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Studies in Dissolution Enhancement of Nifedipine

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ABSTRACT

Solid dispersions containing PVP and PEG, inclusion complex with beta cyclodextrin (Bcyd), and kneaded mixtures with hydrophilic adjuvants such as water-soluble gelatin (WSG) and microcrystalline cellulose (MCC) were prepared in order to enhance the dissolution rate of nifedipine (NF) in simulated gastric fluid. The dissolution rate of NF from solid dispersions increased in the order of PVP K-30 > PEG 6000 > PEG 4000 > pure drug. About a threefold increase in solubility of NF was observed from NF-Bcyd inclusion complex. The drug was released at a quicker rate from hard gelatin capsules containing physical mixture of inclusion complex of NF-Bcyd and WSG and also from tablets. WSG promoted wetting of NF by reducing surface tension. Nifedipine tablets coated with a thin layer of HPMC were found to be stable microbiologically and chemically. The mechanisms of drug release were ascertained using F-test statistics.

INTRODUCTION

Nifedipine is used in the treatment of angina pectoris and hypertension (1). It exhibits limited water solubility; as a result, it shows poor bioavailability. A number of attempts have been made to improve the dissolution of NF; for this purpose, solid dispersions in water-soluble carriers such as urea (2), polyvinylpyrrolidone (2,3), polyethylene glycol (2,4), sodium benzoate and sodium salicylate (5), inclusion complex with cyclodextrins (6), and kneaded mixtures of NF with water-soluble gelatin (WSG) and egg albumin (7) have been reported.

Nifedipine fast-release formulations are available in soft gelatin capsule dosage form. A part of the drug may be washed away from the absorption site, leading to poor bioavailability. Moreover, one of the major disadvantages of soft gelatin capsules is complexity of production.

The present work was undertaken to develop fast-acting solid dosage forms of NF such as hard gelatin capsules and HPMC coated tablets.

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EXPERIMENTAL

Materials

Beta-cyclodextrin (Wacker Chemie, Germany), cross-linked polyvinyl pyrrolidone (GAF Chemicals Corp., U.S.), WSG (Warchem, India), and Avicel pH 101 (FMC Corp., U.S.) were received as gift samples. PEG 4000 and PEG 6000 were obtained from S.D. Fine Chemicals, India. All other materials and solvents were of analytical grade. The experiments were carried out under conditions of protection from light since NF is photosensitive in nature.

Preparation of Solid Dispersions

PEG 4000 and PEG 6000

Solid dispersions of NF and PEG 4000/PEG 6000, in the ratios of 1:1, 1:5, 1:10, and 1:15 w/w, were prepared by the melting or fusion method of Chio and Ringelman (8).

PVP K-30

Solid dispersions of NF and PVP, in the ratios of 1:1, 1:5, 1:10, and 1:15, were prepared by solvent evaporation method (8).

The physical mixtures of NF and the carrier, in a 1:15 ratio, were prepared by mixing in a glass mortar and packing after passing through 100 mesh screen.

Phase Solubility Study

Solubility measurements were carried out as described by Higuchi and Lach (9). An excess amount of NF (25 mg) was added to aqueous solutions containing various concentrations of Bcyd and the dispersions were shaken on a rotary mechanical shaker for 1 day at a controlled temperature of 30 ± 0.5°C. After equilibrium was attained (2 days), the samples were passed through 0.45 μ filter. The concentration of NF was determined spectrophotometrically at 237 nm.

Preparation of Kneaded Mixtures/Complex

Nifedipine-Bcyd and NF-WSG kneaded mixtures were prepared in 1:1 molar ratio. The mixtures were kneaded with 1.5 times the amount of water for 1 hr. The kneaded mixtures were dried under vacuum at room temperature for 48 hr and screened through 100 mesh screen. Avicel pH 101 and WSG were physically mixed with the Bcyd complex at a concentration of 5% w/w. The composition of various batches is shown in Table 1.

Preparation of Physical Admixtures

The physical mixtures of NF with Bcyd and WSG were prepared in the ratio of 1:1 M by simply blending the powders (Table 1).

Preparation of Tablets of NF

The formulations of tablets, prepared by direct compression technique, are shown in Table 2. The tablets were evaluated for hardness, disintegration time, and stability.

The NF-WSG tablets were coated with three coats of aqueous HPMC (4% w/v) by spraying technique.

Surface Tension Study

Surface tension of the kneaded and physical mixtures of NF-Bcyd and NF-WSG as well as pure NF powder was determined by drop weight pipette method (10). Sample equivalent to 10 mg NF was dissolved in hydroalcoholic solution (5%, 1:1) and the surface tension of the solutions was measured at room temperature.

Microbial Growth Study in NF-WSG Tablets

Uncoated tablets of NF-WSG were tested for bacterial/mold load.

Total Bacterial Count

A total of 10 g of sample was aseptically mixed with 90 ml sterile normal saline. One milliliter of the disper-

Table 1

Formulations of Bcyd Complex and WSG Kneaded Mixture

Batch	Formulation
A	Bcyd + Drug (Complex)
B	Bcyd + Drug (P.M.)
C	Bcyd + Drug (Complex) + Avicel (5% w/w)
D	Bcyd + Drug (Complex) + WSG (5% w/w)
E	WSG + Drug (Kneaded Mixture)
F	WSG + Drug (P.M.)
M1	Market Product (S.G.C.)
M2	Market Product (S.G.C.)
M3	Market Product (Tablet)

P.M. = physical mixture.
S.G.C. = soft gelatin capsule.

Table 2

Formulation of Tablets of Bcyd and WSG Complex

Batch	T1 NF-Bcyd Complex + 5% w/w WSG (mg)	T2 NF-WSG (Uncoated) (mg)	T3 NF-WSG (Coated) (mg)
Complex	50	154	154
Lactose	100	100	100
Cross-povidone	7.82	12.7	12.7
PVP	5	7	7
Mg-stearate	1.5	2.54	2.54
Methyl paraben	0.41	0.69	0.69
Propyl paraben	0.041	0.069	0.069

sion was mixed with 15–20 ml of sterile soy bean casein digest agar medium (40°C) in two separate petri dishes. Negative control was also prepared. All plates were incubated at 35–37°C for 48–72 hr in an inverted position.

Total Mold/Yeast Count

For the determination of mold/yeast, saboraud dextrose agar was used and the petri dishes were incubated at 20–25°C for 5–7 days.

Limit

The following limits were selected for the bacterial test:

Total bacterial count: not more than 1000 per g/ml
Total mold/yeast count: not more than 100 per g/ml

Stability Studies

Tablets of NF-Bcyd + WSG and NF-WSG (uncoated and coated) were evaluated for hardness, drug content, disintegration time, and dissolution profile after 30 days at room temperature (RT), 37°C, 37°C/80% RH, and 45°C.

Dissolution Study

Solid dispersions and batches A–F were filled in hard gelatin capsule, while batches T1–T3 were formulated into tablets. Samples equivalent to 10 mg of NF were subjected to dissolution study as per stagnant volume method of USP XXII. The dissolution test was carried out in simulated gastric fluid (900 ml, pH 1.2, 37 ± 1°C, 50 rpm). The samples were filtered through 0.45 μ membrane filter. Two sets of each sample were used for the dissolution study and assayed at 237 nm using Hitachi double-beam UV/VIS spectrophotometer. A straight-line equation was generated from the absorbance values of pure drug applying the weighted linear regression model.

RESULTS AND DISCUSSION

Release of NF from Solid Dispersions

Improvement in NF dissolution was noticed at all the selected ratios of PEG 4000, PEG 6000, and PVP K-30, but the highest increase in dissolution was noticed at 1:15 ratio in all the carriers (Figure 1). The rate of the drug dissolution was faster from solid dispersions than that from physical mixtures. The dissolution rate of

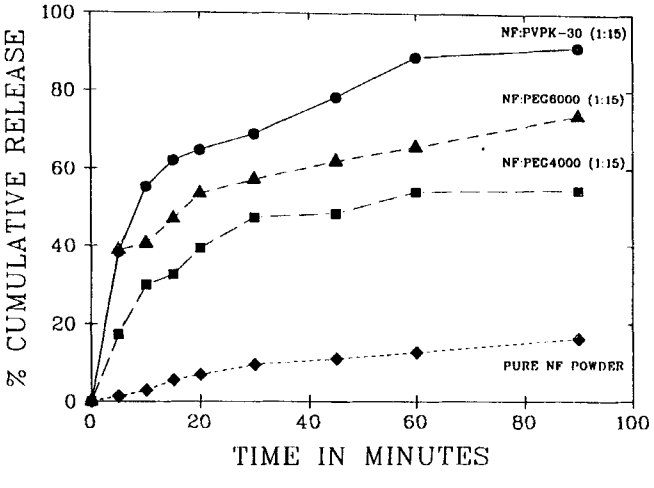

Figure 1. Drug release profiles from solid dispersions.

NF increased in order of PVP K-30 > PEG 6000 > PEG 4000 > pure drug, both in the case of physical mixtures as well as solid dispersions.

Phase Solubility Study

The solubility of NF increased linearly as a function of Bcyd concentration and the solubility curve was found to be of A_L type (9). Maximum increase in solubility was 2.75-fold. The apparent stability rate constant, calculated from the initial straight-line portion of the phase solubility curve, was calculated as 132.78 M^{-1} assuming 1:1 (guest:host) complex. The correlation coefficient was found to be 0.983.

Release from NF-Bcyd Complex and NF-WSG Kneaded Mixtures

The dissolution profile of batches A–D is shown in Figure 2. When Avicel pH 101 and WSG were physically admixed with NF-Bcyd complex, enhancement in dissolution was noted. The results of surface tension measurements indicated that the adjuvants improved wetting characteristics of NF.

Batches C and D released 80% NF in 19 and 10 min respectively. It may thus be concluded that these hard gelatin capsules satisfy the USP specifications of NF soft gelatin capsules. Fastest dissolution was noted in the case of hard gelatin capsules containing Bcyd complex and WSG (batch D). This may be due to the simultaneous effect of complex formation and improved wetting. The kneaded mixture containing NF and WSG exhibited a higher dissolution rate than the physical mixture, which may be due to greater wetting characteristics.

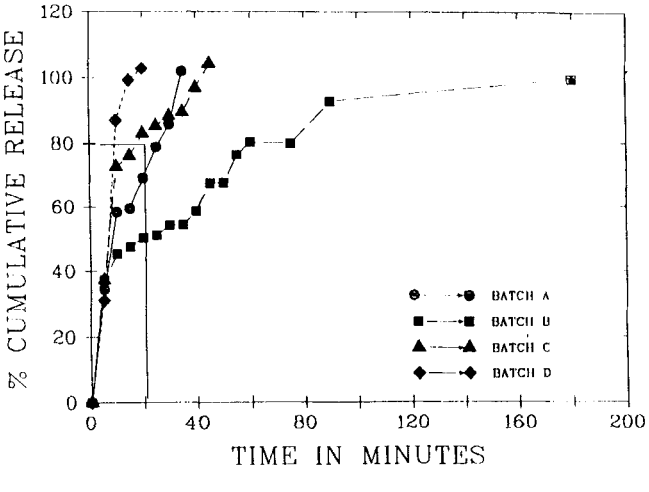

Figure 2. Drug release profiles from Bcyd formulations filled in hard gelatin capsules.

Percentage NF dissolved in 20 minutes from batches D and E was found to be higher than that from commercial soft gelatin capsules containing NF. Significant difference was noticed (F calc. = 12.99, F table = 4.46) between the commercial soft gelatin capsules (batches M1 and M2) and batch D, while difference was not significant between the market products and batch E (F calc. = 3.36).

Release of NF from NF-Bcyd Complex + WSG and NF-WSG Uncoated and Coated Tablets

The dissolution study revealed that the hard gelatin capsules prepared from batches D and E in fact satisfied the USP specification provided for soft gelatin capsules.

The dissolution study results of batches D and E prompted us to further investigate the release profile of NF from tablet dosage form. The formulations are shown in Table 2. Tablets of batches T1 and T2 had an average hardness of 4.2 and 4.6 kg/sq cm and showed an average disintegration time of 75 and 90 seconds respectively. The drug release from batches T1 and T2 was significantly higher as compared to that of the selected market product (80% release of NF from T1 and T2 was achieved within 1 hr).

The tablets containing WSG were coated with a thin layer of HPMC to serve as an environmental protectant (batch T3). Significant difference between the dissolution behavior of coated and uncoated tablets was not found since HPMC is soluble in aqueous medium.

Surface Tension Study

The surface tension of NF-WSG kneaded mixture was found to be lower than that of physical mixture and pure NF powder (53.4 as compared to 59.69 and 72.07 dynes/sq cm). However, surface activity was not significantly changed by Bcyd. The improved dissolution from kneaded mixture of NF and WSG may be attributed to improved wettability. On the other hand, improved dissolution of products containing Bcyd may be attributed to the formation of inclusion complex.

Results of Microbial Growth Study

The results of microbial growth study revealed a small increase in total bacterial count (100 and 130 organisms per gram of sample respectively for fresh and aged sample) and mold count (30 and 50 organisms per gram of sample respectively for fresh and aged sample). Therefore, it may be concluded that uncoated tablets containing WSG comply with the microbial limits specified in the experimental section. The microbial growth may be controlled by the addition of a suitable preservative system.

Stability Studies

Appreciable change in NF content, disintegration time, hardness, and dissolution rate at the specified conditions was not noticed in case of batch T1 containing Bcyd complex and WSG, whereas in the case of uncoated tablets containing WSG (batch T2), NF content decreased (100% to 96.63%) after 30 days of storage at 37°C/80% RH. Moreover, the disintegration time was prolonged (93 to 110 seconds) while the hardness of tablets decreased (4.6 to 4 kg/sq cm). The percentage drug release decreased considerably upon storage (86.7% to 65.7% in 1 hr). The HPMC coated tablets (batch T3, 37°C/80% RH) were found to be comparatively more stable.

The tablets containing both Bcyd complex and WSG (batch T1) and WSG kneaded mixture (batch T2) exhibited better shelf life at RT (Table 3). The film coated tablets showed a much higher shelf life of 532 days at RT.

Dissolution Efficiency (DE)

DE is defined as the area under the dissolution curve up to a certain time t expressed as a percentage of area of the rectangle described by 100% dissolution in the same time (11,12).

The calculated values of dissolution efficiency (PDE) were found to be 86% and 83% respectively for batches D and E, whereas the PDEs from batches M1 and M2 were found to be 72% and 78% respectively. It may be concluded that the formulated hard gelatin capsules exhibited superior PDE than the selected commercial products. Similarly PDEs for batches T1, T2, and T3 were found to be 55%, 56%, and 56% respectively, whereas the commercial tablet showed a PDE value of only 22.96%.

Release Kinetics of NF (13)

The goodness of fit was conducted using mathematical models such as zero order, first order, Higuchi, Hixon and Crowell, and Weibull.

The data of F-test for selected batches are shown in Table 4. In case of uncoated and coated tablets containing WSG, no statistical difference was observed between the selected models. Hence any of the three models can be selected for explaining the mechanism of drug release; however, the priority may be given to a model that exhibits the lowest F value (Higuchi model in this case).

For tablets containing Bcyd + WSG, minimum F value was found to be 8.9 with the Weibull model and hence it may be used for mathematical expression of the

Table 3

Ko Values and Shelf-Life (Days) of NF Tablets Containing Bcyd and WSG Complex/Kneaded Mixture

	NF-Bcyd Complex + 5% w/w WSG			NF-WSG (Uncoated)		
Condition	*r*	*Ko*	Shelf Life	*r*	*Ko*	Shelf Life
R.T.	0.92297	0.02333	429.18	0.97358	0.02584	386.9
37°C	0.89727	0.03263	306.46	0.97829	0.04799	208.37
37°C/80% RH	0.82104	0.04916	238.32	0.97666	0.10624	94.12
45°C	0.98724	0.05225	191.38	0.96085	0.10894	91.79
				NF-WSG (Coated)		
37°C/80% RH				0.99176	0.01878	532.48

R.T. = room temperature

Table 4

Model Fitting of Tablets (Batches T1, T2, and T3)

	Bcyd Complex + WSG 5% w/w		WSG			
			Uncoated		Coated	
Model	r^2	*F* Value	r^2	*F* Value	r^2	*F* Value
Higuchi	0.919338	22.3449	0.980341	8.506905	0.97142	10.81519
Hixon Crowell	0.760724	57.33878	0.946358	25.4431	0.931719	25.33145
First Order	0.719749	66.45008	0.930603	35.53	0.915031	32.53752
Zero Order	0.835169	45.66132	0.969198	13.3286	0.957097	16.2353
Weibull	0.964662	8.93340	0.957246	19.84662	0.93443	20.29171
F calc.						
F w-h	—		2.33		1.87	
F z-h	—		1.56		1.5	
F z-w	5.11		—		—	
F h-w	2.5		—		—	
F Table (6,6) at 1% & 5% = 8.47 and 4.28						

Higuchi = Sqrt of time vs. CPR, Hixon Crowell = time vs. (C.R. 100 - C.R. % D.R.), zero order = time vs. % CPR unreleased, first order = time vs. ln % drug unreleased, Weibull = ln time vs. ln % drug unreleased. CPR = cumulative % released, C.R. = cube root, and D.R. = drug release.
w = Weibull model, h = Higuchi model, z = zero-order model.

dissolution data. The zero-order model showed a significantly different *F* value and hence it was not selected.

The findings of this investigation strongly advocate further efforts in developing bilayer NF tablets and/or sublingual NF tablets.

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