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RESEARCH ARTICLE

Formulation and Evaluation of Eudragit Microspheres Containing Nicorandil

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ABSTRACT

The objective of present study was to develop Nicorandil sustained release microspheres by using Eudragit RS 100 and Eudragit RL 100. The Nicorandil loaded Eudragit microspheres were formulated by non aqueous solvent evaporation method and study the effect of different grade of Eudragit and drug: polymer ratio on % Yield, % Entrapment efficiency, particle size and % drug release of microspheres. The Entrapment efficiency was found to be 82.31 ± 1.58% to 91.25 ± 2.54% and particle size range 60.25 ± 1.42µm to 92.21 ± 2.32µm. The Batch EU6 showed almost 100 % drug release at 12 hrs. % *In vitro* drug release was decreased with increasing the drug: polymer ratio. Drug release was high in Eudragit RL 100 microspheres compare to Eudragit RS 100 microspheres. Fickian diffusion was the mode of drug release from Nicorandil loaded Eudragit microspheres formulations.

KEYWORDS

Nicorandil, Eudragit RS 100, Eudragit RL 100, Microspheres

INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drug to a specific body site have had an enormous impact on the health care system. The last two decades there has been a remarkable improvement in the field of novel drug delivery systems. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc, which modulates the release and absorption characteristics of the drug. Microspheres constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics. Microspheres are one of the particulate delivery systems used to achieve sustained or controlled drug delivery, improve bioavailability and stability and target drug to specific sites. Microspheres also offer advantages such as limiting fluctuation within a therapeutic range, reduction in side effects, decreased dose frequency and hence improved patient compliance.[1]

Nicorandil is potassium channel opener and it is widely used in treatment of angina.[2,3] It has biological half-life of 1 hrs. It has short biological half-life and usual therapeutic dose is in the range of 10 to 20 mg twice daily.[4-7] To reduce the frequency of administration and to improve patient- compliance, a sustained release microspheres formulation of Nicorandil is desirable. Acrylic polymers are widely used as tablet coatings and retardants of drug release in sustained released formulations. The most interesting among acrylic polymers were high permeable Eudragit RL and low permeable Eudragit RS, both are neutral co-polymers of poly (ethylacrylate, methyl meth-acrylate) and

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trimethyl aminoethyl methacrylate chloride are insoluble in water and digestive juices, but both swell and are permeable, which means that the drugs can be released by diffusion. Therefore, the permeability of the drug through Eudragit RS and/or RL is independent of the pH of the digestive tract. The degree of permeability depends on the relative proportion of quaternary ammonium groups in Eudragit. By encapsulating the drug in a Eudragit matrix from which it is released at a relatively slow rate over a prolonged time.[8] Several methods have been used in preparation of microspheres, both for natural and synthetic polymers. Non aqueous solvent evaporation is the most popular method for preparing Eudragit microspheres. [9] The aim of this study was to prepare Nicorandil microspheres using Eudragit polymer by non aqueous Solvent Evaporation method to achieve a sustained release profile and to study effect of the drug: polymer ratio and different grade of eudragit on Percentage Yield, Percentage Entrapment Efficiency, Particle size and its *in vitro* release behavior.

MATERIALS AND METHODS

Materials

Nicorandil was obtained as a gift sample from Torrent Research Centre. Eudragit RS 100 and Eudragit RL -100 were purchased from Yarrow Chem Products, Mumbai. Magnesium stearate, Light liquid paraffin, Methanol, Acetone and N-Hexane were purchased from RFCL, Ltd.

Drug and Excipient Compatibility Study by DSC

The DSC study was carried out using DSC-60 (Shimadzu Corporation, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 10°C/min from 35 to 250°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

Preparation of Microspheres

Eudragit RS 100 or Eudragit RL 100 was dissolved in 10 ml methanol: acetone mixture (1:9). 200 mg Nicorandil was dissolved in above polymer solution. 25 mg magnesium stearate was added in above drug solution and stirrer the dispersion. Above disperse phase was added into continuous phase (90 ml Light liquid paraffin + 10 ml hexane) and continuously stirred using mechanical stirrer for 2 hrs at 1500 rpm until the organic solvent evaporated. The prepared microspheres were filtered by using Vacuum filter. The obtained microspheres were washed repeatedly with n-hexane until free from oil. The collected microspheres were dried at room temperature.

Table 1: Batch description

Sr. no	Batch no.	Nicorandil (mg)	Eudragit RL 100 (mg)	Eudragit RS 100 (mg)
1	EU1	200	400	-
2	EU2	200	600	-
3	EU3	200	800	-
4	EU4	200	200	200
5	EU5	200	300	300
6	EU6	200	400	400
7	EU7	200	-	400
8	EU8	200	-	600
9	EU9	200	-	800

Evaluation Test for Eudragit Microspheres

Percentage Yield

The prepared microspheres were collected and weighed. The measured weight of the dried microsphere was divided by total amount of Drug and polymer which were used for the preparation of microspheres. Results of percentage Yield was calculated using following equation.

$$\text{Percentage yield} = \frac{\text{Weight of microsphere recovered}}{\text{Weight (drug + polymer)}} * 100$$

Percentage Drug Entrapment Efficiency

To determine the incorporation efficiency, 25 mg microspheres were crushed and dispersed in 100 ml 0.1 N HCl and sonicated for 10-15 min. Dispersion was stirred on magnetic stirrer for 24 hrs. The dispersion was filtered and Drug content was analyzed Spectrophotometrically at 261.9 nm. The percentage drug entrapment efficiency was calculated using following equation.

$$\%\text{Entrapment Efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} * 100$$

Particle Size Analysis

Particle size analysis of drug-loaded Eudragit microspheres was performed by optical microscopy using a compound microscope. The slide containing Eudragit microspheres was mounted on the stage of the microscope and diameter of at least 300 particles was measured using a calibrated ocular micrometer.

In Vitro Drug Release Study

20 mg Nicorandil equivalent microspheres were weighed and filled in the empty capsule shells. Dissolution tests were performed in a USP Dissolution Tester Apparatus I (Basket method) at 37 ± 0.5 ˚C. The baskets were rotated at a speed of 50 rpm The dissolution medium consisted of 0.1N hydrochloric acid for the first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours (900 ml), Aliquots of 5 ml were withdrawn at different time intervals, filtered and the content of nicorandil was determined spectrophotometrically at a wavelength of 261.9 nm using UV spectrophotometer.

In Vitro Release Kinetics

The drug release data of controlled-release microspheres was fitted to kinetics models i.e., zero order, first order and Higuchi to find out drug release pattern and mechanism.

Surface Morphology

Morphological characterization of the microspheres was carried out by using scanning electron microscopy under higher and lower resolution.

RESULT AND DISCUSSION

Drug – Excipient Compatibility Study by DSC

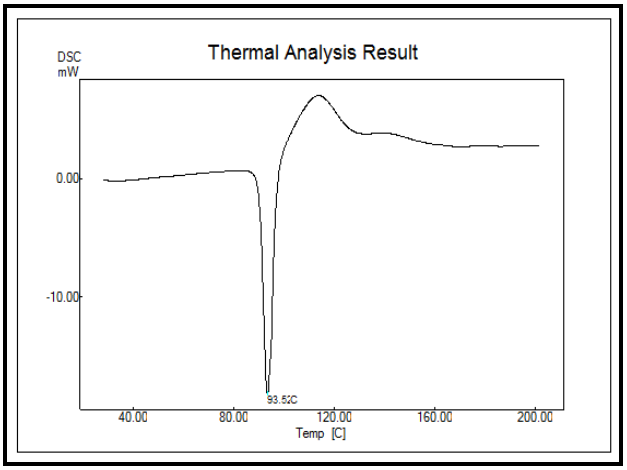

Figure 1: DSC of Nicorandil

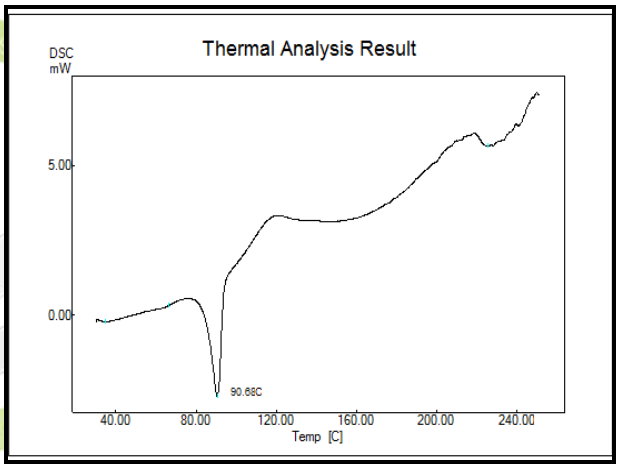

Figure 2: DSC of Nicorandil: Eudragit RS 100 mixture

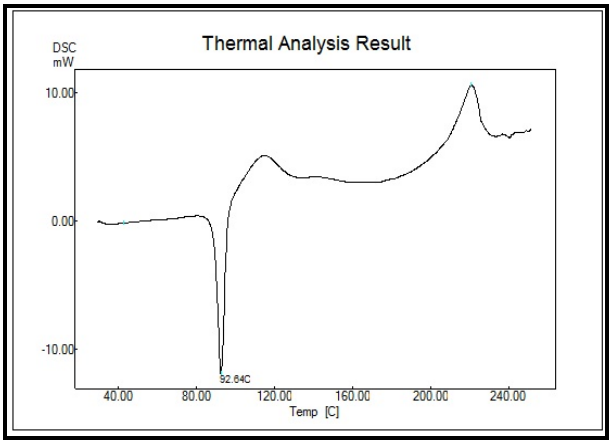

Figure 3: DSC of Nicorandil: Eudragit RL 100 mixture

Result of Eudragit Microspheres

Table 2: Result of various batches of Eudragit microspheres

Sr.No	Batch No	% Yield	% Entrapment Efficiency	Particle Size Analysis
1	EU1	69.04 ±2.37	84.21 ± 1.21	60.25±1.42
2	EU2	74.23 ±2.69	86.21 ± 1.21	68.12 ±1.94
3	EU3	87.9 ±2.21	89.12 ± 1.29	85 ±2.12
4	EU4	71.25±1.29	85.17 ± 1.55	61.14±1.19
5	EU5	80.18 ±2.12	88.21 ±1.14	71.56±2.54
6	EU6	85.23 ±2.45	91.25 ± 2.54	89.58±2.11
7	EU7	70.03 ±1.89	82.31 ± 1.58	65.21±1.23
8	EU8	79.56 ±2.19	85.11 ± 1.49	74.12± 2.11
9	EU9	86.33 ±2.28	90.40 ± 1.88	92.21 ±2.32

DSC of the Nicorandil, Nicorandil: Eudragit RS 100 mixtures and Nicorandil: Eudragit RL 100 mixtures show endothermic peak at 93.52° C, 90.68° C and 92.64 °C respectively. There was no change in the melting endotherm of the Nicorandil, Nicorandil-Eudragit RS 100 mixture and Nicorandil: Eudragit RL 100 mixture. So, it was concluded that drug and different grades of Eudragit were compatible with the each other.

Percentage Yield & Percentage Entrapment Efficiency

From above table 2, it shows that Drug: polymer ratio was increased; the % yield was increased. The drug entrapment efficiency (Table 2) was higher in EU6 batch (91.25). The results obtained clearly indicated that the drug entrapment efficiency increased as the drug to polymer (core to coat) ratio increased. This may be attributed to the availability of more coat material per core molecule. The entrapment efficiency was also higher because the drug was present in a non-aqueous media (light liquid paraffin) in which the solubility of the drug is very low, thereby preventing the loss of the drug into the dispersion medium during the formulation of microspheres.

Here Eudragit grade has no significant effect on % yield and % Entrapment efficiency.[11]

Particle Size Analysis

Particle size of the microspheres was increased with the increasing drug: polymer ratio. As the concentration of polymer increased, the viscosity of the dispersed phase was also increased. When the dispersed phase with higher viscosity was poured into the dispersion medium, bigger droplets were formed and mean particle size of microspheres was increased. [12] Here Particle size was slightly higher in case of Eudragit RS 100 microspheres. Highest Particle size was observed in EU9 Batch (92.21 ±2.32).

% *In Vitro* Drug Release

From the Below figure 4, it can be seen that increased in Drug: polymer ratio decreased the release rate. It was due to as increased in polymer concentration the matrix wall of microspheres became thicker with less no of pores. Here drug release pattern was initially bursting and then sustained. It was due to drug crystal might be present on surface of microspheres.

It was also observed that the release rate of drug from Eudragit RL100 microspheres was a higher than that of Eudragit RS 100 microspheres because Eudragit RL100 contains higher amount of quaternary ammonium groups, which renders it more permeable and accelerates the drug release. Eudragit RS100 microspheres have thicker polymeric surface as compared to RL100 microspheres. The thick polymeric barrier slows the entry of surrounding dissolution medium in to the microspheres and hence less quantity of drug leaches out from the polymer matrices of the microspheres exhibiting slow release.[11,12]

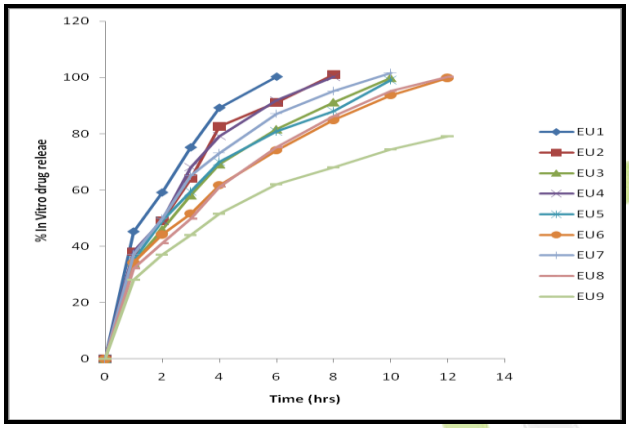

Figure 4: % *In vitro* release data of batches EU1-EU9

In vitro Release Kinetic Models

Here from table 3, it could be seen that when fitted into various mathematical models, the best linearity was found in the korsemeyer-peppas, indicating that the release of the drug from microspheres follows the korsemeyer-peppas model. Here n was found to be below 0.5, which may indicate that the release of Nicorandil from Eudragit microspheres follows Fickian diffusion.

Shape and Surface Morphology of Microspheres

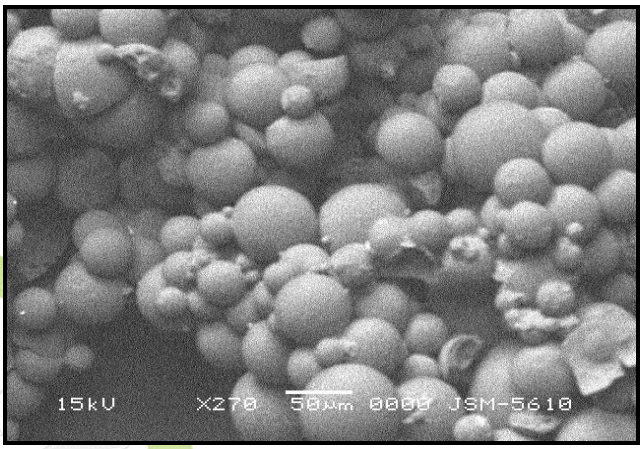

Figure 5: SEM of Nicorandil microspheres

Prepared microspheres shows completely spherical shape as shown in above figure 5.

Table 3: Release kinetic model data of various batches of Eudragit microspheres

Batch No	Higuchi (R^2)	Zero order (R^2)	First order (R^2)	Korsmeyer-Peppas (R^2)	Korsmeyer-Peppas (n)
EU1	0.9836	0.9514	0.9064	**0.9882**	0.4646
EU2	0.9684	0.9250	0.9305	**0.9751**	0.4968
EU3	0.9936	0.9543	0.8770	**0.9954**	0.4760
EU4	0.9765	0.9291	0.8602	**0.9797**	0.4906
EU5	0.9906	0.9471	0.8641	**0.9942**	0.4445
EU6	**0.9974**	0.9720	0.9104	0.9958	0.4459
EU7	0.9828	0.9282	0.8473	**0.9894**	0.4478
EU8	**0.9938**	0.9642	0.8988	0.9928	0.4843
EU9	0.9942	0.9525	0.8802	**0.9974**	0.4260

CONCLUSION

Nicorandil microspheres were prepared successfully by Non aqueous solvent evaporation method. It was found that increase the drug: polymer ratio resulted that increased the percentage Yield, particle size and % Entrapment efficiency. Here % drug release rate was decreased with increasing the concentration of polymer. % Drug release was higher in Eudragit RL 100 microspheres compare to Eudragit RS 100 microspheres. From the SEM study observed that microspheres were spherical in shape.

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