



Research Article

FORMULATION AND EVALUATION OF NIFEDIPINE LIQUID DROPPED TABLETS

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Abstract: Nifedipine is a dihydropyridine calcium channel blocker. Its main uses are as an antianginal (especially in Prinzmetal's angina) and antihypertensive. Nifedipine has been formulated as both a long- and short-acting 1,4-dihydropyridine calcium channel blocker. Therefore the present investigation was to design a formulation of Liquid dropped tablet of Nifedipine. Liquid dropped tablets of Nifedipine were formulated by drug-solution dropping technique by direct compression method. All the formulations were evaluated for disintegration time, hardness and friability, this Superdisintegrant addition method exhibits the lowest disintegration time, hence it is ranked as the best among the methods. They were prepared by using sodium starch glycolate, Ac-di-sol and cross povidone in different concentration. All the formulations were evaluated for weight variation, hardness, friability, drug content, *in vitro* disintegration time, wetting time, *in-vitro* dissolution study. Among all the formulation F5 (cross povidone - 10%) was considered to be the best formulation, which release up to 102.94% of the drug in 60 mins.

Key words: Nifedipine, Sodium Starch Glycolate, Ac-di-sol, cross povidone ; Disintegration time; FT-IR.

Introduction

The dissolution rate of drug from tablet is affected by its active ingredient's surface area and consequently, affects in oral bioavailability of the product. The development of formulations containing poorly-water-soluble drugs for oral delivery can be achieved by improving their dissolution. It has been found that increasing the available surface area by reducing the particle size can often markedly improve dissolution rates and lead to dramatic improvements in bioavailability. In some cases, the decreasing drug particle through micronized powder by milling tends to agglomerate¹ or accelerates the polymorphic conversion.

According to the differences of solubility and dissolution rates of polymorphs, the bioavailability of pharmaceuticals depends on polymorphous crystals². It has been shown that the polymorph in amorphous form of drug usually dissolves more rapidly than the corresponding crystalline form.

Therefore the dissolution and bioavailability of formulation containing active ingredient in amorphous form including pseudopolymorphs form such as solvates would be increased³. On the other hand, the processes in making tablets, including blending, granulating, drying and especially compressing affected therapeutic property of the drug because polymorphic forms, crystal habit, size and surface area would be changed during these processes⁴.

A new technique of tablet preparation was patented, a chargeable pharmaceutical tablet

which could solve the mentioned problems. The tablet was prepared by immersing or loading a blank tablet with liquid form of the active pharmaceutical ingredient.

In this study, nifedipine displays a poorly-water-soluble drug, which results in low and erratic oral bioavailability. Attempts were made to enhance the dissolution of nifedipine using "a drug-solution-dropping" technique which had success for water-soluble drug, chlorpheniramine maleate. The characterization of the preparation was compared to that of conventionally-prepared tablet.

In vitro drug dissolution rate was used as main criteria for comparison between both kinds of blank tablet with dropping drug solution and also with conventional tablet prepared by direct compression methods.

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability⁵.

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. In the other words the solubility can also define as the ability of one substance to form a solution with another substance. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together

form a solution. The process of dissolving solute into solvent is called as solution, or hydration if the solvent is water⁶.

Techniques of Solubility Enhancement

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are⁷:

Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improve the dissolution properties of the drug.

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronisation is used to increased surface area for dissolution.

Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility⁸.

Sonocrystallisation

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size.

The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation. Sono crystallization utilizes ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallisation. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients (API)⁹.

Drug dispersion in carriers:

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961¹⁰. The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method¹¹. Novel additional preparation techniques have included rapid precipitation by freeze drying¹² and using supercritical fluids¹³ and spray drying¹⁴, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion¹⁵.

Microemulsions:

The term microemulsion was first used by Jack H. Shulman in 1959. A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant.

The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is $< 0.1 \mu$ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions¹⁶.

EXPERIMENTAL SECTION

Materials

The following materials were used: Nifedipine (Bari Pharmaceuticals, Hyderabad, India), absolute ethyl alcohol (Bari ScientificTraers, India). A direct compression tablet includes dibasic calcium phosphate dihydrate (DCP direct compression grade, Bari Scientific Traders, India), Ac-Di-Sol® (Croscarmellose sodium, Bari Pharmaceuticals.), Sodium starch glycolate (Bari Pharmaceuticals.), Cross povidone (Croscarmellose sodium, Bari Pharmaceuticals.) and Magnesium stearate (Bari ScientificTraers, India).

Methods

Fourier transform infrared (FT-IR) studies :

Fourier transform infrared (FT-IR) spectroscopy was employed to characterize the possible interactions between the drug and the excipients in the solid state on Perkin Elmer Spectrum GX (organic Chemistry Unit, IISc, Bangalore) by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000–400 cm^{-1} .

Analysing of drug by uv scan

Accurately weighed 10 mg of Nifedipine and transferred into 10 ml of volumetric flask and dissolved in 10 ml ethanol to give stock solution 1 mg/ml. 1 ml was taken from stock solution in another volumetric flask and diluted up to 10 ml with 1.2 phosphate buffer to give a stock solution 100 $\mu\text{g/ml}$. 1ml taken from solution in another volumetric flask and diluted with buffer up to the 10 ml mark that gives 10 $\mu\text{g/ml}$. The absorbance of the solutions were scanned in the UV region and found that Nifedipine showed maximum absorbance at 238nm. Thus λ max of Nifedipine was found to be 238 nm.

Construction of Calibration Curve of Nifedipine

Preparation of Standard solution of Nifedipine

10 mg of Nifedipine was accurately weighed and dissolved in little amount of ethanol

and prepare the final volume up to 10 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 1 ml of stock solution was further diluted with 100ml 0.1 N HCl (pH 1.2) to get 10 µg/ml (working standard). Then 1,2,3,4,5,6,7,8,9 and 10ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 1µg, 2µg, 3µg, 4µg, 5µg, 6µg, 7µg, 8µg, 9µg and 10µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 238 nm against 0.1 N HCl (pH 1.2) as blank. The absorbance so obtained were tabulated. Calibration curve was constructed. The method was validated for linearity, accuracy and precision.

Characterization of formulation blend

The formulation blend was characterised by Bulk density, Tapped density, Angle of repose, Carr's index, Hausner ratio.

Formulation of Nifedipine Liquid dropped

Tablet :

Preparation of blank tablet :

Dibasic calcium phosphate which is a filler and superdisintegrants percentage by weight were mixed thoroughly for five minutes.

Subsequently the homogeneous mixer was mixed with 1% percent by weight of magnesium stearate as lubricant for two minutes. The mixed powder was then compressed on rotary tablet machine-12 station with 10mm flat punch. The obtained blank tablets had a flat surface with a diameter of 10 mm and 300 mg tablet weight.

Preparation of drug solution :

Then the drug-solution was prepared by dissolving 5mg of drug in the 200µl ethanol.

Preparation of Nifedipine Liquid Dropped Tablets :

The Nifedipine drug solution was dropped on to the tablet by using micro syringe. Then the solution was diffused into the tablet, there by the solution was evaporated. All the prepared tablets were dried at 50° C in a hot air oven for 1hr.

Evaluation of prepared tablets

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm².

Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

Wetting time:

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

Assay:

10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in suitable ethanol. The solution was filtered and diluted suitably. Further dilutions were done suitably to get a concentration of 10 µg/ ml with buffer pH 1.2. The drug content was analysed spectrophotometrically at 235 nm.

In-Vitro drug release:

Preparation of 0.1N HCL (pH 1.2) :

Dissolve 8.8ml of conc. HCL in 1000ml of distilled water.

Dissolution test:

USP II Paddle apparatus was used to carry out the dissolution test. 900ml of 0.1N HCL buffer was filled into the basket and paddle was allowed to rotate at 100 rpm, temperature of the bath was maintained at 38°C. The tablet was dropped in to the basket and the samples were taken at regular time intervals and replaced the basket with same amount of buffer 0.1N HCL. Then the absorbance of the samples were measured in UV/Visible spectrophotometer at 235 nm against 0.1 N HCL (pH 1.2) as blank.

RESULTS AND DISCUSSION

Drug and Excipients Compatibility studies by FTIR spectrophotometer

The infrared spectra of pure drug and mixture of polymers and excipients were studied by

FT IR spectroscopy using the KBR. Here spectral changes in the mixture are the basis for the determination of compatibility. The obtained spectrums of different formulation combinations were shown below. The spectral analysis of the pure drug and excipient mixture were done. From the graphs based on peaks and wave numbers that specific functional group, no additional peaks were obtained which indicates that there is no significant interaction between drug and excipients.

Evaluation parameters of formulation blend

Angle of repose of powder are in the range of 25.20 ± 0.41 to 29.50 ± 0.43 , Bulk density are in the range of 0.41 ± 0.01 to 0.50 ± 0.02 and Tapped densities are in the range of 0.50 ± 0.01 to 0.61 ± 0.03 . Hausner's ratio was in the range of 1.16 ± 0.01 to 1.22 ± 0.02 . From the above results it was observed that F8 formulation having better bulk characteristics than compared to remaining formulations.

Evaluation of Liquid dropped tablet

Nifedipine liquid dropped tablet was compressed under 10 mm round shaped standard punch. Thicknesses, length, breadth, hardness, friability of the tablet were evaluated.

- ✓ Weight variation was in range of 297.0 ± 1.41 to 299.6 ± 1.63 and hardness was in range of 2.87 ± 0.17 to 3.07 ± 0.12 . Weight variation and hardness of Nifedipine Tablets was within range.
- ✓ Thickness of the tablet was in the range of 1.90 ± 0.02 to 2.01 ± 0.02 mm. Length and breadth of tablet was as per the punch dimension.
- ✓ Percentage friability of tablet was evaluated in 100rpm and tablet passed the friability test.
- ✓ Tablets from each batch showed uniformity of weight as per IP limits. Each sample was analyzed in triplicate (n = 3).
- ✓ Content uniformity- Assay was done as per IP.

In vitro dissolution studies of drug release:

Table 1 : *In vitro* release of Nifedipine Liquid dropped tablets of F1-F16

Percentage drug release of all formulations:						
Formulation	10min	20min	30min	40min	50min	60min
F1	53.68	54.63	55.94	62.84	72.63	80.84
F2	52.42	61.89	64.10	69.15	71.68	91.26
F3	68.84	71.36	72.0	74.52	77.36	84.0
F4	40.09	49.82	52.63	55.89	58.01	60.92
F5	49.26	53.36	55.26	6.63	62.52	73.26
F6	43.44	48.93	50.10	55.31	61.42	65.89
F7	56.52	61.57	65.68	70.1	74.84	76.73
F8	58.73	76.42	83.26	97.57	98.60	99.47
F9	63.65	70.49	78.32	81.46	85.93	88.42
F10	77.36	82.10	90.31	90.63	90.94	92.84
F11	59.05	61.26	66.94	68.84	70.10	74.21
F12	77.36	78.0	79.89	82.10	83.05	92.47
F13	82.10	84.63	85.26	90.0	93.47	97.26
F14	55.57	58.42	63.15	66.94	74.21	75.15
F15	78.94	82.42	89.68	92.52	94.73	96.0
F16	75.78	87.47	88.42	90.0	90.63	93.15

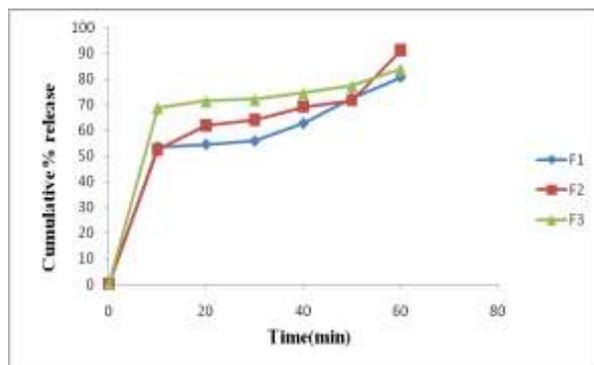


Fig-1 :In vitro release of Nifedipine Liquid dropped tablets of F1-F3

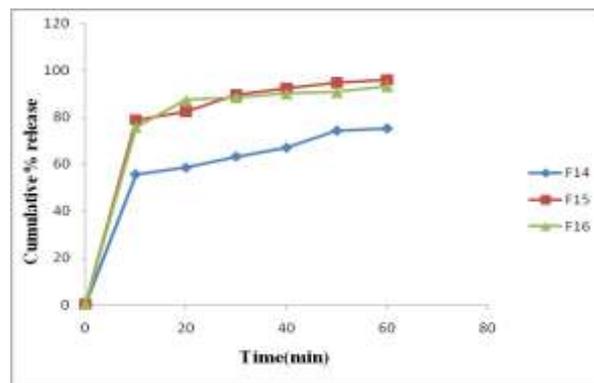


Fig-5 :In vitro release of Nifedipine Liquid dropped tablets of F14-F16

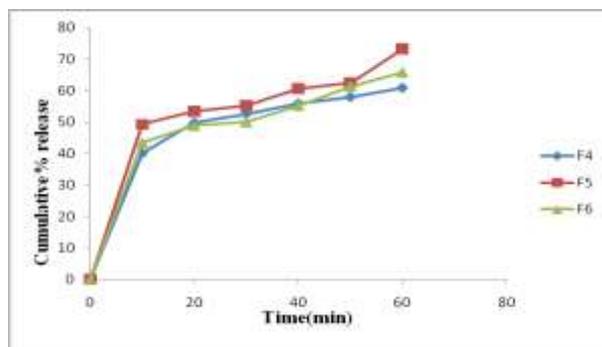


Fig -2:In vitro release of Nifedipine Liquid dropped tablets of F4-F6

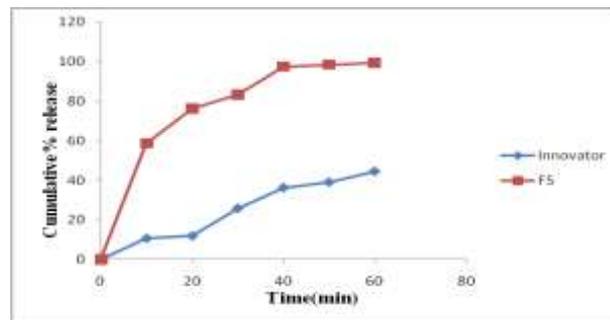


Fig-6: Comparison of dissolution profile of innovator and LDT(F8)

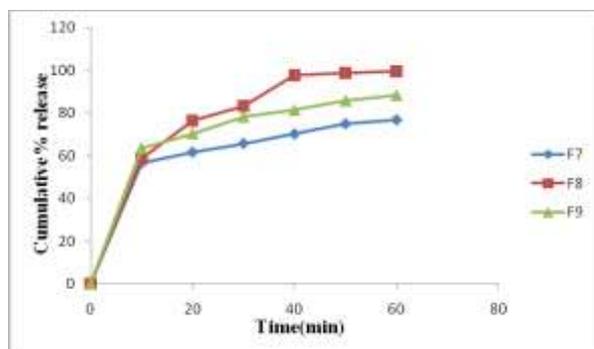


Fig-3 :In vitro release of Nifedipine Liquid dropped tablets of F7-F9

The dissolution study of SSG, CCS and CP (6%) shown above, which shows the release rate 91.26%, 73.26% & 99.47%.

The Dissolution study of various batches from F1- F16 shows that Nifedipine release from tablets containing super disintegrants, at concentration 6% release was more. As concentration of polymer increases the release rate was retarded. The formulation F8 which contain 6% CP release the drug upto 99.47 %.

The drug release of LDT was 99.47% which releases the more than the innovator.

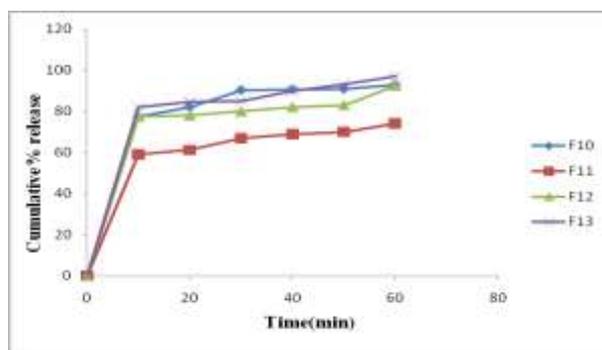


Fig-4 :In vitro release of Nifedipine Liquid dropped tablets of F10-F13

CONCLUSION

In the present work, an attempt has been made to develop drug-solution dropping tablets of Nifedipine. The IR spectra revealed that, there was no interaction between Super disintegrants and drug. All Super disintegrants used were compatible with drug.

The results of physical parameters of preliminary trials by direct compression showed good flow property. Amongst the various combinations of disintegrants used in the study, tablets that were formulated (direct compression) using Crospovidone, Croscarmellose sodium and Sodium starch glycolate exhibited quicker disintegration of tablets.

From the experimental results obtained, F-8 formulation has been selected as the best formulation among all the other formulations. As the concentration of the cross povidone (6%) was optimised. All the evaluation parameters obtained from the best formulation were found to be satisfactory.

Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Nifedipine liquid dropped tablets was found to be successful and the release of the drug was enhanced as compared to the conventional tablets.

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