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COMMUNICATION

Evaluation of Hydrogel-Based Controlled-Release Niacin Tablets

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ABSTRACT

Matrix-based controlled-release niacin tablets were formulated using guar gum. The effect on the in vitro *dissolution profile was examined using variable guar gum content in the formulation. It was observed that the dissolution profile declined with the increase in the guar gum content in the tablet. The* in vitro *dissolution profile was also observed under different pH conditions and there was no marked change. The moisture content of granules also did not cause any considerable change in dissolution profile.*

Three different strength Niacin controlled-release tablets, including 500 mg, were prepared and it was found that applying the same variables of different guar gum content and moisture content of granules resulted in a very insignificant change in the in vitro *dissolution profile. The experimental formulation compared well with commercial products and met the proposed standards for controlled-release products.*

INTRODUCTION

Controlled-release (CR) dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Ideally, a CR dosage form provides therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in the peak/nadir concentration ratio. One of the least complicated approaches to the manufacture of CR dosage forms involves compression of the drug blends, release of the retardant polymer, and the addition of additives to form a tablet in which drug is embedded in the matrix core of the polymer (1–5).

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Hydrogels have attracted considerable attention in recent years as controlled-release devices for the delivery of water-soluble drugs (6).

Lapidus and Lordi have studied the drug release from compressed hydrophilic matrices. Recently, a number of studies have been carried out using hydrogels for oral CR dosage forms, highlighting its importance to control the release of drugs from dosage forms (7).

Niacin is highly water soluble and effective in curing human pellagra and canine black tongue. It has a short blood half-life of 5.3 hr and the drug disappears from the liver with a half-life of 4.4 hr which makes it a suitable candidate to be delivered at a controlled rate.

MATERIALS

Single viscosity grade guar gum (4000 cps viscosity, from Dabur, India) was used. Niacin, starch, lactose, talc, and magnesium stearate used were of USP grade. All other chemicals were of reagent grade.

METHODS

Weighed and sifted niacin, starch, and guar gum was passed through 60 mesh. All three ingredients were dry mixed using a laboratory model planetary mixer. The blend with starch paste was granulated (10%). The granules were dried in a fluid-bed dryer (FBD) at 50–60°C for 20–25 min. The semidried granules were passed through 16 mesh using an oscillating granulator. These granules were then dried to have loss on drying in the range of 3–5% w/w. The dried granules were sifted through 20 mesh. Talc (2%) and magnesium stearate (1%) were sifted through 60 mesh and mixed with dried granules. The lubricated granules were then compressed to capsule-shaped tablets using a hydraulic press (Allied Engg, India).

Drug Release Studies

Six tablets from each batch were taken to evaluate the dissolution rate in three different dissolution media at 100 rpm using 900 ml of medium and maintaining temperature at 37 ± 1°C. USP dissolution test apparatus (Vanderkamp 600, NJ) was used for these studies using a basket (type 1). At predetermined intervals, a 2-ml portion of the medium was diluted with buffer solution and then pipeted for HPLC (Shimadzu, Japan) determination of niacin concentration at 254 nm. Mobile phase consisted of 0.001 M hexane sulfonic acid sodium monohydrate (HSAS) (pH 6.05)/methanol (EL) (50:50).

Dissolution Medium

To study the effect of pH of dissolution medium on drug release, the following dissolution media were prepared: (*a*) potassium chloride–hydrochloric acid buffer, pH 2.0 ± 0.05; (*b*) acetate buffer, pH 4.0 ± 0.05; and (*c*) phosphate buffer, pH 7.0 ± 0.05 and 7.40 ± 0.05.

RESULTS AND DISCUSSION

Effect of Polymer Contents

Figure 1 shows the release patterns of niacin from tablets made with 15, 20, 30, and 40% of high viscosity guar gum. Tablets with low concentration of guar gum showed faster drug release compared to tablets with higher concentrations of guar gum. Therefore, the drug release can be modified by changing the content of guar gum in the tablets.

Figure 2 shows plot of the amount of drug released against time in hours for the developed formulation and for a marketed product. The lines obtained were upward curves indicating a different release mechanism, as expected from the Higuchi equation for release of drug

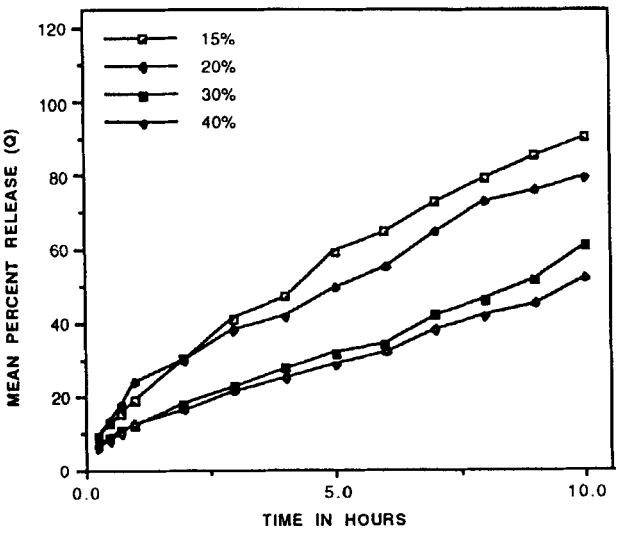

Figure 1. Drug release rate from tablets made with 15, 20, 30 and 40% high viscosity guar gum.

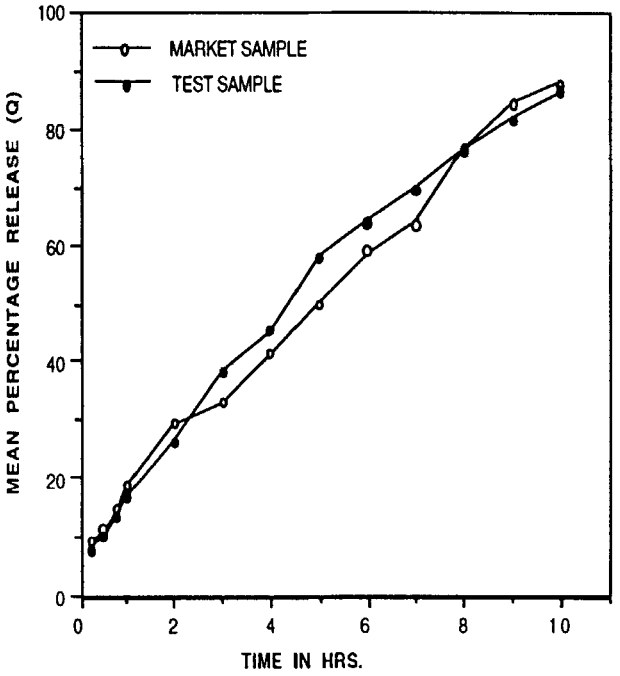

Figure 2. Drug released against time in hours for the developed formulation and for marketed product.

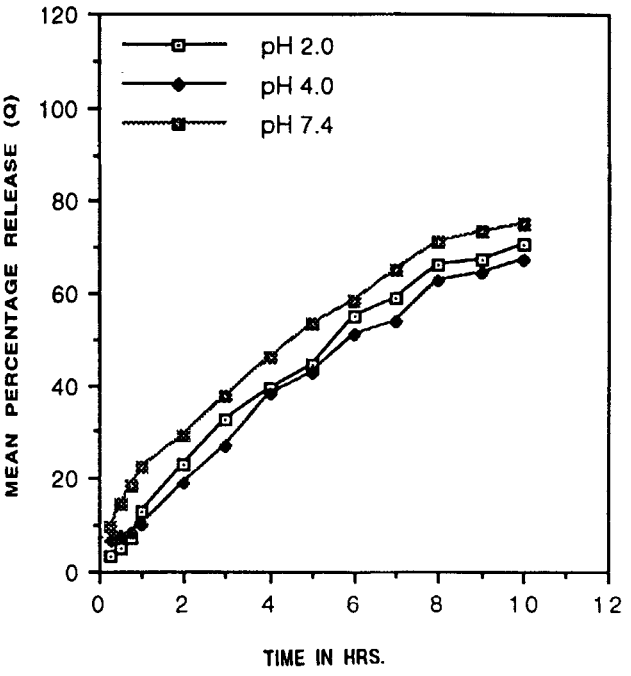

Figure 3. Niacin release from tablets in buffers having different pH.

from solid matrices. It was observed that once the tablet was surrounded by an aqueous environment, the surface of the individual tablet tended to hydrate and form a gel layer to prevent rapid penetration of solution into the inner layer. The size of the tablet increased significantly because of the polymer hydration and remained as a complete gel unit even after the drug was released.

Table 1

Effect of Moisture Content on Dissolution Profile of Niacin Sustained-Release Tablets Using 20% High Viscosity Guar Gum

Batch No.	Moisture Content (%)	SD and Mean[a] Cumulative Percent of Drug Release in Phosphate Buffer (pH 7.0)							
		1 hr		3 hr		6 hr		10 hr	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
8	5.0	22.40	1.714	37.71	1.929	58.86	2.546	81.90	4.213
13	6.0	23.97	1.083	38.01	1.544	54.99	3.798	79.27	1.138
9	8.0	21.59	2.559	36.14	3.199	56.90	1.958	77.07	2.360

a) $p = 0.136$ (not significant), b) $p = 0.137$ (not significant), c) $p = 0.127$ (not significant). Calculated at 1 hr.
a) $p = 0.812$ (not significant), b) $p = 0.125$ (not significant), c) $p = 0.295$ (not significant). Calculated at 3 hr.
a) $p = 0.059$ (marginally significant), b) $p = 0.250$ (not significant), c) $p = 0.359$ (not significant). Calculated at 6 hr.
a) $p = 0.244$ (not significant), b) $p = 0.0107$ (significant), c) $p = 0.114$ (not significant). Calculated at the end of 9 hr.
Statistically no significant difference occurs with batch 8 when compared with batch 13 and batch 9.
a = Batch 8 compared with batch 13.
b = Batch 8 compared with batch 9.
c = Batch 13 compared with batch 9.
[a]$N = 6$.
SD = Standard deviation.

Table 2

Effect of Stability Conditions on the Dissolution Profile of Controlled-Release Niacin Tablets [Batch No. TRN (500) 02.]

Condition/Time	Mean Cumulative Percent of Drug Release in Phosphate Buffer (pH 7.4) ± SD								Degree of Significance *t*-Test (*p*)
	1 hr		3 hr		6 hr		10 hr		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Initial	16.90	0.6802	38.71	0.695	64.38	0.743	86.52	1.849	
45°C/1 M	16.87	0.0721	35.81	0.531	65.15	0.192	87.38	0.515	0.345 (NS)
45°C/2 M	17.07	0.163	34.84	0.358	64.32	0.154	88.18	0.515	0.107 (NS)
45°C/3 M	18.93	0.136	35.81	0.294	65.88	0.901	89.93	0.629	0.106 (NS)
37°C/2 M	17.37	0.597	37.80	0.132	65.56	0.550	87.31	0.173	0.356 (NS)
37°C/4 M	17.90	0.184	36.60	0.365	64.61	0.352	88.19	1.411	0.157 (NS)
37°C/6 M	18.23	0.083	34.89	0.154	65.81	0.434	89.73	0.429	0.502 (NS)
37°C and 75% RH/2 M	18.08	1.171	36.93	1.565	63.09	1.652	87.91	1.648	0.433 (NS)
37°C and 75% RH/4 M	18.23	1.138	36.14	1.687	62.77	1.790	88.54	1.685	0.176 (NS)
37°C and 75% RH/6 M	19.71	1.655	37.15	1.800	63.14	2.011	89.16	2.740	0.122 (NS)
RT/6 M	17.32	1.914	37.79	1.438	65.52	2.287	85.23	1.492	0.313 (NS)
RT/12 M	17.81	1.863	38.19	3.535	66.32	1.425	87.89	1.205	0.25 (NS)

M: Month(s); RT: room temperature; RH: relative humidity; NS: not significant; $n = 6$.

Effect of Moisture Content of Granules

Tablets prepared with granules having moisture content varying from 5 to 8% w/w showed similar drug release. The mean cumulative percent drug release of tablets prepared with different moisture content is shown in Table 1, which indicates that mean cumulative percent of drug release from batches 8, 13, and 9 at 1, 3, 6, and 10 hr show marginally significant to not significant differences. Hence, it is concluded that tablets prepared with granules having moisture content ranging from 5 to 8% had similar dissolution profiles.

Effect of pH of Dissolution Medium

Figure 3 shows the drug release pattern of niacin from tablets in buffers with different pH. The release of niacin is fairly similar in different buffers. This shows that the drug release pattern of niacin is independent of the pH of dissolution medium used in this study.

The pH-independent release demonstrated in this study may be explained by recognizing that the pH inside the matrix controls the solubility of the drug and therefore, the release rate is similar.

If the release of a drug from a slow-release matrix tablet is independent of surrounding pH, then the in vitro dissolution conditions used to assess the performance of the tablet may not be critical.

Stability Studies

Tablets of the final batch were kept at different temperature conditions: at 45°C for 1, 2, and 3 months, at 37°C and 37°C/75% relative humidity for 2, 4, and 6 months, and at room temperature for 6 and 12 months. The samples were critically monitored and in the analysis dissolution was included as the major test. There was no physical change in the tablets; moreover, there was no significant difference between the dissolution profiles of samples kept at different temperatures. In vitro dissolution values were compared using paired Student's *t*-test. Statistically, no significant difference was obtained (Table 2).

CONCLUSION

The results reported here establish that the dissolution of niacin from sustained-release dosage form is affected by a combination of variables. These include percentage of guar gum content, pH of the dissolution medium, and moisture content of the granules. An inverse relationship is found between guar gum concentration and amount of drug released. A larger amount of guar gum causes a greater degree of swelling. Swelling, in turn, reduces the drug release, because the diffusional path length of drug is longer. Conversely, reduction in amount of guar gum reduces the degree of swelling and gel thickness. This enables faster drug release. Drug release was independent of pH of the dissolution media and moisture content of the granules. The in vitro dissolution profile of the test formulation matched well with the leading marketed formulation. The formulation was not affected when subjected to different stability conditions. The release profile remained unchanged after 3 months storage of tablets at 45°C and 37°C/75% relative humidity. Guar gum is suitable for matrix tablets containing low- or high-dose drugs.

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