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Journal of Pharmaceutical and Biomedical Analysis
30 (2002) 1355–1359

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

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Short communication

Simultaneous determination of ibuprofen and hydroxypropylmethylcellulose (HPMC) using HPLC and evaporative light scattering detection

Madelaine R. Whelan, James L. Ford, Mark W. Powell *

School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK

Received 25 March 2002; received in revised form 17 June 2002; accepted 17 June 2002

Abstract

Ibuprofen may be crystallised in the presence of hydroxypropylmethylcellulose (HPMC) to improve its physical properties. This, however, creates problems with the simultaneous analysis of each ingredient. The analytical method developed utilised high performance liquid chromatography (HPLC) with a stationary phase designed for carbohydrate separation (GylcoSep N) and a mobile phase comprising methanol and water. Evaporative light scattering detection (ELSD) proved a suitable method for the analysis of both HPMC and ibuprofen. Data showed that HPMC and ibuprofen could be quantified in each other's presence. Validation studies indicated that the method was adequately accurate and precise. Baseline resolution was achieved between the two components. HPMC (1.1% w/w) was retained in ibuprofen crystals obtained from alcoholic HPMC suspensions.

Keywords: Hydroxypropylmethylcellulose (HPMC); Ibuprofen; Evaporative light scattering detection (ELSD); High performance liquid chromatography (HPLC)

1. Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug. It suffers from inherent formulation difficulties, which include poor compaction and low solubility [1]. Crystal structure can affect the physical, mechanical and processing properties of a material [2]. Crystallisation or precipitation of a material can change its structure. The presence of additives during crystallisation can further induce a change in crystalline form leading to the production of a product with desirable physical properties. The result can be a change in the crystal habit or polymorph.

The crystallisation of ibuprofen has been undertaken by many researchers to improve formulation [3–5]. Methanol was used to produce ibuprofen crystals with good flow and improved compaction [6]. Other solvents, e.g. sulphuric acid, benzene, dichloromethane or polyethylene glycol may alter the habits of ibuprofen [7]. Crystallisation of ibuprofen with polyvinylpyrrolidone (PVP) [8],

* Corresponding author. Tel.: +44-151-231-2494; fax: +44-151-231-2170
E-mail address: m.w.powell@livjm.ac.uk (M.W. Powell).

0731-7085/02/$ - see front matter
PII: S0731-7085(02)00394-1

has also improved the compaction characteristics and mechanical properties of ibuprofen.

Hydoxypropylmethylcellulose (HPMC) is a cellulose ether whose properties depend on the type and degree of substitution [9,10]. HPMC has been used during recrystallisation of other drugs [11] and to modify the crystal structure and ultimately the compression properties of ibuprofen [12]. This was achieved by adding ibuprofen to a suspension of HPMC in ethanol (ibuprofen-HPMC ratio 10:1), heating to 70 °C and precipitating with water.

Methods exist for the analysis of HPMC [13] and ibuprofen [14–16] separately. To the best of our knowledge, however, none exist for their simultaneous determination. Ibuprofen and its main degradation product have been determined in different pharmaceutical products, using liquid chromatography [17]. HPMC has also been examined by size exclusion chromatography [18–20].

In the present study, a method capable of simultaneously quantifying HPMC and ibuprofen was developed using evaporative light scattering detection (ELSD) to analyse the content of ibuprofen crystallised from HPMC suspensions. HPLC-ELSD is an established technique for the determination of a variety of compound types [21–24]. It is particularly suited to the analysis of involatile solutes that do not possess a chromophore, such as HPMC.

2. Experimental

2.1. Chemical and reagents

Ibuprofen B.P. was obtained from Knoll Pharmaceuticals (Nottingham, UK). HPMC 2208 (Methocel K100M) was obtained from Dow Chemical Co., Midland, USA. HPLC grade methanol and ethanol were supplied by Mallinckrodt Baker (Milton Keynes, UK) and BDH Limited (Poole, UK), respectively.

2.2. Calibration standards

Ibuprofen standard solutions contained 0.1, 0.2, 0.4 or 0.8% w/v ibuprofen diluted with the mobile phase. HPMC standards containing 0.02, 0.04, 0.06 or 0.08% w/v HPMC were prepared by dissolving 0.1 g of HPMC in 40 ml of water at 80 °C under constant stirring. The dispersion was allowed to cool and 60 ml of methanol was added to overcome the formation of a gel like mass, which occurs when HPMC is added to cool water [16]. This solution was made up to 100 ml with methanol and diluted to the above concentrations with mobile phase.

Combined ibuprofen and HPMC standard solutions were prepared by dissolving 0.1 g HPMC in 40 ml water at 80 °C, as above. This solution was then cooled and added to 60 ml methanol containing 1.0 g ibuprofen. The resulting solution, made up to 100 ml with methanol, contained 1.0% w/v ibuprofen and 0.1% w/v HPMC. Six calibration standards were prepared containing both HPMC and ibuprofen. The concentrations of HPMC in each standard were 0.01, 0.02, 0.03, 0.04, 0.05 and 0.07% w/v, and the corresponding ibuprofen concentrations were 0.1, 0.2, 0.3, 0.4, 0.5 and 0.7% w/v.

2.3. Preparation of ibuprofen crystals containing HPMC

Samples were prepared by dispersing 0.5 g HPMC in 50 ml ethanol with constant stirring at 40 °C [11]. Ibuprofen (5 g) was added and the dispersion heated to 70 °C. The solution was then added to 500 ml ice cold water. Precipitated crystals were filtered using a Whatman No. 3 filter and dried for 24 h at 45 °C. A portion of the resulting solid (0.5 g) was dissolved in mobile phase (100 ml) to give a solution containing approximately 0.5% w/v ibuprofen.

3. HPLC conditions

The HPLC system comprised an isocratic pump (Model SA 6410C, Severn Analytical, Coventry, UK), an on-line vacuum degasser (Model DEG-103, Kontron Instruments, Watford, UK), a Hewlett–Packard autosampler (1050 Series, Agilent Technologies, Cheadle, UK) and an evaporative light scattering detector (Model 750/14,

Polymer Laboratories Limited, Shropshire, UK). A GlycoSep N column (250 × 4.6 mm i.d, Oxford Glycosystems, Oxford, UK), maintained at ambient temperature, was used to separate the two components. Data collection and analysis was performed using either an Xchrom data system (Lab Systems Limited, Altrincham, UK) or a Spectra Physics data jet integrator (Thermoquest Limited, Hemel Hempsted, UK).

Hundred microliter aliquots of standard and sample solutions were injected onto the HPLC system. The mobile phase comprised methanol:-water (60:40 v/v) at a flow rate of 1.0 ml min^{-1}. The detector desolvation temperature was 60 °C and the nitrogen nebulising gas flow rate was 10 l min^{-1}.

3.1. Method performance

Precision (R.S.D.) and bias were estimated by performing replicate analysis of three solutions. The solutions were made up independently and five determinations of each were performed. The test solutions were, (i) 0.02% w/v HPMC; (ii) 0.1% w/v ibuprofen; and (iii) a mixture containing 0.3% w/v ibuprofen and 0.05% w/v HPMC. The three test solutions were prepared in the same way as the calibration standards.

4. Results and discussion

4.1. Method development

Chromatographic conditions were selected in order to achieve separation of ibuprofen from HPMC in a relatively short time. A typical standard chromatogram is shown in Fig. 1. All chromatograms were similar in appearance, there being no other matrix material present to introduce additional peaks. The resolution (R_s) between ibuprofen and HPMC peaks in this chromatogram is 3.28. Limits of detection were estimated at signal:noise ratios of 3:1. These were 7×10^{-3} and 3×10^{-3}% w/v for ibuprofen and HPMC, respectively.

The mean retention time of a series of individual ibuprofen standards was 2.93 min with a R.S.D. of 0.49% ($n = 10$) and the mean retention time of a series of individual HPMC standards was 1.65 min with a R.S.D. of 1.7% ($n = 10$). The retention times of HPMC and ibuprofen from mixed solutions were not significantly different (1.64 min and 3.03 min, respectively), with corresponding R.S.Ds of 2.31 and 2.18% ($n = 10$). Because of the height of the detector, and the relatively short length of connecting tubing supplied, it was not possible to mount the column in a heater. This is thought to account for the greater variability of the second set of data, since the first set were acquired overnight when temperature variation would have been relatively small.

4.2. Analysis of ibuprofen–HPMC mixtures

Linear calibrations were established for ibuprofen and HPMC using the calibration standards described above. The linear equation for the ibuprofen calibration curve was $y = 10040x + 89.15$, with an associated R^2-value of 0.9957. The corresponding data for HPMC were $y = 57620x - 26.29$ with $R^2 = 0.9983$. Calibration curves constructed using the combined standard yielded similar equations, with R^2-values of 0.9949 and 0.9967 for ibuprofen and HPMC, respectively. Precision and bias were estimated by performing replicate analysis on three separate concentrations of ibuprofen, HPMC and ibuprofen/HPMC mixes. The peak area R.S.D. for the components when analysed individually was 3.3% for HPMC and 0.79% for ibuprofen. When analysed as a mixed sample, R.S.D.s of 3.6 and 7.3% were observed for HPMC and ibuprofen, respectively. The larger R.S.D.s for the second data set are almost certainly a consequence of the integrator assigning different lift-off times for the ibuprofen peak, which is very slightly fronting (Fig. 1), following elution of the HPMC peak. A more consistent integration would probably be achieved by dropping a perpendicular from the valley between the two peaks to the baseline.

Comparison of the nominal and calculated concentrations of the three test solutions yielded the following recovery data. The mixed sample gave recoveries of 101 and 106% for HPMC and ibuprofen, respectively. The corresponding data

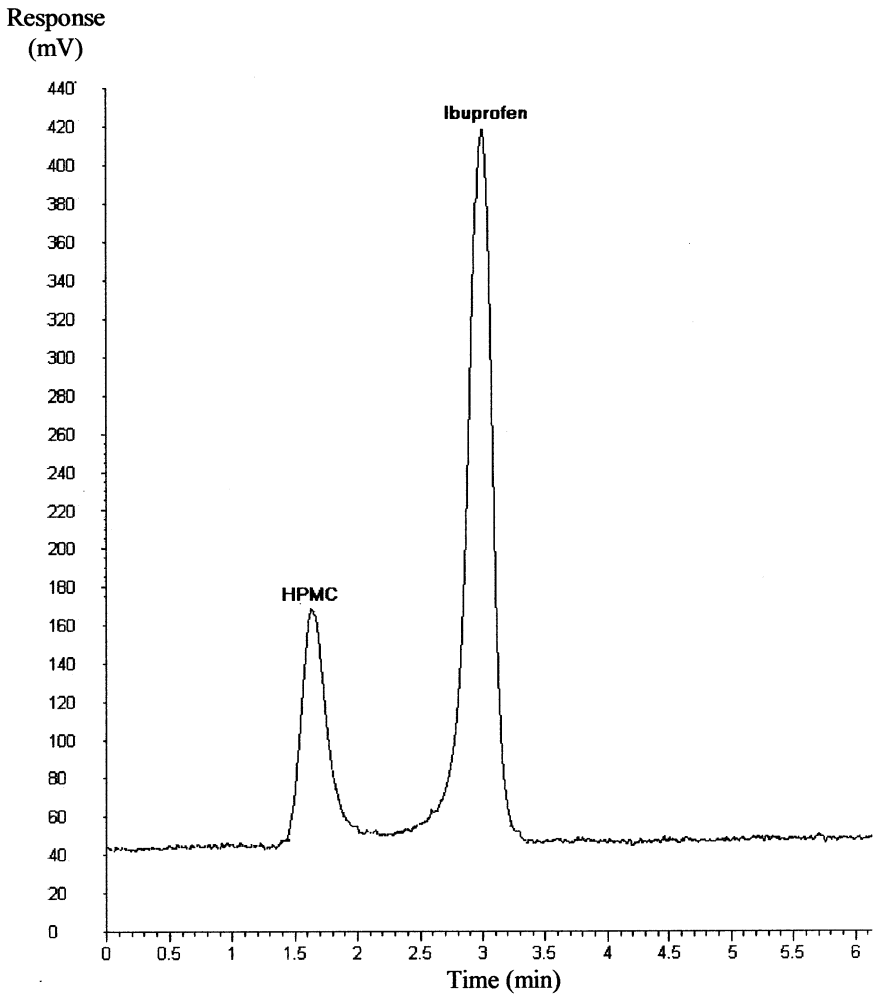

Fig. 1. Chromatogram of a combined standard containing HPMC and ibuprofen at 0.03 and 0.3% w/v, respectively.

for individual solutions were 86% for HPMC and 130% for ibuprofen. It is not surprising that the combined samples should show less bias when quantified against combined standards, given the probability of differences in integration outlined above. Fronting of the ibuprofen peak results in a contribution from ibuprofen to the HPMC peak area in the combined standard, and, similarly, an underestimation of the ibuprofen peak area. A more sophisticated approach to integration is required in order to correct this discrepancy.

Previously published work indicated that ibuprofen recrystallised in the presence of HPMC possessed improved compaction properties [12]. Tablets formed from this material showed an improvement in tensile strength and a reduced tendency to cap or laminate. The authors thought that recrystallisation in the presence of HPMC might lead to the inclusion of some HPMC in the ibuprofen crystals. X-ray diffraction studies are planned to confirm this hypothesis. Analysis of the recrystallised ibuprofen sample showed that

HPMC was present. The chromatograms of the sample showed two distinct peaks at retention times of approximately 1.65 and 2.9 min. The recrystallised sample contained 98.9% w/w ibuprofen and 1.1% w/w HPMC.

5. Conclusion

The simultaneous determination of ibuprofen and HPMC was achieved using HPLC with ELSD. The method was employed to quantify HPMC in ibuprofen recrystallised in the presence of the cellulose-based excipient. The recrystallised sample contained 98.9% w/w ibuprofen and 1.1% w/w HPMC. One tenth of the HPMC added initially was retained in the crystals.

References

[1] L.K. Ghosh, N.C. Ghosh, M. Chatterjee, B.K. Gupta, Drug Dev. Ind. Pharm. 24 (1998) 473–477.
[2] P. York, Int. J. Pharm. 14 (1983) 1–28.
[3] I. Ludlam-Brown, The Physiochemical and Compaction Properties of Powders Modified by Alternative Crystallisation Conditions. Ph.D. thesis, University of Bradford, 1991.
[4] A.J. Romero, C.T. Rhodes, Drug Dev. Ind. Pharm. 17 (1991) 777–792.
[5] M. Jbilou, A. Ettabia, A.-M. Guyot-Hermann, J.-C. Guyot, Drug Dev. Ind. Pharm. 25 (1999) 297–305.
[6] R.E. Gordon, S.I. Amin, European Patent No 0120587A1, 1984.
[7] V. Labhasetwar, S.V. Deshmukh, A.K. Dorle, Drug Dev. Ind. Pharm. 19 (1993) 631–641.
[8] M. Nesic, N. Cvetkovic, D. Polic, Acta Pharm. Jugosl. 40 (1990) 545–550.
[9] K. Jumel, S.E. Harding, J.R. Mitchell, K.M. To, I. Hayter, J.E. O'Mullane, S. Ward-Smith, Carbohydr. Polym. 29 (1996) 105–109.
[10] C. Alverez-Lorenzo, R.A. Lorenzo-Ferreira, J.L. Gomez Amoza, R. Martinez-Pacheo, C. Sonto, J. Pharm. Biomed. Anal. 20 (1999) 373–383.
[11] M.N. Femioyewo, M.S. Spring, Int. J. Pharm. 112 (1994) 17–28.
[12] M.R. Whelan, J.L. Ford, M.H. Rubinstein, A.R. Siahboomi, J. Pharm. Pharmacol. 52 (2000) 152.
[13] United States Pharmacopeia 23, 774, United States Pharmacopeial Convention, Rockville, Maryland, USA, 1995.
[14] British Pharmacopoeia, 1, 307, HMSO, London, UK, 1988.
[15] S. Ojantakanen, M. Marvola, A.-M. Hannula, E. Klinge, T. Naukkarinen, Eur. J. Pharm. Sci. 1 (1993) 109–114.
[16] J.D. Higgings, T.P. Gilmor, S.A. Martellucci, R.D. Bruce, H.G. Brittain, Ibuprofen, in: E.G. Brittain (Ed.), Analytical Profiles of Drug Substances and Excipients, vol. 27, Academic Press, 2001, p. 265.
[17] A. Gasco-Lopez, R. Izquierdo-Hornillos, A. Jiminez, J. Pharm. Biomed. Anal. 21 (1999) 143–149.
[18] G. Delker, C. Chen, R.B. Miller, Chromatographia 41 (1995) 263–265.
[19] K. Mitchell, A study of factors controlling drug release from matrices containing cellulose ethers, Ph.D. thesis, Liverpool John Moores University, 1992.
[20] S.S. Cutie, C.G. Smith, J. Chromatogr. A 693 (1995) 371–375.
[21] D.A. Skoog, J.J. Leary, Principles of Instrumental Analysis, fourth ed., Saunders College Publishing, USA, 1992.
[22] B. Toussaint, A.L.L. Duchateau, S. van der Wal, A. Albert, P. Hubert, J. Crommen, J. Chromatogr. A 890 (2000) 239–249.
[23] B.J. Stith, J. Hall, P. Ayres, L. Waggoner, J.D. Moore, W.A. Shaw, J. Lip. Res. 41 (2000) 1448–1453.
[24] D. Berner, A. Dieffenbacher, Pure Appl. Chem. 71 (1999) 1983–1991.