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Full Length Research Paper

Formulation of solid dispersion and surface solid dispersion of nifedipine: A comparative study

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In this study, an attempt was taken to enhance the solubility and dissolution characteristics of nifedipine, a poorly water soluble calcium channel blocking agent, by preparing solid dispersions (SD) with water soluble carriers; Poloxamer 407, HPMC 5 cPs, polyethylene glycol (PEG) 4000 and 6000 and surface solid dispersions (SSD) with insoluble carriers; sodium starch glycolate (SSG) and croscarmellose sodium (CCS). *In vitro* dissolution study showed that all the preparations were effective to improve the dissolution of nifedipine to several folds when compared with the drug and physical mixtures (PMs). Drug loading in SDs and SSDs was found uniform and they produced satisfactory results on drug content analysis (95 to 102%), compatibility and thermal analysis. PEG 6000, Poloxamer 407 and SSG were found to be the most effective carriers to enhance the dissolution behavior of nifedipine. SDs with water soluble carriers were found more effective in improving solubility of nifedipine than SSDs and PMs. Tablets were prepared using SDs and SSDs, and compared to marketed preparations and to a simple compressed tablet of nifedipine. Tablets prepared from SDs with PEG 6000 and Poloxamer 407 showed better release profile than all the marketed products.

Key words: Bioavailability, hydrophilic carrier, hydrophobic agents, interactions, solid matrix and compatibility.

INTRODUCTION

Solubility and dissolution at the body fluids are the prerequisites for bioavailability of orally administered drugs. Therefore, dissolution is the rate limiting step for the drugs having low aqueous solubility. Solid dispersion (SD) is one of the remarkable techniques for enhancing solubility and improving dissolution characteristics of such drugs. The term SD refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug (Datta et al., 2011). The matrix can be either crystalline or amorphous or blended mixture. The drug can be dispersed molecularly in amorphous clusters or in crystalline particles and thus improves solubility by enhancing wettability.

The surface solid dispersion (SSD) technique has been introduced with newer advantages in improvement of dissolution characteristics of poorly soluble drugs. The technique has successfully overcome some common limitations of SD like tackiness and difficulty in handling. The carriers used in SSD are generally water insoluble, porous materials and hydrophilic in nature. In this technique, drug particles are deposited on the surface of the inert carrier leading to reduction in particle size of the drug and thereby enhanced dissolution. The release of drug from the carrier material depends on hydrophilic nature, particle size, porosity and surface area of the carrier (Kiran et al., 2009). Larger the surface area available for adsorption of the drug, better the release rate (Yang et al., 1979). SSD can be prepared by using different carriers such as crospovidone, croscarmellose

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sodium (CCS), sodium starch glycolate (SSG), kyron T-314, silicified microcrystalline cellulose, etc (Lalitha and Lakshmi, 2011).

Nifedipine is dimethyl 1,4-dihydro-2,6-dimethyl-4-(o-nitrophenyl)-3,5-pyridine dicarboxylate, a dihydro pyridine calcium channel blocking agent. It is photosensitive and poorly water soluble drug with low bioavailability when orally administered in crystalline form (Sugimoto et al., 1982). Nifedipine is widely used in treatment of angina pectoris and hypertension. Diseases like angina, asthma, epilepsy, etc., require immediate drug response to manage the disease condition (Jagdale et al., 2012). But its poor aqueous solubility often resulted in low and irregular bioavailability. Preparation of SD and SSD of such drug is thus highly rational to improve the solubility characteristics. With a goal of enhancing solubility and dissolution characteristics of nifedipine, an attempt was taken to prepare SD and SSD of nifedipine by using water soluble carriers; Poloxamer 407, HPMC 5 cPs, polyethylene glycol (PEG) 4000 and 6000 and water insoluble carriers; SSG and CCS. The efficacy of the SD and SSD to improve the solubility was evaluated and compared with physical mixtures (PMs) and marketed products.

MATERIALS AND METHODS

Nifedipine was a gift sample from The ACME Laboratories Ltd, Bangladesh. Poloxamer 407 and lactose monohydrate were obtained from Incepta Pharmaceuticals Ltd. All other ingredients were of analytical grade and collected from local market.

Preparation of SD and SSD

SD and SSD were prepared by co-precipitation technique (Lalitha and Lakshmi, 2011; Kalpana et al., 2010). The SDs were prepared at the weight ratio of 1:1, 1:5 and 1:10 (drug:carrier) and coded according to Table 2 using Poloxamer 407 (Polo), HPMC 5 cPs (H5), PEG 4000 (P4) and 6000 (P6) as carriers. The SSDs were prepared at the same weight ratio using water insoluble disintegrants SSG and CCS as carriers. Accurately weighed amount of nifedipine and carrier were taken in a glass beaker and dissolved in minimum volume of acetone to obtain a clear solution. The solution was stirred robustly for uniform mixing and evaporated at room temperature by using a hand blower. The viscous residues thus obtained were allowed to solidify and were kept at room temperature for 72 h. The solidified mixture was then powdered and passed through ‘60’ mesh screen and stored in glass vials surrounded by aluminum foil in a desiccator.

Preparation of PM

PMs in the ratio of 1:1 were prepared by mixing the appropriate amounts of nifedipine and carrier for 10 min in a mortar. The mixtures were coded as per Table 2. The mixtures were sieved through a ‘60’ mesh screen and stored in glass vials surrounded by aluminum foil in a desiccator.

Estimation of nifedipine

To determine the mixing uniformity of drug in the SDs, SSDs and PMs, nifedipine and equivalent samples were dissolved in methanol separately as per method described by Datta et al. (2011). The standard and sample solutions were suitably diluted by methanol and absorbance was measured by using a UV Spectrophotometer (UV mini 1240, Shimadzu) at 238 nm.

Fourier transform infrared (FT-IR) spectroscopy

FT-IR spectra were taken in IR-Prestige 21, Shimadzu, Japan by scanning the sample in potassium bromide (KBr) discs. Before taking the spectrum of the sample, a blank spectrum of air background was taken. SD and SSD of 1:5 ratios were scanned over the frequency range 2000 to 400 $cm^{-1.}$ The IR spectra of SD were compared with standard IR spectra of pure nifedipine and respective carrier.

Differential scanning calorimetric (DSC) studies

DSC analysis of the drug, carrier (PEG 6000) and their SD of 1:1 ratio were carried out in Bangladesh Council of Scientific and Industrial Research (BCSIR). Samples were heated under nitrogen atmosphere in an aluminum pan at a rate of 10°C min^{-1} over the temperature range of 30 and 300°C. Thermal data analysis of DSC thermogram was conducted by using STAR software.

In vitro dissolution studies

In vitro dissolution studies were carried out in USP XXI six station dissolution test apparatus using 900 ml of dissolution medium. Simulated gastric fluid without pepsin was selected as the dissolution medium as per recommendation of USP-33 for nifedipine capsule. The temperature of the medium was maintained at 37±0.5°C throughout the experiment. The samples containing 10 mg equivalent nifedipine were placed in the dissolution medium. Paddle was used at a stirring rate of 50 rpm. Samples of 5 ml were taken at 10, 15, 20, 30, 45 and 60 min interval. On each interval, equal volumes of fresh dissolution medium were replaced immediately after taking samples to maintain a constant volume for drug dissolution. The concentration of nifedipine was determined at 238 nm (Lalitha and Lakshmi, 2011), using Shimadzu UV-1201 UV/Visible spectrophotometer (Shimadzu, Japan) against dissolution medium as blank. Percentage of drug release was calculated using the equation obtained from the standard curve prepared in the medium.

Characterization of dissolution data

To characterize the drug release rate in different experimental conditions mean dissolution time (MDT), $T_{50\%}$, $T_{80\%}$ and dissolution efficiency (DE) were calculated from dissolution data according to the following equations (Mockel and Lippold, 1993; Giri et al., 2010):

$T_{50\%} = (0.5/k)^{1/n}$
$T_{80\%} = (0.8/k)^{1/n}$
$MDT = (n/n+1).\ K^{-1/n}$

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \times (t_2 - t_1)} \times 100$$

where *k* is the antilog of intercept and *n* is a release exponent of Korsmeyer's plot and *y* is the percentage of dissolved drug. Mean dissolution time (MDT) value is used to characterize the drug release rate from the matrix. A higher value of MDT indicates a lower drug releasing ability of the SD and vice-versa. Besides, The DE is the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Larger the value of DE, higher is the dissolution rate.

Preparation of tablets

Tablets were prepared by direct compression technique with the SDs and SSDs of 1:5 ratios. The amount of SDs and SSDs were calculated according to the drug content of the preparations (Table 2) and mixed with other excipients. The ingredients were accurately weighed for 30 tablets according to the formulations summarized in Table 1. Particular attention was given to ensure uniform mixing and phase homogenization. Appropriate amount of the mixture was weighed in an electronic balance (AY-200, Shimadzu, Japan) for the preparation of tablet and compressed in a laboratory hydraulic press. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in opaque airtight containers in a desiccator until further study.

Evaluation of tablets

Tablets from each batch were evaluated for thickness, diameter, hardness, average weight and disintegration time. Randomly collected 10 tablets of each batch were evaluated for thickness and diameter by digital slide calipers, average weight by an analytical weighing balance (AY-200, Shimadzu, Japan) and then, the tablets undergo hardness test by Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland). Six tablets were tested for disintegration time by Electrolab disintegration tester ED-2L at 37±0.5°C. Dissolution test was also performed for each formulation using the earlier stated method.

Comparison with marketed products

Nifedipine tablets of two reputed brands were purchased from local drug store. Their physical characteristics were evaluated. *In vitro* drug release of marketed tablets was also determined by the same method described for SD, SSD and PM and the release behavior was compared against prepared tablets.

RESULTS

Physical characterization and drug content of prepared SD and SDS

Nifedipine is a yellow powder having irregular flow property and poor aqueous solubility. Poloxamer 407, HPMC 5 cPs, PEG 4000, SSG and CCS were used as carriers to enhance the dissolution property. All the obtained SDs and SSDs prepared by co-precipitation technique were found granular, non sticky, free flowing and easily compressible. Binary PMs also showed good flow property. All these preparations revealed good uniformity and drug content was from 95 to 102% of the theoretical claim. The results are summarized in Table 2.

Compatibility by FT-IR

The FT-IR spectra of nifedipine showed a C=O stretching at 1683.55 cm^{-1} and C-O ester stretching at 1227.47 and 1120.44 cm^{-1}. Sharp peak of NO_2 stretching was seen at 1529.27 cm^{-1} (Figure 1). The surface SD prepared by SSG and CCS showed characteristic C=O stretching and C-O ester stretching at similar positions. The SD containing HPMC 5 cPs and PEG showed characteristic peaks at similar positions that indicate the compatibility of carriers with nifedipine. SD of nifedipine with poloxamer 407 showed stretching of C=O at 1620 cm^{-1}.

Thermal analysis by DSC

DSC thermogram of drug showed peak of endotherms at 175.01°C corresponding to melting of drug, nifedipine (Figure 2). Onset of melting was on the temperature of 171.43°C and endset was at 179.62°C. The thermogram of carrier PEG 6000 showed that onset of melting started at temperature of 59.22°C and endset was at temperature of 71.51°C (Figure 3). But no peak corresponding to the melting point of the drug was observed in the thermograms of SD (Nif: P6 1:1 SD) indicating amorphous form of the drug (Figure 4).

Effect of carrier on release behavior

All the SDs and SSDs showed significant increase in the *in vitro* drug release. After 1 h of dissolution, pure drug powder released only 8.37% nifedipine, whereas 61.11, 81.44, 98.76, 40.00, 30.71 and 36.56% drug were released from Nif:P6 1:1 SD, Nif:P4 1:1 SD, Nif:Polo 1:1 SD, Nif:H5 1:1 SD, Nif:CCS 1:1 SSD, Nif:SSG 1:1 SSD, respectively (Figure 5). Dissolution rate has also been improved markedly. After only 10 min of dissolution, those preparations released 33.92, 59.88, 36.95, 33.23, 8.13 and 14.02% nifedipine, respectively while the drug was dissolved only 2.42% in same time interval.

Further improvement of the dissolution rate and extent was observed from SD containing higher amount of carriers. 81.44% drug was release from Nif:P4 1:1 SD, whereas 90.18 and 94.44% drug was released from the SD where the carrier was incorporated at 1:5 and 1:10 ratio (Figure 6 and 7).

Table 1. Composition of different formulations of nifedipine tablets containing SD and SSD (mg).

Ingredient	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Nifedipine	10.0	-	-	-	-	-	-
Nif:Polo 1:5 SD	-	63.1	-	-	-	-	-
Nif:P4 1:5 SD	-	-	62.6	-	-	-	-
Nif:P6 1:5 SD	-	-	-	61.7	-	-	-
Nif:H5 1:5 SD	-	-	-	-	61.7	-	-
Nif:CCS 1:5 SSD	-	-	-	-	-	61.2	-
Nif:SSG 1:5 SSD	-	-	-	-	-	-	61.7
Lactose monohydrate	457.0	403.9	404.4	405.3	405.3	405.8	405.3
Sodium starch glycolate	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Magnesium stearate	18.0	18.0	18.0	18.0	18.0	18.0	18.0
Total weight	500.0	500.0	500.0	500.0	500.0	500.0	500.0

Table 2. Drug content of solid dispersion, surface solid dispersion and physical mixtures of nifedipine.

S/N	D:C Ratio	Carrier	Code	Theoretical drug content (%)	Calculated drug content (%) (n=3)
1	1:1	Poloxamer 407 (Polo)	Nif:Polo 1:1 SD	50.00	48.57
2	1:5		Nif:Polo 1:5 SD	16.67	15.84
3	1:10		Nif:Polo 1:10 SD	9.09	9.12
4	1:1		Nif:Polo 1:1 PM	50.00	49.24
5	1:1	PEG 4000 (P4)	Nif:P4 1:1 SD	50.00	48.54
6	1:5		Nif:P4 1:5 SD	16.67	15.98
7	1:10		Nif:P4 1:10 SD	9.09	8.98
8	1:1		Nif:P4 1:1 PM	50.00	50.11
9	1:1	PEG 6000 (P6)	Nif:P6 1:1 SD	50.00	48.62
10	1:5		Nif:P6 1:5 SD	16.67	16.21
11	1:10		Nif:P6 1:10 SD	9.09	9.24
12	1:1		Nif:P6 1:1 PM	50.00	50.32
13	1:1	HPMC 5 cPs (H5)	Nif:H5 1:1 SD	50.00	49.86
14	1:5		Nif:H5 1:5 SD	16.67	16.21
15	1:10		Nif:H5 1:10 SD	9.09	9.25
16	1:1		Nif:H5 1:1 PM	50.00	50.24
17	1:1	Sodium Starch Glycolate (SSG)	Nif:SSG 1:1 SSD	50.00	48.96
18	1:5		Nif:SSG 1:5 SSD	16.67	16.20
19	1:10		Nif:SSG 1:10 SSD	9.09	9.18
20	1:1		Nif:SSG 1:1 PM	50.00	49.71
21	1:1	Croscarmellose Sodium (CCS)	Nif:CCS 1:1 SSD	50.00	49.31
22	1:5		Nif:CCS 1:5 SSD	16.67	16.34
23	1:10		Nif:CCS 1:10 SSD	9.09	8.89
24	1:1		Nif:CCS 1:1 PM	50.00	50.09

D:C ratio, Drug:Carrier ratio; SD: Solid dispersion; SSD: Surface solid dispersion; PM: Physical mixture.

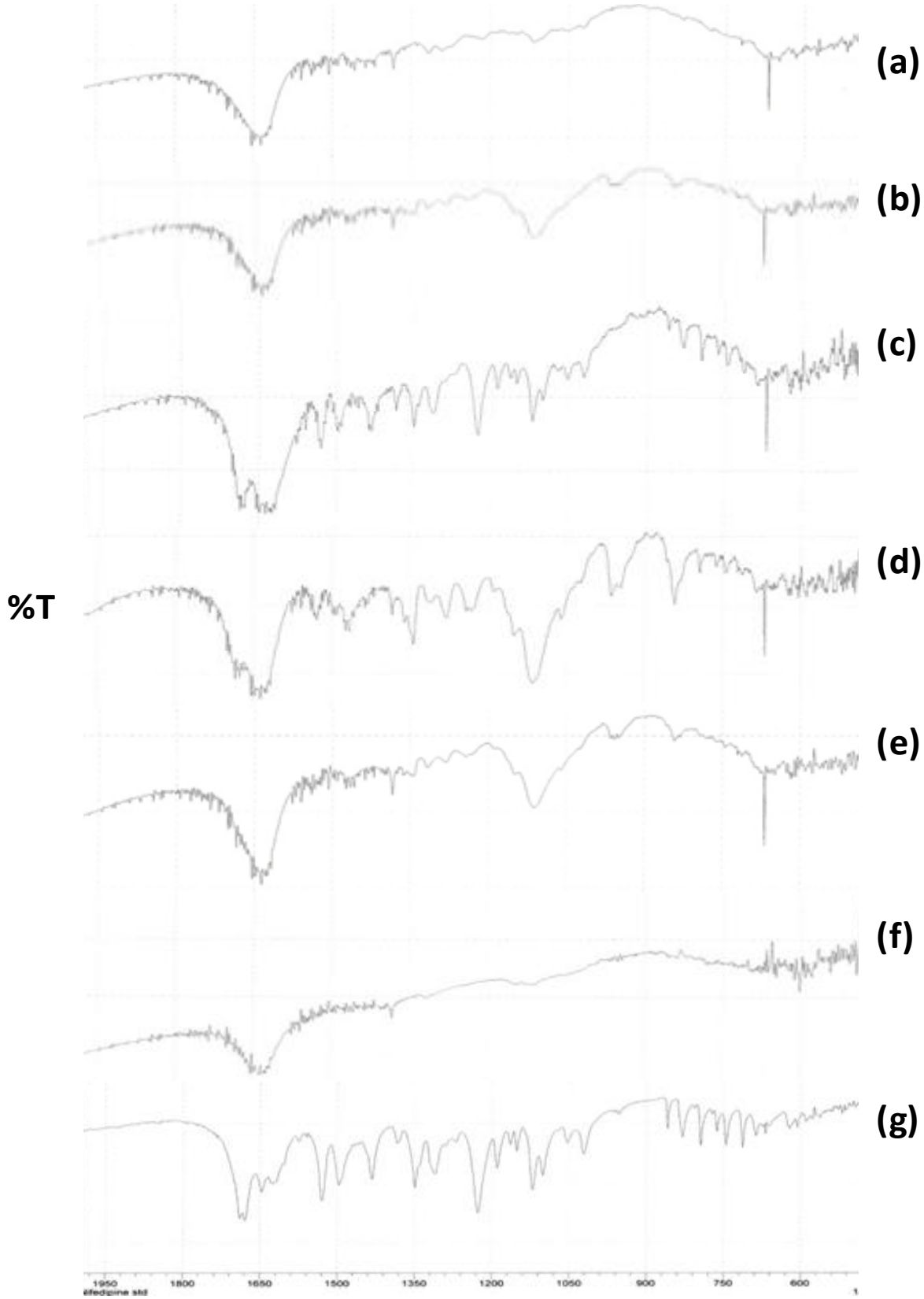

Figure 1. FT-IR spectra of (a) Nif:CCS 1:5 SSD, (b) Nif:SSG 1:5 SSD, (c) Nif:H5 1:5 SD, (d) Nif:P4 1:5 SD, (e) Nif:P6 1:5 SD, (f) Nif:Polo 1:5 SD and (g) Nifedipine.

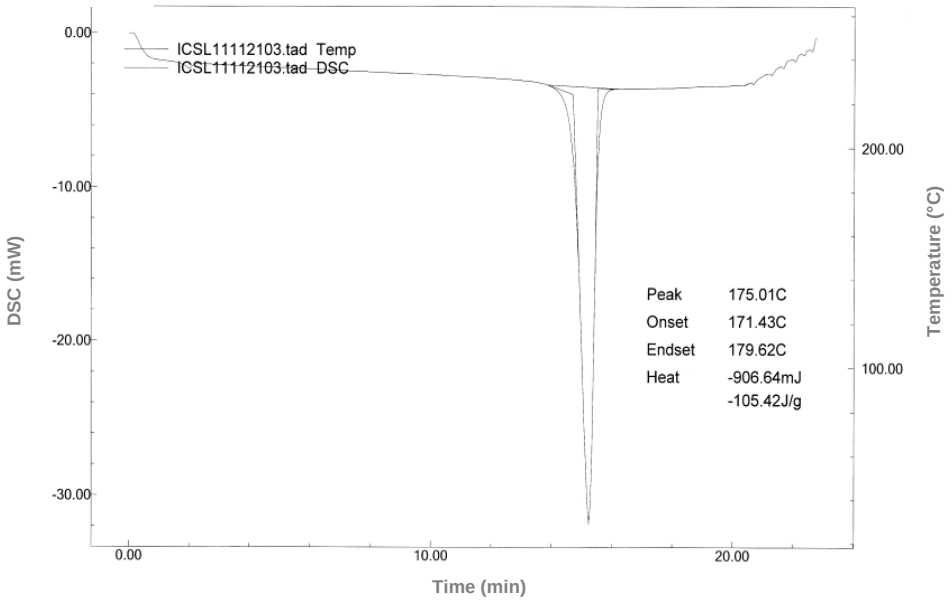

Figure 2. DSC curve of Nifedipine.

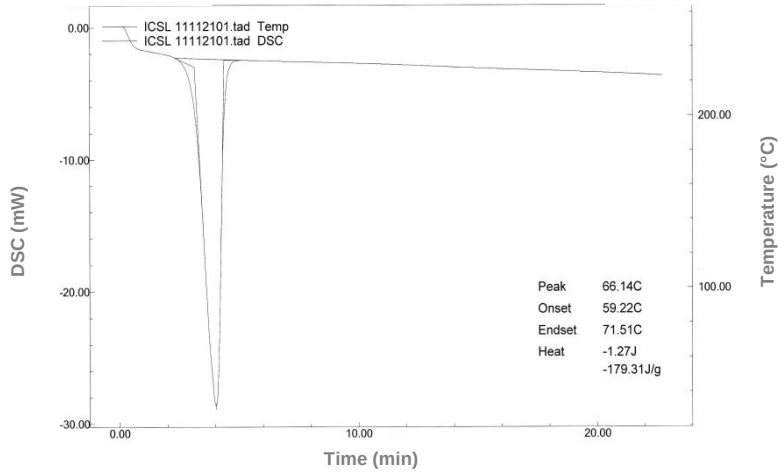

Figure 3. DSC curve of PEG 6000.

Effectiveness of SD and SSD in contrast to the PM

According to the dissolution profiles plotted (Figure 8 and 9), all the prepared PMs, SD and SSD were found capable of enhancing dissolution behavior of nifedipine when compared with the pure drug. PMs showed 27.67 to 93.59% drug release in 60 min when the pure drug showed only 8.37% release at same timeline. This is due to the surface adsorption of the drug on the carriers and thereby increased wetting of the drug in PMs as compared to the pure drug which floats on the surface in the form of aggregates leading to reduced effective surface area (Lalitha and Lakshmi, 2011).

Physical characterization of tablets

Tablets of nifedipine were prepared by direct compression method. The tablets were evaluated for hardness, thickness, diameter, average weight and disintegration time for all the formulations (F-1 to F-7). No significant difference was observed in the weight of individual tablets from the average weight. The hardness of tablets of all formulations was found uniform (5.0 to 6.5 kg/cm^2). Thickness of individual tablet was in acceptable limit. Disintegration time was found less than 6 min for all the formulations. Marketed products also undergo same physical tests and the results are summarized in Table 3.

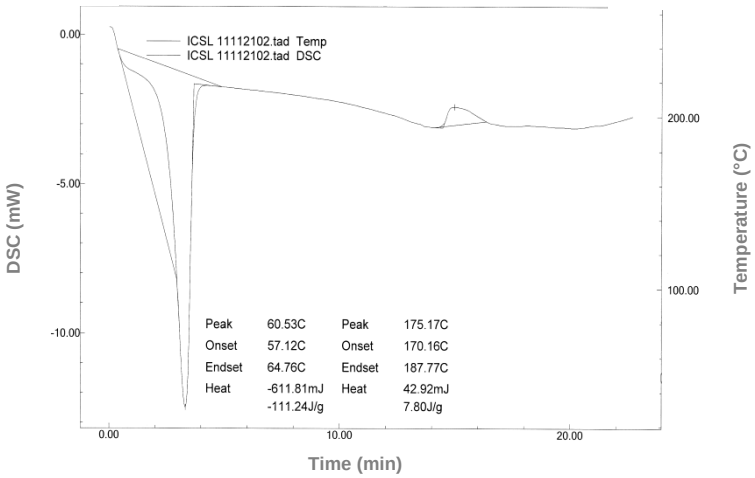

Figure 4. DSC curve of solid dispersion of nifedipine and PEG 6000 at 1:1 ratio.

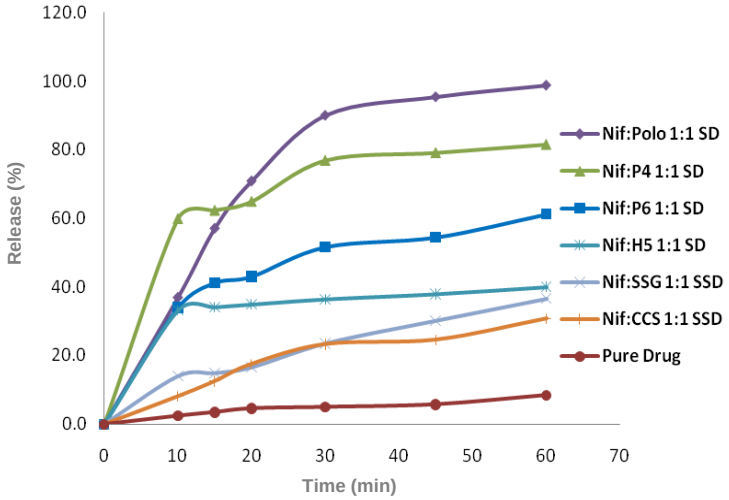

Figure 5. Percent release data obtained from SDs and SSDs of 1:1 ratio.

In vitro drug release study from tablets

Drug dissolution data revealed that the tablets containing SDs and SSDs were capable of releasing the drug in greater extent than tablet containing pure drug (Figure 10). After an hour of dissolution, 94.68, 86.14, 99.41 and 51.44% drug were released from formulation F-2, F-3, F-4 and F-5 containing Nif:Polo 1:5 SD, Nif:P4 1:5 SD, Nif:P6 1:5 SD and Nif:H5 1:5 SD, respectively. Whereas the compacted mass of formulation F-1 containing pure drug released only 12.21% nifedipine at 1 h of dissolution. Thus, each of the carrier used in the SD proved their efficacy to improve the dissolution characteristics even from tablet dosage form.

Similarly, the SSDs was also found capable of releasing the drug at a greater extent. Formulation F-6 and F-7 showed 44.37 and 49.52% drug release after an hour of dissolution, that is, 3.63 and 4.06 times higher than the drug release of formulation F-1.

SDs and SSDs in contrast to brand products

According to the dissolution profiles plotted in Figure 10, brand product A showed good release profile (94.21% drug was dissolved in 60 min) than the brand B (56.00% drug released in 60 min). On the other hand, tablet prepared by SDs and SSDs showed better drug release profiles even from a much bigger matrix tablet without using any wetting agents or surface active agents.

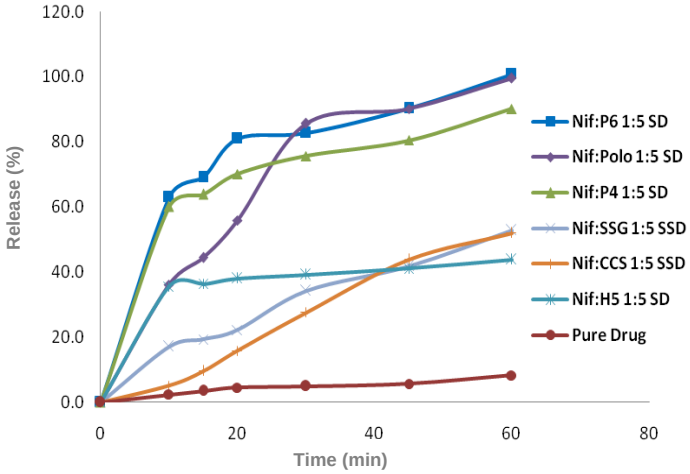

Figure 6. Percent release data obtained from SDs and SSDs of 1:5 ratio.

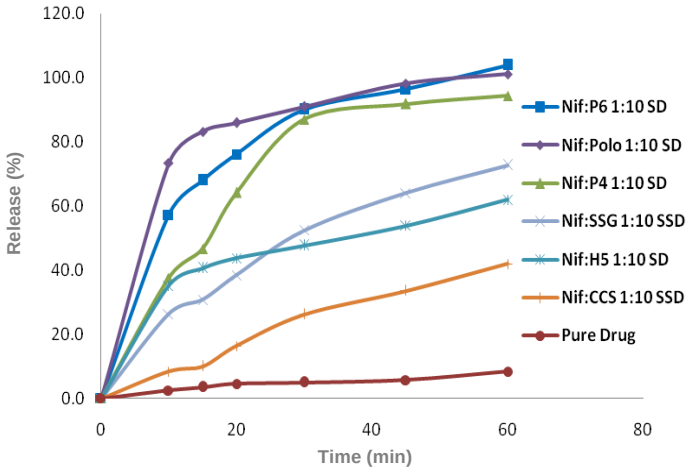

Figure 7. Percent release data obtained from SDs and SSDs of 1:10 ratio.

Particularly, tablets made of Nif:Polo 1:5 SD (formulation F-2) and Nif:P6 1:5 SD (formulation F-4) showed 94.68 and 99.41% drug release within 60 min of dissolution. In addition, the tablets made of SD showed higher dissolution rate when compared with the marketed products. 47.16, 55.47, 64.21 and 34.29% drug was release at 10 min of dissolution from formulation F-2, F-3, F-4 and F-5, respectively where the brand products released only 6.75 and 27.47% drug at the same time.

The MDT value, $T_{50\%}$, $T_{80\%}$ and %DE also indicate the same behavior (Table 4). Formulation F-2, F-3 and F-4 have very small values of MDT, $T_{50\%}$ and $T_{80\%}$ when compared with formulation F-1 and brand products, which indicated the efficiency of solid dispersion system to improve the dissolution behavior. Similarly the %DE of 10 min of these formulations were significantly higher than the formulation F-1 and brand products that denoted the higher drug release rate of the formulations. Rest of the formulations showed acceptable results depending on the properties of the carrier. However, tablets of SSDs showed a lower release profile than the two brands. Statistical analysis of %DE was performed to ascertain the effect of different polymers over pure drug and marketed product using one-way analysis of variance (ANOVA, significance level $p < 0.05$) while the results were confirmed by Bonferroni's multiple comparison as a post-hoc test. The results of ANOVA indicate %DE was significantly different at 0.05 level of significance.

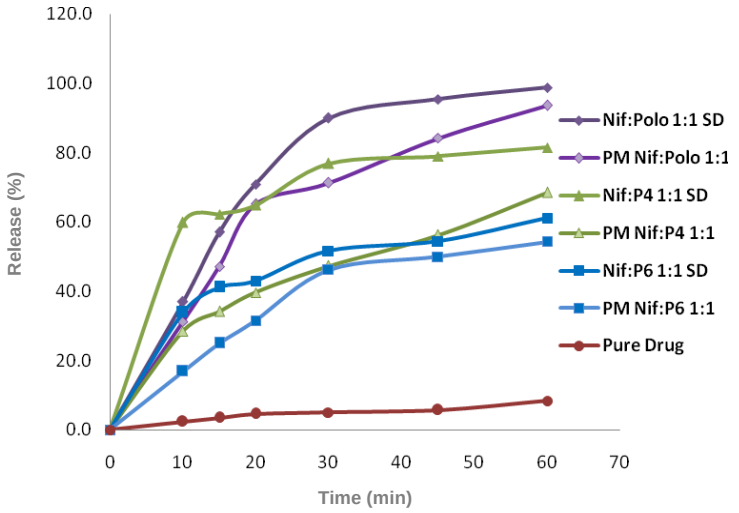

Figure 8. Comparison of release profiles of SDs and PMs of Poloxamer, PEG 4000 and 6000.

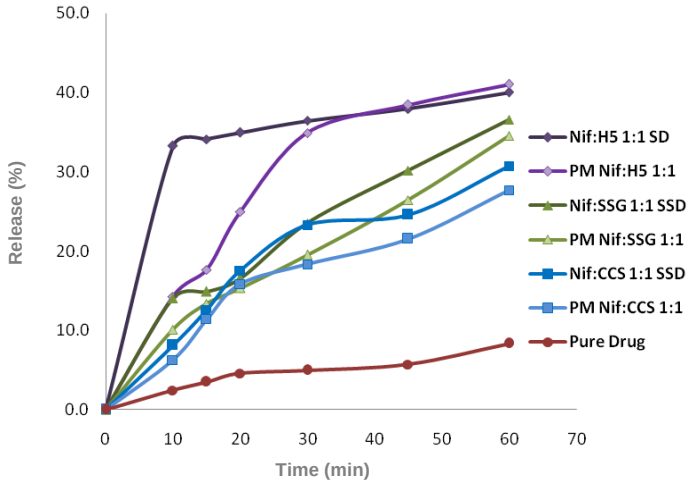

Figure 9. Comparison of release profiles of SDs, SSDs and PMs of HPMC 5 cPs, CCS and SSG.

Study of release kinetics

Obtained *in vitro* drug release data were fitted to kinetic models, namely, zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations to know the pattern and mechanism of drug release from the tablets containing SD and SSD and the marketed products. In this experiment, release profiles of the prepared tablets did not show good fitting with zero order, first order and Hixon-Crowel equation. *In vitro* release profiles of drug from all formulations could be best expressed by Higuchi as the plots showed highest linearity R^2 ranging from 0.879 to 0.981 (Table 5). It indicated that the mechanism of drug release from the tablets was mainly by diffusion. Release profiles of the tablets also showed good linearity with Korsmeyer-Peppas model (R^2 value ranging from 0.826 to 0.992). The value of release exponent (*n*) of Korsmeyer's plot was found from 0.230 to 0.411 for all the formulations that indicated that burst release or Fickian diffusion were the predominant mechanism of drug release from the matrix. Enhanced solubility of drug from SD or SSD may produce pores in the tablet through which more drugs were diffused. On the other hand brand products were found to show best fitting with zero order and korsmeyer release order. Higher values of release exponent *n* of the brand products pointed out that non-Fickian diffusion e.g. diffusion and erosion of the matrix were the governing

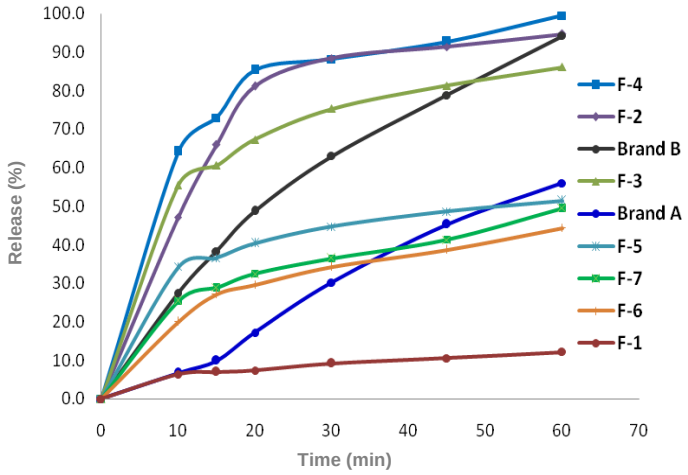

Figure 10. Percent release data obtained from tablets and marketed products.

Table 3. Physical characterization of nifedipine tablets.

Formulation	Diameter *(mm)	Thickness (mm)	Hardness (Kg/cm^2)	Average weight (mg)	Disintegration time (min)
F-1	13.05±0.02	2.75±0.01	6.2±0.04	500±1.30	5.9
F-2	13.06±0.02	2.82±0.02	5.1±0.08	500±1.20	2.3
F-3	13.06±0.01	2.72±0.02	5.4±0.07	500±1.00	2.7
F-4	13.07±0.01	2.83±0.01	5.0±0.08	500±1.20	3.2
F-5	13.06±0.01	2.85±0.01	5.2±0.06	500±0.86	4.7
F-6	13.06±0.00	2.76±0.01	6.5±0.04	500±0.41	6.1
F-7	13.06±0.01	2.79±0.01	6.4±0.03	500±0.36	4.7
Brand A	8.20±0.02	2.65±0.01	3.9±0.07	170±0.45	7.3
Brand B	7.03±0.02	2.24±0.01	4.0±0.04	120±0.59	1.5

*Average±SD.

Table 4. Average successive fractional dissolution time ($T_{50\%}$ and $T_{80\%}$), MDT values (in min) and %DE (10 min) of tablets (n=6).

Formulation	MDT	$T_{50\%}$	$T_{80\%}$	$\%DE_{10\ min}$
F-1	5255.28	2979.71	10649.87	3.20
F-2	14.22	7.78	28.92	23.58
F-3	20.50	6.51	42.01	27.74
F-4	10.57	2.78	21.42	32.11
F-5	186.59	51.35	379.41	17.15
F-6	122.23	77.70	243.83	9.98
F-7	128.36	69.53	261.31	12.71
Brand A	48.56	50.15	73.31	3.38
Brand B	25.25	22.47	44.98	13.74

mechanism of drug release from the tablets (Rahman et al., 2011).

DISCUSSION

SD, SSD and PMs were found to have granular structure with free flowing capacity. All the preparations yielded satisfactory results in drug content analysis. In order to confirm the compatibility and possible interaction between drug and carrier, the dispersions were undertaken for FT-IR spectroscopy and Differential Scanning Calorimetric study.

The FT-IR spectra of nifedipine, SSD with SSG and CCS and SD with HPMC, PEG and Poloxamer showed stretching and vibration peaks at similar positions. Thus the compatibility of drug and carrier in the dispersions was confirmed from the spectra. SD with Poloxamer showed shifting of C=O stretching peak. The shifting of the band might be responsible for the rupture of hydrogen bonds present at crystalline structure of nifedipine. This conversion of nifedipine from crystalline structure to amor-

Table 5. *In vitro* release kinetic data of tablets of nifedipine.

Formulation	Zero Order		First Order		Highuchi		Korsmeyer		Hixon-Crowell	
	K_o	R^2	K_1	R^2	K_h	R^2	*n*	R^2	K_{hc}	R^2
F-1	0.169	0.814	0.000	0.831	1.526	0.981	0.369	0.977	0.026	0.488
F-2	1.326	0.667	-0.020	0.922	12.700	0.907	0.358	0.826	0.052	0.446
F-3	1.120	0.653	-0.012	0.902	10.880	0.912	0.252	0.990	0.048	0.418
F-4	1.257	0.604	-0.032	0.922	12.470	0.879	0.230	0.925	0.050	0.402
F-5	0.660	0.639	-0.004	0.738	6.452	0.902	0.235	0.992	0.040	0.411
F-6	0.625	0.806	-0.003	0.875	5.671	0.980	0.411	0.968	0.041	0.493
F-7	0.670	0.797	-0.004	0.879	6.094	0.975	0.355	0.987	0.041	0.479
Brand A	0.996	0.988	-0.006	0.984	7.655	0.863	1.238	0.985	0.055	0.810
Brand B	1.487	0.950	-0.019	0.952	12.430	0.983	0.677	0.992	0.057	0.619

phous form may be responsible for increased solubility and dissolution rate of the SD. Similar findings were reported by Aparna et al. (2010), who formulated SD of nifedipine with PEG 6000 and Gelucire 44/14.

Melting peak of nifedipine and PEG 6000 were found at 175.01°C and 66.14°C, respectively in the thermal graph from DSC study. Thermal DSC thermograms of Nif: P6 1:1 SD showed absence of melting peak of drug that clearly indicated amorphous formation in the SD (Figure 4). Similar findings were reported by Aparna et al. (2010) who claimed that this was due to attainment of amorphous stage that resulted from increased dissolution rate of the drug. The peak for the melting of carrier was present at the thermograph of SD at similar positions. But only a small exothermic peak having highest value on 175.17°C was observed in the thermogram. It may be due to the oxidation or decomposition of nifedipine at the elevated temperature at the presence of the carrier.

In vitro dissolution study of the SD and SDD revealed remarkable improvement in drug release. All the SD and SSD were found more effective to improve rate and extent of drug release than the PMs and drug powder. This is because the drug is poorly water soluble and in PM, the drug remained in crystalline from. On the other hand, SDs were found more effective in enhancing solubility characteristics of nifedipine when compared with SSDs. Drug release was found proportional to the amount of carrier. Higher drug release was obtained from SD containing higher amount of carrier. At the ratio of 1:1, Poloxamer 407 was found mostly effective in contrast to other carriers. Nif:Polo 1:1 SD showed 98.76% release after 60 min of dissolution. This enhancement of dissolution by Poloxamer 407 might be due to the improvement of drug wetting by the surface active property and micellar solubilization of the carrier (Islam et al., 2010). Although when the content of carrier increased to the ratio of 1:5 and 1:10, PEG 6000 showed highest dissolution rate at the time of study. HPMC showed least enhancement in the drug dissolution as a water soluble carrier. This is may be due to higher viscosity of the medium for the presence of HPMC and for its drug retarding action. SSG, an insoluble carrier, showed remarkable increase in the dissolution as compared to CCS particularly when used at higher ratio. At 1:1 ratio, SSD of CCS and SSG showed 30.71 and 36.56% drug release, respectively, whereas 41.88 and 72.76% drug release was obtained at ratio of 1:10. The order of efficacy to improve dissolution rate at the ratio of 1:10 was found as: PEG 6000> Poloxamer 407> PEG 4000> SSG> HPMC>CCS.

Different water soluble carrier enhanced drug release to different extents. This may be due to the inherent differences in terms of hydration, dissolution and possible complexation with drug which may influence in the improvement of dissolution characteristics (Rupal et al., 2009). Incorporation of such carriers in SD rendered them more efficient in improving wettability of drug and hence, dissolution has been improved. In the SSDs, water insoluble carriers become hydrated in the presence of water and swell rapidly by water intake. Thus the dissolution enhanced as the drug get wetted and dissolved that was primarily adsorbed on the carriers in a finer or molecular form in surface SD.

Distribution of drug particles into a carrier at a fine level is the key factor for enhancing drug dissolution. This molecular dispersion is responsible for the difference between release behavior of PMs and SDs and SSDs. Drug was distributed at molecular level in SDs and SSDs and undergone better wetting and hence, better dissolution. But the PMs were unable to bring the drug dispersed at that fine level and as a result slight improvement of wetting characteristics may happen. Only the PM of nifedipine and HPMC 5 cPs showed similar improvement of dissolution characteristics when compared with SDs at 1:1 ratio. It may be due to the solubility properties of HPMC that is soluble at cold water and becomes a viscous colloidal solution (Rowe et al., 2006) that might turn out to be the barrier for drug dissolution. In a similar fashion, SDs showed better dissolution properties than the SSDs by achieving better

wetting of drug by combining the drug and carrier at molecular level.

This enhancement of release profile of nifedipine was found effective in the finished dosage forms also. Tablets were prepared by incorporating a SD and evaluation for different physical characteristics and dissolution study. Therefore, the dispersions were found to liberate the drug at a faster rate as compared to the brand products. Market products analysis indicated inter brand variation which is a common picture for a poorly water soluble drug product. The release rate was characterized with successive fractional dissolution time ($T_{50\%}$ and $T_{80\%}$), MDT values (in min) and percent DE (10 min). Kinetic study was also performed by fitting the dissolution data to various mathematical models.

Conclusion

SD of nifedipine was prepared by water soluble carriers like Poloxamer 407, HPMC 5 cPs, PEG 4000 and 6000. Insoluble carriers such as SSG and CCS were also used to prepare SSD. All the preparations were found effective to improve rate and extent of drug release when compared with PMs and drug powder. SDs were found more effective in enhancing solubility characteristics of nifedipine when compared with SSDs. Tablets were prepared from each SDs and SSDs. Tablets prepared from SD of nifedipine with Poloxamer and PEG 6000 were found to have better drug release profile than the marketed products.

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