Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Bajpai, S. K. and Tankhiwale, Rasika(2006) 'Examination of the Higuchi Model for the Release of Vitamin B_2 from Multilayered Calcium Alginate/Chitosan Beads in Varying pH Medium', Journal of Macromolecular Science, Part A, 43: 7, 1013 — 1020
To link to this Article: DOI: 10.1080/10601320600739985
URL: http://dx.doi.org/10.1080/10601320600739985

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry, 43:1013–1020, 2006

ISSN 1060-1325 print/1520-5738 online
DOI: 10.1080/10601320600739985

Examination of the Higuchi Model for the Release of Vitamin B_2 from Multilayered Calcium Alginate/Chitosan Beads in Varying pH Medium

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The release of model drug vitamin B_2 from calcium alginate/chitosan multi-layered beads has been studied in the media of varying pH (3 h in the medium of pH 1.0 and for the remaining time in pH 7.4) at 37°C. The quantitative deviation of experimental data from the Higuchi model has been interpretated by using a newly developed 'curve area measurement' (CAM) approach. The higher deviation in the initial phase has been explained on the basis of porous structure of beads due to the use of low molecular weight polymers in the preparation of beads.

Keywords Higuchi, alginate, chitosan, beads

Introduction

The dependence of percent release from an oral single or multiple dosage form on the square root of time was worked out by Higuchi (1) who proposed the following simple mathematical form to express the diffusion controlled release of a drug:

$$Q_t = [2DS\varepsilon(A - 0.5S\varepsilon)]^{0.5} \times t^{0.5}$$

or

$$Q_t = K_H \cdot \sqrt{t} \quad (1)$$

where Q_t is the amount of drug released at time 't', D is the diffusion coefficient, S is the solubility of drug in the dissolution medium, ε is the porosity, A is the drug content per cubic centimeter of matrix and K_H is the Higuchi constant.

A thorough survey of all available literature and other information sources reveals that the drug release data used for the purpose of fitting the Higuchi model for an oral dosage form is usually obtained in the medium of physiological pH 7.4 (2–7). Moreover, not much attempt has been made to quantity the deviation of a release profile from the ideal Higuchi law.

Received and Accepted February 2006.
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In the present work, we have obtained a drug release profile of vitamin B_2 from multi-layered alginate/chitosan beads in a varying pH medium, so that the transition of oral formulation from mouth to colon can be mimicked. The data obtained has been tested for the ideal Higuchi model using a novel 'curve area measurement' (CAM) approach, enabling us to understand the quantitative deviation of the proposed oral formulation from the diffusion controlled, ideal Higuchi model.

Experimental

Mateirals

Sodium alginate (SA; mannuronic acid to guluronic acid ratio 1.75 ± 0.2, medium viscosity 200 cP for 1% aqueous solution at 20°C), and anhydrous calcium chloride was obtained from Research Lab, Mumbai, India. Chitin was purchased from Hi Media, Mumbai, India, and its deacetylation was carried out with 50% NaOH (wt/vol) at 90°C in a nitrogen atmosphere for 2 h (8). Finally, the chitosan (Ch) flakes were washed three times with water and methanol and dried at 50°C in vacuum. Prior to further processing, the flakes were ground and sieved into a particle size range of 0.6–2 mm (10–30 mesh). The drug riboflavin, molecular mass 376.36 and purity 99.7% was obtained from Research Lab. Double distilled water was used throughout the investigations.

Viscosity Measurements

The viscosity average molecular weight ($\bar{M}_v$) of the chitosan was determined by using a dilute solution of chitosan in 2% acetic acid. The intrinsic viscosity of chitosan solution was determined using an Ubbelohde type viscometer. With the help of reported values of k and α for the chitosan–acetic acid system, the intrinsic viscosity $[\eta]$ was calculated. The molecular weight of chitosan was determined using the following equation (9):

$$[\eta] = 1.4 \times 10^{-4} \bar{M}_v^{0.81} \tag{2}$$

Similarly, molecular weight of sodium alginate was determined using the equation (10):

$$[\eta] = 7.3 \times 10^{-5} \bar{M}_v^{0.92} \tag{3}$$

Porosity Measurements

The volume of pores within the beads, which were interconnected and accessible to the surface, was determined by measuring the total volume of porous beads and amount of solvent required to fill the porous component. In brief, individual beads were placed in a graduated cylinder filled with a known volume of ethanol (V_1). The total volume following immersion was recorded (V_2). The beads were removed with the entrapped solvent in the pores and the remaining volume of ethanol in the graduated cylinder was denoted by (V_3). The total volume V_T of the beads was calculated according to equation (4)

$$V_T = V_2 - V_3 \tag{4}$$

$$\text{porosity}, \quad \chi = [(V_1 - V_3)/V_T] \times 100 \tag{5}$$

Preparation of B_2-\Loaded Multilayered Beads

Sodium alginate was dissolved in distilled water at a concentration of 4% (w/v), unless otherwise noted. To this solution, a pre-calculated quantity of model drug vitamin B_2 was added. The solution was stirred thoroughly to ensure complete mixing of the drug. The gelation medium was prepared by dissolving chitosan (1% w/v) in one percent acetic acid, followed by addition of $CaCl_2$ at the concentration of 4% (w/v). The sodium alginate solution was added dropwise into the gelation medium using a 10 ml hypodermic syringe through a needle #21 under constant stirring at room temperature. The beads thus formed were cured in the gelation medium for 20 min and then put into 0.4% chitosan solution for a period of 30 min. Finally, the beads were put in the sodium alginate solution (1% (w/v)) for 30 min and then transferred into a $CaCl_2$ solution [1% (w/v)] for 20 min. The beads were then taken out and allowed to dry till they attained constant weight. Figure 1 shows well shaped spherical beads. Their diameter was found to be 0.146 ± 0.008 cm.

In Vitro Release Study

To carry out a drug release study in a *in vitro* manner, we used the data obtained by Satyanarayan et al. (11), who, after carrying out gamma scientigraphic studies on guar gum tablets using ^{99m}Tc-DTPA as tracer in human volunteers, reported a mean gastric emptying time of 1.08 ± 0.11 h and the mean colonic arrival time of 2.83 ± 0.33 h. Relying on this data, we put the drug loaded beads in artificial gastric fluid of pH 1.0 for 3 h and then transferred them into a phosphate buffer of pH 7.4 at 37°C. Thus, we mimicked the transition of the formulation from mouth to colon. The amount of drug released at different time intervals was determined spectrophotometrically at 437 nm (12). After each measurement, beads were put in a 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. Since riboflavin is

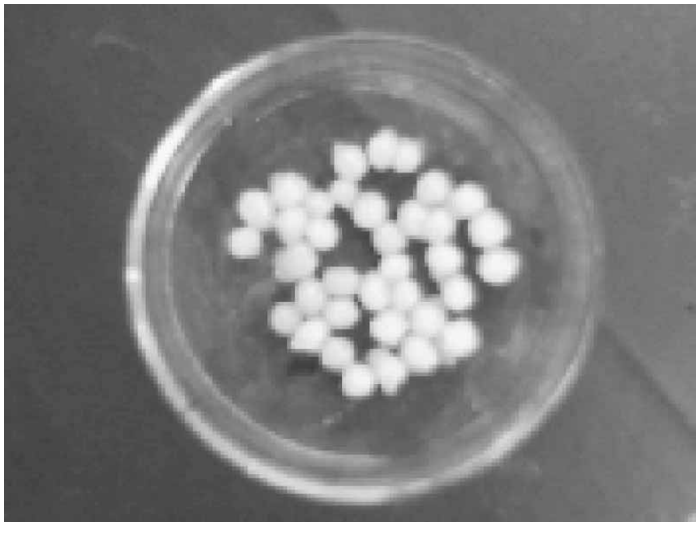

Figure 1. Model drug vitamin B_2 loaded chitosan coated calcium alginate beads.

sensitive towards light, the entire study was carried out using glassware with a completely blackened surface so as to avoid exposure to light.

Theoretical Considerations

According to equation (1), for an oral dosage form which follows the Higuchi model completely, the plot between Q_t and $\sqrt{t}$ must be a straight line passing through the origin (Figure 2). We shall call this as the reference plot.

Now, if Q_t and Q_{t-1} are the percent drug release at time t and t − 1 h, respectively, then:

$$Q_t = K_H\sqrt{t} \tag{6}$$

and

$$Q_{t-1} = K_H\sqrt{t-1} \tag{7}$$

Therefore, if an oral formulation follows the Higuchi model completely, the area under the reference plot [AURP] for the two successive time points (t − 1) and t will be:

$$\begin{aligned}[AURP] &= \text{Area of trapezoid ABCD}\\ &= 1/2(AB + DC)\cdot BC\\ &= 1/2(Q_t + Q_{t-1})[\sqrt{t} - \sqrt{t-1}]\\ &= 1/2[K_H\sqrt{t} + K_H\sqrt{t-1}][\sqrt{t} - \sqrt{t-1}]\end{aligned}$$

or,

$$[AURP]_{1\,h,0\%d} = 1/2K_H \tag{8}$$

where subscript 1 h, 0% dev means the area has been calculated for a 1 h time span and the system follows the Higuchi model completely (i.e., 0% dev). However, if α is the percent deviation of a formulation from the Higuchi model for the same time interval of (t − 1) to t h, then the area under the experimental plot [AUEP] will be given as:

$$[AUEP]_{1h_\alpha\%dev} = K_H/2[1 \pm \alpha/100] \tag{9}$$

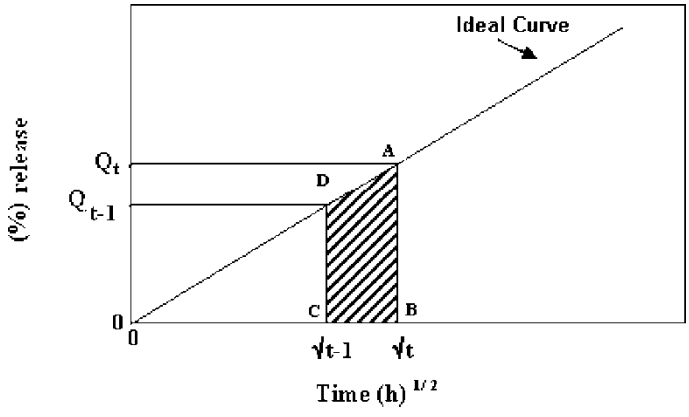

Figure 2. Linear Higuchi plot.

where subscript 1 h, α% dev indicates that for a 1 h time span, the percent deviation is α. Moreover, a +sign is to be used for positive deviation i.e., the experimental curve area is more than the theoretical one.

Dividing equation (9) by equation (8), we have:

$$[\text{AUEP}]_{1\text{h}_\alpha\%\text{dev}}/[\text{AURP}]_{1\text{h},0\%\text{d}} = [1 \pm \alpha/100]$$

or

$$[\text{AUEP}]_{1\text{h}_\alpha\%\text{dev}} - [\text{AURP}]_{1\text{h},0\%\text{d}}/[\text{AURP}]_{1\text{h},0\%\text{d}} = [\pm\alpha/100]$$
$$\therefore \pm\alpha = 100\{[\text{AUEP}]_{1\text{h}_\alpha\%\text{dev}} - [\text{AURP}]_{1\text{h},0\%\text{d}}\}/[\text{AURP}]_{1\text{h},0\%\text{d}} \quad (10)$$

This expression may be used to express percent deviation of the test formulation from the ideal Higuchi law. If the area for test formulation is more than the theoretical one, then the + sign should be used in the above equation.

Using the equation (10), the percent deviation α in the time interval (t − 1) to t h for any oral dosage form can be calculated. The areas can be measured using the 'trapezoidal rule'.

Results and Discussion

Figure 3 depicts the dynamic release of vitamin B_2 from the multilayered beads in the media of varying pH. In order to make quantitative interpretation of this release data, the percent release was plotted against square root of time and the plot (we will call this as experimental plot) was obtained by joining all the data points together in a straight way (Figure 4). Furthermore, the reference plot was obtained by using the fact that the beads demonstrate nearly 100% release in 9 h. So, on putting $Q_t = 100$ and $t = 9$ in equation (1):

$$100 = K_H \cdot \sqrt{9}$$

or

$$K_H = 33.33$$

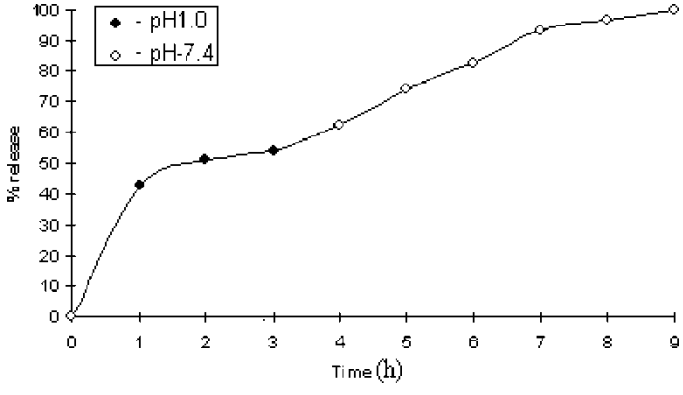

Figure 3. Comparative depiction of release profile of drug–loaded beads in the medium of varying pH., (0–3) h in pH 1.0 and (3–8) h in the phosphate buffer of pH 7.4 at 37°C.

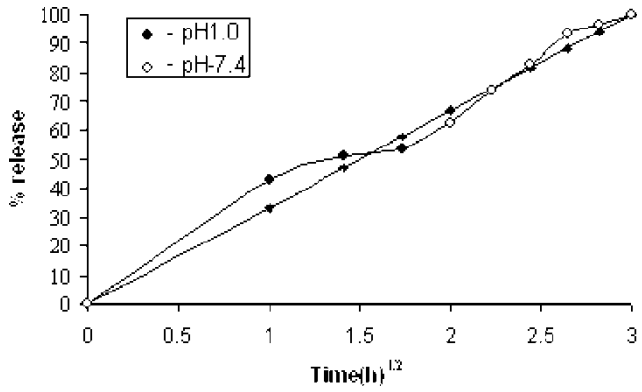

Figure 4. Comparison of K_H vs. (●) t profiles of ideal (◆) and test (○) batch.

Therefore, the Higuchi equation (1) become:

$$Q_t = 33.33 \cdot \sqrt{t} \tag{11}$$

On putting t = 1, 2, 3, 9 in the above equation, corresponding Q_t values (i.e., percent drug released) were determined and the resulting 'Q_t vs. $t^{1/2}$, linear reference plot is also displayed in Figure 2.

The areas under the reference and the experimental plots, as displayed in Figure 4. were determined for various $\sqrt{t-1}$ to $\sqrt{t}$ time-points using 'trapezoidal rule'. The percent deviations α, as calculated from the equation (10), for different 'one hour time-slab' have been listed in the Table 1.

It is clear that the test formulation shows greater positive deviations in the first 2 h and later on, the extent of deviation becomes small. The bar diagram displayed in Figure 5 also shows the same results. The positive deviation, demonstrated by the test formulation from the Higuchi model indicates that release of drugs through the chitosan and alginate coatings is not diffusion controlled. There may perhaps be two reasons for this. First, the layers or coatings are not thick enough to let the drug pass through in a relatively controlled manner. Secondly, the beads might have a porous nature. In order to confirm this hypothesis, we determined the molecular weight of the two polymers namely sodium alginate and chitosan that were used to prepare the beads. The molar mass, determined using equations (2) and (3) were found to be 32075 and 18050 for chitosan and sodium alginate, respectively. The lower values of molecular weight indicate that the two coatings are not very effective and the overall structure of beads may be porous. In order to investigate this further, we determined the porosity of beads using equation (5). The porosity was found to be nearly 63%, supporting our arguments regarding the explanations offered above to justify higher positive deviation of the release data from the ideal Higuchi model.

Finally, we also evaluated the initial, the average and the late time diffusion coefficients, using the formulae described in the previous work (13). The values of various diffusion coefficients were found to be 8.4943×10^{-6}, 1.0423×10^{-5} and $2.89 \times 10^{-5}\,\mathrm{cm^2\,min^1}$, respectively. These abnormally higher diffusion coefficients also support our arguments that due to use of low molecular weight alginates and chitosan, the resulting multi-layered beads are porous and demonstrate faster drug release, extended over a total duration of 9 h.

Table 1
Percent deviation for the test formulation from 9 h ideal Higuchi profile

Time (h)	Ideal Higuchi profile		Experimental profile		Absolute difference of curve areas	%Absolute deviation from Higuchi kinetics	α
	Cumulative release (%)	Area under the curves	Cumulative release (%)	Area under the curves			
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	33.33	16.66	42.60	21.31	+4.65	27.91	+27.91
2	47.13	16.09	51.00	18.72	+2.63	16.34	+16.34
3	57.72	17.30	54.00	17.34	+0.04	0.23	+0.23
4	66.66	16.79	62.60	15.71	−1.08	6.42	−6.42
5	74.52	16.23	74.00	15.72	−0.51	3.11	−3.11
6	81.64	16.39	82.60	16.44	+0.05	0.3	+0.3
7	88.18	16.98	93.30	17.51	+0.53	3.12	+3.12
8	94.27	16.42	96.60	17.02	+0.60	3.60	+3.60
9	99.99	17.48	100	17.62	+0.14	0.80	+0.80

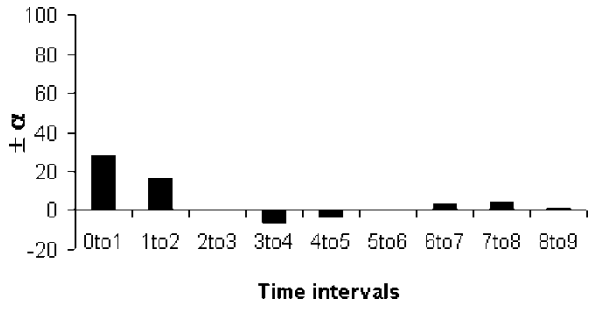

Figure 5. Bar diagram showing % deviations obtained from ideal Higuchi model for 100 % release in 9 h duration.

Conclusions

From the above study, it can be concluded that from the measurement of curve areas between the successive time points for release profile of a test formulation, it may be possible to obtain its quantitative deviation from the ideal Higuchi model. The method may prove to be highly useful for a comparison of a formulated product during the research and development stage, and for a quality control study of drug–loaded hydrogel beads. This work also emphasizes that it is more logical to apply a kinetic model on the drug release data obtained in the media of varying pH, rather than on the kinetics data obtained in the medium of physiological pH only.

Finally, the proposed method can be criticized on the basis of the argument that the comparison of Q_t values (i.e., percent drug released at time t) between theoretical and experimental data for the given time point may directly yield the deviation from ideal Higuchi law. In this regard we would like to emphasize that this shall give the deviation of test formulation at that particular time point only. In other words, by doing so, the deviation during any time-span cannot be evaluated while the proposed method gives the overall deviation between the two successive time points, not at the given time points only.

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