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Optimization of combinational intranasal drug delivery system for the management of migraine by using statistical design

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ABSTRACT

Migraine is a chronic disorder characterized by significant headache and various associated symptoms which worsen with exertion. Zolmitriptan approved for use in the acute treatment of migraine and related vascular headaches but are limited by high pain recurrence due to rapid drug elimination. Combinational formulation of triptans and a nonsteroidal anti-inflammatory drug may provide a quicker and longer duration of relief from the subsequent pain during the attack. In this study, we formulate a Zolmitriptan (ZT) & ketorolac tromethamine (KT) loaded thermo reversible in-situ mucoadhesive intranasal gel (TMISG) formulation which gels at the nasal mucosal temperature and contains a bioadhesive polymer (Xyloglucan) that lengthens the residence time will enhance the bioavailability of the combinational drugs. This study uses Box-Behnken design for the first time to develop, optimize the TMISG and assess factors affecting the critical quality attributes. Histopathological study of the nasal mucosa suggested that the formulation was safe for nasal administration. The statistical difference in absolute bioavailability between oral and intranasal route suggested that intranasal route had almost 21% increases in bioavailability for ZT and for KT there was 16% increase over oral formulations. Optimized formulation would help mitigate migraine associated symptoms much better over the currently available formulations.

1. Introduction

Migraine is a chronic disorder which usually consists of attacks characterized by significant headache and various associated symptoms such as nausea, vomiting, sonophobia, and photophobia (Rapoport, 2009). Migraine occurrence is causing significant impact on quality of life in Asian countries. A study conducted in superspeciality hospital concluded that 68% of medical students had headache of which 42% suffered from migraine (Menon and Kinnera, 2013). Migraine-related disability is high due to paucity of awareness about the disease. A significant finding reported 99% of migraine is predominantly due to poor sanitation, environmental changes, head movements and mental stress (Shivpuri et al., 2003). Serotonin receptor agonists (chemically belong to the class of triptans) are the mainstay in acute migraine treatment (Johnston and Rapoport, 2010). They display high affinity for 5-hydroxytrypamine (5-HT)$_{1B}$ and 5-HT$_{1D}$ receptors, and varying affinity for 5-HT$_{1F}$ receptor (Neeb et al., 2010) leading to vasoconstriction of cranial blood vessels. Zolmitriptan is a synthetic tryptamine derivative (Martin, 1997) recently approved for use in acute migraine and related vascular headaches. They provide immediate analgesia in migraine and cluster headache but are limited by high pain recurrence due to rapid drug elimination. A combinational formulation of triptan and nonsteroidal anti-inflammatory (NASID) drug may provide a quick and long duration relief from the pain during the attack (Dubey et al., 2014). Therefore, ketorolac tromethamine (a NASID) in combination with zolmitriptan will reduce symptom recurrence and have a substantial impact on patient quality of life as well as cost of care. Zolmitriptan nasal spray has limitation due to lower residence time (less than 15 min) followed by its leakage through the pharynx to the gastrointestinal tract resulting lower bioavailability. Although it provides faster onset of action but it cannot preclude re-occurrence and pain persistence. To overcome these constrains, thermoreversible in-situ mucoadhesive intranasal (TMIS) was formulated which gels at nasal mucosal temperature and contains a bioadhesive polymer that lengthens the residence time and thus the bioavailability of the combinational drugs. Several attempts have been made to deliver triptans (Majithiya et al., 2006; Godbole et al., 2014; Kempwade and Taranalli, 2014; Singh et al., 2013) by formulating a TMIS gel using pluronic (Majithiya et al., 2006) and poloxamers (Zaki et al., 2007; Pisal et al., 2004). Preponderance of literature suggested use of conventional optimization techniques where confounding effects of

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excipients over other prevents proper assessment of the factors affecting critical quality attributes of TMISG. The present study uses Pluronic F127 (GRAS approved) (Bromberg and Ron, 1998) and xyloglucan extracted from tamarind kernel powder. Xyloglucan is a highly branched chain carbohydrate polymer having structural similarity with endogenous mucin (Bianchini et al., 2000) allowing better mucoadhesion. This study uses Box-Behnken design for the first time to assess factors affecting the critical quality attributes of TMISG. The main effects and interactive effects of excipients and their role have also been addressed.

2. Materials and methods

2.1. Materials

Zolmitriptan (ZT) supplied by Mylan Pharmaceutical, Hyderabad (India), ketorolac tromethamine (KT) gifted by Torrent Pharmaceuticals, Ahmedabad (India). Pluronic F127 was purchased from Sigma–Aldrich (St. Louis, MO, USA). Tamarind gum was generous gift from Srinivas Agro industries, Solapur, Maharashtra (India). Polyethylene glycol (PEG, molecular weight 6000), potassium dihydrogen orthophosphate, acetonitrile, trimethylamine, orthophosphoric acid and sodium chloride were supplied by CDH, New Delhi (India). All other chemicals and reagents used in the study were of analytical grade.

2.2. Analytical method development and validation

An optimized analytical method was developed as per ICH Q2 (R1) guideline for the simultaneous determination of ZT and KT using RP-HPLC (Waters, USA) equipped with diode array detector (DAD). The developed method was applied for the determination of ZT and KT in formulation studies. A high-performance liquid chromatography (WATERS HPLC) (Milford, USA) was composed of a 515 solvent delivery module, a Waters 2707 auto sampler, injector with a 20 μL fixed loop and a 2998 PDA UV–visible detector. Separation was performed on Agilent HC C-18(2) column (particle size 5 μm; 250 mm × 4.5 mm SN-usjab01584) proceeded by an ODS guard column (10 μm, 10 mm × 5 mm internal diameter) at an ambient temperature. The mobile phase consisted of 146 μL of trimethylamine and about 750 μL of orthophosphoric acid which was added to 530 mL of HPLC grade water. The pH was adjusted to 3.3 using 10% potassium hydroxide solution and finally 470 mL of acetonitrile was added to make up the mobile phase.

2.3. Screening and optimization of pluronic concentration using 2^2 factorial design

Pluronic gel was prepared using cold technique described by Schmolka IR (Schmolka, 1972). Varying amount of Pluronic F 127 (20, 22 and 24% w/v) was dissolved buffer (pH 5.5) with continuous stirring (RQ-122, Remi, India) and kept overnight at 4 °C. The final volume of the aqueous solution was made to 50 mL with the buffer containing pre-dissolved propylene glycol (0.5, 1.0 and 1.5% w/v). A recommended dose of zolmitriptan and ketorolac tromethamine was added such that each 100μL of nasal gel contains 2.5 mg of zolmitriptan and 15.75 mg of ketorolac tromethamine consecutively. The independent variables in 2^2 factorial design were pluronic and propylene glycol concentrations while, gelation temperature was dependent variable.

2.4. Extraction of xyloglucan from tamarind gum

Pure xyloglucan was extracted from tamarind kernel powder (TKP) using method described by Rao et al. (1973). A known amount of TKP was dissolved in 200 mL of cold distilled water to prepare slurry and added slowly to 800 mL boiling water with continuous stirring and kept overnight. This was later subjected to centrifugation at 5000 rpm for 20 min. The supernatant liquid was separated and spray dried.

2.5. Preparation of thermo reversible in-situ nasal gel

From preliminary screening, 20% w/v of pluronic containing 1.5% w/v propylene glycol gelling at 27.4 ± 0.2 °C was selected for further study. Thermoreversible gel (20% w/v of PF127) was prepared by method described earlier in the text and kept overnight at 4 °C. Final volume of aqueous solution was constituted to 50 mL with buffer containing recommended dose of pre-dissolved bioactive. Water soluble additives like mucoadhesive polymer [xyloglucan (0.5, 1.0 and 1.5% w/v) and sodium alginate ((0.5, 1.0 and 1.5% w/v)], PEG (4000 and 6000), osmotic agent (NaCl) and benzalkonium chloride (0.02% v/v) were dissolved prior to Pluronic F127 addition to optimize mixing.

2.6. Measurement of sol–gel transition temperature

A 2 mL aliquot of thermoreversible mucoadhesive *in-situ* gel was poured in a test-tube and placed in heat circulating water bath with digital display and sealed with aluminum foil followed by parafilm. The water bath was set with temperature increment of 0.2 °C/min and equilibration at each new setting. The samples were constantly examined for gelation, a point when tilting of the test-tube at 90° did not cause the meniscus to move. Measurements were done in triplicates and statistical tests of significance were done using Student's *t*-test at $P < 0.05$.

2.7. Measurement of shear viscosity

Shear rate viscosity was measured for the prepared thermoreversible mucoadhesive *in-situ* gel containing ZT–KT using Rheometer Brookfield instrument (R/S-CPS-PI) having cone and plate geometry. Measurements were done under controlled shear rate (CSR) and varying the shear rate from 1 to 100/s. Samples was applied to the lower plate of the rheometer using a spatula to prevent spreading. A spindle number P75-I was attached to the measuring element coupling and micrometer ring was adjusted. The bath/circulator temperature was set at 35 ± 0.1 °C. The shear rate (γ) in s^{-1} and the corresponding viscosity (η) in centipoises (cps) were determined from the instrument reading and substituted in the rheological power-law equation or the Ostwald-de wale relationship (Winter and Chambon, 1986; Abbasbandy et al., 2014; Tung, 1994).

$$\eta = k(\delta u/\delta y)^{n-1}$$

or

$$\eta = k\gamma^{n-1}$$

where η is the viscosity in centipoises (cps), m is the consistency index, γ is the shear rate or the velocity gradient perpendicular to the plane of shear (s^{-1}) and n is the flow behavior index (dimensionless). When $n = 1$, it is a newtonian fluid, $n < 1$, the system behaves as a shear thinning system (pseudo plastic) while with $n > 1$, it is dilatant. As the value of n is decreases than 1, the effective viscosity would decrease with increasing shear rate (van Hemelrijck and Müller-Goymann, 2012). The stability of the thermoreversible mucoadhesive *in-situ* gel containing ZT–KT was examined by comparing the gel placed for 3 months at in stability chamber maintained at ICH IVa conditions (30 ± 2 °C, 65 ± 5% RH).