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A Novel Approach for Testing the Hixon-Crowel Model For *In Vitro* Release of Vitamin B_2 From Chitosan Coated Calcium Alginate Beads

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The dynamic release of a model drug (vitamin B_2) from chitosan coated calcium alginate beads has been studied in the media of varying pH and the Hixon-Crowel model has been applied to the experimental data, using a novel 'curve area measurement' (CAM) approach. The two release profiles, namely experimental and ideal, were found to be in close agreement except for the initial phase of the release process.

Keywords Hixon-Crowel, deviation, vitamin B_2, erosion

Introduction

From time to time, various researchers have proposed different types of drug release mechanisms to interpret the drug release behavior of oral dosage forms (1, 2). It has been proposed that drug release from polymeric hydrogels usually implies water penetration into the matrix, hydration, swelling, diffusion of the dissolved drug and/or surface/bulk erosion of the dosage form. In fact, the kinetic models relating to the drug release from hydrogels depends upon a number of factors, such as the chemical nature of the polymer (ionic or neutral), solubility of the drug in the release media, pH of the release media, etc. The criterion for selecting the most appropriate model is chosen on the basis of goodness-of-fit test. The 'zero-order' kinetics (3) describes the system in which the drug-release rate is independent of its concentration. The 'first-order' kinetics (4) describes the release from the systems in which the release rate is concentration dependent. The Higuchi model describes the release of drug from an insoluble matrix as a square root of a time-dependent process on the basis of Fickian diffusion (5). Finally, the Hixon-Crowel cube root law has been developed to interpret the drug release data for formulations, which undergo erosion (6).

In our previous work (7), we synthesized multi-layered beads, composed of non-toxic biocompatible natural polymers chitosan and sodium alginate, and studied their swelling/degradation behavior in the environment of varying pH (i.e., in the medium of pH 1.0 for 3 h, followed by their immersion in phosphate buffer of pH 7.4) to mimic their transition

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from mouth to colon. It was found that the beads took nearby 8 to 10 h to disintegrate completely.

In continuation of our previous work, we now report the results of an *in vitro* release study carried out with chitosan coated calcium alginate beads, loaded with the model drug riboflavin or vitamin B_2. The kinetic data obtained has been well interpretated by the Hixon-Crowel (1931) erosion based model, using a novel approach developed by us. We shall call the latter the 'curve-area measurement' (CAM) approach. To the best of our knowledge, the cubic root erosion model has not been tested previously using this type of approach.

Experimental

Materials

Sodium alginate (SA; mannuronic acid to guluronic acid ratio 1.75 ± 0.2, medium viscosity 200 cP for 1% aqueous solution at 20°C), anhydrous calcium chloride and barium chloride dihydrate were 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). The final 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 degree of deacetylation, as determined by method of Guibal et al. (9) was found to be 96%. The molar mass was determined to be 3.207×10^4 using the Mark-Houwink equation (10).

$$[\eta] = 1.81 \times 10^{-3} M_v^{0.93}$$

The drug riboflavin, molecular mass 376.36 and purity 99.7 % was obtained from Research Lab. Double distilled water was used throughout the investigations.

Preparation of Drug-Loaded Beads

We prepared vitamin B_2 loaded calcium alginate beads coated with chitosan. To prepare the beads, a definite amount of B_2 was dissolved in sodium alginate solution (4% w/v) and it was dropped into a 4% $CaCl_2$ solution through a hypodermic syringe. After curing the beads for 20 min, they were taken out and put in the 0.4% chitosan solution (prepared in 1% acetic acid) for a period of 30 min. Figure 1 shows the freshly prepared drug-loaded beads Finally, the beads were taken out and allowed to dry at 30°C in a dust-free chamber until they attained constant weight. The average diameter of the dry beads was found to be 0.135 ± 0.007 cm.

Drug Release Study in Media of Varying pH

To carry out the drug release study in an *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 a 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

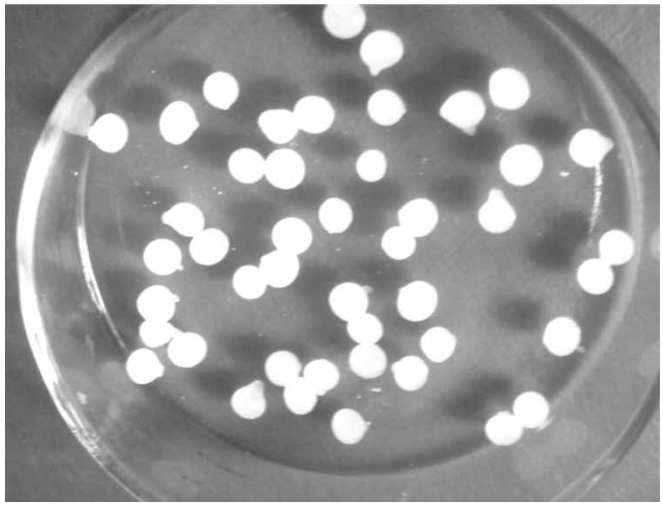

Figure 1. Model drug vitamin B_2 loaded chitosan coated calcium alginate beads.

37°C. The latter step 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, the gels were put in 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 sensitive towards light, the entire study was carried using glassware having a completely blackened surface so as to avoid exposure to light.

Theoretical Considerations

The Hixon-Crowel cube root equation is given as:

$$(1 - F)^{1/3} = 1^{1/3} - k_{HC}t \tag{1}$$

where F is the fractional release, t is the time and k_{HC} is release rate constant.

Since in the present study, 100% release (i.e. $F = 1$) was observed in 8 h, (i.e., $t = 8$), the above equation yields the ideal rate constant:

$$k_{HC} = 1/8$$

Now, as the fractional release term 'F' is present in the form $(1 - F)^{1/3}$ in the above equation 1, it may not be possible to calculate fraction release at different time intervals in the terms of k_{HC} and t.

So, we modified equation 1 as:

$$1^{1/3} - (1 - F)^{1/3} = k_{HC}t \tag{2}$$

On putting $F = 1$ and $t = 8$ in equation 2, we obtained $k_{HC} = 1/8$, so we put $k_{HC} = 1/8$ in the above equation 2 to yield:

$$1 - (1 - F)^{1/3} = t/8 \tag{3}$$

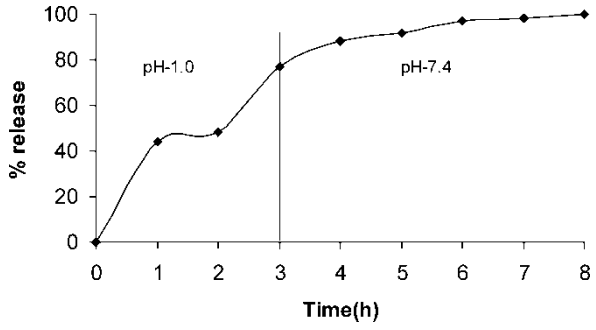

Figure 2. Comparative depiction of release profile of drug–loaded beads in the medium of varying pH., (0–3) h in pH 1.0 and (3–8) h in the phosphate buffer of pH 7.4 at 37°C.

On substituting different values of time 't' (up to $t = 8$) in the above equation, corresponding $1 - (1 - F)^{1/3}$ values can be calculated and an ideal straight line may be obtained by plotting $1 - (1 - F)^{1/3}$ values vs. 't', which passes through the origin. Now, taking the difference between the two successive sampling time points as 1 h, the area under the curve for a time—duration of 1 h over the entire time—the axis can be calculated using a trapezoidal rule. The areas obtained from the above ideal plot are now compared with those obtained from the experimental plot to give the extent to which the oral formulation deviates from the ideal cubic root law.

Results and Discussion

Figure 2 depicts the dynamic release of vitamin-B_2 from drug–loaded beads in the media of varying pH. It is clear that the beads exhibit a total stability of 8 h. In order to apply the cube root law on the experimental data, the $1 - (1 - F)^{1/3}$ values were plotted against time and the experimental, as well as theoretical curves, were well depicted in Figure 3. A close look at Figure 3 reveals that initially, the experimental plot shows appreciable positive deviation. This common phenomenon, observed in hydrophilic polymer matrices, is a result of the release of the drug present at the surface of the beads, thus causing 'burst-release', and resulting in remarkable positive deviation from the ideal plot.

In order to express the deviation of the experimental plot in a quantitative manner, the areas under the curve for 'one hour duration' (i.e., 0–1, 1–2, 2–3 etc.) were calculated for both experimental and theoretical plots, over the complete length of time. The results

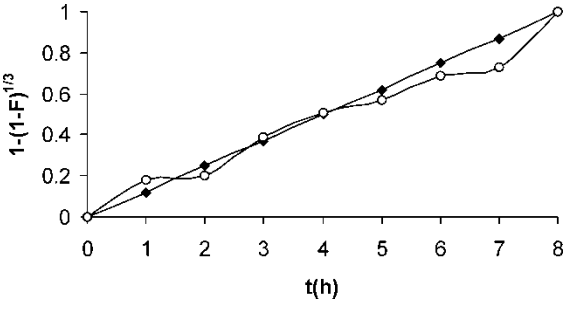

Figure 3. Comparison of $1 - (1 - F)^{1/3}$ vs. time profiles of ideal (◆) and test(○) batch.

Table 1
Percent deviation of curve areas for the chitosan coated alginate beads from the ideal 8 h-Hixon model

	Ideal Hixon-Crowel release profile		Profile for chitosan coated alginate beads			
Time (h)	Cumulative fractional release	Curve areas for 1 h time difference	Cumulative fractional release	Curve areas for 1 h time difference	Difference of curve areas	% Deviation from ideal Hixon-Crowel plot
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.12	0.06	0.18	0.09	0.03	50
2	0.25	0.18	0.2	0.19	−0.01[a]	5.5
3	0.37	0.31	0.39	0.29	0.02	6.4
4	0.5	0.43	0.51	0.45	0.02	4.6
5	0.62	0.56	0.57	0.54	−0.02[a]	3.5
6	0.75	0.68	0.69	0.63	0.05	7.3
7	0.87	0.81	0.73	0.71	0.1	12.3
8	1	0.93	1	0.86	0.07	7.5

[a]Showing negative deviation.

are shown in Table 1. It is clear that deviation from the ideal 8 h Hixon-Crowel plot is always less than 13% at any time point except the first hour. As mentioned above, the exceptionally higher deviation in the first hour is due to 'burst release' of drug present at the surface of the beads. Percent deviations obtained between the experimental and theoretical curve areas are shown in Figure 4. The correlation r, as calculated between the experimental $1 - (1 - F)^{1/3}$and t values was found to be 0.98, thus confirming a

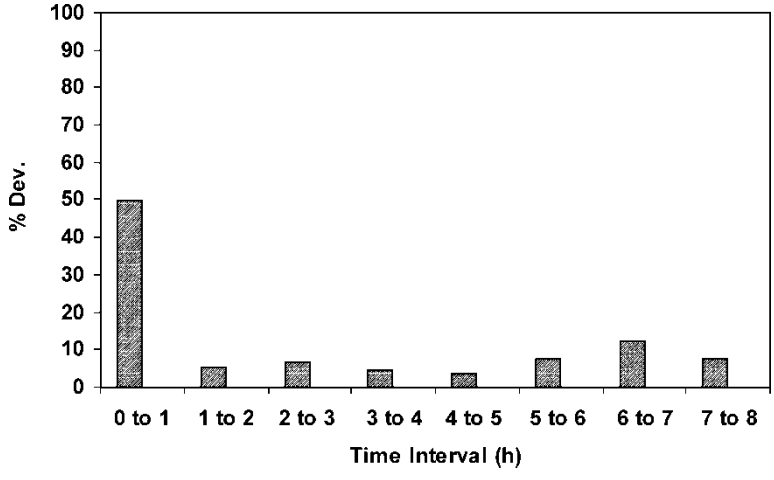

Figure 4. Bar diagram showing % deviations obtained from ideal Hixon-Crowel model for 100% release in 8 h duration.

high degree of correlation between the observed data. In this way, this new method offers a simple approach to test the validity of the Hixon-Crowel model for any test formulation.

Conclusion

This study presents a novel approach for the quantitative expression of the deviation of release behavior of a dosage form from the ideal erosion based cube root law. The chitosan coated calcium alginate beads have demonstrated erosion induced release of vitamin B_2 in the media of varying pH. The drug release pattern fits the Hixon-Crowel model well over the entire length of time except for the first hour, during which an appreciable deviation from the ideal plot has was observed. The deviation is probably due to the 'burst-effect'. The proposed method may be used for the development of oral dosage forms, which demonstrate drug release due to surface erosion. This approach may also be used for promoting products by comparing the performance of a test product with that of an innovator's product.

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