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Original Article

Development and characterization of ethylcellulose based microsphere for sustained release of nifedipine ☆

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ABSTRACT

This article introduced the work of ethylcellulose based polymeric microsphere loaded with nifedipine for reduction in frequency of administration with low solubility in aqueous medium and high rate of absorption in the stomach. The non-aqueous polymeric suspension was put dropwise into an aqueous medium containing polyvinyl alcohol as a surfactant for the synthesis of microsphere by solvent evaporation. The microspheres were characterized by different techniques, namely, XRD, SEM, and NMR. The formation of microspheres was confirmed by SEM. XRD analysis revealed the semi-crystallinity nature of microspheres. The NMR study indicated the presence of hetero-aromatic nucleus in the microsphere.

1. Introduction

Controlled release dosage form covers a wide range of prolonged actions that provide continuous release of their ingredients at a predetermined time. One such approach is using polymeric microsphere as carriers of drugs [1]. As a result, the drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug [2]. Drug release modification has been investigated to control the time of drug release and maintain constant drug bioavailability [3]. An optimal amount of drug delivery to the target tissue with a right period of time is very necessary so that the agent can induce little toxicity and minimal side effects [4]. The drug release from different formulations depend on the extent of cross-linking, morphology and size of microspheres [5]. It has been shown that reduction of either the applied dose or the frequency of administration gives better pharmacological results compared with administration of conventional doses of drugs [4]. Usually an increase in hardness of a dosage form is accompanied by a decrease in release rate, due to a decrease in porosity [6]. Microspheres have been widely accepted as a means to achieve an oral and parenteral controlled release drug delivery system [7]. Microspheres are better tolerated in the form of sustained release of nifedipine for their conventional counterparts and dosage [8]. Nifedipine is a prototype dihydropyridine calcium channel blocker with a rapid onset and a short duration of action [9]. Calcium channel antagonists 1,4-dihydropyridine acting with a high degree of lipophilicity display a slow onset action after administration as vasodilator and hypertensive medication commercialized [10]. However, there have been few studies on ethylcellulose as a polymeric biomaterial through the evaporation method. Formation of porous or hollow microspheres and spherical shapes were controlled during processing which were easy to fabricate due to the solvent/non-solvent phase separation taking place in small polymer-solvent droplets in a continuous non-solvent phase. The solvent evaporation method was a cost-effective process that did not require expensive chemical agents and instruments. Hence, the purpose of this study was to investigate the physico-chemical parameters, such as surface morphology, crystallinity, and elemental composition of microspheres through scanning electron microscopy (SEM), ^{1}H nuclear magnetic resonance (NMR) and X-ray diffractometry (XRD) described in this article.

2. Materials and methods

2.1. Synthesis

Ethylcellulose microspheres were prepared by the solvent evaporation method. Nifedipine (gift from J.B Pharma, India) and

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ethylcellulose (purchased from Merck, India) with a total weight of 1 g were dissolved in 10 mL. Dichloromethane (purchased from Merck, India) was used as the internal phase. Microspheres were prepared with three different drugs to polymer concentration in ratio of 10%, 20% and 30%. The internal phase was then added dropwise to a 0.5% (w/v) solution of polyvinyl alcohol (purchased from S.D. Fine-Chem Limited, India) in water. The mixture was constantly stirred at 500 rpm using an overhead stirrer (Remi Equipments Pvt. Ltd., Mumbai, India) up to 5 h for complete evaporation of methylene chloride. Microspheres were then filtered and rinsed three times with distilled water and dried at room temperature.

2.2. Scanning electron microscopy

Nifedipine microspheres were dried overnight and analyzed through SEM. Microsphere composites were given a conductive platinum coating of 600 Å in a thick, sputter ion coater. These samples were examined through SEM (JEOL JSM-6480LV, Japan) which was well equipped with a backscattered electron detector for imaging and performing the energy dispersive X-ray analysis (EDXA) for elemental composition analysis where particular elements were identified. In this method a focused electron beam was used to scan the sample in parallel lines. For SEM characterization, microspheres were then mounted on a sample holder followed by coating with a conductive metal such as platinum or zirconium using a sputter coater. The sample was then scanned with a focused fine beam of electrons. The surface characteristics of the sample were obtained from the secondary electrons emitted from the sample surface. The microsphere must be able to withstand vacuum and the electron beam can damage the polymer. The mean size obtained by SEM was comparable with results obtained by dynamic light scattering.

2.3. NMR analysis

At room temperature of 21.7 °C, ^{1}H NMR (400 MHz) spectra were recorded using a JOEL FT NMR (AL^{400}) Spectroscope, Japan. The internal standard CDC_{13} ($\delta H = \delta C = 0$) and specific deuterated solvent were used in the experiments. Chemical shift displacement (δ) was expressed in parts per million where 2 mg of sample diluted with 0.5 mL of $CDCl_3$ solution was kept in the sample holder and brought to analysis.

2.4. Powder X-ray diffractometry

X-ray diffracted peaks were obtained using the Philips X'Pert on powder diffraction coordination (Philips Analytical, the Netherlands) set with a directly set up goniometer in the Bragg-

Table 1
Elemental quantification of carbon and oxygen.

Materials	Carbon (%)	Oxygen (%)	Impurity (%)
Nifedipine pure	73.29	26.45	0.26
Ethylcellulose	53.60	40.81	5.59
Dummy microsphere	57.37	35.83	6.8
Nifedipine microsphere	69.58	27.72	2.7
Nifedipine microsphere focused	68.64	29.29	2.07

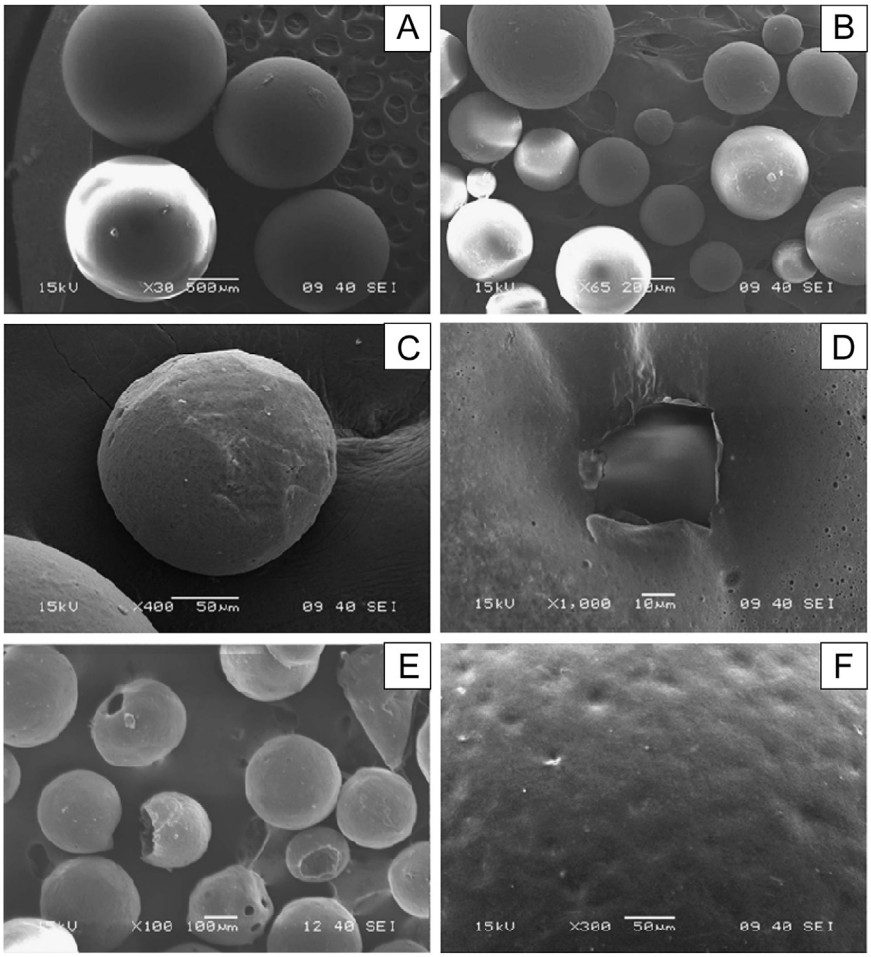

Fig. 1. SEM of solid microspheres (A), microsphere of varying in size (B), surface morphology (C), perforated microsphere (D, E), and smooth surface of microspheres (F).

Brentano focusing geometry. The X-ray generator was operated at 30 kV and 20 mA, using the CuKα line at 1.54056 Å as the radiation source. The samples were ground using a mortar and pestle. The crushed specimen was filled and arranged in a specimen holder made of aluminum. Samples were scanned from 10° to 90° (2θ) and in stage sizes of 0.020, with count time of 2.00 s, using an automatic divergence slit assembly with a proportional detector. The samples were scanned at 25 °C. Relative intensities were read from the strip charts and corrected to fix slit values.

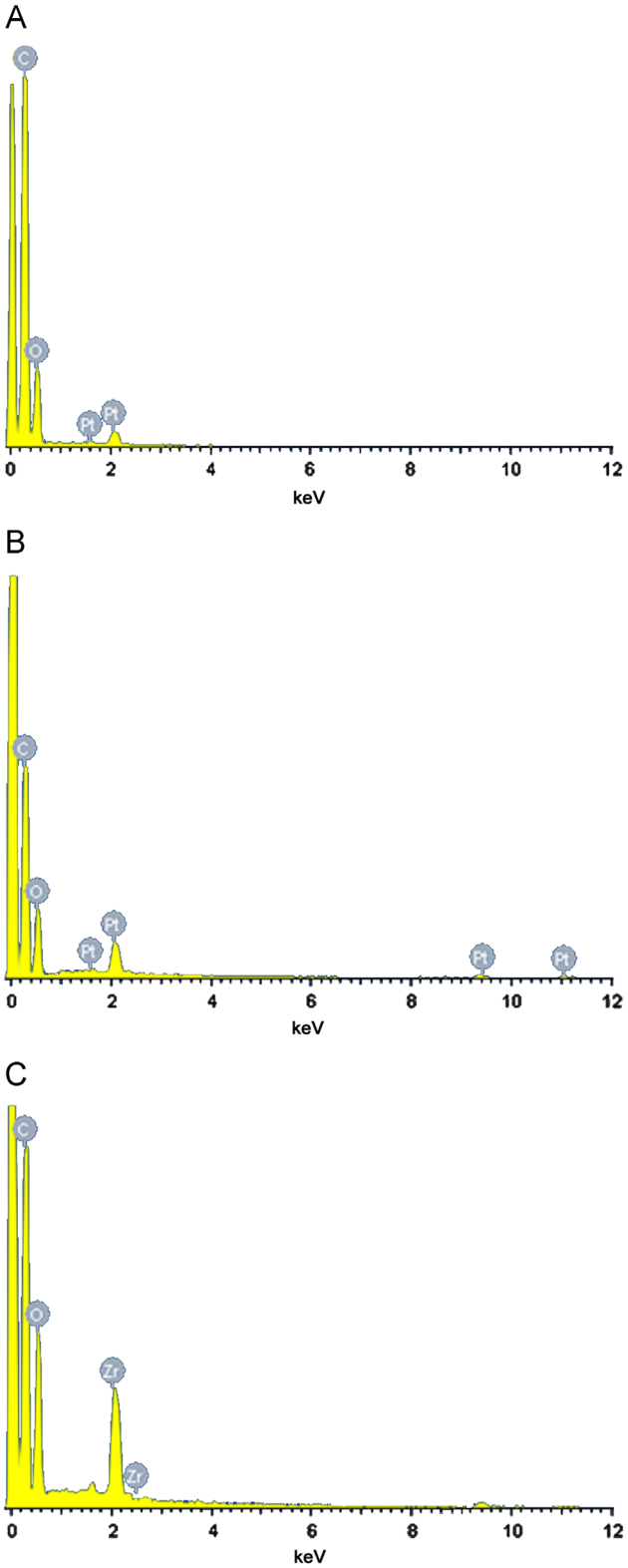

Fig. 2. EDX spectra of nifedipine pure (A), nifedipine microspheres (B), and focused nifedipine microsphere (C).

3. Results and discussion

3.1. Morphology by SEM

Formulation of microspheres depends on some factors like type, amount of solvent, polymer used and processing time. It was

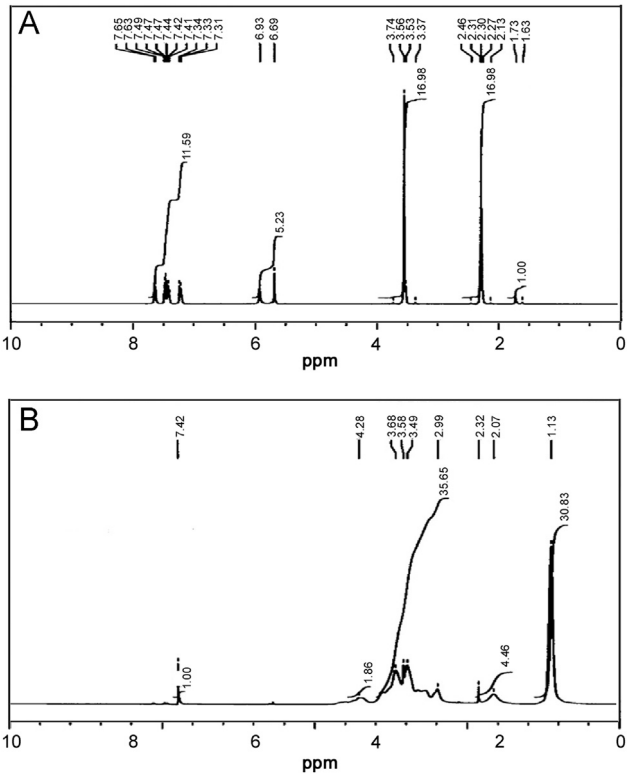

Fig. 3. ^{1}H NMR spectra data for nifedipine pure drug (A) and nifedipine microsphere (B).

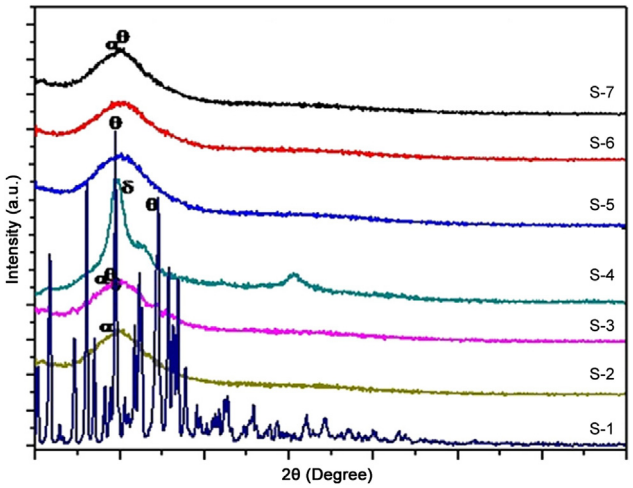

Fig. 4. Combined XRD data for nifedipine (s-1), ethylcellulose (s-2), polyvinyl alcohol (s-3), nifedipine + ethylcellulose (s-4), dummy microsphere (s-5), perforated nifedipine microsphere (s-6), nifedipine microsphere (s-7). Where θ is for nifedipine, α is for ethylcellulose, δ is for polyvinyl alcohol.

found that solid microspheres were 100–1000 μm in size shown in (Fig. 1A and B). Perforated spheres formed due to decrease in solvent from the preparation of polymeric suspension where rapid evaporation took place during processing. The formation of voids might be related to the mechanisms of air bubbles or, entrapped fluid formed during the cross-linking and solidification process. These spheres were naked to achieve more exposure in dissolution media that decreases the sustained release property (Fig. 1D and E). At uniform rotation of stirrer, solidification found to be very sensitive to the time factor for evaporation of solvent from the polymeric suspension led to the formation of solid microspheres. It was observed that when the rotation of stirrer increased above 600 rpm then there were formation of foam-like materials. Uniform stirring rate of magnetic stirrer made the spheres solid and more spherical. The microsphere surface became smooth and non-porous, which was effective in delayed dissolution (Fig. 1A–C). Furthermore, both types of microspheres had a regular spherical morphology (Fig. 1A–E). The surfaces of the two types changed, as could be seen at a high magnification (Fig. 1C and D). The surface of the standard microspheres was smooth (Fig. 1F). Surface irregularity of microspheres was caused by irregular solvent evaporation with respect to time.

3.2. Elemental composition through SEM

Energy dispersive spectroscopy displayed the variations in % composition of pure drug, polymer, dummy microspheres and nifedipine microspheres. The elemental analysis data gave the composition and concentration of carbon and oxygen. The oxygen concentration of nifedipine microspheres slightly decreased due to inter-hydrogen bonding with respect to the nifedipine pure drug as described in Table 1. There were differences in carbon and oxygen concentration at 0.94% and 1.57% in nifedipine microspheres as a whole (Fig. 2B) and back scattered with a single microsphere surface (Fig. 2A) respectively, where 0.63% was the difference in impurities found between them. EDX spectra of drug and nifedipine microspheres with a control region had no other impurities, besides the grid coating material platinum and zirconium shown. The quantitative data indicated about the specific concentration of carbon and oxygen in microspheres (Fig. 2C).

3.3. NMR results

Prominent peaks were observed for ^{1}H NMR ($CDCl_3$) of nifedipine: $\delta = 1.61$ (d, 6H, CH_3), 2.31 (s, 3H, CH_3), 3.56 (d, 6H, OCH_3), 7.24 (s, 2H, aromatic), 7.49 (s, 1H, aromatic) (Fig. 3A) and for nifedipine microsphere: ^{1}H NMR ($CDCl_3$): $\delta = 1.13$ (d, 6H, CH_3), 2.32 (s, 3H, CH_3), 3.56 (d, 6H, OCH_3), 7.24 (s, 2H, aromatic), 7.47 (s, 1H, aromatic) (Fig. 3B). Assay results obtained by NMR confirmed the presence of prominent methyl, carboxyl ester group as well as hetero-aromatic groups. The presence of molecular fragments indicated that, the formulation retained its active nucleus and functional groups of drug in the composite after the preparation. Identical spectral data were found from nifedipine microsphere with respect to nifedipine raw material.

3.4. Phase analysis by XRD

The XRD patterns of raw materials and prepared samples were taken. It was observed that the broad peaks in a diffractogram were at around 19.6° and 21.8° for nifedipine, 18.92° for ethylcellulose, and 19.5° for polyvinyl alcohol (Fig. 4). The following data illustrate the comparative X-ray powder diffraction pattern of nifedipine, physical mixture of nifedipine with ethylcellulose, microspheres without nifedipine, solid and perforated nifedipine microspheres (evaluated from JCPDF, Origin lab, X-pert high score). The XRD profile of nifedipine microsphere indicates that the material is low crystalline. Pure nifedipine and individual polymers were in the crystalline state as is known from its sharp peak. Nifedipine microspheres without drug gave a glassy structure. In the case of perforated microsphere the crystallinity decreased (Fig. 4). However, decreases in the peak intensity and the baseline shift of the diffractogram were observed due to presence of polymers in microspheres when compared to the physical mixture of nifedipine along with ethylcellulose. This might be due to decrease in crystalline of drug that followed dispersal in the polymer matrix of nifedipine microsphere.

4. Conclusions

There is variation in size of microspheres from 50 to 1000 μm. In comparison of elemental composition analysis, it was found that variations at carbon and oxygen contents illustrated the degree of interaction. The microspheres containing nifedipine were partly crystalline state during processing. It is also concluded that NMR spectra identify the presence of active groups of compound in the formulation.

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