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S. K. Bajpai[a]; M. Bajpai[a]; Sutanjay Saxena[a]; Seema Dubey[a]
[a] Polymer Research Laboratory, Department of Chemistry, Govt. Model Science College (Autonomous), Jabalpur, (M.P.), India

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Quantitative Interpretation of the Deviation from 'Zero-Order' Kinetics for the Release of Cyanocobalamin from a Starch-Based Enzymatically Degradable Hydrogel

S. K. BAJPAI, M. BAJPAI, SUTANJAY SAXENA, AND SEEMA DUBEY

Polymer Research Laboratory, Department of Chemistry, Govt. Model Science College (Autonomous), Jabalpur (M.P.), India

In vitro release of the model drug Cyanocobalamin, via enzymatic degradation of a starch based semi-interpenetrating hydrogel network, has been studied in simulated intestinal fluid (SIF) of pH 6.8 at 37°C. The deviation of the formulation from ideal 'zero–order' kinetics was estimated by comparing the experimental 'release rate vs. time' profile with the ideal one and then expressing the deviation in terms of the difference in the curve areas between the two successive time points.

Keywords hydrogel, 'zero–order', deviation, colon, enzymatic degradation

Introduction

Obtaining 'zero-order' release from a oral dosage form is the most desirable phenomenon for chemists and pharmaceutical scientists who work in the field of drug delivery. This is due to the fact that drug delivery at a constant rate provides uniform drug concentration for absorption, and it maintains therapeutic plasma concentration within a therapeutic window to minimize side effects and reduce the frequency of administration. Some of the methods to obtain 'zero-order' release include changing the matrix geometry, preparing polymer erosion-controlled devices, preparing polymer dissolution–controlled systems, synthesizing hydrogels with minimum degree of crosslinking (1–5), etc. Although the almost linear portion of a 'drug release vs. time' profile, obtained for an oral dosage form, suggests the occurrence of 'zero-order' release but this does not provide any quantitative information about the extent to which the system follows 'zero-order'. In the present work, we have studied the dynamic release of Cyanocobalamin from a semi-interpenetrating polymer network composed of starch, polyethyleneglycol, and crosslinked methacrylamide in simulating intestinal fluid of pH 6.8. The constituent starch, present in the gel undergoes

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Address correspondence to S. K. Bajpai, Polymer Research Laboratory, Department of Chemistry, Govt. Model Science College (Autonomous), Jabalpur (M.P.) 482001, India. E-mail: mnlbpi@rediffmail.com

amylase induced degradation with a subsequent release of drug thus mimicking the colonic drug delivery. The release pattern was observed to follow 'zero-order' kinetics. In this work we have suggested a simple mathematical approach to find out the extent of deviation from the ideal 'zero-order' kinetics. To the best of our knowledge, no such report to quantify deviation of 'zero-order' release of a drug from enzymatically degradable hydrogel has ever appeared or been reported.

Experimental

Materials

The monomer methacrylamide (MAAm), crosslinker N,N′-methylenebisacrylamide (MB) and the initiator potassium persulfate (KPS) were of analytical grade. The monomer MAAm was recrystallized in methanol to remove the inhibitor. Polyethylene glycol (PEG; mol. wt. 20,000) and soluble starch (St) were used as received. Injections of Vitamin B_{12} "Cyanocobalamin" (E. Merck, Batch No. 1712) were used as the model drug. The enzyme α-amylase was purchased from Research Lab, Pune, India. Double distilled water was used throughout the investigation.

Preparation of Drug Loaded Formulation

The cylindrical drug-loaded samples were prepared by carrying out free radical polymerization of MAAm in the presence of polyethylene glycol and starch in the drug-containing aqueous solution with MB as crosslinker and KPS as the initiator. For example, to prepare the control set, 1.0 g of MAAm and 4.0 g of polyethylene glycol were dissolved in 1.6 percent (w/v) aqueous solution of starch, containing a precalculated quantity of the drug B_{12}. Crosslinker MB (0.05 g) was dissolved in the solution, followed by the addition of 0.02 g of KPS. The reaction mixture was transferred into PVC straws, each 5.3 mm in diameter, and kept in an electric oven (Tempstar, India) at 50°C for a period of 2 h which was found to be sufficient time for complete polymerization. The formed cylindrical gels were cut into small pieces, 2.50 ± 0.10 cm in length, washed with distilled water, and dried in a dust-free chamber until they attained constant weight. The sample was designated as $HG(X)_y$ where the number X in parenthesis denotes the percent concentration of starch solution and the subscript 'y' denotes the amount of drug (in mg) present per g of the polymer matrix. For example, the control set is $HG(1.60)_{3.45}$.

In Vitro Drug Release Study

In order to carry out dynamic release of B_{12} from the hydrogel sample by a traditional dissolution test (TDT), a completely dried and pre-weight hydrogel sample was put in the 25 ml of α-amylase (5.0 IU/ml) containing a phosphate buffer medium of pH 6.8 (simulating intestinal fluid, SIF) with a constant agitation speed of 50 rpm at 37°C. The amount of drug released at different time intervals was determined spectrophotometrically at 375 nm (6). After each observation, gels were put in the fresh buffer solution. The amount of drug released was computed by comparing the absorbance with the standard curve prepared for the pure drug in the appropriate concentration regions.

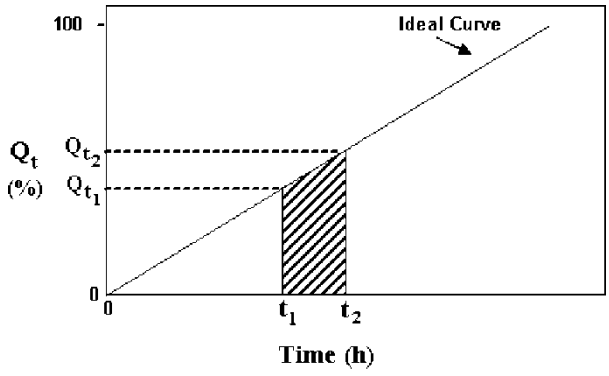

Figure 1. Ideal 'zero-order' "Q_t vs. t" profile.

Results and Discussion

Mathematical Considerations

The 'zero-order' equation (7) may be given as:

$$Q_t = k_o \cdot t \tag{1}$$

where Q_t is the percent drug released at time 't' and k_o is 'zero-order' rate constant.

If Q_{t_1} and Q_{t_2} are the percent drug released at time 't_1' and 't_2', respectively (see Figure 1) then according to equation (1).

$$Q_{t_1} = k_o \cdot t_1 \tag{2}$$

and

$$Q_{t_2} = k_o \cdot t_2 \tag{3}$$

therefore,

$$\frac{Q_{t_2} - Q_{t_1}}{t_2 - t_1} = k_0$$

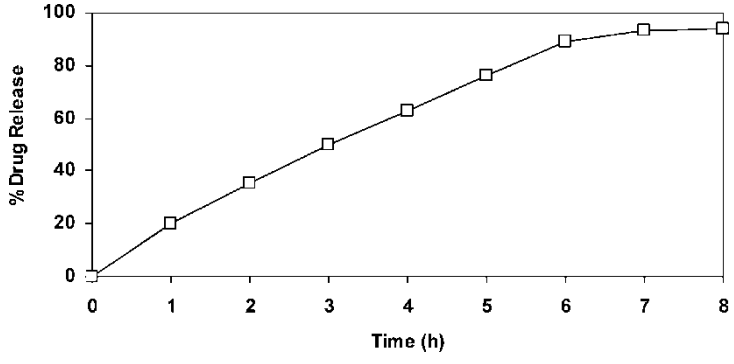

Figure 2. % Drug release as a function of time for the sample HG $(1.60)_{3.45}$ in the amylase containing phosphate buffer of pH 6.8 at 37°C.

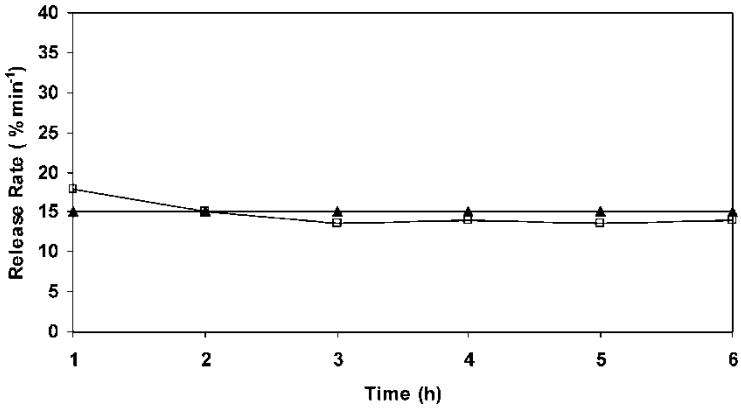

Figure 3. Ideal (▲) and experimental (□) "Release rate vs. time" profiles for 'zero-order' kinetics.

or

$$\text{Rate}(\upsilon) = \frac{\Delta Q}{\Delta t} = k_0 \tag{4}$$

Equation (4) can be used to calculate rates of the 'zero-order' release process at different time intervals.

Figure 2 depicts the dynamic release of vitamin B_{12} in the amylase containing phosphate buffer of pH 6.8 at the physiological temperature 37°C. A close look reveals that the drug profile is almost linear for the first 6 h which may be attributed to the formation of micropores within the gel, due to degradation of starch by α-amylase present in the invading release medium. As a result, the model drug diffuses out through the micropores, following almost 'zero-order' kinetics.

Now in the present study, nearly 90% drug was released in the first 6 h. Thus, putting $Q_t = 90$ and $t = 6$ in equation (1), we obtained $k_0 = 15$ percent min^{-1}. Therefore, the "rate vs. time" profile must be a linear plot, parallel to time-axis.

Table 1
Percent deviation of curve areas for ideal 'zero-order' profile

Time intervals (h)	Curve area		Absolute difference of curve areas	% Deviation[a] from ideal zero order behavior
	Theoretical	Experimental		
1–2	15.00	16.42	1.42	9.46
2–3	15.00	14.32	0.68	4.53
3–4	15.00	13.78	1.22	8.13
4–5	15.00	13.73	1.27	8.46
5–6	15.00	14.0	1.00	6.60

[a] = The % deviation has been calculated by the expression.
% Deviation = (Absolute difference in curve areas/Area of ideal plot) × 100.

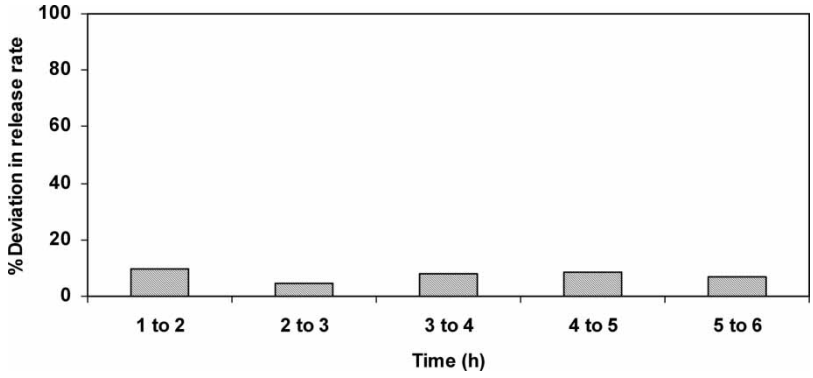

Figure 4. Bar diagram showing percent deviations obtained from ideal 'zero-order' kinetics for 90% release of Cyanocobalamin.

We used equation (4) to calculate the release rates at different time-intervals (putting $\Delta t = 10$ min) from the experimental release profiles and the two 'rate vs. time' profiles have been well depicted in Figure 3.

In order to quantify the deviations of experimental "rate vs. time" profile from the ideal plot at different time intervals, the trapezoidal rule was employed and curve areas at a time span of one hour from the two profiles were calculated. The various curves areas are given in Table 1. Finally, the percent deviations from the ideal 'zero-order' plot have been depicted in the form of a bar-diagram in Figure 4. It is clear from Figure 4 that the values of absolute deviations observed for the entire release process were found in the range 4.53 to 9.46%.

Conclusions

From this study, it can be concluded that quantitative deviation of an oral dosage from the ideal 'zero-order' kinetics can be expressed in terms of a difference between the curve areas of theoretical and experimental 'rate vs. time profiles'. Since the 'zero-order' release process is always characterized by a constant rate, the approach followed by us seems to be more logical and authentic. This method may prove to be highly useful for development of oral controlled release formulations to provide 'zero-order' release of bioactive ingredient entrapped within the device. Finally, the quantitative deviations can enable pharmaceutical scientists to know the extent to which the formulation under development is deviating from ideal 'zero-order' release behavior.

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