

FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLET OF NICORANDIL

Mr. Ashish Pahade*, Dr. V. M. Jadhav, Dr. V. J. Kadam

Quality assurance dept, Bharati Vidyapeeth's College of Pharmacy, CBD Belapur, Navi Mumbai, Maharashtra, India.

*E-mail: ashish.pahade@gmail.com

ABSTRACT

The present study was to develop once-daily sustained release matrix tablet of nicorandil, an anti-anginal potassium channel opener. The tablets were prepared by the direct compression method and wet granulation method. Hydrophilic and hydrophobic matrix materials such as hydroxypropyl methylcellulose, sodium alginate and polyox were used, which can release the drug upto 24hrs in predetermined rate. Binders used were ethylcellulose and pvp k-30. The formulation of nicorandil matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied. The formulated tablet were also characterized by physical and chemical parameters such as for granules, angle of repose, bulk density, compressibility index, total porosity, and drug content and for the tablet thickness, hardness, diameter, weight variation test, drug content, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility and drug content. The in-vitro release rate profile showed the higher concentration of F16 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of a single polymer.

Keywords: Nicorandil, Matrix sustained release tablet, hydrophilic, hydrophobic, polymer.

INTRODUCTION

Oral route is the most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product.

Even for sustained release systems the oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers.¹

With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non toxic for an extended period of time². To achieve better therapeutic action various types of drug delivery systems are available, out of which sustained release systems are gaining much importance because of their wide advantages over others like ease of administration, convenience and non-invasiveness.

Sustained release dosage forms cover a wide range of prolonged action preparations that provide continuous release of their active ingredients for a specific period of time. By prescribing sustained release systems, it is possible to achieve several desirable therapeutic advantages². As the frequency of dosage is reduced, patient compliance can be improved, and drug administration can be made more convenient. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced, because more even blood level is maintained. Total amount of drug administered can be reduced by designing sustained

release systems. In addition, better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced by formulation of extended release form. The safety margin of high potency drug can be increased, and the incidence of both local and systemic adverse side effects can be reduced in sensitive patient. Overall, administration of sustained release forms enables increased reliability of therapy³.

Nicorandil is a vasodilator. It 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 hrs². Nicorandil is rapidly and completely absorbed after oral administration, absolute bioavailability 75±23 %.

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 molecule in case of hypertension and angina successful treatment means maintenance of blood pressure at normal physiological level, for which a constant and uniform supply of drug is desired. Its 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 daily⁴. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained-release formulation of Nicorandil is desirable.



Nicorandil is freely water soluble drug so selection of polymer should be properly done. Preparation of sustain release formulation by matrix technique is commonly employed method because of ease of preparation, flexibility and cost efficiency. In the present study, the polymer hypromellose (METHOCEL K 4M, METHOCEL K 15M, METHOCEL K 100M), polyox and sodium alginate using ethyl cellulose and PVP-30 as an binder were used.

The objective of the present study is 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.

MATERIALS AND METHODS

HPMC K4, HPMC K100, HPMC K15, Polyox, Sodium Alginate, Fumaric acid, Stearic acid, Microcrystalline cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, all the ingredients were of analytical grade.

Formulation of tablet

Different formulations were prepared by two methods:

1: Direct compression method (Table 1)

2: Wet granulation method. (Table 2)

1: Direct Compression Method

The core tablet was prepared by direct compression granulation process. The detail process was as follows:

1. Sifting: The Drug, Fumaric acid, Stearic acid, Microcrystalline Cellulose, HPMC K 4, Magnesium Stearate, and Colloidal silicon dioxide were sifted through sieve # 40.
2. Mixing: The sifted ingredients were mixed thoroughly in a polybag for 15min.
3. Lubrication: Magnesium stearate were sifted through sieve #40 and mixed with the prepared granules in a polybag for 5min.
4. Finally tablets were compressed using single punch machine, tablet compression machine 7.4mm punch were used.

Table 1: Formulations containing various ratios and combination of a hydrophilic polymer by direct compression method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicorandil	20	20	20	20	20	20	20	20	20
Fumaric acid	30	30	30	30	30	30	30	30	30
Stearic acid	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50
Microcrystalline cellulose 102	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)
HPMC K4	80	---	---	---	---	40	40	---	---
HPMC K15	---	80	---	---	---	---	---	40	---
HPMC K100	---	---	80	---	---	---	---	---	40
Polyox	---	---	---	80	---	---	40	40	40
Sodium Alginate	---	---	---	---	80	40	---	---	---
Mag. Stearate (%)	2	2	2	2	2	2	2	2	2
Colloidal silicon dioxide	2	2	2	2	2	2	2	2	2

Table 2: Formulation containing various combinations of polymers (hydrophilic- hydrophilic and hydrophilic-hydrophobic polymer), by wet granulation method

Ingredients	F10	F11	F12	F13	F14	F15	F16	F17	F18
Nicorandil	20	20	20	20	20	20	20	20	20
Fumaric acid	20	20	20	20	20	20	20	20	20
Stearic acid	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50	4.50
Microcrystalline cellulose-102	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)	q.s(160)
HPMC K4	80	---	40	80	---	40	80	---	40
Polyox	---	80	40	---	80	40	---	80	40
Ethyl cellulose (4% solution in ethanol)	6.4	6.4	6.4	---	---	---	3.2 (2% soluton)	3.2 (2% soluton)	3.2 (2% soluton)
PVP-30	---	---	---	10mg	10mg	10mg	5mg	5mg	5mg
Mag. Stearate (%)	2	2	2	2	2	2	2	2	2
Colloidal silicon dioxide	2	2	2	2	2	2	2	2	2



Table 3: Evaluation of nicorandil sustained release tablet

Formulations	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Weight uniformity (Mg)	Angle of repose	Drug content (%)	Compressibility Index (%)
F10	5	3.5	0.081	160±2	25.32±0.021	99.43±1.52	17.22±2.09
F11	5	3.4	0.077	160±1	26.79±0.022	97.33±1.73	16.3±1.13
F12	5.5	3.5	0.052	160±3	29.81±0.028	99.22±1.14	15.71±2.06
F13	6	3.4	0.071	160±1	28.13±0.060	98.21±0.77	14.41±3.05
F14	5.5	3.5	0.055	160±2	29.65±0.051	98.71±1.80	16.10±1.30
F15	5	3.5	0.0359	160±2	28.90±0.019	97.63±0.65	17.33±2.14
F16	6	3.5	0.0595	160±1	30.33±0.038	99.10±0.49	15.21±2.67
F17	6	3.4	0.0763	160±3	28.81±0.018	99.85±1.91	16.08±2.32
F18	6.5	3.5	0.0801	160±3	31.09±0.029	99.78±0.31	15.67±0.58

Wet Granulation Method:**Preparation of the core tablet by using non-aqueous wet granulation process**

The core tablet was manufactured from granules prepared by non aqueous wet granulation method using isopropyl alcohol and methylene dichloride (1:1). The detail process was as follows:

1. Sifting: The Drug, and all other ingredients were sifted through sieve # 40.
2. Mixing: The sifted ingredients were mixed thoroughly in a polybag for 15min.
3. Preparation of Granules: Isopropyl alcohol was added in well mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve #10.
4. Drying: The prepared granules were dried at 30°C for 12 H in presence of dehumidifier, and then it was sifted through sieve #20. Loss on drying was done.
5. Lubrication: Colloidal silicon dioxide, and magnesium stearate were sifted through sieve #40 and mixed with the prepared granules in a polybag for 5min.
6. Finally tablets were compressed using single punch machine, tablet compression machine 7.4mm punch were used.

In vitro Dissolution Studies:

The study was carried out using phosphate buffer 7.4 using USP apparatus type 2, the dissolution medium 900 ml maintained at 37°C ± 0.5°C, the absorbance was measured at 262nm, the dissolution study were carried out for 24hrs⁵.

A) Evaluation of granules^{6,7,8}:

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

Bulk Density/Tap Density of the Drug^{9,10}

Bulk density of the drug API was carried out using bulk density apparatus. Weight of an empty cylinder was taken. Drug was poured in to the cylinder and the volume was measured. The cylinder was kept in the apparatus and tapped for 100 times. The final volume after 100 taps was measured. Then the following calculations were made:

Loose Bulk Density (LBD) = weight of powder/ volume of packing

Tap Bulk Density (TBD) = weight of powder/ tapped volume of packing

Carr's Index = [(TBD. – LBD) x 100] / TBD

Hausners Ratio = Initial volume / Final volume

b) 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.¹¹

Drug content:

An accurately weighed amount of powder Nicorandil granules (100mg) was extracted with water and the solution was filtered through 0.45µ membrane. The absorbance was measured at 262 nm after suitable dilution.¹²



Evaluation of Sustained Released Tablets^{6,7,8}

Tablet Thickness and Size

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier calliper¹³.

Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2 .¹⁴

Friability

Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Tablets equivalent to 6.5g placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.¹⁵

$\% \text{ loss} = [(\text{Initial wt. of tablets} - \text{Final wt. of tablets}) / \text{Initial wt. of tablets}] \times 100$

Uniformity of Weight

Twenty tablets were selected at random and the average weight was calculated. Weight variation was calculated and was compared with I. P. standards.¹⁶

RESULTS AND DISCUSSION

Initially tablet were prepared with drug to polymer ratio 1:2 and 1:3 but the tablet released 100% of drug at 8th hr and 12th hr respectively and hence drug polymer ratio 1:4 was selected. The granules of different formulations were evaluated for the angle of repose, bulk density tap density, carr's index, hausners ratio, angle of repose and

drug content. Angle of repose determined was in the range of 25.32 ± 0.02 to 31.09 and drug compressibility range from 14.41 to 17.33 . The result of loose bulk density ranges from 0.2212 to 0.2433 and tapped bulk density from 0.2612 to 0.3003 . The drug content of the granules found was in the range of 96.93 to 98.14 .

The tablets of different formulation were evaluated for the thickness, hardness, friability, weight variation and drug content (Table 2). The thickness of the tablet ranged from 3.4 to 3.5mm , hardness of the tablet ranged from 5 to $6.5\text{kg}/\text{cm}^2$. The friability was in the range of 0.0359 to 0.0801% and weight variation was in the range of 160 ± 1 to 160 ± 3 . The weight variation test was performed according to the procedure in the pharmacopoeia. In weight variation test, pharmacopoeial limit of the tablet for the percentage deviation is 5% . The average percentage deviation of all the tablets formulation was found to be within the pharmacopoeial limit and hence passed the test for uniformity of weight. Drug content was found to be uniform among different batches of the tablets and ranged from 97.33 to 99.85 .

The sampling point of the drug was at the time interval 1, 4, 8, 12, 16, 20hrs for the dissolution study. The dissolution results for direct compression method, from the formulation F1-F9 it was found that direct compression method showed less hardness and also showed variable dissolution profile. Formulation F5, F6 containing sodium alginate and formulation F2, F8 containing HPMC K15 showed more dissolution variation at 8,12,16,20 hrs the drug release rate of nicorandil was at the higher rate at the end of 24hrs. Formulation F3 and F7 released 100% drug at the end of 16hrs. Formulation F1 and F4 showed satisfactory result but the hardness was very less. And the dissolution profile was at higher rate at the end of 16 and 20 hrs. (Fig 1 & 2).

To overcome less Hardness and variation in dissolution profile next batches were planned with wet granulation method using hydrophobic and hydrophilic binder using non-aqueous solvent.

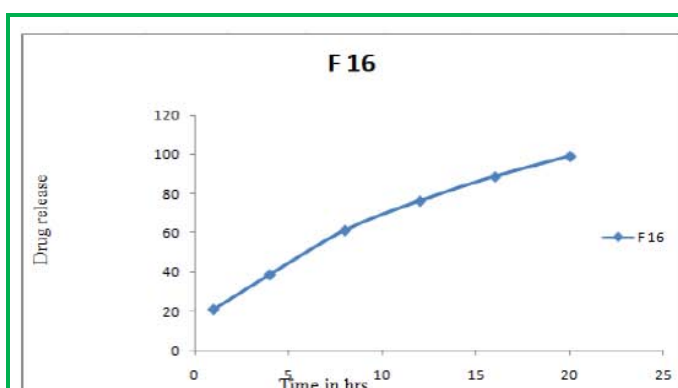


Fig. no. 1 Dissolution profile of optimize batch of Nicorandil sustained release matrix tablet

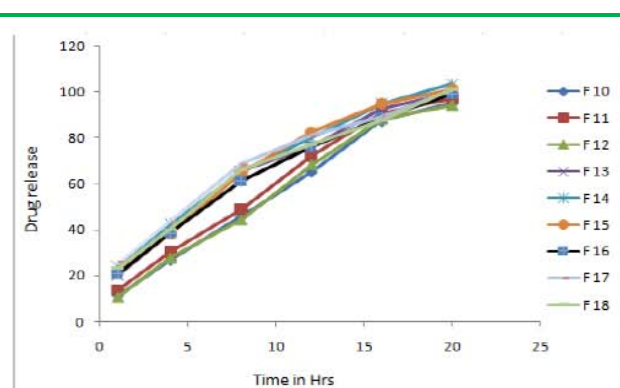


Fig no. 2 Comparative dissolution profile of Nicorandil Sustained Release matrix tablet

The results for wet granulation method for the formulation F10 to F18 were, for formulation F10, F11, F12 showed less drug release at the sampling time intervals this may be due to the presence 4% solution of ethyl cellulose. And formulation F13, F14, F15 showed higher drug release at the sampling time intervals this may be due to higher concentration of PVP-K30. Hence it was decided to go for a combination of 2% ethyl cellulose and 5mg PVP-K30. Formulation F-18 showed higher drug release at the end of 16 hrs. Formulation F-16 and F17 showed satisfactory drug release but as the availability and the higher cost of the polymer POLYOX it was decided to go for polymer HPMC K4 as it is available easily and that to its cost is less compared to POLYOX. The drug release for F-16 was 20.90 at the end of 1st hr and 99.44 at the end of 20hrs.

REFERENCES

- Notari, R., Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York, 1980, p152-54.
- Lechman, L., Liberman, H.A., Kanig, J.L., In., The Theory and Practice of Pharmacy, 3rd Ed., Varghese Publishing House, Bombay, 1987, p 430-453.
- Li, V.H.K., Lee, V. H. L., In., Controlled Drug Delivery: Fundamentals and Applications (Robinson, J. R., Lee, V.H. L., eds.), 2nd Ed., Marcel Dekker, New York, 1987, p 4-36.
- Gennaro, A. R., Remington: The Science and Practice of Pharmacy, 20th Ed., Mack publishing house, Easton Pannsylvania, 2000, p 903-914.
- Raparla DV and Murthy TE. Formulation and evaluation of oral controlled release Glimepiride matrix tablets. *Adv. Phamacol. Toxicol.* 2007; 8(2): 59-62.
- Liberman, H.A., Leon Lachman, Schwartz J.B., Pharmaceutical Dosage forms, 2nd Ed., Vol III, Marcel Dekker Inc., New York, 1992, p 256.
- The Indian Pharmacopoeia, Vol. 2, 4th Ed. The Controller of Publication, Govt. of India, Delhi, 1996, A82-A85.
- The United States Pharmacopoeia, United states Pharmacopoeial convention, Inc., Rockville, MD, 2000, 1944.
- Basak SC, Shrinivasa R, Manavalan R and Rao P. Controlled release HPMC matrix tablet of propranolol HCl. *Indian J. Pharm. Sci.* 2004; 66(6): 827-833
- Shabaraya AR and Narayanacharyulu R. Design and evaluation of chitason matrix of metoprolol tartrate for sustained release. *J. Pharm. Pharmaceutical Sci.* 2000; 8(1): 231-236.
- Shirwaikar AA, Jacob S and Grover V. Formulation and evaluation of sustained release tablets using an insoluble rosin matrix system. *Indian J. Pharm. Sci.* 2005; 67 (1): 80-83
- Roldy RK, Midovert S and Redlen S. Once dailymatrix tablet of azithromicine in-vitro and in-vivo evaluation. *Pharm. Sci. Tech.* 2003; 4(4):55-59
- The British Pharmacopoeia, department of health/by stationary office on behalf of the medicine and health care product regulatory agency, crown copy right, 2005; 5th Ed. 1303-1304, 2588-2589, A133.
- The United State of Pharmacopoeia 24/ Nf19 Asian Edition, The official compendia of standard United States pharmacopoeial convection Inc. Rockville. 1995; 1015,1016, 1791
- Chaudhari PD. Formulation and Evaluation of fast dissolving tablet of famotidine *Indian Drug.* 2005; 42(10): 641-649
- Krishanaiah YS, Lath K, Nageshwara L, Karthikeyan RS, Bhaskar Pand Satyanarayana V. Development of colon target oral guar gum matrix tablet of Albendazole for the treatment of Helminthiasis. *Indian J. Pharm. Sci.* 2003; 65 (4): 378-385

