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Development and Optimization of Telmisartan-loaded Polymeric Nanoparticles: A Novel Approach for enhanced drug delivery and sustained release

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Abstract

Advanced drug delivery systems have gained much attention lately, especially in improving the bioavailability and therapeutic efficiency of poorly water-soluble drugs. Telmisartan is known as an extensively applied antihypertensive drug, which shows relatively low solubility and bioavailability and limits its clinical efficiency. In this paper, for solubility and stability enhancement together with sustained drug release, designed and optimally prepared polymeric nanoparticles (NPs) have been used as telmisartan delivery forms. A PLGA-based nanoparticulate drug delivery system with biodegradability was constructed to ensure better controlled drug release and pharmacokinetic performance. This has been done with the use of different formulation techniques, such as solvent evaporation and nanoprecipitation followed by systematic screening and statistical optimization using Plackett-Burman and Box-Behnken designs.

Keywords: Telmisartan, Nanoparticles, Novel

Introduction

This is the most acceptable and preferred drug delivery system since it is easy and convenient for patients. High patient compliance can be achieved using this method because it is relatively non-invasive and less costly, and several drugs can be accommodated using different formulations. With all these benefits, conventional oral drug delivery formulation usually lacks several limitations due to poor active principles solubility, reduction of bioavailability, and significant first-pass metabolism. Therefore, this sometimes leads to a less than desirable therapeutic performance. New developments have recently occurred through nanoparticle-based drug formulations as promising substitutes for the traditionally formulated systems. Nonetheless, with regard to practical considerations of large-scale production, reproduction, and approval, new formulation systems, even though novel and exciting, remain below par when compared with conventional formulations in popularity. Telmisartan, a widely prescribed antihypertensive agent, belongs to the class of angiotensin II receptor blockers (ARBs) and is known for its poor aqueous solubility and low bioavailability. These pharmacokinetic disadvantages limit its therapeutic potential, and thus, novel methods to improve its delivery and absorption are of utmost importance. Nanoparticle-based drug delivery systems have emerged as an extremely attractive alternative by providing enhanced solubility, controlled release, and targeted delivery to maximize drug efficacy and patient outcome.

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In this paper, polymeric nanoparticles were evaluated as a novel drug delivery system for telmisartan that could improve its pharmacokinetic profile and enhance its therapeutic performance.

Drug Delivery System (DDS)

A DDS is basically the methods, technologies, and formulations used in the transport of a pharmaceutical compound to its target site of action in the body for the accomplishment of the therapeutic effect. Therefore, the key aim of drug delivery systems would be to achieve optimum drug bioavailability, stability, and release profile with minimal side effect. Drug delivery systems can therefore be classified as either route of administration, release mechanism, and the ability to target.

Types of Drug Delivery Systems

1. Conventional Drug Delivery Systems

These are the conventional drug administrations which rely on the drug being absorbed passively by diffusion or dissolution. These include.

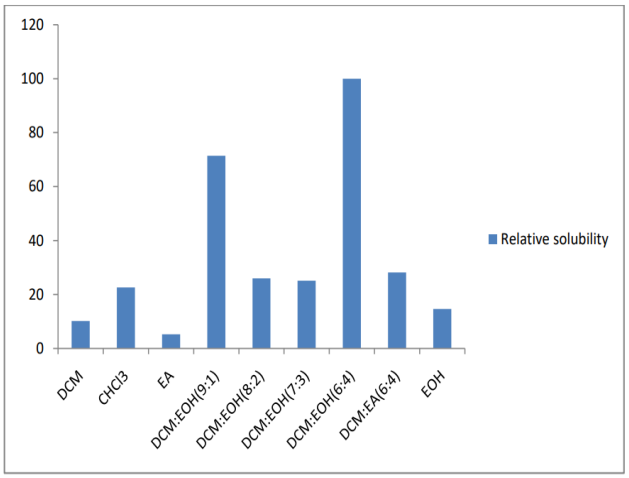
- **Oral (Tablets, Capsules, Syrups)** – Most common, but susceptible to effects like first-pass metabolism and gastric ph.
- **Parenteral (Injections, IV Infusions)** – Provides rapid drug action but may cause discomfort and require trained personnel.
- **Topical (Creams, Gels, Ointments)** – Used for localized drug delivery, such as for skin conditions.
- **Inhalation (Aerosols, Nebulizers, Inhalers)** – Delivers drugs directly to the lungs for rapid action (e.g., asthma medications).

2. Advanced and Novel Drug Delivery Systems

These systems enhance drug absorption, targeted delivery, and controlled release:

A. Controlled and Sustained Release Systems

- **Sustained Release Formulations** – Release the drugs gradually. The drug plasma level is therefore maintained constant during the release duration.
- **Osmotic Pumps** – Utilization of osmotic pressure to sustain the release time of drugs as per the intended schedule.



B. Nanotechnology-Based Drug Delivery Systems

- **Nanoparticles (Polymeric, Lipid, Metallic)** – improves solubility, stability along with controlled delivery at the required site.
- **Examples:** Telmisartan -loaded PLGA nanoparticles Liposomes - Spherical vesicles containing lipids assists in improving solubility coupled with reducing toxicities.
- **Dendrimers** – Polymeric branched chain is used for targeted delivery

C. Targeted Drug Delivery Systems

- **Ligand-Based Targeting** – The drug is targeted to specific cells using ligands such as antibodies or peptides in cancer treatment.
- **Magnetic Nanoparticles** – An external magnetic field directs the carrier drug to a specific location.

D. Stimuli-Responsive Drug Delivery

- **pH-Sensitive Systems** – Systems that release drugs in response to a change in pH, such as stomach compared to intestines
- **Temperature-Sensitive Systems** – These are systems that yield their drugs when exposed to particular temperatures

Advantages of Advanced Drug Delivery Systems

- **Improved Bioavailability** – Enhances the absorption of drugs that are poorly soluble.
- **Targeted Drug Delivery** – Drugs are delivered to targeted tissues or cells, and the systemic side effects are minimized.
- **Controlled Release** – Sustains the concentration of drugs within the body; hence, dosing frequency is reduced.

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- **Reduced Toxicity –** Reduces the exposure of healthy tissues to high concentrations of drugs.
- **Improved Patient Compliance –** The dosing frequency and side effects are reduced, and thus treatment is easy.

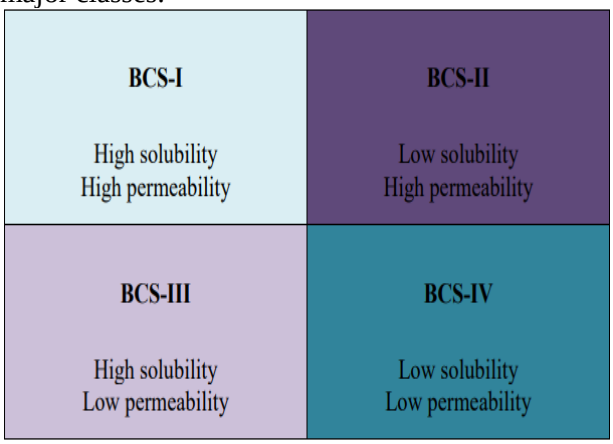
The evolution of drug delivery systems from conventional to nanotechnology-based and targeted has significantly improved the therapeutic outcomes. These advancements are able to have better control over drug release, site-specific targeting, and bioavailability, especially for poorly soluble drugs such as telmisartan. Inclusion of polymeric nanoparticles, liposomes, and controlled-release formulations continues to revolutionize the pharmaceutical industry with more efficient and patient-friendly therapies.

Biopharmaceutical Classification System (BCS) Of Drugs

The Biopharmaceutical Classification System is a scientific approach to classify drugs based on the solubility and permeability characteristics. "This was initiated by the U.S. Food and Drug Administration with the purpose of predicting the process of drug absorption and guiding formulation development." The BCS is also crucial in the approval of generic drugs and development of bioequivalent formulations in the evaluation of how a drug dissolves and is absorbed in the GI tract.

Classifications of drugs under the BCS classification

The aqueous solubility, and intestinal permeability of the drug has divided the classification into four major classes:



Biopharmaceutical Classification System (BCS) of drugs

The main objectives of the Research study are stated as follows:

1. To evaluate the physicochemical property of the drug for the appropriate selection of excipients and implementation in the formulation technique of nanoparticles.
2. To analyze Screening of the major process or product affecting parameters responsible for influencing the desired specifications of NPs with the help of Plackett-Burman design.
3. Implementation of response surface methodology (Box-Behnken design) to identify the accurate ratio of independent variables affecting predetermined dependent variables of telmisartan loaded nanoparticles.
4. To established NPs as a convenient dosage form over the conventional alternatives. • Evaluation of pharmacokinetics of telmisartan in the rat model and determination of inter-subject and intergroup variation.
5. To establish TLM-PLGA-NPs as a safe, biocompatible and sustain release formulation.

Results and Discussion

Pre-Formulation of Nanoparticles

The preformulation study was performed before the development of nano formulation. In this regard, the physicochemical properties of drugs and excipients were thoroughly evaluated to ensure the integrity of the final product to achieve better therapeutic efficacy. In the present study, the preparation of nanoparticles was designed with double emulsion solvent evaporation technique, therefore understanding the basic mechanistic insight of a stable emulsion and drug encapsulation technique into the polymer matrix was emphasized to attain a stable emulsion. To meet study objectives, selection of organic solvent, solubility, crystallinity, FTIR, DSC studies were considered as fundamental preformulation characterization and thoroughly studied.

Determination of Organic Solvent and Solubility

The nano emulsion is a biphasic liquid system that consists of two distinct phases, one is the oil phase, and another is the water phase. Hence the development of polymeric nanoparticles by double emulsion solvent evaporation method by stabilizing both the phases, always remains the toughest part of the study (74). However

physicochemical property like solubility of the drug plays an important role in stabilization of nanoemulsion. To prepare the oil phase, a volatile organic solvent is an essential ingredient that should dissolve drug and polymer homogeneously. It was also observed that the choice of organic solvent and solubility of drugs influence the solid dispersion across the polymer matrix Figure 4.7. In this regard, DCM appeared to be a good solvent for PLGA (75, 76) and TLM but exhibited crystal formation over NPs. On the other hand, the mixture of DCM with ethanol at 6:4 showed maximum solubility value of TLM and resisted crystal growth. "The crystalline nature and high melting point of TLM may influence the solubility in an organic solvent which interferes with the formation of uniform solid dispersed polymeric NPs." Therefore, the solubility of the drug was emphasized and the selection of organic solvents was performed based on the solubility data. The study demonstrated relative saturation concentration of the TLM in selected organic solvents represented in Figure 4.1. The solubility data were characterized to facilitate proper solid dispersion of TLM, confirming alteration of crystalline to amorphous form. Among all organic solvents DCM:Ethanol (9:1) and DCM:Ethanol (6:4) came out with the maximum solubilizing capacity (Figure 4.1). After several trials with the above solvents, the maximum amount of TLM was quantified in a typical mixture of organic solvent (DCM: EOH) (60:40). Though, the formulations were carried out with every other selected solvent and characterized to evaluate the result of other parameters based on organic solvent change.

Determination of Crystallinity

The crystalline API (TLM, Figure 4.2a, d) has a significant impact on drug dispersion across the polymer matrix as it can compromise the therapeutic efficacy of the dosage form. Among diverse formulation technologies, solid dispersion (SD) with various hydrophilic polymers gained great attention since it can enhance drug dissolution via the change in drug crystallinity to an amorphous form as well as better wettability (77). The degree of crystallinity determines the percentages of crystal present in the samples. Accompanying with a high melting point, a drug like TLM has a tendency to crystal growth during formulation or in long term storage (78). Due to the high energy barrier TLM showed heterogeneous solid dispersion with crystal growth into the NPs (Figure 4.2b, e). The X-Ray diffractogram established the percentage of crystallinity associated with each batch, represented in Figure 4.3. In formulation 7, XRD and morphological analysis showed no crystalline structure (crystallinity 9.51%) of TLM over the surface of NPs. Few other batches like formulation 1, 2 and 4 demonstrated 73.49%, 51.36% and 31.86% crystallinity respectively (Figure 4.5 and Figure 4.6). Furthermore, the needle-like crystal lattice had appeared in the morphological analysis was also confirmed as crystalline TLM by XRD analysis (Figure 4.2b, e). A comparative study of saturation solubility and crystallinity showed an inverse relationship in the formulation environment.

Formulation Technique of Polymeric NPS

In the present study, solubility modulated double emulsion (W/O/W) solvent evaporation technique Figure 4.11 was employed to prepare uniform, spherical and drug-loaded polymeric NPs. The double emulsification technique allowed incorporating two different compartments into a single nanodroplet. The appropriate concentration of primary emulsifier (PVA) made the W/O emulsion stable enough to bring uniformity in particle size, which reflected in secondary emulsion (W/O/W) (80, 81). The high-speed homogenization breaks the primary emulsion droplet into a nanosized emulsion droplet which was further isolated (at 26045g) into w/o/w nanodroplet to prepare a homogeneous secondary emulsion.

Discussion

Most newly developed drug molecules have poor aqueous solubility and hence pose an obstacle in clinical development. Drugs of Class II as classified in the Biopharmaceutical Classification System (BCS) pose a problem for dissolution rate-limited bioavailability; hence it becomes difficult to get consistent therapeutic effects. Changes like polymorphs, co-crystals, and amorphous forms do enhance solubility but those methods pose obstacles of manufacturing complexity and stability. In this regard, polymeric NPs provide a promising alternative for enhancing the solubility, stability, and controlled release of drugs. In this

work, TLM was successfully encapsulated into polymeric NPs by using a double-emulsion solvent evaporation technique, thereby ensuring efficient drug loading and sustained release.

The encapsulation process significantly affects drug stability and bioavailability. Crystallization within the polymer matrix can prevent uniform drug distribution and reduce encapsulation efficiency. This was overcome by the use of a mixture of dichloromethane (DCM) and ethanol, which allows for better solubility modulation and prevents premature crystallization. This method enhanced encapsulation efficiency and produced stable nanoparticles with reduced crystal growth. The polymer used was PLGA, which is biodegradable, biocompatible, and has been approved by the FDA for drug delivery applications. The addition of PVA as a surfactant allowed further stabilization of the nanoparticles through the inhibition of droplet coalescence in the course of emulsification.

Formulation Strategies for Targeted Drug Delivery

Assess modifications to surface chemistry through the conjugation of a ligand or PEGylation to increase targeted delivery for diseases characterized by organ damage from hypertension.

Responsive 'smart' nanoparticles that respond to physiological triggers, such as pH or specific enzymes, with controlled release.

Comparative Studies with Other Formulations

Compare TLM-PLGA-NPs to other advanced drug delivery systems like liposomes, dendrimers and solid dispersions to assess the relative advantages.

Pharmacokinetics of nanoparticles in the fed and fasted states should be investigated to clarify variability in absorption

In Vivo Pharmacokinetic and Toxicity Studies in Larger Animal Models

Expand preclinical to larger animal models like dogs or primates for better prediction of human pharmacokinetics.

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