Academic Sciences Asian Journal of Pharmaceutical and Clinical Research

Vol 5, Suppl 3, 2012 ISSN - 0974-2441

Research Article

FORMULATION AND *IN-VITRO* EVALUATION OF NICARDIPINE HYDROCHLORIDE MICROCAPSULES

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Received:30 January 2012, Revised and Accepted:22 April 2012

ABSTRACT

Nicardipine Hydrochloride microcapsules with a coat consisting of Cyclohexane and a polymer such as Ethyl cellulose were prepared by Coacervation phase separation induced by the addition of non solvent. By Scanning Electron Microscopy, the microcapsules were found to be spherical, without aggregation, discrete and free flowing. The maximum percentage of drug content was found to be 82.12 % in formulation F1 with the drug: polymer ratio (4:1) .Entrapment efficiency were found to be in the range of 80 % to 107% .The average particle size were found to be in the range of 123 µm to 88 µm. Percent of loose drug on surface were found to be in the range of 3.54% to 8.65%. All the formulations showed good flowability. The *in-vitro* drug release for all the formulations F1 to F9 were found to be 6.8% to 17.14% drug release in first hour and 56.87% to 98.8% drug release at the end of 12 hrs. Among the nine formulations, F4 shows maximum drug release i.e. 98.8% at the end of 12 hrs. All the formulations F1 to F9 were found to be Zero order drug release with Non Fickian diffusion mechanism. The FTIR study indicates that there was no drug interaction and complexation occur during the manufacturing process.

Keywords: Coacervation phase separation, Entrapment Efficiency, Loose surface crystals study, *in-vitro* drug release

INTRODUCTION

Microencapsulation is the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms and product applications. The application of Microencapsulation might well include sustained-release or prolonged-action medications, taste-masked chewable tablets, powders and suspensions, single- layer tablets containing chemically incompatibility ingredients, and new formulation concepts for creams, ointments, aerosols, dressings, plasters, suppositories and injectables [1]. It has been used in the pharmaceutical industry for the conversion of liquids to solids, taste masking of bitter drugs, acquiring prolonged or sustained release, reducing gastric irritation and environmental protection of labile moieties [2] Microcapsules having core material and coating material. Core material is the drug substance which is to be coated by a coating material generally polymers are used. An important class of polymer mediated drug delivery systems that are applied for controlled drug delivery is the microcapsules [3&4]. Microcapsules continue to be of much interest in controlled release based on relative ease of design and formulation and partly on the advantages of microparticulate system. Ethyl cellulose is a non biodegradable and biocompatible polymer used as encapsulating materials for the controlled release of pharmaceuticals.

Nicardipine Hydrochloride used as a calcium channel blocker [5]. Due to its considerable first pass metabolism and a high clearance, thus necessitating frequent administration of large doses. Microencapsulation provides the prolonged release of drug in a single dose. So to reduce the dose frequency, the purpose of the present work was to prepare and evaluate microcapsules of Nicardipine Hydrochloride by Coacervation phase separation induced by temperature change method.

MATERIALS AND METHODS

Nicardipine hydrochloride was a gift sample from Cipla Ltd, Goa. Cyclohexane and Ethyl cellulose were purchased from Merck Pvt. Ltd, Mumbai. All other reagents used were of analytical grade.

Methods for preparation of microcapsules

Coacervation phase separation by the addition of non solvent developed by Heistand et al. Ethyl cellulose was dissolved in 50 ml toluene to form homogeneous solution. Core material (1.6 g) was then added to the polymer solution and dispersed thoroughly with the aid of a mechanical stirrer (for 10 minutes). Coacervation was then induced by the addition of 30 ml of petroleum ether slowly over a period of 20 minutes while stirring at the same speed. The system was then chilled for 20 minutes with stirring to rigidise the coating of the microcapsules. The encapsulated product was then collected by filtration and air dried to obtain microcapsule

Now repeat the same experiment with same amount of solvent and core material but the amount of coating material was different that is , 400mg, 800mg, and 1200mg. The rotation speed of mechanical stirrer is also a variable that is 200 rpm 400 rpm and 600 rpm.

The results are shown in Table 01.

Table 01: Formulation of Nicardipine hydrochloride microcapsules

Phase separation induced by the addition of non solvent		
Batch code	**Rotation (RPM)**	**Core:coat ratio**
FI	200	4 :1
F2	200	4 :2
F3	200	4 :3
F4	400	4 :1
F5	400	4 :2
F6	400	4 :3
F7	600	4 :1
F8	600	4:2
F9	600	4 :3

Drug polymer compatibility study [6]

Compatibilities among the drug-polymers can be confirmed by carrying out infrared light absorption scanning spectroscopy (IR) studies. Infra red spectra of pure drug and mixture of formulations were recorded by dispersion of drug and mixture of formulations in suitable solvent (KBR) using Fourier Transform Infrared Spectrophotometer (FTIR). A base line correction was made using dried potassium bromide and then the spectra of the dried mixture of drug, formulation mixture and potassium bromide were recorded. The FTIR studies were conducted at National Institute of Technology (NIT), Rourkela, Odisha.

Solubility determination [7].

The solubility was studies in various aqueous and non aqueous solvents.

A cleaned and dried graduated test tube of 10 ml was taken and 10 ml of 0.1 N HCL was poured into it, then unknown quantity of

Nicardipine was added to it and dissolved properly by shaking. The shaking was continued until the drug went into solution that means until a clear solution was obtained. If the drug was undisclosed in the solution even after shaking with hand then the test tube containing the drug with solvent was subjected for shaking in a mechanical shaker for 12 hrs. The above solution was then filtered, dilutions were made and absorbance was noted in UV-Visible double beam spectrophotometer at 238 nm. Likewise, solubility was determined in phosphate buffer of pH 6.8 and 7.2.

Evaluation of microcapsules

Particle size measurement study [8]

Particle size analysis was done by sieving method using Indian standard sieves ≠ 10, 12, 16, 20, 22, 40 and 44. Average particle size was calculated using the formula

$$d_{avg} = \sum dn / \sum n$$

Where n is frequency weight and d is the mean diameter

Rheology properties [9]

Angle of repose, Carr's index, Bulk density and Hausner's ratio were determined to assess the flow ability of the prepared microcapsules.

Drug content estimation [10]

Drug content of the different core:coat ratio of microcapsules were estimated. From each batch of the microcapsules four sample of 100 mg each were taken and analyzed for the drug content. 100 mg of microcapsule were weighed and transfer into mortar and pastel and triturate properly. Remove this powder into 100 ml volumetric flask with the help of 5 ml of methanol and the volume was made up to the mark with 0.1 N HCL, kept for 24 hours and filtered. The drug content was analyzed using UV-Visible double beam spectrophotometer at 238 nm. Percentage of drug content was calculated by the formula

Percentage drug content = weight of pure drug present in microcapsules / weight of microcapsules x 100

Drug Entrapment Study [11]

The Drug Entrapment Efficiency (DEE) was calculated by the equation

EE = (Pc / Tc) X 100

Pc : Practical content.

Tc : Theoretical content.

Loose surface crystals study [12]

Microcapsules of Nicardipine were evaluated by loose surface crystal study to observe the excess drug present on the surface of microcapsules. From each batch, 100mg equivalent of microcapsules was shaken in 20 ml of double distilled water for 5 minute and then filtered through Whattman filter paper no: 41. The amount of drug lost in filtrate was determined spectroscopically and percentage of total drug was calculated.

***In-vitro* drug release study** [13]

Dissolution studies were conducted for microcapsules of Nicardipine by using USP paddle type apparatus at 37 ± 0.5^{0}C at 50 rpm. 900 ml of 0.1 N HCl was used as dissolution medium. At various time intervals, 5 ml of sample was withdrawn from a fixed position of the vessel and replaced with fresh dissolution medium. The absorbance of filtered sample was analyzed by using UV-Visible double beam spectrophotometer at 238 nm. The percentage drug released at various time intervals was calculated.

***In- vitro* drug release kinetic study** [14]

In order to study the exact mechanism of drug release from Nicardipine microcapsules, drug release data was analyzed according to Zero order, First order, Higuchi Equation and Korsemeyer-Peppas model.

Scanning Electron Microscopy (SEM) [15]

Scanning Electron Microscopy (Stereo scan S250 MK III, Cambridge, UK) was carried out to study the morphological characteristics of Nicardipine hydrochloride microcapsules. The dried microcapsules were coated with gold (100 A°) under an argon atmosphere in a gold coating unit and Scanning electron micrographs of both higher and lower resolutions were observed. The scanning electron microscopy was held at Birbal Sahini Institute of Palaeobotany, Lucknow (U.P.)

RESULTS AND DISCUSSION

Drug-polymer compatibility study.

The FT-IR (Shimadzu IR Spectrophotometer, model 840, Japan) was used for these IR analyses in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution. The results indicate that there was no drug interaction and complexation occur during the manufacturing process. The results are shown in Figs 01 to 03.

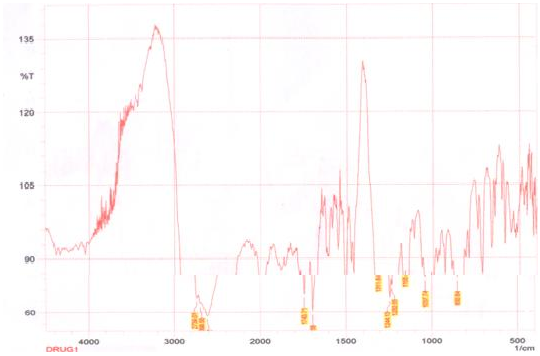

Fig 01: FTIR study of Nicardipine Hydrochloride

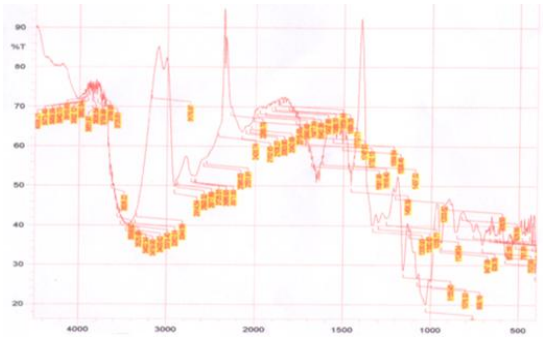

Fig 02. FTIR study of Ethyl cellulose

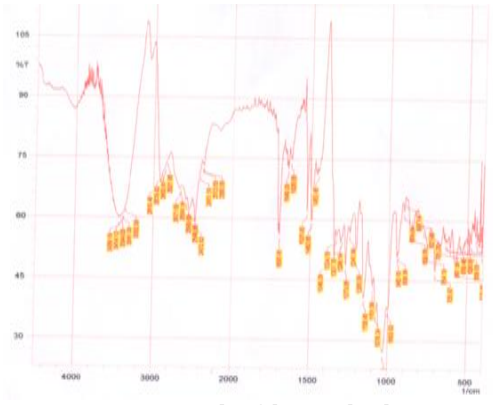

Fig 03: FTIR study of drug and polymer

Solubility determination.

Solubility of Nicardipine Hydrochloride was varied in different pH environment. Nicardipine hydrochloride is more soluble in acidic pH and it was found to be 15.357 mg/ml .The results are shown in Table 02.

Table 02: Solubility values of Nicardipine in different pH ranges

pH	Solubility(mg/ml)
1.2	15.357
6.8	5.252
7.2	4.269

Particle size measurement of microcapsules

The average particle size was found to be in the range of 123 µm to 88 µm. The average particle size of microcapsule increases as the concentration of the polymer increases whereas particle size decreases by increases of rotation speed of stirrer. Particles sizes of different formulations are mentioned in Table 03.

Table 03: Particle size of microcapsules

Batch code	Particle size (micrometer)
F1	98
F2	111
F3	123
F4	92
F5	102
F6	108
F7	88
F8	94
F9	102

Rheological determination of microcapsules

The rheological properties of the microcapsules are presented in Table 04. Particle size of the microcapsules increases as the drug: polymer ratio decreases. Low value of angle of repose indicate that the microcapsules have better flow properties and the better flow properties indicated that non aggregated of microcapsules.

Table 04: Rheological properties of microcapsules

Batch code	Carr's index	Hausner's ratio	Angle of repose (in degree)
F1	9.8	1.11	24.1
F2	10.2	1.21	23.6
F3	10.5	1.08	25.4
F4	11.2	1.15	24.8
F5	12.2	1.18	22.9
F6	10.5	1.19	21.9
F7	10.9	1.07	26.4
F8	10.8	1.13	25.8
F9	11.1	1.17	24.7

Drug content of prepared microcapsules

The minimum percentage of drug content was found to be 53.2% in formulation F9 in the drug : polymer ratio (4:3). Similarly maximum percentage of drug content was found to be 82.12 % in formulation F1 in the drug: polymer ratio (4:1).It seems that value of percentage of drug content decreases with the increase of core:coat ratio probably due to its thick layer of coat formed by increase of coat: core ratio. Percentage drug contents of different formulations of microcapsules are mentioned in Table 05.

Table 05: Percentage drug content of microcapsules

Batch code	Drug: polymer	% drug content
F1	4 : 1	82.12
F2	4 : 2	68.0
F3	4 : 3	62.2
F4	4 : 1	79.7
F5	4 : 2	59.2
F6	4 : 3	58.9
F7	4 : 1	65.9
F8	4 : 2	53.28
F9	4 : 3	53.2

Entrapment Efficiency

Entrapment Efficiency was found to be in the range of 80 % to 107 %. Entrapment Efficiency decreases with increase of rotation speed of stirrer, probably it is due to smaller microcapsules formed by increase of rotation speed of stirrer. The results are shown in Table 06.

Table 06: Entrapment efficiency of the microcapsules

Batch code	Drug : polymer ratio	Theoretical Drug content (%)	Estimated drug Content (%)	Entrapment efficiency(%)
F1	4 : 1	80.00	81.6	102
F2	4 : 2	66.60	68.0	102
F3	4 : 3	57.14	62.2	107
F4	4 : 1	80.00	79.7	99
F5	4 : 2	66.66	59.2	89
F6	4 : 3	57.14	58.9	103
F7	4 :1	80.00	65.9	82
F8	4 : 2	66.66	53.28	80
F9	4 : 3	57.14	53.2	93

Loose surface crystal studies

Loose surface crystal studies were observed to estimate the excess amount of drug attached on the surface of microcapsules after a successful drug entrapment. Percent of loose drug on surface were found to be in the range of 3.54% to 8.65%.The results obtained are mentioned in the Table 07.

Table 07: Loose surface crystal study of microcapsules

Batch code	Percentage drug on surface
F1	8.65
F2	7.43
F3	7.54
F4	4.67
F5	7.54
F6	8.54
F7	3.54
F8	4.36
F9	6.45

***In-vitro* drug release study**

The *in-vitro* drug release study of the microcapsules was performed in 0.1N HCL. All the formulations were found to release Nicardipine hydrochloride in a controlled manner for prolonged periods over 12 hours. The cumulative percent of drug release from the formulations F1 to F9 were found to be 6.8% to 17.4% drug release in first hour and 56.87 % to 98.8 % drug release at the end of 12 hrs. Among the nine formulations, Formulation F3 shows minimum drug release i.e.56.87%, whereas formulation F4 shows maximum drug release i.e. 98.8%. at the end of 12 hrs. It seems that drug release from formulations decreases with increase in drug: polymer ratio and increases with increase in rotation speed of stirrer. The results are mentioned in Fig. 04.

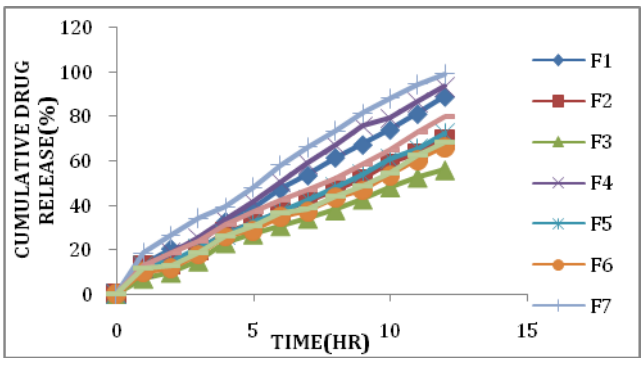

Fig 04:Comparative cumulative drug release profile of formulations F1 to F9

***In- vitro* drug release kinetic study.**

The *in-vitro* drug release data of all the formulations were fit into Zero order, First order, Higuchi Equation and Korsemeyer-Peppas model. The results are shown in Table 08.

Table 08: Release kinetics of microcapsules

Batch code	Zero order R^2	First order R^2	Higuchi R^2	Korsemeyer-Peppas R^2	Diffusion exponent (n)
F1	0.981	0.898	0.897	0.987	0.58
F2	0.975	0.812	0.876	0.981	0.53
F3	0.991	0.821	0.854	0.991	0.68
F4	0.983	0.792	0.992	0.993	0.56
F5	0.986	0.858	0.876	0.998	0.59
F6	0.985	0.875	0.854	0.995	0.61
F7	0.984	0.894	0.812	0.994	0.71
F8	0.982	0.868	0.887	0.992	0.74
F9	0.987	0.843	0.892	0.983	0.69

Among the zero order and first order equations, the Zero order Regression co-efficient (R^2) value was found to be more than the First order. So all the formulations F1 to F9 followed Zero order drug release. Similarly, Regression co-efficient (R^2) value between Higuchi Equation and Korsemeyer-Peppas model, the Korsemeyer-Peppas model (R^2) value was found be more and also 'n' values are greater than 0.5 i.e. all the formulations followed Non-Fickian diffusion mechanism. Hence all the formulations followed the Zero order drug release with Non-Fickian diffusion mechanism.

Scanning Electron Microscopy (SEM)

The microcapsules prepared were found to be spherical to near spherical and without aggregation, (as revealed in SEM studies), discrete and free flowing. SEM of microcapsules are shown in Fig;01. The scanning electron microscopy was held at Birbal Sahini Institute of Palaeobotany, Lucknow (U.P.)

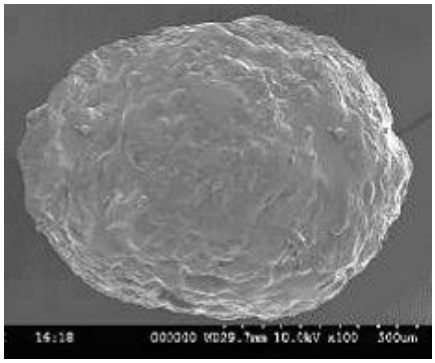

Fig 05: Microcapsules prepared by Non solvent method

CONCLUSIONS

Controlled release Nicardipine Hydrochloride microcapsules could be formulated by using Ethyl Cellulose as a release retardant by Non solvent method. The microcapsules of all the formulated batches were spherical, discrete and free flowing. The drug content was found to be uniform in all batches of microcapsules. Increasing the polymer concentration in microcapsule formulations decreases the rate of drug release dramatically. Further, an elaborate *in vivo* study is to be carried out for the formulated microcapsule using a suitable animal model.

ACKNOWLEDGEMENTS

Authors wish to give thanks to Principal and Management of Malla Reddy College of Pharmacy, Secunderabad, Andhra Pradesh for providing suitable research laboratory to carry out this project work and also my deep greatness to Cipla Ltd, Goa for providing Nicardipine Hydrochloride as a gift sample.

REFERENCES

1. Leon L., Liberman HA., Kang JL.The Theory and Practice of Industrial Pharmacy, 4thed.Mumbai:Varghese publication; 1991.p.413.
2. Naga M, Bindu MB, Arjun G, Pradeep B, Banji D. Formulation and evaluation of cefotaxime sodium microcapsules.Int J Pharm Res Dev.2010;10:80-86.
3. Hidekazu Y. Trends in Microencapsulation Research, KONA. 2004; 22: 23-31.
4. Venkatesan P, Manavalan R, Valliappan K. Microencapsulation: A Vital Technique in Novel drug delivery system. J Pharm Sci Res.2009;1: 26-35.
5. Martindale-The complete drug reference, 33rded. London: Pharmaceutical Press;2002.p. 938-939.
6. Desai KG, Park HJ. Study of gamma-irradiation effects on chitosan microparticles. Drug Del. 2006; 13: 39-50.
7. Martin A, Bustamante P. Solubility and distribution phenomena, 5th ed. New Delhi: B.I.Publications; 2006.p. 241-244.
8. Martin A, Bustamante P.Micromeritics,5thed. New Delhi: B.I.Publications; 2006.p535-536..
9. Leon L., Liberman HA., Kang JL.The Theory and Practice of Industrial Pharmacy, 3rd ed.Mumbai:Varghese publication; 1987.p.34
10. Chowdary KPR, Rao YS. Mucoadhesive microcapsules of glipizide: characterization, *in vitro* and *in vivo* evaluation. Ind J Pharm Sci. 2003; 65(3): 279-284.
11. Choudhary KPR, Rao YS. Preparation and evaluation of mucoadhesive microcapsules of indomethacin . Ind J Pharm sci. 2003 ; 65 (1): 49-52.
12. Bhumkar DR, Maheshwari M, Patil VB, Pokharkar VB. Studies on effect of variabilities by response surface methodology for Naproxane microspheres. Ind Drug. 2003; 40(8):455-461.
13. Abu-lzza K , Garcia LC, Robert D. Preparation and evaluation of zidovudine loaded sustain release microsphere: optimization of multiple response variables. J Pharm Sci. 1996; 85(6): 572-574.
14. Higuchi T. Mechanism of rate of sustained action medication. J Pharm Sci. 1963;52 (11): 1145-1149.
15. Gohel MC, Paric RK , Amin AF, Surti AK. Preparation and formulation optimization of sugar crosslinking gelatin microspheres of Diclofenac sodium. Ind J Pharm Sci. 2005; 67 (8): 575-581.