Journal of Drug Delivery Science and Technology 29 (2015) 238–244

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Research paper

Formulation and evaluation of thermoreversible mucoadhesive in-situ gel for intranasal delivery of naratriptan hydrochloride

Santosh Shelke [a, *], Sadhana Shahi [b], Sunil Jalalpure [c], Dinesh Dhamecha [c], Sushant Shengule [c]

[a] Yash Institute of Pharmacy, Department of Pharmaceutics, Bajaj Nagar, Aurangabad 431134, Maharashtra, India
[b] Government College of Pharmacy, Department of Pharmaceutics, Osmanpura, Aurangabad 431005, Maharashtra, India
[c] KLEU's College of Pharmacy and Dr. Prabhakar Kore Basic Science Research Centre, KLE University, Nehru Nagar, Belagavi 590010, Karnataka, India

ARTICLE INFO

Article history:
Received 4 July 2015
Received in revised form
31 July 2015
Accepted 7 August 2015
Available online 11 August 2015

Keywords:
Naratriptan hydrochloride
Poloxamer 407
Carbopol 934
Thermoreversible
Intranasal gel
Mucoadhesive

ABSTRACT

Intractable migraine presents a significant treatment challenge due to associated throbbing or pulsating headache, which affects one half of the head and lasts from 2 to 72 h. Naratriptan hydrochloride is an approved drug molecule for migraine headaches, but its use is limited due to its poor bioavailability, reoccurrence of migraine and lesser half-life requiring frequent dosing. Therefore, the objective of present study was to formulate a thermoreversible intranasal gel for drug targeting directly to brain *via* olfactory lobe pathway thereby improving bioavailability. Gels were formulated by using poloxamer 407 as thermoreversible polymer and carbopol 934 as mucoadhesive polymer. Formulated gels were characterized for gelation temperature, gel strength, mucoadhesive strength, viscosity, *in-vitro* drug release and *ex-vivo* permeation study using sheep nasal mucosa. *In-vitro* and *ex-vivo* drug release studies suggested that the release rate was directly proportional to the concentration of carbopol 934, whereas poloxamer 407 reduced the rate of drug release. Histopathology study of sheep nasal mucosa showed no signs of damage to columnar epithelial cells, confirming non-toxic nature of the formulated gel. Stability studies performed as per ICH guidelines [Q1A (R2)] suggested that the gels were stable.

1. Introduction

Intractable migraine presents a significant treatment challenge to both patients and physicians. Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches, which is often associated with a several autonomic nervous system symptoms. Typically the migraine headache is unilateral (affecting one half of the head), and throbbing or pulsating, from 2 to 72 h. Associated symptoms include nausea, vomiting and photophobia (increased sensitivity to light), phonophobia (increased sensitivity to sound) or smell and pain which may worsen by any kind of physical activity [1].

Oral route is considered to be the most convenient and economic route of drug administration, however this route of drug administration is sometimes inefficient owing to the properties of drug in use such as poor bioavailability [2], first pass metabolism [3], drug solubility [4] and absorption [5] issues, thus there is an obvious need for alternative but novel drug delivery systems [6]. Parenteral routes of administration like subcutaneous route is another option but the dislike for injection make this dosage form less acceptable for the patients [7]. The percutaneous route is also used for the controlled delivery of drugs which bypasses the first pass metabolism, but has limitations for the permeability of the skin to many drugs [8]. As a preferred alternative to this, transmucosal routes including the nasal, buccal, pulmonary, rectal and vaginal routes can be used to overcome above mentioned issues wherein, intranasal (nasal cavity) route could provide distinctive benefits to drug by low photolytic activity, prevention of harsh environmental conditions, hepatic first pass metabolism and direct delivery to the brain. Intranasal route also provides an advantage of ease of access, improving bioavailability [9], good permeability mainly for lipophilic and low molecular weight drugs [10,11], ease of self-administration, ease of handling and can even be administered to patients in vomiting and unconscious state [12]. Moreover,

* Corresponding author.
E-mail addresses: santoshshelke24@yahoo.com, santoshshel@gmail.com (S. Shelke).

http://dx.doi.org/10.1016/j.jddst.2015.08.003
1773-2247/

recent advancement has revealed that the nasal mucosa can act as the site for directly delivering the therapeutics to the CNS through the olfactory lobes, which helps to circumvent the blood brain barrier (BBB) [13].

Naratriptan hydrochloride (NH) is a selective 5-HT_1 receptor subtype agonist developed for the acute treatment of migraine which acts by stimulating constriction of dilated cranial arteries and by inhibiting the release of neurogenic inflammatory mediators [14]. Naratriptan is available only in oral form with the recommended dose of 2.5 mg, having an oral bioavailability of approximately 60% [15]. It exhibits a six fold higher affinity for the human recombinant 5-HT_1B receptor than Sumatriptan [16].

The physiological characteristics of the nasal mucosa and nasal mucociliary clearance are the two main considerations in designing nasal formulations. With a view to overcome these constrains, development of a thermosensitive mucoadhesive nasal formulation capable of undergoing sol to gel transition at the nasal temperature could serve the purpose. In general, nasal drug delivery is mainly developed to improve drug absorption rate and bioavailability by prolonging the drug residence time at the nasal absorption site through biodegradable mucoadhesive and thermosensitive polymers. The thermoreversible gel formulation helps to prolong the drug contact time and releases the drug in a controlled manner, which results in improved local and systemic bioavailability, reduced dose requirements, improved patient safety and acceptability [17]. Consequently, thermoreversible system helps the drug to be manufactured as liquid dosage form which will perform phase transitions at physiological nasal temperature [18]. Hence at in-situ nasal physiological conditions bioadhesive thermoreversible gels could be very useful for efficient targeted drug delivery to the brain through olfactory lobe. In recent decade different formulations for Sumatriptan [19], Rizatriptan Benzoate [20], Zolmitriptan [21], has been studied to deliver the drug *via* intranasal route, for this the drug was formulated in the form of thermoreversible gel and there was a sustained release of the drug by adhering the gel into the local tissues and releasing the drug to the brain through the olfactory lobes. From the pharmacokinetics standpoint intranasal administration circumvents first pass metabolism and drug absorption is rapid due to the existence of a rich vascular system and highly permeable structures within the permeable membrane [22].

Hence, the objective of the present investigation was to develop thermoreversible gel formulations of NH for intranasal delivery using thermoreversible polymer poloxamer 407 and mucoadhesive polymer Carbopol 934, which would enhance nasal residence time and absorption of the drug across nasal-mucosal membrane.

2. Materials and methods

2.1. Materials

NH was provided as a free sample from Orchid Chemicals and Pharmaceuticals Ltd. (Chennai, India). Poloxamer 407 was obtained as a free sample from Shreya life sciences Pvt. Ltd. (Aurangabad, India). Carbopol 934 and cellophane membrane (12,000–14,000 M.W) were purchased from Hi-Media Lab Pvt. Ltd., (Mumbai, India). All of the other reagents used in this study were of analytical grade.

2.2. Methodology

2.2.1. Compatibility studies

Compatibility studies were carried out at room temperature by Fourier transform infrared (FTIR) (Model-200, Thermo Electron, Shimadzu, Japan) to investigate any physical interactions between the drug and the excipients used in the formulation. The pure drug (NH) and polymers were subjected to FTIR studies alone and in combinations (1:1) and analyzed by KBr pellet technique [23].

2.2.2. Determination of gelation temperature

The temperature at which the liquid (sol) phase is converted to gel form is termed as gelation temperature. The sol–gel transition temperature of the prepared in-situ gel formulations was determined by visual inspection method [19]. Briefly, the solutions of poloxamer 407 in the concentrations (15–20% w/v) were prepared by stirring (magnetic stirrer, IKA India Private Limited, India) in a transparent 10 ml glass bottle sealed with paraffin. The vial was heated at constant rate with an increment of 1 °C and the temperature at which the magnetic bead stopped moving due to gelation was considered as gelation temperature. Gels which showed gelation temperature very close to the nasal temperature (32–34 °C) were selected for further evaluation. The effect of carbopol 934 on phase transition temperature was evaluated by dispersing different concentration (0.1–0.5% w/v) in optimized poloxamer 407 solutions.

2.2.3. Formulation of in-situ nasal gel of NH

Poloxamer 407 gel was prepared by dissolving the optimized poloxamer 407 concentration in cold water (4 °C). The hazy solution formed was kept in the refrigerator (2–4 °C) overnight for complete dissolution resulting in a clear solution. The 'cold' method was adopted for the formulation of NH thermoreversible gels (Table 1) [24], where Carbopol 934 (0.1–0.4% w/v) concentrations were added slowly to the optimized poloxamer 407 solution containing drug with continuous stirring at 4 °C. Formulated gels where then finally stored at 4 °C for further evaluation.

2.2.4. Evaluation of gel

2.2.4.1. Physico-chemical properties of in-situ gel. The formulated gels were evaluated for pH, clarity, drug content, viscosity and gel strength. The pH of each formulation was determined by using pH meter. Initially, the pH meter (Eutech Instruments Pvt. Ltd., Singapore) was calibrated by using standard buffer solutions of pH 4 and pH 7 (Thermo Fisher scientific standard buffers). The clarity was checked against white and black background and was graded as turbid (+), clear (++) and very clear (+++). Drug content was determined using UV–Vis spectrophotometer (Shimadzu 1800, Japan) at 283 nm. Rheological studies were performed with a thermostatically controlled Brookfield viscometer (DV3T Rheometer, USA) fitted with a suitable spindle at varying temperatures (20–40 °C).

Gel strength was determined by placing a standard weight of 35 g onto 50 g of thermoreversible gel (placed in 100 ml beaker) maintained at gelation temperature using controlled water bath. The time in seconds by the weight to penetrate 5 cm deep into the container was recorded as gel strength [25].

Table 1
Composition of NH thermoreversible gel formulations.

Formulation code	Drug (% w/v)	Poloxamer 407 (% w/v)	Carbopol 934 (% w/v)
NS	Pure drug solution (0.5%)	–	–
NG	0.5	18	–
G1	0.5	18	0.1
G2	0.5	18	0.2
G3	0.5	18	0.3
G4	0.5	18	0.4
G5	0.5	18	0.5