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In Vitro Release of Chloramphenicol from Polymer Beads of α-Methacrylic Acid and Methylmethacrylate

S. C. KHANNA* and P. SPEISER

Abstract □ The *in vitro* release behavior of chloramphenicol from four different bead polymers containing methylmethacrylate and α-methacrylic acid in various buffer solutions has been studied. The concentration of α-methacrylic acid in the copolymer beads and the pH and ionic strength of the buffer solutions were observed to influence the release rate of the chloramphenicol from these beads. The beads containing no α-methacrylic acid did not release the drug in any buffer solution, and the beads containing only α-methacrylic acid released the drug at almost the same rate in all buffer solutions. The smaller beads released the drug more quickly than the larger ones.

Keyphrases □ Polymer beads—chloramphenicol release □ Chloramphenicol release—α-methacrylic acid, methylmethacrylate beads □ α-Methacrylic acid, concentration effect—release rates, polymer beads □ pH, ionic strength effects—chloramphenicol release, polymer beads

In an earlier publication (1), the possibility of utilizing the bead polymerization method for the preparation of a sustained-release dosage form was discussed. Physical barriers are used in the majority of the prolonged-release dosage forms to decrease the rate of drug release to the absorption site. The swelling or dissolution property of the polymer materials in which the drug is embedded is the major contributing factor in the release of drug from such dosage forms. Nelson (2) reported that the dissolution or release rate of a drug from a dosage form is the rate-determining factor in the absorption and physiological availability of the drug. Hence, an *in vitro* release procedure may be used to screen the materials worthy of inclusion as a potential physical barrier for sustained-release products. Furthermore, it may show the direction in which the right copolymers or polymers for the purpose may be found. The final required sustained-release dosage form containing these beads may consist of a single specimen of the polymer beads or a mixture of many different polymer and copolymer beads.

As the drug is incorporated in a large number of small individual beads, the chances of consistent availability of the drug at the intended site of the gastrointestinal tract increase considerably. In the present work, the

Table I—Polymeric Beads of α-Methacrylic Acid and Methylmethacrylate with Chloramphenicol

Preparation No.	Monomeric Mixture Polymerized, % α-Methacrylic Acid	Methylmethacrylate	Chloramphenicol in Beads, %
1	100	–	9.5
2	66.6	33.3	15.0
3	33.3	66.6	19.5
4	–	100.0	7.0

influence of the following factors on the *in vitro* release of chloramphenicol USP embedded in beads of α-methacrylic acid, methylmethacrylate, or mixtures thereof has been studied: (*a*) content of α-methacrylic acid in the polymer beads, (*b*) pH and ionic strengths of the buffer solutions, and (*c*) size of the bead.

EXPERIMENTAL

***In Vitro* Release Test**—A modified USP tablet disintegration test apparatus was used under the same conditions as previously described (3). In each glass tube, a fine nylon filter was fitted so that the beads could be separated from the buffer solution from time to time. Approximately 100–150-mg. beads from an 800–1000-μ diameter sieve fraction were accurately weighed and eluted with 50 ml. of buffer solution. At a fixed time interval, selected according to the polymer and the buffer solution used, the buffer solution was filtered through the fine nylon filter fitted in the tube and was replaced with the same amount of the fresh buffer solution. The amount of chloramphenicol released was determined spectrophotometrically at the 278-mμ wavelength. This procedure was repeated until either the whole of the embedded drug was released or a maximum period of 14 hr. was reached. Triplicate experiments were performed with each buffer solution, and the results are the average of these.

Buffer Solution Used—Various buffer solutions in the range of pH of gastrointestinal fluids have been used as eluting liquids for the *in vitro* release of chloramphenicol from the polymer beads. Buffer solutions of pH 1.2 (HCl–NaCl), 3.2, 5.2, 6.2, 7.2, and 8.2 (all phosphates), each with ionic strengths of 0.1, 0.2, and 0.3, were prepared. Buffer solutions of either pH 8.2 or of ionic strength 0.3 are less common in the human gastrointestinal tract, but they were selected in this study to check the effect of these factors at this high limit on the release behavior of chloramphenicol from the polymer beads.

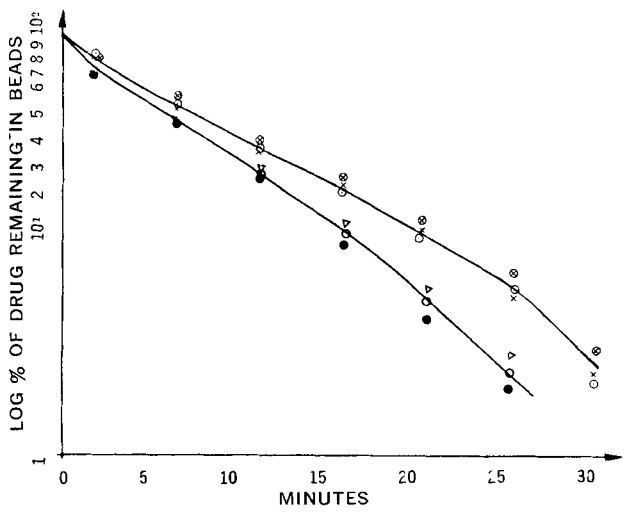

Figure 1—*Release of chloramphenicol from Preparation 1 in different buffer solutions (μ = ionic strength). Key: ○, pH 1.2, μ 0.1; ▽, pH 1.2, μ 0.2; ●, pH 1.2, μ 0.3; ⊗, pH 5.2, μ 0.1; ⊙, pH 5.2, μ 0.2; and ×, pH 5.2, μ 0.3.*

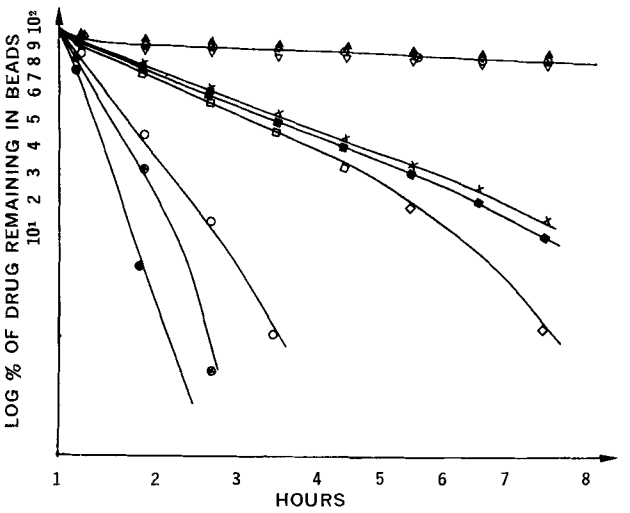

Figure 2—*Release of chloramphenicol from Preparation 2 in different buffer solutions (μ = ionic strength). Key: ▲, pH 3.2, μ 0.1; ⊙, pH 3.2, μ 0.2; ▽, pH 3.2, μ 0.3; ×, pH 5.2, μ 0.1; ■, pH 5.2, μ 0.2; □, pH 5.2, μ 0.3; ○, pH 7.2, μ 0.1; ⊗, pH 7.2, μ 0.2; and ●, pH 7.2, μ 0.3.*

To calculate the amount of the substances for the preparation of the buffer solutions, the following equations were used (4):

$$\text{pH} = \text{pK}_n + \log \frac{(\text{salt})}{(\text{acid})} - \frac{A\,(2n-1)\,\sqrt{\mu}}{1+\sqrt{\mu}} \qquad \text{(Eq. 1)}$$

$$\mu = 1/2 \sum C_i Z_i^2 \qquad \text{(Eq. 2)}$$

All symbols have the same meaning as in the literature (4).

The pH's of the buffer solutions were determined using a Metrohm pH meter, type E 396, and the buffers were adjusted to the correct value if required. The ionic strength, if required, was adjusted by the addition of sodium chloride. All substances used were of analytical quality.

Beads Used—The materials used and the method of preparation of these polymeric beads in the presence of chloramphenicol USP have already been reported (1). The composition of the beads used in the present study is shown in Table I.

Bead Size Used—Sieve analysis of the polymeric beads was carried out (1). The fraction left on each sieve (400–500 μ, 500–630 μ, 630–800 μ, and 800–1000 μ) was used to study the effect of bead size on the release rate of chloramphenicol from the polymeric beads.

RESULTS AND DISCUSSION

To select the appropriate polymer or copolymer of α-methacrylic acid and methylmethacrylate for incorporation into the sustained-release dosage form, the influence of different ionic strengths and the pH's of the various buffer solutions on the release behaviors of chloramphenicol embedded in them has been studied. Although gastric juice varies individually in composition (5), the acidity ranges generally in terms of pH values from 1.2 to 2.5. In some healthy persons, it may even exhibit higher pH values. The pH values of the fluids from the duodenum to the large intestine may vary from 5 to 8 (6). Therefore, the release studies of the drug from the polymeric beads were carried out in buffer solutions from pH 1.2 to 8.2. Although the ionic strengths of the gastrointestinal fluids are constant under normal conditions, they may change due to uptake of ionic substances during meals, *etc.* Therefore, the influence of the different ionic strengths (0.1, 0.2, and 0.3) at all the pH levels of the buffer solutions on the release of drug from beads also has been studied. As the enzymatic activity of gastrointestinal fluids is of minor importance in the release behaviors of the drug from the polymers, pure buffer solutions of either HCl–NaCl or phosphates having the given pH's and ionic strengths have been used.

In the course of the experiments, it became evident that in most cases the release of chloramphenicol from the various polymer and

Table II—Average $t_{20}\%$, $t_{50}\%$, and $t_{80}\%$[a] of Chloramphenicol Released from Different Bead Formulations in Various Buffer Solutions

Buffer Solutions		Preparation No. 1 Time, min.			Preparation No. 2 Time, hr.			Preparation No. 3 Time, hr.		
pH	Ionic Strength	t_{20}	t_{50}	t_{80}	t_{20}	t_{50}	t_{80}	t_{20}	t_{50}	t_{80}
1.2	0.1	1.2	5.0	13.0						
	0.2	1.2	5.4	13.5	—	—	—	—	—	—
	0.3	1.2	5.0	13.0						
3.2	0.1	1.4	6.2	16.4	6.5	—	—			
	0.2	1.4	5.8	16.0	4.75	—	—	—	—	—
	0.3	1.5	6.5	18.5	4.5	—	—			
5.2	0.1	1.4	6.6	17.5	0.8	2.6	5.9			
	0.2	1.3	6.0	16.8	0.65	2.4	5.5	—	—	—
	0.3	1.3	6.5	18.2	0.55	2.1	4.75			
6.2	0.1							25.0[b]	—	—
	0.2	—	—	—	—	—	—	17.0[b]	—	—
	0.3							15.0[b]	—	—
7.2	0.1				0.25	0.8	1.8	1.6	6.5	15.5[b]
	0.2	—	—	—	0.20	0.6	1.35	1.0	2.9	6.4
	0.3				0.15	0.5	0.95	0.45	1.5	3.4
8.2	0.1							1.25	5.5	14.0[b]
	0.2	—	—	—	—	—	—	0.60	2.0	4.5
	0.3	—	—	—	—	—	—	0.35	1.2	2.6

[a] The values for each were taken from Figs. 1–3. [b] The values obtained by extrapolation.

copolymer beads of α-methacrylic acid and methylmethacrylate gave curves of a higher order when plotted as percent cumulative release against time, or as logarithms of the amount of drug remaining in the beads (as a percentage) against time, or as the amount of drug released against the square root of time. However, since most of the drug release data from the various bead formulations showed that up to 80% of the release of the chloramphenicol apparently followed a first-order rate, except the release during the first interval, it was decided to represent the results as logarithms of the amount of chloramphenicol remaining in the beads as a percentage against time (Figs. 1–3). The faster release rate in the beginning may be due to the presence of the drug on the surfaces of the beads. The orthogonal polynomials were used where adequate data were available to calculate the best fitting equations for the regression of the complete curve of log percent of drug remaining in beads against time. In extreme cases, polynomials up to the third degree were required to provide an adequate equation. The comparison of the functions of these equations was rather complex; therefore, the times for release of 20, 50, and 80% of chloramphenicol (represented as t_{20}, t_{50}, and t_{80}) from beads were used as the comparative measures to prove the influence of the various factors in the study on the release behavior of the drug from polymeric beads (Table II). In a few cases, where even 20% release over a study period could not be obtained from the experimental values, it was calculated from the respective regression equations.

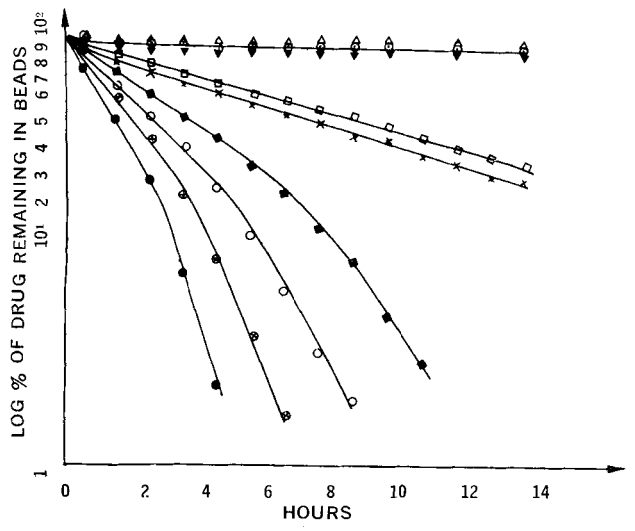

Figure 3—*Release of chloramphenicol from Preparation 3 in different buffer solutions (μ = ionic strength). Key: △, pH 6.2, μ 0.1; ⊙, pH 6.2, μ 0.2; ▼, pH 6.2, μ 0.3; □, pH 7.2, μ 0.1; ×, pH 7.2, μ 0.2; ■, pH 7.2, μ 0.3; ○, pH 8.2, μ 0.1; ⊗, pH 8.2, μ 0.2; and ●, pH 8.2, μ 0.3.*

Influence of α-Methacrylic Acid Content in Bead Polymers on Release of Chloramphenicol—In the absence of α-methacrylic acid in the polymeric beads, Preparation 4, the release of the drug did not take place in buffer solutions of pH 8.2 and below. The release from these beads in buffer solution of higher pH's than this was not carried out. In copolymers, Preparations 3 and 2, incorporating 33.3 and 66.6% α-methacrylic acid, respectively, the release of chloramphenicol started in the buffer solutions of pH 6.2 and 3.2, respectively. The release of chloramphenicol from these copolymer beads in the buffer solutions of pH 5.2 and 2.2, respectively, was almost negligible. The beads containing only α-methacrylic acid, Preparation 1, released the drug quite rapidly in buffer solutions of pH 1.2 and above.

Thus, the content of α-methacrylic acid in the polymer and copolymers influences the onset of the release of chloramphenicol in the buffer solutions. The higher the acidic content in the polymeric beads, the lower is the pH at which the release of drug starts. The results are given in Table III.

There is a rather complicated relationship between the α-methacrylic acid content of the polymer and the properties (pH and ionic strength) of the buffer solutions. This is observed from the irregular release behavior of chloramphenicol from these polymeric beads in the different buffer solutions. For this reason, a quantitative comparison between α-methacrylic acid content in the polymers and the release rates of drug from them in buffer solutions seems difficult to establish. However, it may be observed (Table II) that the higher the α-methacrylic acid content in the polymeric beads, the quicker the release of the drug from them into the buffer solutions.

Influence of pH's and Ionic Strengths of Buffer Solutions on Release Rate of Chloramphenicol from Beads—The polymeric beads containing only α-methacrylic acid showed no significant change in the release rate of chloramphenicol embedded in these beads with variation of either pH or ionic strength of the buffer solution (Table II). It is possible that, due to the large number of acidic groups in the polymer beads, identical solubility and swelling of the beads occurred in the acidic to neutral buffer solutions.

Table III—Influence of Acidic Content in Beads on the Onset of Drug Release

	Preparation No. 1	2	3	4
pH of buffer solution (ionic strength = 0.1)	≥1.2	≥3.2	≥6.2	≤8.2

Table IV—Average Release of Chloramphenicol from Polymeric Beads of Different Diameter

Bead Diameter, μ	Preparation No. 1, Buffer Solution pH 5.2, Ionic Strength = 0.1, Time, min. t_{50}	Preparation No. 1, Buffer Solution pH 5.2, Ionic Strength = 0.1, Time, min. t_{80}	Preparation No. 2, Buffer Solution pH 5.2, Ionic Strength = 0.1, Time, hr. t_{50}	Preparation No. 2, Buffer Solution pH 5.2, Ionic Strength = 0.1, Time, hr. t_{80}	Preparation No. 3, Buffer Solution pH 7.2, Ionic Strength = 0.1, Time, hr. t_{50}	Preparation No. 3, Buffer Solution pH 7.2, Ionic Strength = 0.1, Time, hr. t_{80}
400– 500	1.8	3.5	1.0	1.9	3.5	8.4
500– 630	3.0	7.8	1.3	3.9	4.3	9.2
630– 800	4.0	9.7	2.0	4.0	6.4	15.1
800–1000	7.0	17.4	2.5	5.9	6.5	15.5

However, with the increase of either pH or ionic strength of the buffer solutions, the rate of release of chloramphenicol from the polymer beads containing either 66.6 or 33.3% of α-methacrylic acid was enhanced (Table II, Figs. 2 and 3). In the case of a preparation containing 66.6% α-methacrylic acid in the polymer, the most pronounced increase in the release of chloramphenicol took place in buffer solutions having pH's between 3.2 and 5.2; for a preparation containing 33.3% α-methacrylic acid, the same effect was observed in buffer solutions of pH's between 6.2 and 7.2.

The ionic strength had a more pronounced effect in the case of the bead formulation containing 33.3% α-methacrylic acid than in the case of one containing 66.6% α-methacrylic acid. This change in the release rate of the drug may be due to different swelling and solubility properties of the polymer beads in various buffer solutions.

Influence of the Bead Diameter on the Release Rate—As the release of chloramphenicol from the copolymer beads was found to be dependent on the ionic strengths and pH's of the eluting buffer solutions, it was considered that these beads could be ion-exchange-type resins. The release rate of the drug from such resins is inversely proportional to the radius of the spherical particles. Thus, the release behavior from different bead sizes of the first three preparations was studied. Preparation 4 could not be considered for the study because no release took place from this preparation in any buffer solution below pH 8.2 (Table III). However, no such relationship between t_{50} release and 1/radius could be observed. It may be that the fraction of the sieve-analyzed beads taken in these release studies is not representative of the uniform size distribution of the beads in that fraction. Moreover, the geometry of these beads is altered by swelling and dissolution; hence, the mean radius taken will not be correct for such correlation. However, the results (Table IV) clearly show that the release rate of drug increases with decreasing bead size. Therefore, the uniform release from the sustained-release dosage form may be obtained by varying the particle size in the formulation.

SUMMARY

The release behavior of the drug from these beads in the buffer solutions depends mainly on the amount of α-methacrylic acid content in the polymer. The polymer beads containing 100% α-methacrylic acid released the drug easily in strong acidic buffer solutions of pH 1.2 and above. Hence, these beads may be used to form the initial dose portion in a sustained-release dosage form. The copolymer beads containing 66.6 and 33.3% α-methacrylic acid released the drug in buffer solutions of pH 3.2 and 6.2, respectively, and over. These may be incorporated as a sustained-release portion in such dosage forms. The combination of these beads in the appropriate proportion will show a right release pattern for a sustained-release dosage form.

On the basis of this study, copolymer beads of α-methacrylic acid and methylmethacrylate having the property of predetermined release of drug in specific buffer solution may possibly be prepared. The release rate of the sustained-release portion may also be controlled by varying the bead sizes.

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