STUDIES ON DISSOLUTION BEHAVIOUR OF SUSTAINED RELEASE SOLID DISPERSIONS OF NIMODIPINE

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ABSTRACT

There are various techniques to control the release rate of the drugs, among which, controlling dissolution rate is most popular due to its success and low cost. Although there are numerous reports on sustained action formulations, little studies were reported on the use solid dispersion technique to produce sustained release formulation. Nimodipine is a calcium channel blocker, highly effective in the treatment of classical angina and migraine. There are some reports on solid dispersions of Nimodipine to guarantee the reasonable bioavailability and no reports on sustained released solid dispersion. The present study deals with preparation and evaluation of sustained release solid dispersions of Nimodipine using retarding polymers. Solid dispersions were prepared by solvent evaporation techniques as described in the literature using EVA, EU (RL) – 100 and EC. Solid state and drug polymer interaction were studied by I.R. In – vitro drug release were studied in U.S.P XXIII Electrolab six basket dissolution apparatus using 900 ml of dissolution media (Acetate buffer pH 4.5) at 75 RPM at $37 \pm 0.5°C$. The IR studies confirmed absence of any possible interaction. The dissolution studies indicated that about 99.2% with EC, 95.2% with EU RL 100 & 89.34% with EVA, of Nimodipine dissolved in 12 hours in PH 4.5. It is also seen that the incorporation of PEG 6000 in solid dispersions increases the release of Nimodipine. However, the release of Nimodipine was retarded with an increasing the concentration of EC, EU RL 100 and EVA. The mathematical treatment of the data indicates Fickian diffusion controlled release from the matrix. The use of PEG improved the release of Nimodipine in acidic pH while EC, EVA, EU RL 100 retarded its release.

Keywords: Nimodipine, Sustained release solid dispersions.

INTRODUCTION

More recently, the concept of solid dispersion has been explored using insoluble carrier materials. These sustained release solid dispersion system may be useful for enhancing bioavailability and suitable for sustained release formulations[1]. The sustained solid dispersion offer various potential advantages for drugs having poor bioavailability and can be delivered efficiently there by maximizing their bioavailability and sustained action[2]. Nimodipine is a calcium channel blocker, highly effective in the treatment of classical angina and migraine.[3] Nimodipine is well absorbed upon oral administration. Peak blood levels occur in about one hour, with a half-life of 1 to 2 hours and protein binding is over 95 %. These are used to enhance or reduce the dissolution rate of the drugs[4]. The reduction of the dissolution rate is achieved by incorporating the drug in insoluble carriers which are considered as matrix system, help in prolonging the duration of time over which the drug is released and are considered suitable for formulations as sustained release dosage forms.

MATERIALS AND METHODS

Nimodipine were gift samples from Micro labs Ltd., Bangalore. Methanol (S.D. Fine Chemicals India). EU RL-100 (Degussa India Pvt Ltd. India). Acetone, Ethylene Vinyl Acetate, and EC (S.D.Fine chemicals Mumbai. India). Talc (Laxachem.organic Pvt ltd-Amravati. India). All other reagents and chemicals used were of analytical reagent grade.

Preparation

Preparation of Sustained Release Solid Dispersions by Common Solvent Method: [19]

The sustained solid dispersions of Nimodipine were prepared by the solvent method. The weighed amount of drug was dispersed in a given volume of polymer [Ethyl vinyl acetate (EVA), Eudragit RL (EU RL) 100, and Ethyl Acetate (EC)] acetone solution of required concentration. These were stirred for 15 minutes to ensure homogenous mixing. The dispersion was then evaporated to dryness by storing it in a desiccator under vacuum the mass was then pulverized and fractionated. Two size fractions - the particles which passed through sieve # 40 and retained on # 60 and particles which passed through sieve # 60 but retained on # 80 were subjected for in- vitro dissolution performance. In each case 4 different ratios (1:1, 1:2, 1:3, and 1:4) of the drug and carrier were used in the preparation of sustained solid dispersions.

Preparation of Sustained Release Solid Dispersions by employing physical Mixtures: [11]

The weighed amount of drug was mixed with the corresponding amount of polymer in a glass mortar. This was done by geometric dilution technique to ensure homogenous distribution.

Preparation of Sustained Release Solid Dispersions Containing PEG: [5-10]

The weighed amount of PEG 6000 was dissolved in the polymer-acetone solution. Drug was then dispersed in this

solution, which was then evaporated, to dryness. The dried mass was then pulverized and fractionated. Two size fractions –the particles which passed through sieve #40 and retained on #60 and particles which passed through sieve #60 but retained on #80 were used to study the influence of particle size on *In-vitro* dissolution rate. In each case 4 different ratios (1:1, 1:2, 1:3 and 1:4) of the drug and carrier were used in the preparation of sustained release solid dispersions.

Preparation and evaluation of sustained release tablets employing solid dispersion system: [20]

The tablets containing solid dispersions systems of Nimodipine were prepared by wet granulation method using starch paste as a granulating agent as per the formula given in the Table 1.

Table 1: Composition of Solid dispersions systems of Nimodipine Tablets:

Formulations	Quantity of Ingredients (mg)			
	Nimodipine	EC	EU	EVA
F_1	100	100	-	-
F_2	100	200	-	-
F_3	100	300	-	-
F_4	100	400	-	-
F_5	100	-	100	-
F_6	100	-	200	-
F_7	100	-	300	-
F_8	100	-	400	-
F_9	100	-	-	100
F_{10}	100	-	-	200
F_{11}	100	-	-	300
F_{12}	100	-	-	400

Table 2: Drug content Uniformity

Solid Dispersion	% Drug content
F_1	94.2
F_2	95.1
F_3	95.6
F_4	98.1
F_5	97.3
F_6	97.7
F_7	97.5
F_8	97.8
F_9	97.3
F_{10}	95.7
F_{11}	96.0
F_{12}	95.7

Method Used For Granulation

Accurately weighed quantities of the formulation and lactose were blended thoroughly in a dry motor. Then, starch paste was added slowly with uniform mixing to get a wet mass. The wet mass was passed through sieve no 16 to obtain wet granules. The granules were dried at 50°C for 5

to 6 hours in a tray dryer. The dried granules (passed through Mesh. No.22) after blending with lubricants were compresses into tablets on a REMIK Minipress tablet compression machine.

Evaluation Parameters

Drug Content Uniformity: All the solid dispersions prepared were tested for drug content uniformity. Accurately weighed amount of solid dispersion (120mg) was dissolved in Methanol in 100ml volumetric flask and the volume was made up to the mark with methanol. The solution was then suitably diluted with methanol and assayed for drug content by measuring the Nimodipine content at an absorbance of 317nm. Results were tabulated in table no 2.

I.R. Studies: Infra red spectroscopy is one of the most powerful analytical techniques when it comes to the determination of presence of various functional groups involved in the making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring while in the processing of a formulating I.R. Spectra of Nimodipine and its formulations. The characteristics peaks (N-H – $3298.28 cm^{-1}$) in the spectra of pure drug is super imposable to that of formulations (EVA, EU RL -100 and EC) and there are no extra peaks, which gives an evidence that the drug is intact in the formulations as shown in I.R. Charts.

Dissolution Rate Studies[12-18, 21, 22]: Dissolution of Nimodipine from various solid dispersions were studied by using Acetate buffer. Dissolution of Nimodipine in pure form and from various solid dispersions was studied using USP XXIII dissolution rate test apparatus (Serwell Electronics) employing a paddle stirrer. 900 ml of dissolution fluid and a sample of solid dispersions equivalent to 120 mg of Nimodipine was tied in a mucilin cloth were used in each test. The paddle was adjusted to rotate at a speed of 75 rpm. A temperature of 37 ± 0.5^0C was maintained throughout the experiment. 10 ml of sample of dissolution medium were withdrawn at known time intervals and analyzed for Nimodipine content by measuring the absorbance at 317 nm. The volume withdrawn at time interval was replaced with fresh quantity of dissolution medium. Percent of Nimodipine dissolved at various times was calculated and plotted against time.

***In-vitro*-Dissolution rate studies:** [23-25] The dissolution study for the prepared tablets was carried out using USP XXI Dissolution Test Apparatus- 2(paddle method) in 900 ml of Acetate Buffer (P^H 4.5) maintained at 37 ± 0.5^oC, paddle rotation at 75 rpm. The samples of 5 ml were withdrawn at predetermined time with the pipette. The collected samples were suitably diluted and absorbance was measured spectrophotometrically at 317 nm. The volume withdrawn at each interval was replaced with fresh quantity of 5 ml of dissolution medium. The percentage of Nimodipine released at various time intervals was calculated and plotted against time. The results indicated for each dissolution studies are the average of three determinations. The results are shown in Figures 1 – 3 respectively.

Drug Release Mechanism Kinetics:

In older to establish the mechanism of release of drug, the experimental data was fitted to different kinetic models. The drug release data were subjected to various mathematical kinetic models like zero order, first order etc. The data were also subjected to Higuchi's Model at different ratios (1:1, 1:2, 1:3 and 1:4). The results are showed in Figure: 4, 5, 6 and 7.

Figure 1: *In-vitro* Drug release profile for pure drug and Nimodipine sustained solid dispersions using EC.
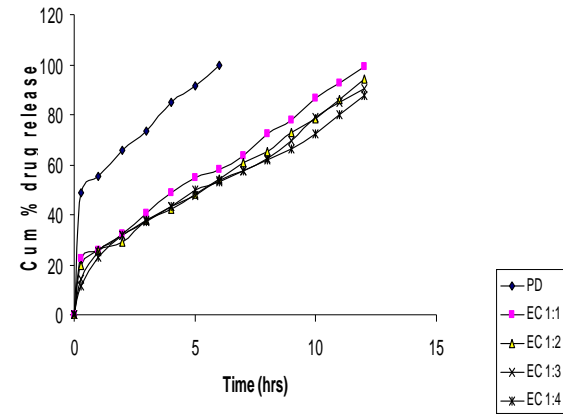
Figure 2: *In-vitro* drug release profile for Pure drug and Nimodipine sustained solid dispersions using EU RL-100
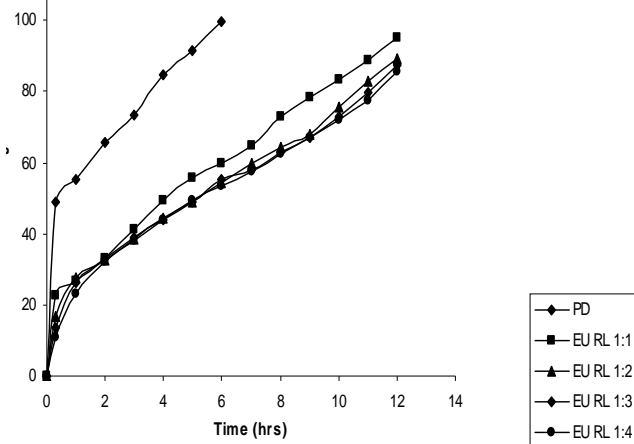

Figure 3: *In-vitro* drug release profile for pure drug and Nimodipine sustained solid dispersions using (EVA).
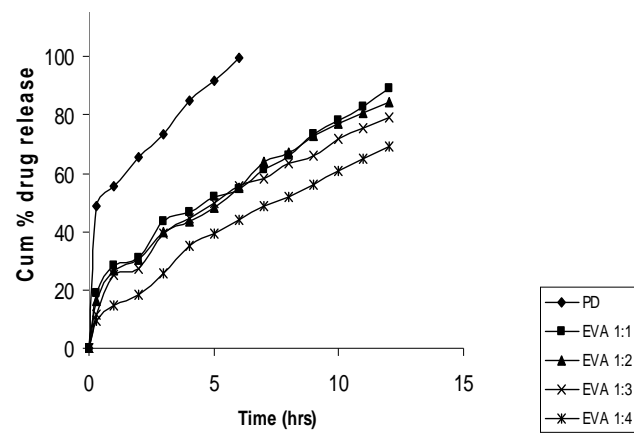

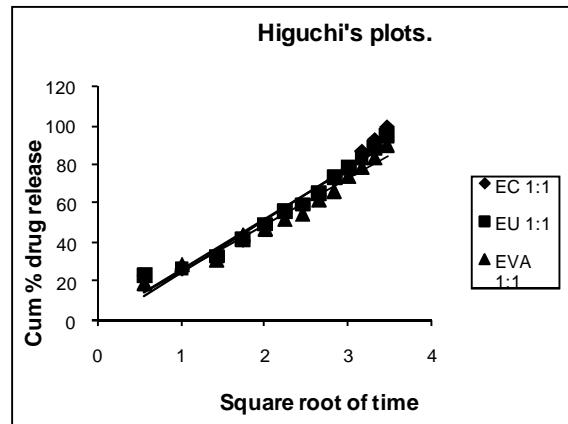**Figure 4:** Higuchi's Plot (Ratio 1:1)
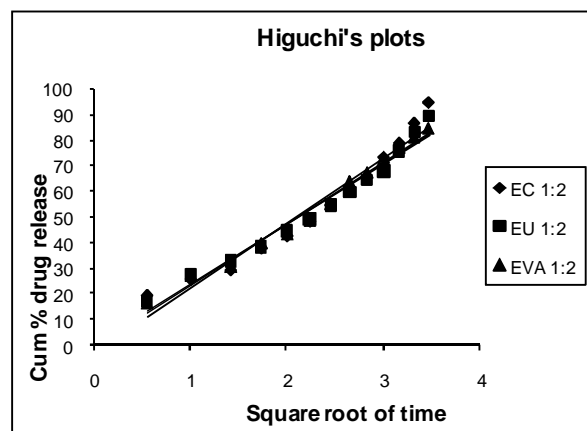

Figure 5: Higuchi's Plot (Ratio 1:2)
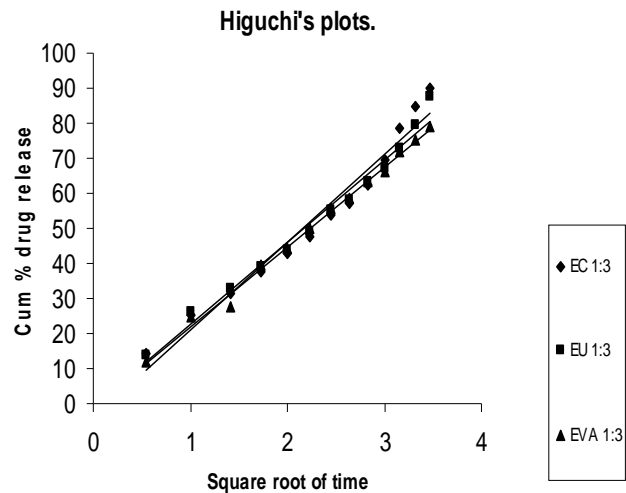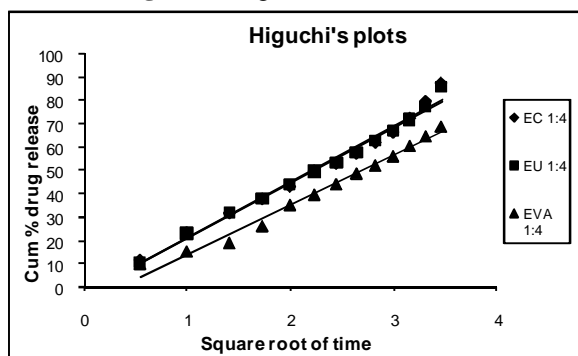

Figure 6: Higuchi's Plot (Ratio 1:3)

Figure 7: Higuchi's Plot (Ratio 1:4)

Stability Studies:[26]

The tablets stored in wide mouth and air tighten containers were subjected to stability performance. Stability studies were carried out at $25^{o}C/60\%$ RH and $40^{o}C/75\%$ RH using Thermo lab instrument, Mumbai. This stability was studied for the period of three months. Different parameters such as hardness, friability were studied for the formulation at first, second and third months.

RESULTS AND DISCUSSION

A simple technique of sustained release solid dispersion was used in the present investigation. Sustained release solid dispersions of Nimodipine were prepared using hydrophobic polymers (EC, EU RL-100 and EVA).Various sustained release solid dispersions were prepared as described in the methodology. The ratio's of Drug: Polymers were 1:1, 1:2, 1:3 & 1:4. These are tabulated in Table no-1. The weighed quantities of drug and polymers were evaluated for drug content uniformity, IR studies and for *In-vitro* drug release profile. The percentage of drug content was found to be 94 - 98%, which was within acceptable limits. The results of the drug

content uniformity in each of solid dispersions are presented in Table no: 2. The IR spectra of the pure drug and sustained release solid dispersions characteristic peak (N-H=3298.28 cm^{-1}) of solid dispersion in the spectra was found to be super imposable to that of pure drug and there are no extra peaks, which gives an evidence that the drug is intact in the solid dispersions. The dissolution rate studies were performed by using USP-XXIII dissolution apparatus employing rotating paddle at a speed of 75 rpm in the dissolution medium of Acetate buffer of pH 4.5 and study was continued up to 12 hrs at suitable time intervals, samples of 5ml were withdrawn by means of pipette and it was immediately replaced with fresh dissolution medium. The withdrawn samples were analyzed for the drug content after appropriate dilutions by measuring the absorbance at 317 nm with UV spectrophotometer. The drug release data and the drug release profiles were shown in Figures in 1, 2, 3 and 4 respectively. Although, they release maximum Percentage of Drug Levels at the end of 12 hours. No consistency in the release behaviour was observed with Ethyl Cellulose (E.C.) Sustained Release Solid Dispersions. Consistent release was observed with EVA & Eudragit RL-100 in all the cases. However, less release was observed in all the cases with EVA solid dispersions. Further, increased consistent release behaviour was observed with increasing polymer concentration in all the cases. Hence, Eudragit (1: 4) 85.66 % was considered as the ideal as it showed optimum and consistent drug release profiles. In view of the reported results, F_8 sustained release solid dispersion was found to be good. Hence F_8 solid dispersion was selected and preceded for preparation of tablets. The tablets were prepared by employing solid dispersion system of Nimodipine and are subjected to stability studies and reports are showed in Table no: 3.

Figure 7: Comparative Drug release Profile of Marketed and prepared Tablets.
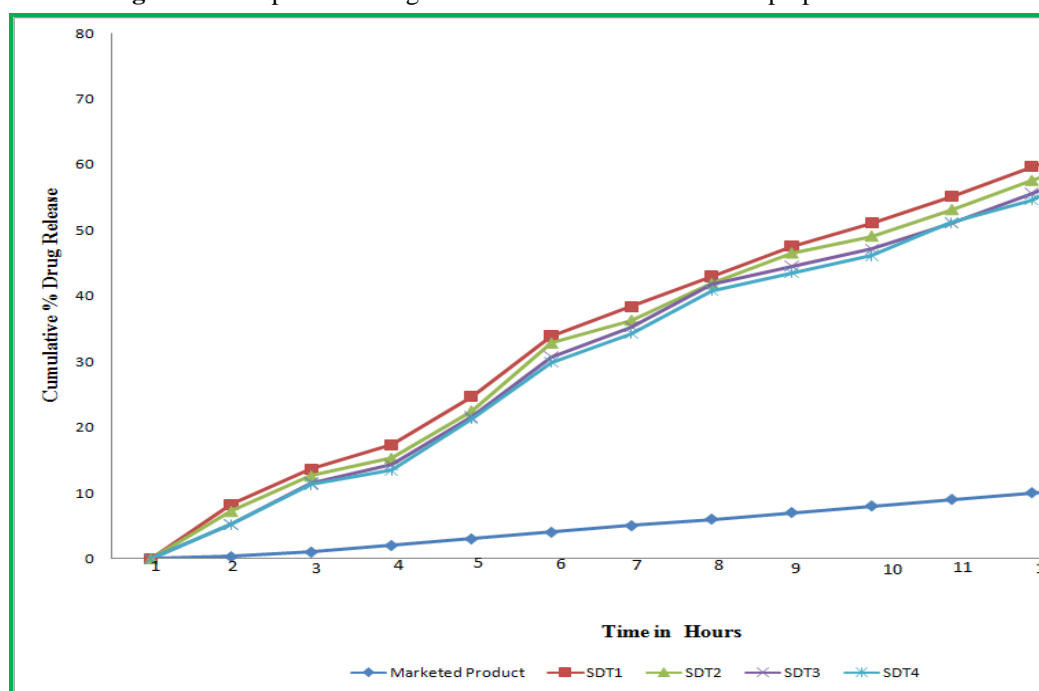
Table 3: Stability Studies of Tablets

Parameters	Initial	Observation					
		I Month		II Month		III Month	
		25°C/60% RH	40°C/75% RH	25°C/60% RH	40°C/75% RH	25°C/60% RH	40°C/75% RH
Nature	Compact Solid	Compact Solid	Compact Solid	Compact Solid	Compact Solid	Compact Solid	Compact Solid
Colour	Light Brown	Light Brown	Light Brown	Light Brown	Light Brown	Light Brown	Light Brown
Hardness (Kg/Cm^2)	7.5	7.6	7.5	7.6	7.7	7.6	7.5
Friability (%)	0.9	0.8	0.8	0.9	0.9	0.8	0.8

CONCLUSION

Drug content uniformity was made for all the prepared sustained release solid dispersions. They are found to be 94 – 98 % and are within the acceptable limits. IR studies were performed and confirmed absence of any possible solid state drug and polymer interactions. *In-vitro* release profiles studies suggested that the drug release has been extended with all the sustained release solid dispersions as compared with the pure drug. Approximately, all the sustained released solid dispersions exhibit polymer concentration dependent release retardation effect. The sustained released solid dispersion technique could be adaptable in laboratory and in Industry as well since it is simple and reproducible. From the stability studies, it was found that all sustained release tablets of Nimodipine exhibited reasonable stability. In conclusion, further studies are needed to monitor to get drug release of 80 – 100 % of drug within 7 – 8 hours which is the average of G.I. residence time. Long term stability studies are needed to establish stable SR products.

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