Thermally reversible xyloglucan gels as vehicles for nasal drug delivery

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Abstract
The aim of this study was to investigate the potential application of thermosensitive gels formed by a xyloglucan polysaccharide derived from tamarind seed for nasal drug delivery. Xyloglucan that had been partially degraded by β-galactosidase to eliminate 45% of galactose residues formed gels at concentrations of 2.5% w/w at gelation temperatures decreasing over the range 27–28°C. The in vitro release of ondansetron hydrochloride from the enzyme-degraded xyloglucan gels followed higuchi kinetics over a period of 5 h at 34°C by anomalous transport mechanism. The ex vivo permeation of ondansetron hydrochloride from the gels was sustained. Histological examination of nasal mucosa following a single administration of the gels showed no evidence of mucosal damage. Finally, the bioavailability study in rabbits revealed that the absolute bioavailability of ondansetron hydrochloride was significantly increased from 28.64% in the case of the oral drug solution to 52.79% in the case of the nasal in situ gel. The results of this study suggest the potential of the enzyme-degraded xyloglucan gels as vehicles for nasal delivery of drugs.

Keywords: Xyloglucan, nasal, in situ gel, drug delivery

Introduction
In the past few years, there are increasing number of in situ forming systems have been reported in the literature for various biomedical applications, including drug delivery, cell encapsulation and tissue repair (Masteikova et al., 2003). In situ gelling systems are the aqueous polymeric solutions that are transformed into gels due to changes in environmental conditions, like temperature and pH. The in situ gels are fluids that can be introduced into the body in a minimally invasive manner prior to solidifying or gelling within the desired tissue, organ, or body cavity (Branl et al., 2007). These systems are currently of interest to the formulation scientists due to their structural and functional benefits. A variety of therapeutic agents has been formulated as in situ gelling systems for their enhanced transport across the mucosal membranes. When the gel is formed under physiological conditions and maintains its integrity for a desired period of time, the process may provide various advantages. Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both in vitro and in vivo (Gil et al., 2004). Temperature-responsive polymers and hydrogels exhibit a volume phase transition at a certain temperature as a consequence of a sudden change in the salvation state (Schmaljohann, 2006). Xyloglucan is neutral, non-toxic polysaccharides (Shirakawa et al., 1998), whose degradation products consist of naturally occurring saccharides and are assumed non-toxic, although the experimental evidence for this conclusion is limited. Xyloglucan is extracted from the tamarind seed (Tamarindus indica, Leguminosae) and is a major component of higher plant cell walls (Reiter, 2002). It is composed of a β-1, 4 linked D-glucan backbone where the O-6 positions of the glucopyranosyl residue are partially substituted with α-D xylopyranose residue (Yamatoya et al., 1997).
Xyloglucan with more than 35% galactose residue removal by using fungal β-galactosidase exhibits thermally reversible gelation in dilute aqueous solution and can serve as thermally responsive material. For xyloglucan with 44% galactose removal, a lower and upper transition temperature from sol-gel and gel-sol, respectively, were found, and the gel was shown to be thermo-reversible upon cooling. A detailed study of effect of galactose removal ratio (GRR) on gelation temperature has been reported by Yuguchi et al. (1997). The potential use of xyloglucan gels for rectal (Miyazaki et al., 1998), intraperitoneal (Suisha et al., 1998) and oral drug delivery (Kawasaki et al., 1999; Miyazaki et al., 2001) is very well studied. The present study is an examination of the potential use of a gel formulation prepared using a xyloglucan polysaccharide for use in nasal drug delivery. The well perfused nasal mucosa provides an excellent site for rapid absorption of drugs. 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 (Ugwoke et al., 2001) Therefore, in situ gel is plausible strategy to decrease MCC. Xyloglucan with more than 44% GRR, because of its ability to form clear gels at physiological temperature it can provide a longer contact time with the nasal mucosa. Ondansetron hydrochloride is a serotonin (5-hydroxytrytamine) subtype (5HT3) receptor antagonist used in the management of chemotherapeutic induced and postoperative nausea vomiting. Its absolute bioavailability is about 60% due to first pass metabolism. From a pharmacokinetic standpoint, intranasal administration circumvents first pass elimination and absorption is rapid due to the existence of rich vasculature and highly permeable structure within the nasal membrane which should increase absorption and improve the bioavailability of the drug.

In this study, we develop nasal in situ gel using a xyloglucan, a temperature responsive polymer containing an antiemetic agent ondansetron hydrochloride. Bioavailability study of nasal in situ gel with favorable gelation, rheological behavior, release and mucosal permeation ability is carried in rabbits.

Materials and methods

Materials
Ondansetron hydrochloride was a kind gift from IPCA Laboratory (India Rep Office, Andheri, India) and Tamarind seed xyloglucan was gifted by DSP Gokyo Food & Chemical Co. Ltd (Fukusima, Japan). All chemicals were of analytical grade and used without any purification.

Preparation of xyloglucan sample
Xyloglucan with a 45% galactose removal ratio was prepared by enzymatic modification from tamarind seed xyloglucan, according to previous method (Shirakawa et al., 1998). Removal of the required percentage of β-D-galactose residues was carried out by reacting a 2% aqueous solution of xyloglucan with an enzyme β-galactosidase from aspergillus oryzae at 7.4 U/mL. (Sigma Aldrich, Ltd). The reaction was carried out at pH 4.5 and temperature 30°C for 24 h. To inactivate the enzyme sample was heated at 100°C for 20 min. The enzyme degraded xyloglucan was precipitated from this solution by addition of ethanol and washed three times with water; the product was dried at 60°C. The supernatant obtained during purification was analyzed for its galactose content by using HPTLC method. The Galactose Removal Ratio (GRR) was determined as

\[
GRR = \frac{\text{Released galactose residue}}{\text{Total galactose residue}} \times 100
\]

The amount of total galactose residues was measured after total hydrolysis by heating the polymer with 2 N Sulphuric acid at 100°C for 3 h (Shirakawa et al., 1998).

Development of HPTLC method for estimation of galactose
Galactose working standard of 1 mg/mL was prepared in ethanol. The calibration curve from 1000–6000 ng/µL was prepared and checked for reproducibility, linearity of the proposed method. The correlation coefficient, coefficient of variance and the linearity of results were calculated. Sample was spotted using Camag microlitre syringe on precoated silica gel aluminum plate (20 × 10 cm with 250 µm thickness). The plates were prewashed by methanol and activated at 60°C for 5 min prior to chromatography constant application rate of 0.1 µL/s was employed and space between two bands was 5 mm. The slit dimension was kept at 5 × 0.45 mm and 10 mm/s scanning speed was employed. The monochromatic bandwidth was set at 20 nm, each track was scanned thrice and baseline correction was used. The mobile phase consisted of n-butanol-acetic acid-water 75/25/6 v/v. Linear ascending development was carried out in 20 × 10 cm glass chamber saturated with mobile phase. The optimized chamber saturation time for mobile phase was 1 h at room temperature at relative humidity of 60%. After the chromatogram run the plate was dried in the hot air oven for 1 h at 60°C and was sprayed with aniline-diphenylamine reagent as visualizing agent (prepared by mixing10 volumes of a solution of 10 mL/l aniline and 10 g/l diphenylamine in acetone with 1 volume of ortho phosphoric acid). Dried plates were scanned on Camag TLC scanner in the reflectance absorbance mode at 340 nm and operated by CATS software the source of radiation utilized was deuterium lamp emitting a continuous UV spectrum between 190 and 400 nm. Calibration curve was plotted to obtain linearity of galactose in the concentration range 1000–6000 ng/µL.

Preparation of gels
A weighed amount of the enzyme degraded xyloglucan was slowly added to cold water or phosphate buffer at pH 7.2. The mixture was slowly homogenized (High Pressure Homogenizer, Inkarp Italy) for 20 cycles at 1500 rpm psi.
An appropriate amount of ondansetron was then dissolved in the resulting solution. Appropriate quantities of sodium chloride and benzalkonium chloride were added simultaneously as a tonicity adjusting agent and preservative respectively. Formulation pH was adjusted between 4.5 and 5.5; by using 0.1 N HCl. The formulations were filled in 10-mL amber colored glass vials, capped with rubber closures and sealed with aluminum caps. Formulation was terminally sterilized in their final pack, by autoclaving at 121°C and 15 Pa for 20 min. Sterilized formulations were stored in a refrigerator (4–8°C) until use.

**In vitro characterization**

**Gel formation temperature of the formulations**

Specific sol–gel transition temperatures determined as the gel formation temperatures (GFT) were obtained through tube inversion experiments (Yu et al., 2008). The samples (1 mL) were sealed in small glass tubes (internal diameter about 10 mm) at 4°C and heated in a temperature controllable water bath from 5°C to 50°C at a heating rate of 1°C/min. When the liquid in the tube was immobile within 30 s, the temperature was recorded as the GFT.

**Measurement of viscosity and rheological studies**

Viscosities of formulations before and after gelation were measured by a Brookfield DV-E viscometer using Spindle number 3 at 100 rpm shear rate. Rheological behavior of resultant gels was evaluated by treating viscosity reading using the following pair of equations (Mitchka, 1982).

\[ \tau_i = K_{\alpha} \alpha_i \]  
\[ \gamma_i = k_n n_i \]  

where \( \tau_i \) = shear stress, \( K_{\alpha} \) = conversion factor (0.279 for spindle number 3), and \( \alpha \) = torque dial.

**Measurement of gel strength**

A measurement of the comparative gel strengths of xyloglucan gels of (2.0% w/w) concentration was carried out using a gel strength measuring apparatus as mentioned by Mahajan et al. (2011). A 50 g sample of the gel prepared was contained in a 50 mL beaker maintained at constant temperature by a water jacket through which water was circulated at 34°C from a thermostat bath.

**Measurement of drug release rate from gels**

*In vitro* drug release studies were performed using Franz diffusion cell with dialysis membrane (Cut off MW-12000). The receptor compartment contained 16 mL phosphate buffer solution (PBS) pH 6.6 that was within the pH range in nasal cavity and maintained at 34 ± 0.5°C. The donor compartment contained formulation equivalent to 2.5 mg of ondansetron hydrochloride was placed in donor compartment. At predetermined time interval 0.5 mL samples were withdrawn from the receiver compartment and concentration of ondansetron hydrochloride was determined spectrophotometrically at 310 nm (Shimadzu, UV-1700, Japan). The buffer contained in the receiving compartment was replaced with an equal quantity to maintain a constant volume (Cerchiara et al., 2005).

**Analysis of drug release data**

The drug release from the dosage form is affected by the polymer type and other formulation parameters. For determining the drug release mechanism from gel matrices; the release data from *in vitro* release studies was analyzed by the commonly used exponential Korsmeyer-Peppas equation as follows:

\[ \frac{M_i}{M} = K t^n \]  
\[ \log \left( \frac{M_i}{M} \right) = \log k + n \log t \]

where \( M_i/M \), fraction of drug released at time \( t \); \( k \), Release rate constant; \( n \), Diffusion exponent indicating the release mechanism.

When \( n \) is equal to 0.5, the drug release is with a fickian diffusion mechanism (Higuchi model). If 0.5 < \( n \) < 1 this indicates anomalous or non fickian release, while if \( n = 1 \) this indicates zero order release (Peppas, 1985).

**Ex vivo drug permeation across nasal mucosa**

Fresh nasal tissue samples removed from the nasal cavity of sheep obtained from the local slaughterhouse were mounted in Franz diffusion cells (permeation area of 3.14 cm² and capacity 16 mL). Phosphate Buffer (pH6.6) was used as diffusion medium. The temperature was maintained at 34 ± 0.5°C. After a pre incubation time of 20 min, formulation equivalent to 2.5 mg of ondansetron hydrochloride was placed in the donor chamber. At predetermined time points, 0.5 mL samples were withdrawn from the acceptor compartment, replacing the sampled volume with PBS pH 6.6 after each sampling, for a period of 5 h (Belgamwar et al., 2009).

Permeability coefficient (P) was calculated by following formula

\[ P = \frac{dQ/dt}{C_o \times A} \]

where \( dQ/dt \), flux or permeability rate (mg/h); \( C_o \), initial concentration in donor compartment; \( A \), effective surface area of nasal mucosa.

**Histological assessment of nasal mucosa**

Immediately after ex vivo permeation study, mucosa was retrieved and fixed in 10% neutral buffered formalin (pH 7.2) at 4°C. Each mucosa sectioned using 5-6 µm size.
Staining was accomplished using hematoxylin and eosin (HE). Sections were examined under a light microscope (Motic Instruments Inc, Canada) to detect and damage to the tissue (Rita et al., 2006).

**In vivo nasal absorption study**

**Animals**

Six New Zealand white rabbits with mean weight of 2.5 ± 0.3 kg were used. The rabbits were accommodated to the dosing for 1 month before the study to prevent withdrawal and defense reaction that may lead to inaccurate dosing. The rabbits were kept in single cage and fasted for 12 h before the study with free access of water during the experiments. A cannula was inserted into the marginal ear vein for blood sampling and flushed with heparinized normal saline solution. The animal experiment was carried out in compliance with the protocol of Institutional animal ethical committee (Registration No: 651/02/C/CPCSEA under CPCSEA, India).

**Study design**

In a crossover study with one week apart as a wash out period, the animals received 5 mL of oral drug solution by an oral tube as well as i.v. bolus of Zofran Inj injected into their marginal ear vein. Nasal formulations were deposited into both the nostrils. Drug was administered to each group at the dose of 2 mg/kg. The blood samples (0.5 mL) were collected at the predetermined intervals to analyze the concentration of ondansetron in plasma. The animal experiment was carried out in compliance with the protocol of Institutional animal ethical committee (Registration No: 651/02/C/CPCSEA under CPCSEA, India).

**Estimation of galactose by HPTLC**

Galactose quantitative estimation was performed by a new, simple, and rapid thin-layer chromatographic method. The method was found to give compact spots for the galactose (Rf = 0.7 ± 0.01). The linear regression analysis data for the calibration plots showed good linear relationship with $r^2 = 0.998$ in the concentration range 1000–6000 ng/mL. The method is precise, accurate, reproducible, and selective for the analysis of galactose. Galactose removal ratio (GRR) obtained was 45.46%.

**Preparation of galactose sample for in situ gel**

Preliminary studies were carried out to determine the xyloglucan concentration in water necessary for in situ gel formation with acceptable consistency for drug delivery. At a xyloglucan concentration of <2% (w/v) there was improper gelation as well as time required for gelation. The optimum xyloglucan concentration was 2.5% (w/v). The pH of the formulation was range 4.5–5.5 which were in the range of absorption site.

**In vitro characterization**

**Gelation studies**

Preliminary investigation of the gelling characteristics of the enzyme degraded xyloglucan was carried out to define the gel region. Sol–gel transition temperatures as a function of concentration over the concentration range of interest were measured. Xyloglucan solutions composed of 2.5% w/w of xyloglucan with 45% GRR, exhibited reversible sol–gel transition property. The thermal gelation characteristics of xyloglucan solution was studied by measuring their GFT values and the measured GFT values of xyloglucan solutions was basically in the range of 25–30°C. The native xyloglucan does not show gel formation at this GFT indicating GFT as a function of galactose removal ratio. The sol gel transition is completely reversible.

**Viscosity measurement and rheological behavior**

The rheological characteristic of the sol–gel systems was temperature-dependent. The apparent viscosity values were measured for liquid formulations and gel using Brookfield viscometer DV-E with spindle no. 3 at 100 rpm. The viscosity of formulations in gel state; was found to be proportionate with the increasing polymer concentration. The viscosity increased markedly with concentration, the higher concentrations showing shear thinning behavior (Figure 1). Shear thinning behavior

![Figure 1. Rheological behavior of xyloglucan gel.](image-url)
will increase spread ability of gel (Owen et al., 2006). This is advantageous as it increases the solutions tendency to stay in place after development.

**Gel strength measurement**

In the development of nasal *in situ* gelling system, the gel strength is important in finding the condition, which can delay the post nasal drip or anterior leakage. The gel strength was found to be affected by concentrations of gelling agent. Although the values produced are not absolute values, they are useful for assessing the influence of concentration on the strength of the xyloglucan gels. The observed increase of gel strength with concentration has been noted previously for xyloglucan gels (Miyazaki et al., 1998) and is a consequence of an increased density of the laterally stacked chains of the enzyme-degraded xyloglucan (Yuguchi et al., 1997). *In situ* gel must have suitable gel strength so as to be administered easily and can be retained at nasal mucosa without leakage after administration. Xyloglucan formulation showed the gel strength values in the range 35–40 s. The gel strength values between 25 and 50 s were considered sufficient as reported previously (Mahajan & Gattani, 2010). The gel strength less than 25 s may not retain its integrity and may erode rapidly while gels having strength greater than 50 s are too stiff and may cause discomfort to the mucosal surfaces.

**In vitro drug release**

Figure 2 shows the release of ondansetron hydrochloride as a function of time from xyloglucan gels loaded with an initial drug concentration, Co, of 2.5% w/v. The drug release from xyloglucan gel was rather biphasic, with a relatively fast release at the initial followed by a slow release at the late, and the amount of drug released was about 98.65% at the end of test (270 min). The initial rates of drug release were very rapid due to incomplete gel formation, but as the time progresses the release rate decreases due to complete gel formation. Xyloglucan forms weak gel (not stiff) at body temperature and there is no use of cross linking agent in formulation. Hence the drug release was complete within 4h. For nasal route of administration rapid drug release is advisable as residence of dosage form at the site of absorption is short. To precisely know the drug release mechanisms from *in situ* gelling systems, the *in vitro* release data of formulation was treated with Higuchi’s diffusion equation \(Q = k t^{1/2}\). The graph between percentage cumulative drug release and square root of time showed almost linear relationship after the initial period. It was not possible to correlate the release in the early stages of drug release study, due to incomplete gel formation. After the complete gel formation, the release profiles were found to be linear with square root of time and followed the Higuchi’s equation. The drug transport mechanism of the same formulations was determined by using the Korsmeyer-Peppas exponential equation. Form the plot of log \( (M/M_0) \); fraction of drug released at time \( t \) versus log of time. The diffusion exponent ‘\( n \)’ was calculated from equation and was found to be 1.25 indicating the anomalous transport mechanism.

**Ex vivo drug permeation studies**

The *in situ* gelling formulation with 2.5% w/v ondansetron hydrochloride was subjected to *ex vivo* permeation studies using sheep nasal mucosa. The percent drug permeated after 4 h was found to be 95.52%. The permeability coefficient (\( P \)) was also calculated and found to be 0.04572 cm²/h.

**Histological examination**

Figure 3a and 3b show photomicrographs of nasal mucosa as a function of time from xyloglucan gels loaded with an initial drug concentration, Co, of 2.5% w/v. The drug release from xyloglucan gel was rather biphasic, with a relatively fast release at the initial followed by a slow release at the late, and the amount of drug released was about 98.65% at the end of test (270 min). The initial rates of drug release were very rapid due to incomplete gel formation, but as the time progresses the release rate decreases due to complete gel formation. Xyloglucan forms weak gel (not stiff) at body temperature and there is no use of cross linking agent in formulation. Hence the drug release was complete within 4h. For nasal route of administration rapid drug release is advisable as residence of dosage form at the site of absorption is short. To precisely know the drug release mechanisms from *in situ* gelling systems, the *in vitro* release data of formulation was treated with Higuchi’s diffusion equation \(Q = k t^{1/2}\). The graph between percentage cumulative drug release and square root of time showed almost linear relationship after the initial period. It was not possible to correlate the release in the early stages of drug release study, due to incomplete gel formation. After the complete gel formation, the release profiles were found to be linear with square root of time and followed the Higuchi’s equation. The drug transport mechanism of the same formulations was determined by using the Korsmeyer-Peppas exponential equation. Form the plot of log \( (M/M_0) \); fraction of drug released at time \( t \) versus log of time. The diffusion exponent ‘\( n \)’ was calculated from equation and was found to be 1.25 indicating the anomalous transport mechanism.

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**Histological examination**

Figure 3a and 3b show photomicrographs of nasal mucosa taken from rabbits 5 h after permeation study of 2% w/w xyloglucan gels with ondansetron hydrochloride and phosphate buffer. Comparison with photomicrographs of control nasal mucosa, the optimized formulation has no significant effect on the microscopic structure. Mucosa shows neither cell necrosis nor removal of the epithelium from the nasal mucosa was observed after exposure to xyloglucan formulation. Examination of mucosa showed normal epithelium layer and there were no alterations in basal membrane and superficial part of sub mucosa as compared with PBS-treated mucosa.
Table 1. Bioavailability parameters of ondansetron for xyloglucan nasal gel, oral solution and intravenous solution.

| Parameters                  | Intravenous solution | Oral solution | In situ nasal gel formulation |
|-----------------------------|----------------------|---------------|-------------------------------|
| C_{max} (ng/mL)             | 63.90 ± 25.23        | 32.06 ± 22.30 | 42.72 ± 12.38                 |
| T_{max} (min)               | -                    | 10            | 15                            |
| AUC_{0-240} (ng/mL·min)     | 69.14 ± 7.30         | 26.54 ± 3.03  | 28.10 ± 2.72                  |
| AUC_{0-∞} (ng/mL·min)       | 71.59 ± 8.93         | 28.64 ± 3.88  | 52.79 ± 4.94                  |
| F abs (%)                   | 100                  | 38.41 ± 2.51  | 72.56 ± 6.15                  |

Each value represents the mean ± S.D. of three experiments.

**In vivo nasal absorption study**

The relevant pharmacokinetic parameters, ondansetron hydrochloride peak concentration (C_{max} ng/mL), T_{max} (min) and area under the concentration Vs time (AUC ng/mL·min) are reported in Table 1. The mean Cmax of ondansetron hydrochloride by nasal route is greater than that by oral route, which was statistically significant (p < 0.05). The AUC_{0-240} after nasal administration was significantly higher than that of oral administration (p < 0.05) and comparable to that after intravenous administration. The time to reach Cmax after nasal administration was somewhat slower than that by oral administration although difference was not significant.

In vivo performance of nasal formulation exhibited better bioavailability (AUC_{0-240} and AUC_{0-∞}, 28.10±2.72 and 52.79±4.94) for in situ nasal formulation in comparison to oral administration of solution (AUC_{0-240}, 26.54±3.03 and AUC_{0-∞}, 28.64±3.88) that could be due to avoidance of first pass metabolism. These values corresponded to absolute bioavailability values (F abs) of 72.56±6.15 and 38.41±2.51% for the nasal in situ gel and oral solutions respectively. The significantly higher bioavailability of its intranasal gel as compared to its oral solution could therefore be attributed avoiding the first pass metabolism associated with per oral drug administration. Consistently, the in situ gel developed in the present study was able to retain the drug in nasal cavity for a time long enough to be absorbed nasally.

**Discussion**

Nasal drug delivery has generated interest as an alternative route for administration of drugs and biomolecules that are susceptible to enzymatic or acidic degradation and first pass hepatic metabolism. However, nasal delivery has limitations which have restricted its use to the delivery of drug molecules is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. It has been reported that for both liquid and powder formulations that are not mucoadhesive, the half life of clearance is in the order of 15–20 min. Therefore, a plausible strategy is to decrease MCC by the use of gel/mucoadhesive formulations to prolong the residence time at the nasal absorption site. The use of in situ gel systems for nasal drug delivery is not new. Poloxomers, thermo responsive polymers have been widely investigated as nasal drug delivery. Xyloglucan is a polysaccharide derived from tamarind seed also forms thermo reversible gel in water.

An important difference between gelation properties of the xyloglucan and poloxomer such as pluronic F127 from toxicity view point is that the xyloglucan polysaccharide forms gels at much lower concentration. In addition xyloglucan is approved for use as food additive. When xyloglucan partially degraded by β galactosidase the resultant product exhibits thermally reversible gelation in dilute aqueous solution. Such gelation does not occur with native xyloglucan. Gelation is also only possible when galactose removal ratio exceeds ~35%. The transition temperature is inversely related to polymer concentration and the galactose removal ratio.

Reid et al (Reid et al., 1988) reported that galactose contents are major structural features determining the water solubility of these molecules. For determination of galactose residue in xyloglucan we developed new, simple and rapid thin layer chromatography.

Thermal gelation characteristic of xyloglucan solution was at concentration 2.5%, which is very low than poloxomers. The gelation time, determined as the time at which lack of movement of the meniscus was first detected on tilting a tube containing the solution at constant temperature decreased with increase of both the temperature and concentration of polymer. Xyloglucan solutions had higher viscosity at all shear rates, which is advantageous for their proposed usage in that leakage of solution from the nose during instillation would be minimized. Sufficient gel strength can be achieved using much lower concentration of xyloglucan with added advantage of more viscous solution that would minimize the leakage of solution from nasal cavity after instillation.

Drug release was complete from gel after 4.5h. Anomalous release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. Drug permeation across the nasal mucosa was rapid and completes within 4h. Histological examination of nasal mucosa shows no detectable tissue damage resulting from exposure to a single dose administration of gel suggested that the xyloglucan was safe for nasal administration.

The results of in vivo studies using rabbits showed that the in situ gel based on xyloglucan were able to promote rapid drug absorption through the nasal mucosa and to remarkably improve the bioavailability of the drug. This improved performance of nasal in situ gel formulation could be attributed avoiding first pass effect. The high drug absorption through nasal mucosa occurs because of xyloglucan which has ability to form gel on mucosal...
surface. The results obtained in rabbits have to be confirmed in human studies.

Conclusion

We have demonstrated the potential of the gels formed by in situ gelation of xyloglucan solution as vehicles for nasal administration of drug. An aqueous solution containing xyloglucan results in the formation of gels in rabbit nasal cavity. Xyloglucan gels have many advantages for use in nasal drug delivery like since it is fluid like prior to nasal administration and thus can be easily be instilled as a drop, allowing accurate drug dosing, convenience of administration for patients, and this function as depots for the release of drug over a period of 4 h. In addition, xyloglucan is non-toxic and has an advantage over other in situ gelling agents such as the poloxamers, of gelation at much lower concentration.

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Declaration of interest

The authors declare no conflicts of interest.

References

Belgamwar VS, Chauk DS, Mahajan HS, Jain SA, Gattani SG, Surana SJ. Formulation and evaluation of in situ gelling system of dimenhydrinate for nasal administration. Pharm Dev Technol 2009;14:240–248.
Brandl F, Sommer F, Goepperich A. Rational design of hydrogels for tissue engineering: impact of physical factors on cell behavior. Biomaterials 2005;28:134–146.
Cerchiara T, Luppi B, Chidichimo G, Bigucci F, Zecchi V. Chitosan and poly(methyl vinyl ether-co-maleic anhydride) microparticles as nasal sustained delivery systems. Eur J Pharm Biopharm 2005;61:195–200.
Eunsook C, Hyesun G, Inkoo C. Formulation and evaluation of ondansetron nasal delivery systems. Int J Pharm 2008;349:101–107.
Gill ES, Hudson SM. Stimuli-responsive polymers and their bioconjugates. Prog Polym Sci 2004;29:1173–1222.
Kawasaki N, Ohkura R, Miyazaki S, Uno Y, Sugimoto S, Attwood D. Thermally reversible xyloglucan gels as vehicles for oral drug delivery. Int J Pharm 1999;181:227–234.
Mahajan HS, Gattani SG. In situ gels of Metoclopramide Hydrochloride for intranasal delivery: In vitro evaluation and in vivo pharmacokinetic study in rabbits. Drug Deliv 2010;17:19–27.
Mahajan HS, Gattani SG. Nasal administration of ondansetron using a novel microspheres delivery system Part II: ex vivo and in vivo studies. Pharm Dev Technol 2010;15:653–657.
Miyazaki S, Shah SK, Surana SJ. Nasal in situ gel containing hydroxy propyl β-cyclodextrin inclusion complex of artehemer: development and in vitro evaluation. J Incl Phenom Macrocycl Chem 2011;70:49–58.
Masteiková R, Chalupová Z, Sklubalová Z. Stimuli-sensitive hydrogels in controlled and sustained drug delivery. Medicina (Kaunas) 2003;39 Suppl 2:19–24.
Mitchka P. Simple conversion of Brookfield RVT readings into viscosity functions. Rheol Acta 1982;21:207–209.
Miyazaki S, Suisha F, Kawasaki N, Shirakawa M, Yamatoya K, Attwood D. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J Control Release 1998;56:75–83.
Miyazaki S, Kawasaki N, Endo K, Attwood D. Oral sustained delivery of theophylline from thermally reversible xyloglucan gels in rabbits. J Pharm Pharmacol 2001;53:1185–1191.
Owen DH, Peters JJ, Katz DF. Rheological properties of contraceptive gels. Contraception 2006;72:321–326.
Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv 1985;60:110–111.
Reid JSG, Edwards M. Dea ICM. In: Phillips GO, Wedlock DJ, Williams PA, eds. Gums and Stabilizers for the Food Industry. Oxford: IRL Press, 1988:391.
Reiter WD. Biosynthesis and properties of the plant cell wall. Curr Opin Plant Biol 2002;5:536–542.
Rita JM, Pradip KG, Manish LJ, Rayasa SR. Thermoreversible mucoadhesive gel for nasal delivery of sumatriptan. AAPS Pharm Sci Tech 2006;7:E1–E7.
Schmaljohann D. Thermo- and pH-responsive polymers in drug delivery. Adv Drug Deliv Rev 2006;58:1655–1670.
Shirakawa M, Yamotoya K, Ninshinari K. Tailoring of xyloglucan properties using an enzyme. Food Hydrocolloid 1998;12:25–28.
Suisha F, Kawasaki N, Miyazaki S, Shirakawa M, Yamatoya K, Sasaki M, Attwood D. Xyloglucan gels as sustained release vehicles for the intraperitoneal administration of mitomycin C. Int J Pharm 1998;172:27–32.
Ugwoke MI, Verbeke N, Kinget R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. J Pharm Pharmacol 2001;53:3–21.
Yuguchi Y, Mimura M, Urakawa H, Kajiwara K, Shirakawa M, Yamatoya K, Shirakawa M, Yamotoya K, Nishinari K. Tailoring of xyloglucan properties using an enzyme. Food Hydrocolloid 1998;12:25–28.
Yu L, Chang GT, Zhang H, Ding JD. Injectable block copolymer hydrogels for sustained release of a PEGylated drug. Int J Pharm 2008;348:95–106.