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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF NICORANDIL

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ABSTRACT : In the present research, an attempt has been made to formulate sustained release matrix tablet of nicorandil, a novel potassium channel opener used in cardiovascular disease. The tablets were prepared by wet granulation method and studied the effect of matrix former xanthan gum and guar gum separately. Tablets were evaluated for uniformity of weight, drug content, friability, hardness, thickness, in vitro dissolution and swelling study. All the formulation showed compliance with pharmacopoeial standard. As the time increases, the swelling index was increased; later on it decreases gradually due to dissolution of outermost –gelled layer of tablet into dissolution medium. Comparison between xanthan gum and guar gum, it has been observed that swelling index of guar gum was significantly more compared to xanthan gum. The dissolution result shows that an increased amount of polymer resulted in retarded drug release. The maximum drug release was found to be 90% over a period of 12 hours in guar gum based tablets (F_4). Similarly maximum drug release was found to be 96% over a period of 12 hours in Xanthan gum based tablets (F_1). This indicates that the minimum quantity of guar gum and Xanthan gum that is drug to gum ratio of 1:1 is required to prepare the sustain release matrix tablets of nicorandil .
Key words: Sustained release, xanthan gum, guar gum, nicorandil

INTRODUCTION

Hypertension and angina pectoris, the most common cardiovascular diseases, require constant monitoring. Potassium channel openers are presently considered an important class of drugs for hypertension and angina pectoris. The first therapeutic drug shown to possess an ability to hyperpolarize smooth muscle cell membranes is nicorandil, a potent coronary vasodilator. Although nicorandil is one of the emerging molecules in the case of hypertension and angina, successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired. Nicorandil has a short half-life, and the usual oral dosage regimen is 5 to 40 mg taken 2 to 4 times a day. To reduce the frequency of administration and to improve patient compliance, sustained-release formulation of nicorandil is desirable. The drug is freely soluble in water, and hence judicious selection of release-retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance (Raghuram, et.al., 2003). Hence, in the present work, an attempt has been made to develop sustained-release matrix tablets of nicorandil using hydrophilic matrix materials such as xanthan gum and guar gum.

MATERIALS AND METHODS

Materials:

Nicorandil was obtained as a gift sample from Torrent Pharmaceuticals (P) Ltd., Gujrat. Xanthan gum and guar gum were purchased from Loba Chemicals., Mumbai. All other chemicals and solvents used were of analytical reagent grade.

Preparation of Matrix Tablets:

Tablets were prepared by wet granulation technique. The composition of formulation is given in Table 1. All the powders were passed through 80 mesh. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of distilled water was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40°C for 12 h and thereafter kept in a desiccator for 12 h at room temperature. Once dry, the granules retained on 44 mesh were mixed with 15% of fines (granules that passed through 44 mesh). Microcrystalline cellulose as a diluent, Talc and magnesium Stearate were finally added as glidant and lubricant. Granules thus obtained were compressed into tablets on a 10 station single punch rotary tablet compression machine (Rimek). A flat-faced punch 12 mm in diameter was used for tableting. Compression force of the machine was adjusted to obtain the hardness of 4-6 kg/cm^2 for different batches.

Table 1: Composition of matrix tablets of nicorandil.

Ingredients (mg/tablet)	**F_0**	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**
Nicorandil	80	80	80	80	80	80	80	80	80
Xanthan gum	---	80	160	240	---	---	---	---	---
Guar gum	---	---	---	---	80	160	240	320	400
Microcrystalline cellulose	410	330	250	170	330	250	170	90	10
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total weight	500	500	500	500	500	500	500	500	500

Evaluation of Tablets:

The prepared matrix tablets were evaluated for weight variation, thickness, friability, hardness, drug content, swelling and *in vitro* studies. Drug content was estimated by UV spectrophotometric method. Nicorandil from accurately weighed samples was extracted into 0.1N HCl and the extracts were suitably diluted and assayed for nicorandil content by measuring the absorbance at 262 nm using 0.1N HCl as blank (Patel, et.al., 2005).

Compatibility studies:

The compatibility of the drug in the formulation was conformed by FTIR spectral analysis. FTIR spectra of pure drug, formulation containing xanthan gum and formulation containing guar gum were determined by using Shimadzu FTIR spectrophotometer by KBr pellet method.

***In vitro* drug Release Studies** (Raghuram, et.al., 2003)**:**

In vitro dissolution studies were carried out using USP XXIV type II apparatus (Electro Lab) at 75 rpm. The dissolution medium consisted of 0.1N HCl (pH 1.2) for the first 2 h and the phosphate buffer pH 7.4 from 3 to 12 h (900 ml), maintained at 37 ± 0.5°C. The drug release at different time intervals was measured at 262 nm by UV-visible spectrophotometer (UV-1700, Shimadzu, Japan).

Swelling behavior of Matrix Tablet (Yeole, et.al., 2006)**:**

The extent of swelling was measured in terms of percent weight gain by the tablet. The swelling behavior of formulation F_1, F_3, F_4 and F_8 was studied. One tablet from each formulation was kept in petri dish containing distilled water. At the end of 1h tablet was withdrawn, soaked with tissue paper and weighed. The process is continued for 12 h. Percent weight gain by the tablet was calculated using formula

$$S.I = \{(M_t - M_0) / M_0\} \times 100$$

Where, S.I = swelling index, M_t = weight of tablet at time't' and M_0 = weight of tablet at time t = 0.

Kinetic analysis of dissolution data (Patra, et.al., 2007)**:**

To analyze the rate and mechanism of drug release from the prepared matrix tablets, the release data were fitted into the zero-order equation:

$$Q = k_0 t$$

where Q is the amount of drug released at time t, and k_0 is the release rate constant, fitted into the first-order equation:

$$\ln (100-Q) = \ln 100 - k_1 t$$

where k_1 is the release rate constant, fitted into the Higuchi's equation:

$$Q = k_2 t^{1/2}$$

where k_2 is the diffusion rate constant, fitted into the Korsmeyer equation:

$$\log (M_t/M_\infty) = \log k + n \log t$$

Where M_t is the amount of drug released at time t; M_∞ is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release. To clarify the release exponent for different batches of matrix tablet, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation 4. A value of n = 0.45 indicates fickian (case I) release; > 0.45 but < 0.89 for non- fickian (anomalous) release: and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-fickian) refers to a combination of both diffusion and erosion controlled-drug release.

RESULT AND DISCISSION

The thickness of the tablets ranged from 4.52 to 5.86 mm. The average percentage deviation of 20 tablets of each formulation was less than ± 5%. Drug content was found to be uniform among different batches of the tablets and ranged from 96 to 99.72 %. The hardness and percentage friability of the tablets of all batches ranged from 4.2 to5.03 kg/cm^2 and 0.68 to 0.82% respectively. FTIR spectral analytical reports confirmed that there was no interaction between drug and polymers/ excipients used (Fig 1).

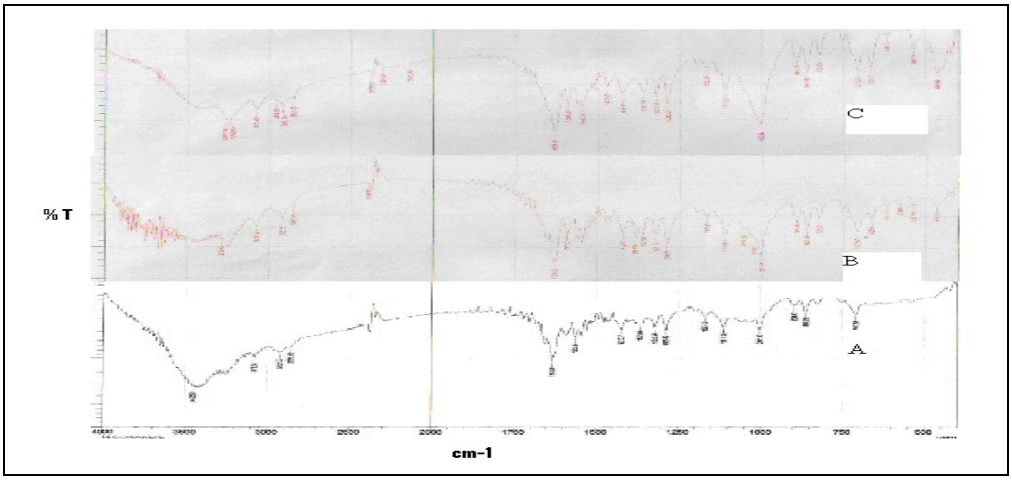

Figure 1: FTIR Spectrum of Drug (A), Formulation containing xanthan gum (B) and Formulation containing guar gum (C).

Swelling index of F_1, F_3, F_4, F_8 formulations are shown in Fig 2, as time increases the swelling index was increased, because weight gained by tablet was increased proportionally with the rate of hydration up to 3 h. Later on it decreases gradually due to dissolution of outermost –gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and gum concentration, as gum concentration increases, swelling index was increased, but drug release decreases. This is due to slow erosion of the gelled layer from tablets containing higher amount of xanthan gum and guar gum. Comparison between xanthan gum and guar gum, it has been observed that swelling index of guar gum was significantly more compared to xanthan gum.

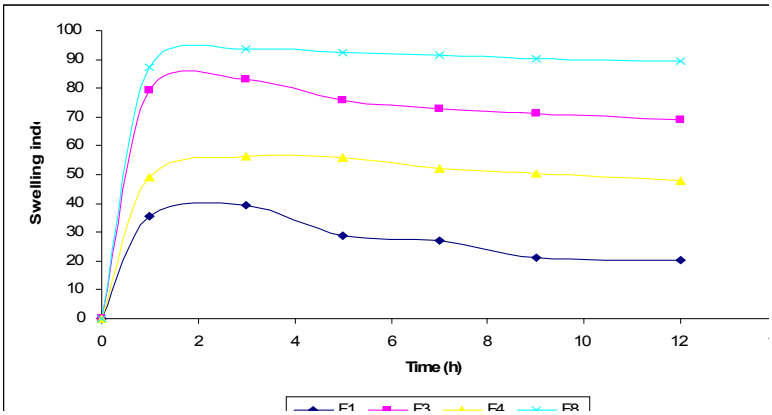

Figure 2: Swelling index of selected formulations.

From the *in vitro* results (Fig 3) it was observed that increasing the amount of gum in the formulation, resulted in slower rate and decreased amount of drug release from the tablet. Comparison between xanthan gum and guar gum based tablets, release of drug from guar gum based tablet was found to be more slowly compared to xanthan gum based tablet. This slow release is because of the formation of more thick gel like structure around the matrix of guar gum compared to xanthan gum that delays release from tablet matrix, where hydration of individual guar gum particles results in extensive swelling (Yeole, et.al., 2006). Thus, maintain the integrity of tablet, and retarding further penetration of dissolution medium, prolong the drug release (Krishnaiah, et.al., 2002). The maximum drug release was found to be 90% over a period of 12 h in guar gum based tablets (F_4). Similarly maximum drug release was found to be 96% over a period of 12 h in xanthan gum based tablets (F_1). This indicates that the minimum quantity of guar gum and xanthan gum i,e., drug to gum ratio of 1:1 is required to prepare the sustain release matrix tablets of nicorandil.

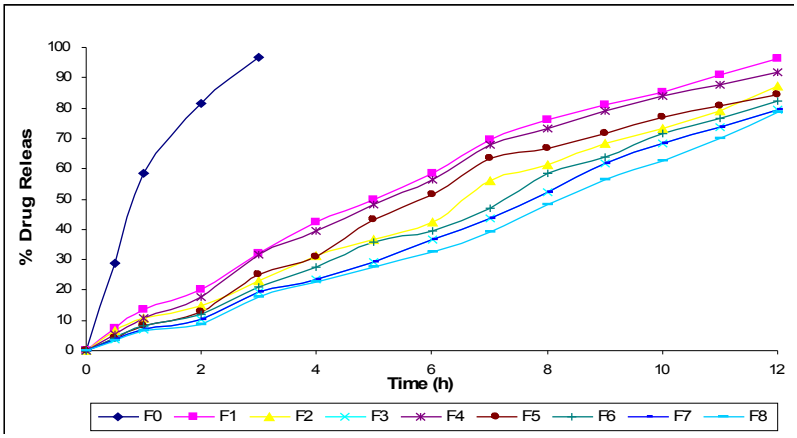

Figure 3: In Vitro Drug release of matrix tablets.

The kinetic values of all the formulations are shown in Table 2. The data clearly shows that, the drug release from all the formulations followed non-fickian diffusion.

Table 2: Kinetic data of matrix tablets of nicorandil.

Formulation	R^2					Order of release
	Zero	First	Higuchi	Korsmeyer	n	
F_0	0.9195	0.9651	0.9962	0.9599	0.4738	Non-fickian
F_1	0.9829	0.9215	0.9807	0.9514	0.7384	Non-fickian
F_2	0.9961	0.9378	0.9818	0.9260	0.7595	Non-fickian
F_3	0.9752	0.9453	0.9827	0.9343	0.8861	Non-fickian
F_4	0.9799	0.9731	0.9818	0.9573	0.8291	Non-fickian
F_5	0.9799	0.9856	0.9818	0.9389	0.8835	Non-fickian
F_6	0.9972	0.9229	0.9818	0.9410	0.8654	Non-fickian
F_7	0.9952	0.9453	0.9327	0.9343	0.8860	Non-fickian
F_8	0.9916	0.9238	0.9192	0.9287	0.8702	Non-fickian

CONCLUSION

It can be concluded that sustained release matrix tablet of nicorandil can be formulated with the minimum quantity of guar gum and xanthan gum that is drug to gum ratio of 1:1.

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