AAPS PharmSciTech, Vol. 9, No. 1, March 2008 (© 2007)
DOI: 10.1208/s12249-007-9019-3

Research Article

Preparation of Spherical Crystal Agglomerates of Naproxen Containing Disintegrant for Direct Tablet Making by Spherical Crystallization Technique

A. Nokhodchi[1,2] and M. Maghsoodi[1,3]

Received 6 March 2007; accepted 25 September 2007; published online 9 January 2008

Abstract. The purpose of this research was to obtain directly compressible agglomerates of naproxen containing disintegrant by spherical crystallization technique. Acetone–water containing hydroxypropyl celloluse (HPC) and disintegrant was used as the crystallization system. In this study croscarmellose sodium (Ac–Di–Sol) was employed as disintegrant. The agglomerates were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD), and scanning electron microscopy and were evaluated for flow, packing and tableting properties and drug release. 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 their fragmentation occurred during compression. DSC and XRPD studies showed that naproxen particles, crystallized in the presence of HPC and Ac–Di–Sol did not undergo structural modifications. The dissolution rate of naproxen from tablets made of naproxen–(Ac–Di–Sol) agglomerates was enhanced significantly because of including the disintegrant in to the particles. This was attributed to an increase in the surface area of the practically water insoluble drug is exposed to the dissolution medium. In conclusion the spherical crystallization technique developed in this study is suitable for obtaining agglomerates of drug with disintegrant.

KEY WORDS: direct tableting; disintegration; naproxen; spherical crystallization.

INTRODUCTION

Direct tableting has been renewed as a preferred process by simply mixing and compressing powder to save time and cost in comparison with granule tableting. The direct tableting technique has been successfully applied to numerous drugs on the industrial scale. The success of any direct-tableting procedure and resulting mechanical properties of tablets are strongly affected by the quality of the crystals used in this process. When the mechanical properties of the drug particles are inadequate and preliminary granulation is necessary, spherical crystallization technique appears to be an efficient alternative for obtaining particle destined for direct tableting (1).

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step. Spherical crystallization technique has been successfully utilized for improvement of flowability and compactibility of crystalline drugs (2).

There are very few reports regarding application of this method for obtaining agglomerates of more than one drug (3). The present spherical crystallization method has been designed to obtain naproxen agglomerates containing disintegrant.

For tablets containing sparingly water soluble drugs, the start of dissolution is often delayed by the poor wettability of the tablet surface and /or slow liquid penetration in to the tablet matrix. This property causes increased disintegration time and retarded drug release that can be overcome by the addition of a disintegrant.

Direct compression as a method of tablet manufacture, however, puts many of the traditional disintegrants at a disadvantage due to the high concentrations needed, poor compression properties and poor disintegration in insoluble systems. A group of super disintegrants such as croscarmellose sodium (Ac–Di–Sol) alleviate most of these problems (4–6). In this study, Ac–Di–Sol was employed as disintegrant and in the process, naproxen was crystallized from acetone-water system and agglomerated with disintegrant. The aim of the present study was to evaluate the suitability of naproxen agglomerates prepared by spherical crystallization technique for direct tableting. This study also investigated the effect of Ac–Di–Sol on the flow, packing, tableting and release properties of the agglomerates.

MATERIAL AND METHODS

Materials

Naproxen (Shasun Chemicals, India), hydroxypropylcellulose, HPC (Nisso HPC-H, Nippon Soda, Japan), magne-

[1] School of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.
[2] Medway School of pharmacy, The Universities of Kent and Greenwich central Ave., ME4 TB, Kent, UK.
[3] To whom correspondence should be addressed. (e–mail: maghsoodim@tbzmed.ac.ir)

sium stearate (BDH, UK), croscarmellose sodium (Ac–Di–Sol, FMC, Philadelphia, USA) and acetone (Merck, Germany) were used.

Methods

HPC (0.25% *w/v*) was dissolved in 50 ml aqueous phase, Ac–Di–Sol (0.5% *w/v*) was added at room temperature and uniformly dispersed. Acetone (4 ml) at 50 °C containing 1 g naproxen was added to the above solution under fixed stirring conditions (200 rpm, paddle type agitator with four blades). The stirring was continued to obtain agglomerates (10 min), which were then filtered and dried overnight. The dried crystals were stored in screw-capped jars at room temperature before use.

The amount of Ac–Di–Sol included in the agglomerates was obtained by following method. Agglomerates were powdered and ethanol was added to the resultant powder under stirring condition. The solution was passed through a membrane filter (0.45 μm). Under these conditions, naproxen and any adsorbed HPC were dissolved in ethanol and the amount of Ac–Di–Sol retained on the filter paper was determined by gravimetric method. As a reference, the naproxen agglomerates were prepared by the same procedure in the absence of disintegrant.

Scanning Electron Microscopy (SEM)

The shape and surface topography of the agglomerates and conventional crystals were observed through a scanning electron microscope (LEO 440I, Cambridge, UK) operating at 15 kV after coating with gold. The shape factor defined as 4π (area/perimeter^2) with an image analyzer (scion image analyzer).

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, particle size of crystals was measured using the scanning electron micrographs. Each determination was carried out on a minimum of 100 crystals.

Measurement of Flowability

Flowability of the crystals was assessed by determining the compressibility index (Carr index) and the angle of repose. The Carr index (7) is a measure of the propensity of a powder to consolidate. Changes occurring in packing arrangement during the tapping procedure are expressed as the Carr index (Eq. 1).

$$\text{Carr index}\,(\%) = [(\rho_t - \rho_b)/\rho_t] \times 100 \tag{1}$$

Where ρ_t and ρ_b are tap density and bulk densities of powder bed, respectively.

The Carr index reflects the compressibility of the powders, and there is a correlation between the compressibility index and the flowability of the crystals.

The angle of repose was measured by a fixed funnel method (8). The results presented are mean value of six determinations.

Measurement of Compressibility

The compressibility of the samples was investigated by tapping them in to a 25-ml measuring cylinder using a tapping machine (Konishi Seisakusho Co., Japan). Initially, 25 g of substance was weighed and then was gently poured into a measuring cylinder. The volume of 25 g samples was recorded. The poured density (minimum density) was calculated from the powder mass (25 g) and the volume. Then the cylinder was tapped and the volume was recorded after every 100 taps until the volume did not change significantly. The compressibility was evaluated by measuring the tapped density according to the modified Kawakita (9) equation (Eq. 2):

$$\frac{n}{C} = \frac{1}{ab} + \frac{n}{a} \tag{2}$$

where a and b are the constants, n is the tap number, C denotes the volume reduction which can be calculated according to the Eq. 3,

$$C = \frac{V_0 - V_n}{V_0} \tag{3}$$

Where V_0 and V_n are the powder bed volumes at initial and nth tapped state, respectively.The data were also analyzed by Kuno (10) equation (Eq. 4):

$$\ln(\rho_f - \rho_n) = -kn + \ln(\rho_f - \rho_0) \tag{4}$$

where ρ_f, ρ_n and ρ_0 are the apparent densities at equilibrium, nth tapped and initial state, respectively, and k is the constant.

The compressibility was assessed by comparing the constants a, $1/b$ and k in Eqs. 2 and 4, respectively. The constant a represents the proportion of consolidation at the closest packing attained and constant $1/b$ describes cohesive properties of powders or the apparent packing velocity obtained by tapping. The constant k in Kuno's equation represents the rate of packing process.

X-Ray Diffraction of Powder (XRDP)

A Siemens (model D5000, Germany) X-ray diffractometer was used at 40 kV, 30 mA and a scanning rate of 0.06°min^{-1} over a range of 2–40 2θ, using $CuK_{\alpha 1}$ radiation of wavelength 1.5405 Å.

Differential Scanning Calorimeter (DSC)

Samples of naproxen crystals (5 mg) were heated (ranging from 25–200 °C) at 10 °C min^{-1} in hermetically sealed aluminum pans. The melting point and onset temperatures were automatically calculated (DSC60, Shimadzu, Japan).

Pressure–Tensile Strength Relationship

The samples (200±10 mg) were compressed using a 8-mm flat-faced punch at a compaction pressure of 10, 15, 20, 25 and

30 MPa, the compacts were held under load for 1 min (dwell time) using a hydraulic press (Riken Seiki Co, Japan). Lubrication of the die and punch was performed using 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 equation [11,12] $T = \frac{2F}{\pi Dt}$, 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 five determinations.

In Vitro Dissolution

The samples (200±10 mg) were compacted using a 8-mm flat-faced punch at a pressure of 10 MPa for a dwell time of 1 minute. As an increase in compression pressure did not improve the tensile strength of tablets significantly, therefore, the lowest compression pressure (10 MPa) was chosen for further studies. The dissolution tests were performed by the rotating paddle method (USP 26). A dissolution apparatus (8ST, Caleva, England) was employed with a stirring rate of 100 rpm and was maintained at 37± 0.1 °C. The dissolution medium was 900 ml pH 7.4 phosphate buffer.

Samples of the solution were withdrawn at definite time intervals (5, 10, 15, 20, 30, 45, 60 and 90 min) and then were passed through a membrane filter (0.45 μm). The amount of dissolved naproxen was analyzed spectrophotometrically (UV-160, Shimadzu, Japan) at 330.8 nm.

Calculation of Dissolution Parameters

The initial dissolution rate (DR_i, mg/ml per min) represented the slop of the dissolution curve between t_0 and t_{15}. The slope was determined through linear regression analysis. The area under the dissolution curve (AUC, mg min/ml) between t_0 and t_{90} was considered as an indication of drug dissolution extent and was calculated using the trapezoidal rule (13).

Disintegration Time

Disintegration testing (six tablets) was performed at 37 °C in phosphate buffer (pH 7.4) using the European pharmacopoeia apparatus (Erweka ZT3, Erweka, Heusensenstamm, Germany) without disc. Disintegration time (DT) and dissolution profile of naproxen–(Ac–Di–Sol) agglomerates was compared with physical mixture of naproxen agglomerates and same amount of Ac–Di–Sol to evaluate efficiency of disintegrant incorporated during agglomeration.

RESULTS AND DISCUSSION

Table I summarizes the micromeritic data obtained for the untreated naproxen and the agglomerates produced without and with Ac–Di–Sol. The geometric mean diameter and the geometric standard deviation of agglomerates were respectively larger and smaller than those of the untreated naproxen, indicating the spherical crystallization process uniformly agglomerated the original single crystals. The mean diameters of the agglomerated particles were approximately 50 times higher than those of the untreated crystals.

Figure 1 illustrates the untreated naproxen, naproxen particles crystallized from media containing HPC in the absence of Ac–Di–Sol and naproxen–(Ac–Di–Sol) agglomerates.

The untreated naproxen particles were plate-like in appearance, whereas naproxen crystallized from acetone-water system in presence of HPC were spherical agglomerates.

SEMs with higher magnification revealed that agglomerates were spherical aggregates of plate shaped crystals. SEMs of naproxen–(Ac–Di–Sol) agglomerates clearly indicate that the use of disintegrant in the crystallization media had no a major effect on the size of naproxen particles in comparison with those obtained in the absence of the disintegrant whereas a marked difference in the surface topography was found. This was due to an increase in the surface roughness of particles in the presence of disintegrant.

As far as CI and angle of repose are concerned (Table I), it is seen that both decrease in the agglomerates as compared to the untreated naproxen. The sphericity of the agglomerates, represented in terms of the shape factor, is shown in Table I. Agglomerates were spherical in shape compared with the untreated naproxen. On the basis of these finding, it was considered that good flowability for agglomerates were attributable to the spherical shape, since the area of contacts in the powder bed for spherical agglomerates was smaller than that for plate-shaped conventional crystals.

Table II summarizes the compressibility parameters data obtained for the samples via the modified Kawakita and Kuno equations (Eqs. 2 and 4)**.** The low values of the Carr index and parameter a of the Kawakita equation for the agglomerates indicated that the agglomerated powders have better compressibility. In other words they are well packed

Table I. Micromeritic Properties of Naproxen Samples

Samples	Geometric Standard Deviation	Geometric Mean Diameter (μm)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	CI (%)	Angle of Repose (o)	Shape Factor
Naproxen–(Ac–Di–Sol) agglomerates	1.27	534.9	0.261±0.002	0.290±0.002	7.61±0.05	36.4±0.5	0.95
Naproxen agglomerates	1.25	548.3	0.215±0.002	0.238±0.001	7.98±0.04	37.5±0.4	0.98
Untreated naproxen	1.75	10.2	0.370±0.002	0.590±0.003	28.50±0.76	58.8±0.6	–

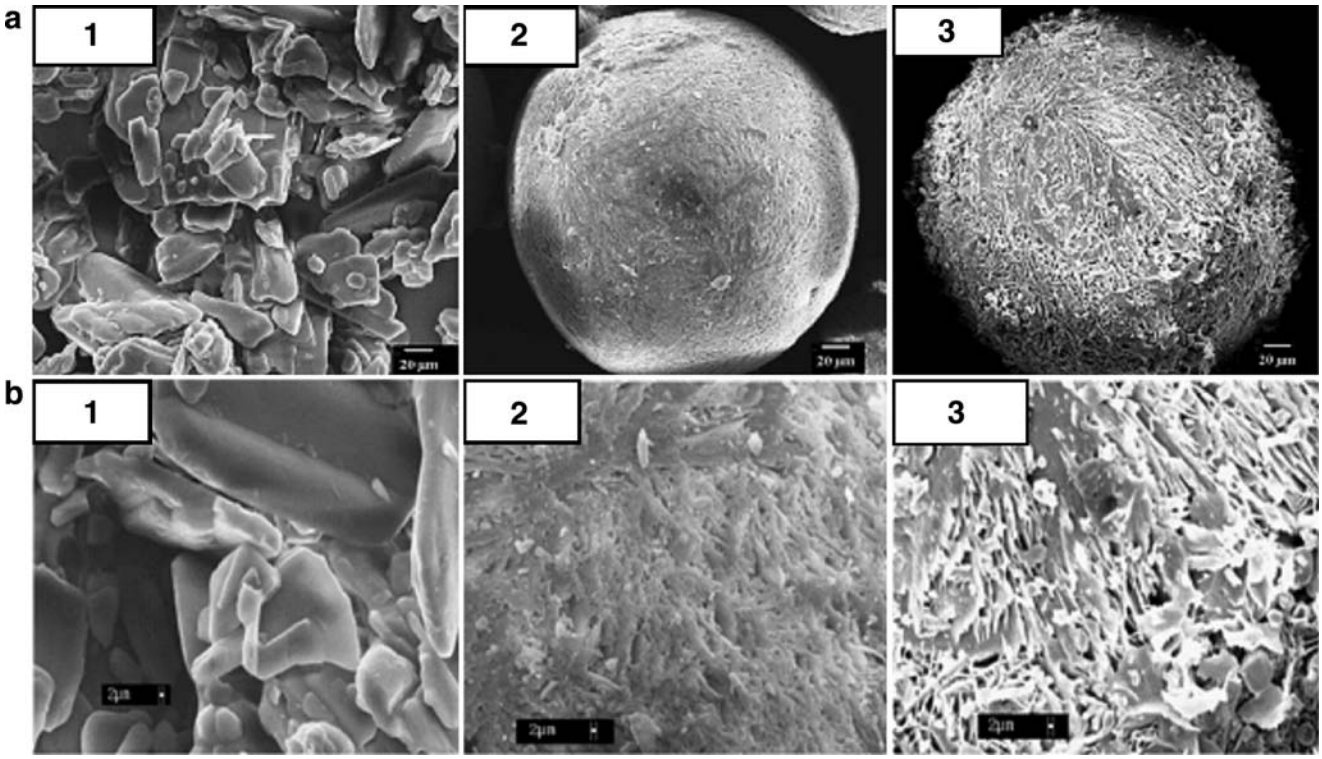

Fig. 1. Scanning electron micrographs of appearance **a** and surface **b** of naproxen particles: (*1*) untreated naproxen (*2*) naproxen agglomerates (*3*) naproxen–(Ac–Di–Sol) agglomerates

before tapping since tapping does not improve the packing significantly.

The large 1/*b*-value of agglomerates indicated that the apparent packing velocity obtained by tapping for the agglomerates was slower or the cohesiveness of the agglomerates was larger than that for the untreated particles, since the agglomerates were packed more closely, even without any tapping, as a consequence of their better flowability and compressibility. The larger k (derived from Eq. 4) obtained for the agglomerates confirmed these findings. According to these results, Ac–Di–Sol in 0.5% (*w*/*v*) concentration in crystallization medium had no significant effect on size, flowability and compressibility of the agglomerates.

In spite of better compressibility of the agglomerates, the bulk and tapped densities of the agglomerates are lower than those of the untreated sample (Table I). In fact, the only way to have better packing and lower bulk density is to have less dense particles and hence porous particles. The results of SEM supported this conclusion. SEMs of the untreated naproxen and the agglomerates with high magnification (Fig. 1) revealed that there was no evidence of porosity in the untreated naproxen whereas the agglomerated particles showed clear evidence of being porous.

The improved flow properties and compressibility of the agglomerated crystals would indicate that they might be directly compressible; whereas, the non-agglomerated drug would be predicted to be not directly compressible due to its poor flow properties.

X-ray powder diffraction pattern (XRPD) in the 10–40 2θ range showed that the diffraction peaks of naproxen were still detectable in the crystallized samples (Fig. 2), suggesting that particles crystallized in the presence of HPC and disintegrant did not undergo structural modifications. How-

Table II. Packability Parameters of Naproxen Samples

Samples	a^a	$1/b^a$	k^b
Naproxen–(Ac–Di–Sol) agglomerates	0.105(r=0.998)	52.632	0.005 (r=0.999)
Naproxen agglomerates	0.098 (r=0.999)	58.823	0.005 (r=0.999)
Untreated naproxen	0.373 (r=0.998)	12.500	0.0035 (r=0.997)

r Correlation coefficient
[a] Parameters in Eq. 1
[b] Parameter in Eq. 3

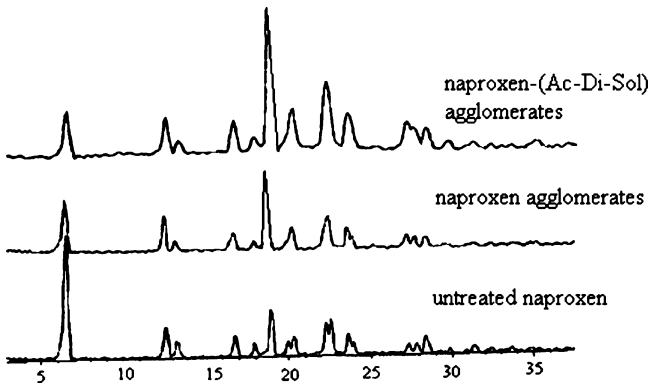

Fig. 2. The X-ray diffraction spectra of naproxen samples

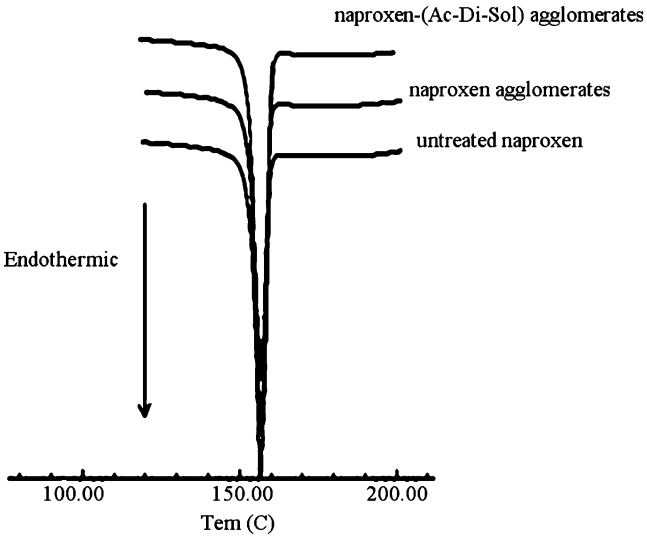

Fig. 3. DSC thermograms of naproxen samples

ever, the differences in the relative intensities of their peaks may be attributed to differences in the crystalinity of the samples (14).

The uniformity of crystalline structure in all batches was confirmed by DSC. The agglomerates showed a sharp melting point with flat baseline, which indicated that the material was not affected by hydration, solvation, polymorphic transition and no interaction with disintegrant, had occurred during crystallization of the particles (Fig. 3). DSC and X-ray analysis, which didn't detect any change of the crystalline form of naproxen or any interaction with disintegrant showed that the Ac–Di–Sol could be incorporated physically into the agglomerates by the adhesion to the surface of the particles.

This was confirmed by SEMs that showed adhesion of fine particles to the surface of the naproxen–(Ac–Di–Sol) agglomerates in comparison with naproxen agglomerates.

The tensile strength of tablets prepared with the agglomerated crystals or the untreated drug crystals is plotted as a function of compression pressure in Fig. 4. The results showed that the tablets made of untreated naproxen particles were prone to capping at compression pressures above 10 MPa. Whereas, the agglomerated crystals were successfully tableted without capping at any compression pressure applied. This was the main reason for higher tensile strength

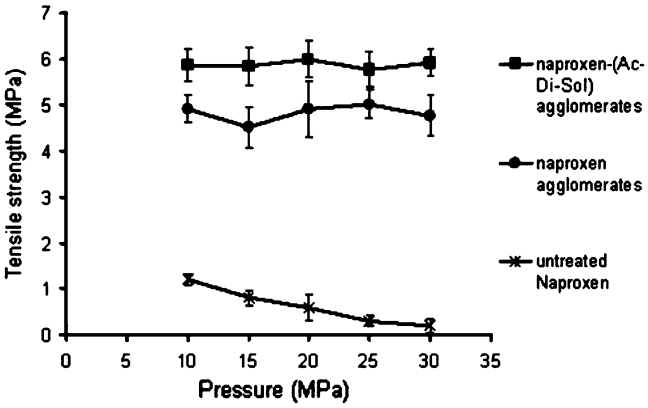

Fig. 4. The tensile strengths of the tablets made from naproxen samples

Table III. The Initial Dissolution Rate (DR_i), Area under the Dissolution Curve (AUC) and Disintegration Time (DT) of Tablets Made from Naproxen Agglomerates, Naproxen–(Ac–Di–Sol) Agglomerates and Physical Mixture of Naproxen Agglomerates and Ac–Di–Sol

	Tablets Made From		
Samples	Naproxen Agglomerates	Physical Mixture Of Naproxen Agglomerates and Ac–Di–Sol	Naproxen–(Ac–Di–Sol) Agglomerates
DT (min)	>30	5.50±0.64	2.10±0.49
$DR_i \times 10^{-3}$ (mg/ml per min)	1.0±0.1	4.3±0.1	6.3±0.1
$AUC \times 10^{-1}$ (mg min/ml)	9.20±1.60	33.90±1.34	68.70±2.14

of tablets made from agglomerated particles in comparison with the tablets made from the untreated sample. The Figure also showed that the tensile strength of tablets made of naproxen agglomerates was not affected by compression pressure. This might be due to the similar porosities of tablets made at the different pressures. It has been shown that during the compaction of highly compressible and compactible agglomerates porosity of the tablets is not affected by the compaction pressure, hence the tensile strength of the tablets (15). In these conditions little pressure is enough to reduce the porosity to the lowest level.

The improved compactability of the agglomerates was attributed to their structural characteristics. The agglomerates were comprised of small crystals, as shown in 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 resulting in increasing the contact point area to produce a strong bond between particles leading to strong tablets (16). It has been shown that Ac-Di-Sol had little effect on the tensile strength of tablets (17), similar to the results obtained in this study and

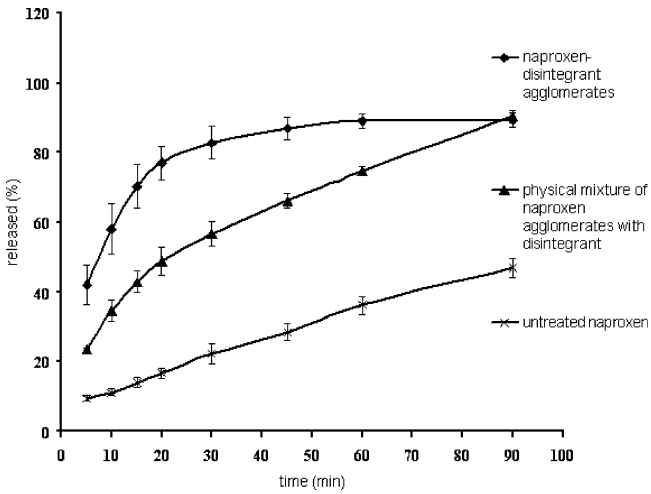

Fig. 5. Dissolution profile of naproxen agglomerates, naproxen–(Ac–Di–Sol) agglomerates and physical mixture of naproxen agglomerates and Ac–Di–Sol

there is no significant difference between the tensile strength of tablets made from naproxen agglomerates and naproxen–(Ac–Di–Sol) agglomerates at all compression pressures applied.

Naproxen tablets without any excipient did not disintegrate even after 30 min. The naproxen agglomerates obtained in presence of 0.5% *w*/*v* Ac–Di–Sol in crystallization medium resulted in a reduction in DT to about 2 min (Table III). This fast disintegration was due to the presence of 4% *w*/*w* Ac–Di–Sol in the agglomerates. It has been shown that the presence of Ac–Di–Sol in tablets improved the dissolution rate through an increase in the rate and extent of liquid uptake by the tablets. This will in turn cause a rapid disintegration of the tablets and thus dissolution rate of the drug (17).

Fast disintegration of tablets is a prerequisite for improving the dissolution of drug. This could be attributed to an increase in the surface area of the practically water insoluble drug exposed to the dissolution medium after disintegration of tablet. Therefore it was expected that any changes in disintegration time would alter the dissolution profiles of naproxen. Our results also showed that a reduction in the disintegration time resulted in an increase in the dissolution rate of naproxen tablets (Fig. 5 and Table III). Table III also showed that a decrease in DT resulted in an increase in the initial dissolution rate (DRi) and the extent of dissolution (AUC). On the basis of these findings, it can be concluded that the difference in dissolution profiles of the formulations was mainly due to the different disintegration times.

The results showed that the method of disintegrant incorporation influenced the disintegration time of the tablets and hence dissolution rate. For the naproxen–(Ac–Di–Sol) agglomerates which contain 4% w/w disintegrant, a higher drug dissolution rate in comparison with the physical mixture of naproxen agglomerates with the same amount of Ac–Di–Sol was observed (Fig. 5 and Table III). This is probably due to the presence of the micronized hydrophilic Ac–Di–Sol particles on the surface of the hydrophobic drug particles during the agglomeration process, resulting in a better disintegrant distribution in the agglomerates.

CONCLUSION

Spherical crystallization technique can be applied to produce drug-disintegrant agglomerates with modified properties. Naproxen-disintegrant agglomerates produced in this investigation showed dramatically improved micromeritic properties such as flowability, compressibility and compactibility and could be compressed successfully by direct tableting. Incorporation of disintegrant during agglomeration significantly enhanced the dissolution rate of naproxen. The results indicate the importance of the spherical crystallization technique to obtain directly compressible agglomerates of combination of drugs and excipients in required proportion.

REFERENCES

1. A. Ribardiere, P. Tchoreoff, G. Couarraze, and F. Puisieux. Modification of ketoprofen bead structure produced by the spherical crystallization technique with a two-solvent system. *Int. J. Pharm.* **144**:195–207 (1996).
2. A. R. Paradkar, A. P. Pawar, K. R. Mahadik, and S. S. Kadam. Spherical crystallization: a novel particle design technique. *Indian Drugs* **31**no. 6, 229–233 (1994).
3. Y. Kawashima, Y. Lin, M. Ogawa, T. Handa, and H. Takenaka. Prolonged release microcapsules of indomethacin through spherical crystallization technique. *J. Pharm. Sci.* **74**:1152–1156 (1985).
4. D. Gissing and A. Stamm. A comparative study of cross-linked carboxy-methylcellulose as a tablet disintegrant. *Pharm. Ind.* **42**:189–192 (1980).
5. N. Munoz, C. Ferrero, A. Munoz-Ruiz, M. V. Velasco, and M. R. Jimenez-Castellanos. Effect of explotab on the tabletability of a poorly soluble drug. *Drug Dev. Ind. Pharm.* **42**:785–791 (1998).
6. C. Ferrero, N. Munoz, M. V. Velasco, A. Munoz-Ruiz, and M. R. Jimenez-Castellanos. Disintegration efficiency of croscarmellose sodium in a direct compression formulation. *Int. J. Pharm.* **147**:11–21 (1997).
7. R. L. Carr. Evaluation flow properties of solids. *Chem. Eng.* **72**:163–168 (1965).
8. N. Pilpel. The flow properties of magnesia. *J. Pharm. Pharmacol* **16**:705–716 (1964).
9. K. Kawakita and Y. Tsutsumi. A comparison of equations for powder compression. *Bull. Chem. Soc. Jap.* **39**:1364–1368 (1966).
10. H. Kuno, T. In Kubo, G. Jimbo, E. Saito, H. Takahashi, and S. Hayakawa, eds. Powder Theory and Application, Chap. 5, Maruzen, Tokyo, 1979, pp. 341–346.
11. A. Rundick, A. R. Hunter, and F. C. Holden. An analysis of the diametral compression test. *Mater. Res. Stand.* **3**:283–289 (1963).
12. J. T. Fell and J. M. Newton. Determination of tablet strength by the diametral-compression test. *J. Pharm. Sci.* **59**:688–691 (1970).
13. M. H. Rubinstein. The effect of disintegrants and processing on the bioavailability of furesemide from compressed tablets. *Drug Dev. Ind. Pharm.* **6**:105–119 (1980).
14. M. Jbiilou, A. Ettabia, A. M. Gguyot-Hermann, and J. C. Guyot. Ibuprofen agglomerate preparation by phase separation. *Drug Dev. Ind. Pharm.* **25**no. 3, 297–305 (1999).
15. A. Nokhodchi, M. Maghsoodi, D. Hassan-zadeh, and Barzegar-Jalali. Preparation of agglomerated crystals for improving flowability and compactibility of poorly flowable and compactible drugs and excipients. *Powder Technol.* **175**:73–81 (2007).
16. Y. Kawashima, M. Imai, H. Takeuchi, H. Yamamoto, K. Kamiya, and T. Hino. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. *Powder Technol* **130**:283–289 (2003).
17. A. F. Marais, M. Song, and M. M. Villiersde. Effect of compression force, humidity and disintegrant concentration on the disintegration and dissolution of directly compressed furosemide tablets using croscarmellose sodium as disintegrant. *Trop. J. Pharm. Res.* **2**no. 1, 125–135 (2003).