

## Enhancement of *In vitro* Dissolution Characteristics of Nifedipine by Co-grinding Technique

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### ABSTRACT

In the present study an attempt has been made to increase the dissolution rate of poorly water soluble drug nifedipine, by employing novel cogrinding method using four carriers, namely, lactose, corn starch, pregelatinized starch and sodium starch glycollate. The coground mixtures were prepared with the above mentioned carriers in four different drug-carrier (w/w) ratios of 1:1, 1:2, 1:4 and 1:9. The prepared coground mixtures were evaluated for drug content uniformity studies by extracting the drug with methanol and measuring the absorbance at 236.8 nm, drug-carrier interactions using fourier transform infrared spectroscopy and dissolution characteristics. Formulation with a drug carrier ratio of 1:9 (nifedipine-sodium starch glycollate) showed promising results with a  $t_{90\%}$  value of 7 min compared to the pure drug ( $t_{90\%}>120$  minutes). Tablets prepared from this cogrinding mixture displayed double the dissolution efficiency compared to the commercial tablet formulation of nifedipine ( $DE_{30min}$  values of 70% and 35% respectively). Short-term stability studies (at 45°C for 3 weeks) of the above tablet formulation showed no significant changes in drug content and  $t_{90\%}$  value ( $p<0.05$ ). This study proves that cogrinding technique can be used for enhancing the *in vitro* dissolution characteristics of the poorly soluble drug nifedipine providing nearly first order release kinetics.

**Keywords:** Cogrinding, Nifedipine, *In vitro* dissolution enhancement.

### INTRODUCTION

Drugs cannot be administered in their pure form. They must be developed into convenient dosage forms for their clinical use and successful commercialization. In recent years much attention has been focused on the problems of drug bioavailability. The dissolution rate of a drug from its dosage form is now considered an important parameter in bioavailability. Dissolution is the rate limiting step in the absorption of drugs from the solid dosage forms, especially when the drug is poorly soluble. The enhancement of oral bioavailability of poorly water-soluble drug remains one of the most challenging aspects of dosage form development. The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action

at a rate and amount sufficient to elicit the desired pharmacologic response. The rate or rapidity with which a drug is absorbed is an important consideration when a rapid onset of action is desired as in the treatment of acute conditions such as asthma attack, pain, etc. In the present work, studies were carried out on the role of cogrinding in enhancing the *in vitro* dissolution characteristics of nifedipine using various excipients, with a view to improve its dissolution rate and develop fast release formulations fulfilling the official dissolution requirements; thus enhancing bioavailability of the drug. Various methods used to enhance the dissolution rate of poorly soluble drugs is by buffering of microenvironment- Buffered aspirin tablets<sup>1</sup>, use of salts of weak acids and weak bases- Sodium and potassium salts of penicillin<sup>2</sup>, use of solvates and hydrates-Ampicillin hydrate<sup>3</sup>, Prodrug approach-21-disodium phosphate ester of betamethasone<sup>4</sup>,

Complexation- Digoxin<sup>5</sup>, use of polymeric forms- Novobiocin<sup>6, 7</sup>, and methods which increase the surface area is by micronization- Griseofulvin, Digoxin<sup>8</sup>, use of surfactants- Phenacetin<sup>9</sup>, Solid dispersion- Griseofulvin with succinic acid<sup>10</sup> and Griseofulvin-PVP<sup>11</sup> and by solvent deposition-Diethyl stilbestrol<sup>12</sup>.

Nifedipine is a calcium channel blocker used as an antianginal and antihypertensive agent acting by blocking L-type calcium channels. It is yellow coloured, crystalline powder, practically insoluble in water, readily affected by exposure to light. Very light sensitive in solution. Hence protected from light. Because of the limited aqueous solubility it exhibits poor dissolution characteristics and its oral absorption is dissolution rate limited<sup>13</sup>. In the present study, an attempt was made to increase the *in vitro* dissolution rate of nifedipine by cogrinding technique using various carriers, namely, lactose, corn starch, pregelatinized starch and sodium starch glycollate. During the process of cogrinding the particle size of the drug is decreased, increasing the effective surface area, thereby enhancing the dissolution rate of the poorly soluble drug. Though the solid dispersion technique is an attractive alternative method, which has been widely used in the dissolution enhancement of poorly water-soluble drugs, many challenges have limited its application in the design of dosage form<sup>14</sup>. Some of the limitations are difficulty in pulverization<sup>15</sup> and sifting of the dispersions, which are usually soft and tacky<sup>16</sup>, poor flow and mixing properties resulted in poor compressibility, drug-carrier incompatibility and poor stability of the dosage forms. Many alternative methods were attempted to enhance the dissolution rate of poorly water-soluble drugs with an aim to the development of suitable formulation for oral use. Ordered mixtures, roll mixing, complexation<sup>17</sup>, cogrinding<sup>18</sup> and cogrinding in presence of small amount of water are some of the reported methods.

## EXPERIMENTAL

## MATERIALS

Nifedipine was received as a gift sample from Unichem India Laboratories, Mumbai. Sodium starch glycollate from Wockhard Research Centre, Aurangabad. Lactose of S.d Fine chem. Ltd., Corn starch of Loba Chemie Pvt.Ltd., Mumbai. Purified Talc from HiMedia Laboratories Ltd., Mumbai. Sodium Chloride from CDH Reagent, New Delhi. All the other chemicals and solvents used were of analytical reagent grade.

## Methods of preparation of cogrinding mixtures

All experiments were carried out under light-protected conditions to prevent the photodecomposition of nifedipine.

## Method of preparation of pregelatinized starch

An aqueous slurry (100 ml) of potato starch (40% w/v) containing 1% of tween 80 was heated at 65°C with continuous stirring until the starch gelatinizes and produces a viscous translucent mucilage. The viscous mucilage was then dehydrated by the addition of acetone while stirring and the solids separated were collected by filtration and further dried at 40°C for 2 hours. Then dried mass obtained was crushed, pulverized and sifted through mesh No. 80. The pregelatinized starch prepared was subjected to identification test and test for oxidizing substances according to USP XX/NF XV as given below.

## Test for oxidizing substances

To a 5 gm of the sample, 20 ml of a mixture of equal volumes of methanol and water was added, then 1 ml of 6N acetic acid was added with continuous stirring until a homogenous suspension was obtained. To this solution 0.5 ml of freshly prepared solution of potassium iodide was added and the mixture was allowed to stand for 5 minutes. No distinct blue, brown or purple color was observed, which complies with the official specification.

## Preparation of Cogrinding Mixtures

Coground mixtures were prepared by using four carriers, namely, lactose (L), corn starch (CS), pregelatinized starch (PGS) and sodium starch glycolate (SSG). All the

ingredients used were separately passed through sieve No. 80.

Cogrounding mixtures of nifedipine and the carrier were obtained by grinding a physical mixture of nifedipine and carrier in four different weight ratios i.e., 1:1, 1:2, 1:4 and 1:9 for 20 minutes in a ceramic mortar and sifted through 100 mesh. To ascertain the effect of method, carrier or both on the dissolution rate of nifedipine, nifedipine alone was ground for 20 minutes and the resultant product is represented as NP<sub>1</sub>. All the samples were stored in a desiccator at room temperature taking precautions to protect from light.

### Physical Mixture

The physical mixture of nifedipine and carrier were obtained by simple blending of the nifedipine and carrier in a 1:9 w/w ratio (drug:carrier) with a spatula. PM-L, PM-CS, PM-PGS, PM-SSG are used to represent the physical mixtures of nifedipine-lactose, nifedipine-corn starch, nifedipine-pregelatinized starch and nifedipine-sodium starch glycolate respectively.

### Evaluation of Coground mixture

A total of 16 different coground mixtures were prepared. The coground mixtures prepared were evaluated for:

1. Drug content uniformity
2. Drug-carrier interactions (by FT-IR)
3. Dissolution characteristics

### PREPARATION AND EVALUATION OF TABLETS OF COGROUND MIXTURE (SSG<sub>9</sub>)

Tablets prepared from the coground mixture of nifedipine (SSG<sub>9</sub>) were evaluated for drug release rates in comparison with commercial nifedipine tablets (5 mg). The tablets of SSG<sub>9</sub> formulations were prepared by wet granulation method using alcohol 90% as granulating agent. Lactose was added as a diluent to improve compressing properties.

### Method used for granulation

Weighed quantities of SSG<sub>9</sub> formulation and lactose were mixed in a glass mortar. Then alcohol was added slowly with

uniform mixing to get a cohesive mass. The wet mass was passed through sieve No. 16 to obtain granules. The granules were dried in a hot air oven at 60°C. The dried granules were passed through sieve No. 16 and then mixed with approximately 2% w/w of talc as lubricant and compressed into tablets of approximately 200 mg. All precautions are taken to protect from light and the work is done under subdued light.

### Dissolution Studies of Tablet Formulation

Dissolution of commercial nifedipine tablets, SSG<sub>9</sub> tablet formulations was studied using USP XXIII dissolution rate test apparatus (Electrolab Electronics) employing paddle stirrer. 900 ml of dissolution medium (1.2 pH buffer) was used. A tablet containing 5 mg of nifedipine was used for the test. The stirrer was adjusted to rotate at 50 rpm and a temperature of 37±0.5°C was maintained throughout the experiment. 5 ml of samples were withdrawn at various time intervals and analyzed for nifedipine by measuring the absorbance at 238.0 nm. The volume withdrawn at various intervals was immediately replaced with fresh quantity of dissolution medium. Each dissolution test was repeated for three times and the average was considered.

### STABILITY TESTING

#### Accelerated stability studies on formulation SSG<sub>9</sub>

Short-term stability studies on SSG<sub>9</sub> formulation were carried out by storing 15 tablets in amber colored screw capped bottle at an elevated temperature of 45±1°C (in hot air oven) over a period of three weeks (21 days) at an intervals one week, the tablets were visually examined for any physical changes and changes in drug content. At the end of the three weeks period, the formulation was also subjected to dissolution rate studies.

### RESULTS AND DISCUSSION

The technique of co-grinding was utilized in the present work to improve the *in vitro* dissolution rate of poorly water-soluble drug nifedipine. All the coground mixtures

prepared were found to be yellow in colour, fine and free flowing powders.

### Drug Content Uniformity Studies

The drug content estimated in various coground mixtures were found to be within  $\pm 2.5\%$  range of the expected percent drug content values, in majority of the cases. The low values of the standard deviation and coefficient of variation ( $<2\%$ ) for the estimated drug contents (except for CS<sub>2</sub> formulation) indicated uniform distribution of the drug within the coground mixtures prepared.

### In Vitro Drug Release Studies

*In vitro* drug release studies were carried out in USP XXIII tablet dissolution test apparatus by rotating paddle method at 50 rpm (apparatus II) using 900 ml of pH 1.2 buffer at  $37 \pm 0.5^\circ\text{C}$  as dissolution medium for 2 hours.

The physical mixture of the drug with various carriers viz., lactose, corn starch, pregelatinized starch and sodium starch glycollate in 1:9 drug-carrier ratio showed no significant improvement in the dissolution rate (approximately 29.5% in 120 minutes) when compared to the pure drug (29%). To ascertain the effect of method, carrier or both on the dissolution rate of nifedipine, the drug alone was ground for 20 minutes and the resultant product (NP<sub>1</sub>) showed dissolution rate of 28.09% in 120 minutes. However, the coground mixtures have showed marked enhancement in the dissolution rate of nifedipine (up to 99.48% in 20 minutes). The dissolution rate of nifedipine from coground mixtures is dependent on the drug-excipient ratio with each excipient studied. As the proportion of the excipient in the coground mixture was increased, the dissolution rate has also increased.

The efficiency of excipients in enhancing the dissolution rate of nifedipine can be evaluated on the basis of D<sub>10</sub>, DE<sub>30min</sub>, t<sub>50%</sub>, t<sub>70%</sub>, and t<sub>90%</sub> values. From this data it can be clearly seen that sodium starch glycollate gives very high rates of dissolution when compared to other carriers. This difference in dissolution rate is more obvious from t<sub>50%</sub>, t<sub>70%</sub> and DE<sub>30min</sub> values. The SSG<sub>9</sub> formulation with the drug-excipient ratio 1:9 has shown t<sub>50%</sub>

value of 3 min, t<sub>70%</sub> value of 4 min and DE<sub>30min</sub> value of 87.30%.

Similarly L<sub>9</sub>, CS<sub>9</sub>, PGS<sub>9</sub> formulations with the same drug-excipient ratio have shown t<sub>50%</sub> values of 4 min, 13 min, 4 min; t<sub>70%</sub> values of 7 min, 24 min, 5 min and DE<sub>30min</sub> values of 67.01%, 52.13%, 78.60% respectively.

The higher dissolution rate enhancement by sodium starch glycollate can be attributed to its aqueous solubility resulting in increased wettability of the micronized drug particles and increase in the effective surface area of the drug.

Out of the 16 cogrinding mixtures, the formulation SSG<sub>9</sub> prepared from sodium starch glycollate was found to give optimum dissolution characteristics (t<sub>50%</sub>, t<sub>70%</sub>, t<sub>90%</sub> and DE<sub>30min</sub> values of approximately 3 min, 4 min, 7 min and 87.30% respectively). Therefore, this formulation was selected for further studies i.e., for designing tablets. These tablets displayed much better dissolution parameters compared to the commercial tablet formulation of nifedipine. The tablets made from SSG<sub>9</sub> formulation have shown t<sub>50%</sub>, t<sub>70%</sub>, t<sub>90%</sub> and DE<sub>30 min</sub> values of 4 min, 8 min, 40 min and 70% respectively. The marketed product has shown t<sub>50%</sub> value of 20 min, t<sub>70%</sub> value of 30 min, t<sub>90%</sub> value of 43 minutes and has shown only 34.93% dissolution efficiency in 30 minutes. The better dissolution parameters of the tablets made from SSG<sub>9</sub> formulation could be attributed to excellent swellability and disintegrant properties of SSG.

### Mechanism of Drug Release

The *in vitro* drug release data obtained from all the formulations were tabulated and fitted into two models of data treatment as follows:

- Cumulative percent drug released versus time plots (zero-order).
- Log cumulative percent drug remained versus time plots (first-order).

When the data was plotted as log cumulative percent drug remaining versus time, the plots obtained were linear indicating first-order release kinetics.

### Drug-Carrier Interaction Study

Drug-excipient interactions were ruled out by IR spectroscopic studies on the promising formulation (SSG<sub>9</sub>) stored for 3 weeks at 45±1°C. The IR spectrum of the pure drug shows the characteristic peaks at 3330.82 cm<sup>-1</sup>, 1678.69 cm<sup>-1</sup> and 1529.0 cm<sup>-1</sup>, due to N-H stretching, carbonyl moiety of acetyl group and nitro group respectively. The IR spectrum of SSG<sub>9</sub> tablet formulation exhibited peaks at 3330 cm<sup>-1</sup>, 1681.91 cm<sup>-1</sup>, 1530.92 cm<sup>-1</sup> due to N-H stretching, carbonyl moiety of acetyl group and nitro group respectively. This confirms the undisturbed structure of drug in the formulation

### Short-term Stability Study

From the stability studies data, it is evident that the drug content and *in vitro* dissolution of SSG<sub>9</sub> tablet formulation (t<sub>90%</sub>) was not significantly affected by storage at 45°C for three weeks. The 't' values were found to be 2.02 and 2.20 respectively, which were much lower than the table value of 4.30 (p<0.05).

### CONCLUSION

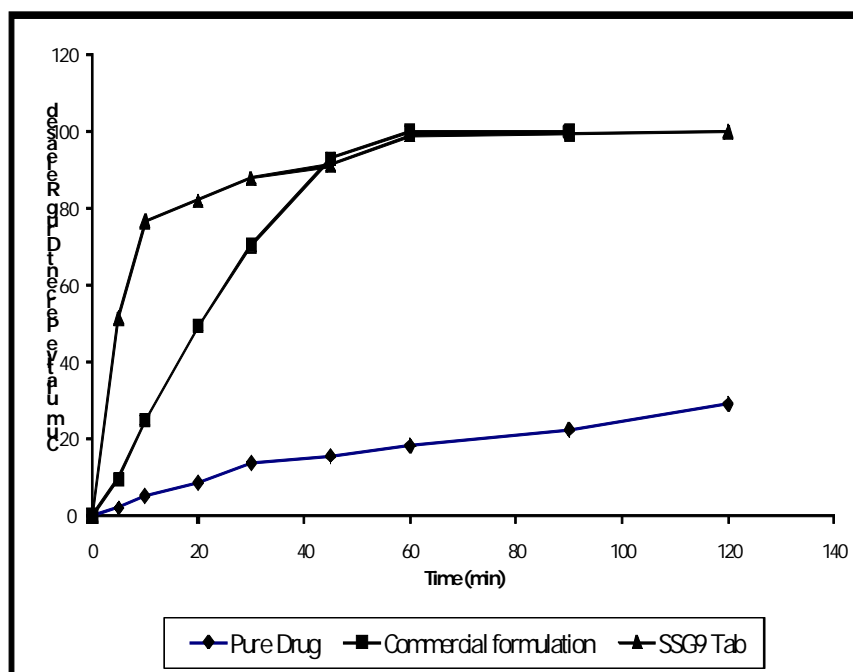
The coground mixtures prepared by cogrinding technique were found to be yellow in colour, fine and free flowing powders with uniform drug content. IR

spectroscopic studies indicated that there are no drug-excipient interactions. *In vitro* dissolution studies indicated that an increase in drug-excipient ratio showed an increase in the percent drug released. The efficiency of various excipients in enhancing the dissolution rate of nifedipine in increasing order according to DE<sub>30min</sub> values can be given as: CS<L<PGS<SSG. Formulation SSG<sub>9</sub> prepared with a drug-carrier ratio of 1:9 (nifedipine: sodium starch glycolate) showed promising results in enhancing the dissolution rate of the poorly water-soluble drug nifedipine (96% drug release in 10 minutes). Tablets prepared from the cogrinding mixture SSG<sub>9</sub> displayed double the dissolution efficiency compared to the commercial tablet formulation of nifedipine (DE<sub>30min</sub> value of 70 and 35% respectively), and 4 to 5 times faster dissolution rate (when t<sub>50%</sub> and t<sub>70%</sub> values are considered). Short-term stability studies on the tablets prepared from the promising coground mixture (SSG<sub>9</sub>) showed no significant changes in the drug content and t<sub>90%</sub> values (p<0.05). Cogrinding method can be used for enhancing the *in vitro* dissolution rate of poorly water soluble drug nifedipine providing nearly first order drug release.

**Dissolution parameters for Pure Drug, Coground Mixtures prepared by using various carriers, SSG<sub>9</sub> Tab and Commercial Formulation**

Formulation Code	Drug-excipient ratio	Mean Percent drug content±SD (CV)*	D <sub>10</sub> (%)	t <sub>50%</sub> (min)	t <sub>70%</sub> (min)	t <sub>90%</sub> (min)	DE <sub>30 min</sub> (%)
Pure Drug	-	-	5.24	>120	>120	>120	7.26
L <sub>1</sub>	1:1	44.793±0.2709 (0.605)	57.38	8.00	24.00	75.00	55.17
L <sub>2</sub>	1:2	32.711±0.598 (1.82)	60.03	4.00	16.00	40.00	63.17
L <sub>4</sub>	1:4	17.01±0.2951 (1.735)	74.95	4.00	8.00	37.00	65.97
L <sub>9</sub>	1:9	8.855±0.142 (1.604)	76.60	4.00	7.00	33.00	67.01
CS <sub>1</sub>	1:1	43.03±0.665 (1.545)	24.89	42.00	73.00	>120	29.16
CS <sub>2</sub>	1:2	30.79±0.99 (3.215)	32.50	25.00	46.00	118.00	34.33
CS <sub>4</sub>	1:4	19.96±0.297 (1.488)	37.49	23.00	29.00	90.00	39.96
CS <sub>9</sub>	1:9	10.06±0.184 (1.829)	43.45	13.00	24.00	45.00	52.13
PGS <sub>1</sub>	1:1	44.552±0.794 (1.782)	38.82	24.00	60.00	>120	39.23
PGS <sub>2</sub>	1:2	31.822±0.479 (1.505)	45.12	16.00	35.00	111.00	46.80
PGS <sub>4</sub>	1:4	19.884±0.080 (0.402)	81.19	4.00	5.00	30.00	78.03
PGS <sub>9</sub>	1:9	9.832±0.1338 (1.361)	91.52	4.00	5.00	10.00	78.60
SSG <sub>1</sub>	1:1	44.421±0.636 (1.432)	39.81	15.00	39.00	90.00	46.96
SSG <sub>2</sub>	1:2	31.023±0.334 (1.077)	52.41	9.00	19.00	55.00	47.80
SSG <sub>4</sub>	1:4	19.764±0.187 (0.946)	81.25	3.00	5.00	17.00	78.83
SSG <sub>9</sub>	1:9	9.853±0.0689 (0.699)	96.16	3.00	4.00	7.00	87.30
SSG <sub>9</sub> Tab	-	-	76.61	4.00	8.00	40.00	70.00
CF	-	-	24.89	20.00	30.00	43.00	34.93

\* Average of three determinations. SSG = sodium starch glycolate, PGS = pregelatinized starch  
SD = Standard deviation, CV = Coefficient of variation.



**Cumulative percent drug release versus time plot (zero order) of pure drug, commercial formulation and SSG<sub>9</sub> Tab**

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