Development of Almotriptan Malate Biodegradable Nanoparticles Loaded for Treatment of Migraine

Krishnaveni R.¹, Halke Naresh², Prasad Gorakshanath Ghugarkar³, Choudhary Priti⁴, Kannan K.⁵, Usha Jinendra⁶, Chalmale Nirbhay² and Gautam Surya Prakash⁷*

¹Department of Microbiology, Vijayanagara Sri Krishnadevaraya University, Ballari, Karnataka, India
²Department of Pharmaceutics, Dayanand College of Pharmacy, Latur, Maharashtra, India
³Dr. N. J. Paulbudhe College of Pharmacy, Ahmednagar, Maharashtra, 414003, India
⁴K.R. Mangalam University, Gurugram, 121103, India
⁵Department of Agricultural Engineering, Sethu Institute of Technology, Autonomous, Pulloor, Kariapatti, Virudhunagar, Tamil Nadu, India
⁶Department of Chemistry, The Oxford College of Engineering, Bengaluru, Karnataka, India
⁷Government Pharmacy College Sullah, Kangra 176084, Himachal Pradesh, India

*Corresponding Author

Received: 2nd February, 2024; Accepted: 15th March, 2024; Published online: 20th March, 2024

https://doi.org/10.33745/ijzi.2024.v10i01.051

Abstract: The manner in which a drug is given can have a big effect on how well it works. When taking certain medicines, the best concentration range is where they work best. Doses above or below this range may be harmful or have no effect at all. On the other hand, the slow progress in effectively treating serious illnesses has shown that a more diverse approach is needed to get medicines to where they need to go inside cells. The purpose of this study was to find a way to fix headaches by creating and testing chitosan nanoparticles that contain almotriptan malate and are given through the nose. The current study tried to create a new dosage form of almotriptan malate nanoparticles that are targeted to the brain through the nose using the biodegradable material chitosan and the ionic gelation process. So, new study has successfully moved the water-loving drug almotriptan malate from the nose to the brain by adding it to biodegradable chitosan nanoparticles, which makes them an effective migraine treatment. The study results are useful for plans to use chitosan nanoparticles and the medicine almotriptan malate to make a new kind of medicine delivery system that can help people with headaches.

Keywords: Almotriptan malate, Nanoparticles, Chitosan, Migraine


https://doi.org/10.33745/ijzi.2024.v10i01.051

This is an Open Access Article licensed under a Creative Commons License: Attribution 4.0 International (CC-BY). It allows unrestricted use of articles in any medium, reproduction and distribution by providing adequate credit to the author(s) and the source of publication.

Introduction

The way in which a pharmaceutical substance is administered can significantly impact its effectiveness. Certain medications possess an optimal concentration range, beyond or falling
short of which may result in detrimental or ineffective effects, rather than therapeutic benefits (Tanna et al., 2023). Conversely, the sluggish advancements in enhancing the effectiveness of treatments for severe illnesses have underscored the increasing necessity for a multidisciplinary strategy to deliver drugs to their intended targets within tissues (Keservani et al., 2016).

Consequently, novel concepts were developed to regulate the non-specific toxicity, pharmacokinetics, pharmacodynamics, immunogenicity, and biorecognition of pharmaceutical substances. These innovative methods, which are referred to as "drug delivery systems" (DDS), are founded upon interdisciplinary principles that merge molecular biology, pharmaceutics, polymer science, and bioconjugate chemistry (Nair et al., 2021). In pursuit of enhanced drug bioavailability, prevention of adverse effects, reduction of drug loss and degradation, and augmentation of drug deposition in the intended site, numerous drug delivery and targeting systems are presently under development (Nair et al., 2020). An innovative, regulated medicine delivery system that was previously an impracticable notion has become a tangible reality (Salem et al., 2020).

Soluble polymers, insoluble or biodegradable microparticles, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles are all viable materials that can serve as drug carriers (Ahire et al., 2020). The carriers have the potential to exhibit specific characteristics of the target area, degrade gradually, be sensitive to pH or temperature, or even be targeted (for instance, through conjugation with antibodies that target particular attributes of the target region). Targeting refers to the capacity to guide a drug-loaded system towards the designated location (Abbas and Marihal, 2014).

Drugs may be directly administered to the central nervous system (CNS) to provide specific activity. Because of its stubborn impediment effect, the blood brain barrier may significantly reduce the effectiveness of many medications (such as antibiotics, antineoplastic medicines, and neuropeptides-- drugs that stimulate the central nervous system) (Rushendran et al., 2017). According to a recent study, almost all big molecule medications and 98% of small molecule medications typically do not penetrate the blood brain barrier. Many strategies with improved pharmacodynamic effects are now being researched to treat brain diseases (Patil et al., 2023). In order to deliver drugs to the brain, advancements are needed in two primary fields: drug discovery and drug delivery technology (Surana et al., 2022). One cutting-edge technique that may be used to transport medication molecules straight into the brain and has shown to be particularly successful against a number of CNS illnesses is the nanoparticle drug delivery system (NDDS) (Singh et al., 2017).

A sizable portion of the global population suffers from the migraine syndrome, which is more common in women (15%) than in males (6%). The hallmark of a migraine is a sharp, throbbing headache that is accompanied by cognitive and motor function impairment, anorexia, nausea, vomiting, photophobia, and phonophobia (Furquan et al., 2023). There is more to migraines than “just a headache.” This is a complicated neurological disorder that may cause several symptoms, sometimes even without a headache, and can affect the whole body. It affects individuals differently and is frequently missed or confused with other ailments (Formica et al., 2022). Although research is ongoing, we still do not know what exactly causes migraines; there is not a reliable diagnostic procedure, and there is not a treatment either. Nonetheless, there are several approaches to assist control the illness and minimise its effects, which will eventually minimize the disturbance to daily living (Bhandari et al., 2022). The purpose of this study was to find a way to fix headaches by creating and testing chitosan nanoparticles that contain almotriptan malate and are given through the nose.

Materials and Methods

*Calibration curve Preparation of almotriptan*
malate:

pH 6.5 phosphate buffer Preparation:

Following the dissolution of 60.5 g of disodium hydrogen phosphate and 46 grammes of potassium dihydrogen phosphate in water, 1 L of mercuric chloride were added to the solution. Additionally, 100 ml of 0.02 m disodium edetate was added (Aher et al., 2023).

 Calibration curve of almotriptan malate:

A volumetric vessel with a capacity of 100 ml was filled with 100 mg of almotriptan malate. This was then mixed with methanol. 6.5 phosphate buffer solution was added to the volume to make the concentration 1000 µg/ml. After removing 10 µl, it was combined with 100 µl of 6.5 phosphate buffer solution to achieve a final concentration of 100 µg/ml. A volume of 1 ml, 0.2 ml, 0.4 ml, and 0.8 ml were extracted from the standard stock solution and diluted with phosphate buffer (pH 6.5) to obtain concentrations of 4, 8, 12, 16, and 20 µg/ml, respectively. To compare the absorption of these solutions, a blank solution of phosphate buffer solution with a pH of 6.5 was utilised at 227 nm (Sonawane et al., 2023; Pardeshi et al., 2024).

Preparation of Nanoparticles:

Making a gel out of chitosan and sodium tripolyphosphate anions produced biodegradable nanoparticles. The chitosan was broken down with a dilute acetic solution that was 1% w/v. The concentration of acetic acid was 1.5 times higher than the concentration of chitosan in water. Blank nanoparticles are made by mixing 4 ml of a sodium tripolyphosphate water solution at strengths of 0.5, 1.0, and 1.5 mg/ml with a magnetic mixer at room temperature (Table 1). Nano-particles with almotriptan were made by adding 4 ml of sodium tripolyphosphate to 10 ml of chitosan solution that had a certain concentration of almotriptan. It was dried, cleaned, and spun at 10,000 rpm for 30 min after the nanoparticle suspension was made (Emad et al., 2021; Fakir et al., 2023).

In vitro drug release study of formulations:

The in vitro drug release study of the improved batch was done using diffusion via the dialysis membrane idea in a USP Type II (paddle type) device. A dialysis bag was soaked in pure water for an hour before it was used. The bag was then attached to the paddle of the equipment. Nanoparticles with drugs that had been spread out in 2 ml of phosphate buffer (pH 6.5) were in the bag. The dissolved medium was a 500-ml phosphate buffer with a pH of 6.5. It was kept at 37±1°C while the paddle turned at 100 rpm. At set times, 5 ml portions of the sample were removed and replaced with the same amount of brand-new dissolving media. Using the right blank, the samples were examined spectrophotometrically at λmax = 228 nm to find out how much medicine was released at different times. The results were shown as the average percentage of medicine released plus the standard variation (Keservani et al., 2017; Nguyen et al., 2022).

In vitro drug release kinetics:

Using the information gathered from in vitro release investigations, the following kinetic models were plotted to calculate the drug release kinetics of almotriptan nanoparticles. The Korsmeyer-Peppas equations were used to ascertain the drug release mechanism (Behera et al., 2010; Keservani et al., 2023).

Results and Discussion

Calibration curve of almotriptan malate:

The spectrophotometric method at 228 for measuring almotriptan malate is very reliable at values between 4 and 20 µg/ml, as shown by confirmation tests (Table 2). The value of 0.9990, which is closer to 1, was found to be the relationship between concentration and absorption (Fig. 1).

Preparation of Almotriptan Nanoparticle:

The ion gelation method was employed to produce four formulations and a blank formulation of almotriptan malate-loaded chitosan nanoparticles, with sodium tripolyphosphate serving as the cross-linking agent.
Table 1: Formulation of Nanoparticle

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Formulation</th>
<th>Chitosan (mg/ml)</th>
<th>Sodium Tripolyphosphate (mg/ml)</th>
<th>Almotriptan (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>1</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>1</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>3</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>4</td>
<td>2.0</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2: Calibration curve of almotriptan

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Concentration</th>
<th>Absorbance At228 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>0.034</td>
</tr>
<tr>
<td>2</td>
<td>8.0</td>
<td>0.048</td>
</tr>
<tr>
<td>3</td>
<td>12.0</td>
<td>0.068</td>
</tr>
<tr>
<td>4</td>
<td>16.0</td>
<td>0.088</td>
</tr>
<tr>
<td>5</td>
<td>20.0</td>
<td>0.096</td>
</tr>
</tbody>
</table>

Fig. 1: Calibration curve of almotriptan malate.

Table 3: Cumulative percentage release studies

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Cumulative percentage release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>45</td>
<td>51</td>
</tr>
<tr>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>90</td>
<td>73</td>
</tr>
</tbody>
</table>
**In vitro drug release study of formulations:**

Figure 2 illustrates the *in vitro* release curve of ZMT across various formulations. Variations in drug release were observed across all formulations. It undergoes constant modification.

The release characteristics of biodegradable chitosan nanoparticles were determined using a phosphate buffer solution at a pH of 6.5. In the beginning, the chitosan nanoparticles released almotriptan malate at a rapid rate, approximately 60% of the substance within 45 min. This may occur due to the drug being released initially from the nanoparticles on the surface, followed by a gradual release of the drug within the CBN. A decrease in particle size results in an increase in the surface area of chitosan nanoparticles laden with drugs, thereby accelerating the release of the drugs (Table 3).

**In vitro drug release kinetics of the optimized formulations:**

We used data from in vitro drug release from the improved formulation and fitted it to models of zero order, first order, Higuchi, and Korsemeyer-Peppas to figure out how the dosage form releases drugs and how fast they release. The data is less straight when the zero-order equation is used to show it. So, we can say that first order dynamics controls the main way that drugs are released. One way to understand how drugs are released is to put the data into a mathematical model of Korsmeyer-Peppas plots. Linearity was seen when the square root of time was plotted against the percentage flow. A lot of the time, first-order model-based data help the drug release diffusion process from devices that give drugs slowly over time.

**Conclusion**

An antimigraine medication is almotriptan malate. Its pharmacological effect is achieved by reducing the activity of trigeminal nerves, inhibiting the release of neurotransmitters from brain neurons, constricting the meningeal arteries, and preventing nociceptive transmission. Additionally, *in vitro* kinetic study was carried out, and the results, when plotted using the zero-order equation, show less linearity. Therefore, it may be...
said that first order kinetics governs the main mechanism of drug release.

Thus, current study has successfully targeted the hydrophilic medication almotriptan malate from the nose to the brain by incorporating it into chitosan biodegradable nanoparticles for effective migraine treatment. In order to treat mild to moderate migraines, the project’s future goals include conducting in vivo studies on the optimised formulation and combining it with free medication and penetration enhancers to improve drug release for both immediate and prolonged action. The study findings provide valuable insights for next investigations that seek to create a medication delivery formulation using chitosan nanoparticles and medicine almotriptan malate for the management of migraines.

References


