International Journal of Biological Macromolecules 87 (2016) 41–47

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

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

Ion activated *in situ* gel of gellan gum containing salbutamol sulphate for nasal administration

Sneha R. Salunke, Sanjay B. Patil*

Shri Neminath Jain Brahmacharyashram's Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Dist. Nashik 423 101, Maharashtra, India

ARTICLE INFO

Article history:
Received 17 June 2015
Received in revised form 26 January 2016
Accepted 14 February 2016
Available online 17 February 2016

Keywords:
In situ gel
Mucoadhesion
Gellan gum

ABSTRACT

Nasal delivery is the promising approach for rapid onset of action and avoids the first pass metabolism. The main aim of present study was to develop a novel mucoadhesive *in situ* gel of salbutamol sulphate using gellan gum and hydroxylpropyl methyl cellulose (HPMC) for nasal administration. The formulations were prepared so as to have gelation at physiological ion content after nasal administration. Developed formulations were evaluated for gelation, viscosity, drug content, *in vitro* mucoadhesion, *in vitro* drug release study, *ex vivo* permeation, and histopathology. Formulations showed pH in the range of nasal cavity and optimum viscosity for nasal administration. The mucoadhesive force depends upon concentration of HPMC and drug release was found to be 97.34% in 11 h. The histopathology did not detect any damage during *ex vivo* permeation studies. Hence, *in situ* gel system of gellan gum may be a promising approach for nasal delivery of salbutamol sulphate for therapeutic improvement.

1. Introduction

In recent years the nasal route has received a great deal of attention as a convenient and reliable method for systemic administration of drugs especially those which are ineffective orally and must be administered by injection. The nasal epithelium has a relatively high permeability, and only two cell layers separate the nasal lumen from the dense blood vessel network in the lamina propria. The nasal route for systemic drug delivery is of interest because it provides several advantages over other routes of drug administrations. These have been suggested as follows: rapid absorption, avoidance of the intestinal and hepatic presystemic disposition, fast onset of therapeutic action, avoidance of irritation of the gastrointestinal membrane, noninvasive administration, ease of convenience, and self medication, improved patient compliance. These factors make nasal drug administration an attractive delivery route [1–4].

The mucosa of the nasal cavity has been examined as a possible route of administration to achieve a rapid and higher level of drug absorption. Presently, nasal mucosa is being recognized for the delivery of therapeutic compounds including biopharmaceuticals. It is used for topical nasal treatments such as antihistamines and corticosteroids, and also for systemic delivery of analgesics, sedatives, hormones, vaccines, and cardiovascular drugs. Intranasal therapy has been accepted as a form of treatment in the ayurvedic system of Indian medicine, and is called "Nasya Karma". Drug delivery through the nose is uncomplicated and convenient, and can include the delivery of solutions, suspensions, powders, *in situ* gel, and ointments [5].

The major disadvantage associated with nasal drug delivery is rapid mucociliary clearance (MCC) that limits the time available for drug absorption from applied dosage form [6]. Consequently, a frequent dosing regimen is required for therapeutic effect. Therefore, a probable strategy is to decrease MCC by the use of gel/mucoadhesive formulations to prolong the residence time at the mucosal site and results in increased absorption. Various approaches have been tried for developing nasal dosage forms like hydrogels, viscous gels with high absorption and lasting drug effects. However, viscous gels have the disadvantage of being difficult to administer. These problems have been overcome by the use of *in situ* gels [7,8]. *In situ* gel is a new dosage form which has been applied in nasal drug delivery recently. Compared with liquid nasal formulations, nasal *in situ* gels are instilled as low viscosity solutions into the nasal cavity, and upon contact with the nasal mucosa, the polymer changes conformation producing a gel, so it cannot only prolong the contact time between the drug and the absorptive sites in the nasal cavity, but also release drug slowly and continuously, hence, it is especially useful for those drugs used chronically. The phase transition can be induced by a shift in pH, a shift in temperature or by the presence of cations [9,10]. This

* Corresponding author. Fax: +91 2556253179.
E-mail address: sbpatil_99@rediffmail.com (S.B. Patil).

http://dx.doi.org/10.1016/j.ijbiomac.2016.02.044
0141-8130/

type of gel combines the advantages of a solution, administration convenience, ease of preparation, no foreign body sensation, exact dosing, with the favorable residence time of a gel and improves patient safety and acceptability [1,11,12].

Gels can offer several advantages over other dosage forms: gels reduce post nasal drip into the back of the throat and therefore minimize any bad taste problems and loss of drug formulation from the nasal cavity; gels decrease anterior leakage of the drug out of the nasal cavity; and also gels help to localize formulation on the mucosa, thereby providing a better chance for the drug to be absorbed [13].

Gellan gum is an anionic, exocellular, deacetylated bacterial polysaccharide discovered in 1978. It is secreted by *Sphigomonas paucimobilis* (formely known as *Pseudomonas elodea*) with a tetrasaccharide repeating unit of 1β-L-rhamnose, 1β-D-glucuronic acid and 2β-D-glucose. The mechanism of gelation involves the formation of double-helical junction zones followed by aggregation of the double-helical segments to form a 3-D network by complexation with cations and hydrogen bonding with water. The gelation mechanism of gellan gum solutions depends on the nature of cations and the divalent cation promotes the gelation much more effectively than the monovalent cation. Deacetylated gellan gum is marketed as Gelrite® or Kelcogel® and is approved in the USA and EU as a gelling, stabilizing and suspending agent in food products. Hence gellan gum is recommended as safe for pharmaceutical use. Moreover, gellan gum is one of the most promising *in situ* gelling polymers in the human body and applicable for biomedicine technology, such as drug delivery vehicles and protein immobilization media [11,14,15].

Salbutamol sulphate is a selective β_2 adrenoreceptor agonist and is readily absorbed from GIT but it is subjected to considerable first pass metabolism. Thus its oral bioavailability is only 50%. It is an antiasthamatic drug used for treatment of asthma, bronchodilator in reversible airway obstruction and to arrest premature labour [16,17]. Oral forms of salbutamol sulphate undergo hepatic first pass metabolism and even under ideal circumstances only small fraction of the aerosolized drug is deposited in the lungs, typically 2 to 10%. Most of the remainder is swallowed. To attain particle size of diameter 1–5 μm inhalation is also major task during formulation. A number of factors in addition to particle size determine effective deposition of drugs in the bronchial tree, including the rate of breathing and breathe holding after inhalation. Due to this factor, inhalation administration is problematic for treatment of asthma in young children, elderly and those suffering from a significant asthma exacerbation [18]. In this regard, the intranasal delivery seems to be an attractive alternative. Previous attempts were made to prepare thermosensitive *in situ* gel of poloxamer 407 and hydroxypropyl methylcellulose (HPMC) and *in situ* gelling nasal inserts of hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose sodium, sodium alginate and chitosan for salbutamol sulphate [19,20].

In the present study, a nasal delivery system of ion-activated *in situ* gel for salbutamol sulphate with gellan gum was developed and its hydrogel formation *in vitro*, viscosity of sol-gel state, drug content, pH, gel strength, *in vitro* mucoadhesive strength, drug release and stability study were investigated.

2. Materials and methods

2.1. Materials

Salbutamol sulphate was a kind gift from Mercury Laboratories, Vadodara, India and Gellan gum (deacylated) a gift sample from CPKelco division of the Monsanto Company, Mumbai, India. Hydroxypropyl methyl cellulose (HPMC E15) and Tween 80 were purchased from Loba Chemie Pvt. Limited, Mumbai, India. All other chemicals used were of analytical grade.

Table 1
Composition of *in situ* gelling systems of gellan gum.

Sr. no.	Ingredients	Formulation compositions (% w/v)				
		G0	G1	G2	G3	G4
1	Salbutamol sulphate	1.2	1.2	1.2	1.2	1.2
2	Gellan gum	0.3	0.1	0.2	0.3	0.4
3	HPMC E15	–	0.2	0.2	0.2	0.2
4	Tween 80	–	0.1	0.1	0.1	0.1
5	D-mannitol	5	5	5	5	5
6	Benzalkonium chloride	0.002	0.002	0.002	0.002	0.002
7	Distilled water	100	100	100	100	100

Table 2
Grades of gelation.

Sr. no.	Degree of gelation	Grade
1.	No gelation	–
2.	Weak gelation; dissolves rapidly	+
3.	Immediate gelation remains for few hours (less stiff gel)	++
4.	Immediate gelation remains for extended period (stiff gel)	+++
5.	Very stiff gel	++++

2.2. Preparation of ion activated in situ gelling system

Accurately weighed quantity of gellan gum (0.2–0.5% w/v) was dispersed in distilled water. The dispersions were then stirred for 20 min at 85–90 °C using magnetic stirrer and then cooled to room temperature. HPMC E15 was added slowly with stirring. D-mannitol, benzalkonium chloride and Tween 80 were also added simultaneously (Table 1). Finally salbutamol sulphate was added with stirring. The pH of all formulations was in the range 4.5–6.5. Formulations were filled in amber colored glass vials, capped with rubber closures and sealed with aluminium caps. Formulations were stored in a refrigerator (4–8 °C) until further use [9].

2.3. Evaluation of in situ gelling systems

2.3.1. In vitro gelation study

Gelation is the process, by which the liquid phase makes a transition to gel. Deacetylated gellan gum was selected in comparison with high acetylated form because it has desirable properties such as responsible for ion activated gelation, having low viscosity, clear in clarity, firm and brittle structure [21]. Beaker containing 2 mL of formulation and a magnetic bead was placed on a magnetic stirrer. The simulated nasal fluid (SNF—aqueous solution containing 8.77 mg/mL NaCl, 2.98 mg/mL KCl and 0.59 mg/mL $CaCl_2$) which had cationic composition of nasal secretions, was added slowly while stirring. Gelation was observed by visual examination [22]. The consistency of formed gel was checked and graded as indicated in Table 2.

2.3.2. Viscosity measurements

Viscosity of all formulations before and after gelation was measured by Brookfield viscometer (RV, Brookfield Engineering Laboratories, USA). Measurements were performed using Spindle number 3 at 50 and 100 rpm and Spindle number 4 at 100 rpm shear rate.

2.3.3. Drug content determination

The vials containing the formulation were shaken for 2–3 min manually and 100 μL of the preparation was transferred to 25 mL volumetric flasks with a micropipette and the final volume was made up with phosphate buffer pH 6.2. The amount of salbutamol