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Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-*co*-agglomeration technique

Maryam Maghsoodi [a], Omid Taghizadeh [a], Gary P. Martin [b], Ali Nokhodchi [c,*]

[a] *School of Pharmacy and Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran*
[b] *King's College London, Pharmaceutical Science Research Division, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK*
[c] *Medway School of Pharmacy, The Universities of Kent and Greenwich, Central Avenue, Kent ME4 4TB, UK*

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Abstract

The purpose of the present research was to obtain directly compactible agglomerates of naproxen containing disintegrant by a novel crystallo-*co*-agglomeration (CCA) technique. Acetone–water containing hydroxypropylcellulose (HPC) was used as the crystallization medium. Acetone acted as a good solvent for naproxen as well as a bridging liquid for agglomeration of crystallized drug with disintegrant and aqueous phase as non-solvent. The agglomerates were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD) and scanning electron microscopy. The agglomerates were compressed at different compression pressures and dissolution studies were carried out for the tablets produced at lowest compression force. The growth of particle size and the spherical form of the agglomerates resulted in formation of products with good flow and packing properties. The improved compaction properties of the agglomerated crystals were due to the fragmentation which occurred during compression. DSC and XRPD studies showed that naproxen particles, crystallized in the presence of HPC and disintegrant did not undergo structural modifications. The dissolution rate of naproxen from the agglomerates could be controlled by the amount of included disintegrant, being enhanced as the latter was increased. Moreover, the results showed that when the disintegrants were included both intragranularly and extragranularly during agglomeration of naproxen particles, tablets containing these agglomerates dissolved at a faster rate than the tablets containing crystallized naproxen with the same amount of disintegrant incorporated only extragranularly by physical mixing. In conclusion, the properties of agglomerated crystals, such as flowability, compactibility and dissolution rate were improved profoundly using the developed technique resulting in successful direct tableting without need to additional process of physical blending of agglomerates and disintegrants.

Keywords: Disintegrant; Crystallo-*co*-agglomeration; Direct tableting; Tensile strength; Disintegration time; Dissolution

1. Introduction

There has been renewed interest in examining the potential of direct compression tableting over recent years since in comparison to the use of the more traditional granulation process. Such manufacture of tablets involves simple mixing and compression of powders, which results in a number of overall benefits including time and cost savings. Direct compression tableting as a technique has been successfully applied to numerous drugs on the industrial scale, although the success of any procedure, and resulting mechanical properties of tablets, is strongly affected by the quality of the crystals used. When the mechanical properties of the drug particles are inadequate a primary granulation is necessary. The use of spherical crystallization as a technique appears to be an efficient alternative for obtaining suitable particles for direct tableting (Ribardiere et al., 1996).

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement of flowability and compactibility of crystalline drugs (Paradkar et al., 1994; Nokhodchi et al., 2007). This technique is also reputed to improve the wettability and dissolution rate of different drugs (Kawashima et al., 1985; Guillaume et al., 1993; Di Martino et al., 1999). Some drugs have also been recrystallized by the spherical agglomeration technique using polymeric materials to modify their release (Akbuga, 1989; Ribardiere et al., 1996). Naproxen is a poorly water soluble drug and its oral bioavailability is limited by the

* Corresponding author. Tel.: +44 1634 883846; fax: +44 1634 883927.
E-mail address: a.nokhodchi@kent.ac.uk (A. Nokhodchi).

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dissolution rate (i.e. it is a class II drug). Accordingly a number of investigations over recent years have been carried out seeking to improve its solubility/or dissolution rate (Liversidge, 1995; Liversidge and Cundy, 1995; Merisko-Liversidge et al., 1996, 2003; Mitchell et al., 2003; Mura et al., 1999, 2003). However one strategy that has not been explored to enhance dissolution is that of crystallo-*co*-agglomeration (CCA), a technique first described by Kadam et al. (1997a,b). Such a method is a modification of a spherical crystallization technique in which a drug is crystallized and agglomerated with an excipient or with another drug, which may or may not be crystallized in the system.

The aim of the current study was to seek to improve the flow, compaction and dissolution properties of a poorly water-soluble and compactible drug, naproxen, by incorporating a disintegrating agent in the drug agglomerates by spherical crystallization technique. The solid state of the produced agglomerates was also investigated to identify polymorphic changes in naproxen during the crystallization process.

2. Materials and methods

2.1. Materials

Naproxen (Shasun Chemicals, India), hydroxypropylcellulose, HPC (Nisso HPC-H, Nippon Soda, Japan), magnesium stearate (BDH, UK), sodium starch glycolate (Yung Zip Chemical, Taiwan), starch (Merck, Germany) and acetone (Merck, Germany) were used.

2.2. Crystallization procedure

Different agglomerates were prepared of the compositions shown in Table 1. The crystallization procedure was similar to the one that reported previously (Maghsoodi et al., 2007). In a vessel 1.25 g HPC was dissolved in distilled water (500 ml), and 1/3 of the total disintegrant, either starch or sodium starch glycolate, was uniformly dispersed in the solution at room temperature by stirring (different ratios of disintegrant:drug were examined) for a period of 20 min. Acetone (40 ml) at 50 °C containing 10 g naproxen and the other 2/3 of disintegrant which was also separately stirred for the same 20 min period. The latter dispersion was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (200 rpm, paddle type agitator with 4 blades). The stirring was continued for 10 min to obtain agglomerates, which were then filtered and dried overnight. The dried crystals were stored in screw-capped jars at room temperature before use. The effect of different concentrations of disintegrant agents was also investigated.

Table 1
Compositions (g) of the naproxen-disintegrant agglomerates and yield (%)

Composition	A1	A2	A3	B1	B2	B3
Starch	–	–	–	0.3	0.15	0.075
NaStarch glycolate	0.3	0.15	0.075	–	–	–
Naproxen	1	1	1	1	1	1
Yield (%)	68 ± 1.2	74 ± 1.7	76 ± 2.3	70 ± 0.9	77 ± 1.4	80 ± 1.1

For comparison purposes, naproxen was crystallized at the same conditions mentioned above in the absence of disintegrant with the disintegrant being added to the agglomerates afterwards. The agglomerated crystals were mixed for 10 min with the amount of disintegrant equal to the amount of disintegrant adsorbed to naproxen agglomerates. This was measured according to the procedure described in the next section.

2.3. Determination of the amount of disintegrant in agglomerates

Agglomerates (1 g) were powdered, and samples equivalent to approximately 100 mg of naproxen were weighed accurately and dispersed in acetone, such that any drug dissolved whereas the disintegrant remained dispersed. The dispersion was then filtered to separate naproxen solution from the disintegrant. After filtration the acetone solution was diluted with phosphate buffer, and the samples were analyzed spectrophotometrically at 332 nm (Shimadzu UV-160, Japan). The drug content was determined by reference to an appropriate standard curve and the amount of disintegrant was taken as the difference between total amounts of powder and the spectrophotometrically determined weight of naproxen.

2.4. Determination of angle of repose

Flow properties of the powders were evaluated by determining the static angle of repose. This was measured according to the fixed funnel and free standing cone method. A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip 2.5 cm height, H, above graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel (H). The mean diameter ($2R$) of the powder cone, was determined and the tangent of the angle of repose was given by:

$$\tan\alpha = \frac{H}{R}$$

where α is the repose angle. The mean of 6 determinations was obtained.

2.5. Compressibility index measurement

Flowability of untreated and agglomerated samples was also assessed from Carr's Index (CI) (Carr, 1965a,b). The CI was calculated from the poured and tapped densities. Tapped density was determined by tapping the samples (10 g) into a 10 ml measuring cylinder using a tapping machine. The CI was calculated according to the following equation:

$$\mathrm{CI} = \left[\frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}}\right] \times 100$$

2.6. Particle size analysis

A total of 25 g of material was sieved using an Erweka vibration sieve (Erweka, Germany) through a nest of sieves. The vibration rate was set at 200 strokes/min and the sieving time was 10 min. The powder fractions retained by the individual sieves were determined and expressed as mass percentages.

In the case of the untreated naproxen, a light blockage technique (FW_DR, Germany) was used to determine particle size distribution (due to the presence of particles with a size less than 50 μm). Approximately 15–20 mg of drug was dispersed in water under stirred conditions.

2.7. Scanning electron microscope (SEM)

The shape and surface topography of agglomerates and conventional crystals were observed using scanning electron microscope (LEO 440I, Cambridge, UK), after coating with gold. The micrographs of at least 100 particles were transferred into the software and the shape factor defined as 4π (area/perimeter^2) obtained using with an image analysis (scion image analyzer).

2.8. X-ray diffraction of powder (XRDP)

The X-ray diffraction patterns of naproxen samples were obtained using an X-ray diffractometer (Seimens, Model D5000, Germany) operated at 40 kV, 30 mA and a scanning rate of 0.06°/min over the range 5–40 2θ, using Cu Kα_1 radiation of wavelength 1.5405 Å. The cavity of the metal sample holder of X-ray diffractometer was filled with the ground sample powder.

2.9. Differential scanning calorimetry (DSC)

Samples of the crystals (about 5 mg) were heated (range 25–200 °C) at 10 °C/min in crimped hemetically sealed aluminium pans under a nitrogen atmosphere. The enthalpy of fusion and melting point could be obtained from the thermograms using the instrumental software (DSC60, Shimadzu, Japan). The calorimeter was calibrated using indium and lead standards.

2.10. Pressure-tensile strength relationship

The naproxen-disintegrant agglomerates (200 ± 10 mg) were compressed using an 8-mm flat-faced punch at a constant compression speed with different compaction pressures (20, 30, 40, 50 and 60 MPa), using a hydraulic press (Riken Seiki Co., Japan). Lubrication of the die and punch was performed using a 1% (w/v) dispersion of magnesium stearate in acetone. The compacts were allowed to relax for 24 h and the force fracturing the compact (F) was measured. The tensile strength (T) of the compact was calculated based on the following equation (Rundick et al., 1963; Fell and Newton, 1970):

$$T = \frac{2F}{\pi Dt}$$

where D and t are the diameter and thickness of the compact, respectively. The results are the mean and standard deviations of a minimum of 5 determinations.

2.11. Disintegration test

Disintegration testing was performed at 37 °C in phosphate buffer (pH 7.4) using the European pharmacopoeial apparatus (Erweka ZT3, Erweka, Heusensenstamm, Germany) without disc. The results are the mean and standard deviations of a minimum of 5 determinations.

2.12. In vitro dissolution

The naproxen-disintegrant agglomerates (100 ± 10 mg) were compacted using an 8-mm flat punch at a pressure of 60 MPa. The USP dissolution test was modified to suit our studies as follows. Dissolution was performed (8ST, Caleva, England) in 900 ml pH 7.4 phosphate buffer (each dissolution vessel contains 225 ml potassium phosphate monobasic 0.2 M and 175.95 ml sodium hydroxide 0.2 M, then water was added to 900 ml) at 100 rpm, 37 ± 0.1 °C using the rotating paddle method.

Samples of the solution were withdrawn at pre-determined time intervals (2, 4, 6, 8, 10, 15, 25 and 40 min) and then were passed through a membrane filter (0.45 μm). The amount of dissolved naproxen, corrected for previously removed samples, was analyzed spectrophotometrically (UV-160, Shimadzu, Japan) at 332 nm.

2.13. Calculation of dissolution parameters

The initial dissolution rate (DR_i, mg/ml min) was determined by linear regression analysis and was taken as the slope of the dissolution curve between t_0 and $t_{8\,min}$. The area under the dissolution curve (AUC, mg min/ml) between t_0 and t_{40} was calculated using the trapezoidal rule (Rubinstein, 1980) and this was taken as an indication of the extent of drug dissolution.

2.14. Statistical evaluation of data

Significance was taken at 95% confidence levels ($p < 0.05$). The mean values of the various parameters determined, i.e., initial dissolution rate (DR_i), normalized area under the dissolution curve (AUC), tensile strength, and disintegration time were compared for significant difference using one-way or two-way analysis of variance (ANOVA) for single factor and two factors comparison, respectively.

3. Results and discussion

3.1. Spherical crystallization mechanism

Naproxen was crystallized from acetone–water and agglomerated with a disintegrant, either starch or sodium starch glycolate. In this process, the crystallization of the drug was performed by the addition of a solution to the anti-solvent

Table 2
Micromeritics of untreated and treated naproxen samples

Samples	Geometric standard deviation	Geometric mean diameter (μm)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	CI (%)	Angle of repose (°)	Shape factor
A1	1.18	583.2	0.25 ± 0.01	0.27 ± 0.01	7.9 ± 1.4	38.6 ± 0.4	0.89
A2	1.20	584.7	0.26 ± 0.02	0.28 ± 0.01	6.9 ± 0.7	37.1 ± 0.5	1.08
A3	1.19	587.2	0.26 ± 0.01	0.28 ± 0.01	7.3 ± 0.7	38.8 ± 0.5	0.97
B1	1.23	587.9	0.25 ± 0.02	0.27 ± 0.01	7.5 ± 1.2	35.6 ± 0.5	0.92
B2	1.25	599.7	0.25 ± 0.02	0.27 ± 0.01	7.9 ± 0.6	36.3 ± 0.3	1.02
B3	1.27	534.9	0.26 ± 0.02	0.28 ± 0.01	7.5 ± 0.1	36.4 ± 0.5	0.95
TN[a]	1.20	550.0	0.26 ± 0.02	0.28 ± 0.01	7.9 ± 1.0	36.1 ± 0.4	0.92
Untreated naproxen	1.75	10.2	0.39 ± 0.02	0.51 ± 0.01	28.5 ± 0.8	58.8 ± 0.6	1.48

[a] Treated naproxen in absence of disintegrant.

phase (water). Acetone served as good solvent and the bridging liquid and aqueous phase as the non-solvent solvent. The acetone dispersion containing the drug was added immediately to the aqueous dispersion and quasi-emulsified droplets of drug solution were produced. The crystallization of the drug then proceeded from the outer surface of the droplet due both to the decreasing the temperature and the counter diffusion of both solvents through the interface of emulsion droplets. The stirring time was found to be an important parameter in this study, since it was observed that stirring the final mixed dispersion beyond 10 min, not only did not result in an increased %yield, but also lead to disruption of the formed agglomerates. However, a stirring period of 10 min after the addition of the drug was necessary for the agglomerates to form. The end-point of the process was apparent when the dispersion (comprised primarily of suspended disintegrant) became essentially a coarse suspension of agglomerates in an otherwise transparent continuous phase (comprised of acetone/water cosolvent).

The spherically agglomerated crystals, produced in yields generally within the range 70–80% (Table 1), were produced simultaneously as crystallization was completed (Kawashima et al., 2003). As both phases (acetone and aqueous) contain the disintegrant, then it is likely that it is distributed both inside the agglomerates (intragranularly) and outside the agglomerate (extragranularly), attached to the surface.

3.2. Micromeritics of agglomerates

The geometric mean diameters of the agglomerates were approximately 50 times larger than those of the untreated naproxen (Table 2). The data indicate that the original single crystals of drug were uniformly agglomerated by the spherical crystallization process employed.

It was found that both CI and angle of repose of the agglomerates decreased as compared to the untreated naproxen. Such a decrease indicated that there were substantial improvements in flow and packing ability of the powder mass in comparison to the original drug. This can be attributed to the increase in sphericity of the powder, since the agglomerates displayed shape factor values close to 1 (Table 2).

The bulk and tapped densities of the spherical agglomerates particles were lower than the corresponding values of the original sample, with the particle size and sphericity, being higher. The lower density is likely to be related to the intraparticle porosity or particle density (Kachrimanis et al., 1998) and hence the reduction in bulk density of the treated samples indicates a greater porosity within the agglomerated particles.

3.3. Morphology of agglomerates

An examination of the SEMs, confirm that the starting material (Fig. 1a-I and a-II) was markedly smaller in particle size than any of the treated crystals (Fig. 1b-I, c-I and d-I). Similar results were obtained in other studies using crystallo-agglomeration procedures for other drugs (Kawashima et al., 1995; Paradkar et al., 2002). SEMs of the untreated naproxen and the agglomerates (Fig. 1a-II, b-II, c-II, and d-II) show no evidence of porosity in the untreated naproxen crystals, whereas the crystallized agglomerated particles indicated clear evidence of porosity. The untreated naproxen particles were plate-like in appearance (Fig. 1a), whereas naproxen crystallized from acetone in presence of HPC but no disintegrant were spherical agglomerates (Fig. 1b-I). It has been shown previously, that HPC at a concentration of 0.25% is necessary to produce spherical agglomerates of naproxen (Maghsoodi et al., 2007).

Table 3
Disintegrant contents of the naproxen-disintegrant agglomerates

Ratio of disintegrant/drug incorporated into crystallization medium (%)	Ratio of disintegrant/drug measured in agglomerates (%)	
	Starch	Sodium starch glycolate
30	14.6 ± 0.5	14.1 ± 0.6
15	8.4 ± 0.3	4.7 ± 0.4
7.5	4.0 ± 0.3	1.9 ± 0.2

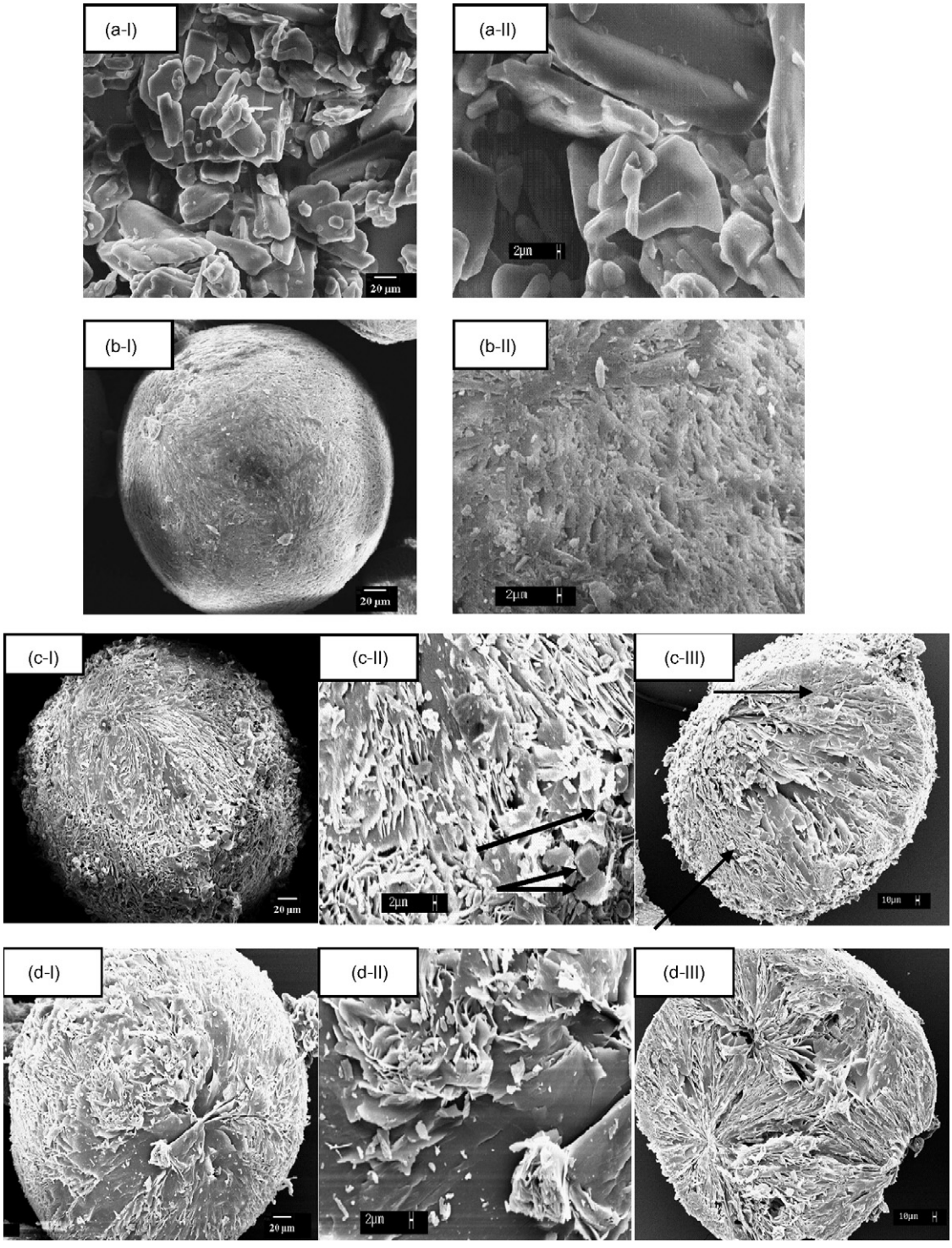

Fig. 1. Scanning electron micrographs of: (a-I) and (a-II) untreated naproxen; (b-I) and (b-II) treated naproxen without disintegrating agent; (c-I), (c-II) and (c-III) naproxen-starch agglomerates; (d-I), (d-II) and (d-III) naproxen-sodium starch glycolate agglomerates. (c-III) and (d-III) are the cross-section of the agglomerates.

SEMs obtained at higher magnifications revealed that agglomerates were spherical aggregates of plate-shaped crystals. Fig. 1c-I and d-I illustrate naproxen particles crystallized from acetone–water system containing HPC and disintegrants. These figures clearly indicate that the use of disintegrant in the crystallization media had no major effect on the overall shape of naproxen crystals in comparison with those obtained in the absence of the disintegrants. However at higher magnification (Fig. 1d-II with c-II), it was apparent that the presence of disintegrating agent in crystallization medium produced agglomerates with a high surface roughness. The presence of disintegrant could be identified in the resultant

spherical agglomerates, as indicated by arrow in Fig. 1c-II.

3.4. Solid state properties of agglomerates

X-ray powder diffractometry (XRPD) is a powerful technique for the identification of crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The X-ray powder diffraction pattern (XRPD) in the 10–40°, 2θ range showed that the diffraction peaks, characteristic of naproxen were still detectable in the crystallized samples (Fig. 2), suggesting that the particles crystallized in the presence of HPC and disintegrants did not undergo structural modifications. However, the differences in the relative intensities of their peaks may be attributed to differences in the crystallinity or particle size of the samples (Jbiilou et al., 1999). It is very difficult to identify the presence of HPC or disintegrants in XRPD spectra as they are polymers with amorphous structure and therefore no sharp peaks are apparent at particular 2θ, due to the very low crystallinity of these components.

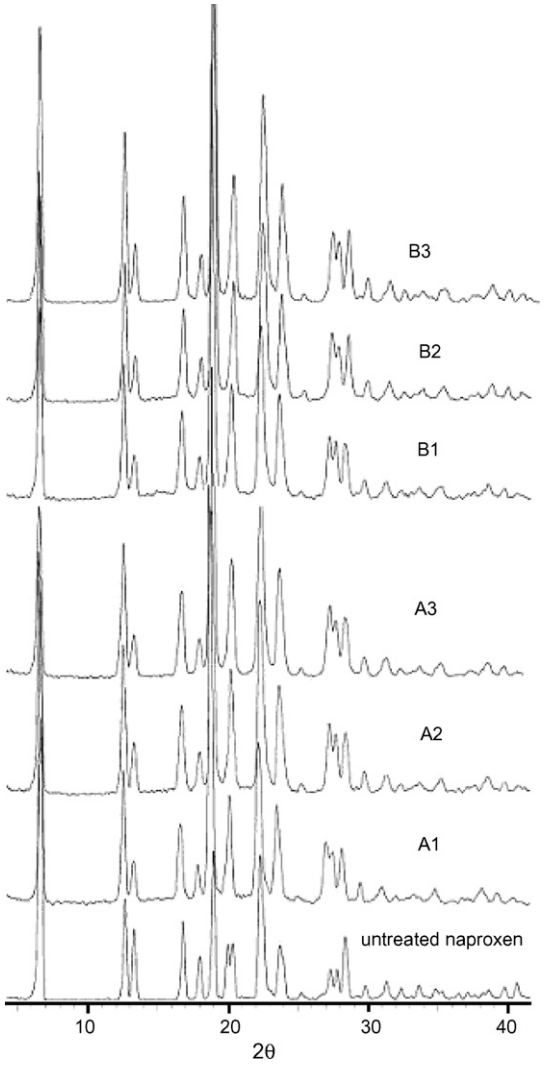

Fig. 2. The X-ray diffraction spectra of untreated and treated naproxen. A samples containing different concentrations of sodium starch glycolate: A1 (14.1%); A2 (4.7%) and A3 (1.9%); B samples containing starch: B1 (14.6%); B2 (8.4%) and B3 (4%).

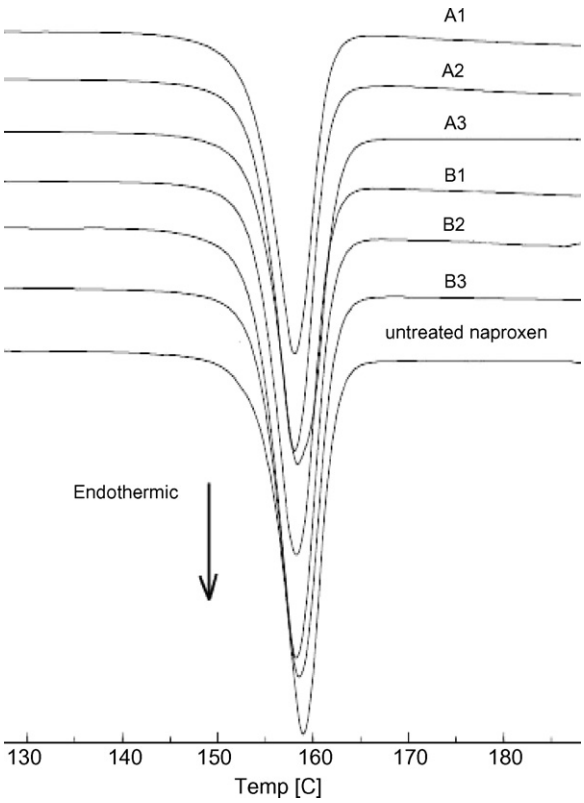

Fig. 3. DSC thermograms of untreated and treated naproxen particles. A samples containing different concentrations of sodium starch glycolate: A1 (14.1%); A2 (4.7%) and A3 (1.9%); B samples containing starch: B1 (14.6%); B2 (8.4%) and B3 (4%).

DSC can be combined with XRPD data to determine the polymorphic composition of pharmaceutical powders, if two or more polymorphs are present. The uniformity of crystalline structure in all batches was confirmed by DSC. All samples, irrespective of disintegrant type and concentration showed a sharp melting point with flat baseline, which indicated that the material was not affected by hydration, solvation, polymorphic transition and in addition there was no indication of interaction of the drug which had occurred with the included disintegrants, during crystallization of the particles (Fig. 3). The results showed that there was no significant difference between melting points of untreated naproxen sample (157.31 °C) and agglomerated samples (ranging from 157.02 to 158.56 °C).

SEMs of the surface and cross-section of the naproxen-disintegrant agglomerates indicated that the disintegrants were incorporated within the voids and physically adhered to the surface of the agglomerates. The physical nature of the mixture was confirmed by DSC and X-ray analysis, since both of the latter methods did not detect any change of the crystalline form of naproxen, or any interaction with disintegrant.

3.5. Mechanical properties of naproxen tablets

The tensile strength of tablets prepared with agglomerated crystals or untreated drug crystals is plotted as a function of

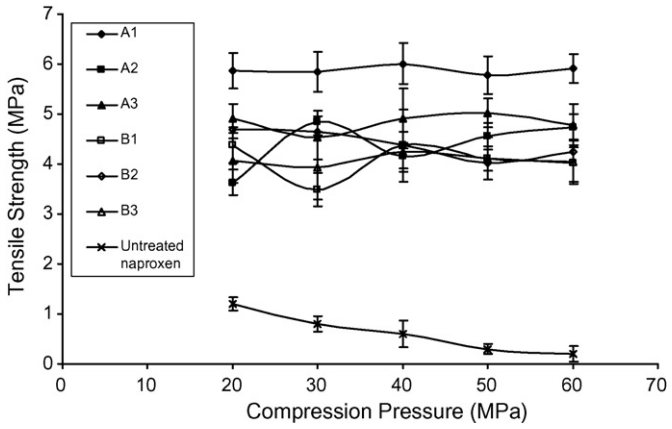

Fig. 4. The tensile strengths of the tablets made from untreated naproxen particles and agglomerated naproxen. A samples containing different concentrations of sodium starch glycolate: A1 (14.1%); A2 (4.7%) and A3 (1.9%); B samples containing starch: B1 (14.6%); B2 (8.4%) and B3 (4%).

compression pressure in Fig. 4. It is clear that all the batches of naproxen containing disintegrant showed higher tensile strength than the original naproxen. A comparison of the tensile strengths of tablets prepared from naproxen samples containing incorporated disintegrant showed that the naproxen tablets containing a high concentration of sodium starch glycolate (formulation A1) had a superior tensile strength compared to other tablets. This could be due to superior compactibility of sodium starch glycolate in comparison with starch as reported by Fassihi (1986). The results showed that the tablets prepared using the untreated (original) naproxen particles were prone to capping at compression pressures above 40 MPa. Whereas, in contrast any of the agglomerated crystals were successfully tableted without capping at any of the compression pressures applied.

The improved compactibility of the agglomerates could be attributed to their structural characteristics. The agglomerates were comprised of small adherent crystals (Fig. 1) and this particular structure was responsible for the large relative volume change, which occurred during the early stage of the compression process, as a consequence of fragmentation. Enhanced fragmentation during compression results in an increased contact point area which produces a strong bond between particles leading to formation of strong tablets (Kawashima et al., 2003).

3.6. Effect of disintegrant concentration on disintegration time of naproxen tablets

The amounts of disintegrant incorporated in naproxen agglomerates for different formulations is shown in Table 3.

Tablets made of naproxen agglomerates crystallized in absence of any disintegrant did not disintegrate even after 30 min. Incorporation of sodium starch glycolate or starch resulted in a reduction in the disintegration time (Table 4). The disintegration time decreased as a function of disintegrant concentration. Tablets containing starch were found to have longer disintegration times than tablets containing sodium starch glycolate (Table 4). Starch does not swell markedly in water and its mechanism of disintegration is based mainly on water penetration due to capillary action. This often develops insufficient internal pressure to induce complete tablet disintegration in low concentration (Gissinger and Stamm, 1980), whereas sodium starch glycolate swells very quickly and results in rapid tablet break-up. The mechanism by which this action takes place involves rapid absorption of water leading to an enormous increase in volume of granules result in rapid and uniform disintegration. Whereas the natural pre-dried starches swell 10–20% in water, the modified starches such as sodium starch glycolate increase in volume by 200–300%. The use of such modified starch enables the disintegration time to become independent of compression force (Liberman et al., 1989). The superiority of sodium starch glycolate in comparison to starch as a disintegrant has also been shown in an earlier study (Visavarungroj and Remon, 1990).

It is apparent that when the disintegrant was incorporated via the crystallo-*co*-agglomeration techniques that the disintegration of the resultant tablets was faster than if the tablets were produced by physical mixing of the disintegrant with naproxen (Table 4). For example when starch was added to the crystallization medium the disintegration time was 3.10 min, whereas the corresponding disintegration time for the naproxen tablets when an equivalent amount of starch was added physically, after obtaining recrystallized naproxen was 14.4 min. Similar results were obtained for the samples containing sodium starch glycolate.

The present results showed that when the disintegrants were located intragranularly (i.e. the disintegrant being present in the acetone solution) and extragranularly (i.e. the disintegrant

Table 4
Disintegration time of naproxen tablets of naproxen-disintegrant agglomerates and physical mixture of naproxen agglomerates with starch and sodium starch glycolate (SSG) as disintegrants

Disintegrant	Disintegrant/drug (%)	Disintegration time (min)	
		Naproxen-disintegrant agglomerates	Physical mixture of naproxen agglomerates with disintegrant
Starch	14.6	3.10 ± 0.12	14.4 ± 0.32
	8.4	13.67 ± 0.62	>30
	4	>30	>30
SSG	14.1	2.99 ± 0.09	7.67 ± 0.22
	4.7	4.76 ± 0.18	12.2 ± 0.35
	1.9	9.79 ± 0.54	>30

being present in the aqueous solution) during crystallization and agglomeration of naproxen then a lower disintegration time is obtained than when the disintegrants were blended physically in the same total concentration. The combined incorporation of disintegrant (sodium starch glycolate) both intra- and extragranularly in the preparation of paracetamol tablets has been shown to produce faster disintegration than extragranular incorporation alone (Khattab et al., 1993), due to the increased distribution uniformity of the disintegrant particle inside the tablet matrix (Zhao and Augsburger, 2006).

3.7. Effect of disintegration time on DR_i and AUC

Fast disintegration of tablets is a prerequisite for improving the dissolution of drug. The dissolution rate of all naproxen tablets were increased by increasing disintegrant content (Fig. 5). Moreover the results obtained indicated that dissolution rate of naproxen tablets made from agglomerated naproxen-disintegrant were higher than the dissolution rate of naproxen tablets made from physical mixtures of naproxen agglomerates with disintegrant. This is likely again to be attributable to the differences in the disposition of the disintegrant within the tablets. The extragranular portion ensures a rapid disintegration of the tablet mass, while the intragranular fraction which contributes

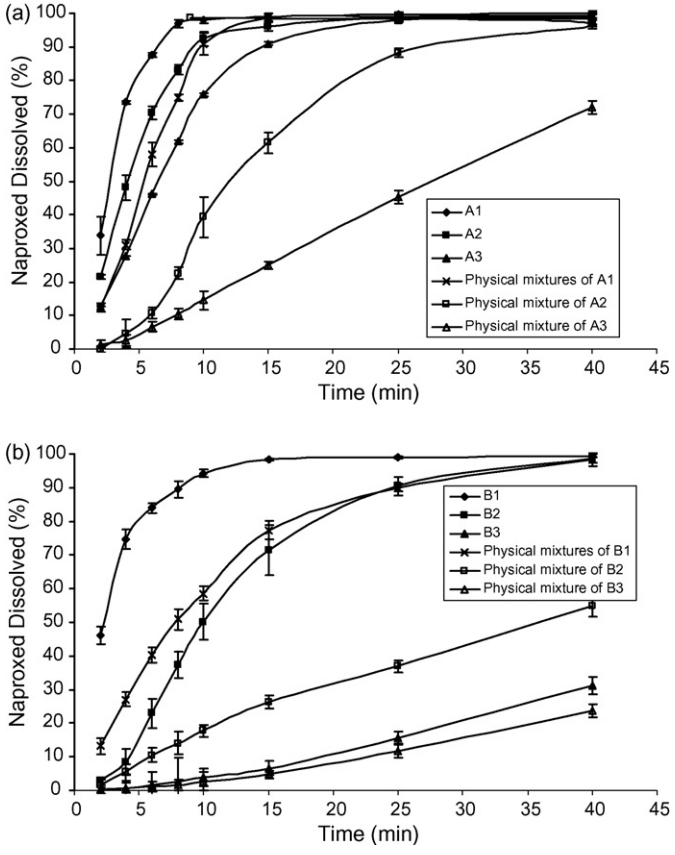

Fig. 5. Dissolution profile of naproxen-disintegrant agglomerates and physical mixture of naproxen agglomerates with disintegrant (a) sodium starch glycolate; (b) starch. A samples containing different concentrations of sodium starch glycolate: A1 (14.1%); A2 (4.7%) and A3 (1.9%); B samples containing starch: B1 (14.6%); B2 (8.4%) and B3 (4%).

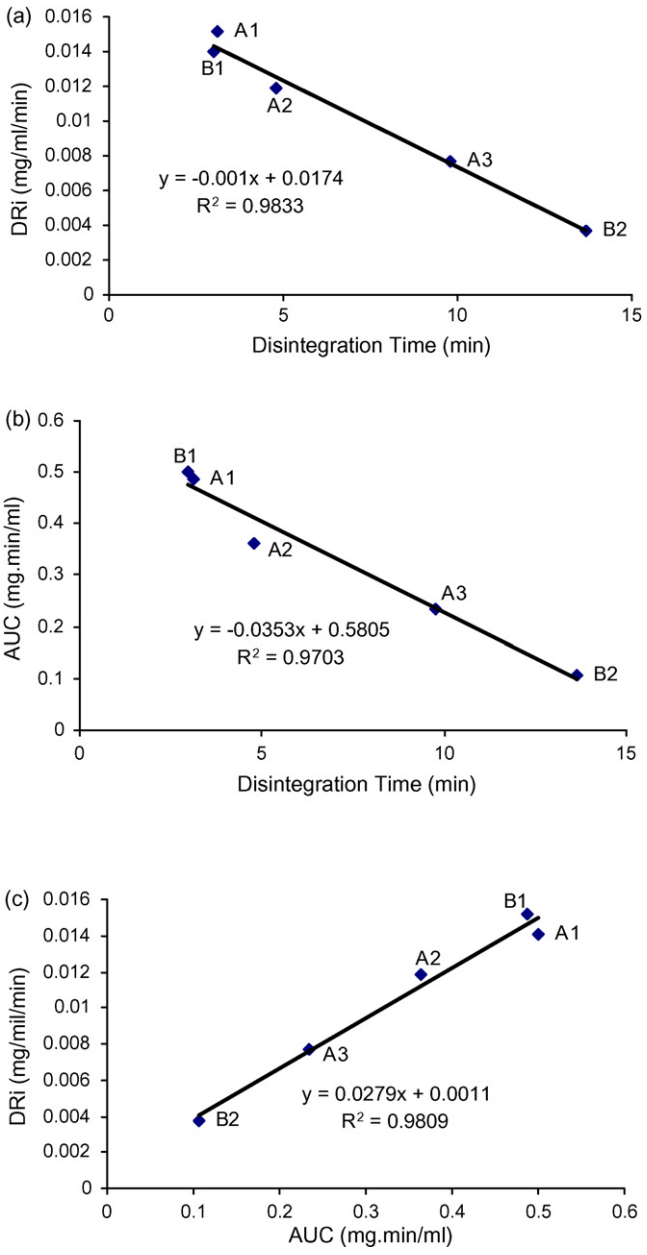

Fig. 6. The effect of tablet disintegration time on dissolution parameters of naproxen-disintegrant agglomerates with disintegrants (a) the initial dissolution rate (DR_i), (b) extent of dissolution (AUC), and (c) the correlation between the initial dissolution rate and extent of dissolution for naproxen-disintegrant agglomerates (for legends see Fig. 5).

to harder tablets leads to a fine size distribution of particles on dispersion which can then promote further disintegration of the aggregates directly into the primary particles. In the case of physical mixtures of drug and disintegrant, all of the disintegrant is included extragranularly then the tablet might be expected to break-up into agglomerates, but the agglomerates rather than disintegrating further, may then only dissolve.

With a poorly soluble tablet base, completely or partially undisintegrated granules can take an extended period of time to dissolve (Fig. 5). This study is in agreement with the findings of Miller et al. (1980) who demonstrated, using a combination of acetaminophen and microcrystalline cellulose tablet, that dis-

tribution of the croscarmellose sodium (a disintegrant) equally between both phases rather than incorporating all of the component extragranularly resulted in a faster dissolution.

Since disintegrant concentration influenced the disintegration time of the tablets as well as the dissolution of naproxen, it was expected that changes in disintegration time would be reflected in the dissolution profiles of naproxen. Indeed the DR_i and AUC increased linearly with decreasing disintegration time for tablets with the disintegration time below 30 min (Fig. 6a and b). The dissolution rate was directly proportional to disintegration rate of the tablets, and a rapid disintegration is especially desirable in the case of slightly soluble drugs (Fassihi, 1986). Extrapolation of these findings indicates that the AUC increases linearly with the initial dissolution rate of the drug (Fig. 6c). These results indicate that the dissolution of naproxen from tablets containing starch or sodium starch glycolate depend primarily on the disintegration time of the tablets.

Three parameters are very important when drug solid particles are used for tableting, flow, tensile strength of tablets and dissolution rate of drug. A comparison of the flow properties of agglomerates containing the two different disintegrants showed that flow was not affected by the disintegrant type ($p > 0.05$). However tablets produced from naproxen agglomerates containing sodium starch glycolate dissolved faster than the tablets containing starch ($p < 0.05$). Generally, the tensile strength of naproxen tablets containing sodium starch glycolate produced harder tablets in comparison with the tablets containing starch.

4. Conclusion

Naproxen-disintegrant agglomerates were successfully prepared for direct tableting by use of a crystallo-*co*-agglomeration technique. The micromeritics of the agglomerates, such as flowability, packability and compactibility were dramatically improved, resulting in successful direct tableting without capping. The main factor in the improvement of the flowability and packability was a significant reduction in interparticle friction, due to the spherical shape of the tableted particles. Compactibility of the agglomerates was much improved. The dissolution rate of naproxen from the naproxen-disintegrant agglomerates was enhanced significantly with increasing the amount of disintegrant. For the tablets prepared from naproxen-disintegrant agglomerates, having a dissolution time below 30 min, a linear relationship existed between disintegration time and DR_i and AUC.

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