

## Original Research Article

# Development of Sustained-Release Microbeads of Nifedipine and *In vitro* Characterization

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### Abstract

**Purpose:** To formulate and evaluate sustained-release microbeads of nifedipine for prolonged delivery.

**Methods:** Nifedipine microbeads were prepared using sodium alginate and pectin in different ratios by ionic-gelation method. The microbeads were evaluated for surface morphology and shape by scanning electron microscopy (SEM), micromeritic properties, microencapsulation efficiency and *in vitro* drug release. The microbeads were also assessed by Fourier Transform Infra-red Spectroscopy (FTIR) and differential scanning calorimetry (DSC) to determine drug-polymer interaction, if any.

**Results:** FTIR and DSC results indicate absence of interaction between the drug and polymers used. Good rheological behavior was demonstrated with an angle of repose < 30°, and Carr's index and Hausner's ratio of < 10% and < 1.12, respectively. Microbead size, yield and entrapment efficiency were in the range of 695 to 733 μm, 69 to 75% and 54 to 63%, respectively. SEM revealed that the microbeads were discrete, largely spherical and free-flowing. Higuchi model was the best fit for the dissolution data and followed non-Fickian diffusion mechanism.

**Conclusion:** The microbead formulation would be suitable for sustained release of nifedipine.

**Keywords:** Microbead, Nifedipine, Alginate, Ionic gelation, Pectin, Higuchi model, Non-Fickian diffusion.

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## INTRODUCTION

Oral sustained release dosage forms provide optimal therapy in terms of efficiency, safety as well as patient compliance. Ideal controlled release dosage forms are such that provide/maintain therapeutic drug concentration throughout dosing interval [1]. To obtain maximum efficacy and minimum side effects it is necessary to deliver the drugs to target site in optimal amount and for required time period [2]. Improved drug stability, optimal duration of therapeutic effect, flexibility of administration via

different routes with minimum drug metabolism/degradation are some of the attributes of sustained release drug delivery system [3].

Microencapsulation is one of the processes designed for the sustained release of drugs. Small solid microbeads are used as carriers with dispersed drug particles either in solution or in crystalline form to allow for sustained action with minimum side effects. In addition, microbeads can be used to provide multiple releases with different active ingredients [4]. Stability in

physiological conditions and ability to reach local areas at therapeutic level make them very useful carriers. Microbeads are produced by technique called microencapsulation which involves entrapping of solid or liquid material with a polymer film around it, thus shielding the active ingredient from the external environment and allow good release characteristics.

Nifedipine (NIF), a model hydrophobic drug, is a calcium channel antagonist [5] widely used for the treatment of angina pectoris, hypertension and other cardiovascular disorders. It has a short half life of 2 - 3 h and is thus a suitable candidate for oral sustained release drug delivery [6]. Previous studies described the preparation of NIF-loaded cellulose acetate butyrate based microspheres using solvent evaporation method for their controlled release behavior [7]. The objective of the present study was to microencapsulate NIF by ionic gelation method using sodium alginate and pectin, to form enteric microbeads, and then evaluate their physicochemical and sustained release properties.

## EXPERIMENTAL

### Materials

Nifedipine was a gift from Tread Pharmaceuticals Lahore, Pakistan. Sodium alginate and pectin were purchased from Yuan-ching Chemicals, China and Merck, Germany respectively. Calcium chloride and sodium hydroxide were also purchased from Merck, Monobasic potassium phosphate and chloroform from Reidel De Haen while all other chemicals and solvents used were of analytical grade.

### Preparation of microbeads

Ionic gelation method was used to prepare microbeads of calcium alginate pectinate [8]. In this method, 2% w/v solution of calcium chloride as gelation medium and different ratios of drug: sodium alginate: pectin polymer at concentrations (2:1.75:0, 2:1.75:0.25, 2:1.75:0.50, 2:1.75:0.75, 2:1.75:1.0) were used and the formulations coded NIF1, NIF2, NIF3, NIF4 and NIF5, respectively. The solution of the drug prepared in chloroform was dispersed in sodium alginate solution and stirred with magnetic stirrer at a speed of 1000 rev/min for 1 h to obtain a viscous homogeneous aqueous dispersion. The dispersion was added dropwise into the gelation medium of calcium chloride using a 5 ml hypodermic syringe with a 22-gauge

needle under constant stirring at room temperature for the development of microbeads.

The microbeads formed were cured in gelation medium for 2 h and then taken out, washed twice with distilled water and allowed to dry at 35°C in a dust-free chamber until they attained a constant weight. Calcium alginate pectinate beads were prepared by the same method.

### Determination of yield

The microbeads were weighed and yield (%) was calculated using Eq 1.

$$\text{Yield (\%)} = \frac{W}{(WD+WP)} \times 100 \dots\dots\dots (1)$$

where W is the weight of the microbeads, and WD and WP are the weights of drug and polymer, respectively, used in formulating the microbeads.

### Assessment of size distribution of microbeads

Microbeads size was analyzed using sieving method [9]. In this method, microbeads of all formulations were placed on a set of standard sieves ranging from sieve No. 10-40, using an electromagnetic sieve shaker (Electro Lab, EMS 8). The sieves were arranged in descending order with the sieve with the largest aperture (2 mm) was on top and the one with least aperture (425 µm) at the bottom. The microbeads passed through these sieves were weighed and mean particle size (P) was determined as in Eq 2 [10].

$$P = \frac{\sum (P_f \times W)}{\sum W} \times 100 \dots\dots\dots (2)$$

where  $P_f$  is the mean particle of the microbead fractions and W is weight of the fractions retained.

### Assessment of flow properties

The microbeads were assessed for flow properties by determining the angle of repose which measures the resistance to particle flow, was determined by fixed-funnel method and calculated as in Eq 3.

$$\theta = \tan^{-1} h/r \dots\dots\dots (3)$$

where, h is height and r is radius of the heap.

Angle of repose < 30° shows excellent flow properties.

Carr's index was evaluated to assess the flowability of the microbeads by comparing the pour and tapped densities of the microbeads, and calculated using Eq 4.

$$\text{Carr's index} = \{(pt-pb) \times 100\}/pt \dots\dots\dots (4)$$

where pb is bulk density and pt is tapped density which was measured in a 10 ml graduated cylinder.

Carr's index < 15% gives good flow characteristics while a value > 25% indicates poor flow characteristics [11].

Hausner's ratio, another index of flowability, was calculated using Eq 5.

$$\text{Hausner's ratio} = pt/pb \dots\dots\dots (5)$$

Hausner's ratio value between 1.00 - 1.11 indicates excellent flowability.

### Scanning electron microscopy (SEM)

The external morphology of microbeads was analyzed by scanning electron microscope (Jeol JSM-5200). Prior to examination, the dried microbeads were sprinkled on adhesive tape which was then smacked on gold coated (thickness; 150-200<sup>o</sup>A) aluminum stub. The pictures of microbeads were taken by random scanning of the aluminium end under reduced pressure [12].

### Fourier transform infrared spectroscopy (FTIR)

FTIR spectroscopy was used to study drug-polymer interactions. The spectra were recorded for pure drug and drug-loaded microbeads. Individual beads were crushed in pestle and mortar and then mixed 1 mg of crushed material with 100 mg of KBr (Merk IR Spectroscopy grade) and dried at 40<sup>o</sup>C. Then FT-IR spectra of the scanning wavelength range 4000-400cm<sup>-1</sup> were recorded by using a FT-IR spectrophotometer (IR-Prestige-21, Shimadzu, Japan) [13].

### Differential scanning calorimetry (DSC)

DSC analysis was done to characterize the changes observed during the preparation of microbeads. Nifedipine, polymers and drug-loaded microbeads were triturated separately and were placed in aluminium pan and the lids were crimped. The analysis was performed at a

rate of 20<sup>o</sup>C/min from temperature range of 30<sup>o</sup>C-400<sup>o</sup>C under nitrogen flow of 25 ml/min and were carried out by using a differential scanning calorimeter (Thermal Analyser SDT Q 600, Shimadzu, Japan). Reproducibility was checked by running the sample in triplicate [14].

### Determination of encapsulation efficiency

Appropriate amounts of microbeads were first crushed, weighed and then suspended in methanol for complete removal of Nifedipine from microbeads and then after 24 h sample was filtered using 0.45 um filter paper. After filtration, nifedipine absorbance from the samples was measured at 235 nm using a UV-VIS spectrophotometer (Pharmaspec 1700, Shimadzu, Japan). The absorbance obtained was then converted to the amount of nifedipine using a standard calibration curve [15]. Encapsulation efficiency (PEE) was calculated using Eq 6:

$$\text{PEE (\%)} = (E/T) \times 100 \dots\dots\dots (6)$$

where E = actual drug content and T = theoretical drug content.

### In vitro drug release studies

In vitro release of nifedipine from various formulations was evaluated for the first 2 h in simulated gastric fluid (0.1M HCl, pH 1.2) and then in simulated intestinal fluid (phosphate buffer, pH 6.8) consecutively. Microbead samples equivalent to 120 mg of nifedipine was transferred to the dissolution medium (900 ml, 37<sup>o</sup>C) in a USP XXII apparatus (Pharma Test, Germany) operating at a speed of 100 rpm. Five milliliter samples were collected from the dissolution medium at definite time intervals with an automated collector after filtering through 10 µm sinter filters. The dissolution medium was kept constant after each withdrawal by adding same volume of fresh dissolution medium. The samples were diluted and analyzed at 235 nm using UV-Visible spectrophotometer. The in vitro drug release studies were conducted in triplicate.

### Analysis of release data

The dissolution data of all formulations were fitted to various commonly used kinetic models [16] i.e., Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas to compare drug dissolution profiles and interpret drug release kinetics using DDSolver software [17].

## RESULTS

### Physical characteristics of microbeads

Nifedipine microcapsules were evaluated for physical parameters. The particle size of microbeads was in the range of 695 - 733  $\mu\text{m}$ , while yield varied within the range of 71 - 76% and entrapment ranged from 54 - 63% for various microbead formulations, as shown in Table 1. The angle of repose, Carr's index and Hausner's ratio of the microbeads ranged from 24.4 - 27.5, 3.4 - 9.0% and 1.03 - 1.09, respectively.

### Shape and surface morphology of microbeads

SEM revealed that the microbeads were almost spherical in shape and had smooth surface on all formulations while cracks were present on the surface of drug-loaded microbeads, as displayed in Fig 1.

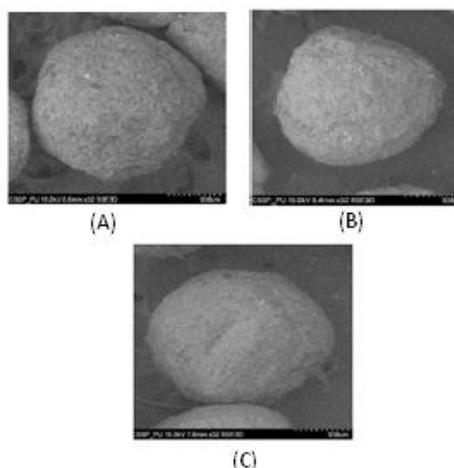


Fig 1: SEM photographs of nifedipine-loaded microbeads (Key: A = NIF1, B = NIF3, and C = NIF5)

### Drug/polymer compatibility

The FTIR spectra of pure nifedipine, polymers and their physical mixtures are shown in Figure 2.

Table 1: Physical characteristics of microbeads

Microbead Code	Mean particle size ( $\mu\text{m}$ )	Yield (%)	Angle of repose ( $^{\circ}$ )	Carr's index	Hausner's ratio	Entrapment Entrapment (%)
NIF1	695 $\pm$ 1.51	71.6 $\pm$ 0.51	27.5 $\pm$ 0.40	6.11 $\pm$ 0.86	1.06	54.01 $\pm$ 0.52
NIF2	700 $\pm$ 1.51	69.1 $\pm$ 0.46	24.49 $\pm$ 0.08	9.07 $\pm$ 2.46	1.09	57.91 $\pm$ 0.63
NIF3	713 $\pm$ 1.72	70.2 $\pm$ 0.21	26.64 $\pm$ 0.43	6.50 $\pm$ 1.46	1.06	60.55 $\pm$ 0.75
NIF4	726 $\pm$ 2.51	73.4 $\pm$ 0.20	26.70 $\pm$ 0.02	3.42 $\pm$ 0.95	1.03	61.59 $\pm$ 0.83
NIF5	733 $\pm$ 3.04	76.5 $\pm$ 0.46	25.87 $\pm$ 0.01	7.63 $\pm$ 1.70	1.08	63.75 $\pm$ 0.94

All values are represented as arithmetic mean; \*n = 3

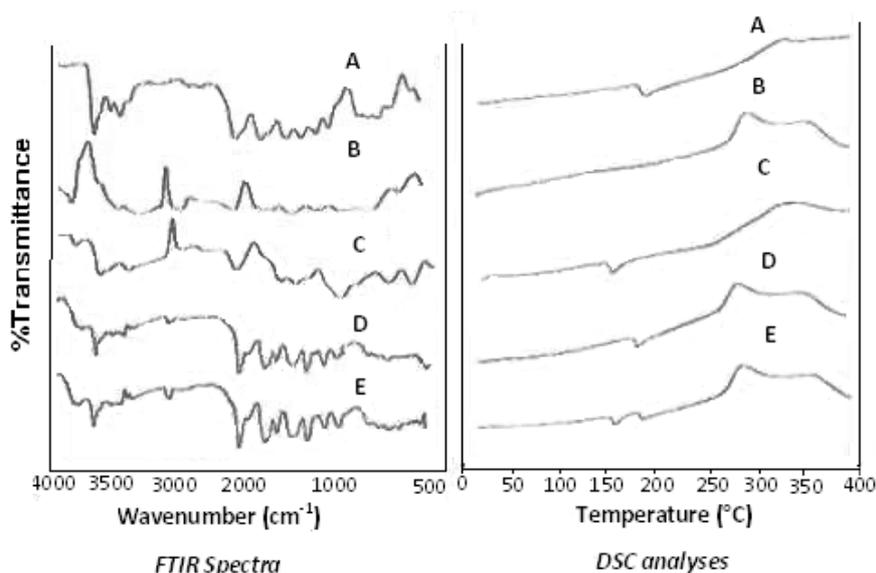


Fig 2: FTIR spectra and DSC thermograms of the formulations (Key: A = nifedipine only; B = sodium alginate; C = pectin; D = nifedipine/sodium alginate physical mixture; E = nifedipine/sodium alginate/pectin microbeads)

**Table 2:** Release kinetics data for the microbeads

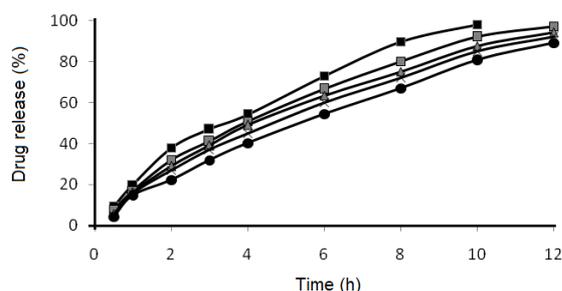
Bead code	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	$k_0$	$R^2$	$K_1$	$R^2$	$k_{HC}$	$R^2$	$k_p$	$n$	$R^2$	$k_H$	$R^2$
NIF 1	9.777	0.978	0.404	0.919	41.62	0.985	0.143	0.864	0.993	0.377	0.984
NIF 2	9.592	0.992	0.352	0.894	40.59	0.987	0.131	0.881	0.994	0.383	0.982
NIF 3	7.749	0.973	0.251	0.960	35.71	0.995	0.121	0.871	0.991	0.333	0.971
NIF 4	7.853	0.979	0.246	0.965	36.01	0.991	0.115	0.881	0.994	0.333	0.967
NIF 5	7.497	0.975	0.210	0.975	34.47	0.993	0.114	0.876	0.990	0.340	0.969

It was observed that the peaks obtained were due to stretching of N-H, C=O and NO<sub>2</sub>. The FTIR spectra of drug and physical mixture showed no shift from original peaks but the intensity of the principle peak corresponding to nifedipine appeared to have been reduced in the mixture.

In the DSC studies, nifedipine showed a sharp endothermic peak (172 – 174°C) at a temperature corresponding to its melting point. Sodium alginate and pectin peaks occurred at temperatures > 300 and 155°C, respectively. The same thermal profile at temperature corresponding to melting point was also observed for drug-polymer microbeads. This indicates the compatibility of drug and polymers.

### In vitro drug release

The effect of variation in drug/polymer ratio on drug release is shown in Fig 3. The release rate of drug formulations NIF3 was seemed to be higher than those of all other formulations but the difference was not significant ( $p>0.05$ ). The drug release kinetic data obtained are listed in Table 2.



**Fig 3:** Nifedipine released from various formulations of microbeads where NIF1 (■), NIF2 (□), NIF3 (Δ), NIF4 (×) and NIF5 (●)

## DISCUSSION

Microbeads of nifedipine with the polymers produced good flow characteristics. All the physicochemical parameters were within acceptable range. The results showed that the

mean particle size of microbeads increased significantly with increasing pectin concentration. Nifedipine microbeads exhibited good flow properties. Higher microbead yield was obtained possibly due to the fact that the polymers served as crosslinking agent for gelation. Thus, due to the presence of more binding sites for the drug with increase in polymer concentration, the entrapment efficiency of the microbeads increased gradually [18].

The drug was compatible with polymers used for the formulation of microbeads as it was evident from FTIR analysis that only a slight shift with overlapping and broadening in some of the peaks characteristic of drugs took place [17]. The compatibility of drug and polymer were also depicted by thermal analysis that the sharpness of the peaks of drugs was reduced when combined in polymer mixture or in microbeads but there was no variation in the melting points of drug as well as polymers [19].

Scanning electron microscopy revealed that the microbead formulations possessed nearly smooth and spherical surfaces. As the drug polymer ratio increased, the cumulative release of nifedipine decreased significantly due to the higher polymer content relative to that of the drug, which implies that polymer/drug ratio can be modulated to achieve the desired release rate of nifedipine and hence sustained effect.

Drug release from NIF1 was 98% in 10 h and this may be due to the presence of cracks on microbead surface while drug release fell to 91% in 12 h in batches containing pectin. This retardation of microbeads led to a gradual decline in drug release from the formulations due to the increased concentration of polymer [20].

Microbeads showed higher values of coefficient of determination ( $R^2$ ) in Higuchi model (Table 2) than the other formulations. Drug release data from various formulations, when fitted to Korsmeyer-Peppas model, yielded 'n' value between 0.864 and 0.881 which indicates that

drug followed non-Fickian anomalous release pattern.

## CONCLUSION

The present work shows that ionic gelation method can be optimized for the production of sustained release microbeads of nifedipine and possibly other similar drugs. The ratio of drug to polymer has an effect on drug release from the microbeads. Higuchi model is the best model to describe its release mechanism. However, drug release is both diffusion- and dissolution-controlled.

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