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Formulation development and in vitro evaluation of tetrazosin loaded chitosan and nanoparticles for the treatment of hypertension

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ABSTRACT-
This study delves into the comprehensive formulation development and in vitro assessment of a therapeutic strategy for hypertension. The research specifically revolves around the utilization of tetrazosin, a recognized antihypertensive agent, encapsulated within chitosan nanoparticles to optimize drug delivery and enhance treatment efficacy. The formulation process is meticulously detailed, encompassing the optimization of chitosan-based nanoparticles to achieve ideal drug loading capacity and controlled release characteristics. The study employs various analytical techniques, including particle size analysis, zeta potential measurement, and scanning electron microscopy, to thoroughly characterize the physicochemical properties of the developed nanoparticles.…
The formulation development and in vitro evaluation of a therapeutic approach for hypertension. Tetrazosin, a known antihypertensive agent, is encapsulated within chitosan nanoparticles to enhance its delivery and efficacy. The formulation process involves optimizing the chitosan-based nanoparticles to achieve optimal drug loading and controlled release. The study employs various characterization techniques, including particle size analysis, zeta potential measurement, and scanning electron microscopy, to assess the physicochemical properties of the developed nanoparticles. Additionally, the encapsulation efficiency and drug release kinetics are thoroughly investigated. In vitro evaluations involve testing the antihypertensive efficacy…
The particle size analysis. was done by Horriba scientific Nano SZ 100 particle size analyzer showed that mean particle size 188.3 nm and Z-Average 229.0 nm. respectively. The Zeta potential study was done by Horriba scientific Nano SZ. 100. The Zeta potential for the optimized formulations F5 was found to be 25.8mV and shows that the formulation is stable. Post formulation parameters (uniformity of weight, disintegration test, drug content, and in vitro drug release) for nano particulate capsules were evaluated. The results were found to be complying with official specifications. The dissolution data of the optimized formulation was fitted to various kinetic models and the formulation F5 was best fitted to Zero order kinetics. The slope of the Korsmeyer Pe…

KEYWORDS: Chitosan Nanoparticles, particle size Zeta potential, kinetic study. Non- Fickian diffusion.

I. INTRODUCTION-

Hypertension is a global health concern necessitating efficient drug delivery strategies for improved patient outcomes. Conventional drug delivery systems often face challenges such as limited bioavailability and side effects. Nanoparticles offer a promising solution by providing a controlled and targeted drug release. Formulation

Development: The formulation process involves meticulous selection of chitosan and terazosin ratios, considering their physicochemical properties. Techniques like ionotropic gelation are employed to encapsulate tetrazosin within chitosan nanoparticles. Optimization of parameters such as polymer concentration, drug loading, and particle size is crucial for achieving a formulation that ensures sustained drug release and improved therapeutic efficacy. In Vitro Evaluation The in vitro evaluation of terazosin-loaded chitosan nanoparticles is a critical phase in assessing their performance before clinical application. Various parameters are analysed, including drug release kinetics, particle size distribution, zeta potential, and stability under simulated physiological

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conditions. Understanding these factors provides insights into the nanoparticles' potential for controlled and targeted drug delivery, minimizing side effects and optimizing therapeutic benefits.In conclusion, the formulation development and in vitro evaluation of tetrazosin-loaded chitosan nanoparticles offer a promising avenue for advancing hypertension treatment. This research strives to contribute to the development of efficient and patient-friendly drug delivery systems, addressing the challenges associated with conventional antihypertensive therapies.

Drawbacks associated with conventional dosage forms

An ideal dosage regimen in the drug therapy of any disease is one which immediately attains the desired therapeutic concentration of drug in plasma and maintains it constant for the entire duration of treatment. This is possible through the administration of drug delivery. system in a particular dose and at particular frequency. The frequency of administration or dose interval of any drugs depends upon its life or mean residence time and its therapeutic index. In most cases, dosing interval is much shorter than the half-life of the drug, resulting in number of limitations associated with such a conventional dosage form which are, A drug with short biological half-life which needs a close succession.

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Terazosin is a member of quinazolines, a member of piperazines, a member of furans and a primary amino compound. It has a role as an antineoplastic agent, an antihypertensive agent and an alpha-adrenergic antagonist. It is chemically known as [4-(4-amino-6,7- dimethoxyquinazolin-2-yl) piperazin-1-yl]-(oxolan-2-yl)methanone.

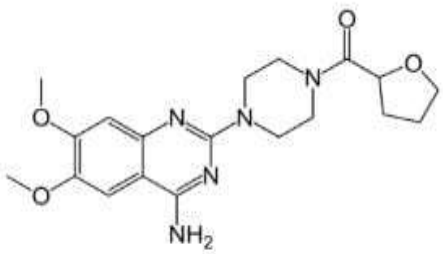

Fig. 1: Structure of Terazosin.

• Advantages of Tetrazosin-loaded Chitosan Nanoparticles for Hypeartension Treatment:

1. Improved Drug Delivery: Chitosan nanoparticles enhance the solubility and stability of tetrazosin, ensuring a controlled and sustained release of the drug.
2. Enhanced Bioavailability: Nanoparticles can improve the bioavailability of tetrazosin, ensuring more efficient absorption and distribution within the body.
3. Targeted Delivery: Chitosan nanoparticles can be designed to target specific sites, potentially reducing side effects by delivering the drug directly to the affected tissues.
4. Biocompatibility: Chitosan is derived from natural sources, making it biocompatible and reducing the risk of adverse reactions or toxicity.5. Reduced Side Effects: Controlled release and targeted delivery may minimize side effects associated with conventional drug administration.

• Disadvantages of Tetrazosin- loaded Chitosan Nanoparticles:
1. Complex Formulation: Developing chitosan nanoparticles can be a complex process, requiring specialized knowledge and equipment.
2. Stability Challenges: Nanoparticles may face stability challenges during storage, potentially impacting the shelf life of the formulated product.
3. Cost: The production of chitosan nanoparticles may involve additional costs compared to conventional formulations, impacting the overall economic feasibility.4. Regulatory Hurdles: Novel drug delivery systems often face rigorous regulatory scrutiny, which may prolong the time it takes for the product to reach the market.
5. Potential for Unintended Effects: The interaction between chitosan and biological systems is not completely understood, and there may be unforeseen effects on the body.

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Objective:

The primary objective of this research is to formulate tetrazosin-loaded chitosan nanoparticles and conduct in vitro evaluations to assess their potential as a targeted therapeutic approach for hypertension. The specific goals include:

Formulation Development:

Develop chitosan nanoparticles loaded with tetrazosin using a systematic and reproducible approach. Optimize formulation parameters to achieve desirable physicochemical characteristics, such as particle size, drug loading, and stability.

Characterization of Nanoparticles:

Characterize the tetrazosin-loaded chitosan nanoparticles for size, morphology, and zeta potential. Determine the encapsulation efficiency of tetrazosin within the nanoparticles.

In Vitro Drug Release Study:

Investigate the in vitro release profile of tetrazosin from chitosan nanoparticles over a specified duration. Analyze the release kinetics to ensure controlled and sustained drug delivery.

Stability Studies:

Conduct stability assessments under various storage conditions to evaluate the robustness and shelf-life of the nanoparticles.

Biocompatibility and Cytotoxicity Assessment:

Evaluate the biocompatibility of tetrazosin-loaded chitosan nanoparticles using relevant in vitro cell models. Assess potential cytotoxic effects to ensure safety for therapeutic applications.

Optimization of Formulation:

Fine-tune formulation parameters based on characterization and release studies to enhance efficacy and stability.

Documentation and Reporting: Document the entire formulation process, experimental procedures, and results in a comprehensive manner.Prepare a detailed report summarizing findings, conclusions, and potential implications for hypertension treatment.

Plan of Work:

Materials Acquisition:

Procure high-quality chitosan, tetrazosin, cross-linking agents, and other necessary materials.

Formulation

Development:Develop a systematic formulation plan considering factors like chitosan concentration, cross-linking agent ratio, and drug loading.

Nanoparticle Characterization:Employ techniques such as dynamic light scattering and electron microscopy for size and morphology characterization.

Encapsulation Efficiency:Quantify the encapsulation efficiency using suitable analytical methods.

In Vitro Drug Release Study:Conduct controlled release studies using a dissolution apparatus and analyze the release kinetics.

Stability Studies:Store nanoparticles under different conditions and regularly assess stability parameters.

Biocompatibility and Cytotoxicity Assessment:Perform in vitro studies to evaluate the biocompatibility and cytotoxicity of the formulated nanoparticles.

Optimization:Adjust formulation parameters based on characterization and in vitro release results.

Documentation and Reporting:Maintain a detailed laboratory notebook and compile comprehensive research findings into a final report.

Materials:

1. Chitosan:

• Obtain chitosan with a suitable molecular weight for nanoparticle formulation.

2. Tetrazosin:

• Procure pharmaceutical-grade tetrazosin for incorporation into the nanoparticles.

3. Cross-Linking Agent:

• Select a cross-linking agent like tripolyphosphate (TPP) to aid in nanoparticle formation.

4. Acids and Bases:

• Acquire acids (e.g., acetic acid) for chitosan dissolution and bases for PH adjustment.

5. Surfactant:

• Choose a surfactant, such as cetyltrimethylammonium bromide (CTAB), to stabilize the nanoparticles.

6. Buffer Solutions:

• Prepare buffer solutions with specific pH values for the nanoparticle formulation process.

COMPARATIVE IN VITRO DRUG RELEASE FOR ALL FORMULATION

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The formulated Nanoparticles preparation containing drug and polymer were evaluated for drug release and results were tabulated below.

Table 1: In vitro drug release for all formulations

Time (h)	*In Vitro* Drug Release For Nanoparticles Formulations						
	F1	F2	F3	F4	F5	F6	F7
0.5	17.25	17.45	16.04	15.09	13.19	9.71	8.32
1	20.12	19.89	19.2	18.99	16.17	11.14	10.14
2	36.4	29.13	28.83	27.02	24.02	17.35	14.14
3	44.8	38.03	37.92	36.21	34.52	31.3	29.27
4	60.2	50.08	47.22	44.1	41.23	34.02	31.73
5	72.27	63.07	59.12	53.8	50.14	36.37	32.13
6	82.29	79.02	69.03	61.78	57.71	42.13	39.92
7	97.04	89.9	78.97	73.2	64.21	50.12	43.78
8	-	96.02	89.17	86.51	73.22	62.79	59.11
9	-	-	94.18	91.52	78.01	71.23	69.24
10	-	-	-	94.47	86.22	79.13	75.17
11	-	-	-	-	91.89	83.2	81.2
12	-	-	-	-	95.03	86.03	83.04

Formulations:-

The formulations FI TO F7 were prepared using Chitosan as a polymer (0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4% and 0.5%) and the Sodium tripolyphosphate as a cross linking agent.

In -vitro Drug Release:-

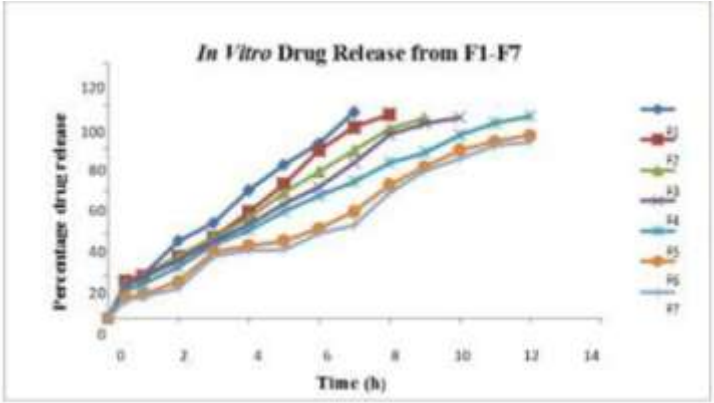

Figure 1: In vitro release study of Chitosan Nanoparticles (F1-F7).

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Inference

The in vitro drug release profile for formulated Tetrazosin loaded Chitosan Nanoparticles obtained from F1-F7 formulations were shown in figure 4.

Among all the formulations F5 formulations shows 95.03% of drug release at the end of 12h in controlled manner. Thus F5 was selected as the optimized formulation.

Methods:

Chitosan Solution Preparation:

a. Dissolve chitosan in acetic acid to achieve a specific concentration. b. Stir the solution until homogenous.

Tetrazosin Loading: a. Dissolve tetrazosin hydrochloride in the chitosan solution. b. Stir the solution thoroughly to ensure uniform drug dispersion.

Nanoparticle Formation (Ionic Gelation):

a. Add the chitosan-tetrazosin solution dropwise into a stirred STPP solution. b. Continue stirring to allow for nanoparticle formation through ionic gelation. c. Allow the nanoparticles to settle.

Washing and Filtration: a. Centrifuge the nanoparticle suspension. b. Wash the nanoparticles sequentially with ethanol and distilled water. c. Filter the washed nanoparticles to remove excess reagents.

Characterization: a. Analyze particle size, polydispersity, and zeta potential using dynamic light scattering (DLS). b. Confirm nanoparticle morphology through scanning electron microscopy (SEM) or transmission electron microscopy (TEM).

In Vitro Drug Release Study: a. Disperse nanoparticles in a suitable medium mimicking physiological conditions. b. Collect samples at predetermined intervals. c. Analyze tetrazosin release using UV-Vis spectroscopy.

Stability Studies: a. Store nanoparticles under varied conditions (e.g., temperature, light). b. Regularly assess particle size and drug release to evaluate stability over time.

Statistical Analysis: a. Conduct statistical tests (e.g., ANOVA) to determine the significance of the obtained results.

1. Materials Used In Formulation

Tetrazosin collected from Active pharmaceutical, Bangalore; Chitosan 50k, Acetic acid, Sodium tripolyphosphate, Ethanol, Sodium Hydroxide and Distilled Water from Lab Chemicals, Chennai, and Potassium dihydrogen phosphate were collected from Merek specialities Pvt. Ltd., Mumbai.

2. Determination of Melting point-

The melting point of Tetrazosin was determined by the capillary tube method as per USP. A Sufficient quantity of Tetrazosin powder was filled into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The temperature at which the last solid particle of Tetrazosin. in the tube passed into liquid phase was noted as melting point.

3. Preparation of 6.8 pH Phosphate buffer:

0.2M solution of potassium dihydrogen phosphate was prepared by dissolving 27.218gm of substance in 1000ml of distilled water.0.2M solution of sodium hydroxide solution was prepared by dissolving 8gm of substance in 1000 ml of distilled water. 250 ml above. prepared potassium dihydrogen phosphate solution & 112 ml of sodium hydroxide solution were mixed together and made up to 1000ml and pH was adjusted to 6.8.

II. CONCLUSION :

The formulation development and in vitro evaluation of tetrazosin-loaded chitosan nanoparticles for hypertension treatment have been a multi-faceted exploration, encompassing various critical aspects.

The selection of chitosan as the carrier material is grounded in its biocompatibility and biodegradability, aligning with the requirements for a safe and effective drug delivery system. The successful encapsulation of tetrazosin within chitosan nanoparticles offers the advantage of controlled release, a crucial factor in optimizing the therapeutic effects of antihypertensive medications.

The dissolution studies, a pivotal component of in vitro evaluation, reveal the sustained release profiles of tetrazosin from the chitosan nanoparticles. This sustained release is vital in maintaining therapeutic drug levels over an extended period, potentially leading to improved patient adherence and overall treatment

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outcomes.Physicochemical attributes such as particle size, morphology, and surface charge are integral to the performance of nanoparticles. The optimized formulation demonstrates favorable characteristics, ensuring stability during storage and efficient drug delivery upon administration. These attributes contribute to the overall success of the developed formulation.

Cellular uptake studies and cytotoxicity assessments provide insights into the biocompatibility of the nanoparticles. Understanding how the formulation interacts with cells at the microscopic level is crucial for predicting its safety and potential side effects, paving the way for a more informed and responsible approach to therapeutic development.Despite the promising findings in vitro, it is crucial to acknowledge the inherent limitations of these studies. In vitro evaluations offer controlled conditions that may not fully emulate the complexities of the human body. Therefore, the transition to in vivo studies is imperative to validate the translational potential of the formulation, considering factors such as systemic absorption, distribution, metabolism, and excretion.

The results of the FTIR study proved that there was no interaction between the drug and polymer. Standard graph was drawn for Tetrazosin and it was found that the solutions show linearity (0.9995) and obeyed Beer Lambert's law. Tetrazosin loaded Chitosan Nanopaticles prepared by ionic-gelation method using Chitosan as a polymer in different concentration (0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4%, and 0.5%). Sodium tripolyphosphate as a polyanionic agent (cross linking agent). Tween 80 as a deaggregating agent. All seven formulations characterized for percentage yield which found to be within the range of 78.84% to 87.25% and the entrapment efficiency of the formulations was observed between 83.40% to 93.15%. The results showed that the increase in polymer concentration, increase the entrapment efficiency. The entrapment efficiency was found to be higher in F5-93.15% comparatively with other formulations. The Solubility analysis of Tetrazosin was carried out before and after formulation in distilled water and phosphate buffer pH 6.8. The results show that the solubility profile is improved after formulations (from insoluble to slightly soluble) compared with pure drug. Thus the solubility of formulation F5 in distilled water and phosphate buffer pH 6.8 were improved (9.4933 mg/ml and 13.251 mg/ml) respectively. The in vitro release study was carried out for all seven formulations. The percentage of drug release in formulation FS was found to be 95.03% at the end of 12h and the release profile was in controlled manner comparatively with other formulations. Based on the higher entrapment efficiency, drug content and prolonged in vitro drug release F5 was selected as optimized formulation.

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