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Research Article

FORMULATION AND EVALUATION OF NICORANDIL MICROSPHERES

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ABSTRACT

Objectives: Nicorandil is a potassium channel opener and used in treatment of angina. It has a short half life of 1 hrs, so it requires frequent administration. The objective of present study was to develop sustained release Nicorandil microspheres.

Method: The microspheres for sustained delivery of Nicorandil were formulated using ethyl cellulose polymer by non aqueous solvent evaporation method and study the effect different variables such as drug: polymer ratio and heavy: light liquid paraffin ratio on % Yield, % Entrapment efficiency, particle size and In vitro drug release.

Results: The Entrapment efficiency was found to be 85.33% to 88.65% and In-vitro release study showed release of drug 98.25 % up to 12 hours.

Conclusions: It was found that increases the concentration of Heavy liquid paraffin resulted in decrease the particle size and increase the release rate. Drug: Polymer ratio had significant effect on % Yield, % Entrapment efficiency, and particle size and release rate.

Keywords: Nicorandil, Ethyl cellulose, Non aqueous solvent evaporation method

INTRODUCTION

Angina pectoris is the most common cardiovascular disease requires constant monitoring. Potassium channel openers are presently considered an important class of drugs for angina pectoris. The first therapeutic drug shown to possess an ability to hyperpolarize smooth muscle cell membranes is nicorandil, a potent coronary vasodilator[1]. Although nicorandil is one of the emerging molecules in the case of angina, successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired [2]. Nicorandil has a short half-life of 1 hr, and the usual oral dosage regimen is 5 to 40 mg taken 2 to3 times a day [3][4]. To reduce the frequency of administration and to improve patient compliance, sustained-release formulation of nicorandil is desirable. One of the methods of sustained drug delivery system is by microencapsulation which is microspheres drug delivery system.

Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000µm, containing dispersed drug in either solution (or) microcrystalline form. Microspheres is a useful approach which prolongs the duration of drug effect significantly and improves patient compliance[5]. Microspheres are one of the multiple unit dosage forms.Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained. Solvent Evaporation, phase-separation and spray drying method are commonly used for the preparation of microspheres. Among the various microencapsulation methods, emulsion solvent evaporation technique is often widely used to prepare microspheres. Solvent evaporation method is the preparation technique that is widely preferred for the preparation of controlled release microspheres. The first stage of this method is to prepare emulsion by adding the dispersed phase consisting of the drug, polymer and appropriate dispersion agent in the organic solvent to dispersion medium which is immiscible with the dispersed phase. At the second stage, minimatrix forms are obtained by removing the solvent used at the dispersed phase from the droplets which are formed in the emulsion[6]. Ethyl cellulose is a hydrophobic polymer and it is widely used in preparation of microspheres[7]. The aim of this study was to prepare Ethyl cellulose microspheres containing Nicorandil by Non aqueous solvent evaporation method to achieve a controlled drug release profile and to study the effect of different formulation variables such as drug: polymer ratio and Heavy: liquid paraffin ratio on particle size distribution, encapsulation efficiency and its *in vitro* release behavior.

MATERIALS AND METHODS

Materials

Nicorandil was obtained as a gift sample from Torrent Research centre, Ethyl cellulose was procured from Yarrow chemicals limited. Magnesium Stearate, Acetone, Methanol,

Liquid paraffin and n-Hexane was purchased from S. D. Fine Chemicals.

Drug and excipient compatibility study by IR

The FT-IR spectra of Nicorandil, Ethyl cellulose and physical mixture were taken by preparing KBr pellets. (Disk method).

Drug and excipient compatibility study was carried out 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.

Table 1: Composition of Batches Nicorandil microspheres

S. No.	Batch no	Drug: polymer	Heavy liquid paraffin	Light liquid paraffin	n-hexane
1	E1	1:2(250 mg: 500 mg)	90 ml	0 ml	10 ml
2	E2	1:3 (250 mg: 750 mg)	90 ml	0 ml	10 ml
3	E3	1:4 (250 mg:1000 mg)	90 ml	0 ml	10 ml
4	E4	1:2(250 mg: 500 mg)	45 ml	45 ml	10 ml
5	E5	1:3 (250 mg: 750 mg)	45 ml	45 ml	10 ml
6	E6	1:4 (250 mg:1000 mg)	45 ml	45 ml	10 ml
7	E7	1:2(250 mg: 500 mg)	0 ml	90 ml	10 ml
8	E8	1:3 (250 mg: 750 mg)	0 ml	90 ml	10 ml
9	E9	1:4 (250 mg:1000 mg)	0 ml	90 ml	10 ml

Preparation of microspheres:

Ethyl cellulose was dissolved in 20 ml methanol: acetone mixture (1:9). 250 mg Drug 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 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 microspheres obtained were washed repeatedly with n-hexane until free from oil. The collected microspheres were dried at room temperature[6].

Evaluation of Microspheres

Percentage Yield

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below.

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

Percentage Entrapment 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 5-6 hrs. The dispersion was filtered and Drug content was analyzed spectrophotometrically at 262 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

Size analysis was performed by the optical microscope. 300 particles of each batch were calculated by calibrated eye piece. The particle size range as well as the average particle size was calculated from a frequency distribution curve.

In vitro drug release

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 for 3 to 12 hours (900 ml), Aliquots of 5 ml were withdrawn at different time intervals, filtered through whatman filter paper and the content of nicorandil was determined spectrophotometrically at a wavelength of 262 nm using UV spectrophotometer[1].

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 microcapsules was carried out by using scanning electron microscopy (JEOL JSM -5200) under higher and lower resolution. The dried samples were coated with gold palladium of 200A° thickness under argon atmosphere of gold coating prior to microscopy evaluation.

RESULT AND DISCUSSION

Drug –Excipient compatibility study by FT-IR

From the above figure and Table show that peak of Nicorandil does not much deviate from the physical mixture of Nicorandil+ ethyl cellulose. As per IR data Nicorandil was compatible with Ethyl cellulose.

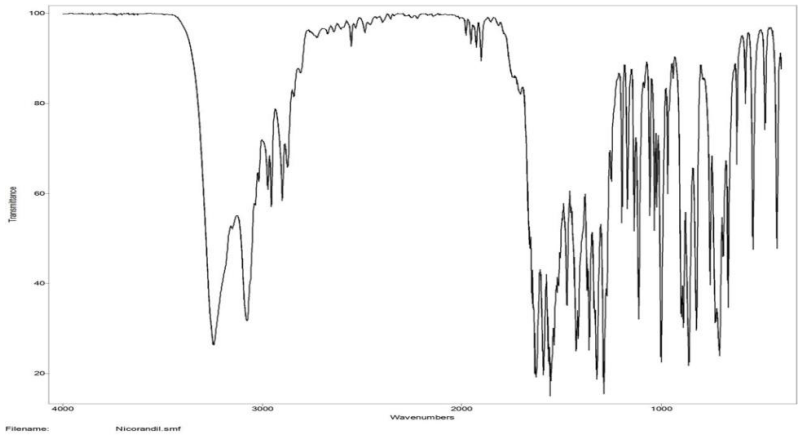


Fig. 1: FTIR of Nicorandil

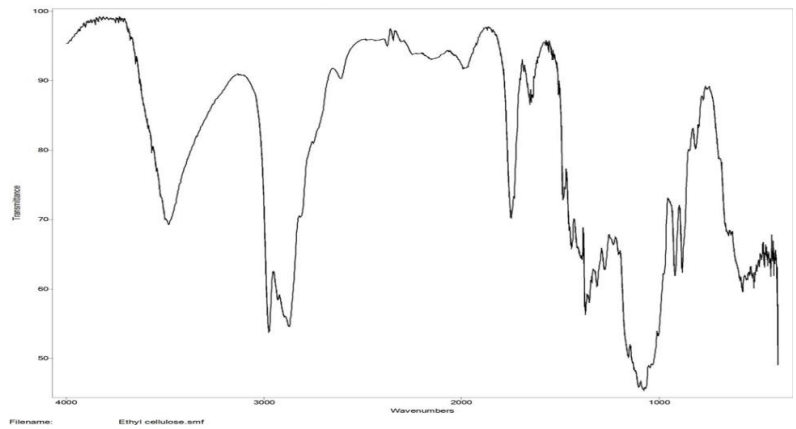


Fig. 2: FTIR of Ethyl cellulose

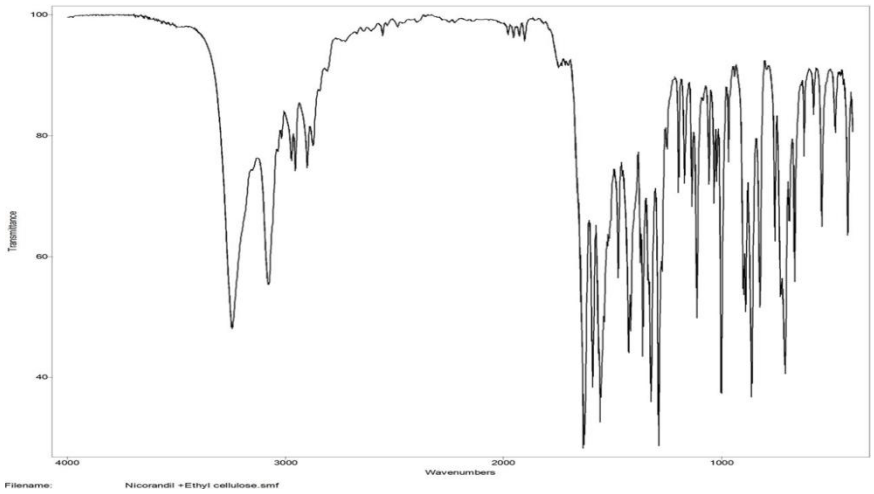


Fig. 3: FTIR of Nicorandil + Ethyl cellulose

Table 2: FTIR data

S. No.	Function group	Wave no.
1	C-H (aromatic)stretching	3077
2	C-H (aliphatic) stretching	2899
3	C-H_3 bending	1424
4	N-H amide bending	1555
5	N-H amide stretching	3243
6	NO_2	1358

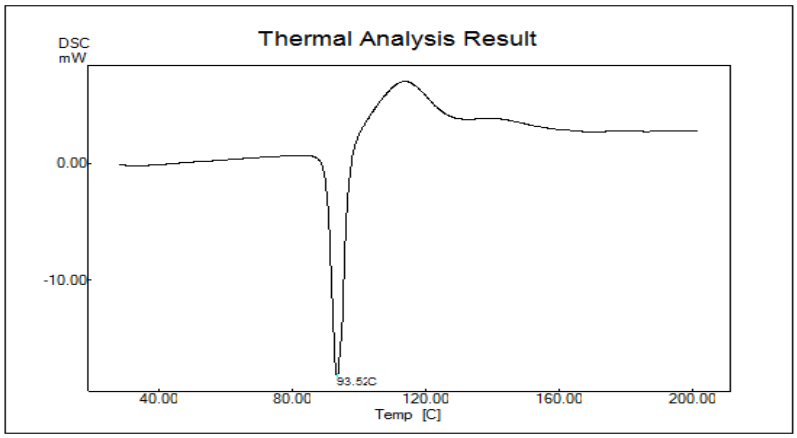


Fig. 4: DSC of Nicorandil

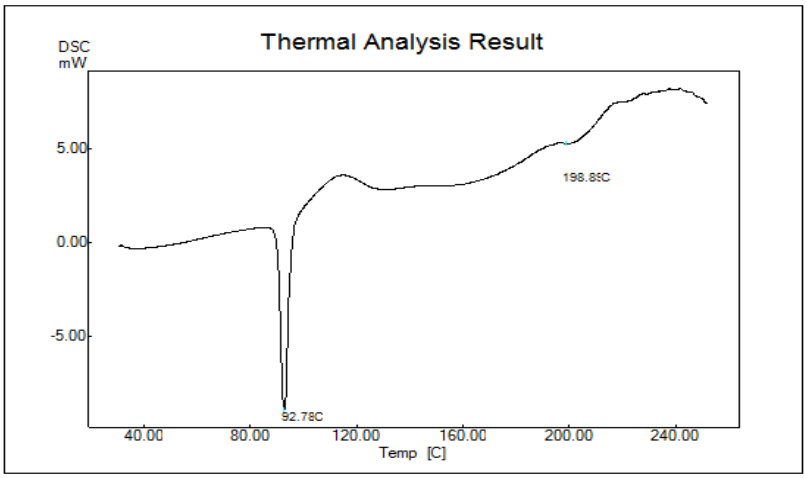


Fig. 5: DSC of Nicorandil+ Ethyl cellulose

Drug –Excipient compatibility study by DSC

The DSC thermogram of the Nicorandil and Nicorandil: ethyl cellulose mixtures show endothermic peak at 93.52 º C and 92.78 ºC respectively. There was no change in the melting endotherm of the drug and drug-ethyl cellulose mixture. So, it was concluded that drug and Ethyl cellulose was compatible with the each other.

Percentage Yield and Percentage Entrapment efficiency

From above table, it shows that Drug: polymer ratio was increased; the % yield and % Entrapment efficiency were increased. Here Heavy: Liquid paraffin ratio had no significant effect on % Yield and % Entrapment Efficiency. Highest % Entrapment efficiency was observed in Batch E6.

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[6][7].

Heavy: Light liquid paraffin ratio had significant effect on particle size. It was observed that size of microspheres was decreased with increasing the viscosity of Liquid paraffin. It can be explained by the increase in viscosity and increase in droplet stabilization power of Liquid paraffin with increasing the Heavy liquid paraffin concentration.

In vitro drug release

Above figure shows that percentage drug release was decreased with increasing the drug: polymer ratio. It was due to as increased in polymer concentration the matrix wall of microspheres became thicker and formation of a thicker matrix wall lead to slower drug release of drug[7][8][10].

Heavy: light liquid paraffin ratio had significant effect on % drug release it was observed that drug release was increased with increasing the concentration of Heavy Liquid paraffin. It was due to reduction of particle size of microspheres might be because of increased the concentration of heavy liquid paraffin this ultimately lead to enhance the drug release.

Table 3: % yield and % Entrapment efficiency of different batches

S. No.	Batch No	% yield	% Entrapment Efficiency
1	E1	75.04 ±2.67	85.33 ± 1.53
2	E2	79.59 ±1.69	87.67 ± 1.53
3	E3	81.9 ±1.55	88.17 ± 1.26
4	E4	77.75±1.18	84.85 ± 1.23
5	E5	81.98 ±1.06	85.15 ±0.57
6	E6	84.42 ±2.12	90.25 ± 2.05
7	E7	74.03 ±1.19	85.15 ± 1.66
8	E8	80.83 ±1.30	86.41 ± 1.43
9	E9	85.33 ±1.52	88.63 ± 0.91

Table 4: Particle sizes of different Batches

S. No.	Batch No	Particle size
1	E1	75.00 ±2.65
2	E2	92.33 ±2.52
3	E3	112.67 ± 2.08
4	E4	87.33 ± 1.53
5	E5	104.33 ± 2.52
6	E6	123.00 ± 2.00
7	E7	102.67 ± 2.08
8	E8	127.67 ± 3.06
9	E9	175.00 ± 3.00

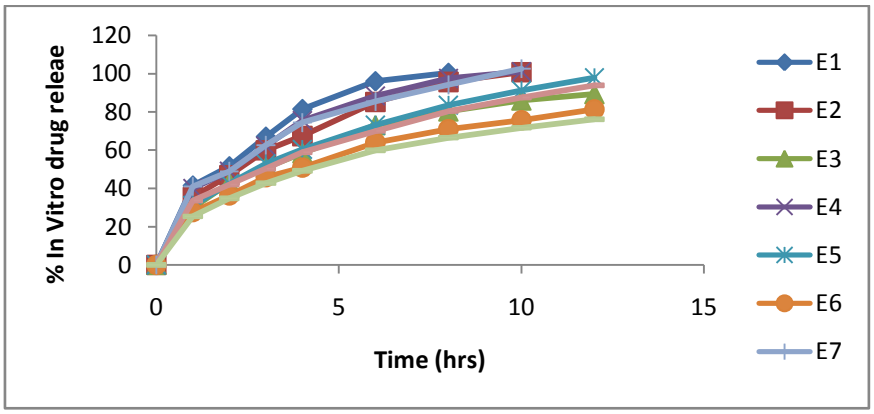


Fig. 6: In vitro drug release profile of Nicorandil microspheres batches

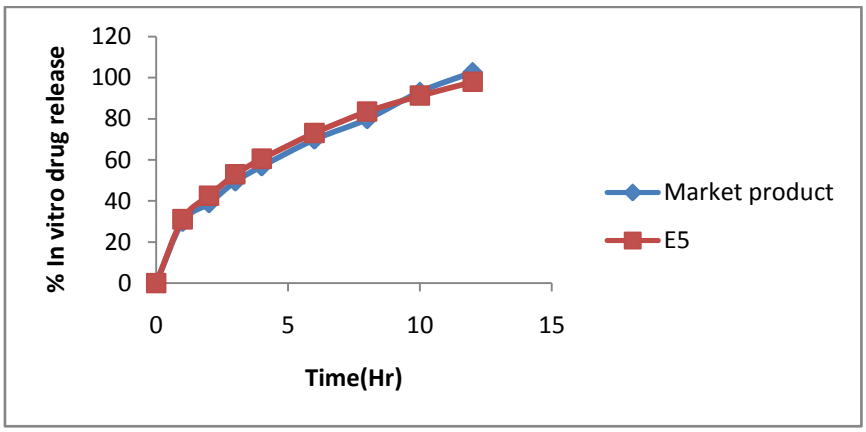
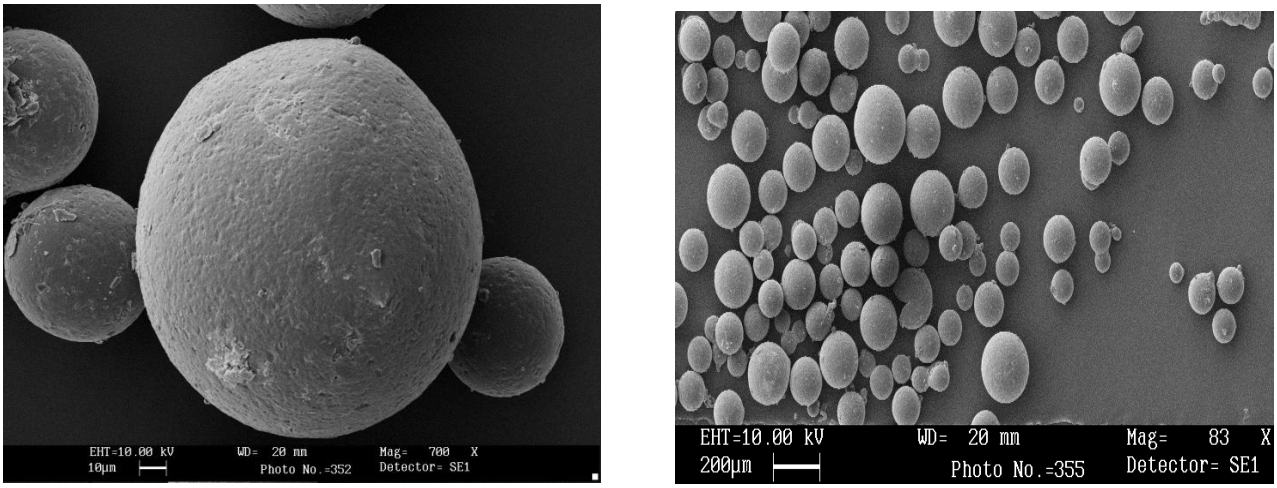


Fig. 7: In vitro drug release profile of marketed formulation and Batch E5

From the above figure shows that E5 batch was match with the drug release profile with marketed formulation.

Table 5: Kinetic Values Obtained from Different Plots of Batches E3, E5& E8

Batch code	Regression values (R^2)		
	Zero order	First order	Higuchi- square root
E3	0.9513	0.9178	0.9631
E5	0.9804	0.9380	0.9987
E8	0.9854	0.9547	0.9988



(a) SEM of Nicorandil microspheres **(b) SEM of Nicorandil microspheres of Batch E5**

Fig. 8: SEM of Nicorandil microspheres

Kinetic models

The release kinetic of the formulation was checked by fitting the release data to various kinetic models. The release was best fitted to Higuchi model.

Surface morphology

From figure 8(a), 8(b) it was observed that surfaces of all microspheres were rough and drug crystals were also present on the surface of microspheres. These drug crystals were responsible for the burst release of drug from the microsphere.

CONCLUSION

Nicornadil microspheres were prepared successfully by non aqueous solvent evaporation method. Drug: polymer ratio had significantly effect on various parameters like % yield, % entrapment efficiency, particle size and % in vitro drug release. It was found that increase the drug: polymer ratio resulted that increased the particle size and decreased the release rate. Liquid paraffin viscosity significantly affects the particle size and in vitro drug release. In continuous phase increase the concentration of Heavy liquid paraffin resulted that decreased particle size and increased the release rate. From the SEM study observed that microspheres were spherical and rough surface.

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