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STUDIES ON DISSOLUTION BEHAVIOUR OF SUSTAINED RELEASE SOLID DISPERSIONS OF NIMODIPINE

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ABSTRACT

Among the various numbers of techniques available for controlled rate of release of drugs, controlling the rate of dissolution is very popular due to its success and economy. Though there are various reports on sustained action formulations, less number of studied s were reported on the use of this technique to produce sustained formulation.. The present study deals with the preparation and evaluation of sustained release solid dispersions of Nimodipine. The solid dispersions were prepared by solvent evaporation technique using EC, EU RL-100 and EVA as carriers in various ratios. Optimized sustained release solid dispersions were evaluated for drug content uniformity, I.R. and In-vitro drug release studies. The results showed that among the various batches containing the polymer being used in the study, F8 formulation containing DRUG: EU RL-100 in the ratio of 1:4 exhibited consistent release profile of the drug. The results were supported by Hardness, Friability, Weight variation, In-vitro drug release and stability studies.

KEYWORDS: Nimodipine, Calcium channel blocker,Sustained Release Solid Dispersions, In-vitro drug release studies

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INTRODUCTION

Nimodipine is Isopropyl (2-meth oxyethyl) 1, 4-dihydro-2, 6-dimethyl-4-(3-nitrophenyl)-3, 5-pyridine-di carboxylate shown in fig.No.1 It is an effective calcium channel blocker used in subarachnoid hemorrhage- associated neuralgic deficits, management of classical angina & migraine[1,2]. The bioavailability of poorly water soluble drug is limited by its dissolution rate, which is controlled by the surface area available for dissolution. Reduction[3] of dissolution rate is achieved by incorporating drug in an insoluble carrier. Such formulations are considered as matrix system since their release has been described by Higuchi[4] which help in prolonging the duration of time over which the drug is released and hence are considered suitable for formulation as sustained release dosage forms. These systems may be useful for enhancing the bioavailability and suitable for sustained release formulations[5]. Sustained release solid dispersions offer various potential advantages for drugs having poor bioavailability which can be delivered efficiently by maximizing their bioavailability and sustained action[6].

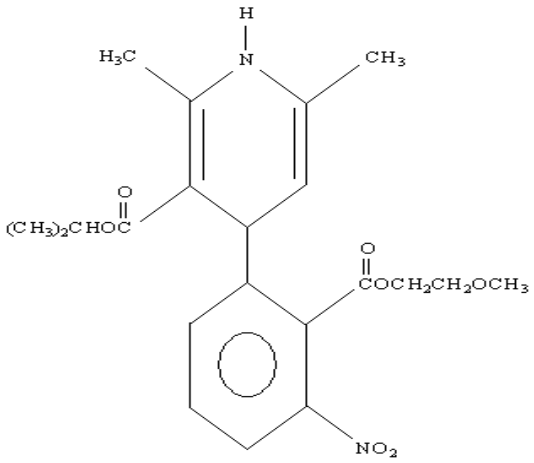

Figure No. 1
Chemical Structure of Nimodipine

In the present work, the sustained release solid dispersions of Nimodipine were prepared by solvent evaporation technique & evaluated for their drug release behaviour.The Nimodipine sustained release tablets were formulated & evaluated by employing solid dispersions.

MATERIALS AND METHODS

MATERIALS

Nimodipine was obtained as gift sample from Micro Labs Ltd. Bangalore, (India). All other chemicals and reagents were of analytical grade.

Technique for the Preparation and evaluation of Sustained Release solid Dispersions

The sustained release solid dispersions were prepared by solvent evaporation technique[7]. In this process; solid dispersions are prepared by dissolving two solid components in a common solvent, followed by evaporation of the solvent. The solvent is removed by evaporation under reduced pressure at varying temperatures. Four different ratios (1:1, 1:2, 1:3 & 1:4) of the drug and carriers were used in the preparation. The resultant mixture is stored in desiccators and used for further studies.

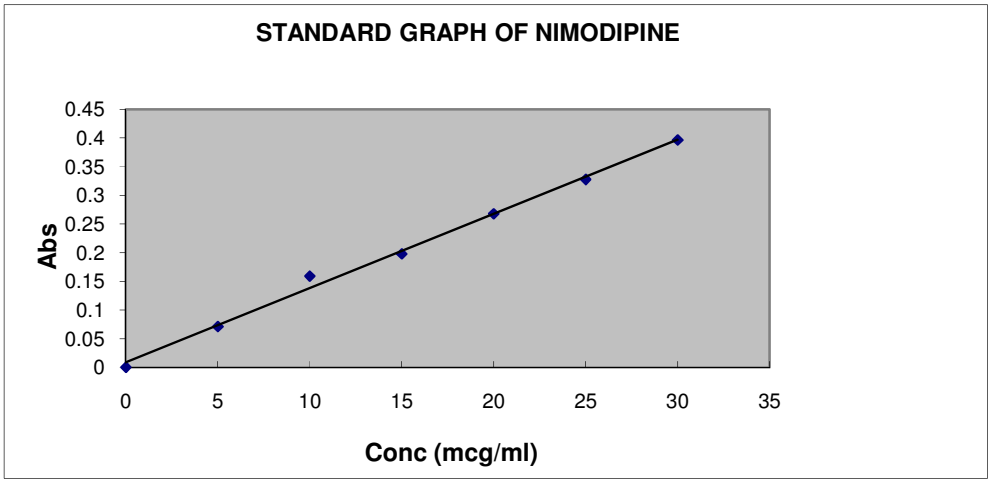

Figure No. 2
Standard graph of Nimodipine

Experimental design

12 batches of solid dispersions were prepared using individual carriers in the ratio of 1:1, 1:2, 1:3 & 1:4

Table No. 1
Formulations of solid dispersions employing water insoluble polymers

DRUG:POLY	F	F	F	F	F	F	F	F	F9	F10	F11	F12
NIM:EC	1	1	1	1	1	1	1	1	1:1	1:2	1:3	1:4
NIM:EU RL-1	1	1	1	1	1	1	1	1	1:1	1:2	1:3	1:4
NIM:EVA	1	1	1	1	1	1	1	1	1:1	1:2	1:3	1:4

Drug Content Uniformity

Accurately weighed amount of solid dispersion was dissolved and was made up to 100ml mark with methanol. The solution was then assayed for drug content by measuring the Nimodipine content at an absorbance of 317nm[8].

Table No.2
Drug Content Uniformity of Solid Dispersions of Nimodipine.

S.No	Solid Dispersions	% Drug Content
1	F_1	94.2
2	F_2	95.1
3	F_3	95.6
4	F_4	98.08
5	F_5	97.3
6	F_6	97.7
7	F_7	97.5
8	F_8	97.8
9	F_9	97.3
10	F_{10}	95.7
11	F_{11}	96.02
12	F_{12}	95.7

Drug: Carrier Interaction Studies

The pure drug Nimodipine and the mixture of pure drug with EC, EURL-100 & EVA were subjected to IR spectra studies.

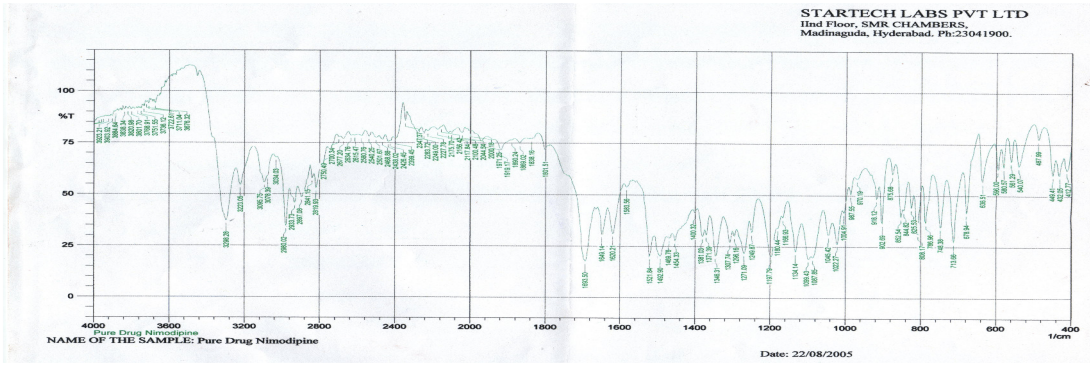

Figure No. 3
I.R. studies of pure drug Nimodipine

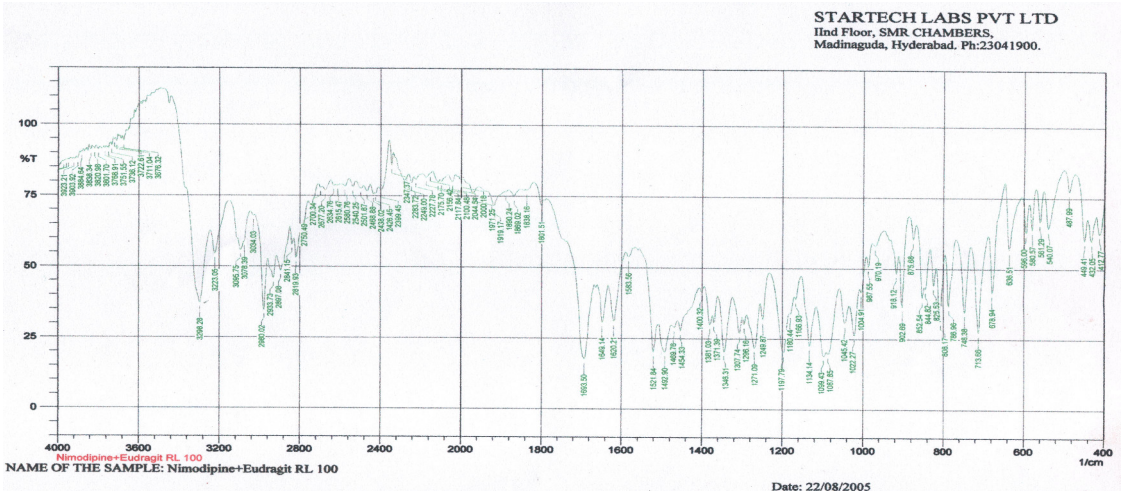

Figure No. 4
I.R. studies of Nimodipine with Eudragit RL-100

Dissolution Rate Studies [9, 10]

Dissolution of Nimodipine from various solid dispersions was studied by using Acetate buffer. Dissolution of Nimodipine in pure form and from various solid dispersions was studied using USPXXIII dissolution rate test apparatus employing a paddle stirrer.900ml of dissolution fluid and a sample of solid dispersions equivalent to 120mg 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 $\pm$ 0.5^{o}c was maintained throughout the experiment. 5ml of sample of dissolution medium were withdrawn at known time intervals and analyzed for Nimodipine content by measuring the absorbance at 317nm.The volume withdrawn at time interval was replaced with fresh quantity of dissolution medium. All the samples were analyzed.

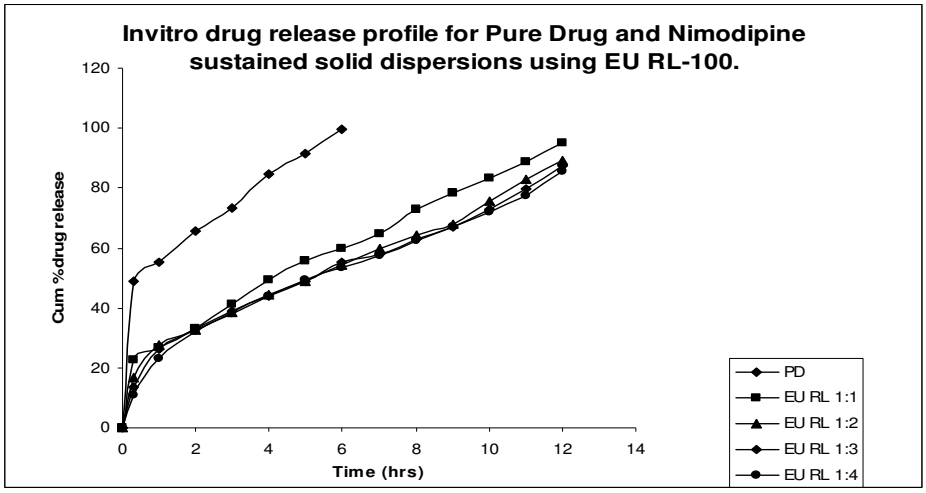

Figure No. 5
In-vitro drug release profile of pure drug and Nimodipine sustained release solid dispersions using EU RL-100.

Drug Release Mechanism kinetics

The Experimental data was fitted to different kinetic models. The drug release data were subjected to various mathematical kinetic models. The data were also subjected to Higuchi plots. The result is shown in Fig.6

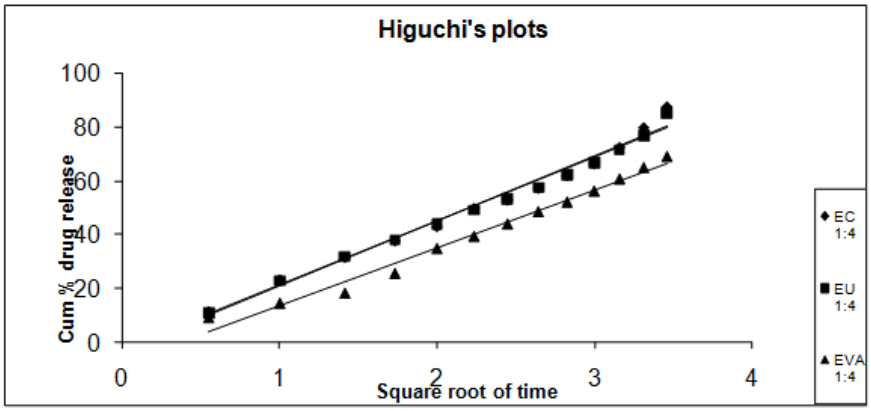

Figure No. 6
Order of release of water insoluble polymers using Higuchi's plots

Preparation and evaluation of Sustained release tablets employing Solid dispersions

The sustained release tablets were prepared by wet granulation technique[11] using starch paste as a granulating agent. Accurately weighed quantities of the F8 formulation and lactose were blended in a dry mortar. Then, starch paste was added slowly with uniform mixing to get wet mass. This wet mass was passed through sieve no.16 to obtain wet granules. The granules were then dried at 50°c for 5-6 hours in a tray dryer. The dried granules were the passed through sieve no22, blended with lubricants and were compressed into tablets on a REMIK Minipress tablet compression machine.

Evaluation of Prepared tablets

The prepared tablets were evaluated for hardness, friability and weight variation

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester.

Six tablets from each of the formulations were tested and the average was noted.

Friability

Ten tablets were weighed and placed in Roche friabilator and rotated at 25rpm. The tablets were then taken out, dedusted and reweighed. The percentage of friability of the tablets was measured as per the following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}}$$

Weight Variation

20 tablets were selected randomly after compression and the mean weight was determined.

Table No. 3

Hardness, Friability and Weight variation of the prepared tablets

Hardness (kg/cm^2)	3.2
Friability (%)	0.03
Weight Variation (mg)	± 5%

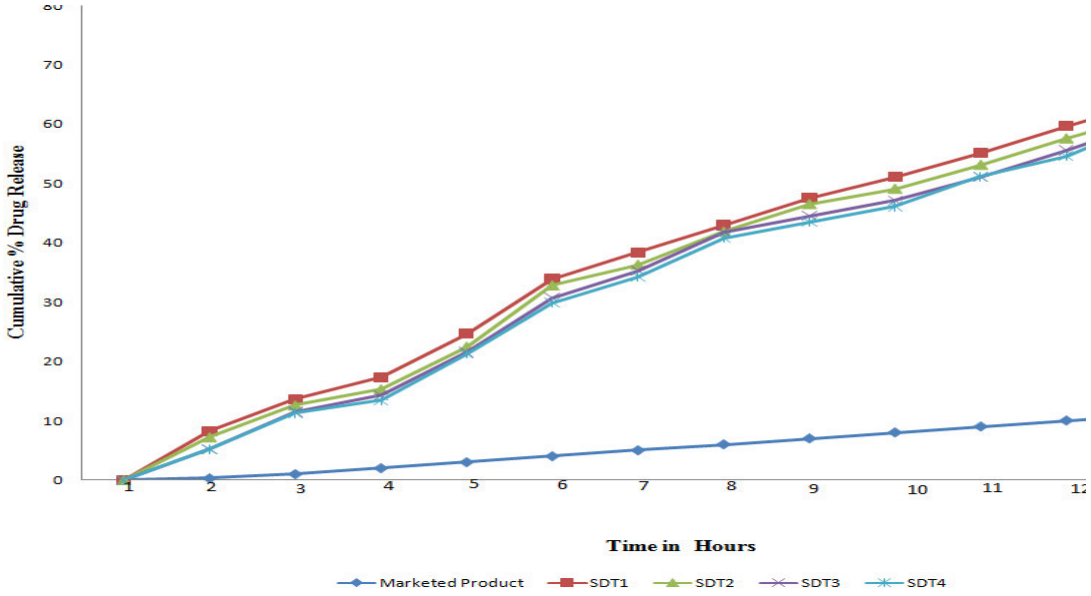

Figure 7

Comparision of %CDR of Marketed product with prepared tablets

Table No. 4

Stability studies of Nimodipine Tablets

PARAMETERS	OBSERVATION						
		I MONTH		II MONTH		III MONTH	
	initial	RT	40^{O}c	RT	40^{O}c	RT	40^{O}c
Nature	Compact solid	Compact solid	Compact solid	Compact solid	Compact solid	Compact solid	Compact solid
Color	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

RESULTS AND DISCUSSION

The supplied drug passed various tests and analysis. The standard graph of Nimodipine was plotted and good linearity was observed with the plot. Its 'r^2'value is0.9953 and hence obeyed beer Lambert's law. The percentage of drug content uniformity was found to be 94-98% which was within the acceptable limits. The pure drug Nimodipine and the solid admixture of pure drug and hydrophobic polymers (EC,EU RL-100 AND EVA) used in the preparation of sustained release solid dispersion formulations were characterized by IR studies. The IR spectrum was found to be super imposable to that of pure drug and there were no extra peaks, which gives evidence that the drug is intact in the solid dispersions. The cumulative percentage release studies showed that consistent release was observed with EU RL-100 and EVA in all the cases. However, less release was observed in all the cases with EVA sustained solid dispersions. With an increase in the concentration of polymer, increased consistency in the behavior of release was observed. Hence, Eudragit RL-100 (1:4) 85.66% showed optimum and consistent drug release profiles. In view of the results, F8 sustained release solid dispersion formulation was found to be optimum and was selected and proceeded for sustained release tablets preparation. The prepared tablets of the selected formulation possessed sufficient mechanical strength of 3 kg/cm^2. Friability values were below 1% which was an indication of good mechanical strength. All the tablets passed the weight variation test, as the percentage weight variation was within the pharmacopoeial limits of$\pm$ 5%. The tablets of the selected formulation were subjected to stability studies with respect to physical appearance, hardness and friability at room and accelerated temperatures for three months using thermo lab stability chamber. The results indicated that the sustained release tablets of Nimodipine exhibited reasonable stability as they did not show any physical changes during the stability study period.

CONCLUSION

It can be concluded that EC, EU RL-100 and EVA can be used to formulate sustained release solid dispersions of Nimodipine with highest cumulative % drug release. Among the various polymer batches being used in the study namely, EC: EURL-100: EVA in the ratio of 1:1, 1:2, 1:3 and 1:4, (Drug: EURL-100) exhibited significant dissolution behavior. In-vitro drug release profiles suggested that the drug release has been extended with all the sustained release solid dispersions as compared with the pure drug. Stability studies revealed that the product does not undergo degradation upon storage and hence maintained its integrity during storage. Further studies are needed to monitor to get drug release of 80-100% of drug within 7-8 hours and long term stability studies are needed to establish stable sustained release products.

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