DESIGN AND CONTROLLED DRUG RELEASE STUDIES ON BENAZEPRIL MICROSPHERES

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ABSTRACT

Microspheres of Benazepril were prepared using the non-aqueous emulsification solvent evaporation method. The impacts of different factors such as stirring rate, concentration of Acrycoat S-100 as matrix polymer on the characteristics of the microspheres were investigated. The morphology of microspheres was studied using optical and scanning electron microscopy and it was shown that microspheres had a spherical shape and smooth surface. The particle size of microspheres analyzed by optical microscopic method was affected by stirring rate and concentrations of Acrycoat S-100. As the stirring rate increased the particle size decreases and as concentration of acrycoat increase the particle size also increases. Larger microspheres showed greater drug loading and smaller microspheres showed a faster drug release. Hence it proves the controlled drug release of this dosage form.

KEY WORDS: Benazepril, Acrycoat S-100, Microspheres, Non-aqueous solvent evaporation.

1.INTRODUCTION

Benazepril is a medication used to treat high blood pressure (hypertension), congestive heart failure and chronic renal failure. Upon cleavage of its ester group by the liver, benazepril is converted into its active form benazeprilat, a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor. It is commercially available as conventional and sustained release tablets and capsules. Slow release formulations of Benazepril are available as both single unit matrix tablets and multiple unit capsule systems. It has been shown that products based on a multiple unit system comprising many small units offer advantages over single-unit preparations such as low dosage matrix tablets which have low content uniformity and, therefore, low release reproducibility (Britishpharmacopoeia,1993;Da-peng,1997; Issaac,1996; Dinarvand,2002). The gastric emptying of multiple unit dosage forms occur gradually, in a more consistent manner, with less inter-subject variability. Multiple unit dosage forms also have the potential to distribute more uniformly in the gastrointestinal tract, thus yielding a more predictable drug release profile by suppressing the effect of many variables in the gastrointestinal environment, results more uniform drug absorption. As multiple unit dosage forms consist of many small units, it avoids fortuitous (all or none) emptying process. The plasma levels of drug from single unit systems were showed more variable than those from multiple unit systems(Parr,1990). In the present study, efforts were made to incorporate Benazepril in Acrycoat S-100 polymer by applying the non-aqueous solvent evaporation technique.

2.MATERIALS AND METHODS

Benazepril is purchased from Uma Brothers, Mumbai, *India*, Acrycoat S-100 purchased from Libraw Pharma, New Delhi, Acetone, Liquid paraffin (LR-grade) SD.Fine Chemicals, Mumbai.

Preparation of Microspheres

Microspheres were prepared by Non-Aqueous Solvent Evaporation Method(Deasy ,1983). Benazepril and Acrycoat S-100 in different proportions 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 (Drug: Polymer) were dissolved in acetone. This clear solution was poured slowly as a thin stream in about 200ml of liquid paraffin solution in a 500ml beaker and stirred at different agitation speed for 1 hour; the microspheres were filtered and dried over night at 30- 40°C.

Evaluation of Microspheres

Micromeritics Studies of Controlled release Microspheres

The microspheres are characterized by their micromeritic properties, such as particle size, tapped density, compressibility index and flow property. Particle size determination using an optical microscope under regular polarized light and the mean particle size was calculated by measuring 200-300 particles with the help of a calibrated ocular micrometer(Martin,1983).

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Microspheres Morphology

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy under a Hitachi Model S-450. The sample was loaded on copper sample holder and sputter coated with carbon followed by Gold.

Drug Content

Samples were analyzed Spectrophotometrically by Elico, SL-164, UV-Vis Double beam spectrophotometer at a wavelength of 240nm. Powdered microspheres containing 0.04gm Benazepril was dispersed in 10ml Acetone followed by agitation with magnetic stirrer for 12hr to dissolve the polymer and to extract the drug. After filtration, the drug concentration in the acetone phase was determined by proper dilution(Dinarvand,2002;Gohel,1996). Finally, drug encapsulation efficiency was calculated.

TABLE 1: Batch specifications of the prepared Microspheres

Batch code	Drug: Polymer	Stirring rate (rpm)	Temperature
A1[a]	1:1	1300	30-40
A2[a]	1:2	1300	30-40
A3[a]	1:3	1300	30-40
A4[a]	1:4	1300	30-40
A5[a]	1:5	1300	30-40
A6[a]	1:6	1300	30-40
B2[b]	1:2	1800	30-40
B3[b]	1:3	1800	30-40
C2[c]	1:2	600	30-40
C3[c]	1:3	600	30-40

Stirring rate: [a] = 1200 rpm, [b] = 1800 rpm, [c] = 600 rpm

In-vitro Drug Release

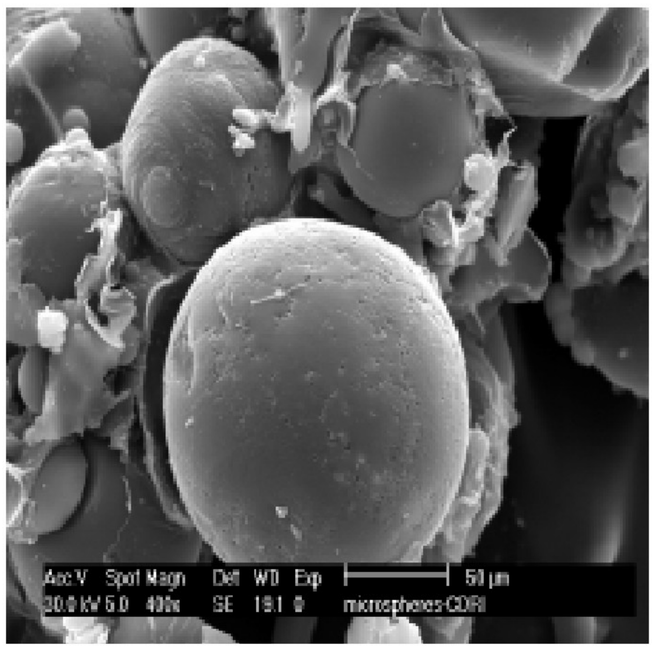
Microspheres equivalent to 0.04gm of Benazepril were subjected for dissolution. Dissolution tests were carried out using USPXXI rotating paddle method (Apparatus 2). The stirring rate was 100rpm. The dissolution medium was 900ml of 0.1N HCl (pH 1.2) and the temperature was maintained at 37 ± 0.5°C. After 2 hr, microspheres were removed and transferred to a medium containing phosphate buffer (pH 7.4) for 10hr. Samples of 5ml were withdrawn at predetermined interval with a pipette and filter(Dinarvand,2002). The collected samples were analyzed spectrophotometrically at 240nm.

TABLE 2: Various formulation parameters for microspheres

Batch Code	Mean Particle Size (µm)	Incorporation efficiency (%)
A1	140.2 ± 8.3	84.24 ± 1.1
A2	175.0 ± 13.7	87.32 ± 1.4
A3	223.8 ± 19.3	89.24 ± 2.1
A4	233.3 ± 23.3	80.12 ± 1.4
A5	245.4 ± 18.6	75.97 ± 2.4
A6	248.7 ± 17.2	78.64 ± 1.8
B2	198.2 ± 12.2	84.56 ± 1.6
B3	215.6 ± 14.3	81.18 ± 2.1
C2	243.5 ± 18.5	74.32 ± 1.7
C3	266.2 ± 17.4	79.21 ± 1.9

3.RESULTS AND DISCUSSION

Controlled release microspheres were prepared by the Non-Aqueous Solvent Evaporation method using a gradually increase in stirring rate and Acrycoat S-100 concentration, to assess the effect of stirring rate and polymer concentration on the size of microspheres. The batch specifications were shown in Table.1. The mean particle size of the microspheres significantly increased with increasing Acrycoat S-100 concentration and was in the range 140.2 ± 8.3 to 248.7 ± 17.24 as shown in Table 2. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension with diminished shearing efficiency and increased particle size. As the stirring rate was increased, the mean particle size decreased. Carr's index is in between 5-15% and Hausner ratio with in 0.5 and angle of repose was found with in the range of 15° to 25 °, which was an appreciable limit for microspheres to show flow property while formulating in the dosage form.



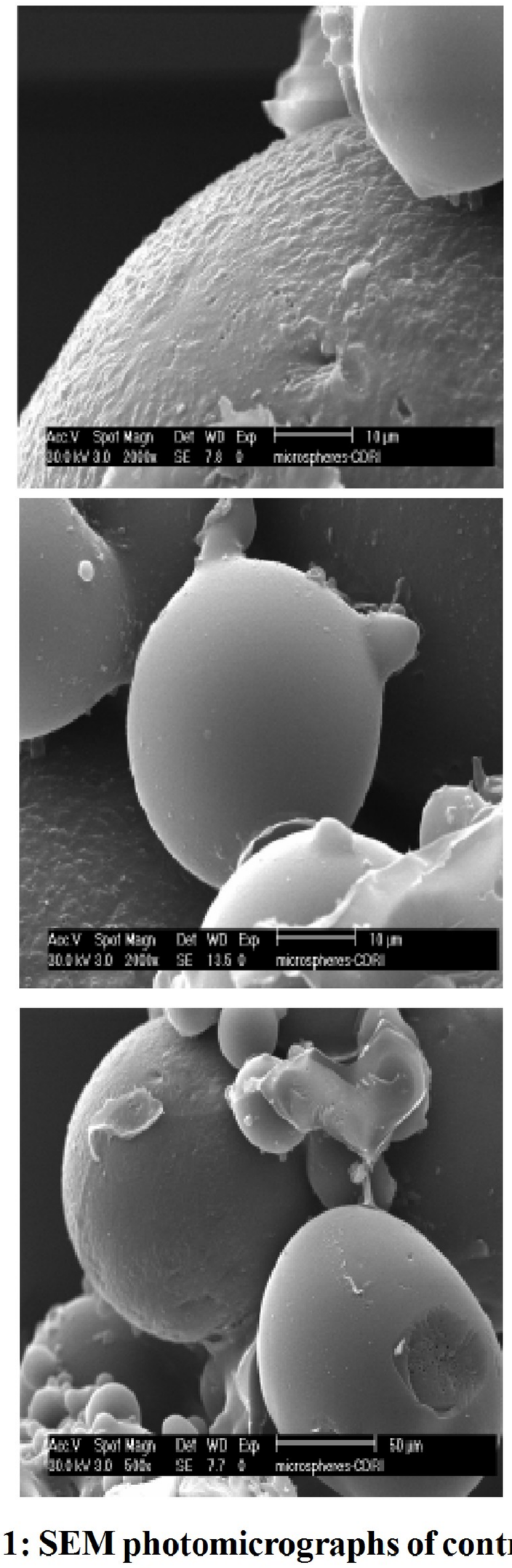


Fig 1: SEM photomicrographs of controlled release microspheres

- Ø SEM 1 shows smooth texture of controlled release microspheres.
- Ø SEM 2 shows pore visibility of controlled release microspheres.
- Ø SEM3 shows dents on the surface.
- Ø SEM4 shows bulb like appearance that reveal solvent evaporation.

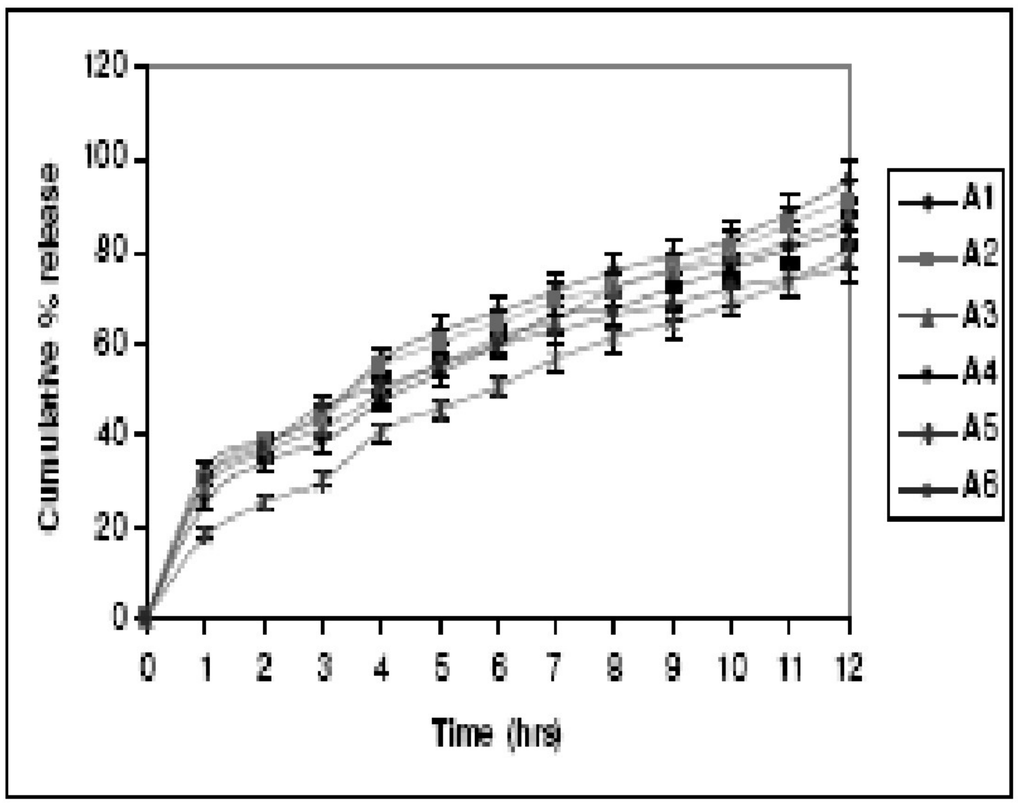


Fig 2: Effect of the polymer concentration during microsphere preparation on in-vitro release of Benazepril (Bars represent mean ± SD; n=3)

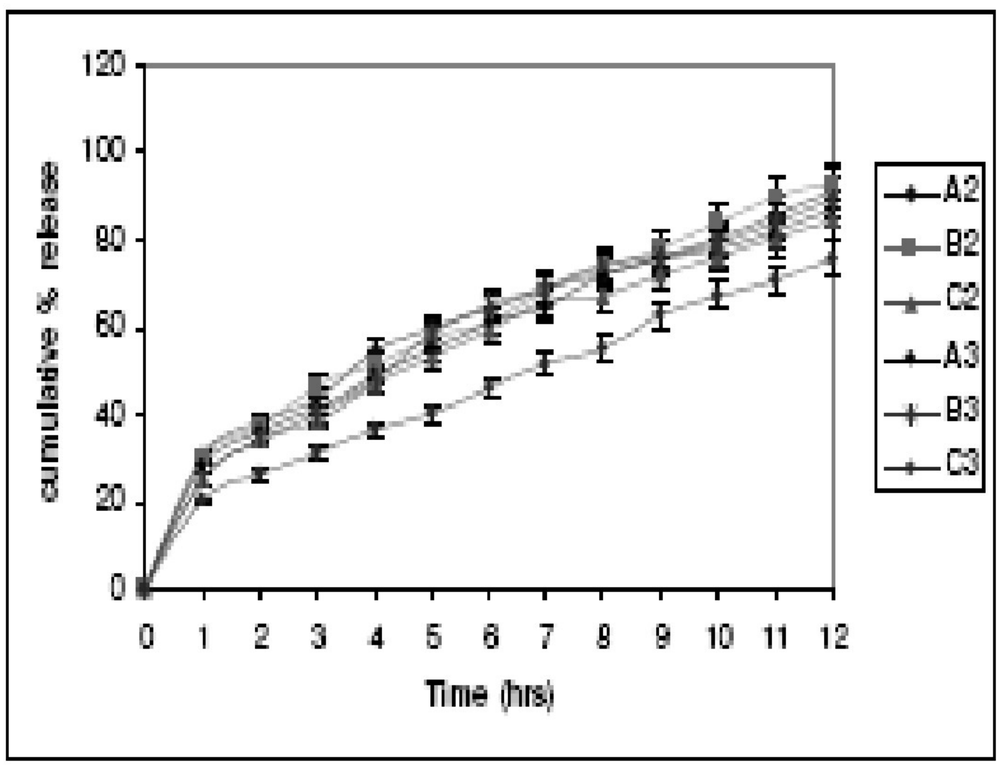


Fig 3: Effect of the stirring rate during microsphere preparation on in-vitro release of Benazepril (bars represent mean ± SD; n=3)

The SEM photographs showed that the fabricated microspheres were spherical with a smooth surface and exhibited a range of sizes within each batch as shown in Fig. 1. The incorporation efficiency of Benazepril was good in all loadings and incorporation efficiency was increased with the polymer concentration. The high entrapment efficiency of the drug was believed to be due to its poor solubility in liquid paraffin. As the polymer concentration increased, the viscosity of polymer solution was increased and responsible for formation of larger microspheres. In-vitro Benazepril release studies were performed in 0.1N HCl for 2hrs

and 7.4pH for 10hrs. The cumulative release of Benazepril significantly decreased with increasing Acrycoat S-100 concentration. The increased density of the polymer matrix at higher concentrations results in an increased diffusional path length. This may decrease the over-all drug release from the polymer matrix. Furthermore, smaller microspheres were formed at a lower polymer concentration and had a larger surface area exposed to dissolution medium, giving rise to faster drug release. Benazepril release was higher in the case of microspheres prepared at a higher agitation speed but the difference in drug release was not statistically significant, but at low agitation speed the release rate was slow (Fig. 3).

4.CONCLUSIONS

In-vitro data obtained for floating microspheres of Benazepril showed good drug entrapment and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main controlled release mechanism. Thus, the prepared microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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