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Studies on enhancement of solubility and dissolution properties of Nimodipine by solid dispersion technique

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Abstract

Nimodipine, a member of calcium channel blocker, specifically binds to L-type voltage-gated calcium channels. The maximum solubility of nimodipine was found at pH 1.2 and solubility decreases up to pH 4.0. At a pH 6.0 and higher pH, solubility reduces drastically. Suitable solid dispersion systems of nimodipine with PVP-K30 and maltodextrin were prepared by physical mixture, solvent evaporation and kneading methods at 1:1 and 1:3 drug: carrier. Drug content, saturation solubility, FTIR, and *in-vitro* dissolution were studied. The drug content was uniform, solubility of the drug increased linearly as a function of the carrier concentration and method. The FTIR studies indicates no chemical interaction between drug and polymer. The DP_{60} and DE_{60} values of solid dispersion systems prepared by solvent evaporation and kneading method were significantly higher ($P<0.05$) when compared to DP_{60} and DE_{60} values of physical mixture and pure Nimodipine. The dissolution follows first order model and obeyed Hixson- Crowell's cube root law.

Keywords: Solid dispersion systems; Nimodipine; Maltodextrin; PVP K-30; *In-vitro* dissolution.

1. Introduction

The formulation of hydrophobic drugs as solid dispersion is a significant area of research aimed at improving their dissolution and bioavailability. Solid dispersions consisting of two components in the solid state are referred to as binary systems [1]. Oral bioavailability of drugs depends on its dissolution rate, therefore major problems associated with these drugs are, its low aqueous solubility, which results in poor bioavailability after oral administration. Solubility of drug candidates may be altered by modifying the crystal form or by changing solvent properties and conditions. It may also be altered by altering the chemical composition, as seen with salt formation, co-crystals and solid complexes. Another means of improving "apparent" solubility is by converting the crystalline drug into an amorphous state. An amorphous phase has higher free energy, enthalpy and entropy than the crystalline counterpart, and thus finds application in improving oral bioavailability for biological classification (BCS) class II or class IV compounds [2]. Various techniques have been used in attempt to improve the solubility and dissolution rates of poorly water soluble drugs, which include solid dispersion, micronization, lipid-based formulations, melt granulation, direct compaction, solvent evaporation, co-precipitation, adsorption, ordered mixing, liquid-solid compacts, solvent deposition, inclusion complexation and steam aided granulation [3,4]. In these techniques carrier is important in improving the solubility and dissolution rate. Dissolution of poorly soluble drugs can be increased by solid dispersion techniques [5].

Nimodipine is a dihydropyridine calcium channel blocker. It has been shown to selectively regulate calcium channels to increase cerebral blood flow. Because of its high permeability, nimodipine can pass through the blood–brain barrier to protect brain cells by increasing their ability to tolerate hypoxia. The major therapeutic indication of nimodipine is for

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the prevention and treatment of delayed ischemic neurological disorders, which often occur in patients with subarachnoid hemorrhages. Nimodipine has also been used in other cerebrovascular disorders, such as ischemic stroke and multi-infarct dementia. Nimodipine is a poorly water-soluble drug and has a low bioavailability and limited clinical efficacy. For "low solubility/high permeability" drugs, dissolution plays an important role in their absorption. Nimodipine belongs to class II under BCS and exhibit low solubility and high permeability[6]. `In the present investigation an attempt was made to prepare solid dispersion systems using hydrophilic polymers and evaluate their solubility and dissolution properties.

1.1. Materials used and the source

The drug Nimodipine was obtained as a gift sample from AET Pharmaceuticals, Hyderabad. Maltodextrin was procured from Sigma Aldrich. PVP K-30, Methanol, Hydrochloric acid, Ethanol and Dichloromethane were obtained from sd fine-chem. Limited, Mumbai.

2. Methods [7-11]

2.1. Determination of Absorption maxima

Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. For the absorption maxima stock solution was prepared by dissolving 100 mg of accurately weighed nimodipine in 100 ml of methanol to get 1mg/ml. Further, 10 ml of the stock solution was pipetted out into a 100 ml volumetric flask and volume was made up with 0.1 N HCl to get 10 µg/ml. From this stock solution, 1 ml was pipetted out and diluted to 10 ml with 0.1 N HCl and subjected for UV scanning in the range of 200-400 nm using double beam UV-VIS spectrophotometer, (Pharmaspec-1700, Shimadzu, Japan). The absorption maxima were obtained at 239 nm with a characteristic peak.

2.2. Preparation of calibration curve

Using absorption maxima a calibration curve was plotted in the concentration range of 1-10 µg/ml. From the second stock solution (10µg/ml), pipetted out 1.0, 3.0, 5.0, 7.0, and 9.0ml into a series of 10ml volumetric flasks and volume was made up to 10ml with 0.1 N HCl to get 1, 3, 5, 7and 9 µg/ml of nimodipine respectively. The optical density values of resulting solutions were measured at 239 nm.

2.3. Preparation of physical mixtures (PM)

Physical mixtures of Nimodipine: PVP K-30 and Nimodipine: maltodextrin at 1:1 and 1:3 ratios were obtained by mixing individual components together with a spatula and kept in desiccator for further study.

2.4. Kneaded systems (KNE)

Solid dispersions containing nimodipine: PVP K-30 and nimodipine: maltodextrin at 1:1 and 1:3 ratios were prepared by kneading method. The drug and excipient were weighed accordingly to the specified drug: carrier ratio and was taken in a glass mortar. The mixture was triturated slowly with methanol for 1 hr take care that the damp mass was maintained throughout the trituration period. Further mass was dried under vacuum, pulverized and sieved through #80 and stored in desiccator for further study.

2.5. Solvent evaporation systems (SE)

Solid dispersions containing nimodipine: PVP K-30 and nimodipine: maltodextrin at 1:1 and 1:3 ratios were prepared by solvent evaporation method. The required amount of drug was dissolved in methanol and excipient was dispersed in the drug solution. The solvent was removed under vacuum until dry. The dried mass was pulverized and sieved through #80 and stored in desiccator until further evaluation.

2.6. Evaluation of solid dispersion systems

2.6.1. Solubility studies

A little excess amount of nimodipine dispersed in 25 ml vials containing different concentrations of PVP K-30 and maltodextrin solutions. The sealed vials were shaken on rotary shaker for 24 hr at room temperature and equilibrated for 48 hr. An aliquot was passed through 0.45µ nylon disc filter and the filtrate were suitably diluted and analyzed on UV at 239 nm.

2.6.2. Saturation solubility

Weighed amount of nimodipine pure drug, physical mixture and all prepared solid dispersions equivalent to 20mg of the drug, dispersed in 25 ml vials containing 20 ml of 0.1N HCl. The sealed vials were shaken on rotary shaker for 24 hr at room temperature and equilibrated for 48 hr. An aliquot was passed through 0.45µ nylon disc filter and the filtrate was suitably diluted with 0.1N HCl and measures the absorbance at 239 nm and estimate the nimodipine content using the calibration curve.

2.6.3. . Drug content uniformity

In each case physical mixture and solid dispersion systems equivalent to 20 mg of nimodipine was accurately weighed and extracted with 100 ml 0.1N HCl and filtered. 1ml of the filtrate was serially diluted with 0.1N HCl and absorbance was measured at 239 nm. The drug content of nimodipine was measured using the calibration curve.

2.6.4. FTIR studies

Fourier transform infrared (FTIR) spectra were recorded on a Shimadzu FTIR-281-spectrophotometer. The spectrum recorded for nimodipine, maltodextrin, PVP K-30, physical mixture and all solid dispersion systems. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of $5.2Tcm^{-2}$ for 3 min. The scanning range was 450-$4000cm^{-1}$ and the resolution was $1cm^{-1}$.

2.6.5. Dissolution studies

In vitro dissolution studies of pure nimodipine, physical mixture and all solid dispersion systems were carried out in 900 ml of 0.1N HCl using a USPXXI type 2 dissolution test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 20 mg of nimodipine, speed of 50 rpm and a temperature of 37^0C were used in each test. A 5 ml aliquot was withdrawn at different time intervals, filtered using a 0.45µm nylon disc filter and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for nimodipine content by measuring the absorbance at 239 nm. The dissolution experiments were conducted in triplicate. The results were computed by using dissolution software PCP DISSO V3.0.

3. Results

3.1. Saturation solubility studies

The saturation solubility of nimodipine from physical mixture and its solid dispersion systems were carried out in 0.1N HCl. The solubility of nimodipine in 0.1N HCl was found to be 0.103±0.005774 mg/ml.

Table 1 Saturation solubility of nimodipine in physical mixture and its solid dispersion system prepared with maltodextrin and PVP K-30

Code	Drug	Excipient	Ratio	Method	Concentration mg/ml ± SD
F1	Nimodipine	PVP K-30	1:1	PM	0.475± 0.0005
F2	Nimodipine	PVP K-30	1:3	PM	0.50± 0.0057
F3	Nimodipine	PVP K-30	1:1	SE	0.362±0.0005
F4	Nimodipine	PVP K-30	1:3	SE	0.2±0.005774
F5	Nimodipine	PVP K-30	1:1	KNE	0.79±0.00577
F6	Nimodipine	PVP K-30	1:3	KNE	0.832±0.0034
F7	Nimodipine	Maltodextrin	1:1	PM	0.6±0.005774
F8	Nimodipine	Maltodextrin	1:3	PM	1.16±0.00574
F9	Nimodipine	Maltodextrin	1:1	SE	0.761±0.0005
F10	Nimodipine	Maltodextrin	1:3	SE	0.31±0.00577
F11	Nimodipine	Maltodextrin	1:1	KNE	0.413±0.00056
F12	Nimodipine	maltodextrin	1:3	KNE	0.528±0.00057

3.2. Drug content studies

The percentage drug content for all the prepared physical mixture and its solid dispersion systems were calculated with SD and CV values.

Table 2 Nimodipine drug content in physical mixture and its solid dispersions prepared with PVP K-30 and maltodextrin

Code	Drug: polymer	Amount of drug taken	Amount of Drug recovered Mean ± SD	%Drug content Mean ± SD
F1	1:1	20 mg	18.42 ± 0.01	92.1 ± 0.1
F2	1:3	20 mg	18.50 ± 0.1	92.5 ± 0.1
F3	1:1	20 mg	18.10 ± 0.1	90.5 ± 0.1
F4	1:3	20 mg	18.15 ± 0.01	90.7 ± 0.1
F5	1:1	20 mg	18.75 ± 0.01	93.5±0.1
F6	1:3	20 mg	19.00 ±0.15	95.0±0.1
F7	1:1	20 mg	18.20 ±0.1	91.0 ± 0.5
F8	1:3	20 mg	19.80 ±0.01	95.4 ± 0.1
F9	1:1	20 mg	18.40 ±0.1	91.5± 0.5
F10	1:3	20 mg	19.74 ± 0.01	98.7 ± 0.1
F11	1:1	20 mg	19.48± 0.15	97.4 ± 0.07
F12	1:3	20 mg	18.75 ± 0.01	93.7 ± 0.01

3.3. FTIR studies

The FTIR spectrum of nimodipine and its solid dispersion systems prepared by physical mixture, solvent evaporation and kneading methods at 1:3 with PVP K-30 and maltodextrin.

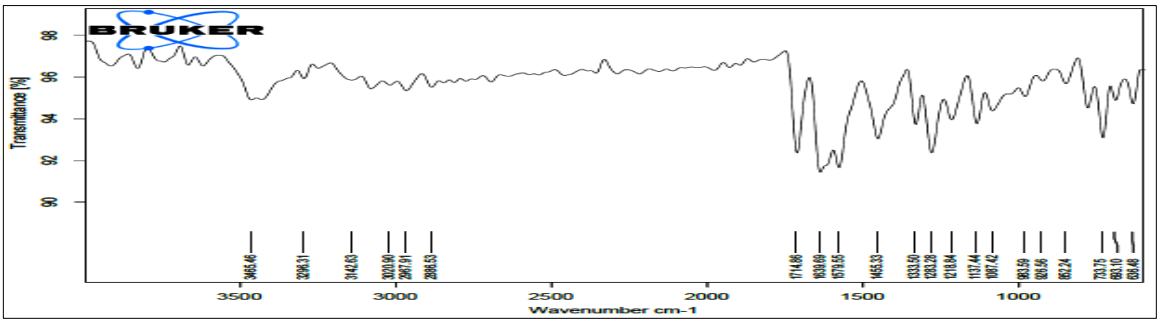

Figure 1 FTIR spectra of Nimodipine

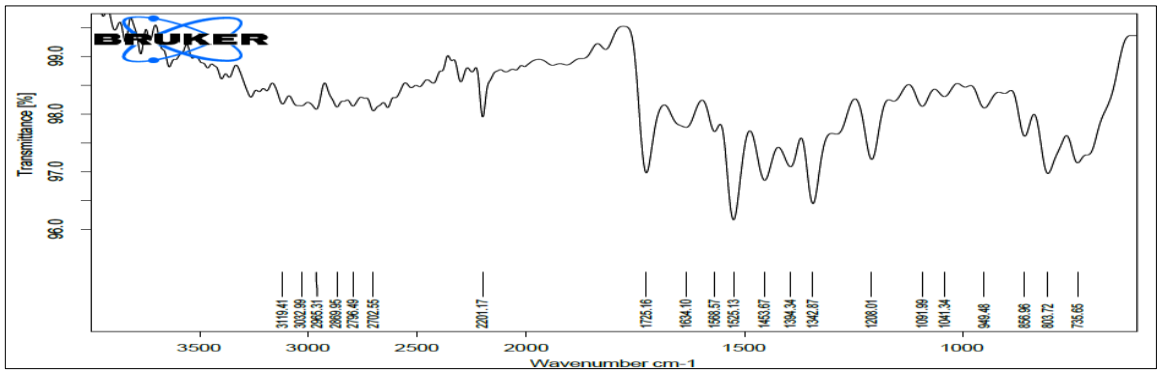

Figure 2 FTIR spectra of F2 formulation

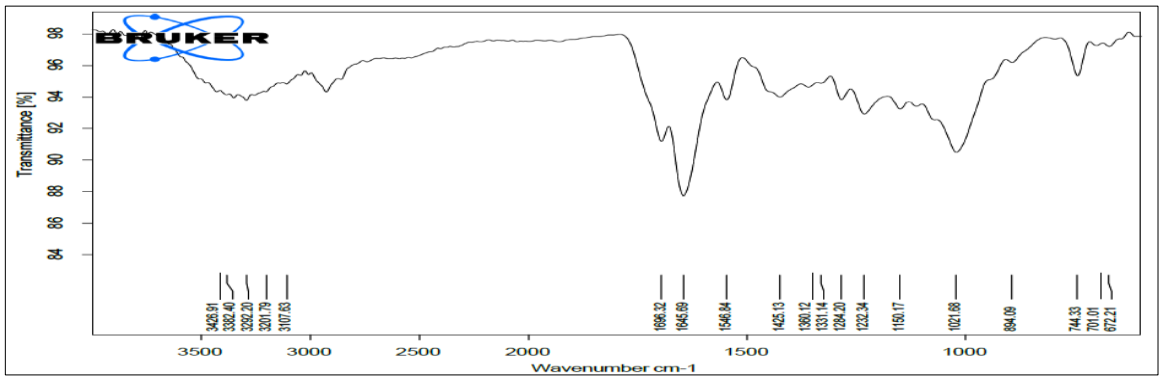

Figure 3 FTIR spectra of F4 formulation.

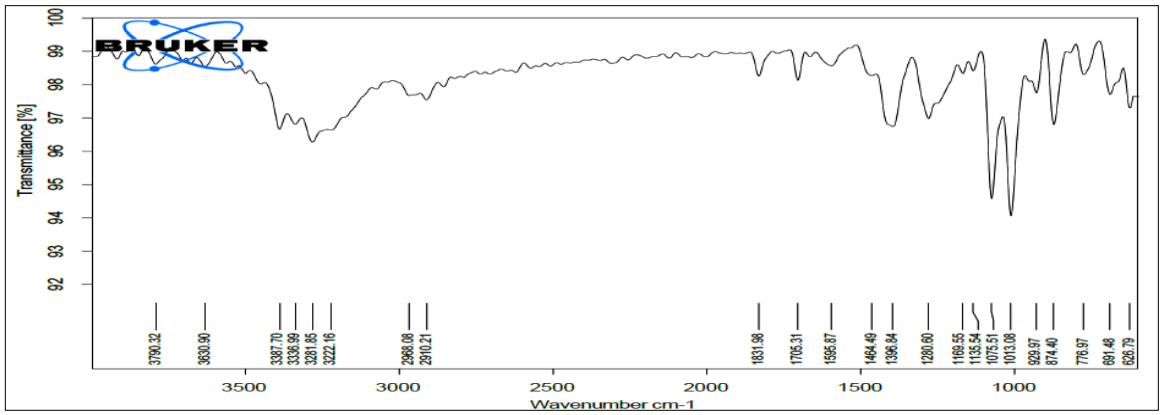

Figure 4 FTIR spectra of F6 formulation.

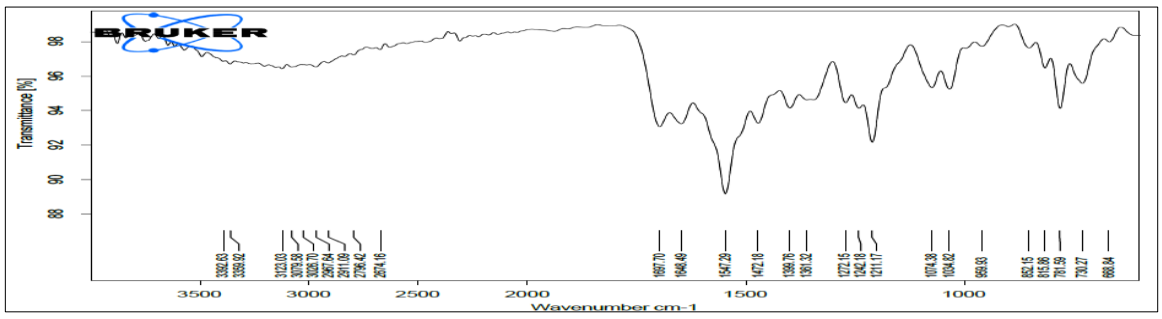

Figure 5 FTIR spectra of F8 formulation

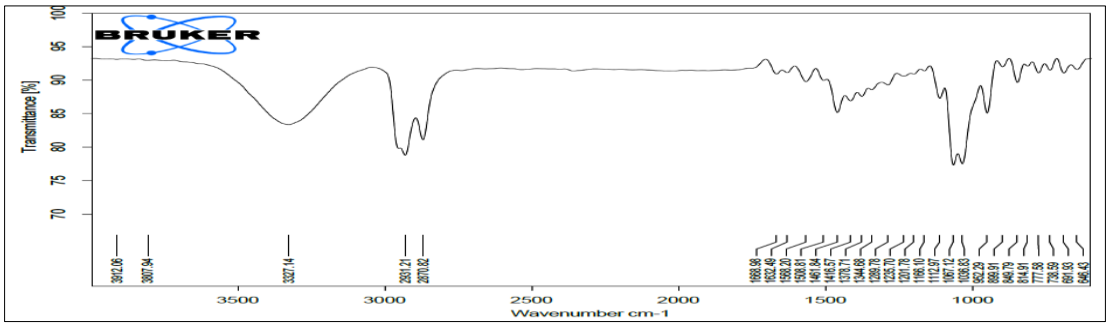

Figure 6 FTIR spectra of F10 formulation.

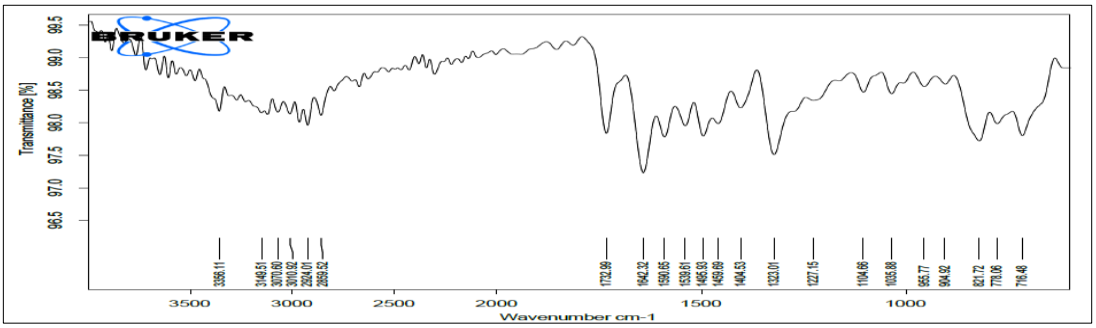

Figure 7 FTIR spectra of F12 formulation.

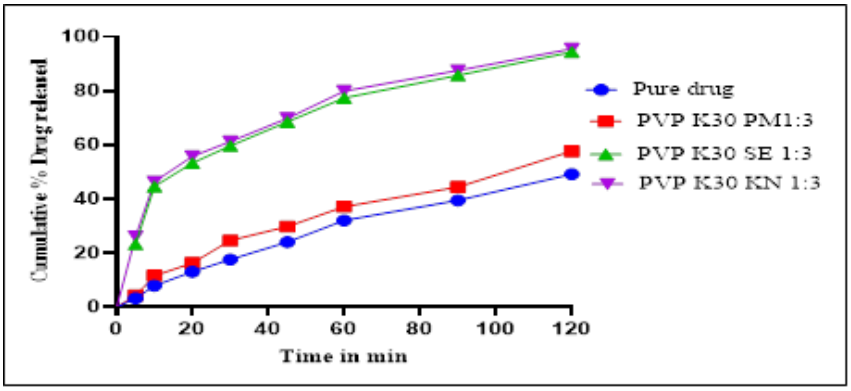

Figure 8 Comparative dissolution profile of pure drug and its solid dispersion systems prepared with PVP K-30 by all methods at 1:3 ratios.

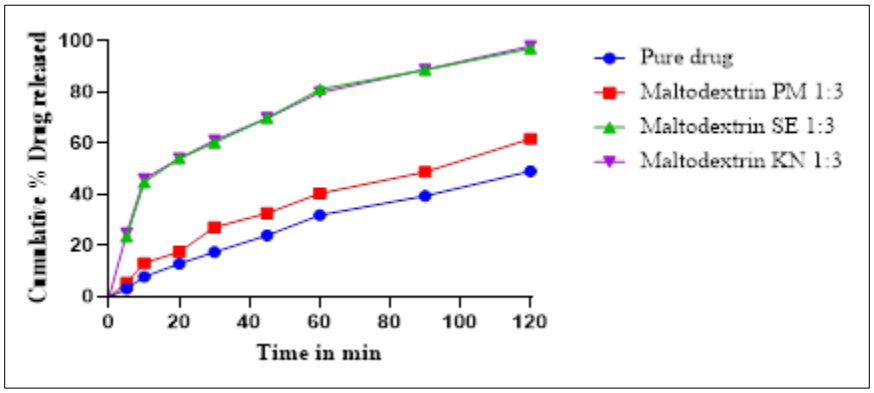

Figure 9 Comparative dissolution profile of pure drug and its solid dispersion systems prepared with maltodextrin by all methods at 1:3 ratios.

3.4. Comparative evaluation of marketed product with prepared solid dispersions

Table 3 Comparative dissolution data of marketed product with prepared solid dispersions.

Time (min)	Cumulative percentage drug released ±SD
5	6.70±0.005774
10	15.70±0.057735
20	26.2±0.057735
30	49.10±0.057735
45	61.54±0.005774
60	73.18±0.005774
90	78.80±0057735
120	89.69±0.005774

Table 4 Various dissolution parameters and best model fitting curve values of pure drug, physical mixtures and its solid dispersion systems prepared with PVP K-30 at 1:1 and 1:3 ratios.

Batches		DE_{30} (%)	DE_{60} (%)	DP_{30}	DP_{60}	T_{50} (min)	RDR_{30}	RDR_{60}	MDT_{30}	First order rates	
										R	K1
Pure drug		9.84	17.17	16.00	29.40	119.2	1	1	13.27	0.9951	-0.0058
PM	1:1	10.34	18.30	17.70	32.20	107.0	1.06	1.07	13.50	0.9953	-0.0065
PM	1:3	13.21	21.80	19.50	35.20	95.8	1.39	1.15	13.94	0.9887	-0.0072
SE	1:1	40.23	52.65	47.20	72.10	32.6	3.31	2.32	9.37	0.9659	-0.0213
SE	1:3	42.79	55.67	51.40	76.40	28.8	3.38	2.41	8.51	0.9748	-0.0241
KNE	1:1	42.92	55.24	50.40	75.40	29.7	3.34	2.38	8.17	0.9706	-0.0234
KNE	1:3	44.76	57.48	53.90	78.80	26.8	3.47	2.49	8.08	0.9762	-0.0258

Table 5 Various dissolution parameters and best model fitting curve values of pure drug, physical mixtures and its solid dispersion systems prepared with maltodextrin at 1:1 and 1:3 ratios.

Batches		DE_{30} (%)	DE_{60} (%)	DP_{30}	DP_{60}	T_{50}(min)	RDR_{30}	RDR_{60}	MDT_{30}	First order rates	
										R	K1
Pure drug		9.84	17.17	16.00	29.40	119.2	1	1	13.27	0.9951	-0.0058
PM	1:1	13.53	22.54	20.00	36.00	93.2	1.45	1.20	14.21	0.9878	-0.0074
PM	1:3	14.71	24.04	21.70	38.60	85.2	1.58	1.26	13.83	0.9894	-0.0081
SE	1:1	42.23	55.52	52.40	77.40	28.0	3.33	2.43	8.49	0.9814	-0.0248
SE	1:3	43.31	56.84	56.90	81.40	24.7	3.42	2.53	8.49	0.9832	-0.0281
KNE	1:1	42.91	56.04	54.10	78.90	26.7	3.39	2.46	8.52	0.9791	-0.0260
KNE	1:3	44.0	57.14	50.46	77.20	25.2	3.47	2.49	8.47	0.9741	-0.0295

Dissolution studies were carried out for commercially available brand of nimodipine in according to USP specifications for dissolution. It's recommended that the percentage of API released in 120 min from immediate release tablets using

0.1N HCl must be not less than 70%. Dissolution profiles of nimodipine from marketed tablets over 120 min in 0.1N HCl are shown in table 3.The results of the dissolution study of nimodipine from solid dispersion found greater solubility of drug compared to pure drug and marketed product. The outcomes of an *in vitro* drug release study show higher cumulative drug release at 120 min, that is 98.02 % of nimodipine from prepared solid dispersions kneading method 1:3 in both the polymers in comparison to pure drug and marketed product, which was only 49.19 % and 89.69 % respectively.

4. Discussion

Solid dispersion systems of nimodipine were prepared using PVP K-30 and maltodextrin at 1:1 and 1:3 ratios by physical mixture, solvent evaporation and kneading methods. The prepared solid dispersion systems were characterized for its drug content, interaction studies by FTIR and in vitro dissolution studies. The dissolution data were further model fitted by using dissolution software PCP Disso V3.0. The parameters were discussed in detail.

The percentage drug content was found to be in the range of 92.1 ± 0.1 to 95 ± 0.1 and 91±0.5 to 93.75±0.1 for solid dispersions prepared with PVP K30 and maltodextrin respectively. The low SD values indicate that method employed resulted solid dispersion systems with uniform drug content. The IR spectra of Nimodipine pure drug shows characteristic absorption bands at 3296 cm-1 (NH stretching), 2967 (aromatic CH=CH stretching), 2886 (-CH3 stretching), 1639 (ester -C=O stretching) and 1455, 1283 cm-1 (NO2 stretching) bands which are specific absorption bands due to various functional groups present in the nimodipine. Whereas the IR spectra of various formulations prepared by employing different polymers viz., PVP K-30 and maltodextrin with nimodipine indicated that there is no chemical interaction between the drug and polymer, which is indicated by presence of prominent absorption bands of principle functional groups of the drug nimodipine viz., - NH absorption band appeared in the range of 3100 -3200 cm-1 and the absorption band of -C=O ester is appeared in the range of 1600- 1680 cm-1 which indicates no chemical interaction between drug and polymer.

4.1. *In vitro* dissolution studies

The cumulative percentage drug release from the pure drug was found to be 49.19± 0.019 after 120 min, whereas physical mixture prepared at 1:1, 1:3 with PVPK30 was found to be 54.54 ± 0.19 and 57.73 ± 0.09 and maltodextrin was found to be 57.97 ± 0.20 and 61.90 ± 0.09.The cumulative percentage drug release from the solid dispersion prepared at 1:1, 1:3 with PVPK30 by solvent evaporation method was found to be 91.77± 0.19 and 94.35± 0.19 and kneading method was found to be 93.86± 0.29 and 95.51 ± 0.20 after 120 min. The cumulative percentage drug release from the solid dispersion prepared at 1:1, 1:3 with maltodextrin solvent evaporation method was found to be 94.76 ± 0.19 and 97.13 ± 0.20 and kneading method was found to be 96.07 ± 0.28 and 98.02 ± 0.10 after 120 min.

The results of the dissolution rate studies indicated higher dissolution rate of nimodipine from solid dispersion systems when compared to nimodipine itself and the corresponding physical mixtures. The slight increase in dissolution rate and efficiency values recorded for the physical mixture may be explained on the basis of the solubility of the drug in aqueous hydrophilic polymeric solutions. Since the hydrophilic polymer dissolve more rapidly in the dissolution medium than the drug alone, it can be assumed that, in early stages of the dissolution process, the hydrophilic excipient molecule will operate locally on the hydrodynamic layer surrounding the particles of the drug. In vitro release studies reveal that there is marked increase in the dissolution rate of nimodipine from all the solid dispersions when compared to pure nimodipine itself. From the in vitro drug release profile, it can be seen that formulation containing 1:3 drug: carrier ratios show higher dissolution rate compared with other ratios in all methods with all the two excipients. This may be attributed to the increase in drug wettability and solubilization of the drug due to hydrophilic carrier at higher concentration.

From the regression coefficient (r) values for formulations, model that gave higher 'r' value was considered as best fit model. The 'r' values for first order model were found to be 0.9953, 0.9887, 0.9659, 0.9748, 0.9706, 0.9762 with all the solid dispersions prepared with PVPK30 and 0.9878, 0.9894, 0.9814, 0.9832, 0.9791, 0.9741 with all the solid dispersions prepared with maltodextrin indicating that the dissolution of nimodipine as such and from all the solid dispersions followed first order kinetics.The DE30 and DE60 values of the nimodipine: polymer kneaded solid dispersion systems were higher than those of the solid dispersion systems prepared by solvent evaporation and physical mixture methods, this may be due to less crystallinity of the nimodipine kneaded systems than that of solvent evaporation and physical mixture solid dispersion systems.The DE30 and DE60 values of the solid dispersion systems that were prepared by the kneading and solvent evaporation methods were relatively high when compared with the values from the physical mixtures and nimodipine alone. Over all the rank order of improvement in dissolution properties of nimodipine with different excipients is maltodextrin>PVPK30 and with methods KNE > SE > PM and ratios in the order 1:3 > 1:1.

5. Conclusions

Solid dispersion systems of Nimodipine were conveniently prepared using PVP K30 and maltodextrin at 1:1 and 1:3 ratios by physical mixture, solvent evaporation and kneading method.The obtained solid dispersion systems were found to be free flowing. With small SD values indicates that method employed resulted solid dispersion systems with uniform drug content.The IR spectra of various formulations prepared by employing different polymers viz., PVP K-30 and maltodextrin with nimodipine indicated that there is no chemical interaction between the drug and polymer. The solid dispersions of the water insoluble drug Nimodipine were successfully prepared by solvent evaporation and kneading method using PVP K30 and maltodextrin. The *in vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure Nimodipine. Mechanisms involved are solubilization and improved wetting of the drug in the hydrophilic carriers rich microenvironment formed at the surface of drug crystals after dissolution rate. One-way ANOVA was used to test the statistical significant difference between pure and prepared solid dispersion systems. Significant differences in the means of DP_{60} and DE_{60} were tested at 95% confidence. The DP_{60} and DE_{60} values of solid dispersion systems prepared by solvent evaporation and kneading method were significantly higher ($P<0.05$) when compared to DP_{60} and DE_{60} values of physical mixture and pure Nimodipine.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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