SYNERGISTIC DRUG COMPATIBILITY OF SUMATRIPTAN SUCCINATE AND METOCLOPRAMIDE HYDROCHLORIDE (IN SITU GEL FORMULATIONS) FOR NASAL DRUG RELEASE OPTIMIZATION

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ABSTRACT

Objective: Migraine is a prevalent neurological condition that causes lifelong tenacious headaches and significantly impacts the daily lives of individuals. Despite being frequently underestimated or neglected, it affects the individual’s routine activities, performance, self-confidence, and identity. Treatment often involves the administration of painkillers, which can lead to various complications. This study aimed to develop and characterize an in situ nasal formulation of sumatriptan succinate and metoclopramide hydrochloride to enhance drug residence time in the nasal cavity and improve drug bioavailability.

Methods: Eight formulations of intranasal in situ gels were prepared using the "Cold Method" and evaluated for various parameters, including appearance, texture, viscosity, pH, gel strength, gelation temperature, drug content, and in vitro/ex vivo drug diffusion. FT-IR studies confirmed no interactions between sumatriptan succinate, metoclopramide hydrochloride, and the excipients. Simultaneous estimation method was used to evaluate drug content, in vitro and ex vivo drug diffusion.

Results: Among the formulations, "Sumatriptan Succinate Metoclopramide Hydrochloride Polymer (SMP8)" exhibited the most favorable characteristics. The percent cumulative drug release was determined to be 96.80±0.0015 for sumatriptan succinate and 92.56±0.0028 for metoclopramide hydrochloride, aligning with the Higuchi model kinetics. In vitro and ex vivo diffusion studies demonstrated that SMP8 provided sustained drug release for up to 9 h, making it the optimal dosage formulation for nasal drug delivery in the treatment of migraine.

Conclusion: This study’s findings suggest that the developed intranasal in situ gel formulation, SMP8, effectively releases sumatriptan succinate and metoclopramide hydrochloride over an extended period. By improving drug residence time and bioavailability, this formulation has the potential to enhance the therapeutic efficacy and patient compliance in the management of migraine.

Keywords: Sumatriptan succinate, Metoclopramide hydrochloride, SMP-sumatriptan succinate metoclopramide hydrochloride polymer, Nasal drug delivery, Intranasal in situ gels.

INTRODUCTION

Migraine is one of the most prolonged, often neglected, wrongly diagnosed, and under-treated neurological conditions leading to years of disability affecting billions of people worldwide [1]. Migraine should not be mistaken for a normal headache, for it is a complicated neurovascular episode causing bouts of moderate-to-severe headache for many hours accompanied by nausea, photophobia, and phonophobia. The second type of migraine includes: "Migraine with Aura" also known as classical migraine which lasts for a few min. The third and most severe is "Chronic migraine" also considered high-frequency migraine for the episodes of headaches is 15 days in a month with 8 days of migraine-like symptoms and can last longer than 3 months [3,5].

Depending on the severity of the migraine, most people use medication to help them get through very unpleasant bouts. Acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs such as acetylsalicylic acid (the ingredient in aspirin), diclofenac, or ibuprofen are among the medications used to treat migraine episodes [3].

Triptans are the first line of antimigraine agents approved by the FDA and preferred for the treatment of migraine headaches with or without aura. They are been reported for selectively binding to the serotonin receptors 5-HT1B and 5-HT1D, thereby leading to vasoconstriction of the cranial arteries, thereby relaxing the painfully dilated arteries hence easing the migraine attacks [6,7].

Among all the triptans, sumatriptan succinate is the first selective 5-HT1B/1D receptor antagonist used in the treatment of migraine. The antimigraine activity of sumatriptan has been ascribed to the constriction of dilated cranial extracerebral blood vessels, especially the arterio-venous shunts in the carotid artery, which express 5-HT1B/1D receptors. Dilatation of these shunt vessels during migraine attacks is believed to divert blood flow away from the brain parenchyma [8]. Migraine is usually accompanied
by nausea and vomiting. The anti-emetic drugs used to treat migraine are metoclopramide and prochlorperazine. These drugs act by antagonizing the dopamine D2 receptor and are used to treat nausea and vomiting seen in acute migraines. Metoclopramide hydrochloride has been noted to increase the absorption of other drugs and relieve gastric stasis by causing gastric dilatation and LES relaxation [9].

Sumatriptan succinate can be administered orally, subcutaneous injections, and through a nasal spray. Oral administration tends to have lower bioavailability for the action, subcutaneous injection administration has a longer effect but the effect to occur is slower; but nasal delivery has appeared to be fast and effective for the immediate relief of migraine attacks [10].

Nasal drug delivery is one of the routes of drug administration that provides high access to the highly vascularized nasal mucosa and can be used for local drug delivery, systemic drug delivery, and targeted drug delivery (CNS) [11]. Apart from other systemic drug delivery systems, such as oral and parenteral (intraavenous, intramuscular), the nasal drug delivery system is a specialized drug delivery technology which results in effective and improved drug delivery as it avoids acidic or enzymatic degradation, does not undergo extensive first-pass effect (hepatic metabolism) following administration, delivers the drug through olfactory region, and bypasses the blood-brain barrier [12]. Further, intranasal drug delivery is easily accessible and can be suitable for self-administration by the patient. The large surface area of the nasal mucosa provides a rapid onset of therapeutic action [13]. However, various factors such as low residence time of drugs in the nasal cavity, rapid mucociliary clearance, inaccurate drug dose due to difficulty in drug administration, and nasal mucosa irritation limit the bioavailability of the drugs given by the nasal route in the form of nasal sprays, nasal drops, ordinary nasal gels, and nasal powders. In situ gels are liquid preparations which when instilled within the body cavity undergo a phase transition from sol to visco-elastic gel due to various types of stimuli [12,14]. In the present research, an attempt is made to develop and evaluate in situ nasal gel consisting of a combination of two drugs sumatriptan succinate (anti-migraine) drug and metoclopramide hydrochloride (anti-emetic) drug with the aim of ease of administration, accuracy of dosing prolonged nasal residence time, and improved nasal bioavailability.

MATERIALS AND METHODS

Materials

Sumatriptan succinate and poloxamer 407 were obtained from Mylan Laboratories, Hyderabad, Telangana, India; metoclopamide hydrochloride from Yarrow Chem Products Pvt. Ltd, Mumbai, India; poloxamer 188 from Ozone Chemicals, Mumbai, India; sodium carboxymethyl cellulose, carbopol 934 LR, sodium lauryl sulfate, propylene glycol, benzalkonium chloride, and sodium metabisulphite from SD Fine-Chem Ltd, Mumbai, India.

Methods

Formulation of in situ gels

The gels (w/v) were prepared using the cold method. The polymers and other excipients were gradually added to cold water (5°C) with constant stirring and the dispersions obtained were stored in a refrigerator until clear. Different concentrations of sodium carboxymethyl cellulose were prepared in distilled water to which a 500 mg mixture of both the drugs sumatriptan succinate and metoclopramide hydrochloride were added. To these prepared solutions, polymers were gradually added with agitation for 1 h. The composition of developed gel formulations was prepared as mentioned by PANDA 2014 with slight modification [15-17]. There were in total of 8 gel formulations prepared and named SMP1 to SMP8, and the composition of the gels is depicted in Table 1.

UV (ultraviolet) spectroscopic studies

a. Determination of λ\text{max} of sumatriptan succinate: The stock solution was prepared by adding 5 mg of sumatriptan succinate to 50 mL of phosphate buffer pH 6.4 and λ\text{max} was scanned in the range of 400 nm-200 nm for 1, 2, 3, 4, 5, and 6 μg/mL sumatriptan succinate obtained from the stock solution [16,18,19].

b. Determination of λ\text{max} of metoclopramide hydrochloride: Metoclopramide hydrochloride stock solution was prepared by adding 5 mg of it in 50 mL of phosphate buffer pH 6.4. Different dilutions of metoclopramide hydrochloride, that is, 5, 10, 15, 20, 25, and 30 μg/mL were prepared from the stock solution and scanned in the range of 400 nm-200 nm to determine λ\text{max} [16,18, and 19].

FT-IR studies

To validate the compatibility of both standard drugs used along with the mentioned polymers and other excipients, the IR spectra studies were carried out using an FTIR spectrophotometer (Cary 630, Agilent Technology). Spectra of a mixture of sumatriptan succinate, poloxamer 407, metoclopramide hydrochloride, poloxamer 188, sodium carboxymethyl cellulose, carbopol 934 LR, sodium lauryl sulfate, propylene glycol, benzalkonium chloride and sodium metabisulphite will be obtained and the spectral scanning will be in the range between 4000 and 450 cm\textsuperscript{-1} [20].

Pre-formulation studies

The drugs that is, sumatriptan succinate and metoclopramide hydrochloride) were evaluated for identity, purity, compatibility, and physical properties. The intranasal in situ gel formulations were examined for appearance (clear/turbid), texture and consistency (stickiness and grittiness), viscosity, pH, gelation time, gel strength, drug content, and in vitro drug release study [16,17].

In vitro diffusion of gel formulations

1 mL of each gel formulation, that is, sumatriptan succinate: SP1 to SP 8 (as per Table 1 but without metoclopramide hydrochloride) were evaluated for identity, purity, compatibility, and physical properties. The intranasal in situ gel formulations were examined for appearance (clear/turbid), texture and consistency (stickiness and grittiness), viscosity, pH, gelation time, gel strength, drug content, and in vitro drug release study [16,17].

Table 1: Composition of developed in situ gel formulations containing sumatriptan succinate and metoclopramide hydrochloride

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>SMP1</th>
<th>SMP2</th>
<th>SMP3</th>
<th>SMP4</th>
<th>SMP5</th>
<th>SMP6</th>
<th>SMP7</th>
<th>SMP8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan Succinate (%w/w)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Metoclopramide Hydrochloride (%w/w)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Poloxamer 188 (%w/w)</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>Poloxamer 407 (%w/w)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>Sodium CMC (%w/v)</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Carbopol 93-4LR (%w/v)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SLS (%w/v)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Propylene Glycol (%v/v)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Benzalkonium Chloride (%w/v)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Sodium Metabisulphite (%w/v)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Distilled Water makes up</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Sodium CMC: Sodium carboxymethyl cellulose, SLS: Sodium lauryl sulfate*
membrane which acted as donor compartment which was placed in 25 mL of phosphate buffer pH 6.4 (receptor compartment). The whole assembly was kept on a magnetic stirrer and was stirred continuously at an optimum speed (100 rpm). A temperature of 37±0.5°C was maintained throughout the experiment. At pre-determined time intervals, 5 mL of the samples was withdrawn and replenished with an equal amount of phosphate buffer. The samples were appropriately diluted and filtered and absorbances were measured spectrophotometrically using a UV spectrophotometer with phosphate buffer (pH 6.4) as the blank. The cumulative percent drug released was recorded for all the gel formulations at each time interval and a graph was plotted between % CDR versus time in min using λmax 227 nm for sumatriptan succinate and 272 nm for metoclopramide [21].

**Ex vivo diffusion of gel formulations**

Ex vivo permeation study was conducted using a Franz diffusion cell containing 10 mL of phosphate buffer (pH 6.4) using an excised goat nasal mucosa. The freshly excised nasal mucosa was mounted on the diffusion cell, and 100 μL of gel containing 200 mg and 100 mg each of sumatriptan succinate and metoclopramide hydrochloride, respectively, was placed on it. Throughout the study, the buffer solution in the chamber was maintained at 37±1°C by connecting the Franz diffusion cell with a water bath. At pre-determined time intervals, 5 mL of the samples was withdrawn and replenished with an equal amount of phosphate buffer. The samples were appropriately diluted and filtered and absorbances were measured spectrophotometrically using a UV spectrophotometer taking phosphate buffer (pH 6.4) as the blank. Cumulative percent of drug dissolved was found at each time interval and the graph was plotted between % CDR versus time in min for SMP8 using λmax 227 nm for sumatriptan succinate and 272 nm for metoclopramide hydrochloride [22].

**RESULTS AND DISCUSSIONS**

**Determination of λmax of sumatriptan succinate**

Sumatriptan succinate (5 mg) was diluted using phosphate buffer pH 6.4 with varying concentrations of 1, 2, 3, 4, 5, and 6 μg/mL. The λmax was determined for each solution, respectively, and based on the results of the spectral studies obtained λmax was found to be 227 nm Fig. 1.

**Determination of λmax of metoclopramide hydrochloride**

Based on the results of the spectral studies obtained, the λmax for the various dilutions (5, 10, 15, 20, 25, and 30 μg/mL) of metoclopramide hydrochloride (5mg) was found to be 272 nm Fig. 2.

**FT-IR studies**

The IR spectra of sumatriptan succinate and metoclopramide hydrochloride obtained were compared with reference standard functional group frequencies as per Indian Pharmacopoeia 2018. The functional group frequencies were in the reported range which indicates that the obtained sample is pure Figs. 3 and 4. The compatibility studies of pure drug sumatriptan succinate and metoclopramide hydrochloride revealed that the characteristic peaks were present in spectra, thus indicating compatibility between the two drugs which shows that there was no significant change in the chemical integrity of the drugs Fig. 5. The IR spectra of the physical mixture of the drugs with all the excipients indicated that the functional group frequencies were in reported range and no new bands were observed in the spectra of the physical mixture when compared with the individual FT-IR spectra of drug and individual polymers which indicates that the ingredients were compatible with each other Fig. 6.

![Fig. 1: λmax of sumatriptan succinate in phosphate buffer pH 6.4](image1.png)

![Fig. 2: λmax of metoclopramide hydrochloride in phosphate buffer pH 6.4](image2.png)

![Fig. 3: FT-IR (KBr cm⁻¹) of sumatriptan succinate](image3.png)
Table 2: Physical appearance, clarity/texture, pH, gel strength, gelation temperature, drug content, and gelling capacity of *in situ* nasal gel of sumatriptan succinate and metoclopramide hydrochloride

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Appearance</th>
<th>Clarity/texture</th>
<th>pH</th>
<th>Gel strength</th>
<th>Gelation temperature</th>
<th>Drug content</th>
<th>Gelling capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMP1</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>6.1</td>
<td>54±0.11</td>
<td>38°C</td>
<td>96.5±0.34</td>
<td>-</td>
</tr>
<tr>
<td>SMP2</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>6.0</td>
<td>63±0.60</td>
<td>43°C</td>
<td>98.3±0.53</td>
<td>-</td>
</tr>
<tr>
<td>SMP3</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>6.0</td>
<td>92±0.22</td>
<td>36°C</td>
<td>99.3±0.34</td>
<td>-</td>
</tr>
<tr>
<td>SMP4</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>6.3</td>
<td>87±0.26</td>
<td>48°C</td>
<td>94±0.15</td>
<td>+</td>
</tr>
<tr>
<td>SMP5</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>6.0</td>
<td>92±0.21</td>
<td>40°C</td>
<td>96±0.46</td>
<td>+</td>
</tr>
<tr>
<td>SMP6</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>6.2</td>
<td>96±0.33</td>
<td>48°C</td>
<td>91±0.23</td>
<td>+</td>
</tr>
<tr>
<td>SMP7</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>6.3</td>
<td>64±0.22</td>
<td>37°C</td>
<td>95±0.41</td>
<td>++</td>
</tr>
<tr>
<td>SMP8</td>
<td>Transparent</td>
<td>Clear/Sticky, non-greasy</td>
<td>5.8</td>
<td>68±0.24</td>
<td>36°C</td>
<td>98±0.16</td>
<td>+++</td>
</tr>
</tbody>
</table>

- No gelation, +: Gels after a few minutes dissolves rapidly, ++: Gelation immediate remains for few hours, +++: Gelation immediate, remains for an extended period.

Fig. 4: FT-IR (KBr cm⁻¹) of metoclopramide hydrochloride

Fig. 5: FT-IR (KBr cm⁻¹) of physical mixture of sumatriptan succinate and metoclopramide hydrochloride

Fig. 6: FT-IR (KBr cm⁻¹) spectrum of formulation SMP8
Physical appearance

All the formulations were transparent and were found to be clear without any turbidity and suspended particles or impurities which is summarized in Table 2. From the study carried out, it was observed that formulation SMP1, SMP2, and SMP3 shows no gelation and formulation SMP8 shows immediate gelation and remains in gel form for a longer time. Further, the % w/w drug content was found to be in the range of 91±0.23–99.31±0.34. The viscosity of all prepared batches of intranasal in situ gels was measured using a Brookfield DV-E viscometer using spindle no. 64 at the rotation speed of 0.6 rpm at room temperature. All the formulations exhibit pseudoplastic flow after gelling. The viscosity increased with the increasing concentration of carbopol 934 LR Table 3.

In vitro diffusion study

In vitro diffusion study was carried out for all eight formulations and the study was carried out for a time period of 11 h. All eight formulations showed a linear increase in drug diffusion across the eggshell membrane with time. Comparatively, the SMP8 formulation showed the maximum
from the FT-IR studies revealed that the drugs were intact and there was no drug-drug and drug-polymer interaction between drug and excipients used in the formulation. The present study also focused on in vitro and ex vivo drug release from prepared gel formulations. The in vitro studies were carried out using the open-ended glass cylinder method in which it was evident that the SMP8 formulation had better penetration of the drug with respect to time duration. Based on these outcomes, SMP8 formulation was further subjected to ex vivo studies using the Franz diffusion cell method, the result obtained revealed that the formulation SMP8 showed the maximum percent cumulative drug release of sumatriptan succinate, that is, 96.803±0.0045 and metoclopramide hydrochloride, that is, 92.569±0.0023 after 9 h with over 50% drug release for both drugs after 3 h, respectively, which is higher compared to the drug given through oral administration. In conclusion, the present study has revealed that SMP8 nasal gel formulation has proven to have no drug compatibility issue and the drugs permeation through the nasal mucosa, displayed that SMP8 nasal gel formulation can be potentially more effective in treating migraine patients than oral drugs which are currently being used, however further pre-clinical studies need to be carried out for the formulation of the proposed drug before human trials initiated.

ACKNOWLEDGMENT

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REFERENCES


Table 3: Viscosity study of in situ gels of sumatriptan succinate and metoclopramide hydrochloride

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMP1</td>
<td>646.15</td>
</tr>
<tr>
<td>SMP2</td>
<td>722.31</td>
</tr>
<tr>
<td>SMP3</td>
<td>764.87</td>
</tr>
<tr>
<td>SMP4</td>
<td>784.45</td>
</tr>
<tr>
<td>SMP5</td>
<td>801.47</td>
</tr>
<tr>
<td>SMP6</td>
<td>821.16</td>
</tr>
<tr>
<td>SMP7</td>
<td>761.72</td>
</tr>
<tr>
<td>SMP8</td>
<td>751.95</td>
</tr>
</tbody>
</table>

*Viscosity in cps

drug diffusion at the end of 11 h for both drugs, respectively, and was recorded to be the best formulation Figs. 7 and 9.

**Ex vivo diffusion study**

Based on the in vitro drug diffusion study, SMP8 formulation was subjected to ex vivo drug diffusion study for a total time period of 9 h. The formulation showed maximum drug diffusion at the end of 9 h through the nasal mucosa. Hence, the SMP8 formulation proved to be the best formulation Fig. 9.

**CONCLUSION**

About 15% of the world population has been reported with migraine headaches in 1-year prevalence out of which some get admitted into the hospital, others as outpatients of neurologists, further affecting their routine life activity and their overall performance [22,23]. Migraine is often accompanied by other symptoms such as nausea, vomiting, photosobia, and phonophobia. Nausea and vomiting have been observed in 60%–95% and 50%–62% of patients, respectively. These symptoms cause more disability than migraine itself as they will delay in oral intake of the medication thereby decreasing the absorption of the drug and ultimately increasing burden on the patient’s life [24].

As discussed above sumatriptan succinate is the choice of drug to relax the dilated cranial extracerebral blood vessels which eases the pain of the migraine.

Metoclopramide hydrochloride is FDA-approved antagonist drug for dopamine receptors to treat nausea and vomiting, especially for patients suffering from gastroesophageal reflux disease or diabetic gastroparesis [25].

At present, there are several drugs available in market using the triptans for treating migraine, most of them are in the form of oral drugs. Nasal drugs in the market such as IMITREX (sumatriptan), MIGRANAL (dihydroergotamine mesylate), ZOMIG (zolmitriptan), ONZETRA, Xsail (sumatriptan) which are approved by the FDA [26]. However, sumatriptan combined with other drugs and checking their compatibility is rarely been observed.

Thereby an attempt is made in the study on combining sumatriptan succinate and metoclopramide hydrochloride drug as a nasal spray to have an immediate effect on patients suffering from migraine and also suppress the symptoms of vomiting and nausea among these patients.

Intranasal in situ gel of sumatriptan succinate and metoclopramide hydrochloride was prepared by cold method using sodium carboxymethyl cellulose, carbopol 934 LR, poloxamer 188, and poloxamer 407 as polymers for controlled release of the drugs. The prepared intranasal in situ gel was evaluated for various parameters such as appearance, texture, viscosity, pH, gel strength, gelation temperature, and drug content in vitro and ex vivo drug diffusion study. The physical appearance of all eight gel formulations (that is, SMP1–SMP8) was found to be uniform in their viscosity, pH, gel strength, and gelation temperature of the gel. The spectra obtained...


