International Journal of Current Pharmaceutical Research
Vol 2, Issue 3, 2010
ISSN-0975-7066

Research Article

ORAL SUSTAINED DELIVERY OF SALBUTAMOL USING IN-SITU GELATION OF SODIUM ALGINATE

S. SANGEETHA, G.HARISH, RAMYA MEDAPATI, PRASANTHI GANTASALA, BOMMA RAJU, N. DAMODHARAN

Department of Pharmaceutics, SRM College of Pharmacy, SRM University, Kattankulathur, Kanchipuram District, Chennai-603 203, Tamilnadu, India. Email: sangeethamadhesh@gmail.com

Received 17 Jan 2010, Revised and Accepted 10 Feb 2010

ABSTRACT

The purpose of this study was to evaluate the potential for the oral sustained delivery of sodium alginate formulation with insitu gelling properties of salbutamol sulphate. Sodium alginate insitu gelling sols were prepared in five different concentrations such as 1, 1.5, 2, 2.5, and 3% (w/v). The formulated insitu gelling sols were evaluated for rheological properties, drug content and stability. The *invitro* release study was performed in acidic medium followed by basic medium for about 8hrs. The stability studies were carried out for 4 month and the drug content and appearance of the formulated sols were examined.

Key words: Salbutamol, Insitu, Sodium Alginate, Stability, Sols.

INTRODUCTION

Some hydrophilic polymers have ion properties. Among these alginate which belong to a family of un-branched binary copolymers of (1, 4)-linked β-D-mannuronic acid and α-L-glucuronic acid residues[1]. The later may be present in various proportions altering the physico-chemical properties of the polymer formed. Alginates show characteristic ion binding for multivalent cations and this forms the basis for their gelling properties. The alginate binding leads to the formation of covalent bonds leading to the perception of the insoluble hydrogel [2, 3]. Such crosslinking processes stiffens and roughen the polymer and reduces the swelling in solvents. This generally leads to a reduction in the permeability of different solutes hindering the release of embodied drugs in alginate matrices, allowing these systems to be used in controlling the drug release. The soluble sodium alginate was cross-linked with calcium chloride resulting in the formation of the insoluble calcium alginate. This system had been used successfully to delay the release of some drugs. Different investigators reached a census that similar systems are only appropriately hinder the release of large molecular weight drugs while fail short to do so with smaller molecular weight compounds. [4] 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) [5]. 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. Also, in the commercially available preparations 10 ml of the formulation should be taken 3 or 4 times daily [10]. In order to overcome a sustained drug delivery system is necessary which can improve the patient's compliance but as in tablet form it is difficult to administer to gediatric and pediatric patients. So on considering the above factors we have planned to formulate an oral insitu gelling sols which can be administered to such patients. [6, 7] The polymer selected for the study is sodium alginate, which is widely used in pharmaceutical formulation. Gelation of dilute solutions of sodium alginate occurs on addition of di- and trivalent metal ions by a co-operative process involving consecutive glucuronic residues in the α-L-guluronic acid (G) blocks of the alginate chain. [8, 9] In the present paper, we assess the potential of sodium alginate as vehicle 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.

MATERIAL AND METHODS

Salbutamol sulphate (Tablets India Ltd), Sodium citrate (Rainbow 2000, B -Pura Laboratories, Chennai), Calcium chloride (Rankem, Ranbaxy fine chemicals, New Delhi). Hydro chloric acids, Potassium dihydrogen phosphate, Sodium hydroxide, Potassium chloride used for the preparation are of analytical grade.

Preparation of sol

Sodium alginate (1%w/v) solution was prepared with distilled water and stirred continuously with magnetic stirrer. Then sodium citrate (0.25% W/V), calcium chloride (0.075% W/V) and salbutamol (400mg) were added and heated to 60ºC for about 30mins then the prepared sol is allowed to cool. This sol is stored in room temperature until further use. [10, 11]

Study on drug to polymer ratio

Four different batches of insitu gelling sols were prepared by varying the concentration of sodium alginate polymer. Sodium alginate solutions (1, 1.5, 2, 2.5 and 3% W/V) were prepared with distilled water and stirred continuously with magnetic stirrer. Then sodium citrate (0.25% W/V), calcium chloride (0.075% W/V) and salbutamol (400mg) were added and heated to 60ºC for about 30mins then the prepared sols were allowed to cool. These prepared sols were stored in room temperature until further use. [12, 13]

Evaluation of the formulated sols

Physiochemical properties

The formulated sols were visually observed. It was found that the sols were clear without any dispersed particles.[14]

Measurement of viscosity of the formulated sols

The rheological behaviors of the prepared sols were determined by Brookfield viscometer. The spindle S34 was selected for the study. The samples containing 0.1, 0.15, 0.2, 2.5 and 3%, w/v sodium alginate sols were filled in the sample holder and the spindle was immersed in the samples. The study was carried out at 25°C with 150rpm. Measurements on each sample were performed in triplicate, to analyze the result. [15, 16, 17]

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. The sample was then centrifuged at 5000 rpm and the filtrate was measured spectrophotometrically at 276.1 nm. [18]

In vitro 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 1.2, contained in the dissolution flask and the temperature was

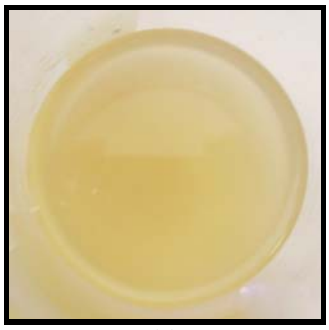
maintained at 37°C with 50 rpm. Aliquots of 5 ml were withdrawn at frequent intervals and equal amount of fresh medium was replaced after each sampling up to 2hrs. At the end of 2 hrs, the medium was changed to pH 7.2. The dissolution was continued in this medium up to 8 hrs. The collected samples were analysed for the drug content through UV spectrophotometer at 276.1 nm. [19, 20]

Stability studies

Stability studies were carried out at room temperature (32- 37 ˚C). The sols prepared were stored in room temperature for about four months. The sols were observed for their physical appearance and drug content at four different intervals. [21, 22]

RESULTS AND DISCUSSION

Although gelation of sodium alginate will occur in the presence of H+ ions, the soft alginic acid gels that are formed are generally suitable as vehicles for drug delivery. In this study Ca++ ions were included in the formulation for induction of alginate gelation. However, for ease of administration we required the formulation to be in the fluid (sol) state [23]. This was achieved by addition of sufficient sodium citrate to the formulation to form a complex with all of the Ca++ ions present in the formulation and hence to effectively remove them from solution. In the acidic environment of the stomach the complex is broken down and the Ca++ ions released cause gelation to occur[24]. The optimum quantities of calcium chloride and sodium citrate which maintained fluidity of the formulation before administration and resulted in gelation when the formulation was added to simulated gastric fluid (pH 1.2), were found from the literatures. The sols formed were clear and viscous with a pleasant appearance[25].



(A)

(B)

Fig. 1 :(A) Sodium alginate *in situ* gelling sol (B) Formation of gel after adding sol to pH 1.2 buffer

Study on drug to polymer ratio

Sodium alginate sols in the concentrations of 1, 1.5, 2, 2.5 and 3% w/v were prepared respectively and their drug loading capacity was determined. From the result it was observed that on increase in polymer concentration the drug loading capacity also increased but after the concentration (2%w/v) the drug loading decreased. This is possibly due to the saturation in the binding sites. [26]

Physicochemical

The sols formed were clear and viscous with a pleasant appearance. The sols when transferred to buffer pH1.2 it was converted to gel. This is due to the acidic environment of the buffer the complex is broken down and the Ca^{++} ions released causing gelation to occur.

Determination of viscosity

The viscosities of the samples were studied through Brookfield viscometer and the viscosities of the samples were found to be 82.5 to 148.2 cps. On increase in polymer concentration the viscosity were also found to be increased.[27] (Table-1)

Determination of drug content

The drug content of the samples were found to be from 37 to 39% for all the batches but the batch SAL-IV showed the highest concentration of drug loading such as 39.96mg. Whereas other batches were found to be comparatively low. (Table-1)

***Invitro* release study**

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 7.2 conditions were studied. The amount of drug release from 1, 1.5, 2, 2.5 and 3% w/v sodium alginate was found to be 72.5, 73.5, 69.7, 81.1, and 72.5% W/V at the end of 8hrs. Figure 2 show significant influence of sodium alginate concentration on the invitro release. 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[28]. (Fig-2)

Stability studies

The stabilities were determined for a period of four months and the results were reported in the table no 3. All the batches showed a slight reduction in the drug content whereas the formulated batch SAL-IV was found to have a least drug loss when compared to other batches. [29, 30] and the batches SAL IV and SAL V loosed its sol properties and converted to gel on storage at the fourth month analysis.

Table 1: Physiochemical properties

S. no.	Formulation code (%w/v)	Viscosity (CPS)	Drug content (mg)
1.	SAL I (1%w/v)	82.5	37.45±0.07
2.	SAL II(1.5%w/v)	84.4	37.89±0.23
3.	SAL III (2%w/v)	104.5	38.86±0.18
4.	SAL IV (2.5%w/v)	120.6	39.96±0.07
5.	SAL V (3%w/v)	148.2	39.02±0.46

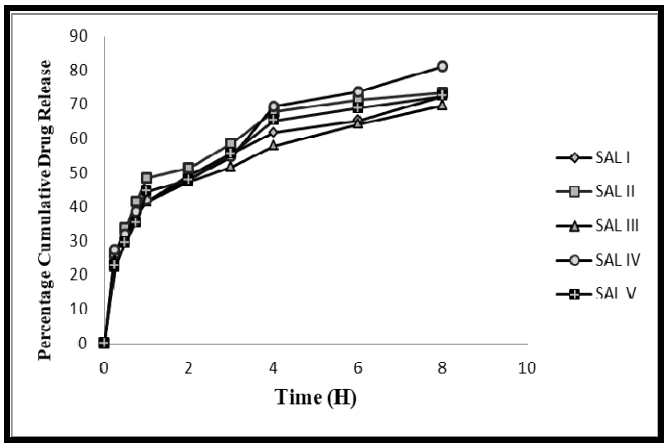


Fig. 2: *Invitro* dissolution study of formulated insitu gelling sodium alginate sols from different batches

Table 2: *Invitro* release kinetics

Sample	Higuchi	Peppa's	
	r	r	n
SAL I (1%w/v)	0.975914	0.983415	0.420669
SAL II(1.5%w/v)	0.958899	0.973904	0.434616
SAL III (2%w/v)	0.978864	0.980695	0.460925
SAL IV (2.5%w/v)	0.983796	0.990639	0.47814
SALV (3%w/v)	0.96572	0.977456	0.4964

Table 3: Data after stability study

S. no	Months	Sal I (1%W/V)		Sal II (1.5%W/V)		Sal III (2%W/V)		Sal IV (2.5%W/V)		Sal V (3%W/V)	
		APR	DC	APR	DC	APR	DC	APR	DC	APR	DC
1.	1st Month	NC	37.45±0.07	NC	37.89±0.23	NC	38.86±0.18	NC	39.96±0.07	NC	39.02±0.46
2.	2nd Month	NC	32.45±0.14	NC	33.31±0.84	NC	33.98±0.09	NC	38.52±0.19	NC	31.77±0.29
3.	3rd Month	NC	30.17±0.46	NC	29.49±0.46	NC	31.45±0.13	NC	37.07±0.68	NC	30.12±0.96
4.	4th Month	NC	28.39±0.67	SCG	28.78±0.59	SCG	30.92±0.02	SCG	36.33±0.59	SCG	28.66±0.06

DC- Drug content, APR- Appearance, NC- No Characteristic Change, SCG-Sols Is Converted in to Gel

CONCLUSION

This study has demonstrated the feasibility of forming gels in the stomach by the oral administration of aqueous solutions of sodium alginate containing Ca^{++} ions in a complexed form. Furthermore, a sustained release of the drug, salbutamol is achievable from the gel vehicles over a period of at least 8 h. so we may conclude that sodium alginate may be a useful oral sustained release vehicle to improve patient compliance and bioavailability and which may be most useful for pediatrics and geriatrics patients.

ACKNOWLEDGEMENTS

Authors thank the Tablets India Pvt Ltd for providing salbutamol sulphate as gift sample. The authors wish to thank the department of pharmaceutics, SRM College of pharmacy for providing all necessary facility and constant encouragement throughout the project work.

REFERENCES

1. Moe ST, Draget KI, Break GS, Smidsrod O, Stephen AM. Food polysaccharides and their applications. Marcel Dekker, New York; 1995: 245–286.
2. Badwan A, Abumalooh A, Sallam E, Abukalaf A, Jawan O. A sustained release drug delivery system using calcium alginate beads. Drug Dev. Indus. Pharm 1983; 11: 239–256.
3. Kwon GS, Bae YH, Cremers H, Feijen J, Kim SW. Release of macromolecules from albumin-heparin microspheres. Int. J. Pharm 1992; 79: 191–198.
4. Susan A and William N. Oral modified release delivery systems. Modified release drug delivery technology. Deckker series 126: 1-8.
5. Gwen NJ and Joseph RR. Sustained and controlled release drug delivery systems. Modern pharmaceutics. Deckker series.3rd edition 72:575-81.
6. Charles SL, Joseph RR. Sustained release drug delivery systems. Remington: The science and practice of pharmacy 19th edition, 1995; 2: 1660.
7. Leon Lachmann, Herbert AL, Joseph LK. Sustained release dosage forms. The theory and practice of industrial pharmacy, 3rd edition, Lea and Febiger 1986 :430-1
8. Kurisawa M, Yui N, Nippon R. Recent trends drug delivery systems using biomaterials 1996; 54 (7): 2004-11.
9. Ruel GE, Leroux JC. Insitu forming hydrogels – review of temperature sensitive systems. Eur J Pharm Biopharm 2004; 2: 409-26
10. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm 2000; 50: 27- 46.
11. Soppinath KS, Aminabhavi TM, Dave AM, Kumbar SG, Rudzinski WE. Stimulus responsive "smart" hydrogels as novel drug delivery systems. Drug Dev Ind Pharm 2002; 23: 957-74.
12. Qiu Y, Park K. Environment sensitive hydrogels for drug delivery. Adv drug deliv rev 2001; 53: 321-39.
13. Anseth KS, Metters AT, Bryant SJ, Martens PJ. Insitu forming degradable networks and their applications in tissue engineering and drug delivery. J control release 2002; 78:199-209
14. Bharadwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and

modified natural gum as sustained release carriers. Drug dev. Ind. Pharm 2000; 26: 1025-38.
15. Guo JH, Skinner GW, Harcum WW, Barnum PE. Pharmaceutical applications of naturally occurring water soluble polymers. Pharm Sci & tech today 1998; 1: 254-61.
16. Podual K, Doyle FJ, Peppas NA. Dynamic behaviour of glucose oxidase containing micro particles of poly (ethylene) grafted cationic hydrogels in an environment of changing pH .Biomaterials 2000; 21:1439-50.
17. Carelli V, Coltelli S , Di Colo G , Nannipicri E , Scrafini MF . Silicon microspheres for pH controlled gastro intestinal drug delivery. Int. J. pharm 1999; 179: 73-83.
18. Kubo W, Miyozaki S, Attwood D. Oral sustained delivery of paracetamol from in situ gelling gellan and sodium alginate formulations. Int. J. pharm 2-3; 258:55-64.
19. Hardman JG, Limbird LE, Gilman AG, Goodman LS. Drugs used in treatment of asthma. The pharmacological basis of therapeutics, 10th edition, New York Mc Graw Hill 2001:736-8.
20. Syed N, Betty S, Bhaskar C, Ananth P. Effect of potassium chloride and cationic drug on swelling erosion and release from Carrageenan Matrices. AAPS Pharm Sci and Tech 2004 ; 05(2) :1-8
21. Lev R, Long R, Mallonga L, Schnnare R, Reilly W. Evaluation carrageenan as a base for topical gels . Pharmaceutics res 1997; 14(11): 42.
22. Lui Y, Schnaare R, Reilly W. Evaluation of carrageenan as suppository base. Pharmaceutic. Res 1997; 14(11): 41.
23. Hariharan M, Wheatley T, Price J. Controlled release tablet matrices from carrageenan: compression and dissolution studies. Pharmaceut dev tech 1997; 2(4): 383-93.
24. John M. Evaluation k- carageenan based microgels in model youghurt systems. The Irish scientist year book 2005.
25. Yoshiaki Y, thanh thi thu thuy, Hiroshi. Structural characteristics carageenan gels: temperature and concentration dependence. Food hydrocolloids 2002; 16(6): 515-22.
26. Lai VMF, Wong PAL and Lii CY. Effects of cation properties on sol gel transition and gel properties of carrageenan. Journal of food science 2000; 65 (8):1332.
27. Miyazaki S, Kawasaki N, Kubo W, Endo K, Attwood D. Comparison of insitu gelling formulation for oral delivery of cimetidine. Int. J. pharm 2001; 2020:161-8.
28. Miyazaki S, Kubo W, Attwood D. Oral sustained delivery of theophylline using in situ gelation of sodium alginate controlled release 2000 ; 67: 275-80
29. Kawasaki, Ohkori R, Miyazaki S, Uno Y. Thermally reversible xyloglucon gels as vehicles for oral drug delivery. Int. J. pharm 1999; 181; 227 -34
30. Kubo W, Itoh K, Miyazki, Attwood D. Oral sustained drug delivery of theophylline and cimetidine from in situ gelling pectin formulations in rabbits. Drug dev. Ind. Pharm 2005; 31 (8); 819-959.