IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE FORMULATON OF TIZANIDINE HCL LOADED SOLID LIPID NANOPARTICLES

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ABSTRACT:

Numerous advancements in drug development have led to effective treatments for complex conditions, yet many drugs cause severe side effects or fail due to degradation by endogenous enzymes in the gastrointestinal tract. Nanotechnology, specifically the creation of nanoparticles (NPs), has revolutionized drug delivery systems by improving the solubility, bioavailability, and targeted delivery of medications. Nanoparticles are solid, colloidal particles ranging from 10 nm to <1000 nm, with a preferred size of less than 200 nm for medical applications. They are composed of a functionalized surface layer, a chemically distinct shell layer, and a core. The versatility of NPs, which include carbon-based, metal, ceramic, semiconductor, polymeric, and lipid-based types, allows for broad applications in drug delivery, manufacturing, cancer therapy, diagnostic testing, HIV treatment, and nutraceutical delivery. By enhancing drug delivery and protecting therapeutic agents from degradation, nanoparticles hold significant potential to advance medical treatments and improve patient outcomes.

INTRODUCTION:

The development of controlled release formulations is crucial for improving the therapeutic efficacy and patient compliance of various medications. Tizanidine Hydrochloride (HCl) is a muscle relaxant used for managing spasticity. However, its short half-life and extensive first-pass metabolism limit its clinical effectiveness, necessitating frequent dosing which can lead to poor patient adherence and fluctuating drug

levels in the body.

Solid lipid nanoparticles (SLNs) offer a promising approach for controlled drug delivery due to their biocompatibility, ability to encapsulate both hydrophilic and lipophilic drugs, and potential for sustained release. SLNs consist of solid lipid cores stabilized by surfactants, providing a matrix for the incorporation of active pharmaceutical ingredients.

This project focuses on the development and evaluation of a controlled release formulation of Tizanidine HCl loaded solid lipid nanoparticles. The aim is to enhance the bioavailability, prolong the release, and maintain consistent therapeutic levels of Tizanidine HCl, thereby improving its clinical efficacy and patient compliance. The formulation process involves selecting appropriate lipids and surfactants, optimizing preparation techniques, and evaluating the physicochemical properties, drug loading capacity, release kinetics, and stability of the SLNs.

Table no 1. Comparative Study between Various Nanoparticles [18].

Srno	Property	SLN.	Polymeric NPs	Liposome.	Liquid emulsion.
1	systemic toxicity	Low	> to sln	Low	Low
2	cytotoxicity	Low	> to sln	Low	Low
3	Residue of organic solvents.	No	No	May or may not	No
4	Large scale production.	Yes	No	Yes	Yes
5	Sterilized by autoclaving.	Yes	No	No	Yes
6	Sustained release	Yes	Yes	Low as compare to sln	No
7	Avoidance of RES	Depend on size coating	No	Yes	Yes

Types of solid lipid nanoparticles

The types of SLNs depend on the chemical nature of the active ingredient and lipid, the solubility of actives in the melted lipid, nature and concentration of surfactants, type of production and the production temperature. Therefore 3 incorporation models have been proposed for study.

- **SLN, Type I or homogenous matrix model**: The SLN Type I is derived from a solid solution of lipid and active ingredient. A solid solution can be obtained when SLN are produced by the cold homogenization method. A lipid blend can be produced containing the actives in a molecularly dispersed form. After solidification of this blend, it is ground in its solid state to avoid or minimize the enrichment of active molecules in different parts of the lipid nanoparticles.

- **SLN, Type II or drug enriched shell model:** It is achieved when SLN are produced by the hot technique, and the active ingredient concentration in the meltedlipid is low during the cooling process of the hot o/w nano emulsion the lipid will precipitate first, leading to a steadily increasing concentration of active molecules in the remaining melt, an outer shell will solidify containing both active and lipid. The enrichment of the outer area of the particles causes burst release. The percentage of active ingredient localized in the outer shell can be adjusted in a controlled shell model is the incorporation of coenzyme Q 10.

- **SLN, Type III or drug enriched core model:** Core model can take place when theactive ingredient concentration in the lipid melt is high & relatively close to its saturation solubility. Cooling down of the hot oil droplets will in most cases reducethe solubility of the active in the melt. When the saturation solubility exceeds, active molecules precipitate leading to the formation of a drug enriched core.

1.2.2. Advantages of SLNs

- Control and / or target drug release.
- Small size and relatively narrow size distribution which provide biologicalopportunities for site-specific drug delivery by SLNs.
- No toxic metabolites are produced.
- SLN can be lyophilized and spray dried.
- Excellent biocompatibility
- Improve stability of pharmaceuticals
- High and enhanced drug content.
- Better control over release kinetics of encapsulated compounds.
- Enhanced bioavailability of entrapped bioactive compounds.
- Chemical protection of labile incorporated compounds.
- Much easier to manufacture than biopolymeric nanoparticles.
- No special solvent required.

General ingredients required for SLNs

Lipids and emulsifiers are generally used for preparation of solid lipid nanoparticles.

Lipids - The matrixes of SLN are the natural or the synthetic lipids which can be degraded, including triglyceride (Tricaprin, Trilaurin, Trimyristin, Tripalmitin, Tristearin), Hydrogenated coco-glycerides (SoftisanÒ 142), Hard fat types (WitepsolÒ W 35, WitepsolÒ H 35, WitepsolÒ H 42, WitepsolÒ E 85), Glyceryl monostearate (ImwitorÒ 900), Glyceryl behenate (CompritolÒ 888 ATO). Glyceryl palmitostearate (PrecirolÒ ATO5), Cetyl palmitate, Fatty acids (e.g., Stearic acid, Palmitic acid, Decanoic acid, Behenic acid), steroid (e.g., cholesterin) waxes (e.g., microcrystal paraffinwax, whale ester wax, cetyl palmitate).

Emulsifiers- Emulsifiers include the phospholipids [Soybean lecithin (LipoidÒ S 75, LipoidÒ S 100), Egg

lecithin (LipoidÒ E 80)], Phosphatidylcholine (lecithin, EpikuronÒ 170, Epikuron 200), Pluronics F 68, 127, Nonionic wetting agent (e.g., poloxamer 188, 182, 407, 908), cholate (e.g., sodium cholate, sodium glycocholate, sodium taurocholate, deoxy-sodium taurocholate) short-chain spirits (e.g., butanol, butanoic acid), Polysorbate 20, Polysorbate 60, Polysorbate 80, Dioctyl sodium sulfosuccinate, Mono-octylphosphoric acid sodium. Amphipathic materials (e.g., ionic and nonionic type) can stabilize the dispersion of SLN, on the surface of SLN, hydrophobic parts stretch to the core, hydrophilic parts stretch to the disperse medium, so drug with low water-solubility can beentrapped in the SLN to form the colloidal drug system.

STERILIZATION OF SLNs

For intravenous and ocular administration SLN must be sterile. The high temperature reach during sterilization by autoclaving presumably causes a hot o/w microemulsion to form in the autoclave, and probably modifies the size of the hot nanodroplets. On subsequent slow cooling, the SLN reformed, but some nanodroplets may coalesce, producing larger SLN than the initial ones. Since SLN are washed before sterilization, amounts of surfactant and cosurfactant present in the hot system are smaller, so that the nanodroplets may be not sufficiently stabilized. For parenteral administration, SLN dispersions must be sterile. The mean particle diameter of SLNs is often more than 200 nm, so sterile filtration is not possible in these cases. Options are therefore limited to aseptic manufacturing processes following sterilization of the starting materials (gamma or e-beam irradiation of the final dispersion) or exposure to ethylene oxide gas (EO).

METHODOLOGY

1. Preparation of Tizanidine HCl Loaded Solid Lipid Nanoparticles (SLNs)

Materials:

- Tizanidine Hydrochloride (HCl)
- Solid lipids (e.g., Glyceryl monostearate, Stearic acid)
- Surfactants (e.g., Poloxamer 188, Tween 80)
- Organic solvents (e.g., Ethanol, Dichloromethane)
- Distilled water

Equipment:

- High-speed homogenizer
- Ultrasonicator
- Centrifuge
- Freeze dryer
- Particle size analyzer
- Differential scanning calorimeter (DSC)
- Scanning electron microscope (SEM)
- UV-Visible spectrophotometer

- High-performance liquid chromatography (HPLC)

Method:

To develop controlled release Tizanidine HCl loaded solid lipid nanoparticles (SLNs), start by melting the selected solid lipid at a temperature 5-10°C above its melting point and dissolve Tizanidine HCl in the melted lipid. Prepare an aqueous surfactant solution and add the lipid-drug mixture to this solution under high-speed homogenization to form a primary emulsion. Subject the primary emulsion to ultrasonication to reduce particle size and create a nanoemulsion. Cool the nanoemulsion to room temperature to solidify the lipid, forming SLNs, and then freeze-dry the SLNs to obtain a dry powder form.

To characterize the Tizanidine HCl loaded solid lipid nanoparticles (SLNs), measure the particle size distribution and zeta potential using a particle size analyzer, and examine the shape and surface morphology with SEM. Determine the encapsulation efficiency (EE) by quantifying the amount of drug encapsulated using HPLC and calculate EE using the formula:

EE (%) = {Amount of drug encapsulated}\ {Total amount of drug added}×100.

Perform thermal analysis with DSC to study the thermal properties and crystallinity of the SLNs. Conduct in vitro drug release studies using a dialysis bag method in a release medium, maintaining the setup at 37°C with constant stirring, and analyze samples for Tizanidine HCl content using UV-Visible spectrophotometry or HPLC. For stability studies, store SLNs under different temperature and humidity conditions and periodically evaluate their physical and chemical stability, particle size, zeta potential, and drug content. Analyze the collected data using appropriate statistical methods, comparing the release profiles of the SLNs with a conventional Tizanidine HCl formulation, and assess the stability data to determine shelf life and optimal storage conditions. Conclude by summarizing the findings, highlighting the effectiveness of SLNs in achieving controlled release of Tizanidine HCl, and discussing their potential to enhance bioavailability and therapeutic efficacy.

Preparation of solid lipid nanoparticles of TIZH

High speed hot homogenization

The selection of preparation method for solid lipid nanoparticles depends on stability, suitability, avalability. Glyceryl Monostearate was melted at 75°C just above the melting point and accurately weighed quantity of TIZH was dispersed thoroughly in it to form a homogeneous dispersion. The aqueous phase consisted of the surfactant tween 80 and span60 dissolvedin specific ml of distilled water. Then heat the solution which was heated up to 75 ° C ina beaker. When temperatures of both the phases became isothermal, a hot surfactant solution was added to molten lipid phase under continuous stirring. Then homogenizationwas carried out using high-speed homogenizer at 4000 rpm for 5 min. Theobtained O/W nanoemulsion was cooled down in an ice-bath to form SLNs. This SLN dispersion in water was freeze-dried in a lyophilizer to obtain a powder. The lyophilized powder was stored in air-tight glass containers at room temperature until further use.

RESULT AND DISCUSSION

The Tizanidine hydrochloride sample was identified as a slightly yellowish, odourless amorphous powder, with a melting point of 281°C, consistent with literature values. The solubility profile showed the drug to be soluble in methanol, 0.1 N hydrochloric acid, and phosphate buffer (pH 6.8), but insoluble in 0.1 N NaOH and water. UV-visible spectroscopy analysis revealed an absorbance maximum at 228 nm in 0.1 N hydrochloric acid, aligning with reported values and selected for in vitro release studies.

The calibration curve of Tizanidine Hydrochloride in 0.1 N hydrochloric acid (pH 1.2) demonstrated linearity within the concentration range of 4–20 µg/ml, with a regression coefficient (R^2) of 0.999 and a slope of $y = 0.037x + 0.143$. Absorbance values at 228 nm ranged from 0.299 to 0.902. Similarly, in phosphate buffer pH 6.8, the calibration curve also exhibited linearity within the same concentration range, with an R^2 of 0.998 and a slope of $y = 0.043x + 0.037$, showing absorbance values from 0.212 to 0.921. Both sets of data confirm the reliability and consistency of Tizanidine Hydrochloride's spectroscopic analysis for in vitro release studies.

The FTIR spectrum analysis of Tizanidine Hydrochloride (TIZH) revealed absorption bands consistent with its chemical structure, confirming the drug's purity. Compatibility studies between the drug and polymer showed no significant interactions. The encapsulation efficiency (EE) of the solid lipid nanoparticles (SLNs) was assessed by measuring the free TIZH concentration in the aqueous medium, with EE ranging from 81.42% to 94.22% across different batches. Particle size analysis indicated sizes between 225.4 nm and 252.1 nm. Optimization using Design-Expert software employed a 3^2 factorial design, evaluating the effects of glyceryl monostearate (GMS) and Tween 80 on EE and particle size. Results demonstrated significant models for both responses, highlighting the formulation's potential for controlled release.

The comparison between experimental and predicted values for the optimized Tizanidine Hydrochloride-loaded SLN formulation (Batch F7) showed a close agreement with minimal errors: a 0.93% error in entrapment efficiency and a 1.25 nm error in particle size. Particle size analysis of Batch F7 revealed an average size of 226.8 nm, while zeta potential measurement indicated a value of -27.7 mV, confirming good colloidal stability. In vitro drug release studies demonstrated a controlled release profile, with Tizanidine Hydrochloride showing 93% release over 24 hours. Kinetic analysis of the release data indicated that the drug release followed zero-order kinetics, suggesting a controlled and sustained release pattern.

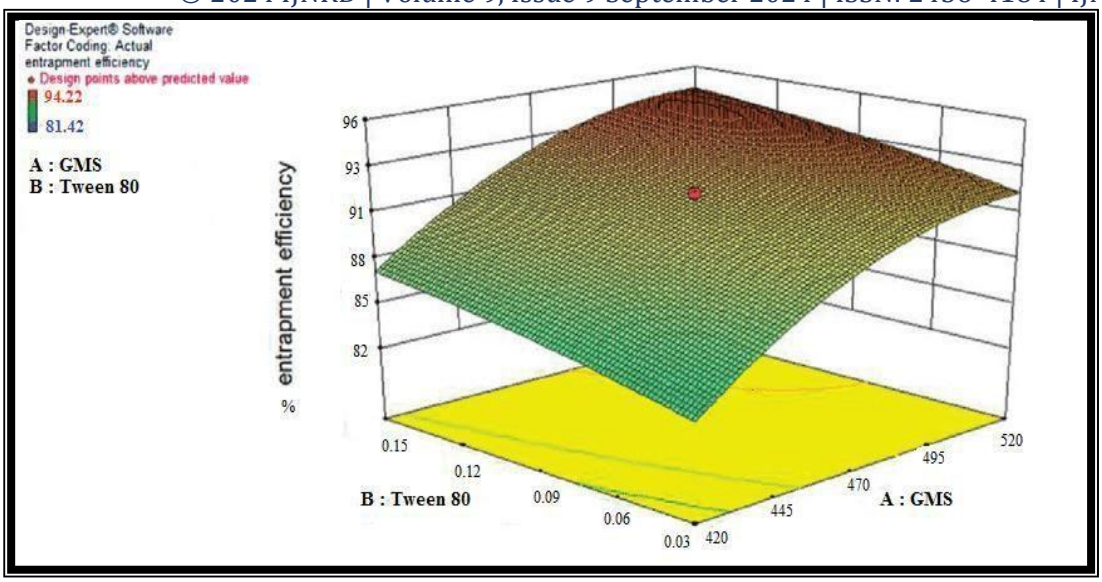

Fig No. 1. – 3D surface response plot of % Entrapment efficiency.

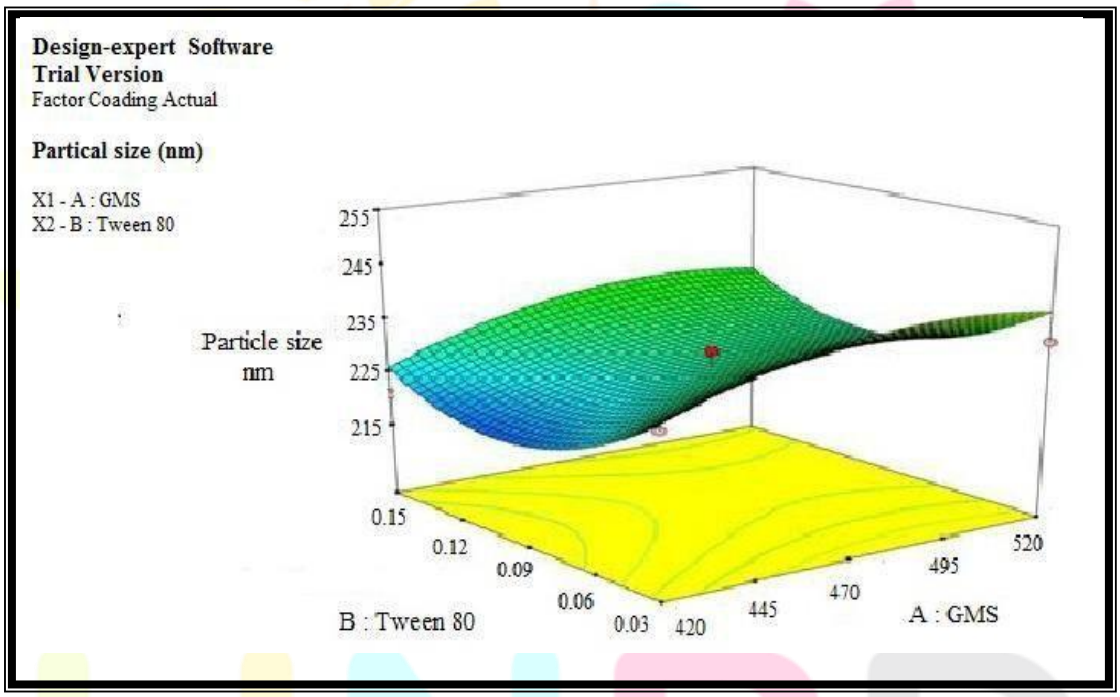

Fig No. 2 - 3D surface response plot of particle size.

The Differential Scanning Calorimetry (DSC) analysis revealed that the melting point of pure Tizanidine Hydrochloride (TIZH) was 280.1°C, consistent with literature values, and exhibited a sharp endothermic peak with a heat of 105.71 mJ. In the DSC thermogram of TIZH-loaded solid lipid nanoparticles (SLNs), the melting peak shifted to 282.4°C with a reduced intensity and a heat of 123.5 mJ, indicating a reduction in crystalline content and no significant drug-excipient interactions. Scanning Electron Microscopy (SEM) of TIZH-SLN showed characteristic nanoparticle morphology, while Transmission Electron Microscopy (TEM) revealed spherical particles with sizes ranging from 70 to 80 nm. Powder flow properties of the SLNs were assessed, showing excellent flow characteristics. For capsule filling, 317.76 mg of dried SLN was required to achieve a 6.87 mg dose of TIZH. Comparative drug release studies demonstrated that the F7 batch SLNs achieved a higher and more controlled release profile compared to the marketed formulation, with 92%

drug release over 24 hours versus 91% from the marketed product.

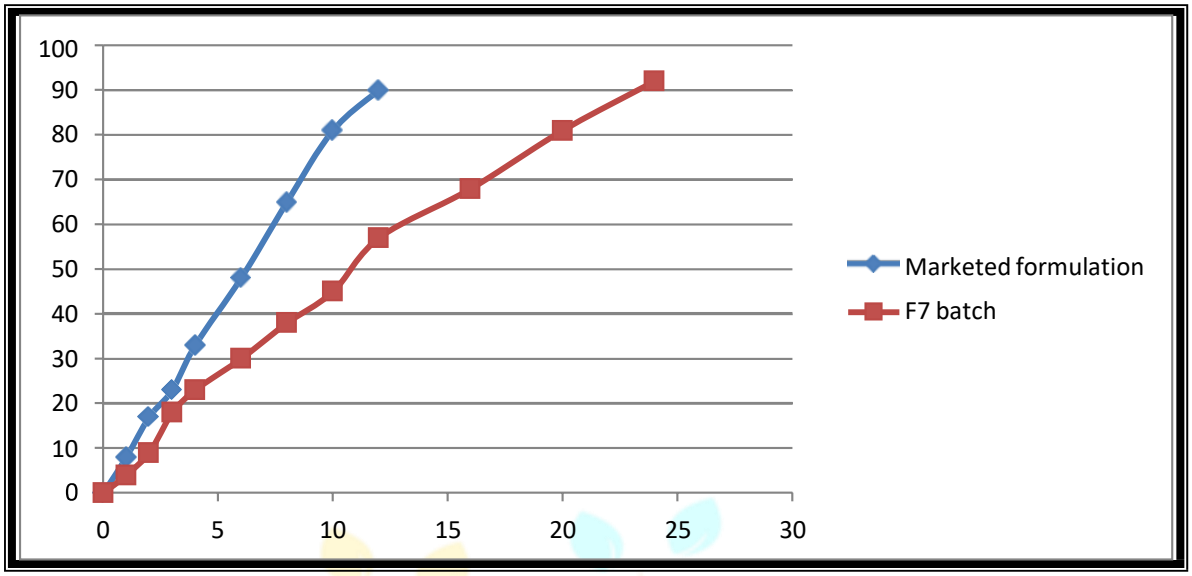

Fig No 3– Graphical comparative study of marketed Formulation and F7 Batch.

Stability study

The stability study of optimized batch was determined by Entrapment efficiency after 3 Months for 40 ^{0}C ± 2 temperature and Humidity 75 RH ± 5. The result was compared withactual entrapment. The lowered entrapment is the result of drug expulsion during lipid modification on storage.

Table No.2. Stability study

Sr no	Actual Entrapment	After 3 months
1	94.22 %	92 .11 %

After the stability study for entrapment was lowered by 2.11 % that is acceptable stability.The F7 batch formulation developed is stable under accelerated condition of 03 months.

SUMMARY AND CONCLUSION

The study demonstrates the successful development of TIZH loaded Solid lipid nanoparticles (TIZH-SLNs) using high speed homogenization. The optimization wasdoneusing a three-level two-factor (3^2) full factorial design. The observed responses were closeto predicted values for the optimized formulation. Addition of Tween 80, Span 60 and GMS to SLN core was more effective to achieve the desired entrapment efficiency, particlesize and release profile. The results of *in vitro* dissolution studies evidenced the significantly better command for release profileof optimized formulation with respected tomarketed formulation. Thus, finally it can be concluded that TIZH-SLNs could be a promising oral drug delivery system for making oral controlled release formulation for long term effect, and augers well in improving the bioavailability of encapsulated drug.

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