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# In vitro evaluation of pellets containing enteric coprecipitates of nifedipine formed by non-aqueous spheronization

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**Abstract**

The process of non-aqueous spheronization was investigated for the in situ formation of an enteric coprecipitate of nifedipine with hydroxypropylmethylcellulose phthalate (HP-55) in spherical pellets. Isolated coprecipitates formed were evaluated by differential scanning calorimetry. The use of various spheronization aids such as lactose, kaolin, Aerosil 972 and 200, Bentone 27, liquid paraffin and magnesium stearate was studied using non-factorial and factorial experiments subject to statistical analysis. Products obtained were evaluated by sieve, packing density and image analysis, scanning electron microscopy and dissolution testing. The final product formed containing sodium lauryl sulphate 2% as wetting agent and sodium starch glycolate 5% as disintegrant processed with optimum solvent level, gave a high yield of acceptable spheres which showed poor drug release at low pH and enhanced release at the pH of the upper small intestine. The mechanism of pellet formation observed differed from that of conventional aqueous spheronization.

*Keywords:* Nifedipine; Hydroxypropylmethylcellulose phthalate; Enteric coprecipitates; Spheronization

## 1. Introduction

Most of the published literature on extrusion-spheronization relates to studies on model mixes containing lactose as a drug substitute/filler and microcrystalline cellulose as spheronization aid to provide plastic, cohesive and lubricant properties on being wetted with the optimum content of water. This project is concerned with a drug application, where the use of water is contraindicated because it causes reversion of an enteric drug coprecipitate formed in situ to enhance solubility in the upper small intestine of a poorly soluble drug and so aids its absorption. In the very limited published work on non-aqueous spheronization, microcrystalline cellulose has been shown to be ineffective (Millili and Schwartz, 1990) and consequently other potential spheronization aids were screened for this application.

Nifedipine is a calcium channel blocker, widely prescribed in the treatment of hypertension,

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angina pectoris and other cardiovascular disorders, which is practically insoluble in water, though more soluble at pH below 3, and hence poorly absorbed unless rendered more soluble by micronized or preferably coprecipitation technology (Sugimoto et al., 1980; Hasegawa et al., 1985a,b,c). Sustained-release multiparticulate dosage formed are preferable to help prevent the high incidence of transient side-effects such as dizziness, headache and flushing associated with plasma spikes produced by conventional oral dosage forms of the drug. Aqueous and ethanolic solutions of nifedipine are unstable in visible light (Majeed et al., 1987). A dispersion of nifedipine and the enteric polymer in a pharmaceutically acceptable solvent was added to a dry powder mix, which contained the necessary plastic components to spheronize successfully. On evaporation of the solvent, the enteric coprecipitate was a constituent of the pellet, unlike the usually employed time-consuming and highly skilled process of drug loading non-pareil seeds (Deasy, 1984), which results in the drug-polymer mix on the surface of inert sucrose cores. Because the drug has low conventional dose (10–20 mg), a low drug loading in pellets formed will still permit a reasonable bulk volume for filling into hard gelatin capsules of convenient size for oral administration.

## 2. Materials and methods

### 2.1. Materials

Acetone, ethanol, sodium acid phosphate, sodium phosphate (Riedel de Haen), Bentone 27 (Steetley Minerals), hydrochloric acid, kaolin heavy, liquid paraffin light, sodium lauryl sulphate (BDH Chemicals), hydroxypropylmethylcellulose phthalate, grade HP-55 (Shin-Etsu), lactose alpha monohydrate, grade D80 (Meggle), magnesium stearate (Organon), nifedipine, micronized (Heterochem), silicon dioxide colloidal, Aerosil grades 200 and 972 (Degussa), sodium starch glycolate, Primojel (Generichem) and glass-distilled water. All reagents were GPR unless otherwise indicated.

### 2.2. Preparation of pellets

All experiments involving the drug were carried out under sodium light. Dry powders were mixed in a planetary mixer (Kenwood) and wetted by gradual addition of the required amount of moistening agent. After being stored overnight (12 h minimum) in a sealed container to ensure uniform solvation of the mix, the wetted mass was extruded at 50 rev/min through a 1-mm diameter screen using a gravity fed cylinder extruder (Alexanderwerk GA 65). The extrudate formed ( $\sim$ 50 g equivalent of dried material) was spheronized on a Caleva 120 mini spheronizer fitted with a radially cut stainless-steel plate.

### 2.3. Sieve analysis

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 $\mu$m, agitated for 10 min on a sieve shaker (Endecott) and retained weight data obtained were used to construct a frequency distribution. The desired size of pellets was in the range 850–1180 $\mu$m 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. Packing density analysis

The packing density of different pellet types was determined by placing 50 g of pellets accurately weighed into a 100-ml graduated cylinder and measuring the volume occupied after standardized tapping 300 times to ensure close packing.

### 2.5. Scanning electron microscopy

Samples from batches of pellets were mounted on aluminium stubs using M-glue (3M) as adhesive, vacuum coated with gold film (Emscope SC 500) and examined using a scanning electron microscope (Hitachi, model S-520) for surface and/or internal morphology.

### 2.6. Image analysis

The sphericity of the pellets was determined using derived pellet parameters measured by an image analyser (Kontron). The maximum diameter, projected area and the perimeter length of 200 randomly selected pellets was determined for each batch. From these parameters two sphericity factors were derived. The first was based on Aspect Ratio (AR) as suggested by Lovgren and Lundberg (1989). The maximum pellet length was expressed as a ratio of the maximum pellet width, which was assumed to be 1 mm. A relative frequency distribution was determined with a class interval of 0.1. The sphericity of the pellets was determined by multiplying the relative frequency of each ratio by the lower class limit of the ratio squared and summing the results. The sum of these figures was then divided into 1 to determine the Sphericity (SphAR) as a percentage of the batch of pellets. Values approaching 100% indicate more spherical pellets. The second sphericity factor was derived from the Form PE factor calculated by the image analysis equipment for individual pellets and is subsequently referred to as Sph PE. The Form PE factor can have values which range from 0 to 1, where 1 is for perfect circularity, and occur as a skewed distribution with the majority of values close to 1. To calculate Sph PE, each Form PE value was subtracted from 1 and multiplied by 1000 before log transformation produced a normal distribution, whose values ranged from 0 to 3. Values approaching 0 indicate more spherical pellets.

### 2.7. Dissolution studies

Flat-faced 13-mm diameter tablets were compressed from 500 mg of nifedipine or a 1:2 coprecipitate prepared with HP-55 under a 4-ton load for 3 min using a hydraulic press (Perkin-Elmer) and after mounting in sealed dies with one exposed face were subjected to intrinsic dissolution testing at 37°C in 500 ml of pH 1.2, 3.0, 5.0, 6.8 or 7.4 medium using a paddle rotating at 100 rev/min (Sotax AT 6). Samples (500 mg) of pellets containing 20 mg drug were agitated at 50 rev/min in 500 ml pH 1.2 medium for 2 h followed by change to pH 6.8 medium at 37°C in an EP dissolution basket assembly (Sotax AT 6), where adequate sink conditions existed. Ten-millilitre samples were withdrawn periodically with immediate replacement of the dissolution medium and following filtration through a 0.45-$\mu$m filter (GA-8, Gelman), were assayed by UV spectroscopy (Shimadzu UV-160) at 348 nm.

### 2.8. Preparation and evaluation of coprecipitate

Nifedipine and HP-55 were mixed and as no single pharmaceutically acceptable solvent was found in which both materials were adequately soluble, they were dissolved in a mixed azeotropic solvent containing 81 parts ethanol and 19 parts acetone, boiling point 63.4°C. HP-55 was chosen over other available enteric polymers such as cellulose acetate phthalate because of its greater solubility in the solvent employed. The solvent was flashed-off using a rotary evaporator (Buchi Rotavapor RE 111) and the recovered cake was dried at 50°C for 48 h to remove residual solvent, prior to grinding to a powder below 180 $\mu$m. Samples were examined by differential scanning calorimetry (Mettler TC 10A TA processor with Epson FX-800 printer) using a ramp rate of 10°C/min over the range 60–220°C.

### 2.9. Model mix and drug coprecipitate studies

Following preliminary development work, initial studies, not involving the use of the expensive drug, were performed with the solvent to determine conditions suitable for good spheronization. As the drug would represent less than 5% of the final product, its omission during development studies was considered unlikely to compromise the validity of the results obtained for the intended drug application. The composition of some of these mixes is shown in Table 1, which were spheronized at 2000 rev/min for 5 min (formulations 1–2) or 10 min (formulations 3–6) prior to drying. Formulations 3–6, 9–12, 13–14 and 15 were examined using factorially designed experiments.

Nifedipine 4% in place of lactose as a coprecipitate with 8% HP-55 (1:2) was included by in situ

Table 1
Composition (%) of some formulations examined

| Formulation | HP-55 | Silicate | Lactose | Liquid paraffin | Magnesium stearate | Solvent |
|---|---|---|---|---|---|---|
| 1 | 8 | 25 (a) | 62 | 5 | 0 | 17 |
| 2 | 8 | 50 (a) | 39.5 | 2.5 | 0 | 17 |
| 3 | 8 | 50 (a) | 39.5/39.25 | 2.5 | 0/0.25 | 22/24 |
| 4 | 8 | 45 (a) + 5 (b) | 39.5/39.25 | 2.5 | 0/0.25 | 22/24 |
| 5 | 8 | 45 (a) + 5 (c) | 39.5/39.25 | 2.5 | 0/0.25 | 22/24 |
| 6 | 8 | 45 (a) + 5 (d) | 39.5/39.25 | 2.5 | 0/0.25 | 22/24 |
| 7 | 8 | 45 (a) + 5 (c) | 39.5 | 2.5 | 0 | 23/24/25/26 |
| 8 | 8 | 45 (a) + 5 (c) | 39.375 | 2.5 | 0.125 | 23/24/25/26 |
| 9 | 8 | 40 (a) + 10 (d) | 39.0 | 2.5 | 0.5 | 23/25 |
| 10 | 8 | 40 (a) + 10 (d) | 38.75 | 2.5 | 0.75 | 23/25 |
| 11 | 8 | 35 (a) + 15 (d) | 39.0 | 2.5 | 0.50 | 23/25 |
| 12 | 8 | 35 (a) + 15 (d) | 38.75 | 2.5 | 0.75 | 23/25 |
| 13 | 8 | 25 (a) + 25 (d) | 39.5 | 2.5 | 0 | 25/27/29/31 |
| 14 | 8 | 50 (d) | 39.5 | 2.5 | 0 | 25/27/29/31 |
| 15 | 8 | 25 (a) + 25 (d) | 39.5 | 2.5 | 0 | 25/27/29/31/33/35 |

(a) is kaolin, (b) is Aerosil 972, (c) is Aerosil 200 and (d) is Bentone 27.

formation arising from solvent evaporation. As initial dissolution studies on pellets formed showed poor disintegration and release of drug, inclusion of a wetting agent (sodium lauryl sulphate 2%) and disintegrant (sodium starch glycolate — Primojel 5%) alone or in combination was examined using factorially designed experiments (formulations 16–19). The final formulation (20) was optimized for solvent content and spheronization time using a 2 factor 4*5 factorial experimental design with replication.

### *2.10. Statistical analysis of data*

The statistical package used in the design and analysis of the factorial experiments was Minitab version 8.2 (Minitab). The results were reported either as an analysis of the constants and coefficients of the various factors, or as an analysis of variance (ANOVA) table. The constants are the average result of the experimental parameter for the whole experiment or sub-experiment, while the coefficients estimate the average variation in the experimental parameter from the constant, as the experimental factors are increased or decreased. These analyses were used in simple two-level designs. Where more than two levels of the experimental factors were employed, regression analysis was performed on the data. This produced a regression equation estimating the coefficients of the linear and quadratic functions, including the regression equation constant. Each regression equation was accompanied by an $R^2$ value, which gave an estimate of the level of variation of the experimental data which may be attributable to the regression equation. The remainder of the variation may be attributed to random effects.

## 3. Results and discussion

### *3.1. Evaluation of coprecipitates*

DSC studies on coprecipitates showed that as the weight fraction of HP-55 was increased, the endothermic peak associated with the melting of nifedipine was progressively depressed and was completely absent in the 1:3 nifedipine/HP-55 scan. As the 1:2 coprecipitate produced a very small peak associated with some free crystalline drug which should preferentially dissolve in the stomach, and had more acceptable lack of bulk and reduced production cost, it was chosen for intrinsic dissolution testing over a range of physiologically relevant pH values. The topographical

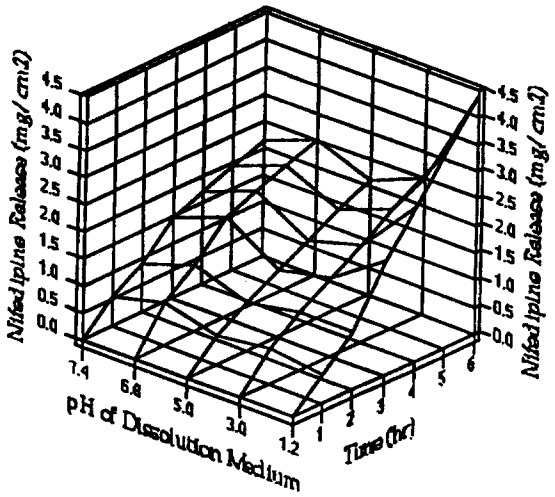


Fig. 1. Topographical release profile on intrinsic dissolution testing of nifedipine over the pH range 1.2–7.4 for 6 h.

profiles for nifedipine and its 1:2 coprecipitate with HP-55 are shown in Figs. 1 and 2, respectively, indicating a large increase in drug dissolution caused by coprecipitation technology at pH greater than 5 corresponding to conditions relevant to the upper small intestine. It was therefore decided to develop a spheronized product based on the in situ formation of the 1:2 coprecipitate formed by the evaporation of the solvent, using

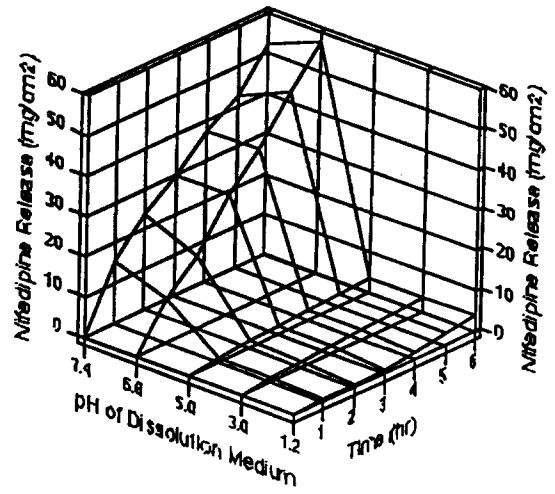


Fig. 2. Topographical release profile on intrinsic dissolution testing of nifedipine/HP-55 1:2 coprecipitate over the pH range 1.2–7.4 for 6 h.

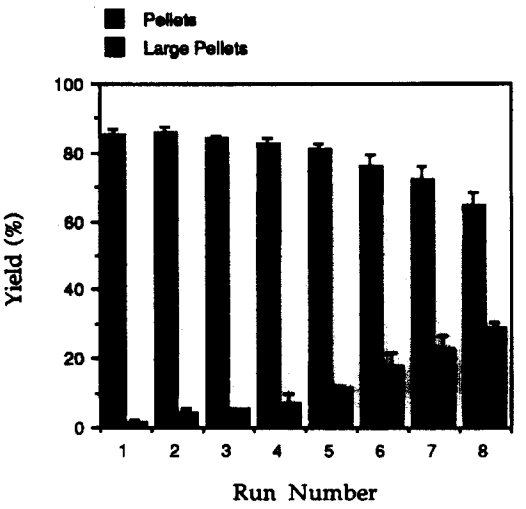


Fig. 3. Effect of run number on the yield of pellets and large pellets of formulation 1. Bar is + S.D.

suitable excipients for this non-aqueous spheronization application.

### 3.2. Non-factorial experiments on model mixes

It has been shown (Millili and Schwartz, 1990) that the use of microcrystalline cellulose in the manufacture of spheronized pellets using ethanol as solvent is unsatisfactory. Accordingly, a range of other excipients were screened as spheronization aids for use with the ethanol/acetone 81:19 solvent and various silicates with liquid paraffin were shown in preliminary experiments to have potential when used with lactose. Formulation 1 was accordingly selected and processed eight times over 3 days to see if it would produce a reproducible yield of product on replicate runs. Fig. 3 shows that the yield of pellets decreased as the run number was increased, remaining relatively constant over the first three runs at approximately 85%. ANOVA indicated that run number had a highly significant effect on the yield of pellets and large pellets ($P < 0.001$), but not of fines. The growth in the yield of large pellets was attributed to progressive surface wetting of the product leading to aggregation due to liquid paraffin build-up in the extruder and spheronizer during replicate runs.

Fig. 4. SEM of formulation 2. Bar is 2.0 mm.

In an attempt to overcome the lack of reproducibility with increasing run number, it was decided to reduce the level of liquid paraffin incorporated as lubricant, while increasing the level of kaolin as silicate. The resultant formulation 2 was again run eight times with an average pellet yield of 88.6% and no progressive loss to large pellets was observed as the run number increased. Further minor modification of this formulation maintaining the total silicates at 50% with increase in lubricant (magnesium stearate) and solvent addition was undertaken (formulations 3–6) to improve the sphericity of formulation 2 (AR 35.2%, PE 2.06). Scanning electron microscopy of formulation 2 (Fig. 4) showed it to be composed mainly of smooth cylinders with rounded ends. Three other silicates were chosen for examination, namely Aerosil 972, Aerosil 200 and Bentone 27. Aerosil 972 and 200 are fine particle grades of silicon dioxide and were chosen to compare their hydrophobic and hydrophilic groups respectively on the properties of resultant pellets. Bentone 27 is an organic derivative of hectorite, which is structurally similar to bentonite, but where the aluminium is replaced largely by magnesium. It is promoted by its manufacturers as a thickening and gelling agent for organic liquids, particularly for solvents containing alcohols and ketones of less than five carbon atoms, as used in this study.

All the mixed silicate formulations gave an overall reduction in the yield of pellets compared to formulation 2 as shown in Table 2, with yield tending to increase with solvent addition and omission of magnesium stearate. Lerk et al. (1977) showed that the addition of magnesium stearate to different excipients, decreased the tablet binding properties of the blends by forming a lubricant film around excipient particles, which effect could be reversed by the addition of Aerosil 200 causing removal of the hydrophobic magnesium stearate layer. The Bentone 27 containing formulation 6 produced yields of pellets comparable to those with kaolin alone (formulation 3). Optimum yield was obtained on inclusion of Aerosil 972 (formulation 4), but on addition of Aerosil 200 (formulation 5), a lower yield of pellets was obtained which appeared very sensitive to the level of solvent used. Packing densities of pellets produced from formulations 3–6 were similar ( $\sim$ 0.93 g/cm$^3$). The biggest improvement in

Table 2
Effect of magnesium stearate and solvent content on the yield (%) of pellets in formulations 3–6 containing various silicates

| Formulation number | Silicate | Mg stearate (%) | Solvent (%) | |
|---|---|---|---|---|
| | | | 22 | 24 |
| 3 | Kaolin | 0 | 73.2 | 85.1 |
| | | 0.25 | 73.4 | 81.5 |
| 4 | Aerosil 972 | 0 | 78.1 | 91.1 |
| | | 0.25 | 53.0 | 86.7 |
| 5 | Aerosil 200 | 0 | 26.5 | 69.6 |
| | | 0.25 | 34.3 | 62.6 |
| 6 | Bentone 27 | 0 | 72.6 | 87.2 |
| | | 0.25 | 78.9 | 84.4 |

sphericity (AR 81.2%, PE 1.88) occurred in the product containing Aerosil 200 as the solvent content increased in the absence of magnesium stearate (formulation 5), which product also tended to produce excess fines presumably due to lack of optimum solvent addition. However scanning electron microscopy of this formulation showed that the product was still composed mainly of short cylinders with rounded ends.

### 3.3. Factorial experiments on model mixes

Arising from the above studies, it was decided to examine the inclusion of Aerosil 200 and Bentone 27 further in an attempt to improve sphericity while still retaining a high yield of pellets. Aerosil 200 was included for additional examination due to the maximum sphericity obtained when spheronized with 24% solvent without magnesium stearate. Bentone 27 appeared to be a promising excipient due to the appearance of dumbbell shapes in the high yield of pellets, which were considered as signs of desirable plasticity in the formulation.

Formulations 7 and 8 were examined containing 5% Aerosil 200 at increased solvent level and reduced magnesium stearate content using a 2*4 level 2 factor design. The yield of pellet data indicated that solvent content was an important determinant, reaching a maximum of 78.6% yield when 26% solvent was used in the absence of magnesium stearate. All the formulation modifications gave negligible yield of large pellets and sizeable but decreasing yield of fines as the solvent content was increased from 23 to 26% (45.4 to 19.4% respectively). Optimum sphericity AR and PE values of 74.5% and 1.85, approaching those obtained for aqueous systems, were obtained when using 23% solvent in the absence of magnesium stearate. The probable cause of differing solvent content for maximum pellet yield and optimum sphericity was that at lower solvent content, fracturing of the brittle extrudate would occur more frequently at about 1-mm intervals along its length with generation of more fines as proposed by Ghebre-Sellassie (1989). The sphericity AR factor uses the maximum length to width ratio in its determination and consequently extrudate with lower solvent level fractured into lengths close to their width would result in sphericity values close to 100%. SEM studies on products obtained supported this theory as they showed that increasing solvent level produced higher yields of longer cylindrical pellets with rounded ends.

A factorial design was used to examine the effect of Bentone 27, solvent and magnesium stearate content as indicated in formulations 9–12. As in the previous section, solvent content was the most important factor, increasing levels increasing yield but decreasing sphericity. The solvent content appeared to be an important parameter in maintaining the integrity of pellets during the spheronization step. The yield of pellets and large pellets was reduced and the yield of fines was increased with increasing magnesium stearate content, which also had a negative effect on sphericity. Increasing addition of Bentone 27 had a marginal increase on yield of pellets and reduced the sphericity of the product. Examination of the pellets and comparison with those produced by aqueous spheronization indicated that the mechanisms of formation were different. This was confirmed by the appearance of the non-aqueous produced pellets which were almost entirely dumbbell shaped, unlike the completely rounded aqueous produced products having improved sphericity values. The increased production of dumbbells in comparison to straight cylinders associated with increasing Bentone content, which still reached only 15% of the final dried product in formulations 11 and 12, was an indication that the plasticity of the mix increased as the level of Bentone 27 in the mix increased, even though this was not reflected in improved sphericity results. None of the factors had a significant effect on the packing density of the pellets.

Formulations 13 and 14 were examined to study the effect of further increase in Bentone 27 and solvent content. The yield of pellets from mixes containing 25% Bentone 27 appeared more sensitive to solvent content reaching optimum yield of 80% pellets at 27% solvent. On increasing the solvent content of the mixes to 31%, there was a large increase in the yield of large pellets to 5%,

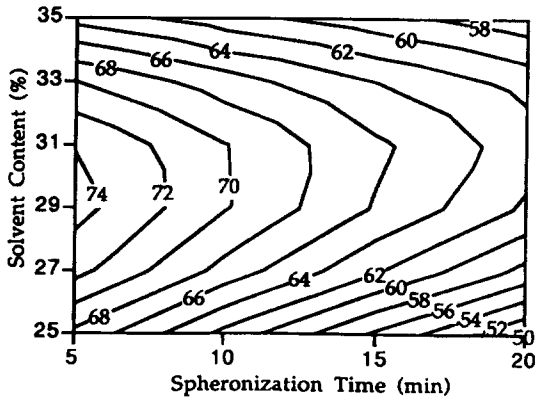


Fig. 5. Contour plot of the regression model fitted to the yield of pellets data. Contour lines represent yield of pellets (%).

indicating that the solvent content was approaching saturation. The effect of varying the solvent content in mixes containing 50% Bentone 27 was negligible in any of the size ranges examined indicating that the solvent was better associated with the Bentone 27 and that the formulation was more robust for routine manufacture. The packing density of pellets was slightly larger when 25% compared to 50% Bentone 27 was used (average 0.93 vs. 0.90 g/cm$^3$), but within each Bentone 27 content formulation variables had negligible effect on packing density. Comparison with the results of formulation 6 indicated that increasing the level of Bentone 27 in the mix increased the requirement of the mix for the solvent to enable successful spheronization. The dumbbell shape of products were more 'dog-bone' like with enlarged rounded ends as the content of Bentone 27 was increased.

Before incorporating the drug and based on the results of the previous studies, a model mix containing 25% kaolin and 25% Bentone 27 was studied with regard to the effect of increasing solvent content and spheronization time on pellet properties (formulation 15) using a 6*4 factorial design. For all the solvent levels examined, the yield of pellets was reduced as spheronization time was increased as shown in Fig. 5. The yield of pellets was highest between 29 and 31% solvent. Above and below these solvent levels, the yield of pellets obtained from the mix decreased. The loss in yield of pellets with increasing spheronization time was accompanied by progressive growth in the yield of fines which was ascribed to loss of bind in pellets by continual evaporation of the volatile solvent. Scanning electron micrographs shown in Fig. 6 show (a) pellets manufactured with a solvent level of 25% for 5 min and (b) pellets manufactured with a solvent level of 35% for 20 min. The long 'dog-bone' structures shown in Fig. 6 (a) were transformed using increased solvent content and spheronization time to the relatively short 'dumbbells' shown in Fig. 6 (b). The micrographs also give an indication of the mechanism of formation of pellets by non-aqueous spheronization. It appears that the proud ends of elongated cylinders are progressively flattened down around the cylinder shaft

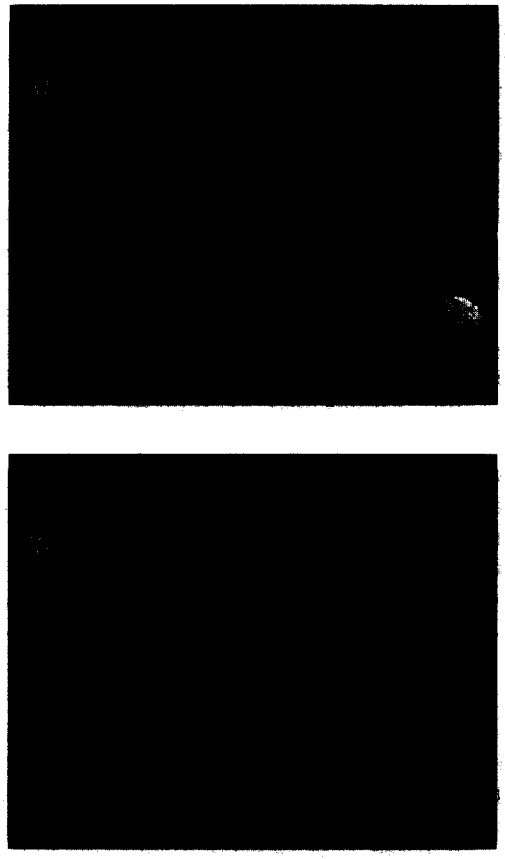

Fig. 6. SEMs showing the effect of increasing solvent level and spheronization time on the pellet appearance of formulation 15: (a) 25% solvent and 5 min, (b) 35% solvent and 20 min. Bar is 2.0 mm.

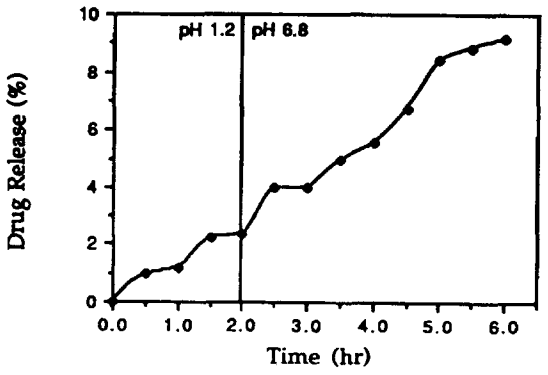


Fig. 7. pH-shift dissolution profile for nifedipine release from pellets of formulation 16.

until they eventually meet to produce a spherical product.

### 3.4. Experiments on drug mixes

The final series of experiments involved substitution of 4% drug for lactose as a 1:2 coprecipitate with HP-55 formed in situ by solvent evaporation. Assuming a capsule fill weight of 500 mg, this drug loading would conveniently provide the normal oral dosage of nifedipine which is 20 mg administered two or three times daily. From preliminary results obtained using formulation 16, it appeared that the addition of nifedipine to the formulation resulted in a mix which was more likely to form large pellets, with reduced yield of both pellets and fines. Also the dissolution rate of nifedipine from the pellets was disappointing (Fig. 7), with only 9% of the total drug content released over 6 h using a pH-shift test to mimic passage along the GIT. As the pellets were intact after the dissolution test, it was concluded that the inclusion of a wetting agent (sodium lauryl sulphate 2%) and/or disintegrant (sodium starch glycolate 5%) in the formulation was necessary (formulations 17–19).

The yield of the various size pellets obtained in comparison to the control formulation without wetting agent and disintegrant is shown in Table 3, while the results of dissolution testing are shown in Fig. 8. Inclusion of sodium starch glycolate appeared to have the least effect and sodium lauryl sulphate the greatest effect on the size

Table 3
Yield of various size pellets (%) on incorporation of sodium lauryl sulphate and sodium starch glycolate into drug mixes

| Formulation | Pellets | Large pellets | Fines |
|---|---|---|---|
| 16 | 59.3 | 10.8 | 29.1 |
| 17 | 47.9 | 12.8 | 39.1 |
| 18 | 57.1 | 10.7 | 31.4 |
| 19 | 50.6 | 7.7 | 40.6 |

distribution of the product. However the presence of both excipients was necessary for optimum dissolution of the drug. Only when sodium lauryl sulphate and sodium starch glycolate were used in combination were the pellets observed to disintegrate fully during the dissolution testing, exposing coprecipitate at the centre to the dissolution medium. Lack of complete drug release was attributed to binding to the adsorptive silicates and possibly other excipients of the formulation, the desorption of which in vivo might be beneficial for the functionality of an extended-release dosage form of the drug.

Finally the most promising drug containing formulation 19 was optimized for solvent content (33–36%) and spheronization time (10–20 min) using a full factorial 2 factor 4*5 replicate experiment (formulation 20). Regression analysis was

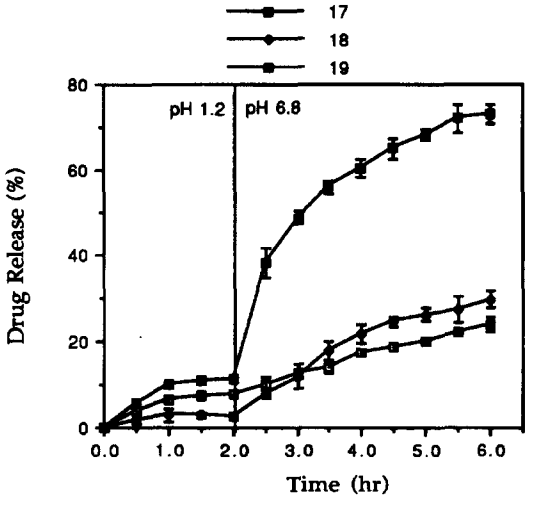


Fig. 8. pH-shift dissolution profile for nifedipine release from pellets of formulations 17–19.

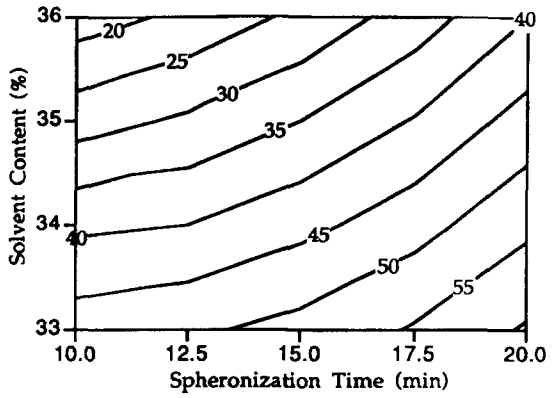


Fig. 9. Contour plot of the regression model fitted to yield of pellet data. Values on the contour lines represent % yield of pellets.

performed on the data to indicate the optimum conditions for yield of pellets in the various size ranges, packing density and sphericity. Dissolution studies were performed on selected products from the experimental matrix. Fig. 9 shows the effect on yield of pellets, where it can be seen that as the solvent content was increased the yield of pellets reduced and as the spheronization time increased the yield increased. However as the solvent content increased and spheronization time reduced, the yield of large pellets increased as expected. Also the yield of fines reduced as the solvent level increased and the spheronization time reduced. The packing density of the pellets ranged from 0.875 to 1.027 g/cm$^3$ and the results were very variable. The sphericity determinations for both sphericity AR and PE were also quite variable and Fig. 10 shows a contour plot for the former values. The most spherical pellets were obtained using high levels of solvent and short spheronization times. The curvature of the lines on the plot indicates a dependency of one variable on the other. SEMs of the pellets produced under the optimum processing conditions in terms of sphericity were made. These pellets were produced with 35% solvent, were spheronized for 12.5 min and had a sphericity AR value of 92%. Fig. 11 shows that the pellets were very spherical but at higher magnification some of the pellets revealed their unclosed folded structure. This confirmed that the rounding mechanism of the pellets occurred through the gradual meeting of the plastic ends of cylinders.

Dissolution profiles for a range of pellets from formulation 20 again showed an enteric effect with retarded drug release ( < 18%) over the first 2 h at pH 1.2 followed by faster release to almost 70% overall drug release during subsequent testing by the pH-shift procedure for 4 h at pH 6.8. There was a tendency for increasing spheronization time of pellets to increase dissolution at low pH and for those formed with 34% solvent to give maximum release at the higher pH. The results are similar to those of Kohri et al. (1987), who showed approximately 65% nifedipine release from sustained-release granules manufactured from hydroxypropylmethylcellulose and ethylcellulose at pH 7.0. When administered to male volunteers as a single dose of 20 mg, the pellets demonstrated prolonged-release, maintaining therapeutic plasma levels over 12 h.

Overall the studies on non-aqueous spheronization indicate that such a procedure is possible provided adequate silicate is used, and that formulation and process factors have an important effect on various properties of the pellets formed. A trade-off existed between these properties such that high yield was often associated with poor sphericity. Lack of adequate yield is unacceptable for this expensive drug, whereas lack of sphericity is a minor aesthetic consideration, unless required for subsequent coating, unlikely to significantly

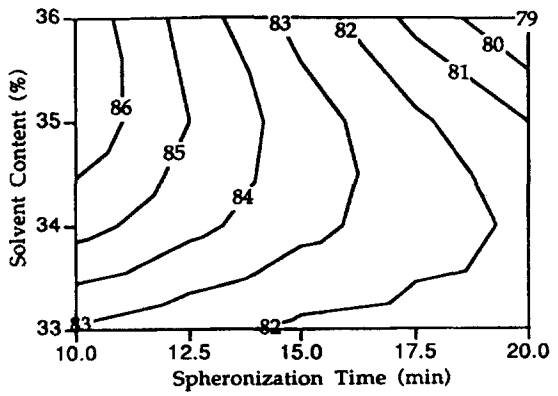


Fig. 10. Contour plot of the regression model fitted to the sphericity AR data. Values on the contour lines represent the % sphericity AR.

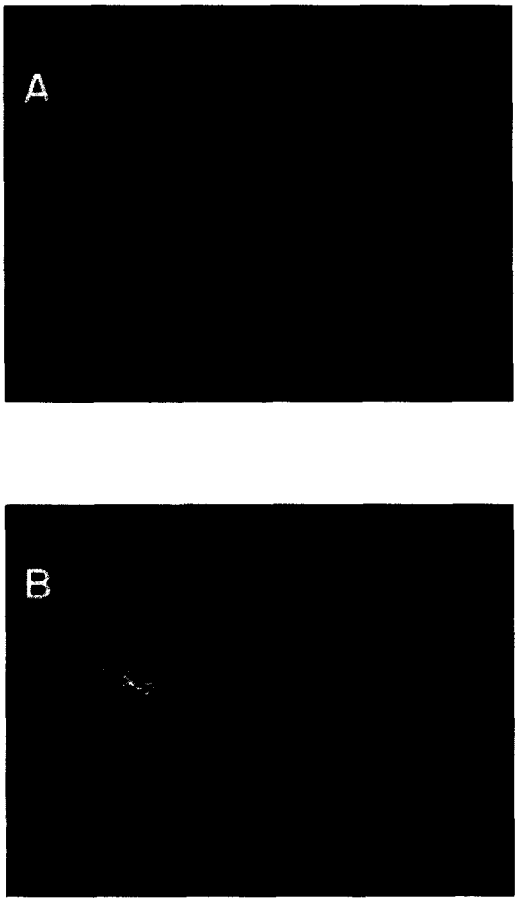


Fig. 11. SEMs of pellets from formulation 20 spheronized with 35% solvent for 12.5 min. Bar is 2.0 mm (a) and 1.0 mm (b).

affect capsule filling and in vivo performance. The mechanism of pellet formation is different to aqueous spheronization, which normally requires microcrystalline cellulose to aid the process. The promising in-vitro dissolution profile of the optimized product based on formulation 20, which readily disintegrates and consequently is less dependent on its initial spherical shape, needs to be confirmed by in vivo testing in humans. However these studies are compromised at present because Bentone 27 does not have regulatory approval. Also the product requires stability testing at a range of temperatures and humidities to confirm the functionality of the coprecipitated drug on long-term storage in its final container.

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