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Indomethacin sustained release from alginate–gelatin or pectin–gelatin coacervates

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Abstract

Gastrointestinal side effects may interrupt essential therapy with indomethacin, a non-steroidal anti-inflammatory drug. Formulation of this drug into sustained release form may reduce some of these side effects by avoiding contact of drug crystals with gastrointestinal mucosa at high concentrations, as may happen with immediate release dosage forms. Indomethacin (IMC) sustained release microparticles (pellets) were prepared from pectin–gelatin or alginate–gelatin hydrocolloid coacervate systems under controlled pH and temperature conditions. Delayed release up to 14 h was obtained with pectin–gelatin or alginate–gelatin systems of varying composition. With the pectin–gelatin systems a low drug to hydrocolloid ratio and low pectin to gelatin ratio was the most optimal composition for sustained release. Incorporation of additives such as carnauba wax was essential for diffusion controlled mechanisms to operate in the alginate–gelatin systems. Additives also showed improvements in particle shape, size distribution and flow properties. The results of this study offer an inexpensive alternative form of sustained release IMC.

Keywords: Indomethacin; Sustained release; Microparticles; Coacervation

1. Introduction

Indomethacin (IMC) is a potent non-steroidal anti-inflammatory drug with analgesic and antipyretic effects widely used in many musculoskeletal and joint disorders. However, one of the adverse reactions of IMC that warrants interruption of therapy is gastrointestinal disturbance (Reynolds, 1993). Also, generation of gastrointestinal ulcers in rats following a single toxic dose have been reported (Cioli et al., 1979; Liversidge et al., 1989). Formulation of IMC as an oral sustained release preparation has been hypothesized to reduce or prevent untoward local actions within the upper gastrointestinal tract, to control the delivery pattern of the drug relative to a desired action, to increase the extent of absorption and to prolong the duration of action of the drug following administration (Dressman et al., 1990; Brune and Beck, 1991) and to improve the side effect profile (Bacon et al., 1990a and Bacon et al., 1990b). The incidence of IMC-induced ulcers is related to the initial systemic concentration

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of IMC (Hilton and Summers, 1986) and ulceration severity follows the order: intravenous IMC > oral IMC suspension > oral IMC in an amphoteric gel (Liversidge et al., 1989). Drug absorption from IMC-SR formulations has been found to be more uniform, prolonged and reliably reproducible when compared with immediate release preparations. There was no effect on the bioavailability of the drug (Bayne et al., 1982; Yeh et al., 1982). There has been some controversy concerning the rationale for IMC-SR formulation (Green, 1984; Tannenbaum, 1985). SR preparations in general, improve patient compliance as a result of less frequent dosing (Tannenbaum, 1985; Yeh, 1985). Some studies have proposed microencapsulation to provide protection towards ulceration, but others have shown no benefit (Rowe and Carless, 1981; Hilton and Summers, 1987). The anti-ulcer effects of alginate have been speculated to have contributed to the reduction in stomach irritation resulting from administering an IMC alginate dispersion formulation to dogs (Shiraishi et al., 1991). The alleviation of gastrointestinal distress by pectin in demulcents has also been reported (Endress, 1991).

Complex ionic coacervation/phase separation has been studied widely using gelatin (cationic) and acacia (anionic) as the hydrocolloids (Deasy, 1984; Keipert and Melegari, 1993; Jizomoto et al., 1993). The process is a result of gelatin acquiring a positive charge below the isoelectric point when the solution pH is altered, to form an ionic complex with the negatively charged acacia. However, the use of some colloids such as pectin has been limited due to poor phase separation when the reaction is carried out at isohydric conditions not offering enough pH changes in the system to result in complex formation (McMullen et al., 1982, 1984). Pectin–gelatin coacervation was achieved after mixing the colloids with pH previously increased to effect a high degree of ionization of the pectin. Upon decreasing the pH of the mixture the amphoteric gelatin acquired a positive charge to form a complex with the pectin. This method, however, produced extremely small irregular particles.

There are no reports demonstrating the use of alginate in ionic complex coacervation/phase separation microencapsulation. Alginate has been used widely for the preparation of gel beads resulting from gelation in the presence of calcium chloride. Colloids (like polylysine and chitosan) have been used with alginate as reinforcing agents on the already formed beads. The process of bead formation usually involved droplet extrusion or dispersion congealing techniques and not phase separation/coacervation (Murata et al., 1993; Ostberg et al., 1993; Ostberg and Graffner, 1994; Polk et al., 1994).

In an attempt to improve microparticle morphology and size distribution, carnauba wax was incorporated in the formulation, and to provide enteric effect Aquateric® was chosen. It was hypothesized that since Aquateric® dissolves in pH 6 and above, it would precipitate in acidic solutions, entrapping the dispersed drug. The formed agglomerates containing the drug would then be coated with pectin– or alginate–gelatin coacervates. Similarly for carnauba wax, it was hypothesized that melting the wax dispersed in the colloid mixture then cooling would result in agglomerates containing the drug. Coacervation by pH reduction would then coat the agglomerates.

The main purpose of this study is to produce a sustained release IMC formulation using a coacervation technique particularly using hydrocolloids including alginate or pectin in combination with gelatin under mainly aqueous environment. The use of alginate and the formation of a protective sheath around IMC particles due to coacervation would potentially contribute toward reduction in ulceration following oral administration.

2. Materials and methods

Gelatin type A, (Pharmagel A, from Ruger Chemical Co. Inc., Irvingham, NJ); citrus pectin N.F. (Pharmaceutical Grade was from S.B. Pennick and Co., NY); sodium alginate and calcium chloride were from BDH Chemicals Ltd (Poole, UK); IMC was a gift from Biovail Research Corporation (Steinbach, Man.); Aquateric® was supplied by FMC Corporation (Newark, DE);

carnauba wax and sodium lauryl sulphate were of B.P. specification.

2.1. Preparation of the coacervation pellets

The method of preparation and recovery of the coacervation pellets was a modification of the method first described by McMullen et al. (McMullen et al., 1982, 1984). The microcapsules were prepared from 100-ml batches of varying concentrations of either pectin or sodium alginate and gelatin containing varying amounts of IMC. First all colloids (pectin, sodium alginate and gelatin) were individually dissolved in distilled water (at 60°C) to give 2% w/v solutions. Selected proportions of the individual colloids (33 ml pectin or alginate and 67 ml gelatin) were adjusted to a mixing pH of 10 with appropriate amounts of 1.0 N sodium hydroxide. The amount of sodium hydroxide required to adjust the pH was about 2.5 ml for pectin, about 1.5 ml for gelatin and 0.2 ml for sodium alginate. The temperature was maintained at 45°C. Either pectin or sodium alginate solution was mixed with gelatin solution with continuous stirring. The pH of the mixture was lowered quickly to pH 5.0 with 0.5 N hydrochloric acid. The amount of hydrochloric acid required to reach coacervation was found to be about 5.5 ml for alginate–gelatin and about 6.0 ml for pectin–gelatin. At this point a desired amount of IMC (0.5 g, 1.0 g, 1.5 g or 2.0 g per 100 ml batch) was added. The dispersion of IMC was aided by the addition of 0.02% (w/v) sodium lauryl sulphate. The pH was further lowered slowly until coacervation and formation of discrete particles was observed, which typically occurred between pH 3.5 and pH 4.5. Agitation was maintained for a further 30 min while allowing the mixture to cool to room temperature. The microparticles (pellets) were then hardened with 10 ml of 37% w/w formaldehyde. After 30 min a suitable stock solution of calcium chloride was added to give a final calcium chloride concentration of 1.5% w/v and product was then left to stand for 15 h. The pellets were filtered and the residue was resuspended under continuous stirring in a mixture of 10 ml glycerin and 50 ml of isopropanol in water (1:2). The flocculated and partially dehydrated pellets were then filtered and washed repeatedly with three 50-ml portions of isopropanol in water and oven dried for 24 h at 37°C or to constant weight. The dry pellets were then sieved through standard 8, 16, 30 and 60 mesh sieves.

In other batch variations, either Aquateric® (hydrophillic polymer) or carnauba wax (lipophilic erodible wax) were incorporated before the drug was added. Aquateric® (1 g, 1.5 g or 2 g) was added to the solution at pH 10.0. The pH was then adjusted to pH 6 followed by addition of the drug and further pH decrease until coacervation. In order to disperse carnauba wax the pH of the colloidal mixture was lowered from pH 10.0 to pH 5.0, and the temperature was raised to about 95°C to melt the wax. The drug was then added with continued agitation as the temperature was allowed to decrease to about 45°C (Kawashima et al., 1981).

Table 1 summarizes all the systems prepared, but only some formulations resulted in spherical, free-flowing pellets with substantial yield in the 16/30 size range. Hence only those were selected for dissolution tests.

2.2. Pellet drug load and degree of encapsulation

The weight, M, of drug encapsulated in a sample of pellets of weight, W, was estimated using a modification of the method described in USP 23 for determining content uniformity. Instead of using methanol and pH 7.5 buffer in a 1:1 ratio, a ratio of 2:1 was used to improve extraction efficiency. Trituration preceded solvent extraction. The experimental drug load (D_e) was given by M/W. The theoretical drug load (D_t) can be determined from the drug/hydrocolloid ratio as shown in Table 1. For example, a ratio of 1:2 suggests 0.33 for D_t. The % encapsulation efficiency (%E) can then be determined by $(D_e/D_t) \times 100$.

2.3. Dissolution test methodology

Drug release patterns were studied using USP Apparatus 1, at a rotational speed of 75 rev./min, a mass of pellets equivalent to 75 mg of IMC using 900 ml of pH 2.0 KCl–HCl buffer at 37°C

for the first 2 h and pH 6.2 phosphate buffer for the next 12 h. The dissolution medium was selected in accordance with USP 23, Drug Release Test 2 for indomethacin extended release. All tests were done in triplicate and the mean values and standard deviation are reported.

3. Results and discussion

The degree of drug encapsulation achieved was high in the range of 75–99%. The bulk of pellets ranged from 30/60 mesh to 16/30 mesh although particles as fine as less than 60 mesh and those larger than 16 mesh were also seen as shown in Fig. 1A and Fig. 1B. The larger particles were a result of aggregation of smaller particles and were not as spherical and as free-flowing as the smaller particles. Additives like Aquateric® or carnauba wax in higher proportions prevented the formation of large aggregated particles that were common in systems containing either pectin–gelatin or alginate–gelatin only. However, addition of these materials yielded pellets containing a larger fraction of very small particles. The yield of particles between the two size limits was not significantly different for the pellets with or without these additives.

Table 1
Summary of pellet composition of all the formulations prepared, selected ones were tested for release characteristics

Formulation no.	Hydrocolloid[a] type and ratio (w/w)	Drug/hydrocolloid ratio (w/w)
1	Pec–Gel 1:0	1:2
2	Pec–Gel 1:1	1:2
3	Pec–Gel 1:2	1:4
4	Pec–Gel 1:2	1:2
5	Pec–Gel 1:2	1:1
6	Pec–Gel 2:1	1:2
7	Alg–Gel 1:1	1:2
8	Alg–Gel 1:1	1:4
9	Alg–Gel 1:2	1:2
10	Pec–Gel–Aq 1:2:3	1:2
11	Pec–Gel–Aq 1:2:3	1:4
12	Pec–Gel–Aq 2:4:3	1:3
13	Alg–Gel–Aq 1:2:3	1:2
14	Alg–Gel–Aq 1:2:3	1:4
15	Alg–Gel–Aq 2:4:3	1:3
16	Pec–Gel–Cw 1:2:3	1:2
17	Pec–Gel–Cw 1:2:3	3:8
18	Pec–Gel–Cw 1:2:3	1:4
19	Pec–Gel–Cw 2:4:3	1:3
20	Alg–Gel–Cw 1:2:3	1:2
21	Alg–Gel–Cw 1:2:3	3:8
22	Alg–Gel–Cw 1:2:3	1:4
23	Alg–Gel–Cw 2:4:3	1:3

Pec, pectin; Gel, gelatin; Alg, alginate; Aq, Aquateric®; Cw, carnauba wax.

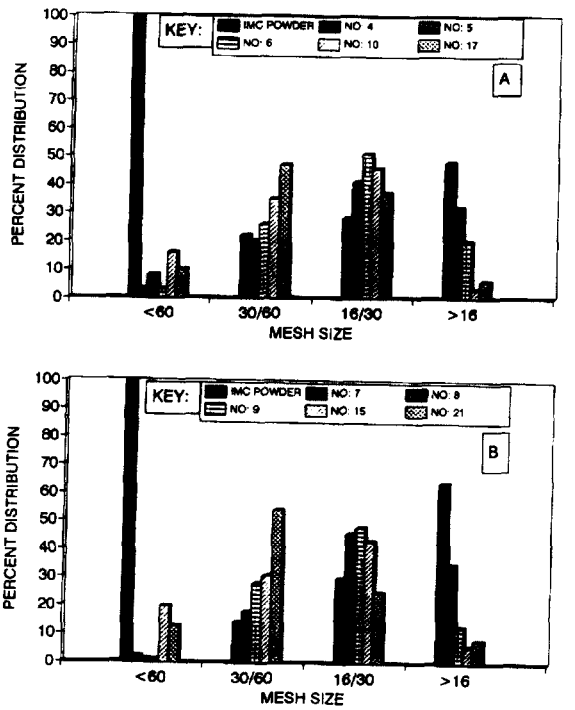

Fig. 1. Percentage size distribution by weight of all sieve-sized fractions of pellets. (A) Pectin–gelatin system. (B) Alginate–gelatin system. (Numbers correspond to formulations summarized in Table 1.)

Complex ionic relations between the negatively charged pectin and the amphoteric protein, type A gelatin have been studied before for the preparation of microglobules (0.5–22 μm in diameter) by McMullen et al. (McMullen et al., 1982). Also, Polk et al. (1994), exploited the complex ionic relations between chitosan (a polysaccharide derived from chitin) and alginate to produce controlled release microcapsules of albumin. However, the aim of this study was to produce SR

pellets of IMC using these complex ionic relations by coacervation under various conditions.

The release profiles of some of the pellet formulations prepared using pectin as the hydrocolloid in combination with gelatin are shown in Fig. 2. The release in pH 2.0 medium was almost negligible in all cases, since these hydrocolloids do not swell in acid pH thereby not allowing water to diffuse for dissolution to occur. Pectin, and even more so, its water insoluble salt form, calcium pectinate have been suggested as agents for delayed release preparations for site specific colonic delivery of drugs (Rubinstein et al., 1993). Although all formulations showed delay in drug release compared with IMC alone, some were more pronounced than the others. IMC alone also showed no release in the acid medium and after buffer change at 2 h, showed a steep initial release of about 63% in the first 1 h, but, the dissolution rate dropped and showed a plateau to reach a final value of 66.5% at the end of 14 h. Previous results have shown that IMC used in this study is Form I, the solubility of which is 11 mg/100 ml in phosphate buffer pH 6.2 at 25°C. However, IMC release from pellets proceeded gradually to nearly 100% in some cases (nos. 5, 6, and 10) and to only

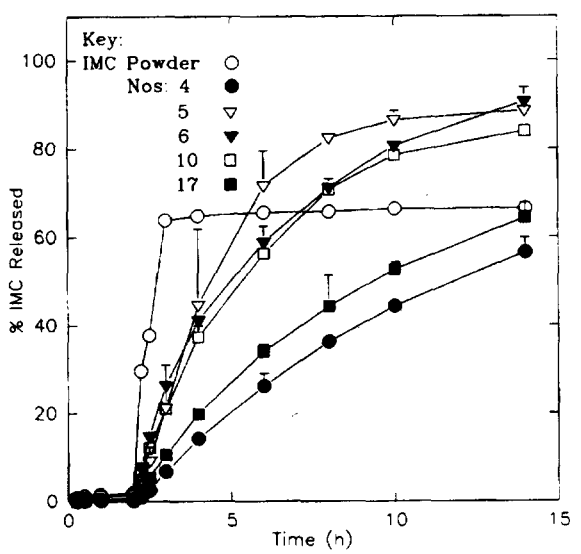

Fig. 2. Cumulative percentage of indomethacin released from pectin containing pellets in pH 2.0 buffer (up to 2 h) and pH 6.2 buffer at 37°C.

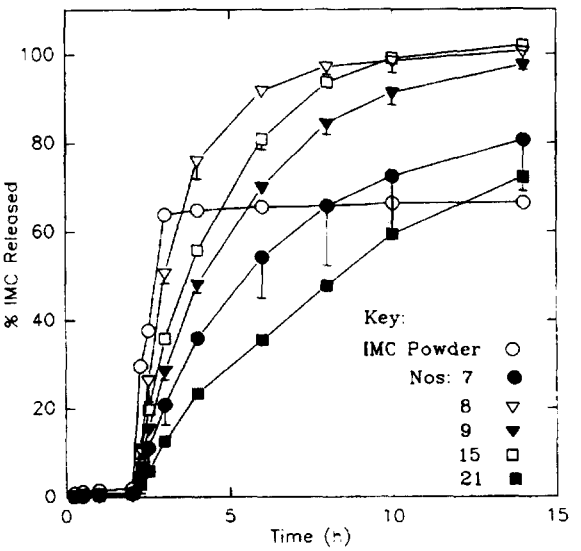

Fig. 3. Cumulative percentage of indomethacin released from alginate containing pellets in pH 2.0 buffer (up to 2 h) and pH 6.2 buffer at 37°C.

50–60% in others (nos. 4 and 17) at 14 h. Formulation no. 4 which had a low drug to hydrocolloid ratio, which could also be considered core to wall ratio, and low pectin to gelatin ratio was most optimal for sustained release over 14 h. Increasing the drug to hydrocolloid ratio at the same pectin to gelatin ratio (no. 5) changed the dissolution profile drastically. A similar effect was observed in formulation no. 6 where the pectin content was increased yet maintaining the same core to wall ratio as no. 4. Introduction of an additive such as Aquateric® (no. 10) at high concentration gave a release pattern similar to nos. 5 or 6. For Aquateric® latex dispersion to be effective the most appropriate method of application is coating along with a plasticizer under specific temperature and other conditions. In this procedure none of these requirements were met. Addition of carnauba wax (no. 17) only slightly increased the release of IMC over the entire range as compared with no. 4.

The results obtained from dissolution tests of the alginate–gelatin systems are shown in Fig. 3. Here, a system containing carnauba wax (no. 21) gave the most prolonged release. Aquateric®, again had no substantial sustaining effect after 4 h

as compared with pure IMC. In general, the 14 h cumulative release was higher for alginate systems as compared with pectin systems. These differences are perhaps due to differences in the degrees of hydration of alginate and pectin and the solubilizing effect of alginate on IMC as reported by others (Shiraishi et al., 1991).

3.1. Kinetics of release

Drug release from matrix diffusion controlled drug delivery systems is dependent on the initial drug load, matrix porosity and tortuosity, leaching solvent (pH, etc), polymer system, and solubility of the drug (Park et al., 1984). The effect of varying drug load in matrix diffusion controlled release systems has been extensively documented (Dressman et al., 1990). Drug release from matrix devices by diffusion has been described by Higuchi's model (Park et al., 1984)

$$Q = [D\acute{\varepsilon}/\tau(2A - \acute{\varepsilon}C_s)C_s t]^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area of matrix exposed to the dissolution medium at time t, A is the amount of drug in the matrix of total porosity $\acute{\varepsilon}$, τ is the tortuosity, and C_s is the solubility of the drug in the matrix and D is the diffusion coefficient of the drug in the matrix. This equation may be simplified if one assumes that D, $\acute{\varepsilon}$, τ, A and C_s are constant, to give

$$Q = Kt^{1/2} \quad (2)$$

Plotting Q against the square root of time would give a straight line with slope equal to K.

From a plot of % IMC released versus square root of time (Fig. 4) and the values summarized in Table 2, formulation no. 4 and to an extent no. 17 showed linear although incomplete release for the entire period which may be due to an effective and complete ionic reaction between pectin and gelatin resulting in a matrix with reduced diffusivity or porosity. The linearity suggests a diffusion controlled release mechanism. Increasing the drug content (no. 5) or increasing the pectin proportion (no. 6) or the addition of Aquateric® (no. 10) led to an increase in drug release and the profile was non-linear with the square root of time suggesting loss of a diffusion controlled mechanism. In the alginate systems, only the pellets containing carnauba wax (no. 21) showed a linear relationship with the square root of time ($r = 0.9933$) and all other pellets failed to show any diffusion controlled release mechanism (Fig. 5).

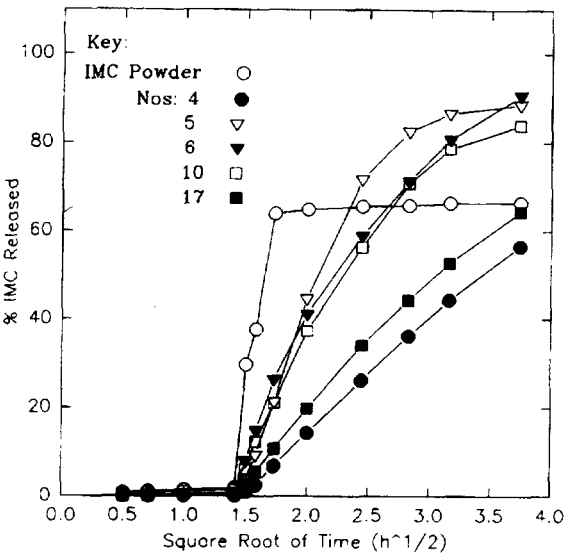

Fig. 4. Indomethacin release from pectin–gelatin coacervate pellets plotted according to the square root of time equation.

Table 2
Slopes and correlation coefficients obtained from square root of time plot of selected formulations

Preparation type	Formulation no.	Slope	R^2
	IMC	12.24	0.4473
Pectin containing			
	4	25.39	0.9980
	5	41.16	0.8743
	6	37.33	0.9553
	10	39.71	0.9409
	17	28.26	0.9914
Alginate containing			
	7	34.74	0.9430
	8	37.62	0.7502
	9	41.82	0.9183
	15	42.55	0.8815
	21	31.40	0.9933

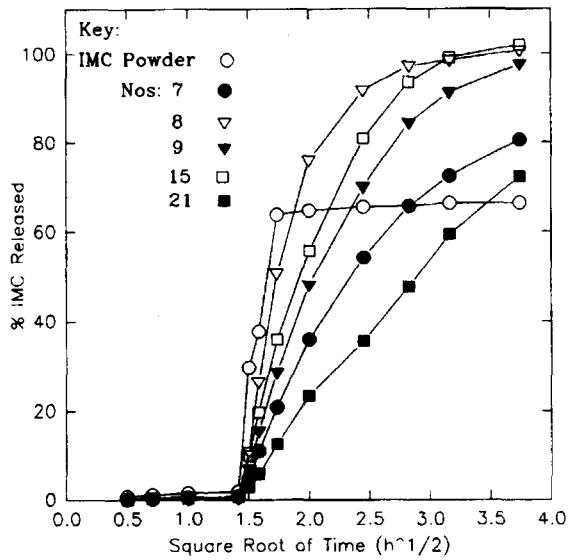

Fig. 5. Indomethacin release from alginate–gelatin coacervate pellets plotted according to the square root of time equation.

4. Conclusions

IMC microparticles (pellets) demonstrating sustained release characteristics up to at least 14 h have been prepared from coacervation of pectin and gelatin or alginate and gelatin. The drug load, ratio of the individual hydrocolloids and also the drug to hydrocolloid ratio affected the release properties substantially. Addition of other materials reduced forces of aggregation and improved particle size distribution and flow.

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