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Development and characterisation of oral fast dissolving tablet of nifedipine using camphor as a subliming material

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ABSTRACT

Mouth fast dissolving drug delivery system has gained high patient acceptability and popularity in the recent times. The aim of this study was to evaluate the effect of increasing nifedipine load on the characteristics of fast-disintegrating sublingual tablets for the potential emergency treatment of anginal pain and hypertension. Nifedipine undergoes first pass metabolism in liver and gut wall which has oral bioavailability of 43-77%. Sublingual dosage form bypasses the metabolism of the nifedipine in liver and offers a fast relieve from anginal pain and hypertension. An attempt has been made to prepare fast dissolving tablets of nifedipine were prepared by wet granulation technique using camphor as subliming agent and sodium starch glycolate together with crosscarmellose sodium as superdisintegrants, flavor and sweetner impart the taste to the formulation. The porous granules were compressed in to tablets by single punch tablet machine. Camphor was sublimed from the tablet by exposing to vacuum drier at 60°c for 12 hrs. All the formulations were evaluated for weight variation, hardness, friability, content uniformity, wetting time, disintegration time and dissolution rate. Among the formulations, (NEF6) one containing to be the best acceptable in terms of palatability, fast dissolving tablet having adequate strength. The disintegration time was found to be 58.0 ± 0.4 seconds, hardness of 3.4 ± 0.41 kg/cm2, wetting time of 39.3 ± 1.80 sec and drug release of 99.96% in 10 mins. All the formulations showed low weight variation. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Key words: Fast dissolving, Camphor as subliming agent, Nifedipin, Tablet

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INTRODUCTION

Difficulties with and resistance to tablet administration is common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with swallowing (dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric, and psychiatric patients [1]. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability. In recent years, rapid-dissolving oral drug formulations have been developed to overcome problems related to swallowing difficulties. The fundamental principle used in the development of the fast-dissolving tablet is to maximize its pore structure [2]. Vacuum-drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets [3]. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly. Fast disintegrating tablets are gaining prominence as new drug delivery systems. These dosage forms dissolves or disintegrate in oral cavity within a minute without the need of water or chewing [4]. Nifedipine is a dihydropyridine calcium channel antagonist originally introduced for the treatment of angina pectoris [5] hypertension and anti-atherosclerotic activity [6]. The sublingual [7] dosage form offers fast release of drug from the formulation and it reaches the systemic circulation directly, which bypasses the metabolism of the nifedipine in the liver and offers a fast relive form the anginal pain, hypertension which will be worth in such conditions. The objective of study was to enhance safety and efficacy of drug molecule, achieve better compliance, solve swallowing problem, enhance onset of action and provide stable dosage form.

MATERIALS AND METHODS

Materials

Nifedipin (Boston Pharmaceuticals Ltd, Gujrat), croscarmellose sodium, sodium starch glycolate, and microcrystalline cellulose (Maple Biotech Pvt Ltd., Pune, India), Saccharine sodium, Polyvinypyrolidone K-30, Mannitol, Raspberry flavor, Ethyl alcohol purchased from Lobachemie, Mumbai, magnesium stearate and Talc purchased from s.d fine chemicals, Mumbai. All other ingredients were of analytical grade.

Methods

The fast dissolving tablets of Nifedipin were prepared using the subliming agent, camphor, sodium starch glycolate and crosscarmellose sodium as super disintegrates, mannitol as a diluent, Sodium saccharine as sweetening agent, alcoholic solution of Polyvinyl pyrrolidone (PVP) (10 % w/v) as binder and magnesium stearate with talc as a flow promoter. The composition of the each batch shown in table 1. The raw materials were passed through a 100-mesh screen prior to mixing. The drug and other ingredients were mixed together, and a sufficient quantity of alcoholic solution of PVP (10%w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granules of the formulations containing either of the superdisintegrants but without camphor (NEF1 or NEF2) were dried in a oven at 60^{o}C for 30 min. Other granular formulations (NEF3 to NEF5) contained a subliming agent and were dried at room temperature, 20-22^{o}C for 8 hrs. During drying, the camphor sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, magnesium stearate and compressed into tablets using flat face rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad). Sublimation was performed from tablets instead of granules at 60^{o} C in selected batch (NEF6).

Evaluation of Tablets

The granules were evaluated for angle of repose, bulk density, taped density, Carr's Index, Hausner ratio [8]. The result obtained for granules were shown in table 2 and evaluation of tablet shown in Table 3.

Thickness: Thickness of tablet was determined by using dial caliper.

Hardness: The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted [9].

Friability: Ten tablets were weighed and placed in a Roche friabilator (Veego, India). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured [10].

Weight variation: Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±10% [11].

Drug content: 20 tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of nifedipin was dissolved in 100 ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 235 nm using UV-Visible spectrophotometer (UV 1601- Shimadzu, Japan).

Wetting time: A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish containing 10ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted [12].

Dissolution study: In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) [Veego Tablet Dissolution Tester] at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as dissolution medium which maintained at 37±0.5°C. Aliquot of dissolution medium (10 ml) was withdrawn at specific time intervals (2 min) and was filtered. The amount of drug dissolved was determined by UV spectrophotometer (Shimadzu, Japan) by measuring the absorbance of the sample at 235 nm [13].

RESULTS AND DISCUSSION

Among the soluble diluents, mannitol was selected as a diluent considering its advantages in terms of easy availability and negative heat of dissolution [14]. Table 3 shows that all the formulated tablets exhibited low weight variation. Addition of a subliming agent had no pronounced effect on hardness and increased friability of the tablets. The drug content of all the formulations was found to be between 99.10 - 99.95% which was within the acceptable limits as per USP XXVII. The batches NEF3 and NEF5 were prepared using camphor at different concentrations to study its effect on disintegration time. The sublimation time (0.5-8 hours) depended on the amount of camphor present initially (0%, 5%, or 10%). Batch NEF5, containing 10% camphor, showed the least disintegrating time. The porous structure is responsible for faster water uptake; hence it facilitates wicking action of sodium starch glycolate in bringing about faster disintegration. Tablets with lower friability (0.5%) may not break during handling on machines and/or shipping. The use of a sublimation agent resulted in increased friability probably due to increased porosity. It was decided to incorporate Talc at a level of 1.5% to decrease the friability of the tablets (batches NEF5 and NEF6). The low value of disintegration time indicates that the porosity of tablets of batch NEF6 would be greater than batches NEF1 to NEF5. In vitro release studies were carried out using USP XXIII tablet dissolution test apparatus paddle method at 37±0.5^{o}C, taking 900 ml of dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Sample of 10 ml were withdrawn after 2, 4, 6, 8, 10 min and analyzed spectrophotometrically at 235 nm. Formulation NEF6 prepared by direct sublimation of camphor from final tablets showed release 99.96% drug at the end of 10 min when compared to tablets prepared by sublimation of camphor from granules. The in vitro dissolution profile (Fig.1) indicated faster and maximum drug release from formulation NEF6.

CONCLUSION

Oral Fast dissolving tablets of Nifedipin is successfully prepared by using sublimation method , Will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability, and its popularity in the near future. From the study, it can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability.

Table 1: Composition of different batches of mouth dissolving tablets of Nifedipine

Ingredients (mg) / Tablet	Formulation Code *					
	NEF1	NEF2	NEF3	NEF4	NEF5	NEF6
Nifedpine	20	20	20	20	20	20
Camphor	--	--	8	8	16	16
Sodium starch glycolate	25	--	25	--	25	--
Crosscarmellose sodium	--	25	--	25	--	25
Sodium Saccharine	3	3	3	3	3	3
Rasberry flavor	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2	2	2	2	2	2
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Disintegration Time (in sec.)	90	85	75	71	60	58
% Friability	0.14	0.31	0.45	1.2	0.14	0.31

*All the quantities expressed in mg. All batches contained 10% Polyvinylpyrrolidone in ethyl alcohol as a binder. Camphor was sublimed from granules in Batches NEF1 to NEF5 and from tablets in Batch NEF6.

Table 2: Granule Properties of all the batches:

Batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (I_C)	Hausner's ratio (H_R)	Angle of repose (θ)
NEF1	0.3111 ± 0.02	0.4101 ± 0.02	21.00 ± 0.11	1.15 ± 0.01	19.10 ± 0.11
NEF2	0.3052 ± 0.02	0.3538 ± 0.04	16.31 ± 0.10	1.16 ± 0.02	19.16 ± 0.12
NEF3	0.3136 ± 0.05	0.3560 ± 0.01	14.76 ± 0.02	1.13 ± 0.03	18.16 ± 0.11
NEF4	0.3222 ± 0.01	0.4155 ± 0.02	16.13 ± 0.02	1.20 ± 0.01	17.17 ± 0.11
NEF5	0.3331 ± 0.03	0.4133 ± 0.03	17.10 ± 0.02	1.21 ± 0.01	17.03 ± 0.12
NEF6	0.3135 ± 0.02	0.3736 ± 0.02	18.05 ± 0.06	1.11 ± 0.04	17.19 ± 0.15

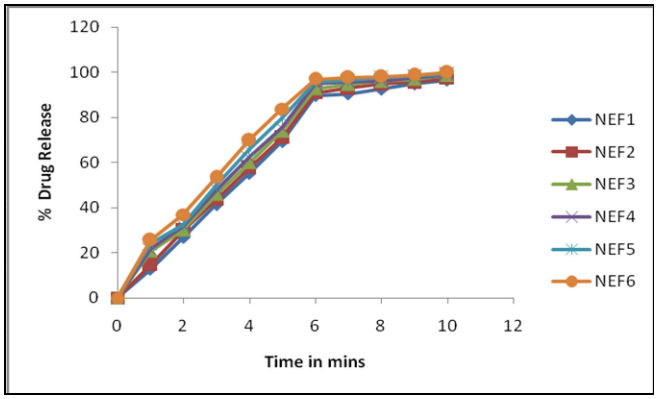
*All reading are average ± (SD)

Table 3: Evaluations of all batches of Nifedipine Tablets

Batch	Average weight (mg) ± SD	Hardness* (Kg/cm^2) ± SD	Wetting time* (sec.) ± SD	Friability (%)	Content uniformity*	DT* (sec.) ± SD	% drug release *
NEF1	151.4 ± 0.10	4.5 ± 0.41	80.6 ± 0.63	0.46	99.10	90.2 ± 1.1	96.46
NEF2	149.0 ± 0.45	4.5 ± 0.54	80.7 ± 1.61	0.53	100.00	85.6 ± 1.0	97.23
NEF3	150.2 ± 0.24	4.0± 0.50	65.1 ± 1.20	0.63	99.16	75.2 ± 1.2	98.65
NEF4	151.0 ± 0.51	3.7 ± 0.42	54.4 ± 0.82	0.74	99.40	71.0 ± 0.6	98.74
NEF5	149.5 ± 0.70	3.5 ± 0.53	40.2 ± 1.13	0.79	99.09	60.0 ± 0.7	99.18
NEF6	150.6 ± 0.22	3.4 ± 0.41	39.3 ± 1.80	0.72	99.95	58.0 ± 0.4	99.96

*Average of three determinate, ± Standard Deviation ± (SD)

Figure 1: Percentage release of NEF1- NEF 6 batches



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