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ORAL SUSTAINED DRUG DELIVERY OF THEOPHYLLINE USING IN SITU GELATION OF SODIUM ALGINATE

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ABSTRACT

In the present paper, we assess the potential of sodium alginate as vehicle for the sustained delivery of theophylline which are to be administered in liquid form and to form gels insitu in the acidic environment of the stomach. Sodium alginate insitu gelling sols were prepared in different concentrations such as 1, 1.5, 2, 2.5 and 3 %w/v by adding Calcium chloride (0.075%w/v), Sodium citrate (0.25%w/v) and Theophylline (1000 mg). The formulated in situ gelling sols were evaluated for viscosity determination, drug content, *invitro* release study and stability studies. The *invitro* release study was performed in acidic pH 1.2 for the first 2 hrs and then for further 4hrs the study was carried out with pH 6.8. Out of all the 5 batches sodium alginate in the concentration of 2%w/v showed best result with *invitro* dissolution, drug content and viscosity. So sodium alginate in the concentration of 2%w/v was selected as the best formulation. Further it may be concluded that sodium alginate can be useful as oral sustained release vehicle to improve patient compliance and bioavailability and which may be most useful for pediatrics and geriatric patients.

KEY WORDS: Sodium alginate, oral *In-situ*, *In-vitro*, *In-vivo*, Theophylline, Calcium Chloride.

1. 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. Matrix systems are the most popular method among innumerable methods used in the development of controlled release formulations. The oral route of drug delivery is typically considered the preferred and most patient compliance means of drug administration. The goal of any drug delivery is to provide a therapeutic outcome of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration. Most sustained release forms are designed so that the administration of single dosage unit provides the immediate release of the amount of drug that promptly produces the desired therapeutic effect and gradual and continual release of additional amount of drug to maintain this level of effect over an extended period, usually 8 to 12 hours (Stockwell, 1986; Badwan, 1983).

Recently a gel formulation for the oral delivery of Theophylline containing Sodium alginate and Calcium chloride as gelling agents has been reported. The sustained delivery of both is designed to be administered in liquid form and to form insitu gel in the acidic environment of the stomach.

Sodium alginate consists of mainly the Sodium salt of Alginic acid which is a mixture of Alginic acid obtained mainly from the algae belonging to the order pharophyceae. It is used as a viscosity increasing agent. Gelation of dilute solutions of Sodium alginate occurs on addition of di – and trivalent metal ions by a co operative process involving consecutive glucoronic residues in the 1- glucoronic acid (G) blocks of the alginate is usually in the form of a matrix. It is slowly soluble in water. Sodium alginate has also been evaluated as a controlled release formulation for drugs like Theophylline, Indomethacin.

The selected drug, Theophylline is a β_2 adrenergic receptor agonist and is used as a bronchodilator. It can be specifically indicated in case of acute asthma, used to treat breathing and in children is > 12 mg/day. It has a short biological half life of about 5-8 hrs. It also has some adverse reactions like vomiting, cardiac arrhythmias which can be lethal (Carelli, 1999).

In the present paper, we assess the potential of sodium alginate as vehicle for the sustained delivery of theophylline which are to be administered in liquid form and to form gels insitu in the acidic environment of the stomach.

2. METHODS AND MATERIALS

i. Preparation of sols containing Sodium alginate: Sodium alginate (1%w/v) solution was prepared with distilled water and stirred continuously with magnetic stirrer. The Sodium citrate (0.25%w/v), Calcium chloride (0.075 %w/v) and Theophylline (400mg) were added and dissolved. Then the solution was heated to 60 °c for about 30 mins and then allowed to cool. The sol was stored in room temperature until further use (Charles, 1995; Guo, 1998).

ii. Measurement of rheological properties of sols: The rheological behaviors of the prepared sols were determined by Brookfield viscometer. The spindle S34 was selected for the study. The samples containing 1, 1.5, 2, 2.5, 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 150 rpm. Measurement on each sample was performed in triplicate, to analyze the result (Hardman, 2001; Hariharan, 1997).

iii. Determination of drug content: A known quantity (40 mg) of the prepared sols was stired with 100 ml of buffer solution pH 6.8 for 6 hrs**.** Then the sample was filtered and the filtrate was measured spectrophotometrically at 273nm (Kawasaki, 1999).

iv.*In-vitro* drug release studies: For the determination of *invitro* drug release, USP dissolution apparatus 2 was used. Dilution method was employed to maintain different pH conditions in the dissolution studies. 30 ml of the solution was added to 200 ml of buffer solution of pH 1.2, contained in the dissolution 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 gap to 3 hrs. At the end of 2 hrs, the medium was changed to 6.8 by adding 500 ml of water with 25 gm of NaOH and 43gm of KH_2PO_4. The dissolution was continued in this medium up to 8 hrs the collected samples were analysed for the drug content through UV spectrophotometer at 273 nm. (Kubo, 2005; Kunihiko, 2008)

v. Effect of gastric acidity on the in vitro drug release: This in vitro release study was carried out at various buffer solutions such as pH 2.0 and 4.0 as to represent the typical gastro intestinal pH variation. The prepared sols, equivalent 40 mg of drug were added to 900 ml buffer solution of pH 2.0 and 4.0 and all other conditions were maintained.

vi. Stability studies: Stability studies were carried out at room temperature (32-37°c). The sols prepared were stored in room temperature for about 4weeks. The sols were observed for their physical appearance. (Kwon, 1992)

3. RESULTS AND DISCUSSIONS

Gelation of Sodium alginate will occur in the presence ok H^+ ions. In this study ca^{++} ions were included in the formulation for induction of alginate gelation. This was achieved by adding sodium citrate to the formulation to form a complex with all the ca^{++} ions. In the acidic environment of the stomach the complex is broken and the ca^{++} ions are released cause the gelation to occur. 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 stimulated gastric fluid (pH 1.2).

Study on drug to polymer ratio: Sodium alginate sols in the concentration of 1, 1.5, 2, 2.5, 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 capacity decreased. This is due to the saturation in the binding sites.

Drug content and viscosity: The viscosities of the samples were studied through brook field viscometer and the viscosities of the samples were found to be 83.2-148.2 cps. On increase in polymer concentration the viscosity was found to increase. The drug content of the samples were found to be from 110 to 118 % for all the batches but the batch ALG V showed the highest concentration of drug loading such as 39.96 mg. Whereas other were found to be comparatively low.

***In-vitro* dissolution studies:** When a solution is administered orally, it first reaches the stomach and it passes in to small intestine, where the pH is alkaline. Hence *in-vitro* drug release under gastric pH, 1 , 1.5 , 2 , 2.5 , 3 % w/v sodium alginate was found to be 98.2 , 96.5 , 70.4 , 68.5 , 60.1 % w/v at the end of 8 hrs. The batch THEO 2 was selected as the best batch because this batch showed a good drug content and satisfactory in vitro release. So the effect of gastric acidity and release kinetics were carried out for these batches.

Effect of gastric acidity on the vitro drug release: On the study of effect of gastric acidity on the in vitro drug release in pH 2.0, it was observed that there was a slight increase in drug release from the formulation when compared to the release profile at the pH 1.2. There is no significant change in drug release pattern. This is because of no marketed difference in the amount of H^+ ions present at pH 1.2 and 2.0, so the sols were able to maintain the integrity of the gel formed. And the pH 4.0 the formulation showed a pronounced increase in amount of drug release when compared to that of dissolution pattern at pH 1.2. This is because of lack of integrity of the gel formed.

***In-vitro* release kinetics:** On the determination of the in vitro release kinetics it was observed that the selected batch follows higuchi diffusion mechanism.

Table.1. Drug content and viscosity

Formulation code (%w/v)	Viscosity(cps)	Drug content(mg)
THEO 1	83.2	110
THEO 2	84.4	118
THEO 3	104.5	116
THEO 4	120.6	114
THEO 5	148.2	111

Table.2. *In-Vitro* Dissolution Studies

Time (hrs)	THEO I	THEO II	THEO III	THEO IV	THEO V
0	0	0	0	0	0
0.25	26.4	23.7	22.4	15.4	13.4
0.5	38.9	37.9	29.8	21.8	19.5
0.75	46.7	48.2	37.5	27.6	25.4
1	55.9	57.9	41.5	33.4	31.2
2	68.4	65.2	47.4	41.5	37.8
3	74.6	73.9	51.6	48.9	43.6
4	81.9	82.8	57.9	55.8	49.8
6	91.2	90.5	66.8	63.9	55.4
8	98.2	96.5	70.4	68.5	60.1

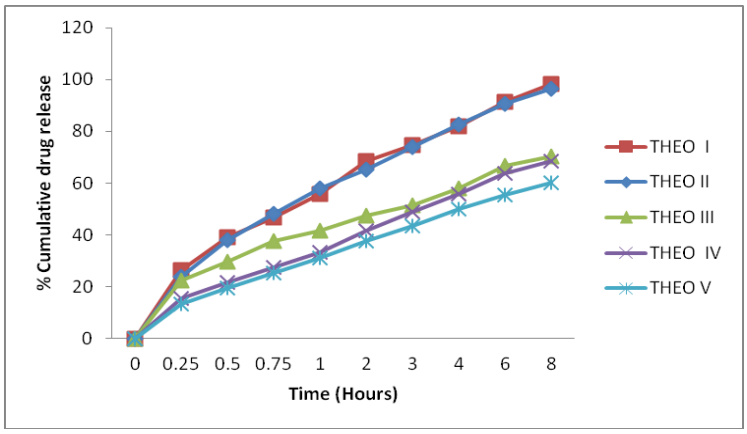

Figure.1.Dissolution Profile for Different Formulations

Table: 3 Effect of Gastric Acidity on the Vitro Drug Release

Time	THEO II IN pH 2	THEO II IN pH 4
0	0	O
0.25	22.5	33.4
0.5	35.9	47.8
0.75	45.0	56.6
1	57.2	68.4
2	64.5	75.4

Table.4. *in-vitro* release kinetics

Samples	Higuchi		Peppa's	
	r	n	r	n
THEO 2	0.9411	1.9021	0.9717	0.3758

Stability studies: The stability studies were determined for a period of 4 weeks. On the physical observation of the five different batches, at the end of 4 weeks the batch THEO 1 and THEO 2 was found to have good stability than the other batches.

4. 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, sustained release of the drug theophylline is achievable form the formulated sol over a period of 8 hrs. So we may conclude that sodium alginate may be useful as oral sustained release vehicle to improve patient compliance and bioavailability and which may be most useful for pediatric and geriatric patients.

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