ELSEVIER

International Journal of Pharmaceutics 146 (1997) 1–9

international journal of pharmaceutics

Research papers

Use of canonical and other analyses for the optimization of an extrusion–spheronization process for indomethacin

Michelle F.L. Law, P.B. Deasy*

Department of Pharmaceutics, Trinity College, University of Dublin, Shrewsbury Road, Dublin 4, Ireland

Received 2 August 1996; accepted 5 September 1996

Abstract

Preliminary experiments with indomethacin 40%, microcrystalline cellulose 20% and lactose 40% wetted with optimum water content, produced pellets in low yield and with poor sphericity, using an extrusion–spheronization process. The difficulty in processing the drug was overcome principally by modifying the formulation to include a newly developed spheronization aid composed of one part hydrophilic polymer coprocessed with 19 parts microcrystalline cellulose by spray-drying. Alternatively addition of 0.5% polyvinylpyrrolidone and 1.25% sodium lauryl sulphate was helpful. When processed under optimum water content and experimental conditions, developed using factorially designed experiment, products with variable dissolution profile and superior sphericity to the proprietary pelletized product, Indocid-R, were produced in high yield. The use of canonical analysis to aid interpretation of experimental results is described.

Keywords: Extrusion–spheronization; Indomethacin; Spheronization aids; Factorial experiments; Canonical analysis

1. Introduction

Indomethacin is a non-steroidal anti-inflammatory drug widely used orally in the treatment of rheumatoid and other disorders. Conventional dosage forms are associated with producing a high incidence of gastrointestinal disturbances as the most common side-effect, the occurrence and severity of which is dose and plasma spike related. The major commercial controlled release dosage form in Ireland is Indocid-R, which has been reported to have a disappointing in vivo profile in humans (Quinn et al., 1993). This project is concerned with the development of a competitor product to Indocid-R by extrusion-spheronization without subsequent coating, using optimization

* Corresponding author. Tel.: + 353 1 2693333; fax: + 353 1 2696457.

0378-5173/97/$17.00
PII S0378-5173(96)04741-2

experiments subject to the novel technique of canonical analysis. Acceptance criteria for products are high yield and adequate sphericity. More extensive in vitro dissolution and also comparative bioavailability testing of selected products against Indocid-R will be reported later.

Canonical analysis is a statistical technique whereby a simplified equation without cross-product terms is produced to augment an understanding of the effect of the process variables leading to optimization. The technique has been used in pharmaceutical applications and has been reviewed by Gonzalez (1993) for the optimization of tablet formulations, based on response surface designs. However the procedure is not widely used in pharmaceutical optimization experiments, possibly due to the complexity of the matrix calculations involved, or simply due to the fact that its usefulness has not been publicised adequately.

2. Materials and methods

2.1. Materials

Citric acid monohydrate (Merck), di-sodium hydrogen phosphate dodecahyrdate, sodium dihydrogen phosphate dihydrate (Riedel de Haen), hydrochloric acid, paraffin wax, sodium carboxymethylcellulose, low viscosity, NaCMC, sodium chloride (BDH), hydroxypropyl cellulose (HPC) (LF, Colorcon), hydroxypropylmethyl cellulose (HPMC) (E50, Dow), Indocid-R capsules batch no 922476 (Thomas Morson), indomethacin (20 μm, Ind. Chimica Farmaceutica, Italy), lactose alpha monohydrate (Granulac 200 mesh, Meggle), microcrystalline cellulose (MCC) (Avicel PH-101, FMC), polyvinylpyrrolidone (PVP) (Povidone K24-26, GAF), Precirol (ATO5, Gattefosse), sodium lauryl sulphate (SLS) (Sigma) and glass-distilled water were used. All reagents were GPR unless otherwise indicated.

2.2. Preparation of pellets

Dry powders were mixed for 10 min in a planetary mixer (Kenwood) and then wetted by gradual addition of the required volume of water. After being stored for 12–24 h in a sealed container to ensure uniform hydration of the mix, the wetted mass was extruded through a 1 mm diameter screen using a gravity fed cylinder extruder (Alexanderwerk GA 65). The extrudate formed was spheronized on a Caleva 120 mini spheronizer fitted with a cross-hatch cut stainless-steel friction plate.

2.3. Sieve analysis and yield of pellets

Sieve analysis on either the whole batch or on random samples obtained by a splitting technique was performed using a nest of standard sieves, 1680, 1180, 850 and 300 μm, agitated for 10 min on a sieve shaker (Endecott) and retained weight data obtained was used to construct a frequency distribution. The desired size of pellets was in the range 850–1180 μm and is referred subsequently to as 'pellets'. Those which occurred above this size range are referred to as 'large pellets', while those below are referred to as 'fines'.

2.4. Image analysis of pellets

The sphericity of the pellets was determined using derived pellet parameters measured by an image analysis system (Quantimet 520, version 4.0, linked to an Ergolux microscope, Cambridge Instruments). A random sample of 200 pellets approx from each batch of product was examined and a roundness function was calculated as follows:

$$\text{Roundness factor} = \frac{P_{m^2}}{4\pi A}$$

where P_m is the perimeter length and A is the projected area. A perfectly round pellet would have a value of 1.0 irrespective of size and the value would tend towards 10.0 for pellets that were progressively non-spherical. However in order to facilitate a correlation between increasing sphericity value and increasing pellet roundness, the reciprocal of the roundness factor was calculated and termed 'sphericity', where values tending toward 0.1 denote progressive lack of roundness and 1.0 indicates a perfect sphere.

2.5. Preparation of spray-dried mixes

The polymer and microcrystalline cellulose in the ratio of 1:19 were prepared as a 10% solids dispersion in water and the continuously agitated slurry was spray-dried using a mini spray-dryer (Buchi 190) with optimized settings of delivery rate at 5 ml/min, air flow rate at 600 NI/h and inlet temperature at 125°C.

2.6. Dissolution studies

Flat-faced 13 mm diameter discs were compressed from 250 mg of 1:1 indomethacin:excipient mix prepared under an 8 t load for 10 min using a hydraulic press (Perkin-Elmer). After mounting with paraffin wax in stainless steel dies with one exposed face, each disc was subjected to intrinsic dissolution testing at 37°C for 6 h (unless premature detachment occurred) in 1 l of Sorensen buffer pH 6.8 using a paddle rotating at 100 rpm, located 15 mm above the disc face (Erweka DT6).

Samples of pellets containing drug were agitated at 100 rpm in 1 l pH 6.8 medium at 37°C in an EP dissolution basket assembly (Erweka DT6), where adequate sink conditions existed. Samples (5 ml) were withdrawn periodically with immediate replacement of the dissolution medium, and following filtration through a 0.45 μm filter (Gelman), were assayed by UV spectroscopy (Shimadzu UV-160) at 318 nm.

2.7. Statistical analysis of data

The statistical package used in the analysis of experiments was Minitab Release for Windows, version 10.1 (Minitab). All tests were conducted at 0.05 level of significance. The second-order equation for canonical analysis was obtained by calculations proposed by Box and Draper (1987).

3. Results and discussion

3.1. Preliminary studies

Indomethacin is a poorly wettable and water soluble drug with high static behaviour, which could prove difficult to successfully extrude and spheronize. A preliminary mix of 40% drug, 20% MCC and 40% lactose wetted with optimum additional water (40%) still tended to give a dry, friable product with many dumbells, confirming that the inclusion of indomethacin would pose difficulties during extrusion–spheronization. Similar findings were reported by Pinto et al. (1992), even when examining formulations containing less than 10% indomethacin.

In an attempt to obtain a satisfactory product with reasonable drug loading, addition excipients were considered necessary. Apart from influencing yield and sphericity of the product, such materials could also affect drug release. Spray-dried mixes of various hydrophilic polymers:MCC 1:19 had been shown previously by us (Law and Deasy, 1996a) to aid extrusion–spheronization. Among a range of other excipients examined, SLS and Precirol were shown to enhance sphericity of a model spheronized product (Law and Deasy, 1996b), apart from the additional effect of SLS improving the dissolution of indomethacin as reported by Najib and Suleiman (1985) and Singla and Mediratta (1988). As a preliminary screen based on intrinsic dissolution testing, Fig. 1 shows the release of drug from compacts prepared from 250 mg mixes of drug with an equal ratio by weight of each of the excipients, compared with an equivalent mix with MCC as control. In general, inclusion of polymers resulted in faster drug release

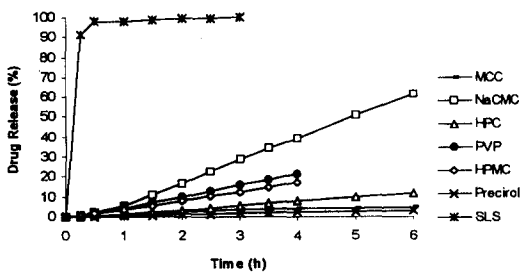

Fig. 1. Dissolution profile of indomethacin from drug:excipient 1:1 compressed discs into phosphate buffer pH 6.8 at 37°C. The key indicates the excipient identity.

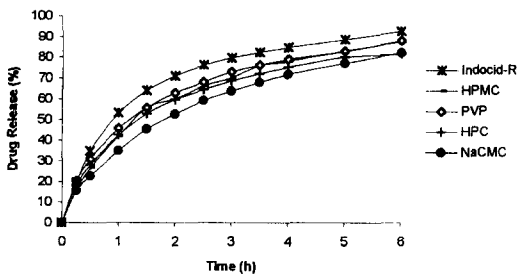

Fig. 2. Dissolution profile of indomethacin from pellets containing 30% drug, 30% spray-dried polymer:MCC 1:19 and 40% lactose into phosphate buffer pH 6.8 at 37°C, compared to Indocid-R pellets. The key indicates the excipient identity.

after an initial lag, the effect being most marked for the NaCMC containing material and attributable to progressive swelling and disintegration of discs, causing those containing PVP or HPMC to prematurely detach from their holder after 4 h. The low release rate obtained from discs prepared with MCC, confirms that this excipient can retard drug release in addition to acting as a spheronizer enhancer. The effect of inclusion of SLS or Precirol is also shown in Fig. 1, where the surfactant promoted almost 100% drug release in 30 min and the waxy material reduced drug release below the control.

Formulations containing 30% indomethacin, 30% spray-dried polymer:MCC 1:19 and 40% lactose, moistened with additional 30% water, were subject to extrusion–spheronization and the dried pellets obtained were dissolution tested, producing the results illustrated in Fig. 2. In contrast to the intrinsic dissolution results on compacts shown in Fig. 1 for single excipient mixes, the spray-dried form of NaCMC:MCC 1:19 produced the slowest drug release profile and none were as rapid as the proprietary product. The effect was attributed to the disintegration of MCC into primary needle shaped particles in the presence of NaCMC during spray-drying as reported by Schott (1995), augmenting its retardant action by enhanced sorption of drug onto the increased area of cellulose crystallites exposed.

Based on these preliminary studies it was decided to include PVP in formulations for pellet production, as use of spray-dried PVP:MCC 1:19 had been shown by us previously to enhance yield and sphericity in a model system (Law and Deasy, 1996a) and did not unduly retard drug release as shown in Fig. 2. In addition PVP was considered desirable, as the polymer has been reported to enhance the dissolution of indomethacin (Corrigan et al., 1985, Najib and Suleiman, 1985). It was decided also to lower the concentration of PVP:MCC as spheronization aid to 20% so as to reduce its retardant effect upon drug release. Finally it was decided to include SLS to aid drug dissolution and to help improve the sphericity of the product.

3.2. Analysis of pellet yield

In order to examine the effect of varying the level of PVP (0, 0.5, 1.0%), SLS (0, 1.25, 2.5%) and water content (22.5, 25, 27.5%) on achieving optimum pellet yield, a 3^3 full factorial experiment was performed. The extruder speed, spheronizer speed and residence time were kept constant at 60 rpm, 1250 rpm and 10 min respectively. The yield of pellets was observed to range from 52.9 to 86.9%. ANOVA of the data showed that the linear, square and interaction terms for the regression model were very significant, indicating a complex system where all the variables examined contribute to the yield of spheronized product.

The effect on pellet yield of variable water and SLS content at each of the PVP levels is shown in Fig. 3 as a series of two-dimensional contour plots. The narrowest range in yield (67.5–85%) was obtained with the mid-level of PVP, the off-centred plots obtained at lower and higher PVP level indicating that their processing conditions were sub-optimal. When the water and PVP content were varied at each level of SLS, a series of contour plots was obtained as shown in Fig. 4, indicating that use of the mid-level of PVP gave the highest and narrowest yield (74.5–85%) of pellets under the most ideal processing conditions. Finally when the water content was held constant at the low, mid- or high level, allowing SLS and PVP content to vary, contour plots as shown in Fig. 5 were obtained, indicating that maximum and narrowest pellet yield under the most optimal conditions was achieved using the mid-level of water. All the pellet yields obtained greatly exceed

those achieved in the reported preliminary experiments using a typical mix for extrusion–spheronization, indicating that the formulation modifications adopted can greatly improve and give an acceptable yield of product having tolerance to minor process variations for this difficult-to-spheronize drug.

With reference to Figs. 3–5, it can be seen that the maximal region of each plot is attenuated in the NW–SE direction. As shown above, the process yield was most centrally optimized when each variable was maintained at the mid-level, while permitting the other two variables to alter. Hence

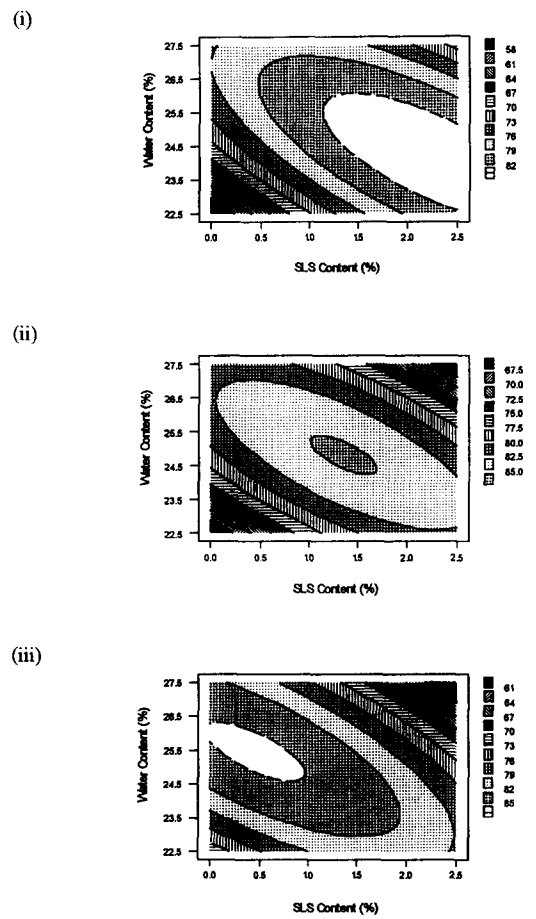

Fig. 3. Contour plots of the regression model fitted to the yield of pellets data maintaining the level of PVP constant at the (i) low level, 0%; (ii) mid-level, 0.5%; and (iii) high level, 1%. The values in the key represent the percentage yield of pellets in the desired size range 850–1180 μm.

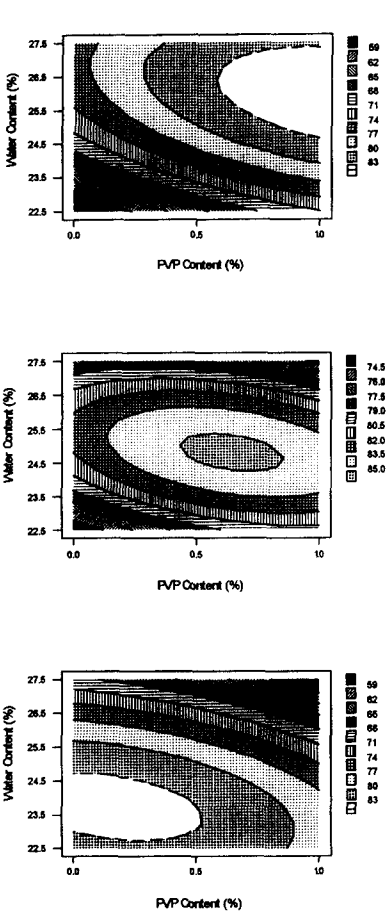

Fig. 4. Contour plots of the regression model fitted to the yield of pellets data maintaining the level of SLS constant at the (i) low level, 0%; (ii) mid-level, 1.25%; and (iii) high level, 2.5%. The values in the key represent the percentage yield of pellets in the desired size range 850–1180 μm.

canonical analysis using a series of matrix calculations was applied to equations describing the yield of pellets, when the third variable was kept constant at the mid-level, giving rise to a pseudo-three-dimensional plot of the response surface for each constant variable. The application of the *B* canonical form brings about a shift in the origin to a new point, *S*, in the centre of the contour region. The fitted equation in matrix form and its *B* canonical form obtained by the procedure, when the PVP level is maintained constant at its mid-level, is shown below and the revised contour plot is shown in Fig. 6.

$$Y_p = -718.394 + [L, W]\begin{bmatrix}78.631\\60.487\end{bmatrix} + [L, W]\begin{bmatrix}-3.287 & -1.405\\-1.405 & -1.142\end{bmatrix}\begin{bmatrix}L\\W\end{bmatrix}$$

where Y_P is yield of pellets, L is SLS level and W is water level, producing the B canonical form

$$Y_p - 85.39 = -3.98X_1^2 - 0.45X_2^2$$

The canonical equation indicates that (i) at the centre of the plot the fitted response is is $Y_P = 85.39\%$, (ii) this Y_p value is maximum because both eigenvalues are negative and (iii) due to the negative slope of the X_2 axis in the direction of the greatest elongation of the ellipsoid, the effect on pellet yield of a reduction in SLS content can be compensated for by a corresponding increase in water content. Thus it can be seen that the exact value of the optimized yield in the experimental series can be readily determined with the aid of the canonical equation.

When similar canonical analysis was applied maintaining the SLS content constant at its mid-level and allowing the PVP and water levels to vary, the visual form obtained is shown in Fig. 7 and the B canonical equation is

(i)

(ii)

(iii)

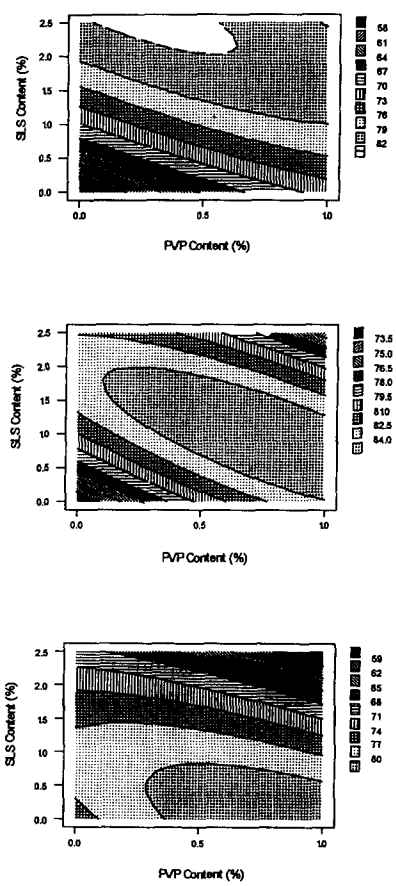

Fig. 5. Contour plots of the regression model fitted to the yield of pellets data maintaining the level of water constant at the (i) low level, 22.5%; (ii) mid-level, 25%; and (iii) high level, 27.5%. The values in the key represent the percentage yield of pellets in the desired size range 850–1180 μm.

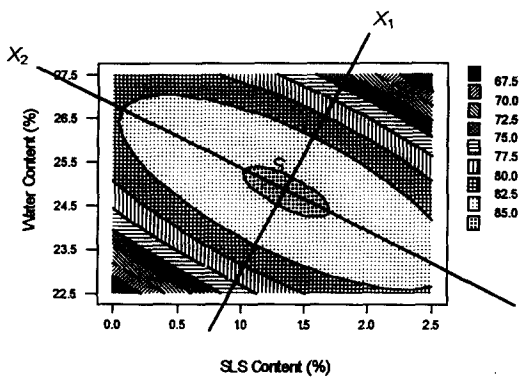

Fig. 6. Contour plot of the regression model fitted to the yield of pellets data maintaining the level of PVP constant at the mid-level (0.5%). The values in the key represent the percentage yield of pellets in the desired size range 850–1180 μm. The cross axes, X_1 and X_2 are associated with the B canonical form.

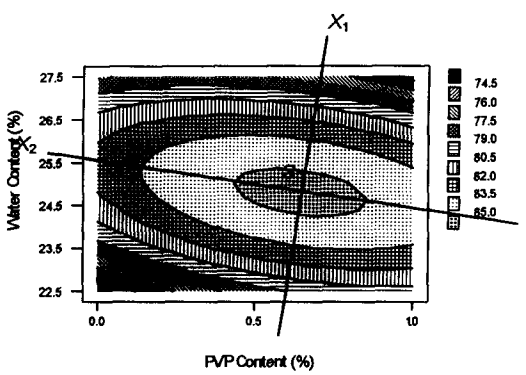

Fig. 7. Contour plot of the regression model fitted to the yield of pellets data maintaining the level of SLS constant at the mid-level (1.25%). The values in the key represent the percentage yield of pellets in the desired size range 850–1180 μm. The cross axes, X_1 and X_2 are associated with the B canonical form.

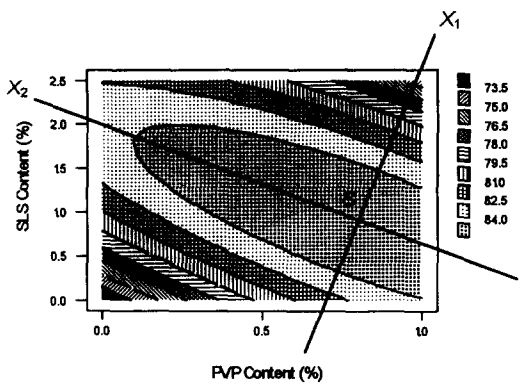

Fig. 8. Contour plot of the regression model fitted to the yield of pellets data maintaining the level of water constant at the mid-level (25%). The values in the key represent the percentage yield of pellets in the desired size range 850–1180 μm. The cross axes, X_1 and X_2 are associated with the B canonical form.

$$Y_p - 85.5 = -8.14X_1^2 - 0.98X_2^2$$

confirming achievement of 85.5% as maximum pellet yield and the interdependence of decreasing PVP content with an increasing water content. The disposition of the X_1 and X_2 axes in an almost NS-EW direction indicates that the PVP content may be varied across the range 0–1% provided the water content is maintained between 24 and 26% in order to obtain pellet yields greater than 82.5%. Likewise when similar analysis was applied keeping the water content constant at the mid-level, the result is shown in Fig. 8 and the B canonical equation is

$$Y_p - 85.61 = -10.36X_1^2 - 0.92X_2^2$$

It can be seen that pellet yields greater than 85% were obtained when each of the three variables was maintained at their mid-level and confirming the desirability of using 0.5% PVP, 1.25% SLS and 25% added water to obtain maximum pellet yield.

When canonical analysis was applied to the equation fitted to the regression model describing the full data set, the following equation was obtained.

$$Y_p - 85.62 = -10.63X_1^2 - 1.57X_2^2 - 0.21X_3^2$$

It is not possible to visually represent the contour plot as it would have to be four-dimensional. The fitted response of 85.62% is maximal and shows that canonical analysis can provide this key information even in cases where graphical representation is not feasible. However the analysis involving three variables make it difficult to visualise the effect of each variable on the process, a situation which may be overcome by maintaining one variable constant as illustrated above.

The yield of large pellets ranged from 1.7 to 46% and was acceptably low (< 10%) under optimal process conditions. The highest yield was obtained when the highest level of all three variables was employed in a single formulation. It appears that increasing water content eventually exceeded the level capable of being bound in the formulation, resulting in an increase in free water on the surface of the forming pellets promoting agglomeration. An increase in PVP content would make the surface of pellets increasingly more adhesive, promoting agglomeration. Likewise increasing SLS would promote wetting by lowering the contact angle of the added water, leading to its easier movement towards the surface of pellets to promote agglomeration, particularly under the influence of the centrifugal force applied in the spheronizer. The yield of fines ranged from 0.5 to 35.8%, being acceptably low (< 10%) when optimum process conditions were employed. Maximum yield of fines was favoured by simultaneously maintaining each of the variables at their lowest level. Hence it was concluded that conditions favouring large pellet formation where opposite to those favouring fines.

3.3. Analysis of pellet sphericity

The sphericity of the pellets was found to range from 0.838 to 0.873 over the experimental design, these relatively high values indicating that the rounding of all products was very good. ANOVA of the regression model for the sphericity data showed that the separate inclusion of PVP or SLS resulted in an increase in pellet sphericity, the effect being confounded with water content.

The effect of formulation variables on pellet sphericity was studied using contour plots exam-

ining two variables at a time, while maintaining the third variable contant at the mid-level. Fig. 9 shows the contour plot obtained while maintaining the PVP content constant, indicating that an increase in SLS content with a corresponding increase in water content resulted in an increase in pellet sphericity. However the trend seems to be more obvious for increments in SLS content than for water content, which is confirmed by the tendency for the contour lines to align parallel to the y-axis (water content). The highest value for pellet sphericity (0.87) was observed for formulations containing 2.5% SLS (and 0.5% PVP) hydrated with 25% water content. An increase in SLS content appears to facilitate plasticization of the mix by lowering the surface tension for water to penetrate and move more uniformly throughout the pellets, resulting in the production of a more spherical product.

When the SLS content was maintained constant at the mid-level of 1.25%, the contour plot obtained is shown in Fig. 10, from which it can be seen that increase in PVP content with a corresponding increase in water content resulted in an increase in pellet sphericity. The corresponding plot obtained when the water content was maintained at the mid-level of 25% is shown in Fig. 11. This latter plot shows that an increase in PVP content with a corresponding increase in SLS content resulted in an increase in pellet sphericity. This trend appears to be more obvious for increments in SLS content than for PVP content,

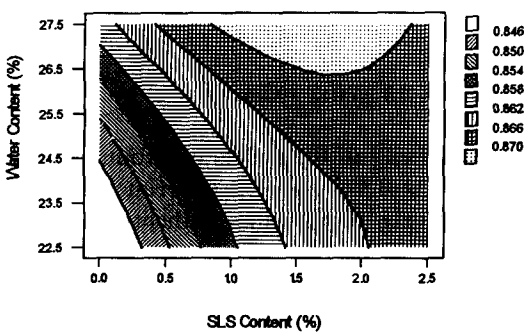

Fig. 9. Contour plot of the regression model fitted to the sphericity of pellets data maintaining the level of PVP constant at the mid-level (0.5%). The values in the key represent the sphericity of pellets in the desired size range 850–1180 μm.

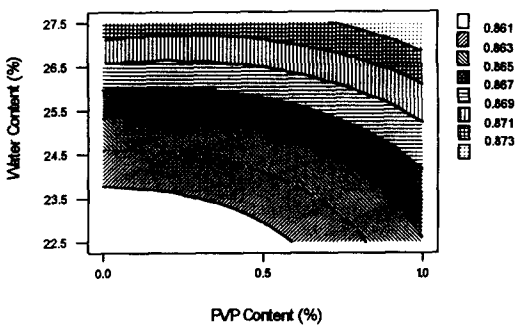

Fig. 10. Contour plot of the regression model fitted to the sphericity of pellets data maintaining the level of SLS constant at the mid-level (1.25%). The values in the key represent the sphericity of pellets in the desired size range 850–1180 μm.

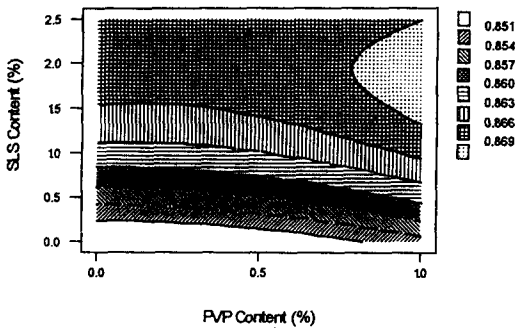

Fig. 11. Contour plot of the regression model fitted to the sphericity of pellets data maintaining the level of water constant at the mid-level (25%). The values in the key represent the sphericity of pellets in the desired size range 850–1180 μm.

which is confirmed by the tendency for the contour lines to align parallel to the x-axis (PVP content), and indicates that an increase in SLS content would have a greater effect than an increase in PVP content on improving pellet sphericity.

Image analysis of Indocid-R, the commercial brand-leader product in Ireland of indomethacin in pellet form, gave a sphericity value of 0.79, which is low in comparison to the formulation developed in this project.

References

Box, G.E.P. and Draper, N.R., Elucidation of stationary regions, maxima, and minima by canonical analysis. *Em-*

pirical Model-Building and Response Surfaces, Wiley, New York, 1987, pp. 332–345.

Corrigan, O.I., Holohan, E.M. and Reilly, M.R., Physicochemical properties of indomethacin and related compounds co-spray dried with polyvinylpyrrolidone. *Drug Dev. Ind. Pharm.*, 11 (1985) 677–695.

Gonzalez, A.G., Optimization of pharmaceutical formulations based on surface-response experimental designs. *Int. J. Pharm.*, 97 (1993) 149–159.

Law, M.F.L. and Deasy, P.B., Use of hydrophilic polymers with microcrystalline cellulose to improve extrusion-spheronization. *Eur. J. Pharm. Biopharm.*, 1996a, submitted for publication.

Law, M.F.L. and Deasy, P.B., Effect of common classes of excipients on extrusion-spheronization. *J. Microencap.*, 1996b, submitted for publication.

Najib, N.M. and Suleiman, M.S., The effect of hydrophilic polymers and surface active agents on the solubility of indomethacin. *Int. J. Pharm.*, 24 (1985) 165–171.

Pinto, J.F., Buckton, G. and Newton, J.M., The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronisation. *Int. J. Pharm.*, 83 (1992) 187–196.

Quinn, N.C., Deasy, P.B. and Donnellan, M.F., Development of a sustained-release product of indomethacin involving microencapsulation, In Kas, S.H. and Hincal, A.A. (Eds.), *Proc. 9th Int. Symp. on Microencapsulation*, Editions de Sante, Paris, 1993, pp. 99–109.

Schott, H., Colloidal dispersions, In Gennaro, A.R. (Ed.), *Remmington: The Science of Pharmacy*, 19th edn., Vol. 1, Mack, Easton, Pennsylvania, 1995, pp. 252–277.

Singla, A.K. and Mediratta, D.K., Influence of sodium lauryl sulphate on indomethacin release pattern from zinc-indomethacin complex and indomethacin capsules. *Drug Dev. Ind. Pharm.*, 14 (1988) 1883–1888.