EFFECTS OF FORMULATION VARIABLES ON NIFEDIPINE MICROSPHERES PREPARED BY SOLVENT EVAPORATION TECHNIQUE

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ABSTRACT

Preparation and characterization of nifedipine microspheres using ethylcellulose as matrix polymer is described. Nifedipine microspheres were prepared by solvent evaporation technique. The influence of different parameters such as the effect of the concentration of internal and external phases, the amount of drug and the rate of stirring of the medium on the size distribution of microspheres were studied. The effect of drug/polymer ratio and mean particle size on the drug release pattern were also evaluated. Drug release from nifedipine microspheres was studied in a medium, which simulated the change in pH of the pathway of the microspheres from stomach to intestine. It was found that with increase in the concentration of the internal phase, the size of microspheres became larger. Increasing the amount of polyvinyl alcohol in the external phase reduced the size of microspheres. Dissolution was found to be inversely related to the pH, in a way that drug release decreased at higher pH. Drug release from microspheres with small mean particle size was faster than those with large mesh particle size and followed Higuchi model of kinetics.

Key words: Microspheres, Nifedipine, Ethylcellulose, Solvent evaporation, Sustained release

INTRODUCTION

The concept of using microencapsulation has received attention in pharmaceutical and biomedical applications. Microencapsulation technology has enormous potential in elimination of formulation and delivery problems associated with many dosage forms such as capsules, tablets, powders, topicals and injectables. Microencapsulation has been employed for many reasons such as protection of the core material (1), reduction of gastric and other gastrointestinal tract irritation (2), and decrease in volatility and conversion of a liquid to a pseudo-solid (3, 4), cell microencapsulation (5,6), peptide and protein delivery (7,8), design of pulsatile drug delivery systems (9) and controlled as well as sustained release dosage forms (10). Nifedipine has been widely used as a calcium channel blocker for treatment of hypertension, various angina, Raynauld's syndrome and other non-vascular diseases. Since most indications of nifedipin are for chronic disease and need long term treatment, development of a sustained release formulation is desirable. Many drug carrier systems have already been proposed for effective use in therapy and most of them are polymeric compounds of natural or synthetic origins. Nifedipine has been microencapsulated by using poly acrylate (11), gelatin (12), poly vinyl pyrolidone-carboxy methyl cellulose and hydroxy propyl cellulose-carboxy methyl cellulose (13) poly (DL-lactide-co-glycolide) (14), and interpenetrating network polyvinyl alcohol-guar gum hydrogel (15). Ethylcellulose has been used extensively in the formulation of oral controlled release delivery systems by coating small beads (16) and in the preparation of microspheres (17). In this investigation the use of ethylcellulose for the preparation of nifedipine was studied. Nifedipine microspheres were prepared using emulsification/solvent evaporation technique. Characterization of the microspheres, drug loading and drug release, the effect of different parameters on particle size of microspheres and the influence of the pH on drug release were investigated. These evaluations characterized the pattern of drug release from the prepared microspheres.

MATERIALS AND METHODS

Materials

Nifedipine was obtained from Tolidaru, Iran. Polyvinyl alcohol (MW 72000), Ethylcellulose (10 cps), HCl (37%), Methylene chloride, Chloroform, Potassium phosphate monobasic were purchased from

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Merck, Germany. All materials were of general standard grade.

Methods

All experiments were carried out under subdued light such as sodium light, to prevent photodegradation of nifedipine.

Microsphere preparation

Microspheres were prepared by solvent evaporation method. Known amounts of nifedipine and ethylcellulose (EC) were dissolved in 6 mL of methylene chloride as the internal phase. The solution was then added dropwise to a solution of polyvinyl alcohol (PVA) in water, which acts as the external phase. The mixture was stirred by a Heidolph stirrer (Germany) constantly at a predetermined speed. The stirring was continued for up to 5 hours until all methylene chloride was evaporated and microspheres were produced. The resulting microspheres were collected and rinsed three times with excess of water and then dried at room temperature. Various amount of ethylcellulose and different stirring rates were employed for the preparation of microspheres in this study.

Microsphere characterization

The morphology of microspheres was studied using optical and scanning electron microscopy (Cambridge F360 UK). The size distribution of microspheres was studied by applying standard sieves with mesh sizes of 250, 500, 710 and 1000 μm.

Drug loading measurement

Known amount of microspheres was dissolved in 10 mL chloroform and filtered through 0.45 membrane (millipore, USA). Nifedipine concentration of the solution was determined spectrophotometrically at 321 nm using calibration curve. Ethylcellulose does not have UV absorbance at this wavelength.

Drug release study

Drug release from microspheres was determined by USP XXIV method applying basket using a six station dissolution apparatus (Kavosh, Iran), and 40 mg of microspheres was put in each basket. Drug release from microspheres was determined in 900 mL of HCl (pH 1.2) and phosphate buffer (pH 7.2) media. Drug release was also studied in HCl medium for 2 hours followed by phosphate buffer for 22 hours. The dissolution medium was stirred at 100 rpm and maintained at 37±0.5°C. Samples of 5 mL were taken at ¼, ½, 1, 2, 2½, 3, 4, 6, 8, 10 and 24 hours and filtered through 0.45 μm membranes (millipore, USA). Nifedipine concentration of samples were determined spectrophotometrically at 239 nm and 240.2 nm for acid and buffer media respectively.

RESULTS AND DISCUSSION

Different formulations of nifedipine microspheres were prepared in this study (table 1). The effect of polymer (EC), drug/polymer ratio, and emulsifier (PVA) concentrations on particle size distribution of microspheres are shown in figures 1, 2 and 3 respectively. By increasing the amount of EC in internal phase, from 150 mg to 600 mg, the mode fraction size of microspheres increased from <250 μm to 500-710 μm. This could be attributed to the increase in the viscosity of internal phase, which consequently reduces the diameter of microemulsion droplets. The higher the viscosity of the internal phases (microemulsion droplets), the greater amount of energy was required to break the droplets into smaller particles. Figure 2 shows that as the ratio of nifedipine to polymer (EC) changed from 1:16 to 1:2 while keeping the amount of EC constant, the mode fraction size of microspheres increased from <250 μm to 500-710 μm. This effect seems to be as the result of the same argument mentioned for the effect of EC on particle size of microspheres. Since the amount of EC is the same (400 mg), increasing the amount of drug content, increases the total (drug and polymer) content of internal phase and as a result bigger droplets and bigger microspheres are formed. Figure 3 shows that as the amount of PVA (emulsifier) increased from 400 mg to 800 mg, the mode fraction size of the microspheres decreases from 500-710 μm to <250 μm. This effect demonstrates that the effect of PVA concentration on particle size is related to droplet stabilization. At low PVA concentration, the droplets are poorly stabilized and tend to coalesce and therefore become larger particles. This effect of PVA concentration on particle size distribution of microspheres are in agreement with previous finding by Arshady (1990) (18). Figure 4 shows that, consistent with other reports by increasing the stirring rate from 150 rpm to 300 rpm, the mode fraction size of microspheres is reduced from >1000 μm to 500-710 μm (19).

Figures 5 shows the SEM photograph of microspheres. As can be seen, nifedipine microspheres prepared in this study had smooth surface and spherical shape. Table 1 shows that the yield of drug loading of microspheres was not affected by EC, PVA, drug concentration and stirring rate.

Figure 6 shows the drug release from microspheres with the same ratio of drug to polymer content (1:3)

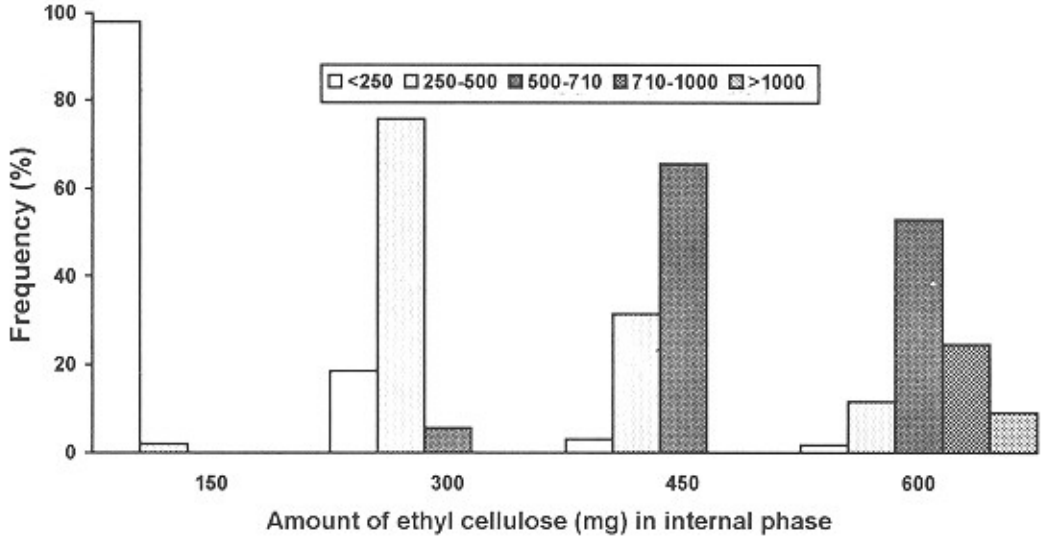

Figure 1. Effect of ethylcellulose content of internal phase (mg) on particle size distribution of microspheres prepared at stirring rate of 200 rpm and drug/polymer ratio of 1:3.

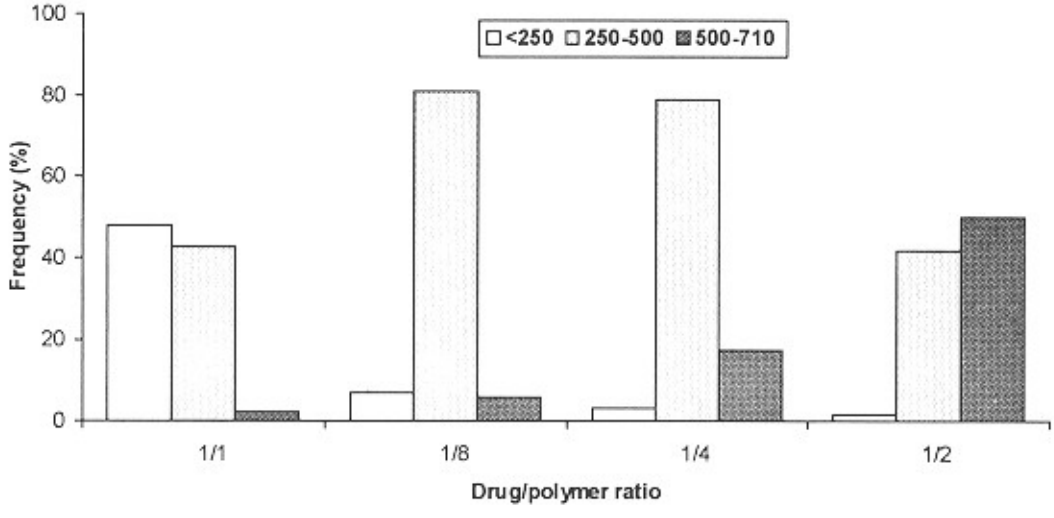

Figure 2. Effect of drug/polymer ratio on particle size distribution of microspheres prepared at stirring rate of 200 rpm, internal phase containing 400 mg EC and external phase containing 400 mg PVA.

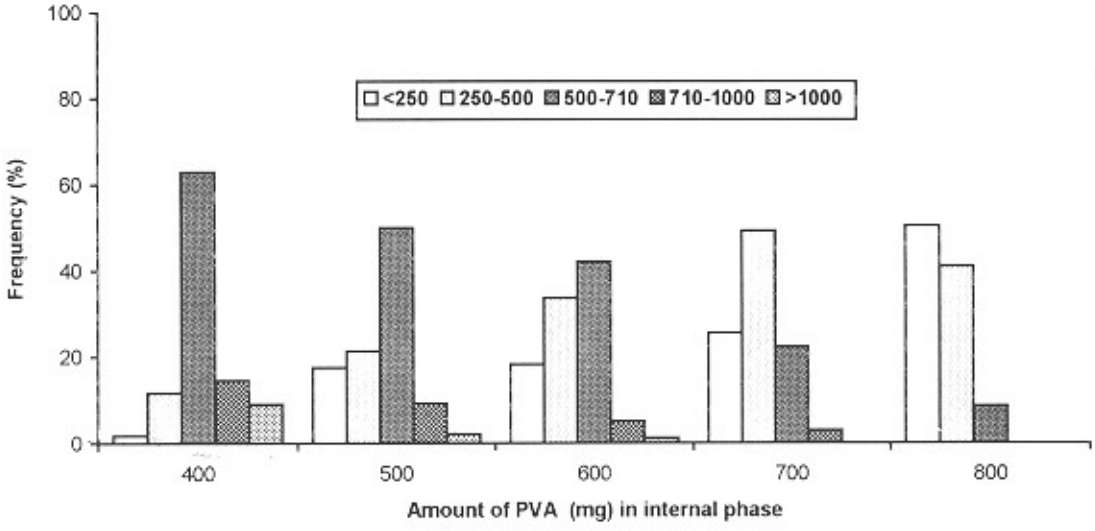

Figure 3. Effect of PVA content of external phase (mg) on particle size distribution of microspheres prepared at stirring rate of 200 rpm and drug/polymer ratio of 1:4.

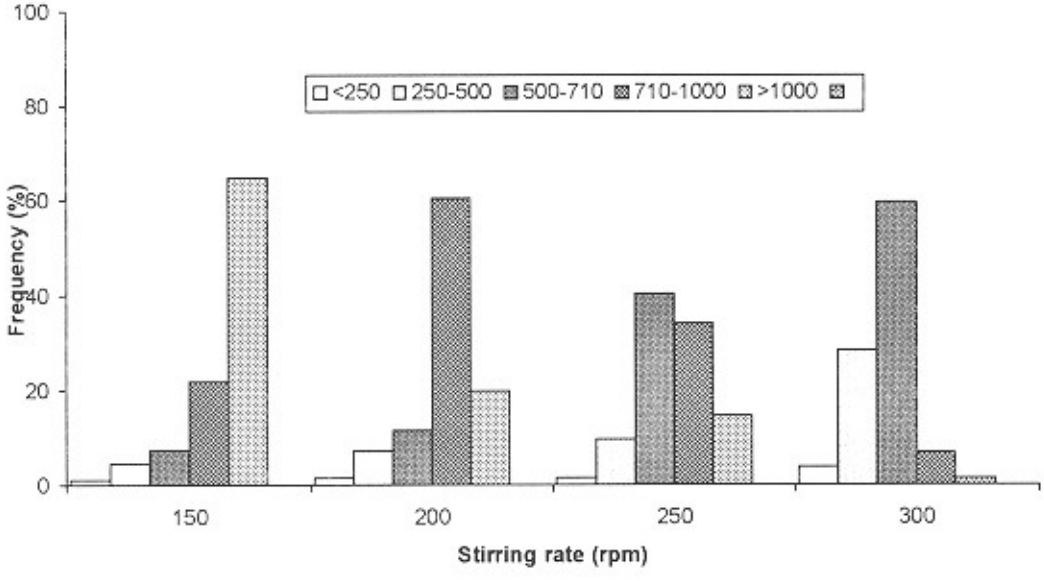

Figure 4. Effect of stirring rate on particle size distribution of microspheres prepared with drug/polymer ratio of 1:4, internal phase containing 800 mg EC and external phase containing 400 mg PVA.

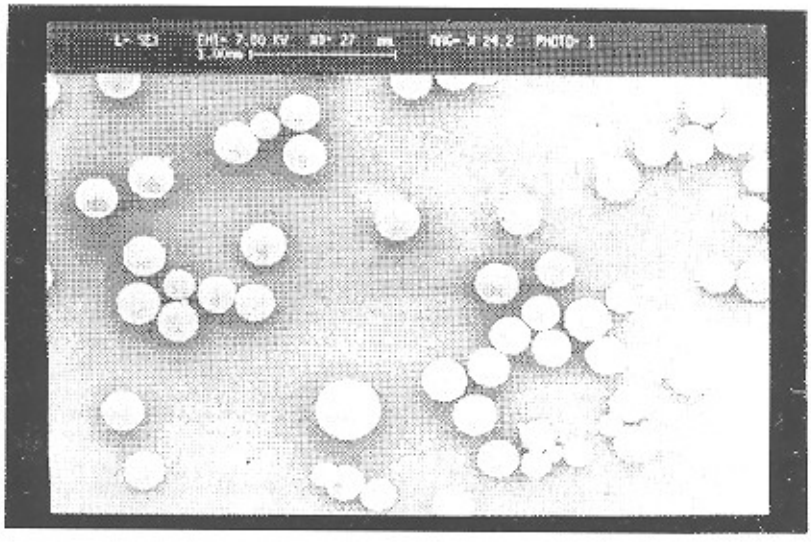

Figure 5. Scanning electron microscopy photograph of nifedipine microspheres.

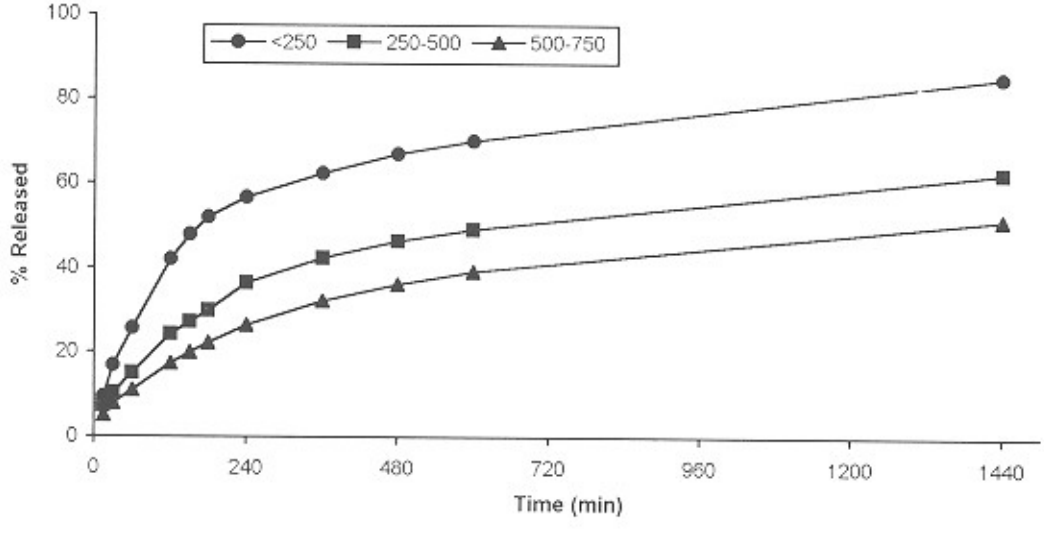

Figure 6. Effect of particle size on drug release from nifedipine microspheres with drug/polymer ratio of 1:3 in acid-buffer media (2-22 h).

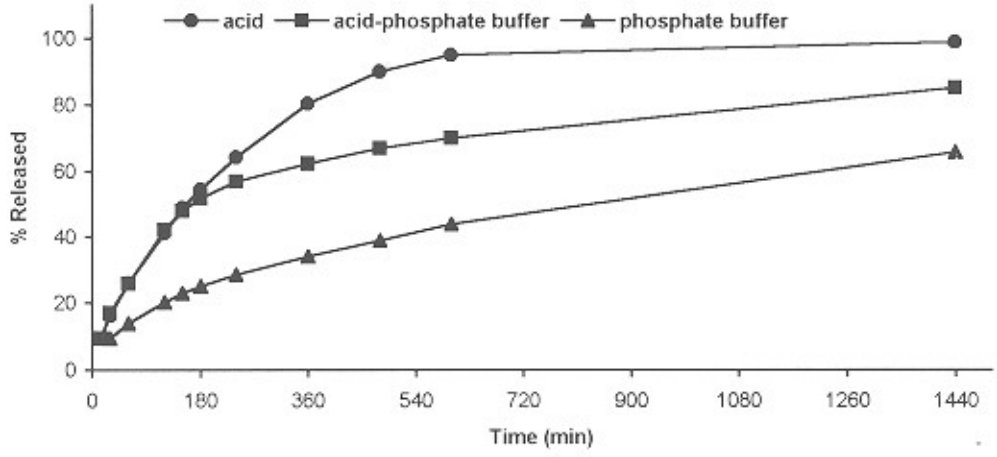

Figure 7. Effect of particle size on drug release from nifedipine microspheres with drug/polymer ratio of 1:3 and mode fration size of <250 μm in acid, phosphate buffer and acid-phosphate buffer media

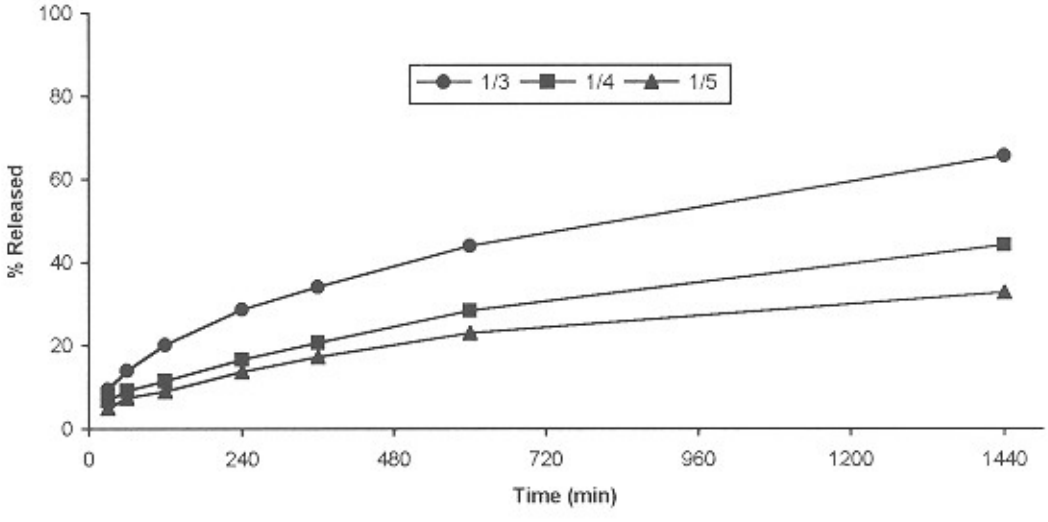

Figure 8. Effect of drug/polymer ratio on drug release from nifedipine microspheres with mode fraction size of <250 μm in buffer media (2-22 h).

Table 1. Nifedipine microspheres formulations and their mode fraction size and drug loading yield.

Code	EC (mg)	PVA (mg)	Drug:polymer ratio	Stirring rate (rpm)	Mode size fraction (μm)	Drug loading yield (%)
N1	150	400	1:3	200	<250	99.1
N2	300	400	1:3	200	250-500	98.4
N3	450	400	1:3	200	500-710	98.1
N4	600	400	1:3	200	500-710	98.2
N5	600	500	1:4	200	500-710	98.3
N6	600	600	1:4	200	500-710	97.6
N7	600	700	1:4	200	250-500	97.8
N8	600	800	1:4	200	<250	97.6
N9	400	400	1:16	200	<250	99.2
N10	400	400	1:8	200	250-500	99.0
N11	400	400	1:4	200	250-500	98.4
N12	400	400	1:2	200	500-710	97.6
N13	800	400	1:4	150	>1000	97.3
N14	800	400	1:4	200	710-1000	97.8
N15	800	400	1:4	250	500-710	98.2
N16	800	400	1:4	300	500-710	99.0
N17	200	400	1:4	200	<250	99.1
N18	250	400	1:5	200	<250	98.3

Table 2. Correlation coefficient (r^2) and release constant (K) for Higuchi model, Zero and first order release from microspheres

	Higuchi						Zero order						First order					
	r^2			K			r^2			k			r^2			k		
Release media	<250	250-710	>710	<250	250-710	>710	<250	250-710	>710	<250	250-710	>710	<250	250-710	>710	<250	250-710	>710
HCl (pH 1.2)	0.98	0.97	0.99	-12.7	-8.78	-3.97	0.95	0.94	0.92	0.17	0.12	0.05	0.81	0.86	0.81	0.002	0.002	0.001
Phosphate buffer (pH 7.2)	0.98	0.99	0.98	-11.5	-8.90	-7.70	0.92	0.91	0.92	0.04	0.03	0.03	0.75	0.71	0.73	0.001	0.001	0.000
HCl-Phosphate buffer	0.98	0.97	0.99	-12.7	-8.78	-3.97	0.95	0.94	0.92	0.17	0.12	0.05	0.81	0.86	0.81	0.002	0.002	0.001

but with different particle size in HCl-phosphate buffer (2-22 h) media. This figure indicates that the release rate of nifedipine from smaller microspheres with mode fraction size of <250 μm is higher than that from larger microspheres with mode fraction size of 500-710 μm. This is due to the greater surface area of the smaller microspheres. Figure 7 shows the drug release from microspheres with the same ratio of drug to polymer content (1:3) with particle size of <250 μm in HCl, phosphate buffer and HCl-phosphate buffer media respectively. It can be seen that drug release from microspheres in acid medium is markedly higher than that in buffer media. This may be attributed to the higher solubility of nifedipine at lower pH. Figure 8 shows the release rate of nifedipine from microspheres of the same particle size (<250 μm) but with higher drug content, in buffer medium is higher than those with lower drug content. Drug release from all microsphere formulations, except those with drug content of higher than

30% and particle size of less than 250 μm, did not exceed than 80%. This observation shows that ethylcellulose, when used as matrix polymer for the preparation of microspheres, slows the drug release dramatically. Drug release from all microsphere preparations confirms the Higuchi model (square root of time) release characteristics (table 2) which is due to the fact that microspheres are matrix type and no swelling or erosion of microspheres takes place during drug release experiments.

CONCLUSION

It can be concluded that, emulsification/solvent evaporation technique is a reproducible and simple method for the preparation of nifedipine microspheres. However, the use of ethylcellulose for the microsphere preparation has limitations, since it delays drug release at a longer period which is suitable for oral drug delivery systems. Only microspheres smaller than 250 μm in size with drug content higher than 30% (w/w) released more than 80 % of their drug content in 24 hours.

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