Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(7):112-120

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Development of Controlled Release Tablets of Nisoldipine with Improved Pharmaceutical Properties

Buchi N. Nalluri*, Satish K. Bonagiri, V Saisri Anusha, R. Sribramhini, Karna M. Maheswari

KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, AP, INDIA

ABSTRACT

The present investigation was undertaken with an objective of formulating controlled release (CR) matrix tablets of Nisoldipine (NIS), an anti-hypertensive and anti-anginal drug based on the formation of inclusion complexes with β-Cyclodextrin (β-CD) & Hydroxy Propyl-β-Cyclodextrin (HP-β-CD) i.e., NIS-β-CD and NIS-HP-β-CD at 1:1 and 1:2 M ratios. Binary systems of NIS-CD were prepared by kneading method (KS) and physical mixtures (PM). KS exhibited superior dissolution properties when compared to PM, pure NIS and the improvement in dissolution rate values were in the order of KS > PM > pure NIS. The dissolution properties for NIS-CD binary systems were in the order of HP-β-CD > β-CD. These binary systems prepared by kneading technique were further compressed into tablets by direct compression process using Hydroxy Propyl Methyl Cellulose (HPMC K 100 LV) as drug release retardant and were evaluated for various physico-chemical/mechanical parameters. Formulation containing NIS-HP-β-CD 1:1M gave superior release 99.39 ± 0.53 % at the end of 6 hrs when compared to NIS-β-CD (1:1M) and pure NIS formulations. The dissolution data was also evaluated for drug release kinetics and mechanism.

Keywords: Nisoldipine, Controlled release matrix tablets, HPMC, binary systems.

INTRODUCTION

Over the past few decades several new chemical entities (NCEs) have been discovered, out of which 40% are the lipophilic and poorly soluble drugs [1]. Solubility of the drug is the main obstacle in the delivery of the NCEs and also existing drugs. The ability of improving the solubility and delivery of poorly soluble drugs is very important step in formulation development. It can be enhanced through either altering the macromolecular characteristics of the drug particles, or chemical or mechanical modification of the environment surrounding the drug molecule. Particle size reduction, addition of surfactant, pH adjustment, self-emulsifying systems and inclusion in cyclodextrin-drug complexes are the best examples for the solubility enhancement techniques [2]. Together with the solubility, the permeability behavior should also be considered in the development of formulation for oral administration. Drug absorption from solid dosage forms after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two steps, *in vitro* dissolution may be relevant to the prediction of *in vivo* performance.

NIS is used in the treatment of hypertension, angina pectoris with a terminal half life of 7-12hrs. The low oral bioavailability of the drug (15-24%) is due to the hepatic first pass effect and its absorption is dissolution rate limited [3]. Improving the dissolution properties of NIS can improve its absorption and also bioavailability and onset of action. Currently NIS is marketed in US as controlled release oral tablet in different strengths. So far no research works were published on CR dosage forms of NIS. However, some patents were published [4].

Hence, the present investigation was aimed to develop once or twice a day oral CR tablet dosage forms for NIS

based on HPMC K 100 LV as drug release retardant. Since, NIS is poorly water-soluble drug, its release from the CR tablets is incomplete and therapeutically effective drug levels may not be achieved. So, binary systems of NIS were prepared with β-CD and HP-β-CD by physical mixing and kneading techniques to form inclusion complexes thereby enhancing the solubility.

EXPERIMENTAL SECTION

Material and Methods

NIS (Gift sample from Orchid Pharmaceuticals Pvt. Ltd, Chennai, India), Beta Cyclodextrin (Rouette Pharma, France), Hydroxy Propyl Beta Cyclodextrin (Rouette Pharma, France), Methanol (Loba Chemie, Mumbai, India), Hydroxy Propyl Methyl Cellulose K 100 LV (Colorcon, India), Microcrystalline cellulose-Avicel PH 105 (FMC Biopolymers, USA), Magnesium stearate (Finar, Mumbai, India), Colloidal silicon dioxide (Loba Chemie, Mumbai, India) were used. All the chemicals and reagents are of analytical grade.

Analytical Procedures

An UV-VIS Spectrophotometric method [5] based on the measurement of absorbance at 245nm in methanol stock solution was used in the present research work for estimation of NIS. As the dissolution studies of NIS were carried out in 0.1N HCl with 0.5% SLS calibration curve was also constructed in the same medium.

Solubility studies

Excess of NIS (50mg) was added to 15mL of each fluid in 25mL stoppered conical flasks and the mixtures were shaken for 48 hours at room temperature (28 ± 1°C) on a rotary flask shaker. 1mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were suitably diluted and assayed for NIS by measuring absorbance at 245nm. Shaking was continued until three consecutive estimations were same. The solubility experiments were run in triplicate.

Preparation of NIS-CD Binary Systems:

In the present investigation two types of binary systems namely physical mixtures, kneaded systems of NIS and CDs were prepared in 1:1 and 1:2 molar ratios in order to study the possibility of improving dissolution rate of NIS. The formulae of binary systems are given in Table 1.

Table 1: Formulae of the NIS and NIS-CD binary systems

Composition	Formulation
Pure drug (NIS)	F1
Physical mixture of NIS with β-CD at 1:1M	F2
Physical mixture of NIS with β-CD at 1:2M	F3
Physical mixture of NIS with HP- β-CD at 1:1M	F4
Physical mixture of NIS with HP- β-CD at 1:2M	F5
Kneaded system of NIS with β-CD at 1:1M	F6
Kneaded system of NIS with HP-β-CD at 1:1M	F7

Physical mixtures (PM)

The Physical mixtures of NIS and CDs in 1:1M and 1:2M were prepared by mixing pulverized powders (# 100) together with a spatula.

Kneaded systems (KS)

The physical mixtures of NIS and CDs in 1:1M and 1:2M were triturated in a mortar with a small volume (5mL) of water-methanol (1:1v/v) solution. The thick slurry was kneaded for 45 minutes and then dried at 45°C until dryness. The dried mass was pulverized and sieved through # 100.

Drug excipients compatibility of Binary systems by FTIR Spectroscopy:

FTIR spectra were obtained on Spectrum 100 FTIR (Perkin-Elmer). Samples were prepared in KBr disks and data were collected over a spectral region from 4000 to 400 cm^{-1}.

Preparation of NIS CR tablets

Compressed tablets of NIS and NIS-CD 1:1M kneaded binary system was prepared by direct compression method, as per formulae given in Table 2.

Table 2: Formulae of the tablets of NIS and NIS-CD kneaded binary systems

Ingredients (mg/Tab)	FORMULATIONS		
	F8	F9	F10
NIS	**20**	**-**	**-**
NIS-β-CD KS 1:1M	**-**	**80**	**-**
NIS-HP-β-CD KS 1:1M	**-**		**92**
HPMC K 100 LV	**50**	**50**	**50**
MCC	**128**	**68**	**56**
Colloidal Silicone dioxide	**1**	**1**	**1**
Magnesium stearate	**1**	**1**	**1**
Total Weight of the Tablet (mg)	**200**	**200**	**200**

HPMC K 100 LV was used as release retardant material. Colloidal silicon dioxide and magnesium stearate at 1%w/w concentrations were used as glidant/lubricants. Sufficient quantities of MCC were used to raise the total bulk of the tablets to a weight of 200mg each. The resulting powder blend was compressed on single punch tablet press (Cadmach, India) using 8 mm punches (round shape) to the hardness of 4-6Kg/cm^2.

Evaluation of Flow Properties of Binary systems

The binary systems were evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio [6].

Evaluation of NIS tablets:

The tablets were evaluated for following properties: drug content, uniformity of weight, hardness, friability, and *in vitro* drug release profiles [7].

Drug content

Five tablets were weighed and powdered in a mortar. Accurately weighed powder samples equivalent to 20 mg of NIS was transferred to a 100mL volumetric flask, and NIS was extracted in to 75mL methanol. This solution was filtered and collected in to a 100mL volumetric flask and made volume up to 100mL with methanol. The solution was suitably diluted with 0.1N HCl with 0.5% SLS and the absorbance was measured at 245nm. The estimations were carried out in triplicate.

Uniformity of weight of tablets

The individual and total weight of 20 tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated.

Hardness

The hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average of 6 tablets for each formulation.

Friability

For each formulation 10 tablets were weighed, placed in Friabilator (M/S Cambell Electronics, India) and were subjected to 100 rotations in 4min. The tablets were reweighed and friability was calculated by the following formula: $$Friability = \frac{W_2 - W_1}{W_1} \times 100$$

Where W_1 is the initial weight and W_2 is the final weight of the tablets.

***In vitro* Dissolution studies**

In vitro dissolution studies of pure drug, the binary systems and prepared CR tablet formulations were carried out in 900 mL of 0.1N HCl with 0.5% w/v SLS using USP XXI type 2 (paddle method) Dissolution Rate Test Apparatus (DISSO 8000, Lab India). In the case of powders, the samples were dispersed on dissolution medium. Samples equivalent to 20mg of NIS, a speed of 50 rpm and a temperature of 37 ± 1°C were used in each test. A 5mL aliquot was withdrawn at different time intervals, filtered using a 0.45µ nylon disc filter and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for NIS by measuring absorbance at 245nm. The dissolution experiments were conducted in triplicate.

Release kinetics and mechanism

In order to describe the kinetics of the release process of NIS, various equations were used such as the zero-order rate equation [8], which describes the systems where the release rate is independent of the concentration of the

dissolved species. The first-order equation [9] describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. The Higuchi square root equation [10], describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion. Two factors, however, diminish the applicability of Higuchi's equation to matrix system. This model fails to allow for the influence of swelling of the matrix upon hydration and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the Peppas equation [11], which is often used to describe the drug release from polymeric system.

$$Mt/Ma = K\, t^{n} \qquad (1)$$

Where Mt/Ma is the fractional drug release at time t; K is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is a kinetic constant which depends on and is used to describe the transport mechanism. The value of n for a tablet, n = 0.45 for Fickian (Case I) release, > 0.45 but < 0.89 for non Fickian (anomalous) release and 0.89 for case II (zero-order) release and > 0.89 for super case II type of release. Equation one was used to calculate the n values and to identify the drug release mechanism of drug.

Due to the differences in drug release kinetics, the Peppas constant k, though is one of the measures of release rate, should not be used for comparison. Therefore, to characterize the drug release rate in different formulations, mean dissolution time (MDT) was calculated from dissolution data using the formula:

$$MDT = (n/n+1) \times k^{-1/n}$$

Where n is the release exponent and k is the Peppas constant [12]. MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice-versa [13].

RESULTS AND DISCUSSION

Solubility Studies

NIS is not yet official in any pharmacopoeia; official dissolution rate test is not available. However, dissolution rate tests were reported where 0.1N HCl with 0.5% SLS was used as dissolution medium for evaluating *in vitro* dissolution profiles for extended release NIS formulations. Based on these published FDA reports solubility of NIS in 0.1N HCl and 0.1N HCl with different concentrations of SLS and also in water was carried out and results were shown in Fig.1. An 8-fold increase in NIS solubility with 0.5% SLS in 0.1N HCl was observed when compared to without SLS and the solubility of NIS increased with increasing the SLS concentration in 0.1N HCl. Based on the data form the solubility studies and keeping in view of the discriminating power of the selected dissolution medium and excipients selected in the formulation development studies, all the dissolution experiments were carried out in 0.1N HCl with 0.5% w/v SLS as dissolution medium.

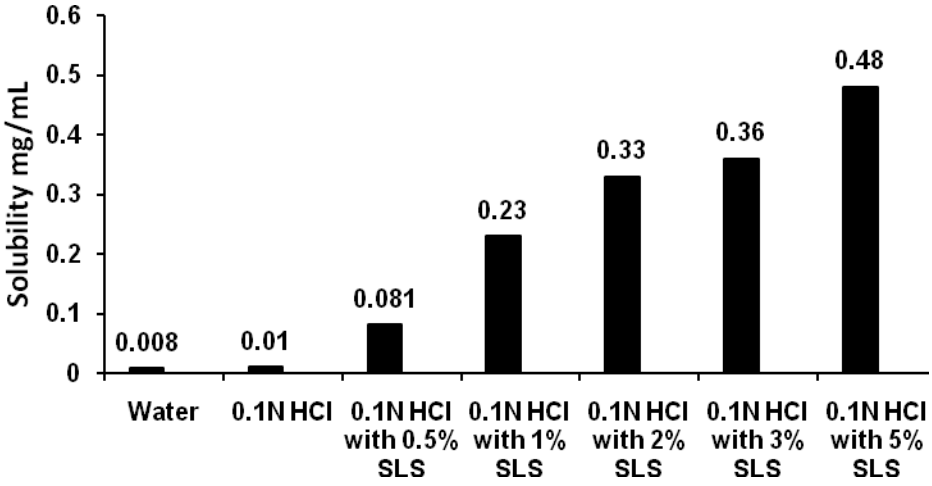

Figure 1 Solubility of NIS in different fluids

FTIR Studies

FTIR studies were carried with a view to evaluate the *in situ* drug and excipient/s compatibility. Fig.2. shows the IR spectra of pure NIS and different NIS-CDs kneaded systems (1:1M). Pure NIS showed IR absorption bands at 1705

cm^{-1} for the ester carbonyl-stretching band, 1114 and 1216 cm^{-1} for ether absorption bands of C3 and C5, respectively. The absorption bands at 1492 and 1531 cm^{-1} were denoted for stretching vibration of C = C in the aromatic ring while, 1310 cm^{-1} was denoted for NO_2 group and 3323 cm^{-1} for N-H group. The spectra of pure CDs showed the vibration of free -OHs between 3300 and 3500 cm^{-1} and those of the bound -OHs at 2930 cm^{-1}.

The spectra of all NIS-CD systems did not show new peaks, indicating no chemical bonds were created in the formed compounds. Although no appreciable changes were observed at the bands of ether groups (1114 and 1216 cm^{-1}), the band at 1114 cm^{-1} has nearly disappeared between NIS and both CDs. These results served to confirm the existence of a strong interaction between NIS and both CDs whereas, the band at 1310 cm^{-1} denoted for NO_2 group was disappeared for NIS-HP-β-CD kneaded system indicative of inclusion of aromatic ring in to HP-β-CD cavity.

Moreover, the absorption band at 3323 cm^{-1} ascribed to stretching vibrations of the N-H bond in the dihydro pyridine ring was broaden, slightly shifted or nearly disappeared in the kneaded system samples spectra. Thus, the FTIR spectral studies may indicate that NIS molecule is partially included into CD cavities through the dihydro pyridine ring.

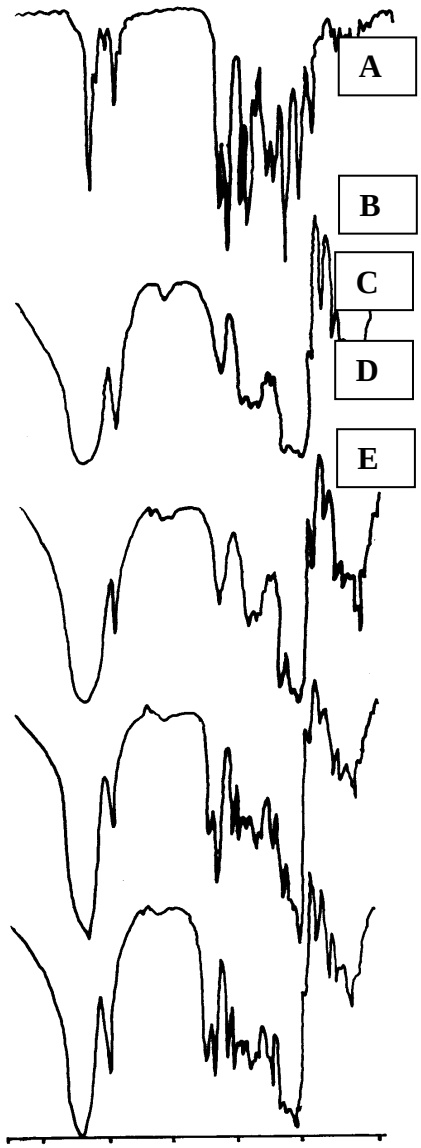

Figure 2 FTIR spectra of NIS (A); β-CD (B); HP-β-CD (C); NIS-β-CD-KS 1:1M (D) ;

NIS-HP-β-CD-KS 1:1M (E)

Determination of pre and post compression parameters

The results of various pre compression parameters are given in Table 3.

Table 3: Pre compression parameters of NIS and NIS-CD binary systems

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner ratio	Angle of repose (°)
F8	0.353	0.256	37.8	1.37	29.8
F9	0.339	0.253	33.9	1.33	30.4
F10	0.332	0.251	32.2	1.32	29.5

These results indicated that the binary systems of all formulations are suitable to prepare tablets by direct compression technique. The compressed tablets fulfilled the official compendia requirements regarding drug content, uniformity of weight, hardness and friability. The results are given in Table 4.

Table 4: Post compression parameters of NIS and NIS-CD CR tablet formulations

Formulation	Drug content (mg/tab)	Weight Variation (mean ± SD)	Hardness (Kg/cm^2)	Friability (%wt. loss)
F8	**19.98**	**200 ± 1.25**	**5**	**0.53**
F9	**20.12**	**198 ± 2.52**	**5**	**0.51**
F10	**20.25**	**202 ± 1.98**	**4.5**	**0.32**

***In Vitro* Dissolution Studies**

NIS-CD Binary Systems

When an assumed drug-CD binary system is dispersed in a dissolution medium, a very rapid dissolution is often observed. Dissolution rate tests are based on this observation in order to characterize the inclusion complexation between drug and cyclodextrin. The most often used dissolution rate tests are the rotating disk method and dispersed amount method. In the present investigation dispersed amount method is used to investigate the various dissolution parameters of NIS and NIS-CD binary systems. The dissolution experiments were carried out in 0.1N HCl with 0.5% w/v SLS as dissolution medium.

The drug percent dissolved at 30 min (DP_{30}) values for NIS, NIS-β-CD PM at 1:1M and 1:2M were 40.97 ± 3.30, 48.98 ± 1.78 and 56.81 ± 3.20 respectively, whereas NIS-HP-β-CD PM at 1:1M and 1:2M were 63.89 ± 1.40 and 86.73 ± 0.44 respectively. When compared to the pure NIS the DP_{30} values were significantly higher for PMs at both molar ratios for both CDs. However, the values for NIS-HP-β-CD PMs were significantly higher when compared to that of NIS-β-CD PMs. The DP_{30} values for NIS-β-CD and NIS-HP-β-CD KS at 1:1M were 91.38 ± 1.19 and 100 ± 0.00 respectively and were significantly higher when compared to that of pure NIS and NIS-CD physical mixtures. The RDR (relative dissolution rate) values were also in the same order as above Table 5.

Table 5: Mean ± SD dissolution parameters of NIS and NIS-CD binary systems

Formulation	DP_{30} (Mean ± SD)	RDR	k(min^{-1})
F1	**40.97 ± 3.30**	**-**	**0.0215**
F2	**48.98 ± 1.78**	**1.19**	**0.0270**
F3	**56.81 ± 3.20**	**1.36**	**0.0351**
F4	**63.89 ± 1.40**	**1.56**	**0.0409**
F5	**86.73 ± 0.44**	**2.11**	**0.0790**
F6	**91.38 ± 1.19**	**2.23**	**0.1026**
F7	**98.42 ± 0.76**	**2.40**	**0.1305**

The comparative cumulative percent drug release profiles of the prepared binary systems are given in Fig.3.

When compared to pure NIS, the first order release rate constant 'k' (min^{-1}) values were significantly higher for PMs at both molar ratios for both CDs. However, the values for NIS-HP-β-CD PMs were significantly higher when compared to that of NIS-β-CD PMs whereas; the 'k' values are significantly higher for kneaded system when compared to pure NIS and NIS-CD physical mixture. A 4.77 and 6.06 fold increase in 'k' values for NIS-β-CD and NIS-HP-β-CD 1:1M kneaded system was observed when compared to pure NIS.

Overall, binary systems prepared by kneading method exhibited superior dissolution properties when compared to physical mixtures and pure NIS and the improvement in dissolution rate values were in the order of KS > PM > NIS. Overall, the dissolution properties for NIS-CD binary systems were in the order of HP-β-CD > β-CD. The increase in dissolution rate recorded for the physical mixtures may be explained on the basis of the solubility of the drug in aqueous CDs solutions. Since the CDs dissolve more rapidly in the dissolution medium than the pure drug, it can be assumed that, in early stages of the dissolution process, the CD molecules will operate locally on the hydrodynamic

layer surrounding the particles of the drug, this action resulting in an *in situ* inclusion process, which produces a rapid increase of the amount of the dissolved drug. The marked increase in the dissolution rate and efficiency values of physical mixtures could be also due, although to a lesser extent, to the hydrophilic effect of CDs, which can reduce the interfacial tension between water insoluble drugs and the dissolution medium, thus leading to a higher dissolution rate values. The higher dissolution rate values observed with NIS-HP-β-CD kneaded systems may be attributable to the reduction in crystallinity and enhanced wettability of NIS. The superiority of dissolution characteristics observed with kneaded systems than those of physical mixtures may be due to the better interaction of NIS with CDs during kneading process.

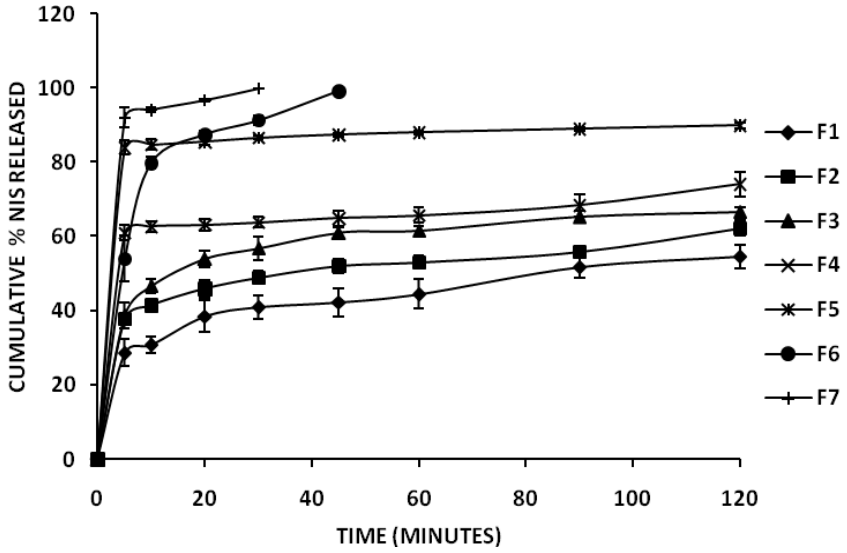

Figure 3 Comparative dissolution profiles of NIS and NIS-CD binary systems

The cyclodextrin inclusion complex of a poorly soluble drug is usually more hydrophilic than the free drug itself. It wets more easily and the drug dissolves faster and better. A compound in the crystalline state dissolves more slowly than that in the amorphous state. In general, it can be concluded that the increased dissolution rate of CD-entrapped drug molecules is a result of various factors: an increased solubility, an improved wettability, decrease in crystallinity, molecular dispersion and the large surface area available for dissolution. Based on the results obtained with dissolution studies kneaded systems of NIS with both β-CD and HP-β-CD were selected and further formulated in to CR tablets along with pure NIS for comparison.

NIS CR tablets

All the tablet formulations were subjected to *in vitro* drug release studies using 0.1N HCl with 0.5% SLS as dissolution medium, in order to assess drug release profiles including release kinetics and drug release mechanisms from tablets.

Swellable systems consisting of hydrophilic polymers, in the presence of water, absorb a significant amount of dissolution medium to form gel. As the dissolution medium penetrates the matrix, polymer material swelling starts and drug molecules begin to move out of the system by diffusion. Swelling therefore modifies the drug release; and compared with a porous, inert, non swellable matrix, the porosity and tortuosity of a swellable matrix are primarily attributed to the polymer swellability. In swellable systems, the drug release occurs by water absorption, matrix swelling, and subsequent drug diffusion through the gel layer.

The dissolution profiles of these formulations (F8-F10) clearly indicated a controlled release pattern over a period of 6-12 h, because HPMC tablet formulations swelled upon contact with the dissolution media and a gel layer was formed on their surface. This gel retarded further ingress of fluid and subsequent drug release. Nevertheless, drug release was nearly complete in the end of the dissolution experiment, almost certainly because of higher solubility and dissolution performances of NIS in the presence of CDs. F8 formulation containing pure NIS only 54.00 ± 4.12 percent of drug was released at the end of 12 hours. Whereas, F9 and F10 formulations with kneaded systems of NIS-β-CD and NIS-HP-β-CD 1:1M instead of pure NIS gave a complete drug release. However, with F9 formulation a complete drug release was observed within 10 hrs, whereas with F10 formulation a complete drug release was observed within 6 hrs. The complete drug release with F9 and F10 formulations may be because of improved solubility and dissolution properties of NIS with β-CD and HP-β-CD respectively. The higher and complete release observed with F10 formulation can be better explained by the fact that HP-β-CD itself is more

hydrophilic and soluble when compared to the β-CD. These results were further confirmed by the MDT values as given in Table 6.

Table 6: Values of R^2, *k* and n values for CR tablet formulations

Formulation	Zero order		First order		Higuchi		Peppas		MDT (min)
	R^2	*K*	R^2	*k*	R^2	*K*	R^2	n	
F8	0.9454	4.15	0.9607	0.058	0.9602	17.83	0.8865	0.97	571.42
F9	0.9799	10.63	0.8794	0.428	0.993	44.31	0.9599	1.27	378.13
F10	0.8871	17.27	0.9683	0.841	0.909	53.89	1.0000	1.40	309.40

The comparative cumulative percent drug release profiles of the prepared CR tablet formulations are given in Fig.4.

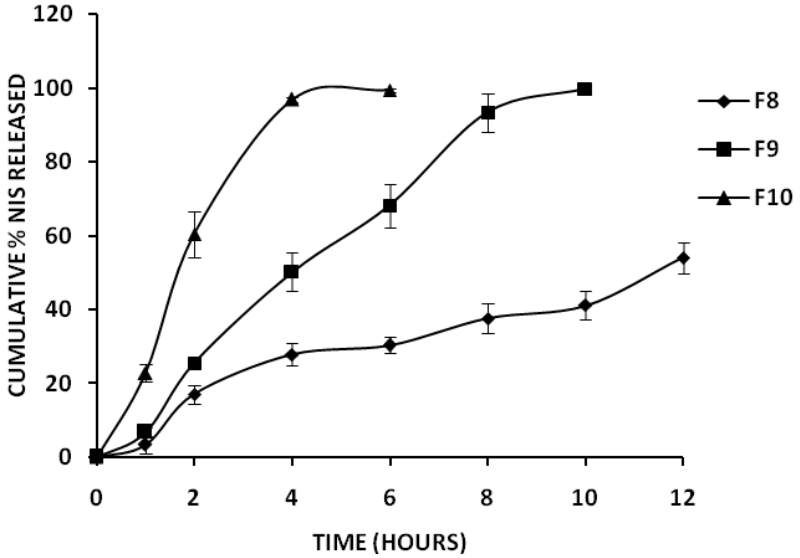

Figure 4 Comparative dissolution profiles of NIS and NIS-CD CR tablets

Drug release kinetics and mechanisms

R^2 values for F8 and F10 obtained with first order plots were found to be superior when compared to the R^2 values obtained with zero order plots. These results indicated that the NIS release from F8 and F10 followed first order kinetics Table 6. In case of F9, the R^2 values obtained with zero order plots were found to be superior when compared to the R^2 values obtained with first order plots. These results indicated that the NIS release from F9 followed zero order kinetics. The Higuchi square root model showed higher correlation coefficient values (0.9098-0.993) and diffusion is the release mechanism for NIS from the tablets.

The graphs of **Log Qt/Q *versus* Log t** showed a linear relationship with R^2 values ranged from 0.88-1.000 and 'n' values from 0.97-1.40 and demonstrated Super Case II transport i.e., the release of NIS form these tablets especially, with F9 and F10 formulations were likely due to the combination of NIS diffusion and polymer relaxation/dissolution as opposed simple Fickian diffusion. It is evident that dissolution or erosion of the HPMC matrices would account for the increasing values of 'n' and this may explain the burst and complete release of NIS from these tablets. The results are given in Table 6.

CONCLUSION

Overall, the binary systems of NIS prepared by kneading technique gave superior dissolution properties when compared to physical mixing technique and pure NIS. Among the 10 formulations, F9 formulation (NIS-β-CD 1:1M) gave 99.74 ± 1.07 at the end of 10 hrs, F10 formulation (NIS-HP-β-CD 1:1M) gave 99.39 ± 0.53 at the end of 6 hrs and fulfils the regulatory requirement. The CR tablets gave a controlled release of NIS over a period of 6-12 hrs depending on formulation. The controlled release formulations containing NIS-CD binary systems gave higher NIS release when compared to tablets containing pure NIS and further investigations are needed to extend the drug release from the tablets over a period of 12-24 hrs as required.

Acknowledgements

The authors are thankful to the Orchid Pharmaceuticals Pvt Ltd, Chennai for providing Nisoldipine sample and Siddhartha Academy of General and Technical Education, Vijayawada, for providing necessary facilities to carry

out this research work**.**

REFERENCES

[1] D Mudit; GK Ashwini; PK Kulkarni. *Int J Pharm & Pharm Sci*., **2011**, 3(2), 231-35.
[2] PS Mohanachandran; PG Sindhumol; TS Kiran. *Int. J. Comp. Pharm.*, **2010**, 4 (11), 1-10.
[3] K Parfitt; JE Reynolds; AV Parsons; CS Sweetman. Martindale: The Extra Pharmacopoeia, 13th Ed, Pharmaceutical Press, London, **1993**; 381.
[4] G Pascal; N Alain; V Guy. US patent **2007**, 2008/0063711A1.
[5] MS Mohammed. Der Pharma Chemica., **2011**, 3 (4), 275-78.
[6] L Lachman; HA Lieberman; JL Kanig. The Theory and Practice of Industrial Pharmacy, 3rd Ed, Varghese publishing house, Mumbai, **1987**; 296-300.
[7] The United State Pharmacopoeia, 23rd Ed, United State Pharmacopoeial Convention Inc, Rockville, **2007**; 643-45.
[8] CS Brazel; NA Peppas. *Eur. J. Pharm. Biopharm*., **2000**, 49(1), 47-58.
[9] H Lapidus; NG Lordi. *J. Pharm. Sci*., **1966**, 55(8), 840-43.
[10] T Higuchi. *J. Pharm. Sci*., **1963**, 52(12), 1145-48.
[11] RW Korsmeyer; R Gurny; EM Doelker; P Buri; NA Peppas. *Int. J. Pharm*., **1983**, 15(1), 25-35.
[12] JE Mockel; BC Lippold. *Pharm Res*., **1993**, 10(7), 1066-70.
[13] AM Hamzah; AA Othman; AK Reem; KS Ashok; M Anwar. *Drug Res Acta Poloniae Pharmaceutica*., **2010,** 67 (1), 93-97.