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Research Article

DESIGN AND EVALUATION OF ONCE-DAILY SUSTAINED RELEASE MATRIX TABLETS OF NICORANDIL

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ABSTRACT

In this study, effect of viscosity and hydration properties of matrices in once daily sustained release tablet formulation release of Nicorandil was studied. Different matrix tablet formulations prepared by using wet granulation method by using ethanolic solution of ethyl cellulose as granulating agent. The effect of combination of different polymers and the different concentration of granulating agent studied. The granules and tablets were tested various physicochemical parameters. The release profile of formulation was compared with theoretical release profile of the drug. The results suggested that the Nicorandil release from matrix system was controlled by diffusion and erosion mechanism (i.e. anomalous behavior).

Keywords: Nicorandil, Drug release, Matrix tablet, Sustained release, Ethyl cellulose, Hydroxypropyl methylcellulose

INTRODUCTION

Nicorandil is potassium channel opener providing vasodilation of arterioles and large coronary arteries and its nitrate component also produces venous vasodilation through stimulation of guanylate cyclase. It is used in the treatment of angina pectoris and hypertension. It has biological half-life of 1.33 hrs. Nicorandil is rapidly and completely absorbed after oral administration, absolute bioavailability 75±23 %[1-2]. The first therapeutic drug shown to possess ability to hyperpolarize smooth muscle cell is Nicorandil, a potent coronary vasodilator. Although Nicorandil is one of the emerging molecules in case of hypertension and angina, for successful treatment i.e. maintenance of blood pressure at normal physiological level, a constant and uniform supply of drug is desired. It has short biological half-life and usual initial dose is 10 mg twice daily (or 5mg twice daily for patient susceptible for headache), increased as necessary to a maximum of 30 mg twice daily; the usual therapeutic dose is in the range of 10 to 20 mg twice daily. To reduce the frequency of administration and to improve patient- compliance, a once-daily sustained release formulation of Nicorandil is desirable. Preparation of sustain release formulation by matrix technique is commonly employed method because of ease of preparation, flexibility and cost efficiency. Compressed hydrophilic matrices are commonly used as oral drug delivery systems because of their good compatibility. Drug release from hydrophilic matrix tablets is controlled by formation of a hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water into tablet and also movement of dissolved solutes out of the matrix tablets. The overall drug release process is influenced not only by drug solubility but also by the physical and mechanical properties of the gel barrier that forms around the tablet. The extent of matrix swelling, erosion, and diffusion of drug determines the kinetics as well as the mechanism of drug release[3]. The release mechanism from matrix tablet was also sufficiently described[4]. Hydroxypropyl methyl cellulose was used as release retardant for once daily formulation for various drugs [5-9]. In the present study, different grade of hydroxypropyl methylcellulose (METHOCEL K 4M, METHOCEL K 15M, METHOCEL K 100M) and ethyl cellulose were used.. The objective of the present study was to formulate once-daily sustained release formulation of Nicorandil, to study effect of polymer viscosity, polymer ratios and combination of hydrophilic as well as hydrophobic polymers on the pattern of drug release by in vitro dissolution testing and to compare it with theoretical release profile. For water soluble drug hydrophilic polymers and hydrophilic polymers were used successfully. These polymers may be used in combination or individually. In present study hydrophilic polymers, different grades of hydroxypropyl ethylcellulose were used as matrix forming system which has many advantages [10-11]. Hydrophobic polymer, ethyl cellulose was used as granulating agent as well as direct excipient added during mixing.

MATERIALS AND METHODS

Nicorandil was obtained as gift sample from M/s. Torrent Pharmaceuticals Ltd., Ahmadabad. Different grades of hydroxypropyl methylcellulose (HPMC) i.e. METHOCEL were obtained as gift samples from M/s. Colorcon, Mumbai. Ethyl cellulose was procured from Ms. SD Fine Chemicals, Mumbai. Other chemicals were of analytical grade.

Preparation of tablets

Firstly, drug excipient compatibility studies were conducted. For the compatibility-testing program, binary powder mixtures were prepared in 1:1 ratios with bulk excipients and 1:10 ratio with trace excipients (lubricants). The binary mixture were ground in a mortar, and screened through mixture was filled in the vial and sealed. All samples were stored at 55°C for 10days. Sampling was done after every 2days. Samples were analyzed for drug content, TLC and UV spectra. The viscosity of the polymers provided were measured by using Brookfield viscometer model DV III and found within the range of theoretical values given by the supplier.

The tablets were prepared by wet granulation method. The corresponding amount of drug, hydroxypropyl methylcellulose, ethyl cellulose, magnesium stearate and talc were accurately weighed. The powders were screened through screen #60. The screened powders were transferred to mortar and mixed for 10 minutes. The powder mixture was granulated using granulating solution. The wet mass was passed through sieve # 16 and granular material was dried in oven for 12 hours at 45°C. The dried mass was passed through sieve # 20. After addition of lubricant and glidant, compression was carried out using 9 mm flat-faced circular punches on rotary compression machine (Remi Electronics, Mumbai).

Evaluation of granules

Granules prepared by wet granulation method were evaluated for bulk density, angle of repose and drug content.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 1.5 g of powder from each formula was introduced in a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall onto a hard surface from a height of 2.5 cm at 2 sec intervals. The tapping was continued till no volume change was noted. LBD and TBD were determined by following formula:

LBD = weight of powder/ volume of packing

TBD= weight of powder/ tapped volume of packing

Angle of repose

The angles of repose of the granules were determined by using funnel method. The accurately weighted granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated by using the equation

$\tan\theta = h/r$

Where h and r are the height and radius of the powder cone respectively.

Drug content

Accurately weighed a quantity of granules equivalent to 100mg of Nicorandil, was extracted with water for 36 hrs and the solution, and filtered through 0.45µ membrane. The absorbance of the resulting solution was measured at 261.8 nm after suitable dilution by using spectrophotometer (UV 9PC2501, Shimadzu, Japan).

Evaluation of tablets

The compressed matrix tablets were evaluated for thickness, weight variation, hardness and drug content.

Thickness

The thickness of tablet was determined using Vernier caliper. Six tablets from each batch of formulation were used and mean thickness value and standard deviation were calculated for each formulation.

Hardness

For each formulation, the hardness of six tablets was measured using the Monsanto hardness tester and mean value and standard deviation was calculated.

Weight variation

To study the weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated and the percentage deviation in weight was calculated.

Friability

For each formulation the friability of six tablets was determined using Roche Fribilator. The friabilator was rotated for 4 minutes at 25rpm.The percent weight loss was then calculated.

Drug content

Five tablets were weighed and powdered. Weighed accurately a quantity of the powder equivalent to 0.1 g of Nicorandil and shaken with 50 ml of water for 10 minutes, and added sufficient water to produce 100.0 ml and filtered. After suitable dilution with water and the absorbance of the resulting solution was measured at the maximum at about 261.8 nm. Calculate the content of Nicorandil, at the maximum at about 261.8 nm.

***In vitro* drug release study**

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 24 hours using an eight station USP XXII type 2 apparatus (Labindia, Mumbai, India). The agitation speed was 75 ± 1 rpm. The dissolution medium used in each flask was 600 ml of 0.1N HCl (pH 1.2) for initial 2 hours, after that the pH was raised to 6.8 by addition of 300 ml of solution of tribasic sodium orthophosphate to each flask (15.2 g in water). The dissolution study was carried out for 24h (initial 2 hours in 0.1N HCl of pH1.2 and rest in pH 6.8) under sink condition. At every 1 hour interval samples of 5 ml were withdrawn from the dissolution medium and the volume was readjusted with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 261.8 nm by UV spectrophotometer. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard.

Calculation of theoretical release profile of Nicorandil from sustained release formulations:

The total dose of Nicorandil for a once-daily sustained release formulation was calculated by using the fallowing equation[5]

$D_t = \text{Dose}\ (1 + 0.693 * t/t_{1/2})$

Where,

D_t = total dose of drug,

Dose = dose of immediate release part,

t = time during which sustained release is desired i.e. 24 hrs, and

$t_{1/2}$ = half life of the drug

Hence

$D_t = 5.92\ [1 + (0.693*24)/1.33] \approx 80.0$ mg.

Hence, the formulation should release 5.92 mg in 1 hour like conventional tablet, and 3.21 mg per hour up to 24 hours thereafter.

RESULTS AND DISCUSSION

Nicorandil with all available information proved to be a suitable candidate for development of sustained release formulation. Hydrophilic Polymers (METHOCEL K4M, METHOCEL K15M, and METHOCEL K100M) with different viscosity were tried to formulate sustained release formulation of Nicorandil. Here, different ratios of drug: polymers were tried, and then after selecting the specific ratio of drug: polymer for polymer of particular viscosity, the formulation were modified with different approaches such as increasing conc. of granulating agent to get formulation which shows least deviation from theoretical release. The effect of combination of hydrophilic and hydrophobic polymers on drug release was also evaluated. The effect of addition of hydrophobic polymer (Ethyl cellulose) as a solution and as directly added excipient was evaluated. Drug-excipient compatibility study shows no interaction between Nicorandil and selected excipients as there was no significant shift of λmax, R_f value and drug content values (the results are not shown).

Granules prepared by wet granulation method were evaluated by measurement of bulk density and angle of repose, compressibility index and drug content. The results of **angle of repose** (<30) indicate good flow properties and the values for prepared formulations ranges from 26-32.Generally, **compressibility index** values up to 15% result in good to excellent flow properties and values for all formulation ranges from 14-21%. **Drug content** for all the formulations were in the ranges from 97-101%. All these results obtained indicate that the granules possessed satisfactory flow properties, compressibility, and drug content (Result shown in Table 2).

The tablet formulations were subject to various evaluation tests such as thickness, diameter, uniformity of weight, drug content, hardness, friability, and *in vitro* dissolution. All the parameters pass the pharmacopoeial limits. The formulations given kinetic data treatment and results were shown in Table 3.

Dissolution studies

Effect of drug to polymer ratio

It was found that for different grade of HPMC polymers (K4M, K15M, and K100M), with 1:3 drug: polymer ratios it is not possible to extend the release for 24 hours. With 1:3.5 drug: polymer ratios with HPMC K4M and HPMC K15M it was found that drug release was extended beyond 18 hour but relatively much faster as compared to theoretical release profile while HPMC K100M extend drug release much better. With 1:4 drug: polymer ratios the HPMC K4M and HPMC K15M it was possible to extend the drug release up to 24 hours and HPMC K100M released 96% of drug at the end of 24 hours (Fig 1). Here, it was found that with all these different ratios also, the effect of viscosity on the drug release was significant and

release was retarded in the order HPMC K100M> HPMC K15M> HPMC K4M.

Effect of increased concentration of hydrophobic polymer as granulating agent:

All the formulations for ratio effect were prepared with 2% ethyl cellulose as granulating agent. Then formulations were prepared with increased concentration of granulating agent i.e. 4% ethyl cellulose. It was found that formulation containing 1:4 ratio of HPMC K15 M and using 4%ethyl cellulose as granulating agent shows least deviation from theoretical release (Fig.2). These formulations were then subjected to data treatment to know the release rate of the drug from matrices. From the Korsmeyer treatment it was found that many of prepared formulations which are suitable for once-daily dose showed anomalous type of release mechanism (i.e. by diffusion and erosion) [12-13].

Effect of combination of polymers:

Different combination of HPMC K4M, K15M, K100M were prepared to get required release profile for sustained release formulation of Nicorandil. For studies the effect of combination of polymers 2% ethylcellulose solution was used as granulating agent. Different combination i.e. K4M: K15M and K4M: K100M in the ratio 2:1 (i.e. drug: polymer ratio 1:3) were found to extend drug release beyond 18 hours near to 24 hours but it was too fast in the initial hours. Other combinations were tried in the ratio 2:2, formulation (i.e. drug; polymer ratio 1:4).

It was found that these formulations extend the drug release up to 24 hours; still the initial fast release was observed and needs further optimization to get the desired release pattern (Fig.3). Other combinations of hydrophilic polymers (HPMC K4M, HPMC K15M and HPMC K100M) and hydrophobic polymer (ethyl cellulose) were tried. These combinations extend the drug release up to 24 hours but the initial release was fast as the combination of hydrophilic polymer and hydrophobic polymer was not able to form the strong release retardant layer initially (Fig.4). Ethyl cellulose retarded drug release effectively when used as alcoholic solution of granulating agent, while in the formulation in which it is used as formulation additive, the release was not retarded effectively.

Table 1: Formulations of Nicorandil tablets

Formulation Code	Ingredients (mg)								
	Nicorandil	HPMC K4	HPMC K15	HPMC K100	EC (2% Sol. qs)	EC (4% Sol. qs)	EC	Mag. Stearate (%)	Talc (%)
F_1	80	240		------	10	------	------	2	2
F_2	80	------	240	------	10	------	------	2	2
F_3	80	------	------	240	10	------	------	2	2
F_4	80	280	------	------	12	------	------	2	2
F_5	80	------	280	------	14	------	------	2	2
F_6	80	------	------	280	14	------	------	2	2
F_7	80	320	------	------	16	------	------	2	2
F_8	80	------	320	------	16	------	------	2	2
F_9	80	------	------	320	16	------	------	2	2
F_{10}	80	160	80	------	10	------	------	2	2
F_{11}	80	160	------	80	10	------	------	2	2
F_{12}	80	160	160	------	16	------	------	2	2
F_{13}	80	160	------	160	16	------	------	2	2
F_{14}	80	240	------	------	16	------	80	2	2
F_{15}	80	------	240	------	16	------	80	2	2
F_{16}	80	------	------	240	16	------	80	2	2
F_{17}	80	320	------	------	------	32	------	2	2
F_{18}	80	------	320	------	------	32	------	2	2
F_{19}	80	------	------	280	------	28	------	2	2
F_{20}	80	160	160	------	------	32	------	2	2
F_{21}	80	160	------	160	------	32	------	2	2

Table 2: Evaluation of granules*

Formulations	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Drug content (%)
F_1	31.36	0.2343	0.2803	15.73	99.17
	±0.016	±0.003	±0.004	±2.49	±0.50
F_2	28.46	0.2365	0.2830	15.84	97.11
	±0.022	±0.0057	±0.0046	±2.40	±0.67
F_3	30.43	0.2419	0.2885	16.11	99.81
	±0.021	±0.0034	±0.0048	±2.56	±1.74
F_4	30.35	0.2299	0.2830	18.77	99.66
	±0.056	±0.0045	±0.0046	±0.25	±0.75
F_5	29.99	0.2361	0.2885	18.10	100.40
	±0.042	±0.0031	±0.0048	±2.47	±1.76
F_6	27.96	0.2307	0.2727	15.37	98.84
	±0.046	±0.003	±0.0043	±1.24	±0.71
F_7	30.74	0.2522	0.2912	13.42	97.01
	±0.027	±0.002	±0.0024	±0.53	±1.04
F_8	28.92	0.2459	0.2873	14.34	97.33
	±0.012	±0.003	±0.01	±2.04	±1.98
F_9	30.61	0.2481	0.2970	16.47	98.70
	±0.026	±0.009	±0.0051	±2.25	±0.57
F_{10}	31.70	0.2372	0.2792	15.01	99.04

	±0.037	±0.006	±0.0108	±1.80	±0.53
F_{11}	29.73	0.2367	0.2913	20.76	97.74
	±0.009	±0.003	±0.003	±2.54	±1.54
F_{12}	26.82	0.2381	0.2913	19.11	100.23
	±0.027	±0.0057	±0.0048	±2.07	±1.64
F_{13}	27.73	0.2289	0.2678	14.5	98.73
	±0.022	±0.003	±0.004	±1.23	±1.73
F_{14}	30.86	0.2238	0.2678	15.77	100.16
	±0.028	±0.0028	±0.001	±2.06	±1.14
F_{15}	29.93	0.2206	0.2654	16.87	98.21
	±0.065	±0.0057	±0.004	±3.00	±0.79
F_{16}	30.55	0.2157	0.2632	18.00	97.89
	±0.056	±0.0026	±0.0069	±1.36	±1.80
F_{17}	29.00	0.2381	0.2913	19.11	98.23
	±0.014	±0.0057	±0.0048	±2.07	±0.65
F_{18}	31.44	0.2361	0.2819	16.14	99.42
	±0.042	±0.0031	±0.0107	±2.98	±0.53
F_{19}	29.08	0.2419	0.3000	19.33	100.33
	±0.015	±0.0034	±0.0051	±2.19	±1.71
F_{20}	32.04	0.2370	0.2955	19.78	98.74
	±0.024	±0.0016	±.0025	±0.62	±0.38
F_{21}	26.25	0.2361	0.2885	18.12	98.59
	±0.011	±0.0031	±0.0048	(±1.26)	±0.57

*all values expressed as mean+ standard deviation (n=3)

Table 3: Kinetic Treatment of prepared Nicorandil matrix tablets

Formulation code	Coefficient of determination (r^2)			
	Zero order	First order	Higuchi square root	Korsmeyer plot
F_1	0.7539	0.8696	0.9653	0.9524
F_2	0.776	0.9247	0.9918	0.9838
F_3	0.8289	0.8923	0.9771	0.9369
F_4	0.929	0.7966	0.9336	0.8984
F_5	0.9329	0.8042	0.9043	0.8549
F_6	0.9462	0.6847	0.8913	0.8360
F_7	0.9362	0.6554	0.9284	0.9053
F_8	0.9372	0.7318	0.8774	0.8699
F_9	0.9460	0.8057	0.8897	0.9045
F_{10}	0.8182	0.7322	0.9623	0.9093
F_{11}	0.8489	0.6647	0.9280	0.8742
F_{12}	0.8781	0.7258	0.9718	0.9277
F_{13}	0.8980	0.7802	0.9718	0.9247
F_{14}	0.7475	0.9641	0.9560	0.9782
F_{15}	0.8176	0.8941	0.9835	0.9681
F_{16}	0.8424	0.8859	0.9840	0.9535
F_{17}	0.9728	0.6842	0.9524	0.9453
F_{18}	0.9806	0.7962	0.9707	0.9755
F_{19}	0.8985	0.9474	0.9914	0.9784
F_{20}	0.9159	0.8983	0.9924	0.9879
F_{21}	0.9309	0.8778	0.9957	0.9967

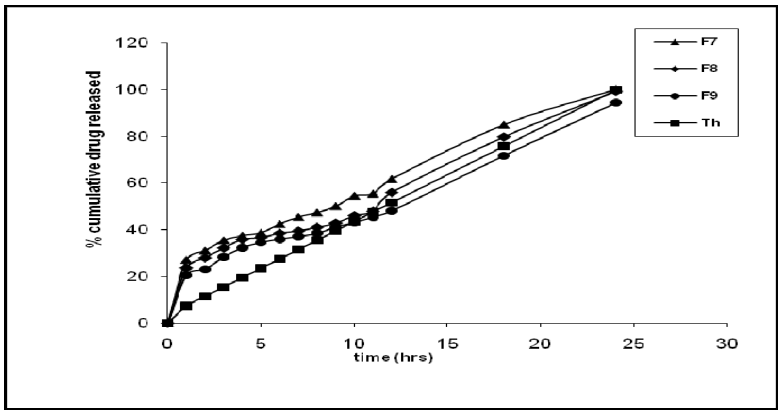

Fig. 1: Cumulative drug released with different viscosity grade HPMC at Drug: Polymer ratio 1:4

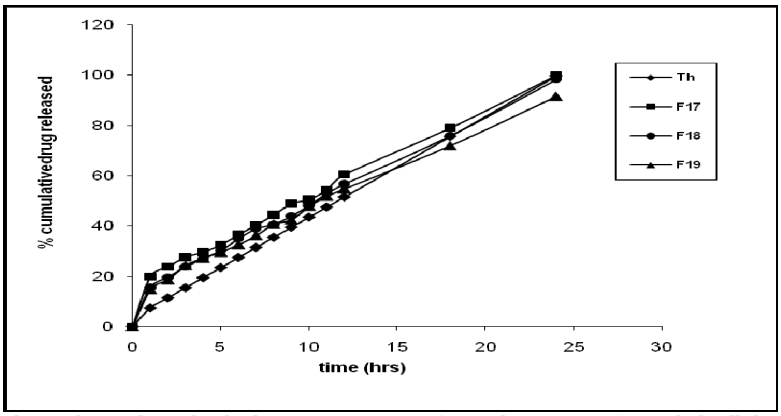

Fig. 2: Cumulative drug released at higher concentration of granulating agent (4% ethyl cellulose solution)

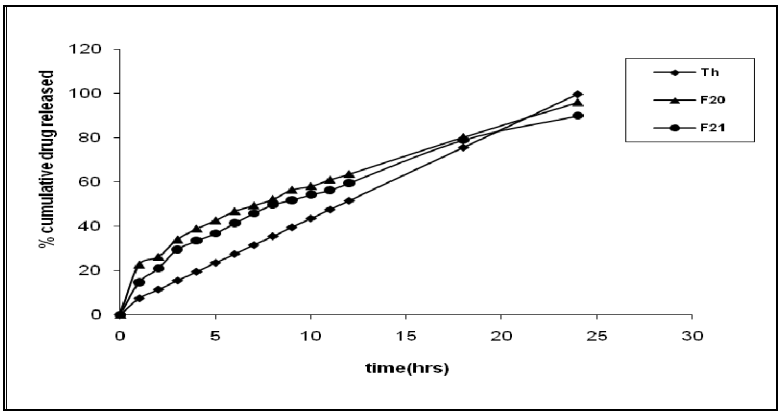

Fig. 3: Cumulative drug released at different combination of hydrophilic polymers

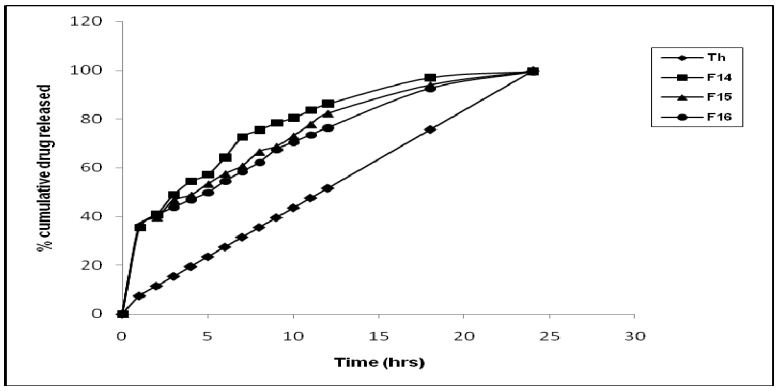

Fig. 4: Cumulative drug released with combination of hydrophilic and hydrophobic polymers

CONCLUSION

Sustained release matrix tablets of Nicorandil can retard drug release up to 24 hrs using hydroxypropyl methylcellulose as the release retardant polymer and solution of granulating agent of ethylcellulose. By using different combination of hydrophilic polymers it was also possible to retard release of Nicorandil up to 24 hours. The concentration of granulating agent has significant effect on release of Nicorandil from once-daily formulation. Ethyl cellulose, a hydrophobic polymer retarded drug release better when used as granulating agent as compared to formulations in which it is added directly. The viscosity of the polymer was a found to affect the drug release rate. An inverse relationship appeared to exist between polymer viscosity and drug release rate. Thus, higher the viscosity of the polymer, lower the release rate. The results suggested that the Nicorandil release from matrix system was controlled by diffusion and erosion mechanism (i.e. anomalous behavior) and the formulation followed typical Higuchian pattern.

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