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Sustained-Release Formulations of Nifedipine

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The effects of various polymers on the release of nifedipine from their matrices have been evaluated. *In vitro* release profile of nifedipine from Eudragit RS matrices showed that increasing the concentration of Eudragit RS resulted in a reduction in the release rate of nifedipine. *In vitro* release profiles of nifedipine matrices containing methylcellulose showed that more than 90% of the drug was released after 2 h at PH 1.2 indicating that methylcellulose could not produce sustained release matrices of nifedipine. A linear relationship was established between the T90% and the percent Eudragit RS, used. Relationships, such as predicted by the Korsmeyer equation ($Q=Kt^n$), were considered appropriate to describe accurately the quantity of drug released. Values of n were 0.564-0.629, indicating that release was controlled by both diffusion and erosion.

NIFEDIPINE is a calcium channel antagonist originally introduced for the treatment of angina pectoris and more recently for hypertension. Nifedipine is a slightly water-soluble and light sensitive drug whose biovailability is very low when it is orally administered in crystalline form[1]. Its biological half-life is, on the other hand, very short[2,3] sustaining its antihypertensive effect only for a few hours. Therefore several attempts have been made to enhance biovailability[1,4] of nifedipine and to prolong the duration of its action[5-9].

Nifedipine is also ideal since the drug exhibits all the required pharmacokinetic and physicochemical properties which make it a good candidate for the development of an oral sustained release dosage form[10]. The aim of the present study was to achieve sustained release formulation of nifedipine.

MATERIALS AND METHODS

Nifedipine (Asma, Italy), Eudragit RS (Rhom Pharma), Calcium hydrogen phosphate (Chemisch Fabrikkirsch -Via, Germany), polyvinyl pyrolidone (BASF), magnesium stearate (F-Paris), polyethylene glycol 4000, methylcellulose, lactose and starch (Merck, Germany) were used.

Formulation of nifedipine matrices using hydrophilic polymers:

Nifedipine matrices were produced by mixing nifedipine with lactose, granulating with starch solution and passing the mixture through a no.16 sieve. The sieved fractions were dried at room temperature (the entire manufacturing process was protected as much as possible from light). The granules were sieved again and mixed with methylcellulose and powdered polyethylene glycol 4000 for 10 min, then magnesium stearate was added and mixed for an additional 2 min. The granules were compressed on a 9-mm punch and die using a single-punch machine (formulation F1). Formulation F2 was prepared by mixing nifedipine with calcium hydrogen phosphate, granulating with PVP solution (10%w/v), then passing the mixture through a no.16 sieve. Methylcellulose, PEG 4000 and magnesium stearate were added and then made into tablets by the same method as mentioned in formulation F1. Formulations E3, F4 and F5 were prepared by mixing nifedipine with calcium hydrogen phosphate and Eudragit RS, granulating with a PVP solution (10% w/w), then

passing the mixture through a no.16 sieve. The sieved fraction were dried at low temperature. The granules were sieved again and mixed with magnesium stearate for 2 min.

Dissolution Studies : The USP paddle method was used for all the *in vitro* dissolution studies. In this method distilled water containing 0.02% polysorbate 80 (Tween 80) which simulated gastric fluid (pH 1.2) and intestinal fluid (pH.6.8) without enzyme were used as dissolution media. The rate of stirring was 100 ± 4 rpm. The amount of nifedipin was 20 mg in all formulations. The matrices were placed in 900 ml of gastric fluid and maintained at 37 ± 0.1° for 2 h. At appropriate intervals, 5 ml of each sample was taken and filtered through a 0.45-µm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. After 2 h, the dissolution medium pH was increased from 1.2 to 6.8 using phosphate buffer to simulate intestinal fluid. The samples were then analyzed at 334 and 340 nm by UV-visible spectrophotometer at pH 1.2 and pH 6.8 respectively. The mean of six determinations was used to calculate the drug release from each of the formulations.

RESULTS AND DISCUSSION

All formulations were relatively robust in terms of friability and hardness. The composition of matrices containing nifedipine are listed in Table 1. Figure 1 shows the dissolution characteristics of matrices prepared with methylcellulose (formulations F1 and F2). *In vitro* release profiles of nifedipine matrices containing methylcellulose showed that firstly, above 90% of the drug was released after 2 h at pH 1.2, secondly replacing methylcellulose and lactose with calcium hydrogen phosphate did not alter the length of release. It can be concluded that using methylcellulose in the formulation of nifedipine matrices could not produce sustained-release matrices.

Figure 1 also shows the dissolution characteristics of matrices prepared with different amounts of Eudragit RS (formulation F3, F4 and F5). An increase in percent of Eudragit RS from 7% (F3) to 9% (F5) resulted in a reduction in the release rate of the drug. In other words, matrices of the batch F5 showed the least release among all the formulations of matrices due to the high percentage of Eudragit RS.

The effect of Ph on dissolution rate was investigated at pH 1.2 and 7.2 Faster dissolution rates are displayed by all formulations at pH 1.2 (Fig. 1). All matrices are similarly affected by pH changes, and thus it can be concluded that drug dissolution rate of nifedipine is a function of pH dissolution media.

The only difference between F2 and F5 is that methylcellulose was replaced by Eudragit Rs. Comparing F2 and F5 clearly revealed that Eudragit RS significantly reduced the release rate of nifedipine.

For comparison purposes, the data in this study was subjected to the following equation, which may be considered a simple, Higuchi-type equation.

$$Q = Kt^{0.5}+c \quad \text{Equation (1)}$$

Equation 1 for release data dependent on the square root of time, would give a straight line release profile, with K presented as a root time dissolution rate constant and c as a constant. The lag period, prior to the commencement of release is defined as -c/K[11].

To analyze the mechanism of release of drug from these tablets, the following equation was used :

$$Q\text{-}K^{tn} \quad \text{Equation (2)}$$

where Q is the percentage of drug released, t is the release time, K is a constant incorporating structural and geometric characteristics of the release device, and n is the release exponent indicative of the mechanism of release. When n approximates to 0.5, a fickian/diffusion-controlled release is implied, where $0.5<n<1$ non-fickian transport and n=1 for zero-order release. When the value of n approaches 1.0, phenologically one can conclude that the release is approaching zero-order[11].

The best fit parameters, calculated according to equation 1 and 2 given in Tables 2 and 3 respectively. The information criteria were calculated based on the methods of Akaike[12] and Schwartz[13], this corresponding to the limits of applicability of the equations[11,12,15]. The model producing the lowest value for the information criterion is considered to be the most appropriate. The high value of the sum of squares and information criteria suggest that the empirical equation 1) does not provide a fit for the results. On the other hand, the second model (equation 2) is more

Table 1: Different formulations of nifedipine matrices and their composition*

Formulation Code	Matrix Composition (mg)							
	Starch	Lactose	MC[a]	PEG[b]	PVP[c]	CHP[d]	Eud[e]	MgS[f]
F1	100	60	18	3	—	—	—	1
F2	—	—	18	3	3.6	160	—	1
F3	—	—	—	—	8	154	14	4
F4	—	—	—	—	8	152	16	4
F5	—	—	—	—	8	150	18	4

[a]Methyl Cellulose, [b]Polyethylene glycol 4000, [c]Polyvinyl Pyrolidone, [d] Calcium Hydrogen Phosphate, [e]Eudragit RS, [f]Magnesium stearate, *All formulations containing 20 mg nifedipine

Table 2: Best Fit Parameters, Sums of Squares (ss) and Information Criteria (Akaike and Schwartz) based on equation ($Q=Kt^{0.5}+c$)

Formulation code	K	c	ss	Akaike	Schwartz	No.of data points
F3	6.23	-16.2	476	53	53	8
F4	5.71	-14.5	766	63	64	9
F5	5.35	-17.2	192	51	52	9

TABLE 3: Best Fit Parameters, Sums of Squares (ss) and Information Criteria (Akaike and Schwartz) based on equation ($Q=Kt^n$)

Formulation code	K	n	ss	Akaike	Schwartz	No.of data points
F3	3.24	0.584	619	55	56	8
F4	3.36	0.563	924	65	66	9
F5	2.07	0.628	312	55	56	9

appropriate than the equation 1. Negative values of c indicate a burst release of drug and high positive values imply a delay to release. the data in Table 2 indicate the matrices containing 7, 8 and 9% Eudragit RS had a burst of release. Comparing F3 (7% Eudragit RS, n=0.584), F4 (8% Eudragit RS, n=0.564) and F5 (9% Eudragit RS, n=0.629) showed that an increase in the amount of eudragit resulted in a slight increase in values of n. It can be concluded that using Eudragit in formulation of nifedipine matrices in range of 7-9% w/w, produces matrices with diffusion and erosion controlled release. The influence of polymer concentration within a matrix is of great importance. Generally, the greater the concentration of Eudragit RS within a matrix, the slower the release of nifedipine. Attempts were made to determine relationship between the time to release 90% of the drug and

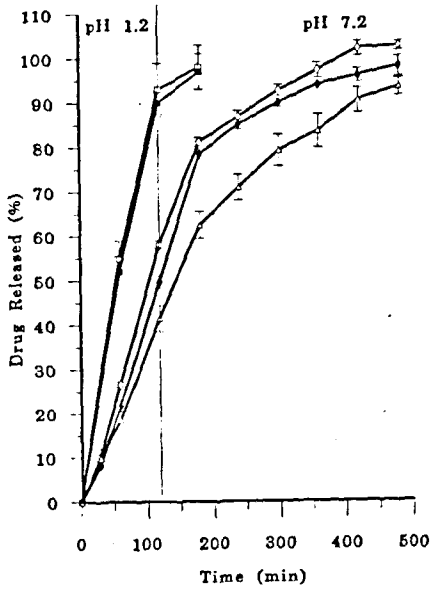

Fig. 1: Release of nifedipine from (❑) F1, (⧈) F2, (✧) F3, (◆)F4, (Δ) F5 tablets

percentages of Eudragit RS. The authors observed that there was a linear relationship (correlation coefficient of 0.996) between the time to release 90% ($t_{90\%}$) of the drug *in vitro* and the percentage of Eudragit in the matrix. Therefore, it is possible to predict the release rate of nifedipine from matrices containing different percentages of Eudragit Rs.

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