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Engineering Spherical Beads as an Approach to Improve the Physico-Mechanical Properties of Poorly Soluble Drugs

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Abstract

Improving oral bioavailability of drugs given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. To address this encumbrance, ionotropic gelation technique has attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by engineering spherical agglomerates. Spherical beads of poorly water soluble drug, piroxicam, were formulated by dispersing the drug in solutions of ionic polysaccharide sodium alginate and then dropping these dispersions into a solution of the counterion calcium chloride. The droplets rapidly created gelled spheres by ionotropic gelation. Strong spherical beads could be engineered with high yield and a drug content approaching 100%. The flow characteristics of micronized rods like crystals were significantly enhanced by this agglomeration technique when compared to the non-agglomerated drug crystals. Furthermore, scanning electron microscopy, size, image analysis, dissolution profiles and compression properties of piroxicam beads were evaluated. Beads engineered by using 1% sodium alginate and 3% calcium chloride gave the most desirable results as compared to other compositions.

Key words: Spherical beads; piroxicam; agglomeration technique;physico-mechanical properties.

1. Introduction

Piroxicam belongs to the class of acidic non-steroidal anti-inflammatory drugs. It is used as an effective analgesic and anti-inflammatory agent in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute pain in musculoskeletal disorders and acute gout [1]. It has been shown to be an effective analgesic in fracture, dental, postoperative and postpartum pain[2] .Piroxicam is practically insoluble in water , resulting in unpredictable absorption from the gastrointestinal tract. This water insolubility urged the trials to enhance its dissolution via crystal modification technique [3,4]. The polysaccharides used to agglomerate the drug have a well- established pharmaceutical and biomedical history. Alginates are hydrophilic colloidal polysaccharides obtained from cell walls of certain algae and seaweeds. These molecules are block copolymers of D-mannuronic acid and L-guluronic acid [5]. Sodium alginate forms gels with multivalent cations such as calcium. In pharmaceutical formulation technology, alginates have been used as tablet binders, disintegrants, viscosity-enhancing agents, and sustained-release matrices [6].The aim of our work was to employ a simple technique which allows the conversion of drug crystals into free-flowing beads in a completely aqueous environment and as a result improving the dissolution profiles of the drug. Spherical agglomerates of piroxicam were engineered by extruding sodium alginate-drug dispersions as droplets into an aqueous solution of the counterion $CaCl_2$.

2. Materials and methods

2.1. Materials

Piroxicam (Batch No. SBML/TMZ/708030) was kindly supplied from El-Nasr Pharmaceutica Company, Egypt. Calcium chloride ($CaCl_2$), pepsin, pancreatin and sodium alginate were purchased through Sigma-Aldrich, USA. Magnesium stearate, sodium hydroxide, sodium chloride, hydrochloric acid, acetone, ethanol and monobasic potassium phosphate were purchased from ADWEC, Egypt. Double-distilled water was used throughout the study.

2.2. Beads formation

The percent composition of the prepared piroxicam beads is reported in Table 1. The drug [100% (w/w) of total solids] was dispersed into aqueous solutions of sodium alginate [0.5, 1 and 1.5% (w/v) in deionized water]. These dispersions were formulated using a magnetic stirrer (jenway L1D, UK), under constant stirring (500 rpm) at $25 \pm 0.5\ ^{o}C$ for 15 min. The beads were engineered by dropping the dispersion (3mL/min) through a disposable syringe (6 gauge needle) onto 30 mL of gently agitated aqueous solutions of the counterion $CaCl_2$ (1, 3 and 7% v/v). The gelled beads were separated after 5 minutes, rinsed with deionized water and air dried for 24 hours, followed by drying at 60 ºC for 6 hours in oven (Stork Tonic, Germany). All batches were prepared in duplicate. Piroxicam powder was allowed to crystallize from an ethanolic solution by fast cooling where the drug was precipitated as rods and used for comparisons.

2.3. Evaluation of the engineered beads

2.3.1. Drug content and solubility

The drug content of the prepared beads was determined spectrophotometrically(Shimadzu UV-1601 PC, Kyoto, Japan) after extracting the beads within a simulated intestinal fluid (SIF) at 356 nm. The solubility of piroxicam beads was evaluated by placing an excess amount of drug in contact with water, simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Samples were shaken in a thermostatically controlled mechanical shaker (Gallenkamp, England) at 160 rpm for at least 48 h at 22 ºC. The samples were filtered and solubility was obtained by measuring the drug concentration spectrophotometrically at 356, 333 and 356 nm, respectively. Experiments were carried out in triplicates.

2.3.2.Bead size and morphology by scanning electron microscopy (SEM).

The morphology of the piroxicam beads was evaluated using Scanning Electron Microscope (Jeol JXA-840A, Japan) and compared to that of untreated piroxicam. Prior to imaging, the samples were sputter-coated with gold for 3 min. The size of the prepared beads was also determined by light scattering based on laser diffraction using the Malvern Mastersizer (Malvern Instruments Ltd., Worcestershire, UK). The measurements were performed using a 45 mm focus objective and a beam length of 2.4 mm.

2.3.3. Image processing analysis

Shape analysis of piroxicam beads under study was determined by optical microscopy (Leica Galen III, Japan). A small amount of each powder was spread on a glass slide and distributed using a camel-hair brush. The slide was then mounted on an optical microscope and the images of the particles were transferred to an IBM compatible computer through a digital color camera (Samsung model SDC – 312, Japan). Particle images were analyzed automatically using image processing and analysis software (Scion Image Beta 4.03, Scion Corporation, Maryland, USA). Approximately, 40-60 particles were examined for each powder type. The particle shape and surface texture were quantified by two parameters derived from perimeter, area and convex area of the projected images of particles, namely, circularity [7] and fullness ratio [8,9]. Circularity = $(4\ \pi\ \text{x area}) / \text{Perimeter}^{2}$Fullness ratio = $(\text{area} / \text{convex area})^{½}$

Where, convex area is the area of the polygon circumscribing the particle projection, formed by tangents to its boundary. Results were reported as the mean (±S.D.) of five replicates.

2.3.4. Flowability characteristics

The flow properties of the prepared beads as well as drug powder as received and crystals were assessed by angle of repose ($\tan \theta = h / r$), the determination of Bulk Densities, Hausner ratio (Tapped density / initial density) and Carr's index (C_i) [(Tapped density –initial density)/ Tapped density X 100%] [10,11].

2.3.5. Dissolution studies

The release properties of piroxicam beads (40 mg) were studied in 900 ml SGF or SIF using USP Dissolution apparatus 2 (Hanson research, chatsworth, USA).The paddle speed was set at 50rpm and the dissolution medium was maintained at a temperature of 37 ± 0.5 ºC. At predetermined time intervals for a total period of 3 h, aliquots were withdrawn and the drug content was determined spectrophotometrically. The results were the mean values of three runs. The obtained data was subsequently analyzed to determine the order of release.

2.3.6. Compression properties

2.3.6.1. Preparation of compacts

Compacts were prepared directly from piroxicam powders using 8 mm flat-faced punches on a hydraulic press (International Crystal laboratories, Garifield, USA). The material for each compact was weighed (200 mg), introduced into the die and compacted at increasing compression pressures of 3000, 5000 and 7000 psi. The compaction surfaces were lubricated with 2% w/v, magnesium stearate in acetone before compaction. The compacts were held under load for 15 seconds, ejected and stored in a dessicator at room temperature for 24 hours before testing to allow for possible elastic recovery.

2.3.6.2. Determination of compact dimensions, porosity and crushing strength

Thickness and diameter of intact compacts were measured with a vernier caliper (Shanghai, China) having an accuracy of 0.01 mm. The porosity, ε, of the compacts was calculated by the equation [12]: $\varepsilon = 100\ (1 - V_c / V_o)$

Where, V_c is the volume of the resulting compact, which is calculated from the measured diameter, and thickness and V_o is the compact volume at zero porosity. Crushing strength was measured with a tablet hardness tester (model 6 D, Pharmatron, USA). It was not possible to obtain the idealized diametrical breaking because of the fragile nature of the compacts, so the crushing strength was employed instead of tensile strength. The results of porosity and crushing strength were the mean of three measurements.

2.3.6.3. Determination of powder immediate elastic recovery

The immediate apparent elastic recovery was calculated according to Armstrong and Haines – Nutt [13] :% Immediate apparent elastic recovery (E) = $[t2 - t_1) / t_1]X100$

Where, t_1 is the minimal thickness of the powder in the die when the upper punch displacement was maximal and t_2 is the powder thickness at the end of compression, before ejection. The results are the mean of triplicate measurement.

3. Results and Discussion

3.1. Piroxicam beads can be successfully generated by spherical agglomeration technique

In the spherical crystallization methods, agglomerates of pure drug were formulated from drug solutions using a partially miscible solvent system such as water: ethanol: chloroform. Drug crystallization during agglomeration resulted in the formation of different polymorphs[14]. Spherical agglomerates of almost pure drug were engineered from drug dispersions, thus probably eliminating polymorphic transformations during bead formation. Moreover, the drug crystals were agglomerated in a completely aqueous environment under mild conditions [6].

The entrapment efficiency of piroxicam beads within calcium alginate is shown in Table 2. High drug loadings were achieved for all beads. Except for the small amount of drug lost to the external phase, the product recovery or yield was complete. Mechanically, strong spherical beads with drug content up to 100% could be prepared. The actual drug content was very close to the theoretical content, indicating minimal diffusion or loss of drug to the external phase during bead formation.All beads possessed higher solubility in water and most of them except B6 and B9 showed higher solubility in SIF compared to drug powder and crystal (Table 2). This may reflect the improvement in the solubilization process due to the process of spherical agglomeration of piroxicam. In SGF, most beads exhibited lower solubility compared to drug powder and crystal except B1, B4, B5 and B7. The solubility results were consistent with the molar solubility of alginate salts in acidic and alkaline media where calcium alginate beads stayed intact in SGF but rapidly disintegrated and solubilized in SIF.

Visual inspection of the raw material showed small, rectangular or “columnar-like” particles with smooth surfaces and sharp edges (Fig. 1a). The effect of alginate pelletization on piroxicam particles shape and surface texture was quite variable depending significantly on alginate level. Piroxicam beads obtained in presence of 0.5% alginate (B1) were irregular structures with smooth surfaces (Fig. 1b). Beads obtained in presence of 1% and 1.5% (B5 and B9, respectively) exhibited high spheronisation with extensive surface cavitation and roughness [Fig. 1c &d].

The particle size of the wet beads was determined by the size of the droplets extruded from the syringe. The size of the dried beads depended primarily on alginate ratio. The average particle size could be varied between 99.35µm to 1.02mm. There was no significant difference in the particle size of the beads, so the main influence on flowability and compression could be attributed to particle sphericity and surface properties, not to particle size. Minute differences between piroxicam beads were further characterized by Image Processing Analysis. The analysis system allows the calculation of two shape descriptors namely, circularity (the approximation for the shape of a sphere) and fullness ratio (the ratio of particle surface area to the area of the polygon circumscribing the particle projection, formed by tangents to its boundary). Circularity is mainly related to particle geometry [7] and fullness ratio to surface smoothness [8,9]. These shape parameters assume a value of one for a sphere with a smooth surface. Therefore, the closer the values of the shape parameter to one, it will be the higher the shape symmetry and the smoother the particle surfaces. As shown in Table 3, Beads (B1, B4, B7) exhibited lower circularity compared to other beads, meaning a less spherical shape. On the other hand, no significant alterations could be observed between beads (B2, B5, B8) and (B3, B6, B9). This fact may suggest that the influence of alginate on the morphology of the beads is a non-continuous process and it starts to level off after 1%. In contrary to SEM, the image analysis revealed homogenous fullness ratio values suggesting that surface texture is not affected by alginate or calcium chloride levels. However, the image analysis results indicated that (B5 and B6) showed the most spherical shape and the smoothest surfaces.

3.2. Piroxicam beads achieved improved Flowability

The flow properties of the drug powder or rode-like crystals were significantly improved by the spherical agglomeration method. Piroxicam beads had higher initial and tapped densities than that of the drug powder and crystals. This may be attributed to the effect of granulation on the bulk density where granules were denser than the parent powder mix; occupy less volume per unit weight [15].Angle of repose, Hausner ratio and Carr's index are considered as indirect method for quantifying powder flowability. The followings are the values assigned to be indicative of good flow properties [10,11]:25-30° for angle of repose, < 1.25 for Hausner ratio and 5-15% for Carr's index. Drug beads had lower values of angle of repose, Hausner ratio and Carr's index than drug powder indicating better flow behavior. The values of the drug granules were all lying in the range of good flowability. Piroxicam is a fine fluffy cohesive powder; pharmaceutical granules produced from cohesive powders will be larger and more isodiametric, both factors contributing to improve the flow properties[15]. B5 and B6 exhibited the lowest angle of repose with the lowest values of Carr᾿s index and Hausner ratio for B5. The results of flowability could be explained by the interplay of bead size, bead surface texture and bead circularity.

3.2. **Spherical agglomerates showed improved dissolution rates.**

Piroxicam crystals in SGF exhibited higher rate of dissolution when compared with the drug powder and beads (Fig. 3). The in-vitro dissolution of the drug powder and crystals reached 37.58% and 52.76% within 1 h, respectively. On the other hand, the dissolution of the drug beads ranged from 19% to 48. In SIF, drug beads showed faster dissolution compared to the drug powder and crystals except B6 and B9. The explanation to this finding was that the process of agglomeration is a means of improving the dissolution process of a poorly soluble drug. It is clear that the dissolution of the drug beads varied depending mainly on the percent of sodium alginate. The increase in the concentration of sodium alginate led to slight retardation of drug dissolution. Beads (B1) reached 100% of the drug dissolution after 45min. This may be attributed to the fact that beads (B1) contain the least amount of both $CaCl_2$ and sodium alginate followed by beads B4 which exhibited 100% after 1 h. It is noted that beads (B5) exhibited better dissolution results, 98% after one hour, than that of beads (B7), 97%, although it contained higher percent of sodium alginate. This may be due to the fact that B5 showed better flowability. Moreover, there was a difference in the percent of $CaCl_2$ where beads (B5) contained 3% $CaCl_2$ and beads (B7) contained 7% $CaCl_2$. The amount of the drug released in SGF is much slower than that in SIF because of the limited solubility of the drug in SGF. In addition, calcium alginate beads stayed intact in SGF and did not disintegrated within one hour but rapidly disintegrated in SIF. Kinetic analysis of the dissolution data of piroxicambeads, powder and crystals in SGF and SIF was done using linear regression according to zero-order, first-order and Higushi diffusion model.The correlation coefficient [r^2] of the kinetic treatment of the release data was calculated in each case. These data reveals that in SGF, drug powder, B5, B7 and B9 exhibited zero order kinetics while the other beads and drug crystals exhibited first order kinetics. In SIF, drug powder, B4 and B9 exhibited zero order release while the other beads and drug crystals exhibited first order release. The two-way Analysis of Variance (ANOVA) was performed to determine the significance of difference between the increased concentrations of sodium alginate and $CaCl_2$ on the dissolution characteristics of piroxicam beads at a significant level of $\alpha = 0.05$. It was found that there was no significant difference between different piroxicam beads upon changing the concentration of $CaCl_2$. There was a significant difference concerning different piroxicam beads upon changing the percent of sodium alginate. This may verify that the recorded improvement in the rate of drug dissolution for the drug beads was significant.

3.3. Compression properties

Compression of untreated piroxicam and piroxicam crystals, at all compaction pressures, produced weak compacts with low crushing strength, Table 4. Piroxicam beads showed considerable improvement in the strength of the resulting compacts. The influence of the initial particle size on the compact tensile strength is often conflicting. For most powdered pharmaceuticals, compaction of smaller particles resulted in stronger tablets because the smaller particles provide a large total area for bonding than larger particles. However, the effects of the initial particle size on the strength of tablets depend on the mechanical properties of the materials. For example, tablet strength more or less independent of particle size was observed for materials undergoing extensive fragmentation such as calcium phosphate dihydrate and sucrose[16].For materials known to undergo a combination of brittle facture and plastic deformation such as lactose and sodium citrate, the most common relationship found was an increase in tablet strength with a decrease of particle size. For the plastically deforming or low-fragmenting materials, as cubic sodium chloride, the general tendency is increased tablet strength with increased particle size[16]. In a later study[17], tablet strength more-or-less independent of particle size was observed for another low-fragmenting material, sodium bicarbonate. To account for the increased hardness of piroxicam beads and to elucidate the effect of alginate and $CaCl_2$ levels on the hardness of these beads, both the tablet porosity, as a measure for the volume reduction properties, and the tablet elastic recovery as a measure for the inter-particulate bonding strength, were determined at different compaction pressures, Table 4.

The larger beads exhibited lower porosities for given applied pressure than the smaller untreated powder and crystals. Thus, the degree of densification that occurred during compression was greater for the beads. This may be attributed to increased frictional and cohesive forces associated with the smaller size of the untreated material that tends to restrict particle sliding and thus reduce densification[18,19]. Furthermore, fragmentation of the beads during compaction produces small particles which fill the remaining inter-particulate voids between the crystals leading to further decrease in porosity of the compacts made from the treated crystals. In a previous study, the larger size fraction of paracetamol exhibited higher relative density and lower porosity than the smaller size fraction [20]. This result was attributed to the greater fragmentation of the larger particles. The inter-particulate bonding strength was increased, as suggested by the significantly lower elastic recovery values. It is reasonable to assume that the distribution of the binder within the piroxicam powder increased the strength of the bonds developed between the piroxicam particles when compacted, and hence, produced tablets with acceptable crushing strength. Moreover, the fragmentation of the loose aggregates produced by the binder created fresh and clean particle surfaces available for bond formation. It is worth mentioning that the preparation of compacts from untreated piroxicam and piroxicam crystals was extremely difficult. The prepared compacts suffered inherent weakness, capping and lamination; therefore, crushing strength was used instead of tensile strength for evaluation of mechanical properties. On the other hand, beads compacts survived compression and decompression stages and exhibited uniform diametric breaking on hardness testing.

Conclusion

The proposed spherical agglomeration technique for piroxicam was simple, mild and rapid. It resulted in strong beads with high drug loading, good flowability and compressibility. The ionic character of the polysaccharides allowed pH-dependent disintegration of the beads. Considering the final dosage form, the beads could be readily filled into capsules, or alternatively, smaller agglomerates could be compressed into tablets. Beads (B5) exhibited the most preferable compilation of properties including sphericity, smoothness, flowability, compressibility and in-vitro release. Accordingly, this formula was highly recommendable for better manufacture of piroxicam.

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References.

1. Nagabhushanam M. Formulation studies on cyclodextrin complexes of piroxicam. Rasayan J Chem. 2010;3(2):314-20.
2. Hyllested M, Jones S, Pedersen J, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. British journal of anaesthesia. 2002;88(2):199-214.
3. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. European Journal of Pharmaceutics and Biopharmaceutics. 2000;50(1):47-60.
4. Nokhodchi A, Maghsoodi M, Hassan-Zadeh D, Barzegar-Jalali M. Preparation of agglomerated crystals for improving flowability and compactibility of poorly flowable and compactible drugs and excipients. Powder technology. 2007;175(2):73-81.
5. Rinaudo M. Main properties and current applications of some polysaccharides as biomaterials. Polymer International. 2008;57(3):397-430.
6. Bodmeier R, Paeratakul O. Spherical agglomerates of water-insoluble drugs. Journal of pharmaceutical sciences. 1989;78(11):964-7.
7. Hausner H. Friction conditions in a mass of metal powder. Polytechnic Inst. of Brooklyn. Univ. of California, Los Angeles, 1967.
8. ÖZEN M. Investigation of relationship between aggregate shape parameters and concrete strength using imaging techniques: Middle East Technical University; 2007.
9. Russ JC. The image processing handbook. CRC press; 2011. p. 553-5.
10. Kumar V, Kothari SH, Banker GS. Compression, compaction, and disintegration properties of low crystallinity celluloses produced using different agitation rates during their regeneration from phosphoric acid solutions. AAPS PharmSciTech. 2001;2(2):22-8.
11. JN S. Powder flow. In: ME A, editor. Pharmaceutics: The Science of Dosage Form Design. London: Churchill Livingstone; 2002. p. 205-8.
12. Nokhodchi A, Bolourtchian N, Dinarvand R. Crystal modification of phenytoin using different solvents and crystallization conditions. International journal of pharmaceutics. 2003;250(1):85-97.
13. Armstrong N, Haines-Nutt R. Elastic recovery and surface area changes in compacted powder systems. Powder Technology. 1974;9(5):287-90.
14. Kawashima Y, Lin S, Ogawa M, Handa T, Takenaka H. Preparations of agglomerated crystals of polymorphic mixtures and a new complex of indomethacin—epirizole by the spherical crystallization technique. Journal of pharmaceutical sciences. 1985;74(11):1152-6.
15. Raja Shekhar S, Vedavathi T. Recent Trends of Oral Fast Disintegrating Tablets: An Overview of Formulation and Taste Masking Technology. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2012;3(1):771-92.

16. Alderborn G, Nyström C. Studies on direct compression of tablets. IV. The effect of particle size on the mechanical strength of tablets. Acta Pharmaceutica Suecica. 1982;19(5):381.

17. Alderborn G, Borjesson E, Glazer M, Nystrom C. Studies on direct compression of tablets. XIX: The effect of particle size and shape on the mechanical strength of sodium bicarbonate tablets. Acta pharmaceutica suecica. 1988;25(1):31-40.

18. Roberts R, Rowe R. The effect of the relationship between punch velocity and particle size on the compaction behaviour of materials with varying deformation mechanisms. Journal of pharmacy and pharmacology. 1986;38(8):567-71.

19. York P. Particle slippage and rearrangement during compression of pharmaceutical powders. Journal of Pharmacy and Pharmacology. 1978;30(1):6-10.

20. Garekani HA, Ford JL, Rubinstein MH, Rajabi-Siahboomi AR. Effect of compression force, compression speed, and particle size on the compression properties of paracetamol. Drug development and industrial pharmacy. 2001;27(9):935-42.

Table 1: Composition of Piroxicam Beads

$CaCl_2$ % (v/v)	**Sodium alginate % (w/v)**		
	0.5 %	**1 %**	**1.5 %**
1 %	B1	B2	B3
3 %	B4	B5	B6
7 %	B7	B8	B9

Table 2: Drug Loading in SIF and Equilibrium Solubility in Water, SGF and SIF of Piroxicam Beads.

Beads No.	**Drug content in SIF (mean±S.D.[*])**	**Drug solubility in water (µg/mL) (mean±S.D.)**	**Drug solubility in SGF (µg/mL) (mean±S.D.)**	**Drug Solubility in SIF (µg/mL) (mean±S.D.)**
B1	100 ± 4	59 ± 3	142 ± 5	878 ± 18
B2	90 ± 3	51 ± 3	96 ± 2	454 ± 12
B3	94 ± 4	38 ± 2	87 ± 3	377 ± 14
B4	95 ± 2	52 ± 1	113 ± 3	571 ± 26
B5	101 ± 3	79 ± 1	112 ± 4	789 ± 25
B6	93 ±4	61 ± 2	74 ± 3	108 ± 2
B7	87 ± 2	31 ± 1	100 ± 4	543 ± 9
B8	99 ± 3	60 ± 2	88 ± 4	404 ± 9
B9	93 ± 5	50 ± 3	72 ± 3	58 ± 2
Powder	N/A	22 ± 1	97 ± 3	91 ± 4
Crystals	N/A	25 ± 1	99 ± 2	364 ± 9

[*] **Standard Deviation**

Table 3.Shape of Piroxicam Beads.

Samples	**Fullness ratio (mean±S.D.*)**	**Circularity (mean±S.D.)**
B1	0.88 ± 0.01	0.84 ± 0.07
B2	0.84 ± 0.01	0.97 ± 0.06
B3	0.88 ± 0.02	0.96 ± 0.06
B4	0.88 ± 0.01	0.85 ± 0.07
B5	0.91 ± 0.01	0.98 ± 0.07
B6	0.89 ± 0.02	0.98 ± 0.06
B7	0.88 ± 0.01	0.86 ± 0.07
B8	0.87 ± 0.02	0.98 ± 0.08
B9	0.87 ± 0.02	0.97 ± 0.06

Table 4. The Effect of Compression Pressure (psi) on the Hardness, Porosity and Elastic Recovery of Compacts Obtained with Various Piroxicam Samples.

Samples	**Elastic recovery (%)** (mean ± S.D.*)			**Porosity (%)** (mean ± S.D.*)			**Hardness (Kg)** (mean ± S.D.*)		
	7000	**5000**	**3000**	**7000**	**5000**	**3000**	**7000**	**5000**	**3000**
Untreated	7 ± 1	8 ± 1	8 ± 1	18 ± 2	20 ± 1	26 ± 1	15 ± 1	11 ± 1	8 ± 1
Crystals	7 ± 1	8 ± 1	8 ± 1	15 ± 1	18 ± 1	20 ± 1	15 ± 1	13 ± 1	9 ± 1
B1	4 ± 0.1	4 ± 0.3	5 ± 0.1	11 ± 2	15 ± 2	17 ± 1	24 ± 1	15 ± 1	12 ± 1
B2	2 ± 0.4	2 ± 1	4 ± 1	6 ± 1	8 ± 1	18 ± 1	33 ± 2	20 ± 2	14 ± 1
B3	1 ± 0.1	2 ± 0.4	3 ± 1	7 ± 1	8 ± 1	14 ± 1	34 ± 1	28 ± 1	17 ± 1
B4	6 ± 0.4	7 ± 1	5 ± 0.3	11 ± 2	14 ± 2	14 ± 1	29 ± 1	22 ± 1	17 ± 2
B5	6 ± 1	6 ± 1	7 ± 1	14 ± 1	14 ± 1	17 ± 1	27 ± 1	20 ± 2	15 ± 1
B6	5 ± 0.4	5 ± 1	6 ± 0.1	12 ± 1	13 ± 1	18 ± 1	26 ± 2	19 ± 2	15 ± 1
B7	5 ± 0.4	5 ± 1	5 ± 0.3	12 ± 2	14 ± 2	18 ± 1	30 ± 1	23 ± 1	13 ± 2
B8	5 ± 1	5 ± 1	7 ± 2	12 ± 2	13 ± 1	18 ± 2	26 ± 2	20 ± 1	15 ± 1
B9	2 ± 1	2 ± 1	3 ± 1	7 ± 1	7 ± 1	12 ± 1	35 ± 2	29 ± 1	18 ± 1

*Standard Deviation

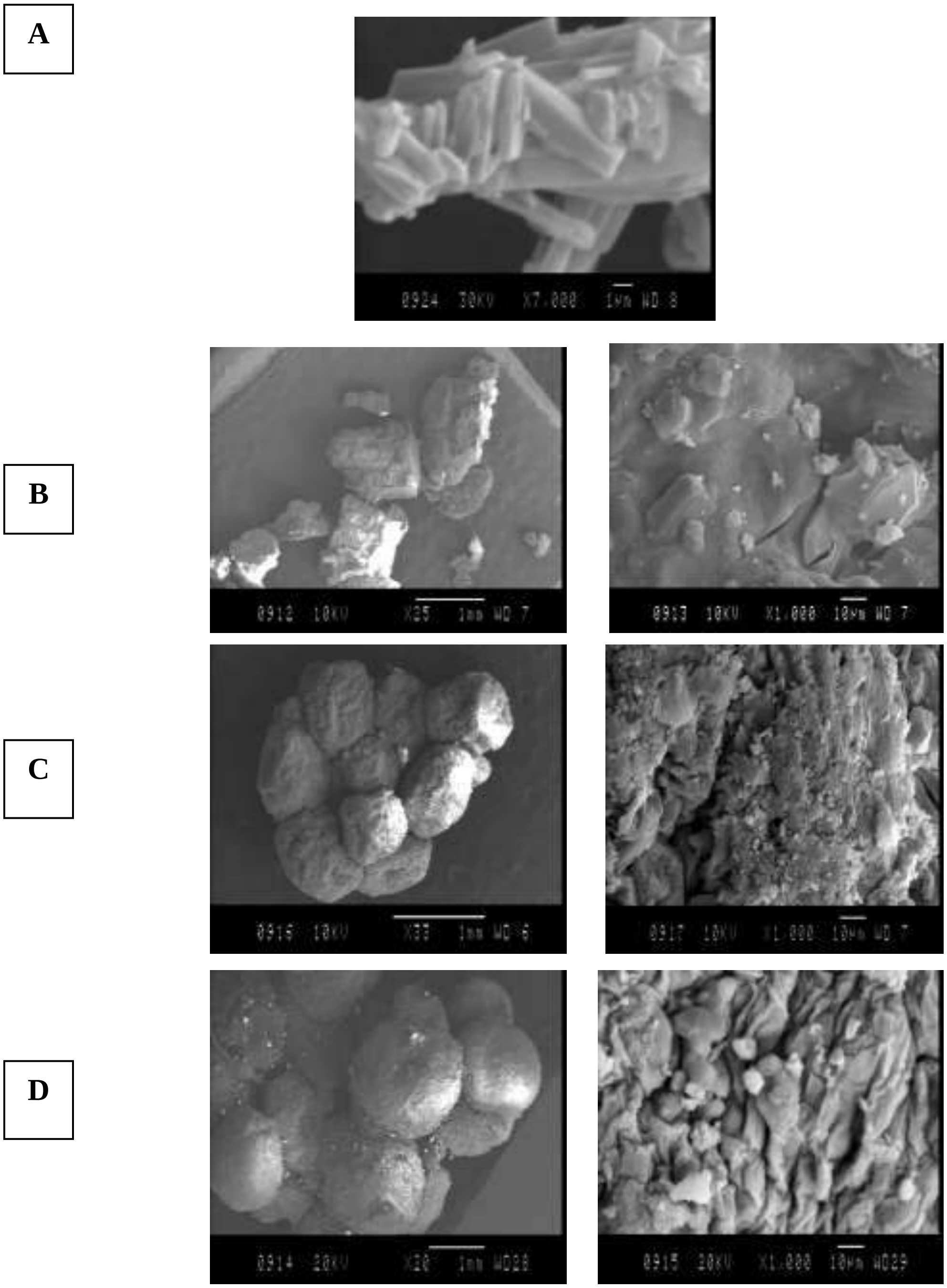

Fig. 1. SEM of a) Untreated piroxicam, b) beads B1 (two magnifications), c) beads B5 (two magnifications) and d) beads B9 (two magnifications).

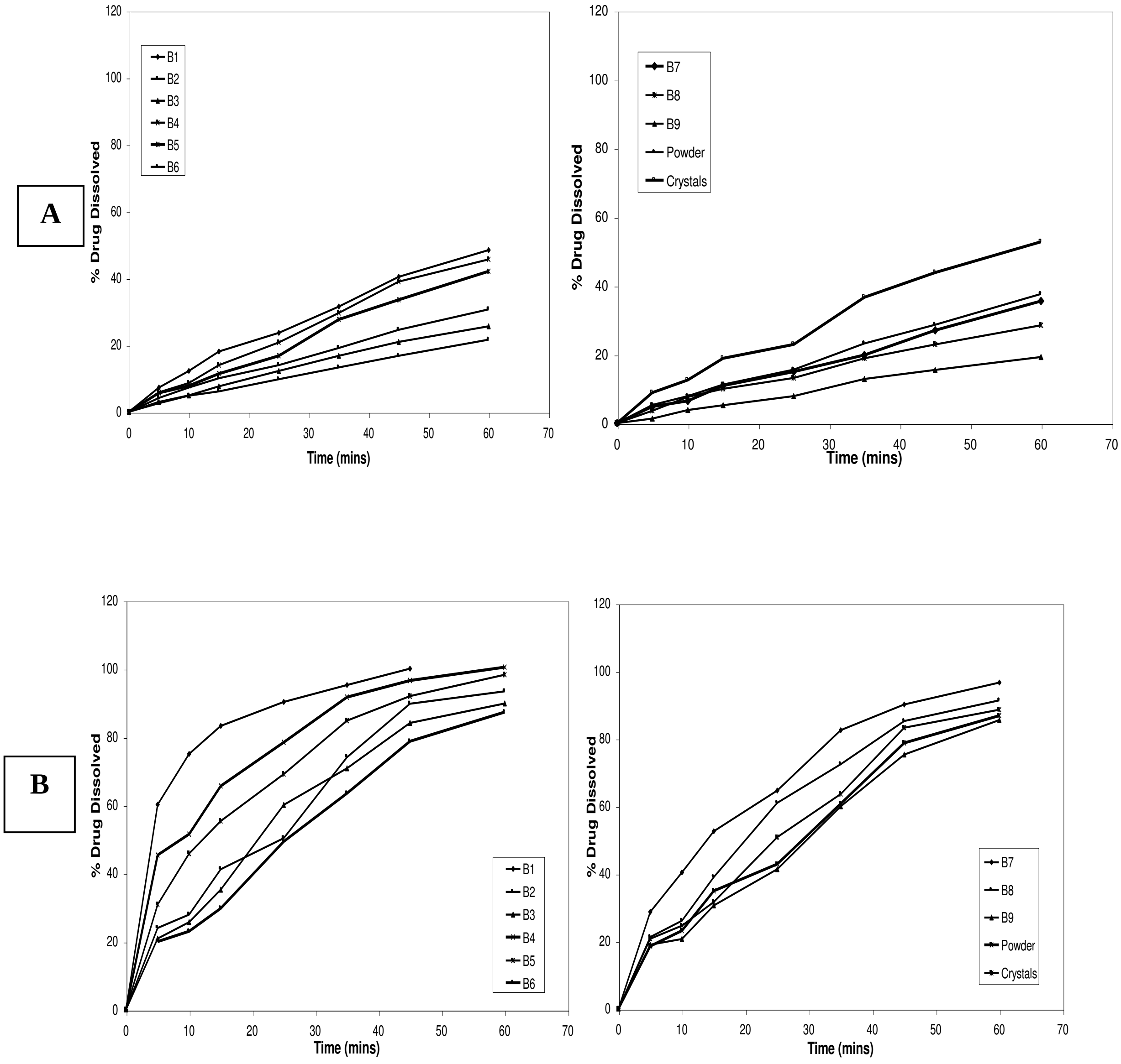

Fig. 2. Dissolution profiles of piroxicam beads, powder and crystals in a) SGF and b) SIF.