

FORMULATION AND EVALUATION OF NIFEDIPINE SUSTAINED RELEASE PELLETS

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Article Received on: 17/06/11 Revised on: 20/07/11 Approved for publication: 08/08/11

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ABSTRACT

Nifedipine is a dihydropyridine derivative effectively used in management of various cardio vascular diseases in long-term therapy. The main objective of this work is formulation of Nifedipine sustained release capsules. This drug has low half life of 2 hr and is rapidly eliminated. Nifedipine is practically insoluble in water. Solubility of drug plays a major role in absorption and ultimately affects bioavailability. As it is poorly soluble it shows irregular bioavailability upon oral administration. Nifedipine lacks to maintain its concentration at site of action and side effects are more in conventional dosage form. Hence to minimize these affects we found it as an excellent candidate for sustained released oral drug delivery system. Drug release from marketed tablet modified release formulation showed 98.27% and Nifedipine sustained release pellets in capsules showed 98.80%. After stability studies sustained release capsules showed 99.18%. It is concluded that formulation F9 sustained release pellets in capsule was concluded as superior than marketed sustained release tablet formulation. Among the different formulations prepared, trial no F9 with ethyl cellulose N20 of 0.5% concentration and HPMC E5 with 20% concentration was found to have satisfactory dissolution profile.

Key words: Nifedipine, Sustained release pellets, Bioavailability, Dissolution profile, In-vitro drug release, Stability studies

INTRODUCTION

Pellets^{1,2} can be defined as small, free flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients typically from about 0.5mm to 1.5mm, by using appropriate processing equipment. Nifedipine is a dihydropyridine derivative effectively used in management of various cardio vascular diseases in long-term therapy. The biological half-life of Nifedipine is 2 hours. It requires multiple dosing to maintain therapeutic drug blood level so it is a best candidate to formulate as modified release dosage form. The present study was to develop a pharmaceutically equivalent, stable and quality improved formulation. The active pharmaceutical ingredient Nifedipine was subjected to preformulation study^{3,4}, which encompasses the “Accelerated drug excipients compatibility study” and the results obtained with selected excipients showed good compatibility with Nifedipine. The manufacturing procedure was standardized and found to be reproducible. At accelerated stability conditions formulation F9 was found to be stable for 60 days.

MATERIALS AND METHODS

Nifedipine, Sodium lauryl sulphate, Sodium starch glycollate, Kyron, Titanium dioxide, Ethyl cellulose, Hydroxy propyl methyl cellulose, Methylene dichloride, Isopropyl alcohol

Melting point

Melting point of the sample was determined by capillary method.

Solubility data of Nifedipine by saturated solubility method

Different solvents were prepared according to the procedure given in I.P. Drug was added in excess to 3 ml of each solvent in separate test tubes. The test tubes were kept in an ultrasonicator for 15 min and on mechanical shaker for 6 hours for equilibration. After 6 hours, contents of each test tube were filtered, suitable diluted and analyzed for the drug content using U.V. spectroscopy.

Calibration curve of Nifedipine in pH 6.8 phosphate buffer

The standard solutions of Nifedipine was subsequently diluted with pH 6.8 phosphate buffer containing 1% sodium lauryl sulphate to obtain series of dilutions containing 5, 10, 15, 20 and 25 µg/ml of Nifedipine in solution. The absorbance of the above solutions was measured in U.V. spectrophotometer. The absorbance values were plotted against concentration of drug.

Preformulation study

Compatibility study

Nifedipine was mixed with excipients in (1:1) ratio. The mixtures were kept in a 5 ml amber colored glass vials

and packed properly. These vials were stored at 40°C/75% RH for a period of 30 days.

Differential Scanning Colorimetry

The DSC study was performed on pure drug and drug + polymer. The study was carried out using a Shimadzu DSC 60. 2 mg of sample were heated in a thermally sealed aluminum pans in the temperature range of 25°C to 300°C at heating rate of 10°C minimum under nitrogen flow of 30 min.

Formulation development

Drug loading solution preparation

The raw materials were collected. 0.975g (750ml) of methylene chloride was weighed and to this 100grams of Nifedipine was added and stirred for 10 minutes (solution 1). Weighed quantity of HPMC E5, kyon, sodium starch glycollate, sodium lauryl sulfate and titanium dioxide was mixed with Isopropyl alcohol and stirred for 10 minutes (solution 2). Solution 1 and solution 2 were mixed under continuous stirring for 10 minutes and filtered through #100 mesh.

Drug loading

The non-pariel seeds were loaded into fluidized bed coater and the solution from step 1 was sprayed onto it. The operation was repeated till the solution is fully sprayed or until to get a desired size. The drug pellets were unloaded from the fluidized bed coater and loaded onto a tray drier for drying.

Drying and sifting of drug coated pellets

The pellets were dried for 30 min at a temperature maintained at 48°C-50°C and sifted by using #18 and #20 mesh and those retained on #20 mesh were collected.

Preparation of sustained release coating solution

Isopropyl alcohol and methylene di chloride were taken in a stainless steel container. To this a weighed quantity of Ethyl cellulose or HPMC E5 or both in combination were added under stirring continuously until it is completely dissolved.

Sustain release coating

The drug loaded pellets were loaded into fluidized bed coater and the sustain release coating solution was sprayed.

Drying and sifting for sustained release coated pellets

The pellets were dried under maintained temperature of 48°C-50°C for 30 min and sifted using 18-20# mesh. The pellets retained on #20 mesh were collected. 30mg equivalent of Nifedipine pellets were filled in capsules according to the bulk density data obtained. These capsules were used for drug content analysis and the in-vitro dissolution studies. The whole process of preparation of solution, coating and capsule filling

performed under mercury lamp to avoid photo degradation of the drug.

Evaluation of pellets

Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into graduated cylinder.

Friability test

The essential requirement of pellets is to have an acceptable friability to with stand further processing. Friability less than 0.08% is generally accepted for tablets, but for pellets this value could be higher due to the higher surface area/ unit and subsequent involvement of frictional force. 45g of pellets were placed in friabilator which was then operated for 100 revolutions at 25 rpm.

Angle of repose

The angle of repose of Nifedipine pellets was determined by the funnel method (Reposgram).

Evaluation of Sustained release Capsules

Drug content Analysis

Standard preparation

Accurately 100mg of Nifedipine was weighed and transferred into 100ml volumetric flask. 50ml of methanol was added to dissolve and made up to volume with water. From the above solution 2ml was transferred into another 100ml volumetric flask and made up to volume with methanol.

Sample preparation

Accurately weighed pellets equivalent to 100mg of Nifedipine was transferred into 100ml volumetric flask and 50ml of methanol was added to dissolve and made up to volume with water. From the above solution 2ml was transferred into another 100ml volumetric flask and made up to volume with methanol.

Dissolution procedure

In vitro drug release of the sample was carried out using USP – type I dissolution apparatus^{5,6,7} (basket type). The dissolution medium, used was phosphate buffer pH 6.8 containing 1% SLS, which was placed into the dissolution flask at temperature of 37 ± 0.5 °C at 50 rpm. Accurately weighed pellets filled in capsules were placed in each flask of dissolution apparatus. The apparatus was allowed to run for 12 hours. During the release studies, a 5ml of medium was taken out in amber colored glass vials and filtered through Whatmann filter paper (no. 40) and subjected to drug analysis by U.V. The removed volume was replaced each time with fresh medium. The % cumulative drug release was calculated.

Stability studies

The stability study⁸ was conducted on optimized formulation at accelerated condition of 40°C at 75%RH

condition for a period of 2 months. The capsules were individually wrapped using aluminum foil and packed in amber colored screw capped bottle and kept at above specified conditions in stability chamber for a period of 60 days. After 60 days the capsules were evaluated for content uniformity and in-vitro drug release.

RESULTS AND DISCUSSION

Compatibility study data at 40⁰C/75%RH for one month revealed that there were no physical or chemical change and discoloration observed between drug and different excipients. DSC Thermogram showed that there was no major difference in onset temperature, end set temperature and peak temperature when compared with pure drug's thermogram. No interaction was found between drug and polymers. Therefore it shows that there is no incompatibility between drug and different polymers. All formulation trials were passed in bulk density, friability and angle of repose test. All parameters were found within the limit. On the basis of in vitro dissolution data, various kinetic models were plotted such as percentage drug release, zero order, first order, Higuchi and Korsmeyer-peppas. It was observed that the release from first hour is improved and it is maintained as the time progress and reaches to 98.809% after 12 hours. The result of stability studies of formulation F9 indicates that there was no significant change in the drug content and dissolution profile of the formulation.

Drug release from marketed tablet modified release formulation showed 98.27% and Nifedipine SR pellets in capsules showed 98.809% and after stability studies SR capsules showed 99.18%. When compared SR capsule with SR tablet the drug release from SR pellets in capsule was more after 12 hours than the marketed tablet modified release formulation. It is concluded that

formulation F9 sustained release pellets in capsule superior than marketed sustained release tablet formulation. Among the different formulations prepared, trial no F9 with ethyl cellulose N20 of 0.5% and HPMC E5 with 20% concentration was found to have satisfactory dissolution profile.

ACKNOWLEDGEMENT

The authors are thankful to the Management, R.V.S College of Pharmaceutical Sciences, Suler, Coimbatore for their constant encouragement and support.

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Table-1: DISSOLUTION DATA OF FORMULATION F9 IN PHOSPHATE BUFFER WITH 1% SLS, PH 6.8

S. No	Time in hours	% cumulative drug release
1	0	0
2	1	22.11
3	3	53.61
4	4	68.48
5	6	84.91
6	8	93.52
7	12	98.809

Table-2: DISSOLUTION DATA OF FORMULATION 9TH KEPT FOR STABILITY

S. No	Time (hrs)	% Cumulative drug release of F9	
		Initial	60 days
1	0	0	0
2	1	22.11	21.78
3	3	53.61	53.32
4	4	68.48	68.60
5	6	84.91	85.04
6	8		92.30
		93.52	
7	12	98.809	99.18

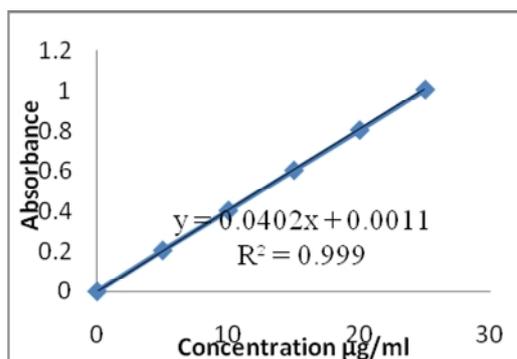


Fig.1: Calibration curve of Nifedipine

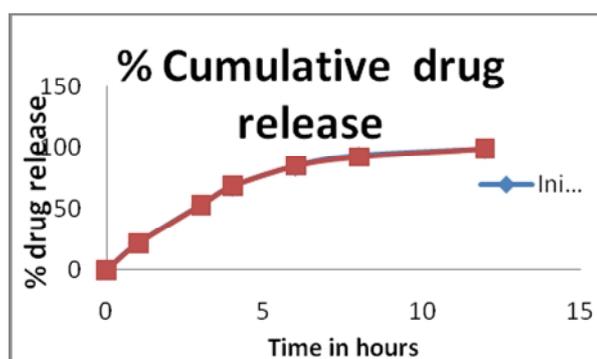


Fig.-2: Dissolution profile of formulation 9

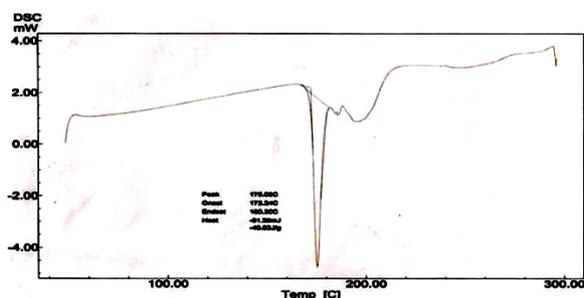


Fig 3: Thermogram of Nifedipine

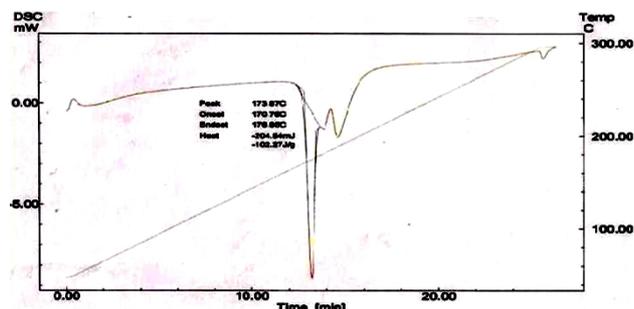


Fig.4: Thermogram of Nifedipine + HPMC E5

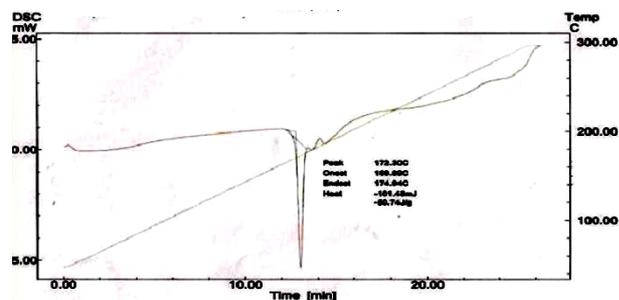


Fig.5: Thermogram of Nifedipine + Ethyl cellulose N-50

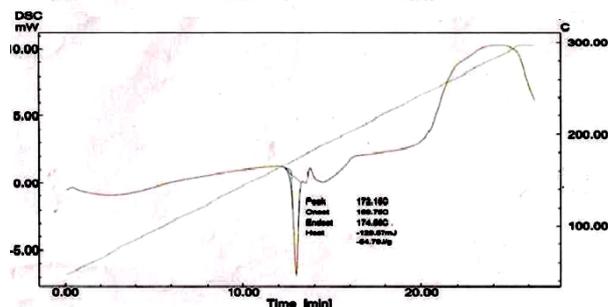


Fig.6: Thermogram of Nifedipine + Ethyl cellulose N-20

Source of support: Nil, Conflict of interest: None Declared