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FORMULATION AND EVALUATION OF NICORANDIL MICROSPHERES

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ABSTRACT

Present investigation describes preparation of microspheres by solvent evaporation followed by in vitro characterization of microspheres to evaluate the effect of method of preparation on physical properties and drug release profile of microspheres. The microspheres were found to be discrete, spherical with free flowing properties. The particle size distribution, entrapment efficiency and their release profiles were investigated. The yield was found to be maximum in case of solvent evaporation method. The microspheres formulation prepared by solvent evaporation method the drug carrier interactions were investigated in solid state by Fourier Transform Infrared (FT-IR) spectroscopy study. In vitro drug release rate for a microsphere was found to be sustained over 24 hours. Hence, it can be concluded that the Formulation prepared by solvent evaporation method, has potential to deliver nicorandil in a controlled manner in a regular fashion over extended period of time in Comparison to all other formulations and can be adopted for a successful oral delivery of nicorandil for safe management of hypertension.

Key words: nicorandil, Solvent evaporation, Ethyl cellulose,HPMC, and chitosan

INTRODUCTION

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. More precisely, sustained drug delivery can be defined as "Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. This goal can be achieved on the basis of proper design of the dosage regimen.

Microspheres have potential to deliver drug in a controlled fashion. nicorandil is an effective antihypertensive drug but is extensively bound to plasma proteins and also causes gastrointestinal disorders, neutropenia, acute hepatotoxicity, migraine and pancreatitis. It may there fore be more desirable to deliver this drug in a sustained release dosage form. The present study was focused on development of sustained release nicorandil microspheres using solvent evaporation method and to study the effect of method of preparation on physical properties and drug release profile of nicorandil microspheres[1].

The purpose of this work is to develop multiparticulate sustained release drug delivery system of Nicorandil, a low soluble drug, to improve the bioavailability with reduction in dosing frequency along with good patient compliance. A sustained release system is designed to release the drug at a predetermined rate in order to maintain a constant drug concentration for a specified period of time with minimum side effects [2]. The microspheres are prepared by incorporating varying concentrations of Hpmc K 100 and Ethyl cellulose & chitosan.

Present work includes the development of multi-particulate dosage form because it offers several advantages like improving patient compliance by

decreasing dosing frequency, less inter and intra subject variability[7] , reduced risk of local irritation, no risk of dose dumping[8]. Microspheres can provide sustained release properties with more uniform distribution of drugs within gastrointestinal tract [9] [10]. Hence the bioavailability of beads can be enhanced.

MATERIALS AND METHODS:

Materials: Nicorandil was obtained as a gift sample from, MSN Libratory Private Limited, Hyderabad, India. HPMC K100 was obtained from Colorcon India Pvt.Ltd Ethylcellulose, Chitosan were obtained from SD Fine –Chem Private Limited, Mumbai, India. All other ingredients, reagents and solvents were of analytical grade.

Method: The microspheres containing the angina pectoris drug Nicorandil, as the core material were prepared by a non-aqueous solvent evaporation method. Here the drug (250 mg) and the polymers like Ethyl cellulose, Ethylcellulose +Hpmc and chitosan.(F1toF5 Ethyl cellulose F6 toF10 Ethyl cellulose+Hpmc) was dissolved in 20 ml in the ratio of 1:9 (methanol: acetone) mixture, F10toF15 Chitosan was dissolved in 20 ml of (1:9) acetone& acetic acid mixture ,(250,375,500,625 and 750) were mixed in various ratios. F1to F15formulations the slurry was introduced into 30 ml of liquid paraffin while stirring (600-1800 rpm) with a mechanical stirrer equipped with a three-blade propeller at room temperature. The solution was stirred for 4 h to allow the solvent to evaporate and the microspheres were collected by filtration by Whatman filter paper. The microspheres were washed repeatedly with petroleum ether (40 - 60 °C) until free from oil. The microspheres were collected and dried for 3 h at room temperature and subsequently stored in a desiccator over fused calcium chloride. Total fifteen formulations were prepared with different drug polymer ratio. These fifteen formulations were included in the optimization study and evaluated.

Table No.1 various formulations of Losartan potassium microspheres

S.no	Formulation	Nicorandil (mg)	Ethyl cellulose	Ethyl cellulose+Hpmc	Chitosan
1	F1	1%	1%		
2	F2	1%	1:5%		
3	F3	1%	2.00%		
4	F4	1%	2:5%		
5	F5	1%	3%		
6	F6	1%		1%	
7	F7	1%		1:5%	
8	F8	1%		2.00%	
9	F9	1%		2:5%	
10	F10	1%		3%	
11	F11	1%			1%
12	F12	1%			1:5%
13	F13	1%			2.00%
14	F14	1%			2:5%
15	F15	1%			3%

EVALUATION PARAMETERS: The prepared microspheres were evaluated for particle size, drug content, entrapment efficiency, invitro dissolution studies and stability studies.

Particle size analysis: The particle size of microsphere was determined using optical microscopy method. Particle size of all the batches of the formulated beads in a sample was measured with an optical micrometer fitted with a calibrated eye piece. Calibration of the microscope was done prior to particle size measurement of the beads[14]. Approximately 625 particles were counted for particle size using a calibrated optical microscope. All readings are average of three trials ± SD.

Scanning electron microscopy analysis (SEM): The shape and surface characteristics were

determined by scanning electron microscopy (model-JSM, 35CF, jeol, Japan) using gold sputter technique. The particles were vacuum dried, coated to 200 Ao thicknesses with gold palladium using prior to microscopy. A working distance of 20nm, a tilt of zero-degree and accelerating voltage of 15kv were the operating parameters. Photographs were taken within a range of 50-500 magnifications.

Drug entrapment efficiency: Drug entrapment efficiency of Nicorandil microspheres was performed by accurately weighing 100mg of drug equivalent microspheres and suspended in 100 ml of 6.8 pH phosphate buffer and it was kept on a side for 24 hours. Then, it was stirred for 15 mins and filtered. After suitable dilution, Nicorandil in the filtrate was analyzed spectrophotometrically at 258nm using U.V.Spectrophotometer.

Nicorandil drug content: Equivalent weight of microspheres was weighed and dissolved in 5ml of water and methanol mixture in a standard flask Shake for 30min and then make up with 6.8 pH phosphate buffer and then centrifuge it. From that take 5ml of solution in 50 ml standard flask make up with 6.8 PH phosphate buffer. Generally, the drug content in any formulation should fall within the limit of 90 – 110%.Then solution was filtered and the drug content was estimated at230 nm spectrophotometrically after suitable dilution.

In vitro drug release studies: In vitro drug release from Nicorandil was performed using USP Apparatus I in 900 mL of buffer pH 1.2 for 2hrs and pH 6.8 for remaining time period stirred at 37 °C and 50 rpm maintaining sink conditions. The accurately weighed Nicorandil microspheres were enclosed in a sieve, placed in the basket, and processed for dissolution testing. All the nicorandil microspheres stayed in the basket during 24-h dissolution testing (i.e., no particles diffused out of the sieve). Dissolution samples (5 mL) were withdrawn at regular intervals (0, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24h) using an auto sampler with replacement of equal volumes of fresh medium. The samples were filtered through a 0.45-µm filter and analyzed spectrophotometrically at 258 nm in triplicate. Drug concentration was calculated using a calibration curve.

Stability Study: Stability studies were carried out at accelerated condition (25º C ±2º C at 60% RH ±5% RH), (30º C ±2º C at 65% RH ±5% RH) and (40˚ C ±2˚ C at 75% RH ±5% RH) for the optimized formulation F10. The beads were stored at (25º C ±2º C at 60% RH ±5% RH), (30º C ±2º C at 65% RH ±5% RH) and (40˚ C ±2˚ C at 75% RH ±5% RH) for accelerated temperature in closed high density polyethylene bottles for 3 months. The samples were withdrawn after predetermined period of 1 month, 2 month and 3 month. The samples were analyzed for its drug content and *In-Vitro* drug release.

DRUG RELEASE KINETICS:

Zero order release rate kinetics: To study the zero order release kinetics the release rate data are fitted to the following equation

F=K0t Here,

F is the fraction of drug release

K0 is the rate constant

T is the release time

First order model: This model has also been used to describe absorption and/elimination of drug, the release of the drug which followed first order kinetic can be expressed by the equation

Log C=log c0-kt/2.303

Where, Co is the initial concentration of drug

K is the first order rate constant

t = is the time

Higuchi release model: To study the higuchi release kinetics, the release rate data was fitted to the following equation

F =KH.t1/2

Where, F is the amount of the drug release

Kh is the release time t is the release time

Korsmeyer and peppas model: The release rate date were fitted to the following equation,

Mt/M8 =KM.tn

Where, Mt/M8 is the fraction of drug release

KM is the release constant

t is the release time.

RESULTS AND DISCUSSION:

Evaluation parameters of microspheres

The various parameters in the production of microspheres were evaluated and reported in Table 2 and 3. The angle of repose was found to be between 23.19 to 29.1. The bulk density and tapped density was found to be between 0.30 to 1.04 and 1.03 to 1.95. The Car's index and Hausner's ratio was found to be between 7.12 to 13.17 and 1.07 to 1.114. The entrapment efficiency was found in the range of 75.85±1.91 to 91.21±1.07. The drug content is in the range of 95.41±2.1 to 99.82±2.67.The particle size is in the range of 100.5±1.3 to110.2±2.9.

Dissolution Studies: All the 15 formulations of Nicorandil microspheres are subjected to dissolution studies. Dissolution is carried out in USP type 1

apparatus at 100 rpm in the volume of 900ml dissolution media (ph 6.8 phosphate buffer) for 24hours. The results are shown in Table 4 to 6 and Figures 1 to 4. Formulations F1, F2, F3,F4&F5 containing Ethylcellulose (1:1,1:1.5,1:2,1:2.5,1:3) shows percentage drug release of 99.6% , 99.62% , 99.61% ,98.54% & 99.18% in 9 hrs. Formulations F6, F7, F8,F9&F10 (1:1,1:1.5,1:2,1:2.5,1:3) which contained Ethylcellulose with HPMC K100M shows percentage drug release of 97.82% , 99.59% , 99.75% ,98.41% & 99.59% in 24hrs respectively. Formulations F11, F12, F13,F14&F15 which contained Chitosan (1:1,1:1.5,1:2,1:2.5,1:3) shows percentage drug release of 99.47% , 100.57% , 98.61%,98.46% & 98.46 in 22 hrs respectively . Formulation F10 containing Ethyl cellulose+HPMC K100M shows percentage drug release of 99.59% in 24 hrs. It has been observed that the dissolution rate was found to decrease linearly with increasing concentration of HPMC K100M.

The graph indicates F10 formulation shows better drug release when compared with other formulations, and followed by the zero order kinetics. The mechanism of release F17 formulation as shown in fig 4-8, and it fits into Korsmeyer Peppas non fickian diffusion.

Table no 2 Micrometric properties of Nicorandil

Formulation Code	Tapped density	Bulk Density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (θ)
F1	1.14±2.5	0.967 ±0.01	8.38±0.16	1.43 ±0.07	26.46±0.2
F2	1.05±3.21	0.687±0.01	7.12±0.13	1.07 ±0.06	22.92±0.21
F3	1.14±2.56	0.903±0.02	9.82±0.17	1.10 ±0.03	23.96 ±0.63
F4	1.10±2.23	0.306±0.01	10.0 ±0.09	1.11 ±0.07	24.30 ±0.55
F5	1.17±4.19	0.815 ±0.03	12.5±0.21	1.14 ±0.08	26.56 ±0.41
F6	1.13±1.15	0.923±0.02	13.17±0.19	1.15±0.05	28.29 ±0.37
F7	1.16±1.13	0.781±0.03	7.26±0.16	1.08±0.04	24.56±0.25
F8	1.43 ±1.72	1.055 ±0.01	7.68 ±0.16	1.08 ±0.02	22.61 ±0.18
F9	1.41 ±2.59	1.049 ±0.03	9.37 ±0.23	1.10 ±0.02	23.19 ±0.13
F10	1.64 ±1.87	1.039 ±0.02	10.0 ±0.31	1.11 ±0.08	24.77 ±0.26
F11	1.95±2.57	0.932 ±0.03	11.45 ±0.26	1.13 ±0.06	27.40 ±0.31
F12	1.17±2.34	0.826 ±0.01	12.40 ±0.19	1.14 ±0.02	28.78 ±0.13
F13	1.16±0.12	1.041±0.3	9.5±0.210	1.11±0.016	28.14±0.2
F14	1.12±0.4	1.02±0.4	11.02±0.237	1.08±0.018	29.1±0.19
F15	1.03±0.17	0.96±0.24	10.12±0.238	1.07±0.015	28.2±0.15

Table No.3 Particle size, Drug Entrapment Efficiency:

Sl.no	Formulation code	Percentage yeald	Drug content (%)	Entrapment effeciancy(%)	PARTICLE SIZE (µm)
1	F1	89	97.83	76.68	100.5±1.3
2	F2	87	95.63	88.85	106±2.21
3	F3	96.6	96.59	82.63	102.1.33
4	F4	85.6	96.82	78.55	105.2±0.3
5	F5	86.6	95.41	75.85	110.2±2.9
6	F6	98	97.72	83.9	112±2.8
7	F7	87.5	96.31	85.65	103.16±2.7
8	F8	93	99.64	81.7	105±2.05
9	F9	96	98.42	85.2	108.2±0.8
10	F10	97.98	99.82	91.21	100.10±2.3
11	F11	96.71	96.69	89.84	104.4±2.4
12	F12	91.08	96.38	86.72	105.7±0.7
13	F13	91.37	97.67	79.64	107.4±1.2
14	F14	90.46	96.52	90.42	101.3±1.0
15	F15	91.84	98.17	89.41	102.9±2.3

Table No.4 Invitro drug release data of F1-F5 Formulations

S.No	Time(hr)	F1	F2	F3	F4	F5
0	0	0	0	0	0	0
1	1	57.86	47.86	31.57	41.82	31.35
2	2	68.63	61.75	37.34	53.42	47.74
3	4	78.48	69.84	42.09	58.51	51.72
4	6	99.76	74.12	51.26	66.74	62.41
5	8		83.51	63.78	75.76	71.49
6	10		97.49	67.48	84.82	78.84
7	12		99.62	91.42	90.48	83.58
8	14			99.61	98.54	92.49
9	16					99.18
10	18					
11	20					
12	22					
13	24					

Table No.5 Invitro drug release data of formulations F6-F10

S.No	Time(hr)	F6	F7	F8	F9	F10
0	0	0	0	0	0	0
1	1	34.84	25.56	18.41	22.24	21.48
2	2	48.59	34.61	32.49	32.47	27.86
3	4	51.68	46.28	43.71	37.76	41.84
4	6	62.43	58.43	54.71	42.06	49.6
5	8	74.28	66.47	62.32	57.91	54.32
6	10	84.81	82.58	81.67	70.14	67.63
7	12	97.82	99.59	92.45	78.38	73.57
8	14			99.75	82.36	78.48
9	16				88.34	82.62
10	18				98.41	88.32
11	20					91.64
12	22					94.78
13	24					99.59

Table No .6 Invitro drug release data of F11-F15 formulations

S.No	Time(hr)	F11	F12	F13	F14	F15
0	0	0	0	0	0	0
1	1	62.84	57.36	48.75	11.84	11.56
2	2	73.41	63.47	57.32	22.84	14.42
3	4	86.26	71.55	63.84	31.64	22.85
4	6	93.72	78.14	70.41	43.84	32.22
5	8	99.47	82.87	76.21	49.48	33.64
6	10		86.67	84.13	51.41	56.47
7	12		96.83	88.89	67.58	57.88
8	14		100.57	93.38	86.74	66.08
9	16			98.61	92.38	72.38
10	18				98.46	83.64
11	20					91.87
12	22					98.46

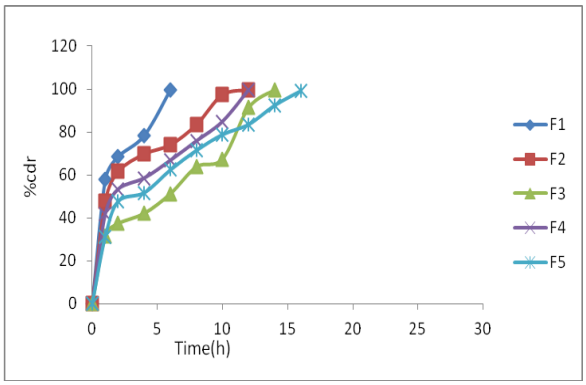

Fig. 1 Dissolution profile of F1 –F5

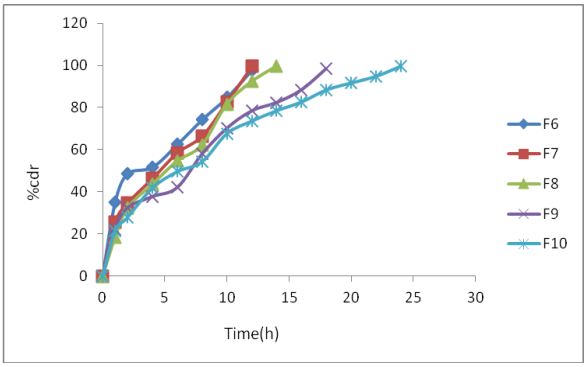

Fig.2 In vitro dissolution profile of F6 –F10

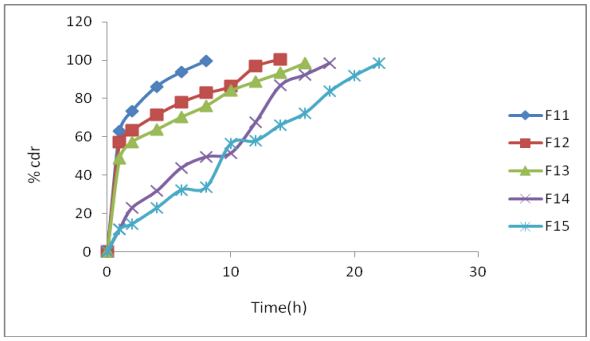

Fig. 3 In vitro dissolution profile of F13 –F17

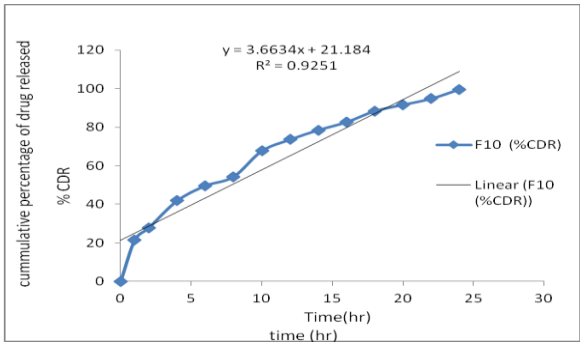

Fig. 4 Zero order plot of best formulation (F10)

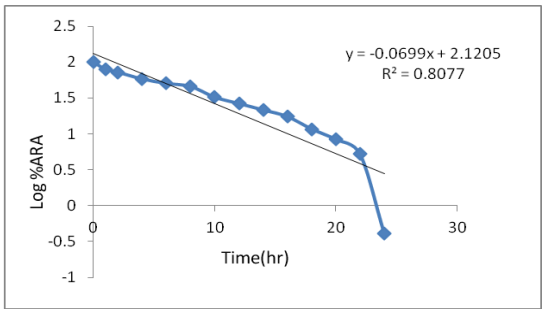

Fig.5 First order plot of best formulation (F10)

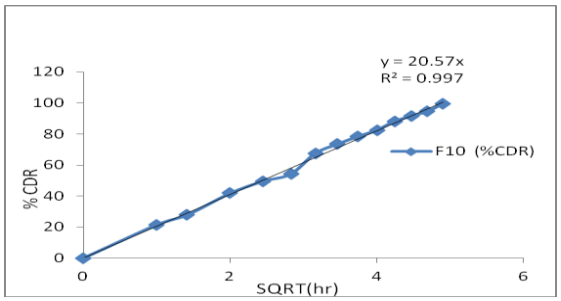

Fig.6 Higuchi plot of best formulation (F10)

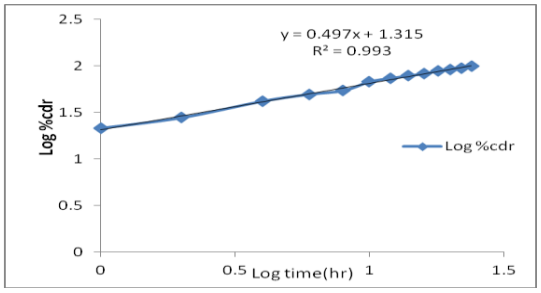

Fig .7 Koresmeyer peppas plot of best formulation

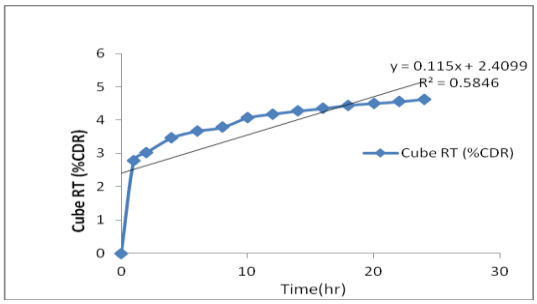

Fig.8 Hixson plot of best formulation

Conclusion:

The concept of formulating microspheres containing Nicorandil offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. Microspheres of Nicorandil were prepared successfully by solvent evaporation method using the different concentration of polymers, especially by means of improving the oral bioavailability of the drug. It would be faster and more economical to alter beneficially the properties of the existing drugs than developing new drug entities. Hence this formulation will be a boon to novel drug dosage forms.

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