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RESEARCH ARTICLE

DEVELOPMENT & CHARACTERIZATION OF NISOLDIPINE LOADED MICROSPHERES

Vinod Dhote[1]*, KanikaDhote[2], Dinesh Kumar Mishra[3], Subhendu Mishra[2]

[1]Truba Institute of pharmacy, Bhopal (M.P)

[2]Ravishankar College of Pharmacy, Bhopal (M.P)

[3]College of Pharmacy, IPS Academy Indore-452012 (M.P)

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***Correspondence for Author:**

Mr. Vinod Dhote*

Truba Institute of Pharmacy, Bhopal (M.P.)

Email: vinoddhote@gmail.com

Abstract:

The aim of the present research is to develop multiple unit dosage form as microspheres of a drug meant for management of hypertension (high blood pressure) using Nisoldipine. In the present study microspheres containing nisoldipine were prepared by Solvent evaporation method and characterized by optical microscopy and scanning electron microscopy. The microspheres were analyzed for drug entrapment, bulk density, angle of repose, particle size and In-vitro release pattern. The effect of process variables on microsphere size was studied and based on these preliminary studies, different batches of microspheres were prepared by altering the drug: polymer ratio and cross-linking with calcium chloride. The size of microspheres was in range of 130-140µm. They were spherical in shape as evidenced by photomicrographs and scanning electron microscopy. The percent drug entrapment was in the range of 86-88 % and they could sustain drug release over a period of 8 hrs.

Key words: Microspheres, Solvent evaporation method, optical microscopy, *in-vitro* release

INTRODUCTION:

Conventional drug delivery systems achieve as well as maintain the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day.[1] In order to avoid the unnecessarily frequent administration, higher cost of therapy and other undesired features of conventional dosage forms, controlled release preparations have been designed.[2] However, these systems have been of limited success in the case of drugs with a poor absorption window throughout the GIT. Microspheres are one of the microparticulate systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites.[2-4] Microsphere drug delivery system is a unique technology which provides controlled release of active ingredients.[3-5] It offers numerous advantages over other technologies like reduced side effects, improved stability, increased elegance and enhanced formulation flexibility.[6-8] Microsphere are porous, polymeric systems that are used mostly for topical and recently for oral administration. They can be incorporated into conventional dosage forms such as creams, lotions, gels, ointment, tablet and powder and share a broad package of benefits & thus provides formulation flexibility. [5, 9-12]

Nisoldipine is a 1, 4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, nisoldipine prevents calcium-dependent smooth muscle contraction and subsequent vasoconstriction. Nisoldipine may be used in alone or in combination with other agents in the management of hypertension. [7, 13]

By deforming the channel, inhibiting ion-control gating mechanisms, and/or interfering with the release of calcium from the sarcoplasmic reticulum. The decrease in intracellular calcium inhibits the contractile processes of the myocardial smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.[12-16]

The purpose of this research was to develop a controlled delivery system containing drug Nisoldipine with different ratio of polymer.[17-18] Their convenience and ease of manufacture may cut down the cost of the final product for efficient parentral administration in management of hypertension.[19-20]

METERIAL AND METHOD:

Nisoldipine obtained as gift sample from Torrent Pharmaceutical private limited, Ahmedabad.

PVA from Fisher scientific, eudragit RS 100 were purchased from Finar scientific. Methanol and other chemical was purchase from Loba Chemical Private Limited Mumbai.

Method:

Preparation of microspheres containing Nisoldipine:

In order to produce the microspheres, modified quasi-emulsion solvent diffusion method was used (20). Weighed amounts of ibuprofen and acrylic polymer were dissolved in 5 mL of ethanol at 45^{O}C. The formed ethanolic solution was poured into water containing polyvinyl alcohol (0.025- 0.1% w/v) and stirring continuously with a propeller type agitator (Model RZR-2000; Heidolph Electro).[13-14] The system was thermally controlled at 20^{O}C. Ethanol solution was finely dispersed in the aqueous phase as discrete droplets. The finely dispersed droplets of the polymer solution of the drug were solidified in the aqueous phase via counter diffusions of ethanol and water out of and into the droplets. After 30 min of stirring, the microspheres were separated by filtration, washed twice with 50 mL of water and then dried in oven at 37^{O}C for 24 h.[4, 15] Dried microspheres were stored in desiccators containing $CaCl_2$. Three independent batches were prepared. In Figure 1, the processing of this technique is illustrated. The representative formulations for the preparation of microspheres are tabulated in Table 1.

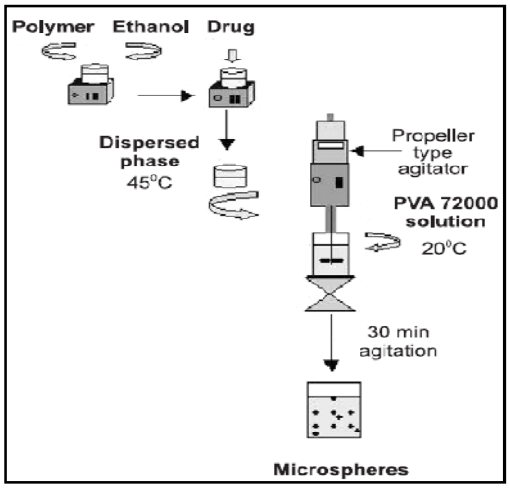

Figure 1. Formulation procedure for drug loaded microspheres.

Table 1: Composition of microspheres containing Nisoldipine

Formulation code	F1	F2	F3	F4	F5	F6
Inner phase						
Drug (mg)	2.5	2.5	2.5	2.5	2.5	2.5
Eudragit RS 100 (g)	0.50	0.83	2.5	3.0	3.5	4.0
Methanol (ml)	3	3	3	3	3	3
Outer phase						
Distilled water (ml)	200	200	200	200	200	200
PVA (mg)	50	50	50	50	50	50

Evaluation of Microspheres:

Determination of Production Yield and Loading Efficiency

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the microspheres obtained.[16]

$$\text{Production yield} = \frac{\text{Practical yield of Microparticles}}{\text{Therotical yield of Microparticles}} \text{ X } 100$$

The loading efficiency (%) of the microspheres can be calculated according to the following equation:

$$\text{Loading Efficiency} = \frac{\text{Actual drug content in microparticles}}{\text{Therotical drug content}} \text{ X } 100$$

Particle Size Analysis

Particle size analysis of prepared microspheres was carried by using Malvern Particle Size Analyzer Hydro 2000 MU (A). Microspheres were dispersed in double distilled water before running sample in the instrument, to ensure that the light scattering signal, as indicated by particles count per second, was within instrument's sensitivity range.[17-18]

During the measurement, particles are passed through a focused laser beam. These particles scatter light at an angle that is inversely proportional to their size. The angular intensity of the scattered light is then measured by a series of photosensitive detectors. The map of scattering intensity versus angle is the primary source of information used to

calculate the particle size. The scattering of particles is accurately predicted by the Mie scattering model. The Mastersizer 2000 software, allows accurate sizing across the widest possible dynamic range.[19]

Scanning Electron Microscopy

For morphology and surface topography, prepared microspheres were coated with platinum at room temperature so that the surface morphology of the microspheres could be studied by SEM.

The SEM, a member of the same family of imaging is the most widely used of all electron beam tools (Goldstein J. I., 2003). The SEM employs a focused beam of electrons, with energies typically in the range from a few hundred eV to about 30 keV, which is across the surface of a sample in a rectangular scan pattern. Signals emitted under this electron irradiation are collected, amplified, and then used to modulate the brightness of a suitable display device which is being scanned in synchronism with probe beam.[20]

Infrared Spectroscopy

FTIR spectroscopy was conducted using Perkin Elmer, Spectrum 100 FT-IR spectrometer. Spectrum was recorded in the wavelength region of 4000 to 400 cm-1. The procedure consisted of dispersing a sample in excess of potassium bromide nearly at the ratio 1:100, mixed well, after which the mixture was kept into the sample holder for analysis.[12]

Differential Scanning Calorimetry (DSC)

Thermal analysis is an important evaluation technique to find any possible interaction between the drug and used polymers. Any of such interaction may reduce the drug entrapment efficiency of the polymer and may also alter the efficacy of the drug. Such interaction can be identified by any change in thermogram.

***In-vitro* Release Study of microspheres**

Accurately weighed loaded microspheres (5 mg) were placed in 50 ml of ethanol/methanol in 100 ml glass bottles. The later were horizontally shaken at 37°C at predetermined time intervals. Aliquot samples were withdrawn (replaced with fresh medium) and analysed UV spectrophotometrically at 236 nm for Nisoldipine. The contents of drugs were calculated at different time intervals up to 6hrs.[15]

Results and Discussion:

- **Yield of the product**
  - **Percentage Yield**

Table 2. Percentage yield of formulated microspheres

Formulation code	Production yield (%)
F1	73.37±1.23
F2	76.64±1.37
F3	83.38±1.96
F4	86.76±1.22
F5	85.74±1.83
F6	84.42±2.23

*****Each value is average of three separate determinations ±SD

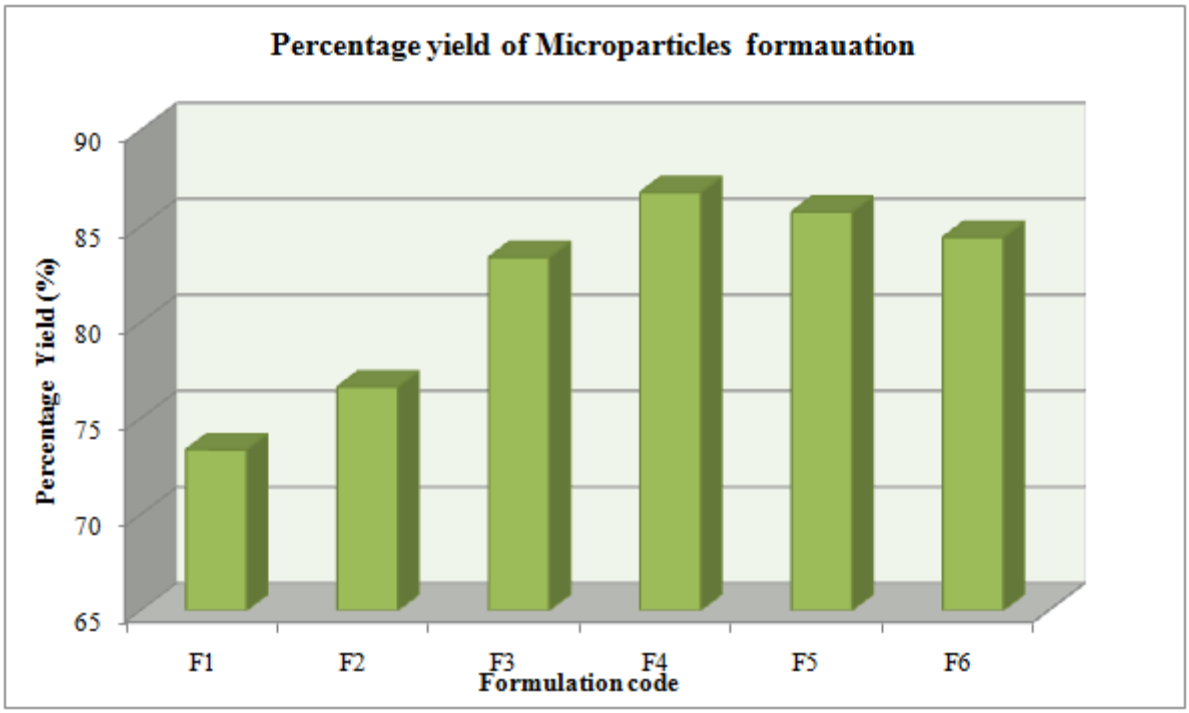

Figure 2: Percentage yield of microspheres formulations

Production yield of microspheres were between 73.37 to 86.76%. In case of Eudragit RS 100 microspheres, means on increasing drug: polymer ratio there is increase in the production yield of the microspheres.

- **Drug Loading Efficiency**

Table 3: Drug loading efficiency of microspheres formulations

Formulation code	Drug Loading efficiency (%)
F1	73.17±1.56
F2	75.74±1.26
F3	69.38±1.18
F4	87.76±1.23
F5	83.94±1.80
F6	80.42±2.03

*****Each value is average of three separate determinations ±SD

The loading efficiency was found to be high i.e. 69.38 to 87.76 % in drug loaded microspheres it was found that as drug: polymer ratio increases, drug loading efficiency also increases.

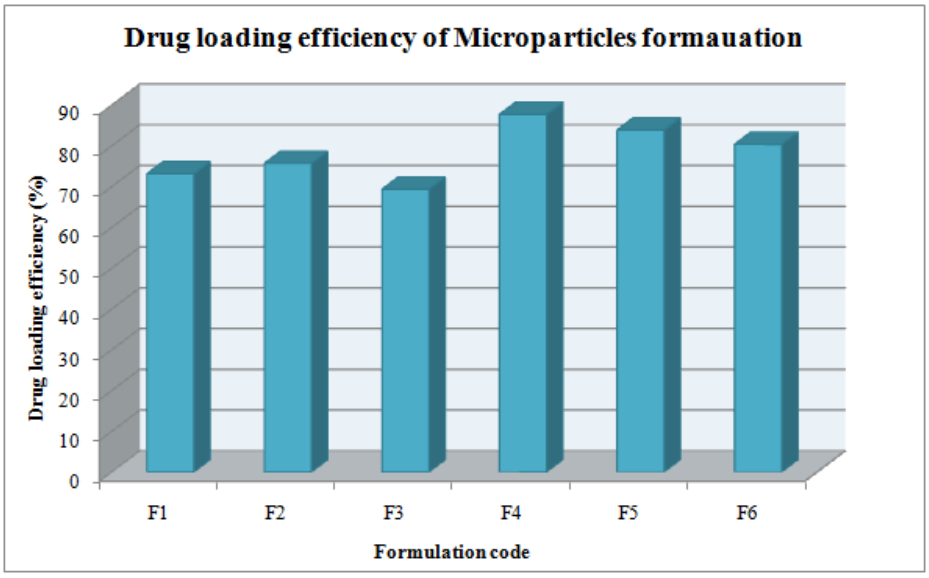

Figure 3: Loading efficiency of Nisoldipine microspheres formulations

- **Particle Size Analysis**

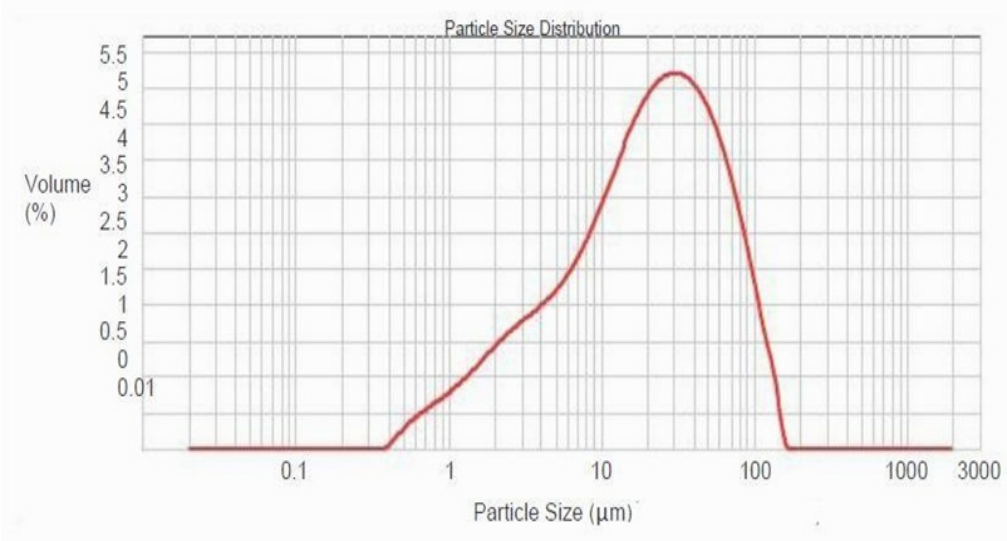

Figure 3: Particle size distribution of microspheres

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during both the polymerization methods. The mean particle size of nisoldipine microspheres found to be 39.92µm.

Scanning Electron Microscopy

The morphology of the microspheres prepared by entrapment method and quasi-emulsion solvent diffusion method were investigated by SEM. The representative SEM photographs of the microspheres are shown in Figure 4.

SEM images showed that microspheres prepared by liquid-liquid suspension polymerization method were finely spherical and uniform; no entire drug crystals were observed visually.

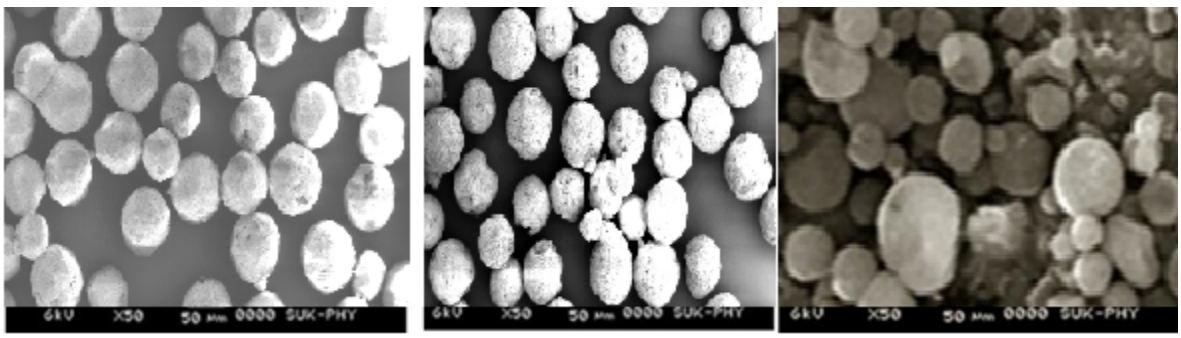

Figure 4: SEM Photographs of Nisoldipine microspheres (F4)

Infrared Spectroscopy

FTIR spectra of Nisoldipine microspheres

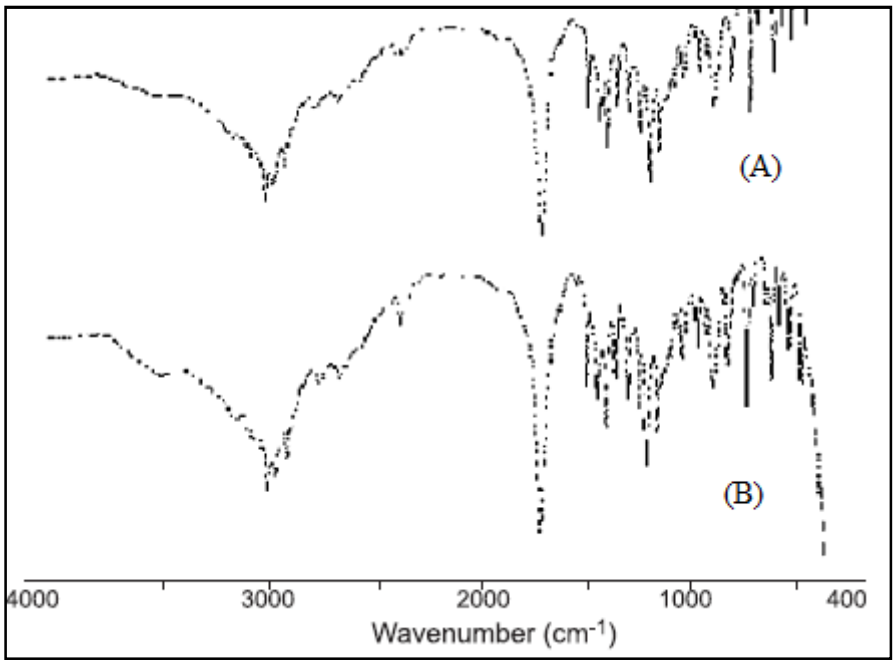

Figure 6: Overlay FTIR Spectra of: (A) Nisoldipine and (B) Nisoldipine microspheres formulation.

All characteristic peaks of drugs in the IR spectra of F 6 formulation were observed to be concordant with respective pure drugs.

Differential Scanning Calorimetry (DSC)

The results of DSC were observed for the integrity of the drug in microspheres formulation prepared by the entrapment process. In the DSC curve of selected F6 formulation. According to this data, there was no interaction between drug and Eudragit RS 100 in microspheres results showed that there was no interaction between the drugs and the polymer.

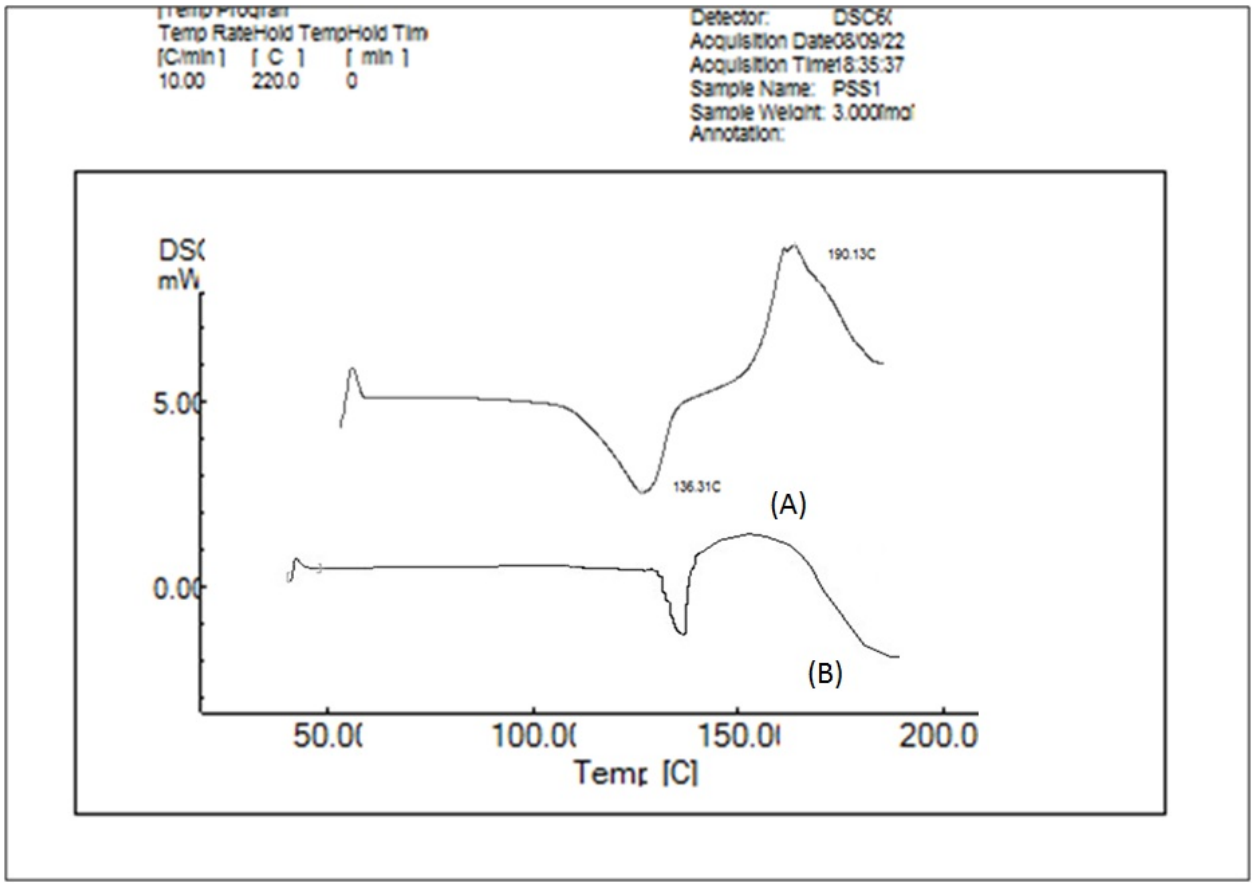

Figure 6: DSC Thermograms of A: Pure Drug, B: drug loaded microspheres formulation

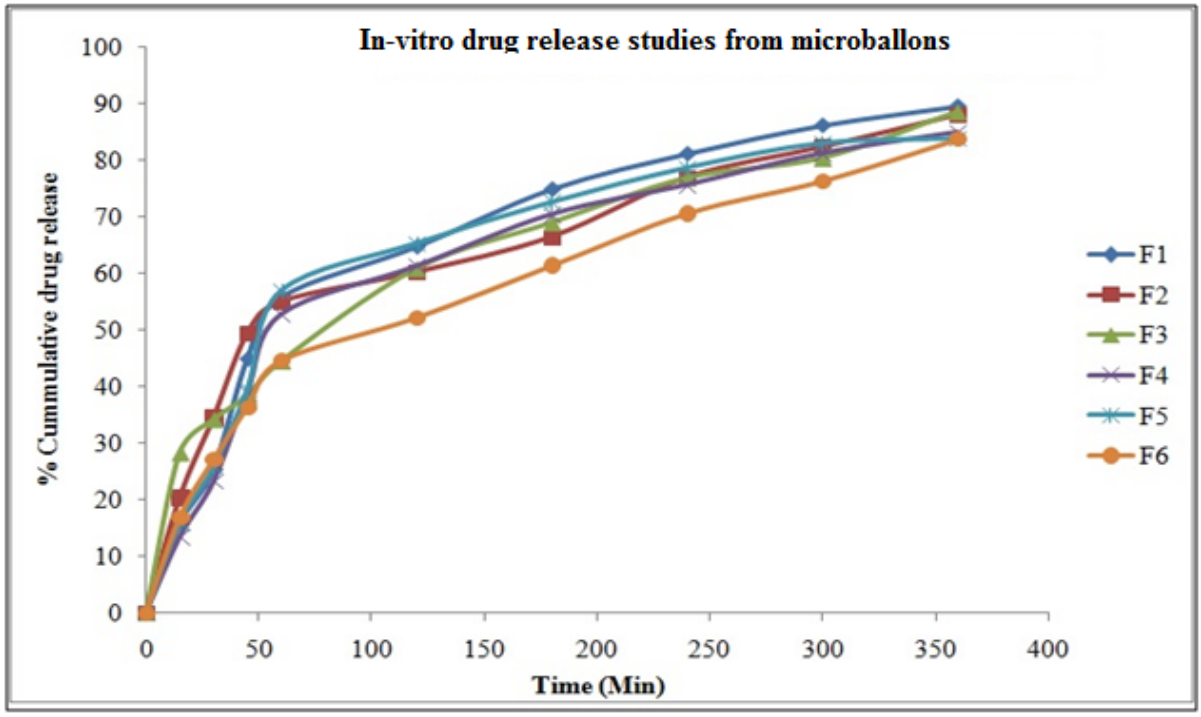

Figure 8: In-vitro drug release profiles of drug loaded microspheres formulations

The drug release profiles of the microspheres formulations are illustrated in Table 4 and Figure8. Drug release from nisoldipine microsphere was found to range from 81.32 % to 89.34 % from all formulations.

From the results it was found that, as concentration of polymer increases, percentage of drug released decreases. The initial high drug release could be due to two reasons: first, the drug near or on the surface of the microspheres and second, well known porous nature of microspheres, the pores providing a channel for release of the drug.

The microspheres differ from regular microspheres with their highly porous surface. This characteristic gives property to release the drug at a faster rate through the pores. Release from F6 formulation has Higuchi release pattern followed zero order reaction kinetics (R^2= 0.998, 0.925 and 0.970).

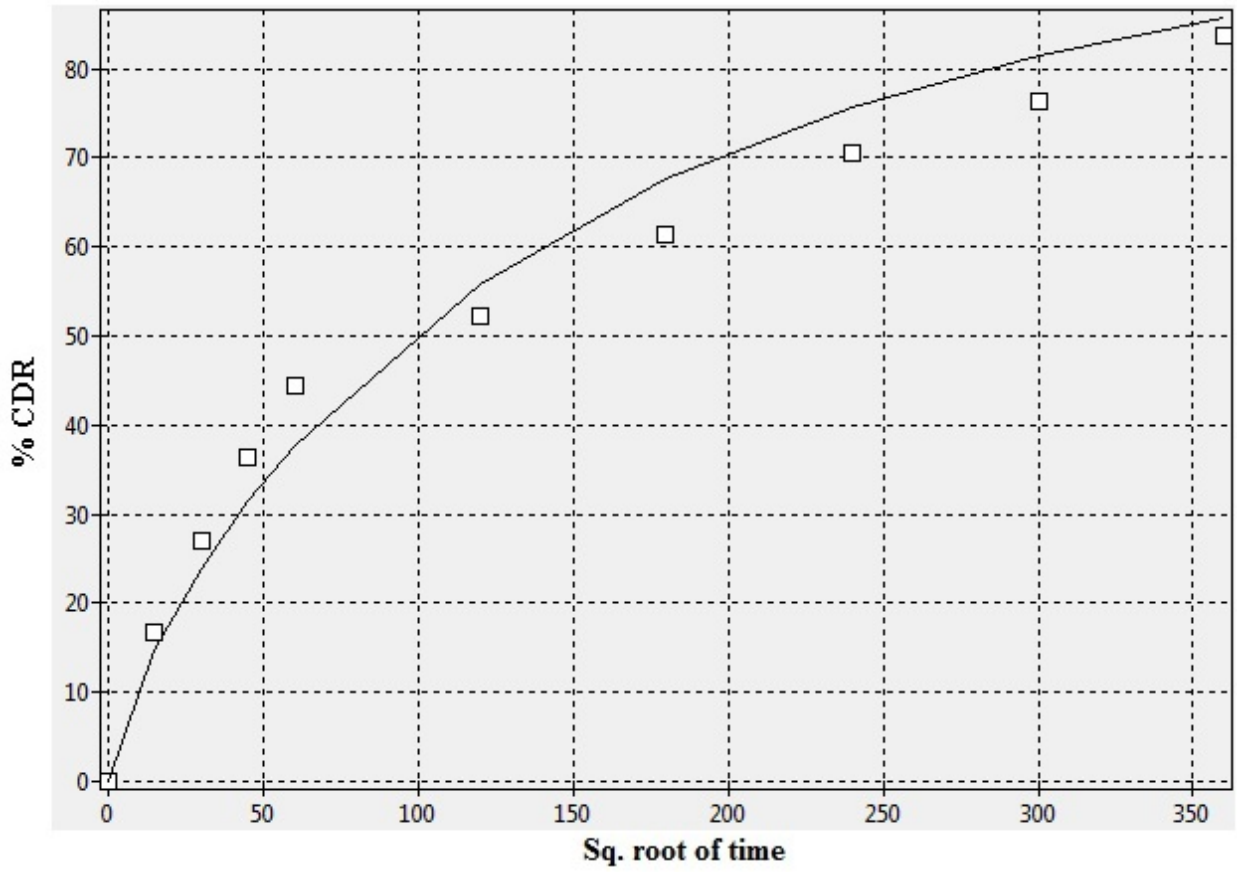

Figure 9: Higuchi release plot

Conclusion:

The primary benefit of controlled release preparation compared to conventional dosage forms is that more uniform maintenance of blood plasma level of active agent which is helpful to avoid undesirable peaks and troughs achieved with multiple immediate release preparations. From the overall investigation, one can conclude that the optimized microspheres of nisoldipine using both polymers can meet ideal requirements for microspheres. The relatively high percentage yield and loading efficiency of microspheres indicated that the method is suitable for preparing the microspheres formulations. Quasi-emulsion solvent diffusion method is simple, less time consuming and involves use of safer ingredients than free radical polymerization and hence more preferred.

The microspheres differ from regular microspheres with their highly porous surface. This characteristic gives property to release the drug at a faster rate through the pores. Due to smaller pore diameter, the Eudragit Rs 100 microspheres showed less and slower drug release in the *in-vitro* release studies. Release from all the microspheres followed zero order reaction kinetics.

With this kind of formulation, the undesirable side effects and presystemic metabolism of the drug can be eliminated and a sustained effect can be obtained. Therefore, drug loaded microsphers prepared in thus study are promising as being more useful than conventional formulation in therapy. Finally it can be concluded that the objective of this study is achieved.

FUTURE PROSPECTUS

In future microspheres can be used to prepare suitable dosage form and its *in-vivo* absorption studies in animals/ humans can be carried out to know the bioavailability from sustained release formulation.

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