point exceeding 70 °C in the spray-drying process. Optimal outcomes have been achieved with a concentration of 1% SLNs in an aqueous trehalose solution or a 20% trehalose concentration in a mixed solvent of ethanol and water (10/90 v/v). While the spray-drying technique is comparatively more economical than lyophilization, it induces particle aggregation due to elevated temperatures, shear forces, and the partial melting of the particles. Consequently, it is imperative to employ lipids with a high melting point or to incorporate trehalose into the formulation.[7]

Each methodology employed for the fabrication of SLNs presents distinct advantages and limitations; thus, modifications must be made to align with the characteristics of the active ingredients utilized, the accessibility of equipment and materials, and the associated costs.

Advantages of the nasal route of drug delivery

- Non-invasiveness
- By pass the BBB, direct transport to CNS
- Avoidance of first pass metabolism and drug degradation
- Improved bioavailability
- Lower dose/ reduced side effects
- Reduce blood borne exposure risks of HIV
- Improved convenience and compliance

Target properties for intranasal drug delivery systems[8]

In this segment, we delineate the essential characteristics that may facilitate the efficacy of intranasal drug administration. These characteristics will subsequently be elaborated upon when evaluating specific candidates.

Biocompatibility: The delivery systems must exhibit safety profiles that preclude irritation or cumulative toxicity, particularly for those intended for frequent drug administration. Consequently, established pharmaceutical excipients or food additives possessing Generally Recognized as Safe (GRAS) designation are preferentially employed wherever feasible. Prolonged retention: The nasal cavity is anatomically linked to the throat via the nasopharynx. Upon the application of liquid drug formulations, there is a propensity for them to flow into the nasopharynx and subsequently enter the gastrointestinal tract. This phenomenon impedes the therapeutic efficacy of local, systemic, or central nervous system delivery. Thus, delivery systems demonstrating adherence to the nasal cavity are deemed advantageous. Chitosan, sodium alginate, cellulose derivatives, and Carbopol (refer to Table 1) are exemplary mucoadhesive polymers that have been utilized for this objective.

In situ gelling: Hydrogels that exhibit responsiveness to external stimuli are of significant academic interest, as they can be administered in a liquid form (for example, via a nozzle), and subsequently transition to a gel state at the targeted site; this characteristic also mitigates the challenge of post-administration dripping in the throat region. Ease of application: To optimize the therapeutic efficacy of drugs, devices such as nasal drops, atomizers, or sprays are frequently employed for intranasal delivery. Consequently, it is crucial to evaluate their performance when utilized with gels. For instance, sprays represent the predominant administration devices for the nasal cavity, and gelling systems must maintain a “fluid-like” consistency during spraying to ensure an evenly distributed plume across the nasal cavity. Appropriate rheology: Several target characteristics of in situ gelling nasal formulations pertain to their rheological properties. In the context of in situ gelation, parameters such as the gelation rate (time required to achieve gel formation post-application) or gelation temperature (Tgel) (for thermoresponsive systems) are critical factors to be examined. Furthermore, gels must exhibit an appropriate rheology for administration (moderate viscosity) and regain robust mechanical properties at the site of action; that is, they must be adequately strong and cohesive to guarantee optimal coverage of the targeted area.

In-situ gel formulation[9]

Numerous mechanisms for the formulation of in-situ gels are delineated as follows:

Stimuli-responsive in situ gelling system

Thermally triggered system

Within this paradigm, the formation of in-situ gel is achieved by employing a polymer that undergoes a transition from a solution to a gel state upon an elevation in the physiological temperature of the body. As the temperature escalates, the biomaterials utilized for the synthesis of in-situ gel undergo a transformation from a sol state to a gel state, thereby producing the in-situ gel.

pH triggered systems

In-situ gel can also be synthesized through the modulation of the gel's pH in response to physiological stimuli, utilizing pH-sensitive polymers in this context. When the polymer is characterized by weakly acidic groups, the hydrogel's swelling is augmented with an increase in external pH; conversely, swelling diminishes if the polymer comprises weakly basic groups.

Osmotically induced in situ gelling system

In this methodology, the gelling process of the administered solution is activated by variations in ionic strength. The kinetics of gelation is contingent upon the osmotic gradient established across the gel's surface. The aqueous polymer solution generates a transparent gel in the presence of monovalent or divalent cations. Polymers responsible for inducing gelation include gellan gum, hyaluronic acid, alginates, among others.

Chemically induced in situ gel system[11]

Ionic cross-linking

Certain ions exhibit sensitivity to polysaccharides such as carrageenan, gellan gum, pectin, and sodium alginate, which experience phase transitions in the presence of assorted ions such as K+, Ca2+, Mg2+, and Na+. These polysaccharides are categorized as ion-sensitive entities.

Enzymatic cross-linking in situ

The formation catalyzed by naturally occurring enzymes has not been extensively explored but appears to offer advantages over chemical and photochemical methodologies. For instance, enzymatic processes function effectively under physiological conditions without the necessity for potentially deleterious chemicals, including monomers and initiators.

Photo-polymerization

In situ photopolymerization has been applied in biomedical contexts for over a decade. A solution comprising monomers or reactive macromers along with an initiator can be administered at a tissue site, with the application of electromagnetic radiation facilitating gel formation. Typically, acrylate or analogous polymerizable functional groups are employed as the polymerizable entities on the individual monomers and macromers, as they rapidly undergo photopolymerization in the presence of an appropriate photoinitiator. Upon injection at the designated site, photopolymerizable systems undergo photo-curing in situ with the aid of fiber optic cables, subsequently releasing the drug over an extended duration.

Factors affecting nasal drug absorption[12-17]

Factors influencing absorption are related to nasal physiology, physicochemical characteristics of drugs and formulation aspects.

Biological factors

- Structural features
- Biochemical changes
- Physiological factors
- Blood flow
- Nasal secretions
- pH of the nasal cavity
- Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental factors
- Temperature
- Humidity

Physicochemical properties of drugs

- Molecular weight
- Size
- Solubility
- Lipophilicity
- pKa and Partition coefficient

Physicochemical properties of formulation

- Dosage form
- Viscosity
- pH and mucosal irritancy

Device related factors

- Particle size of the droplet/powder
- Size and pattern of disposion

Biological factors[18]

Physiological factors encompass, first and foremost, mucociliary clearance, a pivotal mechanism for expulsing pharmacological agents from the nasal cavity, which entails the synergistic function of the mucus layer and the cilia. The tips of the cilia engage with and transport the superficial viscoelastic mucus layer towards the nasopharynx, whereas the relatively less viscous lower layer of mucus remains predominantly stationary. Furthermore, a diverse array of metabolic enzymes resides within the nasal mucosa. This presence can constrain the bioavailability of drugs administered via the nasal route; however, the enzymatic activity observed is comparatively diminished relative to that in the gastrointestinal tract and the liver. Additionally, pathological states such as rhinitis and the common cold may also interfere with the absorption of therapeutics from the nasal cavity, and the pH level within the nasal cavity significantly influences drug permeation. Alterations in the pH of mucus can impact ionization, thereby either enhancing or diminishing drug permeation, contingent upon the specific characteristics of the drug.

Physicochemical properties of drugs[19-20]

A multitude of physicochemical attributes of the drug may also influence its nasal absorption.

Molecular Weight and Size

The degree of drug absorption is contingent upon molecular weight, particularly for hydrophilic substances. The nasal delivery route is efficacious for administering drugs weighing up to 1000 daltons. Absorption experiences a marked decline when molecular weight exceeds 1000 daltons, except in the presence of penetration enhancers. It has been documented that a robust linear correlation exists between the logarithm of the percentage of drugs absorbed nasally and the logarithm of the molecular weight of water-soluble compounds, indicating the involvement of aqueous channels in the nasal absorption of hydrophilic molecules. It has also been observed that particulate sizes exceeding 10 μm are predominantly deposited within the nasal cavity. Particles sized between 2 to 10 μm may be retained within the pulmonary system, while particles smaller than 1 μm are typically exhaled.

Solubility and Dissolution

The solubility of a drug is a critical determinant in assessing its absorption across biological membranes. If

the drug exhibits insufficient solubility in the intended vehicles, it not only restricts drug absorption but may also limit a formulator's capacity to develop a product.

Chemical form

The chemical configuration in which a drug is administered to the nasal mucosa can significantly influence its absorption. For instance, converting a drug into a salt or ester form may modify its absorption characteristics. This phenomenon is associated with the enhancement of lipophilicity consequent to esterification, which augments both the rate and extent of nasal absorption.

Physical form of formulation

The absorption of drugs via the nasal route is contingent upon the physical characteristics of the formulation employed. A pivotal parameter in the development of formulations is the product's viscosity. Typically, formulations exhibiting higher viscosity tend to diminish systemic drug delivery efficacy through the nasal pathway. In the context of desmopressin nasal delivery, the incorporation of viscous agents may confer a relatively prolonged therapeutic effect. It appears rational to posit that formulations with increased viscosity, such as gels, are more suitable for drugs that exert local action.

pH of Formulation

The pH level of both the formulation and the nasal mucosal surface can significantly influence the permeation characteristics of a drug. The pH of the nasal formulation is critical for several reasons:

To mitigate potential irritation to the nasal mucosa. To facilitate the availability of the drug in its unionized form conducive to absorption. To inhibit the proliferation of pathogenic bacteria within the nasal cavity. To preserve the efficacy of excipients, including preservatives. To ensure the maintenance of normal physiological ciliary movement, as lysozymes present in nasal secretions are effective in degrading specific bacteria at an acidic pH. In alkaline environments, lysozyme becomes inactivated, rendering the nasal tissue more vulnerable to microbial infections. Consequently, it is advisable to maintain the formulation within a pH range of 4.5 to 6.5.

Buffer capacity

Typically, nasal formulations are administered in minimal volumes, generally ranging from 25 to 200µl, with 100µl being the predominant dosage volume. As such, nasal secretions can potentially modify the pH of the administered dose, which can subsequently influence the concentration of the unionized drug that is available for absorption. Therefore, it may be necessary to ensure an adequate buffer capacity within the formulation to stabilize the pH.

Osmolarity

The tonicity of the formulation can considerably impact drug absorption. The phenomenon of epithelial cell shrinkage has been documented in the presence of hypertonic solutions. Furthermore, hypertonic saline solutions are known to impede or completely halt ciliary activity. A low pH can produce effects analogous to those observed with hypertonic solutions. Generally, isotonic formulations are preferred.

Gelling/Viscofying agents or gel forming carriers

Certain formulations necessitate gelation or increased viscosity to augment nasal residence time. An elevation in solution viscosity may extend the therapeutic duration of nasal preparations. A drug carrier such as hydroxypropyl cellulose has demonstrated efficacy in enhancing the absorption of low-molecular-weight drugs, albeit without similar outcomes for high-molecular-weight peptides. A combination of carriers is frequently advocated from a safety perspective, specifically regarding nasal irritancy.

Solubilizers

The aqueous solubility of a drug consistently poses a challenge for nasal drug delivery in solution form. Traditional solvents or co-solvents, including glycols, small amounts of alcohol, Transcutol, medium-chain glycerides, and Labrasol, can improve drug solubility. Alternative strategies involve the utilization of surfactants or cyclodextrins, such as HP-β-cyclodextrins, which function as biocompatible solubilizers and stabilizers in conjunction with lipophilic absorption enhancers. In such scenarios, consideration must be given to their potential impact on nasal irritancy.

Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzyl alcohol are some of the commonly used preservatives in nasal formulations.

Antioxidants

Depending upon the stability profile of a given drug in the formulation chosen, it may be necessary to use antioxidants to prevent drug degradation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylatedhydroxy toluene and tocopherol.

Humectants

Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel based nasal products to avoid nasal irritation and are not likely to affect drug absorption. Some common humectants used include glycerin, sorbitol and mannitol.

Absorption enhancers

When it becomes difficult for a nasal product to achieve its required absorption profile, the use of absorption enhancers is recommended. The selection of absorption enhancers is based upon their acceptability by regulatory agencies and their impact on the physiological

functioning of the nose. Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation. Once a suitable enhancer is identified, its optimal concentration should be experimentally determined. Generally higher concentrations of enhancers are likely to result in nasal irritation and damage to the nasal mucosa. On the other hand, lower enhancer concentrations would generally provide lower or no improvement of absorption.

Evaluation of in situ gel[21-23]

In situ gels may be evaluated and characterized for the following parameters,

Fourier Transform Infrared Spectroscopy and Thermal Analysis

During gelation process the nature of interacting forces can be evaluated using this technique by employing KBr pellet method. Thermogravimetric analysis can be conducted for in situ forming polymeric systems to quantitate the percentage of water in hydrogel. DSC is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions.

Clarity

The clarity of formulated solution was determined by visual inspection under black and white background.

Texture analysis

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringe ability of sol so the formulation can be easily administered in vivo.

Gelation point

It is temperature at which the liquid phase makes a transition to gel. A gelation temperature range suitable for thermos reversible nasal gel would be 30 to 36°C. Gelation point was considered as the temperature where formulations would not flow when test tubes were tilted to 90° angle as the temperature was gradually increased.

pH of the Gels

The pH of each batch was measured using pH meter which was calibrated using buffers of pH 4 and pH 8 before the measurements.

Content uniformity

Weighed amount of the formulation was dissolved in medium and after suitable dilution the absorbance was measured using UV/visible spectrophotometer. The amount of the drug present in the formulation was calculated by measuring the absorbance of a standard solution of known concentration of drug prepared in distilled water.

Rheological studies

Viscosity of the prepared formulations was measured by using Brookfield Viscometer. The gel under study was placed in the small sample holder and the spindle was lowered perpendicularly into it. The spindle was rotated at varying speeds and the suitable speed was selected.

Gel strength

This parameter can be evaluated using a Rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker from the sol form. This gel containing beaker is raised at a certain rate so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

Measurement of gel strength

Formulated gels were placed in the test tubes and gelled in a thermostat at 37°C. The apparatus for measuring gel strength was then placed onto the in situ gel. The time taken by the apparatus to sink to a depth of 5 cm through the prepared gel was measured for each formulation. Weights that detached the two vials using the following equation, Detachment stress (dynes /cm2) = mg /A where m is the weight added to balance in grams, g is the acceleration due to gravity taken as 980 cm/sec2, A is the area of the tissue exposed and is equal to $\pi r2$ (r is the radius of the circular hole in the aluminium cap).

In vitro nasal diffusion cell

The nasal diffusion cell was fabricated in glass. Drug release from gel was tested with nasal diffusion cell using dialysis membrane (mol.wt.12, 000-14,000 kDa) with permeation area of 0.785 cm2.20ml of diffusion medium was added to the acceptor chamber. Gel containing drug equivalent to its dose was placed in donor compartment. At predetermined time points, 1ml sample was withdrawn from the acceptor compartment replacing the sampled volume with diffusion medium after each sampling. The samples were suitably diluted and measured spectrophotometrically. The concentration of drug was determined from a previously constructed calibration curve.

CONCLUSION

Nasal drug delivery represents an innovative platform and serves as a viable alternative to the injectable mode of administration. There is a potential for an increased number of pharmaceuticals to be introduced into the market soon as nasal formulations aimed at systemic therapy. The evolution of a pharmaceutical compound alongside its corresponding drug delivery system is subject to many influencing factors. New nasal formulations are also anticipated to emerge in the market for treating pulmonary disorders, including diabetes, osteoporosis, and reproductive health interventions. The bioavailability of nasal drug formulations constitutes one of the primary obstacles in advancing nasal product development. Conversely, pharmaceutical enterprises allocate substantial financial resources toward developing nasal formulations due to the escalating demand for such products within the global

pharmaceutical landscape. Therefore, to mitigate adverse effects and enhance the efficacy of nasal formulations, it is imperative to prioritize fundamental research in the domain of nasal drug delivery.

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