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Interlot variability of carbomer 934

B. Pérez-Marcos [a], R. Martínez-Pacheco [a], J.L. Gómez-Amoza[a], C. Souto [a], A. Concheiro[a] and R.C. Rowe [b]

[a] *Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago, 15706 Santiago de Compostela (Spain) and* [b] *ZENECA Pharmaceuticals, Macclesfield (UK)*

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Summary

Seven carbomer 934 lots exhibiting no appreciable differences in IR spectra, density or carboxylic acid group content were found to differ significantly as regards the rheological characteristics of their aqueous dispersions. These differences are attributed to differences in mean molecular weight, and explain significant differences between the two most dissimilar lots as regards the dissolution profiles of theophylline and hydrochlorothiazide tablets in which they were used as matrices.

Introduction

Carbomers, marketed by BFGoodrich under the trade name Carbopol® (BFGoodrich, 1985), are acrylic acid polymers crosslinked with polyalkyl ether (American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, 1986; Cosmetic, Toiletry and Fragance Association, 1992). Since the 1950s, when they were introduced as better thickening agents than natural gums (Barry and Meyer, 1979a), their pharmaceutical use has progressively increased (Secard, 1962; Perotti, 1970a,b; Cosmetic, Toiletry and Fragance Association, 1992). Pharmaceutical grade carbomer 934 (Carbomer 934P), in which the polyalkyl ether is alkylsaccharose, is authorized by the FDA for use in dosage forms for internal administration. Available data on the basic properties of carbomers are nevertheless scarce in comparison with those concerning other hydrophilic polymers with similar uses, such as cellulose ethers (Doelker, 1987). Particularly important among such properties are those related directly or indirectly to the rheological properties of aqueous dispersions of carbomer, which are of relevance both to its technological characteristics and to the release of drugs from solid dosage forms in which it is used as binder (Concheiro et al., 1987; Vila-Jato et al., 1987) or matrix (Vázquez et al., 1992). Official standards for the viscosity of aqueous dispersions of carbomer (British Phar-

Correspondence to: R. Martínez-Pacheco, Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Santiago, 15706 Santiago de Compostela, Spain.

macopoeia, 1988; The National Formulary XVII, 1990), which refer only to a single concentration of the polymer (and differ as to the procedure used), may not be sufficient to guarantee interlot homogeneity among dosage forms in which it is used. In this work we investigated variability among carbomer lots, from different points of view, and its consequences for the release of theophylline and hydrochlorothiazide from carbomer-based formulations.

Materials and Methods

Materials

We studied samples of Carbomer 934 NF lot A91121 (hereinafter lot 1) and Carbomer 934P NF lots 8902185 (lot 2), 8902160 (lot 3), 8801779 (lot 4), 8902161 (lot 5), 9004705 (lot 6) and 8902162 (lot 7). Nominal viscosity was 2050–5450 cP for neutral 0.2% w/v aqueous dispersions, and 30000–39400 cP for 0.5% w/v dispersions (both at 25°C). All carbomer samples were desiccated under vacuum at 80°C for 1 h before use, and results are referred to dry weight when relevant. Theophylline USP, solubility 8.3 mg/ml (Cohen, 1975), and hydrochlorothiazide USP, solubility 0.61 mg/ml (Deppeler, 1981), were from J. Escuder, Spain (theophylline lot 016, hydrochlorothiazide lot 0014).

Carboxylic acid group content

Carboxylic acid group content was calculated following The National Formulary XVII (1990) from neutralization curves obtained potentiometrically in duplicate with a Crison MicropH 2001 pH-meter.

IR spectra

IR spectra between 200 and 4000 cm^{-1} were recorded in KBr pellets on a Perkin-Elmer 1330 spectrophotometer.

Density

True density was determined in triplicate with a Quantachrome MCY-2 helium pycnometer.

Equilibrium moisture curves at 20°C

Duplicate 1 g samples were stored until their weight became constant under atmospheres with relative humidities controlled by aqueous sulphuric acid solutions. Equilibrium moisture content was calculated from the final weight gain.

Viscosity

The viscosity of 0.005, 0.010, 0.015, 0.020, 0.025 and 0.030% w/v dispersions of carbomer was measured in triplicate at 37°C in a Canon-Fenske U-type viscosimeter (Afora, Ref. 5354/2) after neutralization as per The National Formulary XVII (1990). The rheological behaviour of more viscous 0.1% w/v dispersions was determined from shear stress-shear rate curves recorded at 25°C (after neutralization as above) in a Brookfield DV-II digital rotatory viscosimeter using spindle speeds of 0.3–60.0 rpm. For lots 3 and 6, curves were also obtained for 0.2% w/v dispersions.

Release of theophylline and hydrochlorothiazide

Direct compression carbomer/theophylline and carbomer/hydrochlorothiazide tablets were produced, using carbomer lots 3 and 6 (four formulations in all), in a Korch EKO excentric press equipped with piezoelectric pressure transducers (Martínez-Pacheco et al., 1985) and flat 12 mm teflon punches lubricated with a suspension of magnesium stearate in acetone. Tablet weight was 500 mg, drug content 10% w/w with a maximum compression force of 2250 N; dies were filled by hand. Dissolution profiles were obtained using a US Pharmacopeia XXII (1990) Type II apparatus (Turu Grau) operated at 150 rpm (tablets were prevented from floating by retention in $2.8 \times 2.8 \times 1$ cm cages with 1.6 mm meshes). All assays were carried out over 8 h using six tablets and 900 ml of distilled water as dissolution medium. The quantities of theophylline and hydrochlorothiazide released were determined spectrophotometrically at 272 and 274 nm, respectively. Higuchi's dissolution rate equation (Higuchi, 1962, 1963) was fitted to the data for theophylline, and a zero-order rate equation to those for hydrochlorothiazide (Pérez-Marcos et al., 1991a). The corresponding rate constants

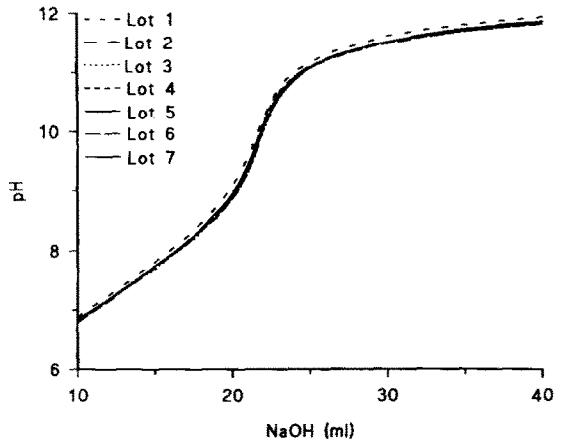

Fig. 1. Mean neutralization curves of the seven carbomer 934 lots studied.

for each carbomer lot were compared using Wilcoxon's test (Siegel and Castellan, 1988).

Results and Discussion

The carboxylic acid group content of carbomer 934 should be between 56 and 68% (British Pharmacopoeia, 1988; The National Formulary XVII, 1990). The contents of the seven lots studied, as calculated from the corresponding neutralization curves (Fig. 1), satisfied this standard and were virtually identical, all lying between 59.4 and 60.3% (Table 1). The IR spectra of the seven lots were also very similar (Fig. 2), with carbonyl and hydroxyl bands at 1722 and 3420 cm^{-1}, respectively (Graf et al., 1983) and an 800–1000 cm^{-1} region showing that the spatial configuration of the polymer is the same in all seven lots (Bardet and Alain, 1975a).

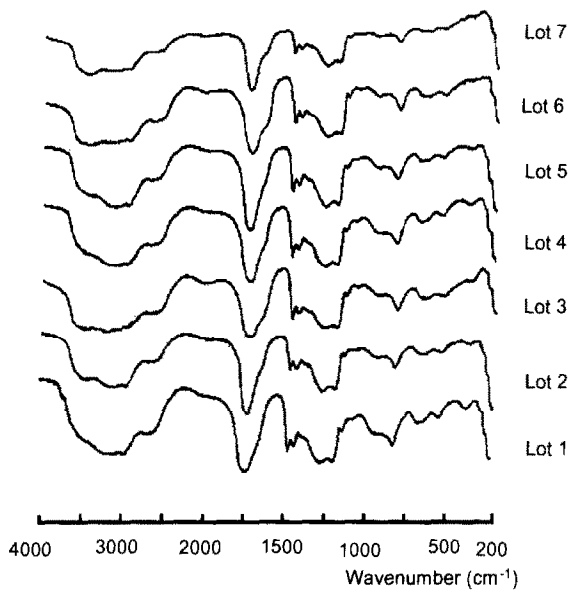

Fig. 2. IR spectra of the seven carbomer 934 lots studied.

Though there is no official specification for the true density of carbomer, the manufacturer declares a value of 1.41 g/cm^3 regardless of variety (BFGoodrich, 1985). The true densities measured

TABLE 1

Mean carboxylic acid contents, true densities and equilibrium moisture (20°C, R.H. = 58.3%) of the seven carbomer 934 lots studied (SD in parentheses)

Lot	Carboxylic acid content (%)	True density ($g\ cm^{-3}$)	Equilibrium moisture (%)
1	59.59 (1.12)	1.489 (0.021)	8.40 (0.09)
2	60.00 (0.97)	1.505 (0.006)	9.07 (0.43)
3	60.09 (1.93)	1.489 (0.006)	8.67 (0.03)
4	59.41 (0.96)	1.510 (0.015)	8.62 (0.01)
5	60.09 (0.00)	1.512 (0.018)	8.95 (0.20)
6	60.09 (0.00)	1.446 (0.007)	8.84 (0.07)
7	60.28 (2.09)	1.481 (0.026)	8.67 (0.13)

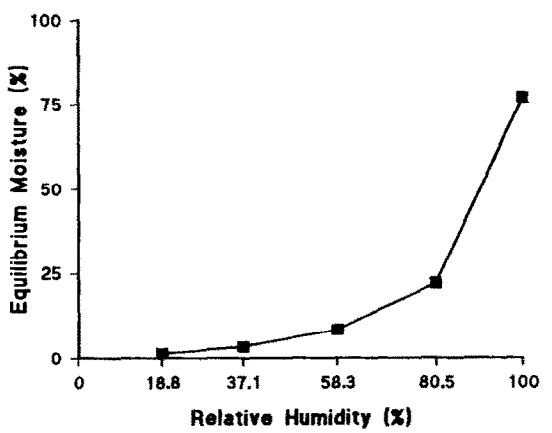

Fig. 3. Equlibrium moisture curve at 20°C of carbomer 934 lot 1. The six lots omitted superimpose lot 1.

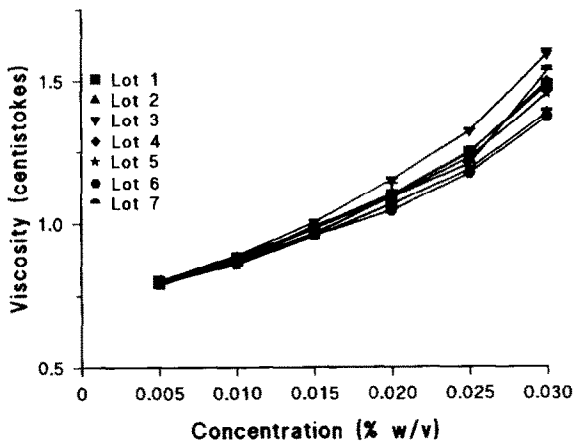

Fig. 4. Mean viscosities of dilute aqueous dispersions of the seven carbomer 934 lots studied, as measured with a Canon-Fenske U-type viscosimeter.

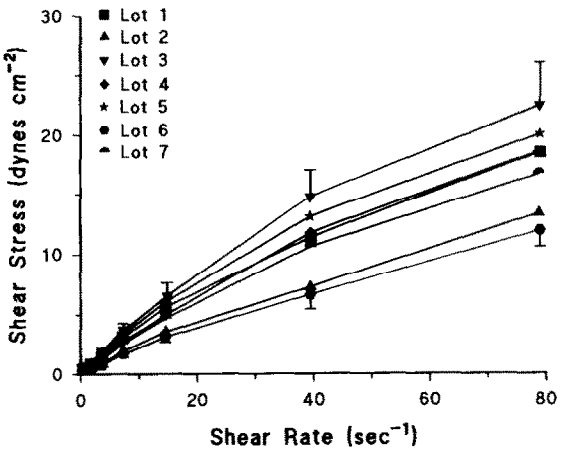

Fig. 5. Mean shear stress-shear rate curves of 0.1% w/v aqueous dispersions of the seven carbomer 934 lots studied (for clarity, standard deviations are indicated only for the most and least viscous lots).

in this work (Table 1) were slightly greater than the declared value, but very similar to each other.

The above findings show that the lots studied did not differ significantly as regards their chemical and structural characteristics.

Because of its hygroscopic nature, special attention is paid to the moisture content of carbomer (British Pharmacopoeia, 1988; The National Formulary XVII, 1990). The equilibrium moisture curves of the seven lots studied were practically identical (Fig. 3 and Table 1). At concentrations of 0.030% w/v or less, lot 3 produced the most viscous aqueous carbomer dispersions, and lot 6 the least (Fig. 4 and Table 2). In conjunction with the Mark-Houwink equation (Mark, 1938; Houwink, 1940), the intrinsic viscosities of lots 3 and 6 (Table 2), calculated by Martin's method (Bardet and Alain, 1975b), suggest that these lots have different mean molecular weights (Florence and Atwood, 1988).

The rheological behaviour of 0.1% w/v dispersions in the rotatory viscosimeter (the apparatus stipulated by The National Formulary XVII (1990), used by the manufacturer and commonly employed for characterization of highly viscous fluids) was clearly pseudoplastic (Fig. 5) (Barry and Meyer, 1979a,b). Interlot variability was considerable, with lots 3 and 6 again producing re-

TABLE 2

Mean viscosities (cSk) of dilute aqueous dispersions of carbomer lots 3 and 6 (SD in parentheses), and their intrinsic viscosities.

Lot	Concentration (% w/v)					Intrinsic viscosity (ml g^{-1})
	0.010	0.015	0.020	0.025	0.030	
3	0.8910 (0.0064)	1.0036 (0.0073)	1.1516 (0.0043)	1.3232 (0.0043)	1.5888 (0.0177)	17.870
6	0.8597 (0.0115)	0.9589 (0.0167)	1.0425 (0.0201)	1.1732 (0.0032)	1.3730 (0.0221)	15.636

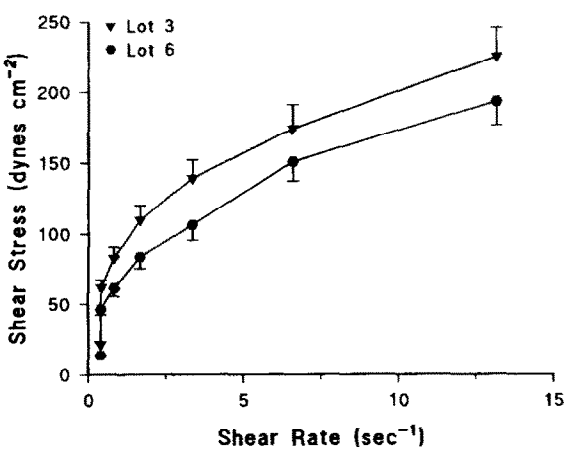

Fig. 6. Shear stress-shear rate curves (mean ± SD) of 0.2% w/v aqueous dispersions of lots 3 and 6.

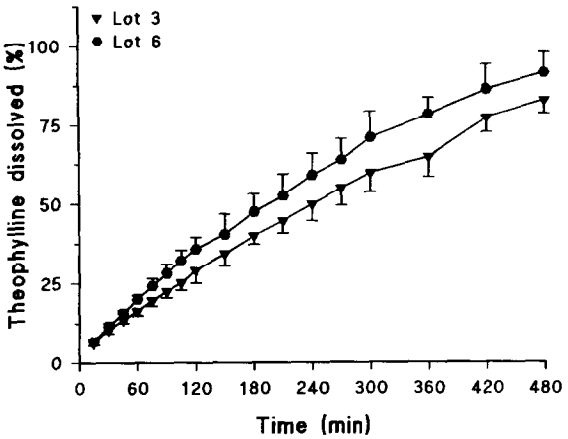

Fig. 7. Cumulative dissolution curves (mean ± SD) of theophylline tablets made with carbomer lots 3 and 6.

spectively the most and the least viscous dispersions. These two lots also differed (Fig. 6) as regards the behaviour of 0.2% w/v dispersions (one of the standard concentrations used for characterization of carbomers) (BFGoodrich, 1985; American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, 1986; British Pharmacopoeia, 1988; The National Formulary XVII, 1990)

In recent years, a considerable amount of research has been performed on the controlled release of various drugs from carbomer matrices

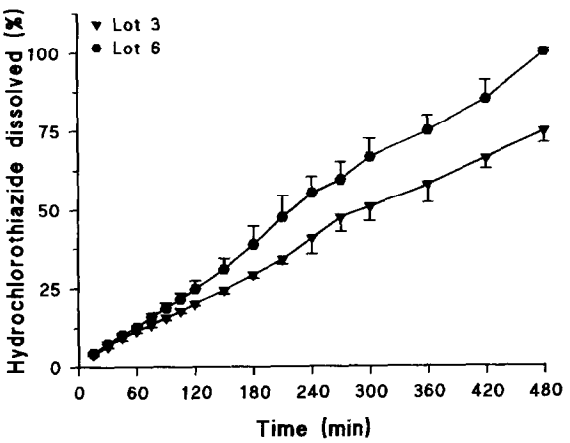

Fig. 8. Cumulative dissolution curves (mean ± SD) of hydrochlorothiazide tablets made with carbomer lots 3 and 6.

TABLE 3

Results of fitting Higuchi's equation or the zero-order kinetic equation to the data for release of, respectively, theophilline and hydrochlorothiazide from matrices of lot 3 and lot 6 carbomer: rate constants and correlation coefficients

Lot	Theophilline		Hydrochlorothiazide	
	k (% min$^{-1/2}$)	r	k (% min^{-1})	r
3	4.363	0.9819	0.155	0.9912
6	4.943	0.9806	0.208	0.9899

(Vázquez et al., 1992). To investigate the potential influence of the above viscosity differences on the quality of carbomer-based dosage forms, we studied the rate of release of two drugs with widely differing solubilities in water (theophylline and hydrochlorothiazide) from matrices of lot 3 and lot 6 carbomer. Release of both drugs was slower from the matrix composed of the more viscous carbomer (Figs 7 and 8). As previously reported for carbomer matrices, release kinetics depended on the solubility of the active principle in water: theophylline release complied with Higuchi's equation, while hydrochlorothiazide release exhibited zero-order kinetics (Table 3) (Pérez-Marcos et al., 1991a,b). For both drugs, there was a statistically significant difference between the kinetic constants determined for lot 3 and lot 6 matrices ($p > 0.99$ from Wilcoxon's test). The fact that the difference was greater for hydrochlorothiazide than for theophylline may be attributed to the difference between the release mechanisms involved in the two cases (Vázquez et al., 1992).

Conclusions

In spite of the chemical and structural similarity of the seven carbomer 934 lots studied, they differed considerably as regards the rheological behaviour of their aqueous dispersions, possibly due to differences in mean molecular weight. These differences had a significant effect on the rates at which theophylline and hydrochlorothiazide were released from carbomer matrices.

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References

American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, *Handbook of Pharmaceutical Excipients,* The Pharmaceutical Press, London, 1986, pp. 41–42.

Bardet, L. and Alain, M., Caractérisation physicochimique d'un haut polymere d'acide acrylique utilisé en pharmacie: I. Détermination de la tacticité. *Trav. Soc. Pharm. Montpellier,* 35 (1975a) 257–262.

Bardet, L. and Alain, M., Caractérisation physicochimique d'un haut polymere d'acide acrylique utilisé en pharmacie: II. Détermination de la masse moléculaire. *Trav. Soc. Pharm. Montpellier,* 35 (1975b) 263–272.

Barry, B.W. and Meyer, M.C., The rheological properties of Carbopol gels: I. Continuous shear and creep properties of Carbopol gels. *Int. J. Pharm.,* 2 (1979a) 1–25.

Barry, B.W. and Meyer, M.C., The rheological properties of Carbopol gels: II. Oscillatory properties of Carbopol gels. *Int. J. Pharm.,* 2 (1979b) 27–40.

BFGoodrich Co., *Bulletin Carbopol®* Water Soluble Resins, Cleveland, 1985.

British Pharmacopoeia, HMSO, London, 1988, pp. 98–99.

Cohen, J.L., Theophylline. In Florey, K. (Ed.), *Analytical Profiles of Drug Substances,* Vol. 4, Academic Press, New York, 1975, pp. 466–493.

Concheiro, A., Vila-Jato, J.L., Martínez-Pacheco, R., Seijo, B. and Ramos, T., Effect of aging on the bioavailoability of nitrofurantoin tablets contaning Carbopol 934. *Drug Dev. Ind. Pharm.,* 13 (1987) 501–516.

Cosmetic, Toiletry and Fragrance Association, Final report on the safety assessment of Carbomers -934, -910, -934P, -940, -941 and -962. *J. Am. Coll. Toxicol.,* 1 (1992) 109–41.

Deppeler, H.P., Hydrochlorothiazide. In Florey, K. (Ed.), *Analytical Profiles of Drug Substances,* Vol. 10, Academic Press, New York, 1981, pp. 405–441.

Doelker, E., Water-swollen cellulose derivatives in pharmacy. In Peppas, N.A. (Ed.), *Hydrogels in Medicine and Pharmacy,* Vol. 2, Polymers, CRC Press, Boca Raton, 1987, pp. 115–160.

Florence, A.T. and Attwood, D., *Physicochemical Principles of Pharmacy,* 2nd Edn, Macmillan, Houndmills, 1988, pp. 282–334.

Graf, E., Fawzy A.A. and Tsaktanis, J., Interaction of Carbopol® 934 with diphenhydramine and dexchlorpheniramine. *Acta Pharm. Tech.,* 29 (3) (1983) 209–215.

Higuchi, T., Mechanism of sustained-action medication. theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.,* 52 (1963) 1145–1149.

Higuchi, W.I., Analysis of data on the medicament release from ointments. *J. Pharm. Sci.,* 51 (1962) 802–804.

Houwink, R., Relation between the polymerization degree determined by osmotic and viscosimetric methods. *J. Prakt. Chem.,* 157 (1940) 15–18.

Mark, H., The formation and properties of highly polymerized solids. *Der. Feste Körper,* 31 (1938) 64–104.

Martínez-Pacheco, R., Gómez-Amoza, J.L. and Vila-Jato, J.L., Diseño de un sistema de registro de presión en máquinas de comprimir excéntricas. *Cienc. Ind. Farm.,* 4 (1985) 207–211.

Pérez-Marcos, B., Gutiérrez C., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C. and Concheiro, A., Usefulness of certain varieties of Carbomer in the formulation of hydrophilic furosemide matrices. *Int. J. Pharm.,* 67 (1991a) 113–121.

Pérez-Marcos, B., Iglesias, R., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C. and Concheiro, A., Mechanical and drug-release properties of atenolol-Carbomer hydrophilic matrix tablets. *J. Controlled release,* 17 (1991b) 267–276.

Perotti, A.G., I Carbossivinilpolimeri nella tecnica farmaceutica. *Il Farmaco. Ed. Prat.,* 11 (1970a) 651–688.

Perotti, A.G., I Carbossivinilpolimeri nella tecnica farmaceutica. Parte II. *Il Farmaco. Ed. Prat.,* 12 (1970b) 721–743.

Secard, D., Carbopol pharmaceutical. *Drug Cosm. Ind.,* 90 (1962) 28–116.

Siegel, S. and Castellan, N.J., *Nonparametric Statistics for the Behavioral Sciences,* McGraw-Hill, New York, 1988, pp. 73–101.

The National Formulary XVII, US Pharmacopeial Convention, Rockville, 1990, pp. 1910–1911.

US Pharmacopeia XXII, US Pharmacopeial Convention, Rockville, 1990, pp. 1578–1580.

Vázquez, M.J., Pérez-Marcos, B., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C. and Concheiro, A., Influence of technological variables on release of drugs from hydrophilic matrices. *Drug Dev. Ind. Pharm.,* 18 (1992) 1355–1375.

Vila-Jato, J.L., Concheiro, A. and Seijo, B., 'In vitro'-'in vivo' correlations of eight nitrofurantoin tablet formulation: effect of various technological factors. *Drug Dev. Ind. Pharm.,* 13 (1987) 1315–1327.