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Formulation and Evaluation of Nifidepine Mouth Dissolving Tablet by Direct Compression Method

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Abstract: *Nifedipine, the prototype of the dihydropyridine class of calcium channel antagonists which used to treat Prinzmetal's angina, hypertension and other vascular disorders by blocking the calcium channels. In such cases, mouth dissolving dosage forms will be an effective solution for patient compliance and efficient medicine regimen. In the present research, mouth dissolving tablet of Nifedipine was made using various tabletiing aids. The prepared tablets were evaluated for weight, thickness, hardness, friability with disintegration time of less than 30 seconds and drug dissolution of about 75 % achieved within 30 minutes. The prepared tablets were stability tested at 40°C having 75 % Relative Humidity for 3 months and were found to be stable. Prepared mouth dissolving tablets of Nifedipine 10 mg was found to be bioequivalent under fasting and fed conditions with the marketed product.*

Keyword*: Nifedipine, mouth dissolving, Direct compression method, orodispersible.*

1. INTRODUCTION

Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a conventional dosage form for administration and to achieve better patient compliance. One such an approach is fast mouth dissolving tablet. Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted the scientist to develop orally disintegrating tablet (ODTS) with improved patient compliance and convenience.[1] Fast disintegrating or orodispersible tablets (ODTs) are one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self administration without water or chewing. This delivery system offers convenience for treatment-resistant population who has difficulty in swallowing unit oral dosage form, namely tablets and capsules. The demand for these formulations is particularly beneficial to pediatric and geriatric patients. It is estimated that 50% of the population is affected by dysphagia which results in high incidence of non- compliance and ineffective therapy. To overcome this problem it is necessary to design a formulation which rapidly disperse and dissolve in the oral cavity without the need of water for swallowing. Such dosage form should disintegrate when placed in the mouth and can be swallowed in the liquid form.[2,3] The bioavailability of a drug is significantly greater than those observed from conventional tablet dosage form by avoiding first pass metabolism. Moreover they overcome the swallowing difficulty associated with geriatric, pediatric or psychiatric patients and for the conditions where patients may not have ready access to water thus it provides convenience of administration, greater patient compliance and quick onset of action,[3] indeed, the mouth dissolving tablet is an important and attractive alternative to liquid dosage form. And it is also possible to increase the solubility of poorly soluble drug by formulation of fast mouth dissolving tablets. These fast disintegrating tablets can also be designed in such a way that the drug is absorbed through the buccal and esophageal mucosa as the saliva passes into the stomach.

The bioavailability of the drug is greater than that observed for conventional dosage form furthermore, the side effects caused by first pass metabolism may be reduced.[5] Fast disintegrating dosage form has been successfully commercialized and because of increased patient demands, these dosage forms are expected to become more and more popular.

The growing importance was highlighted recently when the European Pharmacopoeia adapted the term 'Orodispersible tablets' as a tablet to be placed in the mouth where it disperses rapidly before swallowing.[6]

Justification of research:

The few research articles reported have formulated the fast dissolving tablets by Direct compression method [5,6] In few articles, the fast dissolving tablets by direct compression method.[8, 9]

2. MATERIALS AND METHODS

Excipients and reagents:
Nifedipine was obtained from Pharmalink laboratories Pvt Ltd, Mumbai, India; Sodium Starch Glycolate was obtained from Loba Chemicals Pvt Ltd, Mumbai.; Sodium Carboxy methyl cellulose was obtained from Loba Chemicals Pvt Ltd, Mumbai; Aspartame was obtained from Merck Chemicals Pvt Ltd, Mumbai.; Camphor was obtained from Vishal Chemicals Pvt Ltd, Mumbai., Ammonium Bicarbonate was obtained from Loba Chemicals Pvt Ltd, Mumbai.; Magnesium Stearate was obtained from Molychem Chemicals Pvt Ltd, Mumbai.

Equipments and instruments:
Tablet Compression Machine by Jaguar JMD4_9 LtdUSP Tablet dissolution apparatus Type II by Electrolab Limited., Model No- TDT- 08L; 16 Station Single Rotary Tablet Compression Machine manufactured by Cadmach Machinery; UV-Visible double beam Spectrophotometer by Shimadzuj Japan Model No- UV - 1800; FTIR Spectrophotometer by Shimadzu, Japan. Model No- IR Affinity -1; Electronic Balance Model, Sansui; pH meter by Hanna Instrument, Italy; Pfizer Hardness Tester, Roche Friability test apparatus; Hot Air Oven by Metalab Scientific Industries, Mumbai.

Disintegration and dissolution parameters:
Disintegration test is performed in USP disintegration test apparatus in Purified Water. Dissolution is performed in 6.8 phosphate buffer. The parameters include, USP-II (Paddle), 50 RPM, 900 ml. Time Points: 5, 10, 15, 30, 45 and 60 minutes.

Method for blend Uniformity, content uniformity / uniformity of dosage units and dissolution:
Nifedipine is official in USP and the same method is utilized for the determination of Blend Uniformity, Content Uniformity, Uniformity of Dosage Units and Dissolution.

Method for bulk density, tapped density, repose angle and friability measurements:
USP guidelines followed in the measurement of Bulk Density, Tapped Density, Compressibility Index, Repose Angle and % Friability Measurements.

3. EXPERIMENTAL/ METHODOLOGY

API characterization:
Nifedipine was characterized with respect to Description, Form, Bulk Density, Tapped Density, Compressibility Index, Hausner Ratio, Repose Angle, Loss on Drying and Particle Size Distribution.

Drug-excipient compatibility study:
IR spectroscopy was also used to determine the molecular interaction between polymer and drug. The all physical mixtures and drug sample were mixed with dried KBR and physical mixture of drug and polymer were filled in the prewashed, dried ampoules and sealed. The sealed ampoules were stored at 37°C ±0.5 for 28 days in stability chamber. At the end of 28 days ampoules were removed from stability chamber and subjected for interaction study.

Formulation:
Weigh accurately 10 mg of Nifedipine in each eight batch and place in the mortar and add the Sodium Starch Glycolate (SSG) On contact with water the superdisintegrants swell, hydrate, change volume or produce disruptive change in the tablet. Depending upon the type of carrier in formulation, 5% (w/w) of Sodium starch glycolate and Sodium Carboxy Methyl Cellulose (SCMC) as disintegrant were mixed with mixture for 5-10 minutes. Final mixture was compressed on 8 mm punch and die. The batch design is reported in Table 1.

Table 1: Formulation of Nifedipine tablet by Disintegrant addition technique or direct compression method.

Ingredient	D1	D2	D3	D4	D5	D6	D7	D8
Drug	10	10	10	10	10	10	10	10
Sodium Starch Glycolate	2.4	3.6	4.8	6.0	0	-	-	-
Sodium CMC	-	-	-	-	2.4	4.8	7.2	9.6
Magnesium Stearate	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Aspartame	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Tale	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Lactoseq.s.	120	120	120	120	120	120	120	120

(n= mean of three determinations)

4. EVALUATION

The prepared granules were evaluated for the blend property like Bulk density, Tapped density, Carr's index, Hausner ratio and Angle of repose.

Determination of L max:

10 mg of Nifedipine was accurately weighed and was first dissolved in 10 ml methanol. 10ml of this solution was then diluted to 100ml using 6.8 pH phosphate buffer to get a final solution of concentration l00µg/ml. UV spectrum was recorded in the wavelength range 200-400 nm. The wavelength of maximum absorbance λ max was determined.

Construction of calibration curve for Nifedipine:

Preparation of standard stock solution: 10 mg of Nifedipine was first dissolved in 10ml of methanol. 10 ml of this solution was then transferred to a 100 ml volumetric flask. The volume of solution was made up by using the 6.8 pH phosphate buffer to give a solution concentration l00µg/ml.

Working stock solution: The standard stock solution was then appropriately diluted with 6.8 pH phosphate buffer, to obtain a series of Nifedipine solution in the concentration range of 1-12µg/ml. The absorbance of all the solutions was measured against blank at 340 nm using double beam spectrophotometer. A standard graph of absorbance verses concentration of concentration of drug was plotted. This graph was used for the estimation of drug concentration in the orodispersible tablets for in vitro drug release studies.[12]

5. RESULTS AND DISCUSSION

API characterization:

Nifedipine was characterized with respect to Description, Form, Bulk Density, Tapped Density, Compressibility Index, Hausner Ratio, Repose Angle, Loss on Drying and Particle Size Distribution. The results are shown in Table 2.

Table 2: Characterization Parameters of Nifedipine.

Parameters	Details
Description	Yellowish crystalline powder having faint odor
Bulk Density	1.70 g/ml
Tapped Density	1.17g/ml
Compressibility Index	23.3%
Carr's index	0.74%
Hausner ratio.	0.92%
Angle of repose	0.54º

Drug-excipient compatibility study:

To study the compatibility of drug with excipients FTIR spectra of drug in combination with excipients was studied. The IR spectrum indicates that there was no physicochemical interaction in between drug and excipients under study. Drug Excipient compatibility suggests that drug polymer blend do not affect the stability of mixture indicating compatibility of drug with excipients.

Hardness variation study:

Hardness was measured using the Pfizer hardness tester. Measure the pressure required to break diametrically placed matrix tablet, by a coiled spring. Disintegrant strongly affected by tablet size and hardness. Orodispersible formulation prepared by both methods showed less hardness as it is necessary to achieve faster disintegration. In comparison, hardness achieved by Direct Compression method (2.6-3.6 kg/cm^2) was quite low than that of disintegrant addition method (2.6-3.8 kg/cm^2).

Determination of λ max:

The λmax for Nifedipine was found to be 340 nm in 6.8 phosphate buffer.

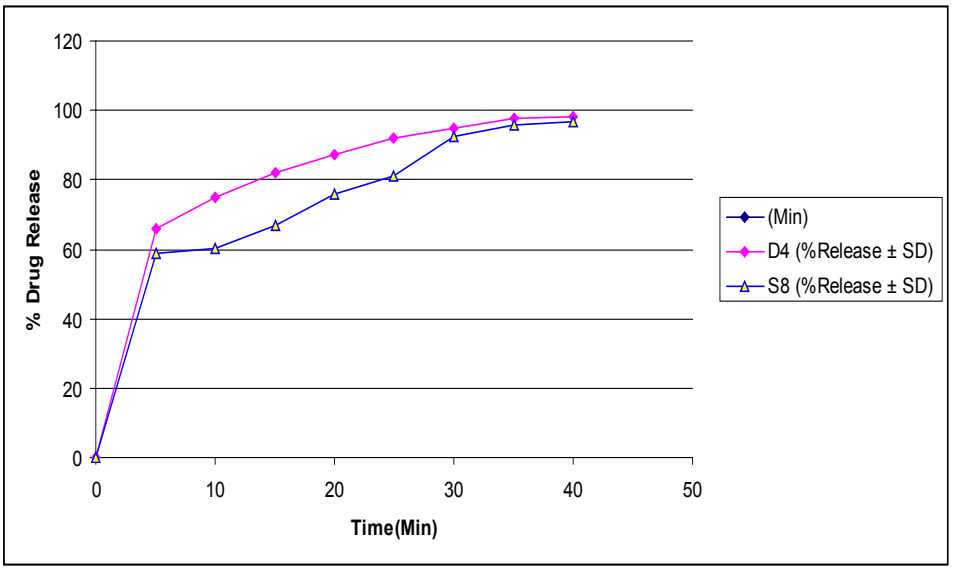
Preparation of calibration curve of Nifedipine:

The calibration curve of Nifedipine was prepared in pH 6.8 phosphate buffer with the Linearity was found in the concentration range of 2-14 µg/ml. Regression coefficient obtained in pH 6.8 phosphate buffer was found to be 0.998 with the equation of line y = 0.016x + 0.000.

In-vitro dissolution studies:

The dissolution study was carried on optimized formulations D4 and DS it shows the release of drug was largely depended on the disintegration time that is faster the disintegration of tablets better and faster is the release which can be clearly marked in Figure 1.

Figure 1: Dissolution profiles of optimum formulations (D4 and D8) phosphate buffer prepared by employing disintegrant addition or compression technique.



Accelerated stability study:

The study of the effect of temperature on optimum formulations D4 and D8 of orodispersible tablets reveled that no significant changes in the physical parameters when stored at temperature of 40°C at a relative humidity (RH) of 75% and at room temperature. No significant reduction in the content of the active drug was observed over a period of two months hence shelf life of the formulation could extrapolate to a minimum of two years. The optimum formulations did not show any significant change in disintegration time, friability and drug content when kept at different condition and periods, data for effect of temperature.

6. CONCLUSION

It concluded that fast dissolving tablet of Nifedipine can be successfully prepared by disintegrant addition method and was found to have potential advantages over conventional dosage forms, with their improved patient compliance, convenience, bioavailability and rapid action.

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