J. Pharm. Pharmacol. 1998, 50 (Supplement): 161

Thermal studies on spray-dried biodegradable microspheres from various organic solvents

D. F. BAIN, D. L. MUNDAY AND A. SMITH*

*School of Pharmacy, The Robert Gordon University, Schoolhill, Aberdeen AB10 1FR, and *Knoll Pharmaceuticals, Pennyfoot Street, Nottingham NG1 1GF*

The substitution of dichloromethane and chloroform with less toxic acetone (Rafler & Jobmann, 1994) and halothane (Guiziou et al, 1996) has been proposed for the preparation of biodegradable microspheres. However, little consideration has been paid to the technological consequences of such substitution on drug release. This report describes thermal characterization of compositionally identical microspheres prepared from different organic solvents and its correlation with other determined characteristics.

Microspheres were prepared from solutions of the (co)solvents listed in Table 1 (3 % w/v total solid) comprising 24, 56 and 20 % w/v poly(D,L-lactide) Resomer® R104, R202H (Boehringer Ingelheim) and rifampicin (Lepetit) respectively. DSC (Pyris 1, Perkin Elmer, USA) was performed at various scanning rates to compute Arrhenius derived activation energies (E_a) of glass transition (Tg). Other thermal data in Table 1 was gathered at a rate of 10 °C min^{-1}. Solvent residue and drug release were determined as described previously (Bain et al., 1998).

Table 1. Preparative conditions, thermal and residual solvent data

Batch	Solvent(s)		Tg / °C	enthalpy / kJ g^{-1}	E_a / J g^{-1}	residue / ppm x10^{-3}
	nature	ratio				
1	DCM	100%	58.3	4.15	5.47	60.69
2	HAL	100%	49.9	5.57	3.50	125.51
3	ACT	100%	42.3	3.69	7.59	24.73
4	DCM:CFM	1:1	58.1	5.60	4.61	93.52
5	DCM:ACT	2:1	51.7	5.40	4.11	40.50
6	CFM:ACT	2:1	53.5	6.74	3.84	106.29

Key: DCM, dichloromethane; ACT, acetone: CFM, chloroform; HAL, halothane

Solvent change led to variation in thermal behaviour and release character (see Figure 1) which can be related to the microsphere formation mechanism (Bain et al, 1998). In general, rapid polymer deposition associated with highly volatile solvents e.g. ACT produced a porous matrix and rapid drug release, whereas other solvents resulted in a slower release. However, high and persistent solvent residue permitted significant polymer enthalpy relaxation upon storage due to its plasticizing action. This ageing process can be followed by the up-scale shift of the Tg and the progressive development of an anomalous endotherm. These changes marked the loss of excess enthalpy generated by rapid microsphere formation during spray-drying. After exhaustive *in vacuo* drying, activation energies in Table 1 for the Tg were inversely related to the enthalpy of the endotherm. The latter parameter was, in contrast, directly related to the level of solvent residue which facilitates molecular movement associated with relaxation and Tg elevation.

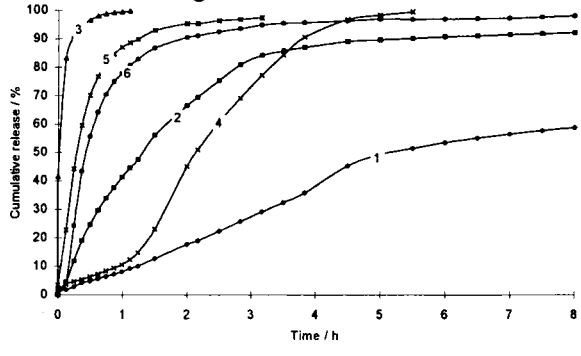

Figure 1. Release profiles of microspheres

Relaxation corresponds to the formation of a more stable microsphere matrix. Thus, based on this factor, those prepared from HAL (2) and CFM:ACT (6) should result in slowest drug release. However, related to relaxation, the Tg of the matrices formed proved a more reliable indicator of microsphere stability, release rate decreasing as Tg increased. Clearly, other factors influenced by the drying process, such as matrix density, have a role in determining the magnitude of the Tg and relaxation recovery, which in turn modulate drug release. In conclusion, solvent selection for spray-drying has significant technological implications in addition to toxicological considerations.

Bain DF, Munday DL & Smith A, 1998, *Fifth European Symposium on Controlled Drug Delivery*, Noordwijk aan Zee, 92-4.

Rafler G. & Jobmann M., 1994, *Drugs made in Germany*, 37(4), 37, 115-19.

Guiziou B, Armstrong D, Elliot E, Ford J and Rostron C, 1996, *J. Microencap*, 10, 466-80.