



ENHANCEMENT OF DISSOLUTION OF NIFEDIPINE BY SURFACE SOLID DISPERSION TECHNIQUE

Y. LALITHA^{1*}, P. K. LAKSHMI¹

¹Department of Pharmaceutics, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Andhra Pradesh, India
Email: drlakshmisuresh@gmail.com

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ABSTRACT

The main objective of the study was to enhance the dissolution of nifedipine, a poorly water soluble drug by surface solid dispersion technique using different carriers and to study the effect of each carrier on the in vitro dissolution profile. The formulations were optimized in the preliminary trials by using various ratios of different carriers like kyron T-314, croscarmellose sodium, crospovidone, silicified microcrystalline cellulose and sodium starch glycolate. Resultant formulations were evaluated using FTIR, X-ray diffraction, DSC, GC, SEM and in vitro dissolution. Solid dispersion with kyron T-314 at 1:9 ratio gave good release when compared to pure drug and physical mixtures. The optimized dispersion was formulated in to sublingual tablets by using kyron T-314, crospovidone, croscarmellose sodium and sodium starch glycolate as disintegrants and was evaluated for friability, hardness, weight variation, disintegration and in vitro dissolution. The sublingual tablets prepared with kyron T-314 as disintegrant gave good disintegration.

Keywords: Nifedipine; Surface solid dispersion; Sublingual tablets; Kyron T-314; In vitro dissolution

INTRODUCTION

Bioavailability of poorly water-soluble hydrophobic drugs is limited by their solubility and dissolution rate. Several studies were carried out to increase the dissolution rate of drugs [1]. One such study was solid dispersion which has shown promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability [2]. The mechanism by which solid dispersion enhances the solubility and dissolution involves particle size reduction to fine form or molecular level, conversion of crystalline form to amorphous form and by enhancing wettability [3]. This technique has been used for various poorly aqueous soluble drugs such as nimesulide [4], ketoprofen [5], tenoxicam [6], nimodipine [7] and nilvadipine [8].

Despite of having so many advantages, only few commercial solid dispersion products are available [9]. The surface solid dispersion technique overcame the shortcomings of solid dispersion prepared by water soluble carriers like tackiness and difficulty in handling of the product. The carriers used in surface solid dispersion are water-insoluble, porous materials and hydrophilic in nature. In this technique drug gets 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 [10]. Larger the surface area available for surface adsorption of the drug better is the release rate [11]. In preparing surface solid dispersion various carriers like crospovidone, croscarmellose sodium, sodium starch glycolate, kyron T-314 and silicified microcrystalline cellulose have been employed.

Nifedipine is a dihydro pyridine calcium channel antagonist originally introduced for the treatment of angina pectoris and hypertension. Nifedipine which is a poorly water soluble drug coming under BCS class-2 undergoes first pass metabolism in liver and gut wall. Sublingual administration bypasses the metabolism of the nifedipine in liver and offers a fast relieve from anginal pain and hypertension.

As nifedipine has poor solubility and dissolution, the dissolution was enhanced by surface solid dispersion technique. The surface solid dispersion was prepared with different carriers at different ratios. The optimized solid dispersion product was then evaluated and sublingual tablets were prepared. As sublingual tablets prevent the first pass metabolism and are easy to manufacture, the tablets of nifedipine were prepared with various disintegrants like kyron T-

314, croscarmellose sodium, crospovidone and sodium starch glycolate.

MATERIALS AND METHODS

Nifedipine, kyron T-314, crospovidone, croscarmellose sodium, sodium starch glycolate and silicified microcrystalline cellulose were obtained as gift samples from Dr. Reddy's laboratories, Hyderabad. All the solvents used were of analytical grade from SD Fine Chem, Mumbai, India.

Preparation of nifedipine surface solid dispersion (SSD) and physical mixture (PM)

The surface solid dispersion of nifedipine with different carriers at different ratios were prepared by solvent evaporation method. The drug to carrier ratios of 1:1 and 1:9 were used for preparing both solid dispersion and physical mixtures. The drug was first dissolved in required quantity of dichloromethane and to this solution, carrier was dispersed. The above prepared mixture was then placed in a rotary flash evaporator for evaporation of the solvent by adjusting the temperature to 40-45°C and under reduced pressure. The obtained mass was passed through a 60 # sieve and was dried at 40°C in an oven for at least 3 hrs until a constant mass was obtained. The obtained product was stored in desiccators for carrying out evaluation. Physical mixtures (PM) containing one part of drug and 9 parts of carrier were prepared by mixing in a double cone blender for 15 minutes. The prepared mixtures were sifted through 60# sieve and were used for evaluation.

Calibration curves by blank correction method

In order to correct the interference of the carriers in the UV measurement, some methods reported [10] were employed. Stock solutions were prepared by dissolving 100 mg of drug in few ml of methanol and then made up with the appropriate buffer. Calibration curves in the range of 2 to 20 mcg/ml were obtained by diluting aliquots with appropriate buffer solution. The interference of the carriers on UV measurements was blanked out by preparing stock suspension of the carriers in appropriate buffer solution. Aliquots of suspensions were added to drug solutions to obtain a 1:9 drug-to-excipient ratio on dilution. The suspensions were diluted and filtered through 0.45 mm membrane filter before going for the determination of absorption at a λ_{max} of 238 nm. The blanks were mixtures of corresponding buffers and appropriate carrier. The method obeyed Beer's law in the concentration range of 2 to 20 mcg/ml.

Assay

Accurately weighed samples (n=3) equivalent to 10 mg of drug was taken in a 100 ml volumetric flask, a few ml of methanol was added and shaken for few minutes until the drug gets dissolved. The volume was made to 100 ml with 6.8 pH phosphate buffer containing 0.5% SLS solution and this solution was filtered using 0.45 mm membrane filter. A 10ml aliquot of the above prepared solution was taken and diluted to 100 ml with buffer solution. The absorbance of sample solution was determined at 238 nm against carrier blank by using blank correction method.

In vitro dissolution studies

In-vitro dissolution studies of samples were carried out as per conditions reported by [12] using USP apparatus II paddle method by powder dispersion technique. Accurately weighed sample equivalent to 10 mg of nifedipine was placed in a dissolution vessel and 900 ml of 6.8 pH phosphate buffer containing 0.5% SLS dissolution medium, maintained at $37 \pm 0.50^\circ\text{C}$ was transferred into the vessel and rotated at 50 rpm. At different time intervals, aliquots were withdrawn and filtered through 0.45 mm membrane filter. To maintain sink conditions, an equal volume of fresh dissolution medium was immediately replaced. The concentration of nifedipine at each sampling time was analyzed spectrophotometrically at 238 nm by blank correction method.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra were recorded on drug, carrier, PM and SSD samples which were prepared in potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan) facility (model - 8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The scanning range was 4000 cm^{-1} to 500 cm^{-1} .

Differential scanning calorimetry (DSC)

DSC analysis of drug, PM and SSD was performed using TA Instruments (New Castle, DE) Q1000 differential scanning calorimeter (DSC) at a heating rate of $10^\circ\text{C}/\text{min}$ under nitrogen environment. The temperature range used was $0 - 210^\circ\text{C}$.

Powder X-ray diffraction analysis (PXRD)

X-ray diffraction of drug, physical mixture and SSD Samples were obtained on a Siemens X-ray diffractometer using Copper K α ($\lambda = 1.5406\text{ \AA}$) radiation. The data were recorded over a scanning 2θ range of 5° to 50° .

Scanning electron microscopy (SEM)

The surface morphology of nifedipine SSD on kyron T-314 (1:9) and PM were observed by using an analytical scanning electron microscope (JSM- 6360A, JEOL, Tokyo, Japan). The samples were lightly sprinkled on a double-sided adhesive tape stuck to an aluminum stub. The stubs were coated with platinum to a thickness of about 10 \AA under an argon atmosphere. Afterwards, the stubs containing the coated samples were placed in the scanning electron microscope chamber.

Preparation and evaluation of sublingual tablets

As the dissolution profile of nifedipine SSD on kyron T-314 at 1:9 ratio showed good results, it was selected for the preparation of sublingual tablets of surface solid dispersion. Amount of SSD in the tablet was selected on the basis of nifedipine equivalent to 10 mg present in the SSD. Tablets were prepared by direct compression method using different disintegrants like kyron T-314 (NSK), crospovidone (NSCP), croscarmellose sodium (NSCM) and sodium starch glycolate (NSSG) and compressed on a 10 station rotary tablet compression machine. Tablets were prepared even without disintegrant (NS). Other ingredients incorporated in the tablets were saccharine sodium, talc, magnesium stearate, avicel PH101, silicified microcrystalline cellulose and mannitol. The tablet weight was

adjusted to 200 mg. The tablets prepared were evaluated for parameters like weight variation, hardness, friability, disintegration time, assay, content uniformity and in vitro dissolution.

Solvent residue

The residual solvent concentration of the prepared solid dispersion of nifedipine SSDK-5 was studied by GC. The solvent used was dichloromethane and the concentration of it was detected. GC analysis was performed using Shimadzu GC 2010 plus with Teledyne tekmar HT3 head space auto sampler, fitted with flame ionization detector. Packed column was DB-17 capillary column. Carrier gas was nitrogen. Headspace GC is used to detect solvent residues. Temperature of oven was 35°C , injection port 140°C and detector 250°C . Oven was programmed at $35-250^\circ\text{C}$.

RESULTS AND DISCUSSION

According to the dissolution profiles plotted below (fig. 1), the dissolution rates of nifedipine were increased by surface solid dispersion technique than when compared to pure drug and physical mixtures. The pure drug showed (Table 1) only 32% release in 30 minutes when compared to physical mixtures which showed more release than the pure drug. This is due to the surface adsorption of the drug on the hydrophilic carriers and thereby increased wetting of the drug in physical mixtures than compared to the pure drug which floats on the surface in the form of aggregates leading to reduced effective surface area. The release of nifedipine was enhanced to a greater extent by surface solid dispersions when compared to both pure drug and physical mixtures due to the drug getting adsorbed in a finer form or molecular form on the carriers. The release of drug varied from one carrier to other carrier in terms of both PM and SSD's. The release of drug with SSD on kyron T-314 showed greater results when compared to other carriers. All carriers employed displayed enhancement in dissolution rate.

As the carrier concentration is increased, the dissolution of drug (Table 1) got increased. In between different ratios (1:3, 1:5 and 1:7) of drug: carrier SSD's were prepared and evaluated by dissolution. These ratios showed slighter increase in dissolution rate which is between the 1:1 and 1:9 drug: carrier SSD ratios. The release of drug with 1:9 drug: kyron T-314 SSD was more when compared to 1:1 drug: kyron T-314 SSD due to the availability of more carrier for coating the drug. The improvement in dissolution rate was less for crospovidone SSDs when compared to other carriers which may be due to the poor hydration capacity of it [13].

Silicified microcrystalline cellulose SSDs showed great improvement in dissolution rates, which may be due to greater surface area available in combination of both microcrystalline cellulose [10] and colloidal silica [11] in the form of silicified microcrystalline cellulose for coating the drug. At 1:9 ratio, carriers like sodium starch glycolate and croscarmellose sodium SSDs showed good release with a greater enhancement of dissolution which may be due to the good hydration capacity of these carriers than crospovidone [13]. Kyron T-314 SSDs has shown highest dissolution profile at all ratios when compared to other carriers. Around 72% of the drug was released within 10 minutes at 1:9 drug: carrier ratio which may be due to good disintegrating properties of it when compared to other carriers. The dissolution rate in increasing order for all carriers was as follows: kyron T-314 > croscarmellose sodium > sodium starch glycolate > silicified microcrystalline cellulose > crospovidone.

FTIR spectra of nifedipine (fig. 2) revealed the peaks characteristic of the N-H stretching vibration at 3331 cm^{-1} and a band with main peak at 1688 cm^{-1} indicative of the C=O stretch of the ester group. The above characteristic peaks appear in the spectra of both physical mixtures and surface solid dispersion of the drug with kyron T-314 as carrier at the near wave numbers with broadening. From these results, it was concluded that there were no intermolecular interactions between the drug and kyron T-314. Further characterization was done using XRD and DTA to determine the interaction.

DSC of the pure drug showed a sharp peak at 172.46°C corresponding to the melting point of nifedipine (fig. 4). The peak showed an onset at 171.82°C. Kyron T-314 showed a broad peak at 100.10°C with peak onset from 56.09°C. DSC of SSD showed peaks characteristic of kyron T-314 and the drug with no additional peaks. However, the peak of kyron T-314 had shifted to 108.75°C, while the drug showed a sharp melting point peak at 172.21°C. From DSC, it can be concluded that drug and carrier showed no interaction.

The X-ray diffraction pattern of nifedipine (fig. 3) exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. It showed diffraction peaks at 2θ degree of 8, 10.3, 11.7, 19.5 and 24.5. The x-ray diffraction pattern of the surface solid dispersion was just an superimposition of each component with respect to the peaks of nifedipine and kyron T-314. The relative 2θ angle of nifedipine peaks remained unchanged but relative intensity of the peaks was decreased which may be probably due to dilution of the drug. So, there was no amorphization of the drug and its original crystalline form was retained. No new peak was detected and hence there was no polymorphic transition of the drug taking place. IR and DSC studies support the same data, which is confirmed by x-ray diffractometry.

Residual solvent concentration in SSD of nifedipine prepared using dichloromethane was analyzed by gas chromatography. The levels of dichloromethane were below detectable limits (LOD was 10ppm and 1ppm respectively). Hence, the solvents in the SSD's were efficiently

removed by solvent evaporation method in an efficient way well below permissible levels.

The SEM of physical mixture as shown in (fig. 5) showed dusting of drug powder on the carrier, while the SEM of surface solid dispersion showed a more porous nature of carrier with fine crystals of nifedipine deposited on it when compared to physical mixture. This change in structure may be one of the causes for increase in dissolution rate.

Sublingual tablets containing SSD of nifedipine: kyron T-314 in 1:9 ratio were prepared by direct compression technique. The tablets complied with the official specifications. The results of various parameters (Table 2) for the prepared sublingual tablets were evaluated. The percent drug dissolved in 10 minutes and disintegration time from these sublingual tablets prepared using SSD with different disintegrants like kyron T-314, croscarmellose sodium, crospovidone, sodium starch glycolate and without disintegrant were evaluated. The tablets prepared with kyron T-314 as disintegrant got disintegrated immediately than compared to others which may be due to the greater disintegrating properties of it over the other disintegrants. The tablets with kyron T-314 (NS) as disintegrant showed immediate availability of nifedipine when compared to tablets prepared with crospovidone (NSCP), croscarmellose sodium (NSCM), sodium starch glycolate (NSSG) and the tablets without any disintegrant (NS), which showed more disintegration time and slow release in the first 10 minutes indicating requirement of external disintegrants.

Table 1: Percent drug dissolved of nifedipine from pure drug, physical mixtures and surface solid dispersions

Carrier	Formulation	D: C ratio	Percent drug dissolved in 30 minutes
Nifedipine	Pure drug	-	32.8
Crospovidone	SSD	1:1	62.39
		1:9	69.11
		PM	34.48
Silicified microcrystalline cellulose	SSD	1:1	34.48
		1:9	40.64
		1:1	65.75
		1:9	72.18
		PM	36.15
Sodium starch glycolate	SSD	1:1	42.04
		1:9	68.53
		1:9	74.42
Croscarmellose sodium	PM	1:1	38.97
		1:9	43.17
		1:9	76.39
Kyron T-314	SSD	1:1	83.68
		1:9	39.53
		1:9	45.44
	PM	1:1	82.83
		1:9	92.39
		1:9	40.93
		1:9	46.01

SSD is surface solid dispersion and PM is physical mixture of different carriers at 1:1 and 1:9 ratios respectively.

Table 2: Evaluation of sublingual tablets

Formulations	Weight variation****	Hardness* (kg/sq.cm)	Percent friability***	Disintegration time** (seconds)	Percent drug dissolved in 10 minutes*
NS	200.42 + 0.34	3.46 + 0.10	0.34	185	65
NSK	200.32 + 0.40	3.32 + 0.12	0.38	25	74.83
NSCP	200.18 + 0.27	3.35 + 0.12	0.30	30	71.2
NSCM	200.23 + 0.29	3.37 + 0.12	0.27	34	70.38
NSSG	200.27 + 0.23	3.48 + 0.07	0.37	36	69

*values are average of three determinations, **test has been performed for 6 tablets, ***test has been performed for 10 tablets, ****test has been performed for 20 tablets.

NS is sublingual tablets without disintegrant; NSK, NSCP, NSCM and NSSG are sublingual tablets with kyron T-314, crospovidone, croscarmellose sodium and sodium starch glycolate as disintegrant respectively.

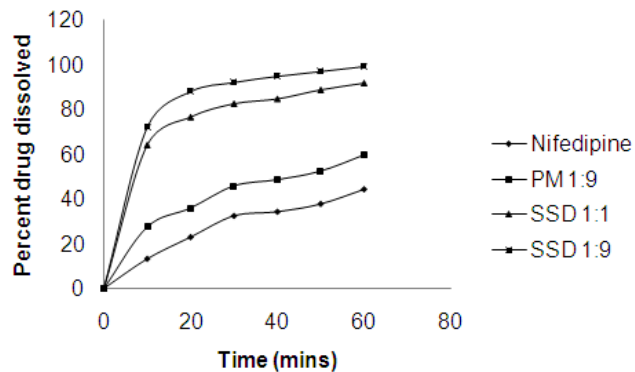


Fig. 1: In vitro dissolution profiles of nifedipine, PM of nifedipine with kyron T-314 at 1:9 ratio, SSD of nifedipine with kyron T-314 at 1:1 and 1:9 ratios.

SSD is surface solid dispersion and PM is physical mixture of nifedipine.

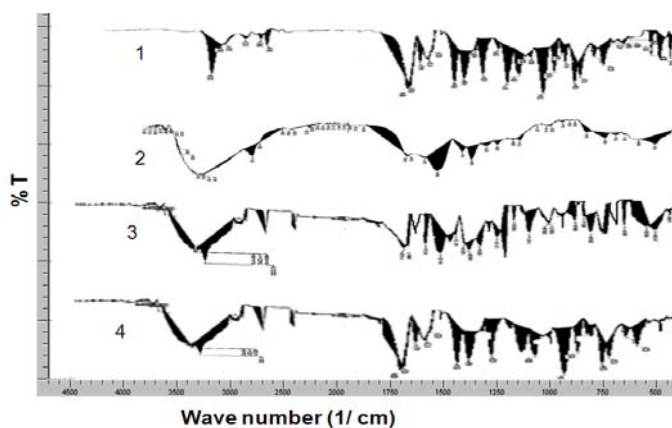


Fig. 2: IR spectras of nifedipine (1), kyron T-314 (2), 1:9 ratio of nifedipine: kyron T-314 PM (3) and 1:9 ratio of nifedipine: kyron T-314 SSD (4)

SSD is surface solid dispersion and PM is physical mixture of nifedipine.

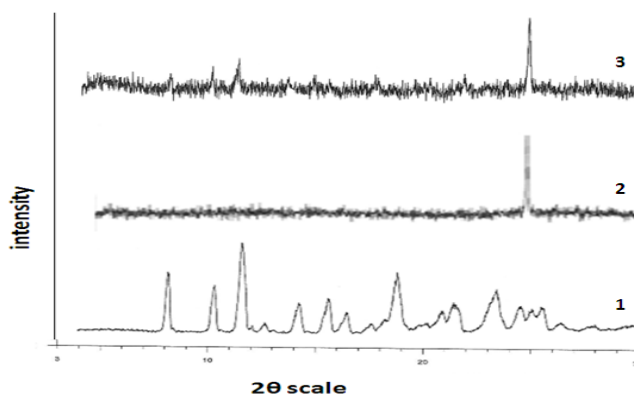


Fig. 3: PXRD of nifedipine (1), kyron T-314 (2), 1:9 ratio of nifedipine: kyron T-314 SSD (3)

SSD is surface solid dispersion and PM is physical mixture of nifedipine.

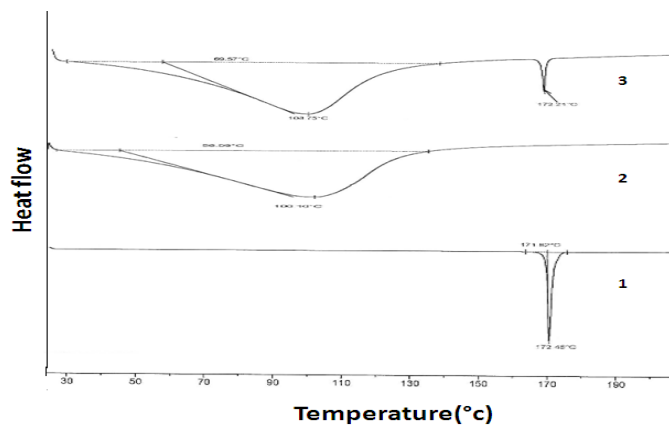


Fig. 4: DSC thermograms of nifedipine (1), kyron T-314 (2) and SSD of nifedipine and kyron T-314 at 1:9 ratio (3)

SSD is surface solid dispersion and PM is physical mixture of nifedipine.

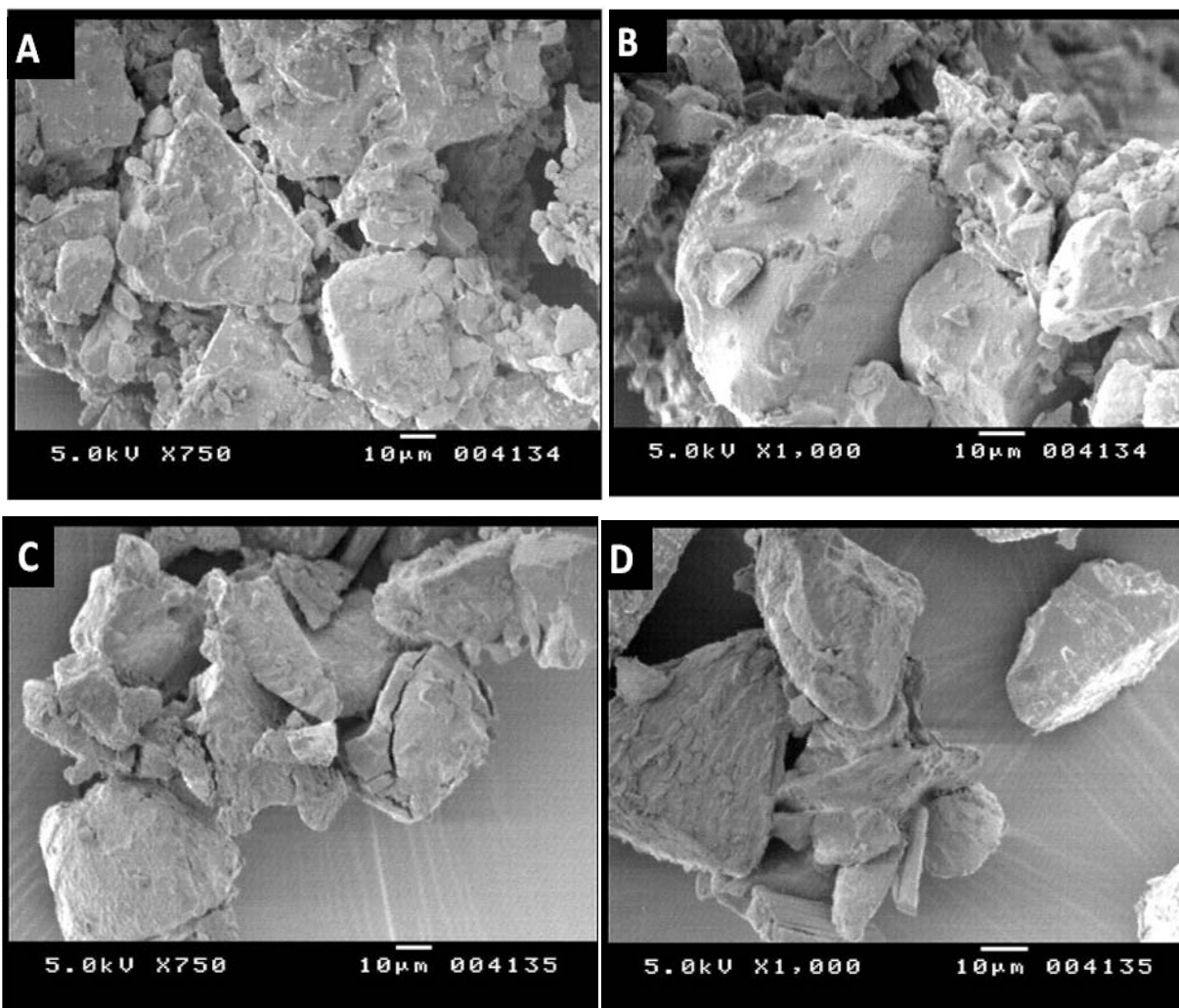


Fig. 5: SEM photographs of PM of nifedipine: kyron T-314 at 1:9 ratio at 750X (A), 1000X (B) and SSD of nifedipine: kyron T-314 at 1:9 ratio at 750X (C), 1000X (D)

SSD is surface solid dispersion and PM is physical mixture of nifedipine.

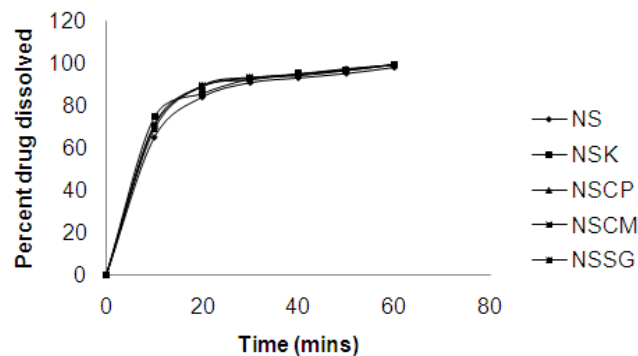


Fig. 6: *In vitro* dissolution profiles of sublingual tablets (NS, NSK, NSCP, NSCM and NSSG) of nifedipine prepared with 1:9 ratio of nifedipine: kyron T-314 SSD.

NS is sublingual tablets without disintegrant; NSK, NSCP, NSCM and NSSG are sublingual tablets with kyron T-314, crospovidone, croscarmellose sodium and sodium starch glycolate as disintegrant respectively.

CONCLUSION

The dissolution rate of nifedipine was successfully achieved by surface solid dispersion technique. The type and the amount of the carrier played a very important role in the enhancement of the dissolution rate. This enhancement in dissolution rate helped in providing rapid onset of drug. The sublingual administration of prepared SSD tablets help in bypassing the first pass effect.

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REFERENCES

1. B. Venkat Yadav, V. Adhikrao Yadav. Enhancement of solubility and dissolution rate of BCS class II pharmaceuticals by nonaqueous granulation technique. *International Journal of Pharma Research and Development*. 1: 1-12 (2010).
2. A.T. M. Serajuddin. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* 88: 1058-1066 (1999).
3. Christian Leuner, Jennifer Dressman. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* 50: 47-60 (2000).
4. G. V. Babu, N. R. Kumar, K. Himasankar, A. Seshasayana, K. V. Murthy. Nimesulide-modified gum karaya solid mixtures: preparation, characterization and formulation development. *Drug Dev. Ind. Pharm.* 29: 855-864 (2003).
5. J. A. Rogers, A. J. Anderson. Physical characteristics and dissolution profiles of ketoprofen-urea solid dispersions. *Pharmaceutica Acta Helvetiae*. 57: 276-281 (1982).
6. O. N. El-Gazayerly. Characterization and evaluation of tenoxicam coprecipitates. *Drug Dev. Ind. Pharm.* 26: 925-930 (2000).
7. G. V. Murali Mohan Babu, C. H. D. S. Prasad, K. V. Ramana Murthy. Evaluation of modified gum karaya as carrier for the dissolution enhancement of poorly water soluble drug nimodipine. *Int. J. Pharm.* 234:117 (2002).
8. N. I. Hirasawa, S. Shise, H. Miyata, K. Danjo. Physicochemical characteristics and drug release studies of nilvadipine solid dispersions using water insoluble polymer as carrier. *Drug Dev. Ind. Pharm.* 29: 339-344 (2003).
9. J. L. Ford. The current status of solid dispersions. *Pharm Acta Helv.* 53: 93-98 (1986).
10. T. Kiran, Nalini Shastri, Sistla Ramakrishna, M. Sadanandam. Surface solid dispersion of glimepiride for enhancement of dissolution rate. *International Journal of PharmTech Research*. 1: 822-831 (2009).
11. K. Y. Yang, R. Glemza and C. I. Jarowski. Effects of amorphous silicon dioxides on drug dissolution. *J. Pharm. Sci.* 68: 560-565 (1979).
12. Natalija Zajc, Ales Obreza, Marjan Bele, Stane Srcic. Physical properties and dissolution behaviour of nifedipine/mannitol solid dispersions prepared by hot melt method. *Int. J. Pharm.* 291:51-58 (2005).
13. RP Dixit, MS Nagarsenker. In vitro and in vivo advantage of celecoxib surface solid dispersion and dosage form development. *Indian. J. Pharm. Sci.* 2007;69(3):370-7.