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FORMULATION AND EVALUATION OF ORO-SUSTAINED RELEASE INSITU GELLING SOL USING XANTHAN GUM

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ABSTRACT

The purpose of this study was to evaluate the prospective of the oral sustained delivery of xanthan gum formulation with insitu gelling properties. Xanthan gum insitu gelling sols were prepared in three different concentrations such as 0.1, 0.15, and 0.2 %(w/v) by adding bentonite as complexing agent at 0.5% (w/v). The formulated insitu gelling sols were evaluated for rheological studies and drug content. The *invitro* release study was performed in acidic medium followed by basic medium for about 8hrs. The bioavailability of salbutamol from the gels formed insitu in the stomach of rabbits following oral administration of the liquid formulation had the ability to sustain the drug release over a period of 6hours.

KEYWORDS

Xanthan gum, Oral, In-Situ, *Invitro*, *Invivo*, Salbutamol, Bentonite.

INTRODUCTION

Increased compliance and expense involved in marketing of new drug entities has focused greater attention on development of sustained release or controlled release drug delivery systems[1]. Matrix systems are the most popular method among innumerable methods used in the development of controlled release formulations. Hydrophilic polymeric matrix systems are widely used in controlled drug delivery, since they make it easier to achieve a desirable drug release profile, are cost effective and have broad FDA acceptance[2].

Recently a gel formulated for the oral delivery of paracetamol containing xanthan gum and gelatin as gelling agents has been reported [3]. Where the sustained delivery of both are designed to be administered in liquid form and to form gels insitu in the acidic environment of the stomach. The other insitu gelling compound examined sodium alginate is a widely used pharmaceutical formulation.

Xanthan gum is a high molecular weight extra cellular polysaccharide, produced in commercial scale from the fermentation of gram negative bacterium *Xanthomanas campestries*. It is a hydrophilic polymer, which until recently had a limited use as thickening, suspending and emulsifying agent in water based systems. It is now being used in gum

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based sustained release tablet matrices. Xanthan gum not only retards drug release, but can also provide time independent release kinetics with added advantage of compatibility and inertness. Release of soluble drugs from this biopolymer occurs mainly through diffusion, whereas sparingly soluble or insoluble drugs are released as a result of matrix erosion. It is also recommended for use in both acidic and alkaline media[4]. Xanthan gum has been evaluated as a controlled release formulation for model drugs, including theophylline [5], cefalexime [6] and indomethacin[7].

The selected drug, Salbutamol is a β_2-adrenergic receptor agonist used as a bronchodilator. It can be specifically indicted in case of acute asthma and also for symptom relief during maintenance therapy of asthma and other conditions with reversible airways obstruction (including COPD). This drug has a daily dose of 4-8 mg because of shorter biological half-life (1.2 hrs); it needs multiple administrations, which often results in dose related side effects and poor patient compliance [8, 9]. Also, in the commercially available preparations 10 ml of the formulation should be taken 3 or 4 times daily [10].

In the present paper, we assess the potential of bentonite as complexing agent for the sustained delivery of salbutamol which are to be administered in liquid form and to form gels insitu in the acidic environment of the stomach [11, 12].

METHODS AND MATERIAL

(i) Preparation of Sols Containing Xanthan gum (SXG)

Xanthan gum solutions of concentrations 0.1, 0.15 and 0.2% (w/v) were prepared by adding the xanthan gum to distilled water containing 0.5% (w/v) bentonite and stirred. Appropriate amounts of Salbutamol Sulphate (0.4%, w/v) and flavouring agents (5, 10, 20 or 40% w/v of D-sorbitol) were then dissolved in the resulting solution. The concentrations mentioned were after the optimization process [13, 14].

(ii) Measurement of Rheological Properties of Sols

The rheological behaviors of the prepared sols were determined by Brookfield viscometer. The spindle S15 was selected for the study [15]. The samples containing (0.1, 0.15 and 0.2%, w/v) xanthan gum were filled in the sample holder and the spindle was immersed in the samples. The study was carried out at 20°C. Measurements on each sample were performed in triplicate, to analyze the type of rheological system[16].

(iii) Effect of Taste Masking Agent on the Rheological Behavior of In Situ Gelling Sols

The same procedure as mentioned above was carried out for the sols and after addition of drug D-sorbitol was added and stirred. The D-sorbitol was added in four different concentrations such as 5, 10, 20 and 40%w/v. Then the D-sorbitol added sols were subjected to viscosity studies [17].

(iv) Determination of Drug Content

A known quantity (40 mg) of the prepared sols was stirred with 100 ml of buffer solution pH 6.8 for 6 hrs. Then the sample was filtered and the filtrate was measured spectrophotometrically at 276 nm.

(v) Invitro Drug Release Studies

For the determination of *invitro* drug release, USP Dissolution Apparatus-II was used. Dilution method was employed to maintain different pH conditions in the dissolution studies. 10 ml (40 mg of drug) of the solution was added to 750 ml of buffer solution of pH

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1.2, contained in the dissolution flask and the temperature was maintained at 37°C with 50 rpm. Aliquots of 5 ml were withdrawn at frequent intervals and equal amount of fresh medium was replaced after each sampling up to 2hrs. At the end of 2 hrs, the medium was changed to pH 6.8. The dissolution was continued in this medium up to 8 hrs. The collected samples were analyzed for the drug content through UV spectrophotometer at 276 nm[18].

(vi) Effect of Gastric Acidity on the Invitro Drug Release

This *invitro* release study was carried out at various buffer solutions such as pH 2.0 and 4.0 as to represents the typical gastro intestinal pH variation. The prepared sols, equivalent 40mg of drug were added to 900ml of buffer solution of pH 2.0 and 4.0 and all other conditions were maintained same as explained earlier [19].

(vii) Bioavailability Studies

White male rabbits weighing 3.4-3.8 kg were divided in to three groups and fasted for overnight prior to the experiments but were allowed free access to water. The formulated xanthan gum sol (0.15%w/v) 2ml containing 4mg of salbutamol was orally administered to one group using a needle fitted in to a disposable syringe. A similar procedure was followed for the administration of 4mg of commercial (Asthalin) preparation to the second group and the third group was treated with water. At predetermined intervals blood samples was collected from the ear vein and centrifuged at 3000rpm for 10min. The plasma concentration was determined chromatographically by using schimadzu LC 2010 HT HPLC system and the various pharmacokinetic parameters were calculated. The above mentioned study was approved by Institutional animal ethics committee (IAEC) baring the proposal number JSSCP/IAEC/M.PHARM/PH.CEUTICS/05/2006-07.

RESULTS AND DISCUSSION

In xanthan gum insitu gelling sol, bentonite itself is a complex forming agent so it does not require any addition of complexing agent to prevent the release of cations. The optimum quantities of bentonite that maintained fluidity of the formulation before administration and resulted in gelation when the formulation was added to pH 1.2, were determined by preliminary test in which XG sols (0.1, 0.15 and 0.2 % w/v) containing bentonite concentrations (0.5, 0.8, and 1.0 %w/v) were added drop wise to 50 ml of pH 1.2 the minimum concentration required for gelation of sols with these three bentonite concentration(0.5, 0.8 and 1.0%w/v) were added drop wise to 50ml of pH 1.2 the minimum concentration required for gelation of sols with these three bentonite concentration was 0.5%(w/v). Gelation occurred without exposure to acidic condition in formulations containing either 0.8 and 1.0% (w/v) bentonite and at concentration of 0.25 % (w/v) or less these formulation were not able to form rigid gels when exposed to pH 1.2, therefore of no interest for the present study. The optimum concentration for maximum gel strength was 0.5 % (w/v) bentonite, with this three (0.1, 0.15 and 0.2% w/v) different concentration of xanthan gum insitu gelling sols were prepared.

The viscosities of the formulations at different RPM were determined using Brookfield viscometer. The viscosity was found to decrease at increasing rpm exhibiting shear thinning behavior and also increase in viscosity was observed with increase in concentration of polymer. However all the batches obeyed Newtonian system (Table-1). On addition of

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taste masking agent such as D-sorbitol in the concentrations 5, 10 and 20w/v to the formulations there was only a slight difference in the viscosity. But there was a marked increase in viscosity after addition of 40%w/v D-sorbitol. The observed increase of viscosity with increase of concentration of D-sorbitol is an expected consequence of increasing polyhydric alcohol (in D-sorbitol) molecules interaction with increase of polymer concentration [19]. It was also found that sols containing 40%w/v D-sorbitol gelled at room temperature after storage for a week, hence it was not suitable for oral administration. So the optimum concentration of D-sorbitol to be used as taste masking agent was found to be 20% or less. On determination of drug content about 99.6% of percentage drug loading was observed in all the batches of xanthan gum. (Table-1)

Table 1
Determination of Drug content and Rheological properties

S.NO	FORMULATION CODE (%W/V)	RHEOLOGICAL SYSTEM	DRUG CONTENT (mg)
1.	SKC 0.1	NEWTONIAN	39.91±0.17
2.	SKC 0.15	NEWTONIAN	39.84 ± 0.24
3.	SKC 0.2	NEWTONIAN	39.82±0.32

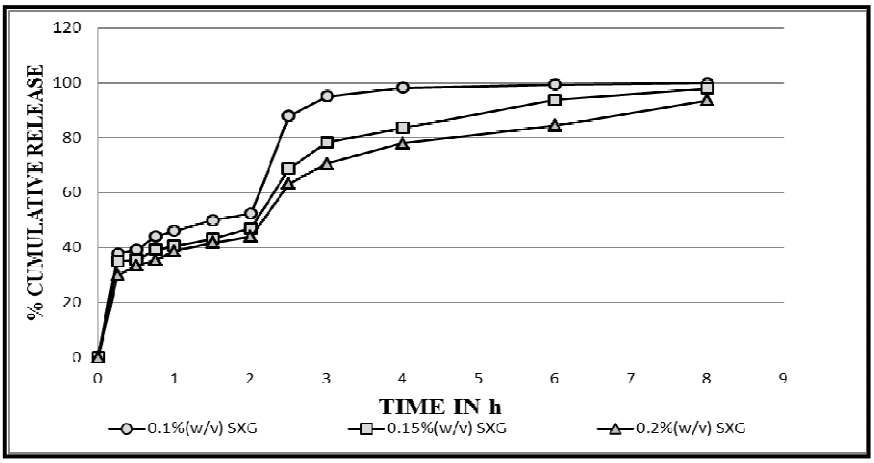

Figure 1.
Invitro dissolution profile of different concentration of SXG

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When a solution is administered orally, it first reaches the stomach and it passes in to small intestine, where the pH is alkaline. Hence invitro drug release under gastric pH 1.2 and intestinal pH 6.8 conditions were studied. The amount of drug release from 0.1, 0.15 and 0.2%w/v xanthan gum was found to be 52.36%, 47.07% and 44.09% at the end of 2hrs in pH1.2 and 99.85%, 97.95% and 93.63% in pH6.8 at the end of 8hrs. Figure 1 show significant influence of xanthan gum concentration on the invitro release. Rigid gels are formed when the sols are placed in contact with dissolution medium at pH1.2 and the amount of drug released was lower than that at pH6.8. The reason for this difference in release behavior is attributable to the large difference in the H+ ion concentrations of the two dissolution medium. The H+ ion concentration at pH6.8 is insufficient to cause the formation of rigid gels. Precisely to know the mechanism of drug release the data was plotted in Higuchi's classical equation (Table-2).The correlation values obtained from Higuchi model was found to be 0.9679, 0.9084 and 0.9603 respectively for all the three formulations. This value show that the mechanism of release of the gel formed insitu after addition in to the acidic medium followed Higuchi diffusion controlled release. To verify the fact that whether the diffusion follow's Fick's law or not, the data was also plotted according to Peppa's equation in which, log cumulative percentage of drug released is plotted against log time. The slope obtained from the linear plot of peppa's model was found to be 0.3475, 0.3561 and 0.3566 respectively, because the values are less than 0.5 and it follows diffusion controlled mechanism [20].

Table 2.
Invitro release kinetics

Sample	Higuchi	Peppa's	
	r	r	n
SKC 0.1 (%w/v)	0.9084	0.9219	0.3561
SKC 0.15 (%w/v)	0.9603	0.9364	0.3566
SKC 0.2 (%w/v)	0.9679	0.9422	0.3475

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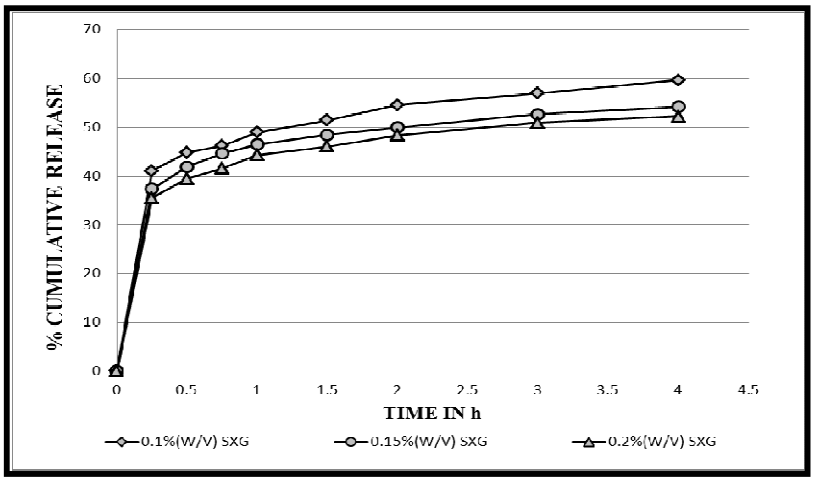

Figure 2.
Invitro dissolution profile of different concentration of SXG at pH 2.0

On the study of effect of gastric acidity on the *invitro* drug release in pH2.0, it was observed that there was a slight increase in drug release from all the three SXG formulations when compared to the release profile at the pH 1.2 (Figure-2). There is no significant change in drug release pattern. This is because of no marked difference in the amount of H^+ ions present at pH1.2 and 2.0, so the sols were able to maintain the integrity of the gel formed. And with the pH 4.0 the formulations SXG 0.1% showed a pronounced increase in amount of drug release when compared to that of dissolution pattern at pH 1.2 (Figure-3). This is because of lack of integrity of the gel formed. Whereas 0.15% SXG and 0.2 % SXG there was no significant difference in drug release from that of pH 1.2 and 2.0, though we observed a slight increase in amount of drug released.

The formulation 0.15 % SXG was selected for the *invivo* study in rabbit models. The drug concentration was estimated from the plasma samples and various pharmacokinetic parameters (AUC_{0-t}, $t_{1/2}$, t_{max}, c_{max}) were calculated. The bioavailability of the formulation (0.15%SXG) and commercial syrup (Conventional) following oral administration exhibited highest AUC followed by the commercial syrup [19]. The increased AUC represent better absorption and bioavailability of the drug from the formulated SXG, which may be due to retarded release of drug from the dosage form. (Table-3)

Table 3.
Various pharmacokinetic parameters for 0.15 %(w/v) SXG

Formulation	C_{max}	T_{max}	AUC_{0-6hr}	$t_{1/2}$	K_e

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0.15%(w/v)SXG	607.22	2.0	2204.21	2.72	0.1465
Commercial conventional syrup	308.10	1.0	1404.84	1.84	0.1959

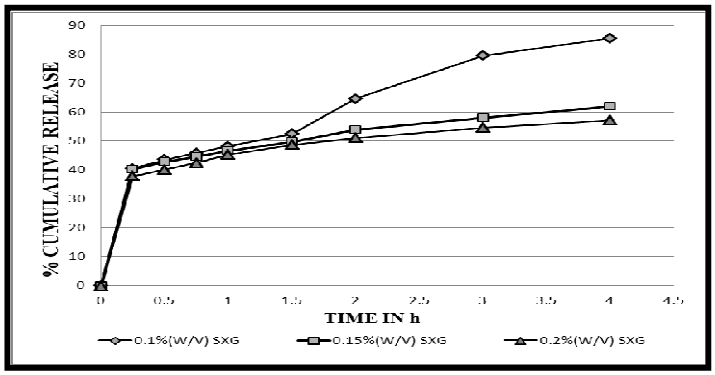

Figure 3
Invitro dissolution profile of different concentration of SKC at pH 4.0

CONCLUSION

This study has demonstrated that insitu gels formed by oral administration of solutions of xanthan gum and that release of salbutamol sulphate is sustained over a time period of at least 6hours. In addition, xanthan gum has an advantage to gel at much lower concentration over other insitu gelling agents such as pectin and sodium alginate, so we may conclude that xanthan gum can be useful oral sustained release vehicle to improve patient compliance and bioavailability and which may be most useful for pediatrics and geriatrics patients.

REFERENCE

1. Gwen M J, Joseph RR, Banker GS and Rhodes GT, Ed. Modern Pharmaceutics. 3rd Edn, Marcel Dakker Inc Publisher, New York 72: 575, (1996).
2. Dissolution for delayed release dosage forms, the United States pharmacopoeia XXIX, United States pharmacopeial convention Inc, 2006, 2680.
3. Endo H, Atanabe W, Matsumato M et al, Preparation and evaluation of heat sensitive melting gel-acetaminophen gel, Journal of hospital pharm, 26: 250-258.

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4. Hardman JG, Limbird LE, Gliman AG, Goodman LS eds, Drugs used in the treatement of asthma, The pharmacological basis of therapeutics, 10th edition, New york Mc Graw-Hill 2001, 736-8.
5. Alderman DA, A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms. Int. J. Pharm. Tech. Prod Mfr. 931: (1984).
6. Yeole P G, Galgatte U C, Babla T B, Nakhat P D, Design and evaluation of xanthan gum-based sustained release matrix tablets of diclofenac sodium. Indian J.Pahrm. Sci 68: 185-189, (2006).
7. Fu Lu M, Woodward L, Borokin S, Drug Develop. Ind. Pharm. 20: 1987, (1994).
8. Dhopeswarkar K, O'Keeffe J C, Horton M, Drug Develop. Ind. Pharm 20: 1851, (1994).
9. Watanabe K and Yakou S, Biol.Pharm. Bull: 16: 391, (1992).
10. Ruel-gariepy E, leroux JC, Insitu-forming hydrogels-review of temperature sensitive systems, Eur J Biopharm 50: 27-46, (2000).
11. Soppinath KS, Aminabhavi TM, Dave AM, Kumar SG, Rudzinski WE, Stimulus-responsive "smart" hydrogels as novel drug delivery systems, Drug Del. Ind. Pharm, 23: 957-74, (2002).
12. Kubo W, Miyazaki S, Attwood D, Oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulation, Int J Pharm, 2-3: 258, 55-64.
13. Lev R, Long R, Mallonga L, Schnaare R, Reilly W, Evaluation of carrageenan as a base for topical gels, Pharmaceut Res, 14(11): 42, (1997).
14. Lui Y, Schnaare R, Reilly W, Evaluation of carrageenan as a suppository base, Pharmceut Res ,14(11): 41, (1997).
15. Kubo W, Itoh K, Miyazahi S, Attwood D, Oral sustained delivery of theophylline and cimetidine from in situ gelling pectin formulation in rabbits, Drug. Dev. Ind. Pharm,31(8): 819-825,(2005).
16. Yoshiaki Yuguchi, Thanh Thi Thu Thuy, Hiroshi U, Kanji K, Structural characterization of carrageenan gels, temperature and concentration dependence, food hydrocolloids, 16(6): 515-22,(2002).
17. Lai V.MF, Wong P A, Lii C Y, Effect of cation properties on sol-gel transition and gel properties of α-carrageenan, Journal of food science, 65(8): 1332, (2000).
18. Wataru kubo, Miyazaki S, Attwood D, Oral sustained delivery of paracetamol from insitu gelling gellan and sodium alginate formulations, Int. J. Pharm, 258:,54-64,(2003).
19. Shozo Miyazaki, Wataru K, Kunihiho I, Yasuhiro K, Mariko F, The effect of taste masking agents on insitu gelling pectin formulations for oral sustained delivery of paracetamol and ambroxal, Int. J.Pharm, 297:38-49,(2005).
20. Koresmeyer RW, Gurny R, Doelkar E, Buri P , Peppas NA, Mechanisms of solute release from porous hydrophilic polymer, Int J Pharm, 15: 23-25, (1983).