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The influence of variation of gastric pH on the gelation and release characteristics of *in situ* gelling sodium alginate formulations

Rishad R. Jivani[1], Chhagan N. Patel[2], Nurudin P. Jivani[1]

[1] Department of Pharmaceutics, Smt. R.B.Patel Mahila Pharmacy College, Atkot, Gujarat, India
[2]Department of Pharmaceutical Analysis, Shari Sarvajanik Pharmacy College, Mehsana, Gujarat, India

Abstract

The aim of present study was to examine the influence of variation of gastric pH over the range 1–3.5 on the gelation of liquid formulations of sodium alginate and on the *in vitro* release of baclofen from the resultant gels. Gels suitable as vehicles for sustained delivery of these drugs were formed *in vitro* at pH < 3.5 from sodium alginate solutions of concentrations 1.0–2.5% w/v. Very weak gels were formed at pH 3.0 resulting in poor sustained release characteristics compared with those at pH 1.2; no significant *in vitro* gelation was observed at pH 3.5. Visual observations showed *in situ* gelation of 1.5% (w/v) sodium alginate formulations under conditions of both high (pH 1.0–1.6).

Keywords: *In situ* gelation, Sodium alginate gels, Baclofen

Introduction

Possibility of using *in situ* gelling sodium alginate formulations to achieve sustained release of drugs following oral administration have been investigated by many scientist (Kubo et al. 2004a, 2004b and 2005, Miyazaki et al. 2005). Alginic acid is a linear block copolymer polysaccharide made up of β-D mannuronic acid (M) and α-L-guluronic acid (G) residues joined by 1,4 glycosidic linkages. The proportion of all block and the arrangement of blocks along the molecule much depending on the algal source. Dilute aqueous solutions (1.0–2.0% w/v) of sodium alginate readily form gels in aqueous solution in the presence of free Ca^{++} ions. They are widely used in the food industry and because of their nontoxicity and biocompatibility have found many pharmaceutical and cosmetic applications. A property of aqueous solutions of alginates has been widely exploited for the preparation of vehicles for the sustained delivery of bioactive molecules and their ability to form firm gels in presence of di- and trivalent metal ions by a co-operative process involving consecutive guluronic residues in the G blocks of he alginate chain (Grant et al. 1973, Morris et al. 1973, Liang et al. 1980)

A soluble complex of calcium ions was included in our formulation that was designed to break down to release free calcium ions on encountering the acidic environment of the stomach, so ensuring gelation of the orally administered sodium alginate solution. A similar procedure was employed previously in the design of *in situ* gelling formulations of the sodium alginate (Miyazaki et al. 2000 and 2001, Kubo et al. 2003), aqueous solutions of which also readily form gels in the presence of Ca^{++} ions.

***Corresponding author:** hellorishad@yahoo.com

A perceived problem with such formulations is that the gastric hydrogen ion concentration may not be sufficiently high in some circumstances, even in the fasted state, to ensure adequate release of complexed calcium. It is known that in healthy young Caucasians the gastric pH is less than pH 3 during 90% of the fasted state, although on a minute-to-minute basis may reach as high as pH 7 (Dressman et al. 1990). After ingestion of a meal, the gastric acidity can vary over a wide range depending on the composition of the meal but is typically in the range pH 3–7. This article examines the *in vitro* gelation and release characteristics of the sodium alginate formulations containing baclofen over the pH range 1–3.5

Materials and Methods

Baclofen was received as a gift sample from Sun pharmaceutical Ltd., Vadodara, India. Sodium Alginate was received as a gift sample from Shital Chemicals, Ahmedabad, India. Calcium bicarbonate purchased from S.D. Fine chemicals, Mumbai, India. All other ingredients were procured from Lesar chemicals, Vadodara, India and of analytical grade. All materials used through out the study conformed to USP 24 standards.

Preparation of in situ gelling solution

Different concentrations of sodium alginate solution were prepared in deionized water containing sodium citrate (0.25%). Present of less concentration of cations in the solution was sufficient to hold the molecular chains together and inhibit hydration. Sodium alginate solution was heated to 70°C with stirring. After cooling below 40°C different concentrations of calcium bicarbonate and drug were added and dispersed well with continuous stirring. The resulting sodium alginate *in situ* gel solution containing baclofen was finally stored in amber color bottles until further use.

Gelation of sodium alginate sols

The influence of pH on the gelation characteristics of 1.0, 1.5, 2 and 2.5% w/v sodium alginate sols was determined by immersion of 30 mL sol enclosed in dialysis tubing into dilute solutions of HCl (150 mL) with pH values over the range 1.0–3.5. After equilibration for 24 h at room temperature, the contents of the tube were passed through a sieve (No. 6.5, 2.80 mm) over a period of 30 s and the weight of the gel remaining in the sieve was determined (BL-220H, Shimadzu Ltd., Kyoto, Japan).

In vitro drug release study

The release of baclofen from *in situ* gel preparation was carried out as described Woodford et al. 1987 with some modification using USP dissolution test apparatus (USP 24) with paddle stirrer at 50 rpm. Slow speed avoids the breaking of gelled formulation and was maintaining with low agitation conditions. The dissolution medium used was 500 mL of 0.1 N HCl (pH 1.2), and temperature was maintained at 37°C. 10 mL formulation was withdrawal using disposable syringe, the needle was wiped clean and excess formulations removed from the needle end. The syringe end was then placed into the Petri dish and plunger pusses slowly to remove 10 mL formulation and than Petri dish containing formulation was kept in the dissolution vessel containing dissolution fluid without much disturbance. At every 1h interval an accurately measured sample of the dissolution medium was removed and replace with pre-warmed (37°C) fresh medium. Absorbance of baclofen was measured at 267 nm using UV spectrophotometer (UV-1601, Shimadzu, Japan).

Result and Discussion

Effect of variations in gastric pH on gelation of sodium alginate sols

Figure 1 shows the weight of gel formed from 30 mL solutions of 1, 1.5, 2.0 and 2.5% w/v sodium alginate after dialysis in solutions of HCl over the pH range 1.0–3.5. Gel formed from 2% sodium alginate solution at pH 1 to 2.5 and for 1.0 and 1.5% solution at pH 1.0 to 2.0 had a well-defined cylindrical form indicative of effective gelation as a consequence of the release of the complexed calcium ions under these acidic

conditions. Although complete gelation of 1.0 and 1.5% solutions was observed at pH 2 the resultant gels were not sufficiently strong to maintain their cylindrical form. Figure 1 also shows that the hydrogen ion concentrations at pH 3.0 and 3.5 were not sufficiently high to cause effective breakdown of the calcium complex in the sodium alginate solutions and gelation was poor or non-existent under these conditions. Figure 2 shows sodium alginate solution and formation of *in situ* gel in 0.1 N HCl (pH 1.2)

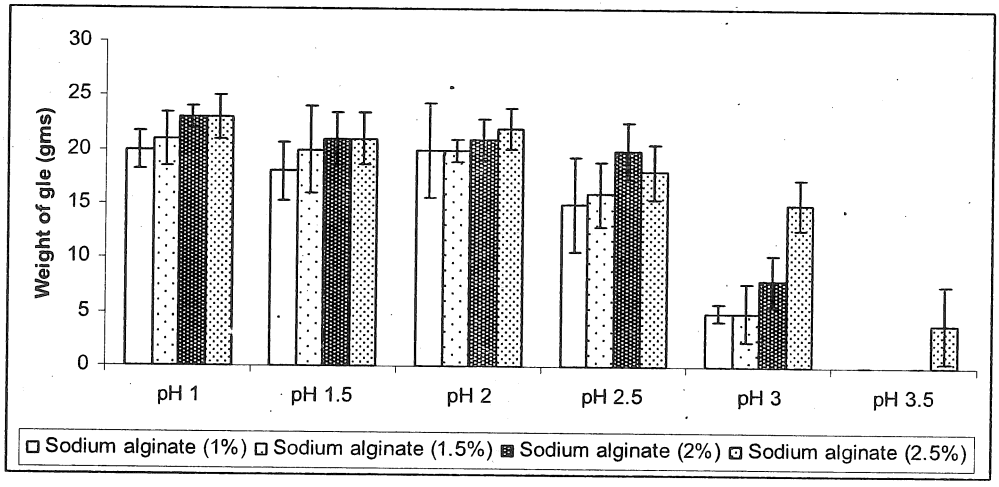

Figure 1. Effect of variations in gastric pH on gelatin of baclofen *in situ* gelling formulations

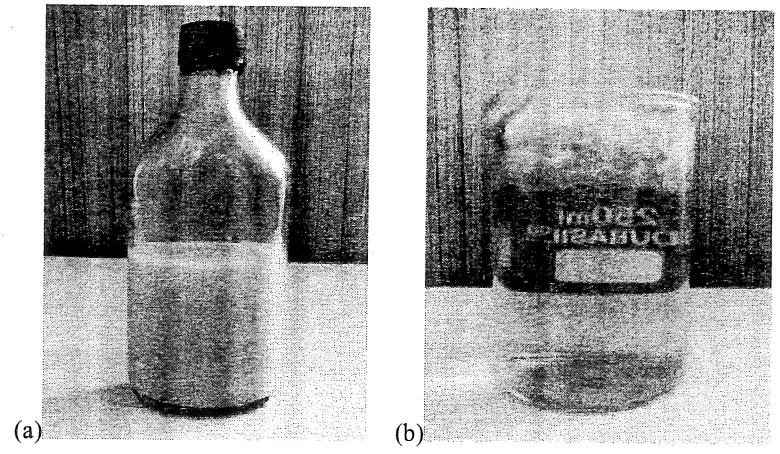

Figure 2. *In situ* gel formation of sodium alginate solution; (a) solution of baclofen, (b) formation of *in situ* gel in 0.1N HCl.

Effect of variations in gastric pH on in vitro drug release of baclofen in situ gelling formulations

The release profiles of baclofen from the 2.0 % w/v sodium alginate formulations at various gastric pH are shown Figure 3. Release of drug from each of the formulations was appreciably faster when the sodium alginate was exposed to a receptor solution at pH 3.0 over the initial release period; observation of the donor cells showed that the formulations were predominantly in sol form throughout the duration of the release period. Diffusion through the dialysis membrane of H^+ ions from the receptor solution at this pH was insufficient to cause the release of complexed calcium ions and consequently gelation of the sodium alginate was incomplete. No further analysis of the data for these formulations was undertaken.

The slower release from formulations initially maintained at pH 1.2 was a consequence of effective gelation under these conditions as confirmed by visual observation of the diffusion cell.

The release data over the whole time period of release for these formulations were analysed using the Higuchi equation for drug release from semisolid vehicles containing dissolved drug (Higuchi 1962), Higuchi model showed least sum of square of residuals (SSR=149.59) and Fischer's ratio (F=13.59). The mechanism of release of baclofen from in situ gel was by anomalous diffusion controlled mechanism.

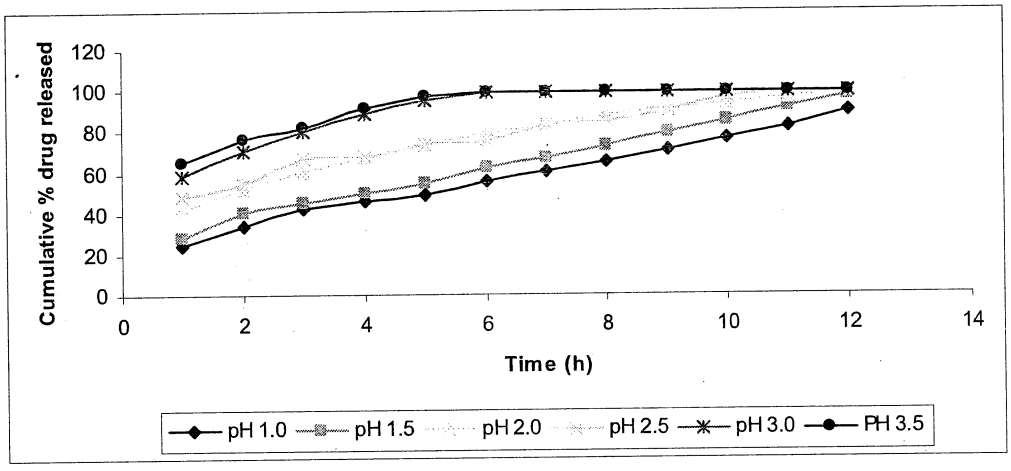

Figure 3. Effect of variations in gastric pH on *in vitro* drug release of baclofen *in situ* gelling formulations

Conclusion

This study has demonstrated that 2% w/v sodium alginate sols formulated with a source of calcium in complexed form can form gels under *in vitro* condition. *In vitro* gelation is not observed at low acidity (pH ≥ 3.0). *In vitro* drug release studies have indicated no significant influence on the sustained release characteristics of baclofen from gels formed *in situ*.

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