University Department of Pharmaceutical Sciences[1], Utkal University, Vani-Vihar, Bhubaneswar, Orissa, Kanakmanjari Institute of Pharmaceutical Sciences[2], Rourkela, Orissa, Gayatree Institute of Pharmaceutical Sciences, Sambalpur, India

Effect of processing temperature on Eudragit RS PO microsphere characteristics in the solvent evaporation process

S. K. Sahoo[1], S. Dhal[1], P. Mohapatro[2], B. Ch. Behera[2], B. B. Barik[1]

Received February 8, 2007, accepted February 27, 2007

Sunit Kumar Sahoo, University Department of Pharmaceutical Sciences, Utkal University, Vani-Vihar, Bhubaneswar, Orissa, Pin-751004, India
sahoosunitkumar@rediffmail.com

Pharmazie 62: 638–639 (2007)
doi: 10.1691/ph.2007.8.7041

Eudragit RS PO microspheres containing stavudine as a model drug were prepared by the solvent evaporation method using acetone liquid paraffin system. The influence of processing temperature: 10, 30 and 40 °C on various parameters like particle shape, size distribution, drug loading, drug polymer interaction and release kinetic were studied. It was found that at lower temperature (10 °C) small particles of irregular size, rough and wrinkled surface were formed, whereas higher temperature gradually increases the particle size as well as improves the shape and smoothness of microspheres. It was found that temperature had no effect on encapsulation efficiency and drug polymer compatibility. Drug release rate from microspheres were found to be a function of mean particle size distribution.

Microencapsulation by the solvent evaporation method is popular method and has been utilized successfully for developing therapeutically effective sustained release drug formulations. This complex process can be influenced by several parameters (Ronik et al. 2005; Jones et al. 1995) as for example rate of solvent evaporation, stirring rate, viscosity of polymeric phase, drug polymer ratio, volume ratio between inner phase and outer phase and amount of surfactant. Several extensive studies has been done earlier considering the above mentioned factors but a literature study shows that a few works have been done considering the effect of processing temperature on Eudragit RS PO microsphere formation, particle shape, mean particle size, particle size distribution, drug loading, drug polymer compatibility, and release studies.

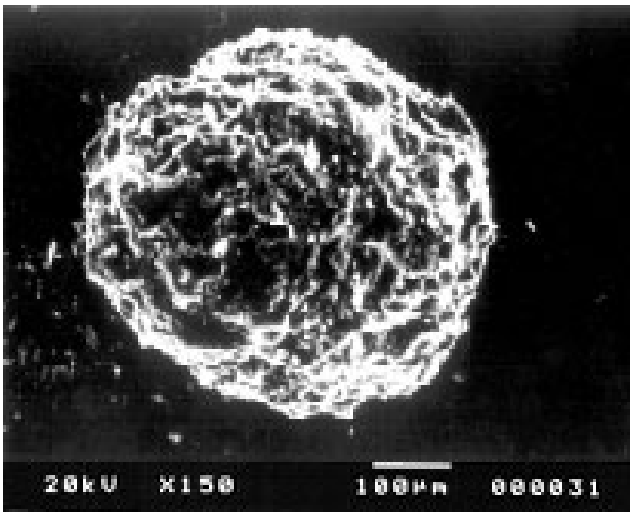
The main objective of the present investigation was to investigate the effect of preparation temperature on Eudragit RS PO microspheres in a different temperature range (10 °C, 30 °C and 40 °C) and to study its effect on various parameters like particle shape, mean particle size, particle size distribution, drug loading, drug polymer compatibility, and release.

Eudragits are a class of biocompatible copolymers synthesized from acrylic and ethacrylic acid esters. Eudragit RS PO is referred to as ammoniomethacrylate copolymers, with having 5% functional quaternary ammonium groups (Kimy et al. 2002). These polymers are well tolerated by the skin and have been used in the formulation of dosage forms, most commonly in the preparation of matrix tablets for oral sustained release and in tablet coating. They have also been used in other types of dosage forms, e.g. in the microencapsulation of drugs (Esposito et al. 1999).

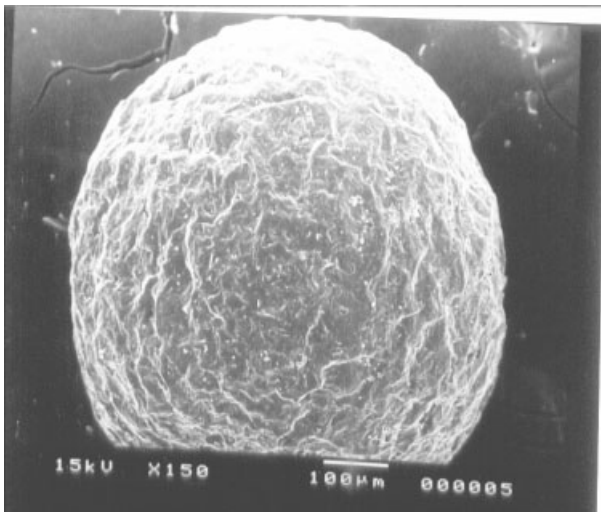
In the above study stavudine has been used as the model drug. Stavudine (D4T, thymidine) is a FDA approved drug for clinical use for the treatment of HIV infection, AIDS and AIDS related conditions either alone or in combination with other antiviral agents. Stavudine is typically administered orally as a capsule or an oral solution. The virustatic drug has a very short half life (1.30 h)

Evaluation of microspheres formulated at different temperature shows that the temperature has a strong effect on mean particle size (303.35, 381.93 and 440.37 μm for formulation 1, 2 and 3 respectively) and particle size distribution. The mean particle size of the microspheres was found to increase with increasing processing temperature. This may be due to the fact that at low temperature (10 °C), when the polymeric phase was added to the oil phase and stirred, extensive emulsification of the polymeric phase takes place and then the solvent from polymeric phase diffuses in to the outer oil phase and evaporates from the system resulting in small size microparticles, but higher preparation temperature (40 °C) increases the rate of solvent evaporation and the emulsion droplets harden faster and stirrer shear force is not able to break the droplets and leads to formation of larger particle size (Ronik et al. 2005). The drug entrapment study shows more than 95% drug entrapment in all cases (96.1 ± 3.7, 99.2 ± 2.4 and 95.7 ± 2.5 for formulation 1, 2 and 3 respectively), indicating the entrapment is not affected by temperature. Surface topography (Fig. 1) shows that the microspheres formulated at lower temperature had irregular, rough and wrinkled surfaces becoming smoother and more regular as the processing temperature increases. At lower temperature the rate of solvent removal from the inner phase (droplet) is slow and gradually its viscosity increases to a very high viscous droplet stage and at this stage when the rotating stirrer hits it its shape deforms and solidifies as such before recovering to regular and thermodynamically more favorable spherical shape and hence the microspheres have irregular structure. IR spectroscopy shows that there was no significant difference in the IR spectra of pure stavudine and drug loaded microspheres (1, 2 and 3). The characteristic OH stretching, NH stretching of secondary amine, C−H stretching and C=O stretching of pure drug remained unchanged in the case of microspheres. The results suggest that processing temperature had no effect on drug polymer compatibility.

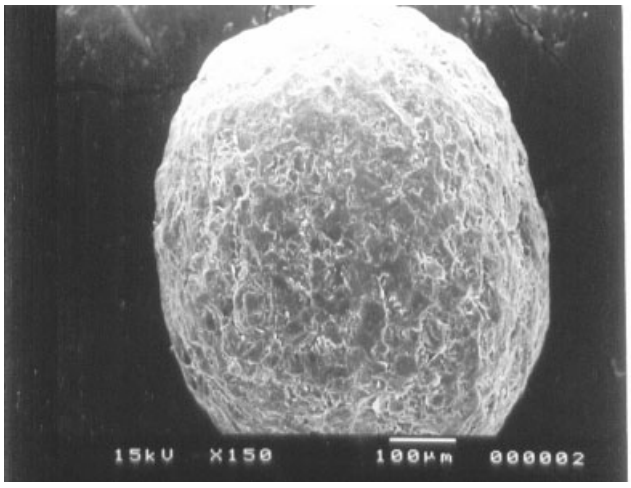
When the *in vitro* drug release data from various formulations were analyzed it was found that the formulation prepared at higher temperature showed a longer sustained release action as compared to formulations prepared at lower temperature (Fig. 2). At lower processing temperature the mean particle size of the microspheres was less than that at higher processing temperature. Therefore, drug release from microspheres prepared at lower temperature was faster than that of microspheres prepared at higher temperature because of the small size of the microspheres, which provided a large surface area for faster drug release (Wakiyama et al. 1981). This finding is consistent with the general rule (that is, small size of microspheres provides large surface area for faster drug release).



(A)



(B)



(C)

Fig. 1: SEM photomicrographs of formulation 1 (A), 2 (B) and 3 (C). Effect of processing temperature on particle surface structure

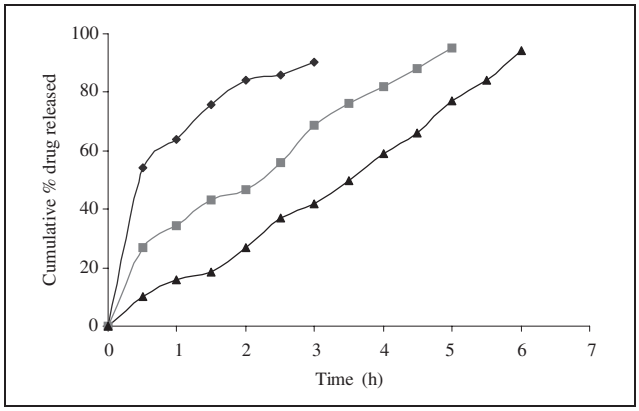


Fig. 2: Effect of processing temperature on drug release pattern. Drug release profile from formulation 1 (—●—), 2 (—■—) and 3 (—▲—)

Experimental

Stavudine was obtained as a gift from Macleod, Mumbai. Eudragit RS PO from Röhm Pharma, GmbH, Darmstadt, Germany. All other reagents and solvents used were of pharmaceutical or analytical grade.

Stavudine microspheres were prepared by solvent evaporation techniques keeping drug to polymer ratio 1 : 3. Eudragit RS PO (1.5 g) was dissolved in 8.5 ml acetone using a magnetic stirrer (Remi Equipments, model 2 MIH). Stavudine (500 mg) and magnesium stearate (75 mg) were dispersed in the polymer solution. The resulting dispersion was then poured into 250 ml beaker, containing the mixture of 100 ml liquid paraffin light and 10 ml n-hexane maintained at desired temperature, while stirring at 750 rpm. A mechanical stirrer with a blade (4 cm diameter) (Remi Motors, Model No.RO-123R, Mumbai) was used. Stirring was continued for 3–5 h then microspheres were filtered through a Whatman no. 1 filter paper. The residue was washed 4 to 5 times in 50 ml N-Hexane each. Microspheres were dried at room temperature for 24 h. Formulations at processing temperature 10, 30 and 40 °C assigned batch code as: 1, 2 and 3 respectively.

The microspheres were evaluated for % yield, % drug content by a UV-Visible spectroscopic method (Systronic 2101) in phosphate buffer, pH 6.8 at 266 nm. A scanning electron microscope (JEOL JSM-5200) was used to characterize the shape and surface topography of the microspheres, particle size distribution and mean particle size by sieving (using standard ASTM sieves), drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for pure drug and drug-loaded microspheres using a FTIR JASIO Model No. 410. The *in vitro* release studies of drug loaded microspheres were carried out at 37 °C using phosphate buffer pH 6.8 (500 ml) in a USP dissolution apparatus rotated at 100 rpm (LABINDIA, DISSO-2000, Mumbai, India) under sink conditions (Chowdary et al. 2004; Lee et al. 2000). The samples were analyzed by UV-Visible spectroscopy at 266 nm.

References

Chowdary KPR, Koteshwara Rao N, Malathi K (2004) Ethyl cellulose microspheres of glipizide: Characterization, *in vitro* and *in vivo* evaluation. Indian J Pharm Sci 66: 412–416.

Esposito E, Sebben, S, Cortesi R, Menegatti E, Nastruzzi C (1999) Preparation and characterization of catioinic microspheres for gene delivery. Int J Pharm 189: 29–41.

Jones DS, Pearce KJ (1995) Investigation of the effects of some process variables on, microencapsulation of propranolol HCl by solvent evaporation method. Int J Pharm 118: 199–205.

Kimy BK, Hwang SJ, Park JB, Parky HJ (2002) Preparation and characterization of drug loaded polymethacrylate microspheres by an emulsion solvent evaporation method J Microencapsul 19: 811–822.

Lee JH, Park TG, Choi HK (2000) Effect of formulation and processing variables on the characteristics of microspheres for water soluble drugs prepared by w/o/o double emulsion solvent diffusion method. Int J Pharm 196: 75–78.

Ronik TM, Frlan R, Bogataj M, Bukovec P, Mrhar A (2005) Effect of preparation temperature in solvent evaporation process on eudragit RS microsphere properties. Chem Pharm Bull 53: 143–146.

Wakiyama N, Juni K, Nakano M (1981) Preparation and evaluation *in vitro* of polylactic acid microspheres containing local anesthetic. Chem Pharm Bull 29: 3363–3368.