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# Controlled-release cellulose esters matrices for water-soluble diclofenac sodium: compression and dissolution studies

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Matrix tablets comprising of a blend of cellulose acetate butyrate (CAB) or cellulose acetate propionate (CAP) and α-lactose monohydrate were prepared by direct compression to control the release of diclofenac sodium. Tablet formulations containing CAP75000 or CAB50-54 exhibited highest extents, but lowest onsets of plastic deformation and lowest release rates in buffer medium, while tablets containing CAP15000 or CAB35-39 exhibited lowest extents, but highest rates of plastic deformation and highest release rates in buffer medium. The $D_A$ values obtained from Heckel plots and the $D_I$ values obtained from Kawakita plots showed similar trends. A plot of compression pressure or crushing strengths against T50% showed curvilinear relationship for all tablets. Tablets containing 40 % CAB35-39 (formulation F7D) was considered the best formulation in terms of T50%, compressibility and compactability.

## 1. Introduction

Polymers suitable for direct compression tablets that control the release of water-soluble drugs are of great interest. Hydrophobic polymers are valuable in this regard because of their tablettability advantages over hydrophilic polymers. For example, ethyl cellulose has been extensively studied as a controlled release matrix to modify drug release rates of some drugs (Shaikh et al. 1987a; Katikaneni et al.1995a, b; Dabbagh et al. 1996; Pollock 1996; Pather 1998).

Cellulose acetate butyrate (CAB) and cellulose acetate propionate (CAP) are cellulose esters and share some properties with ethyl cellulose; they are water insoluble and lack enteric properties. The physical properties of cellulose esters depend on the cellulose chain length and on the type and amount of ester groups attached to the chain. Pharmaceutically, cellulose acetate butyrate has been extensively used in microspheres fabrication (Shukla and Price 1991; Bhardwaj et al. 1995; Obeidat and Price 2005; Obeidat and Obaidat 2007; Barakat and Ahmad 2008), film formation (Sobral et al. 2008), tablet coating to mask taste or control drug release and for osmotic pump drug delivery (Roche 1991; Zentner et al. 1990; Shanbhag et al. 2007). However, despite their wide applications, only limited resources are available for their use in direct compression of tablets for controlled/sustained release applications. For example, tablets made of CAB of different grades were used to control the release of vitamin C (Yuan and Wu 2000) and theophylline (Yuan and Singleton 2010). In a similar work, CAP was directly compressed to achieve sustained release of aspirin (Wyatt 1991).

Diclofenac sodium is an anti-inflammatory drug with short biological half life of 1–2 hours. Thus, repeated dosing of 3 to 4 times a day is required to maintain therapeutic drug levels in the body. Diclofenac sodium is considered an ideal candidate for sustained release dosage forms to obtain prolonged clinical efficacy, reduced frequency of administration with less side effects.

During compression several changes may occur such as transitional repacking, deformation at points of contact, fragmentation and/or deformation, bonding, decompression, and ejection. Transformation into compact with certain strength during compression or densification is known as compactability (Joiris et al. 1998) which is usually represented by a plot of tensile strength versus solid fraction or porosity. Compactability can also be characterized by crushing strength - compression pressure (Higuchi et al. 1953; Carstensen 1993).

Compression of powders is usually associated with a reduction of their bulk volumes inside the die. Volume reduction can be evaluated by fitting different empirical or semi-empirical models such as Heckel (Heckel 1961a, b) and Kawakita (Kawakita and Lüdde 1970/71) to the obtained data using ejected (out of die) tablets. Particle rearrangement, consolidation mechanism and onset of deformation can be obtained from Heckel plots, while degree of volume reduction in the powder bed and extent of deformation is obtained from Kawakita and Lüdde plots.

The current work addressed the utility of powdered cellulose esters (CAB and CAP) of different molecular weights for the manufacturing of direct compression tablets to control the release of diclofenac sodium. Another purpose was to investigate the effects of polymer plastic deformation, molecular weight, viscosity grade and particle size on tablet mechanical properties and drug release.

## 2. Investigations, results and discussion

### *2.1. Tablet formulations and mechanical properties*

Preliminary studies on tablets mechanical properties and dissolution rates revealed that the ratio of the polymers to the diluent was a major factor in optimizing tablet properties. Hence, at low ratio of polymer to diluent of less than 2:1 in formulations F1, F2, F4, F5 and F6 (data not shown) yielded tablets with relatively rapid drug release rates and inappropriate crushing

strengths. This can be attributed to the presence of a high percentage of the water-soluble diluent (α-lactose monohydrate) that allowed rapid drug release. However, α-lactose monohydrate is known to be physically and chemically stable, flowable, non-hygroscopic and cost effective (Guo 2004). In addition, its particle size ($317.6 \pm 52.4$ μm) is close to that of diclofenac sodium ($230 \pm 36.6$ μm) and hence would reduce drug particles segregation (Guo 2004) and facilitate tabletting by direct compression (Gohel 2005).

Therefore, to compensate for the rapid drug release rates, the ratio of the polymers to the diluent was increased gradually whereas drug loadings were kept constant. Tablet formulations (F7) where polymers to diluent ratio of approximately 2:1 (about 40% of polymer and 21% of diluent) are an adequate compromise between mechanical and dissolution properties. However, in order to further investigate the behaviour of F7 tablet formulations, diclofenac sodium-free tablets comprising almost entirely (about 94%) of cellulose ester polymers (formulations F9) or of α-lactose monohydrate (formulation F8), and tablet composed almost entirely of pure diclofenac sodium (about 94%) were prepared and their mechanical properties were studied. All Tablet formulations are presented in Table 1 which shows the percentage of each component within each tablet. The moisture contents of tablet formulations were found to be 1.924- 2.264% as determined by Karl Fischer titration method.

The relative densities of F7 tablet formulations (n = 6) were calculated as described in the experimental part (section 3.4.1), and Heckel plots were constructed by plotting the value of ln (1/1-$D_r$) against compression pressures, $P$ (kg/cm$^2$) to evaluate the compressibility of tablet formulations. Heckel Plots showed linear portions with high correlation coefficients ($R^2 = 0.90$–$0.98$) only after an initial characteristic curvatures. Researchers have attributed the presence of initial curvature in Heckel plots to particles rearrangement (Seelig and Wulff 1946; Heckel 1961b), brittle fracture (Alderborn et al. 1985) and/or to the presence of aggregates of the primary particles (Shapiro 1994). Careful microscopic examination of powders of F7 formulations revealed the absence of particle aggregates. On the other hand, non-linearity was observed in Heckel plots for F3 and F8 tablet formulations made of almost entirely pure drug (diclofenac sodium) or diluents (α-lactose) as shown in Table 1 over the entire range of compression pressures (figures not shown) indicated that densification occurred through particles fragmentation which is consistent with reported data (Gohel 2005; Vromans 1987). Therefore, the initial curvature in Heckel plots may be attributed to the behaviour of lactose and diclofenac sodium during compression. Nevertheless, due to the presence of different components that vary in their particle sizes, it is plausible that significant particle rearrangements took place and thus contributed to existence of the initial curvature. However, since size reduction by brittle fracture or fragmentation cannot continue indefinitely, ultimately, a transition to compaction by plastic deformation has occurred as the pressure increased as evident by the straight line that followed the initial curvature in Heckel plots of F7 tablet formulations. Therefore, the behaviour of Heckel plots of F7 tablet formulations could be attributed to particle fragmentation initially followed by plastic deformation. The reciprocal of slopes of those linear portions yielded material's mean yield pressure, $P_y$. Values of $A$ in Heckel equation (Eq. 1) were obtained from the intercepts of the linear portions after extrapolation to y-axis and from which the relative densities ($D_A$) were calculated using Eq. (2). The relative density ($D_B$) due to rearrangement at low pressures was calculated using Eq. (3). The values of $P_y$, $D_A$, $D_o$ and $D_B$ for F7 formulations are presented in Table 2. In order to get more insight into the behaviour of F7 tablets, Heckel plots were also constructed for F9 tablet formulations comprising almost entirely pure polymers. Heckel plots for formulations F7 and F9 are shown in Figs. 1a and 1b, respectively, and related parameters ($P_y$, $D_A$, $D_O$ and $D_B$) are presented in Table 2. Unlike Heckle plots for F7 tablet formulations, those for F9 tablet formulations were apparently linear throughout the compression pressures employed in this study indicating that plastic deformation was the predominant mechanism of densification.

The mean yield pressure, $P_y$, is inversely related to the rate and onset of a formulation to deform plastically under pressure (Odeniyi and Jaiyeoba 2007; Itiola 1991). Comparing $P_y$ values listed in Table 2, it was apparent that $P_y$ values were larger for F7 than for F9 tablets. This indicates that F9 formulations experience faster onsets and were able to deform plastically on higher rates since they were composed almost entirely of single polymers, while F7 formulations exhibit slower rates of plastic deformation due to low percentage of polymers (compared to F9) and also due to the presence of other constituents; diclofenac sodium and α-lactose which were found not to deform plastically. Since F9 tablet formulations were found to experience plastic deformation based on parameters obtained from Heckel plots, they were extremely resistant to test of failure or break, and thus insufficient data were obtained regarding their mechanical strengths.

Generally, for both F7 and F9 tablet formulations, the onset or rate of plastic deformation decreased in the order FB > FD > FA > FC. Within each group of polymers it was found that the compressibility was inversely related to the mean yield pressure. For CAP-containing tablets, the lower viscosity grade polymer; CAP1500 resulted in tablets (FB) that were less easily deformed than FA tablets containing the higher viscosity grade polymer; CAP75000. This finding is consistent with data reported for ethyl cellulose of controlled particle sizes (Upadrashta et al. 1994), polyethylene glycol (AI-Angari et al. 1985) and HPMC (Nokhodchi et al. 1995). However, for CAB-containing tablets, the lower viscosity grade polymer; CAB50-54 resulted in tablets (F7C) that were less easily deformed than F7D tablets containing the higher viscosity grade polymer; CAB35-39. This can be explained by the difference in the particle sizes of CAB polymers (Rue and Rees 1978) where CAB35-39 polymer being the finest as shown in Table 3. Therefore, CAB35-39 polymer could produce more easily compressible and, therefore, more easily deformed FD tablets especially at the relatively high compression pressures employed in this study (Nokhodchi et al. 1995; Sun and Grant 2001a). These explanations were also supported with the measured crushing strengths values of F7 tablet formulations; where F7D tablets possessed higher crushing strengths than F7C tablets at all compression pressures employed in this study as shown in Table 4. In addition, a fairly good correlation between the particles sizes of all CAB and CAP polymers employed in this study and the tensile strengths of the corresponding tablets existed; the smaller the polymer particle size (e.g. CAP75000 and CAB35-39), the higher was the tablets tensile strength. This is in agreement with reported relationships of particles sizes and tablet mechanical strengths (Hersey et al. 1967; Alderborn and Nyström 1982; McKenna and McCafferty 1982; Alderborn et al. 1985; Nokhodchi et al. 1995; Sun and Grant 2001). However, unlike the influence of CAB and CAP polymers particle size, the viscosity grade of these polymers did not seem to correlate well with the corresponding tablets tensile strengths in this study.

It is worth mentioning that differences in mean plasticity constants between F7 and F9 tablet formulations was due to a complex interplay of percentage, particle size, viscosity and molecular weight of polymers involved, in addition to behaviour of the diluent and the active ingredient in F7 tablets.

The $D_o$ values which represent the degree of initial packing in the die due to powder filling were calculated using the bulk

**Table 1: Composition of different cellulose acetate butyrate (CAB) and cellulose acetate propionate (CAP) tablet formulations containing constant percentages of diclofenac sodium, Talc and Mg stearate**

| Formulation | Polymer | Diclofenac Na % | Lactose % | Methocel E5 % | Talc % | Mg stearate % | Total % |
|---|---|---|---|---|---|---|---|
| F3 | – | 94.3% | – | 4.7 | 0.5 | 0.5 | 100 |
| F8 | – | – | 94.3% | 4.7 | 0.5 | 0.5 | 100 |
| F7A | 40% CAP75000 | 33.3 | 21 | 4.7 | 0.5 | 0.5 | 100 |
| F7B | 40% CAP15000 | 33.3 | 21 | 4.7 | 0.5 | 0.5 | 100 |
| F7C | 40% CAB50-54 | 33.3 | 21 | 4.7 | 0.5 | 0.5 | 100 |
| F7D | 40% CAB35-39 | 33.3 | 21 | 4.7 | 0.5 | 0.5 | 100 |
| F9A | 94.3% CAP75000 | – | – | 4.7 | 0.5 | 0.5 | 100 |
| F9B | 94.3% CAP15000 | – | – | 4.7 | 0.5 | 0.5 | 100 |
| F9C | 94.3% CAB50-54 | – | – | 4.7 | 0.5 | 0.5 | 100 |
| F9D | 94.3% CAB35-39 | – | – | 4.7 | 0.5 | 0.5 | 100 |

**Table 2: Parameters derived from density measurements and from Heckel and Kawakita plots**

| Formula | $P_y$ | $A$ | $D_A$ | $D_0$ | $D_B$ | $P_k$ | $a$ | $b$ | $D_l$ |
|---|---|---|---|---|---|---|---|---|---|
| F3 | 4444 | 1.31 | 0.730 | 0.385 | 0.345 | 24.44 | 0.243 | 0.031 | 0.757 |
| F8 | 4545 | 1.34 | 0.738 | 0.585 | 0.153 | 24.44 | 0.200 | 0.031 | 0.800 |
| F9A | 6191 | 1.43 | 0.755 | 0.291 | 0.474 | 21.28 | 0.180 | 0.047 | 0.820 |
| F9B | 5860 | 1.48 | 0.772 | 0.363 | 0.409 | 38.02 | 0.165 | 0.026 | 0.835 |
| F9C | 7020 | 2.36 | 0.907 | 0.406 | 0.501 | 24.44 | 0.142 | 0.031 | 0.858 |
| F9D | 5962 | 1.79 | 0.833 | 0.363 | 0.470 | 32.46 | 0.156 | 0.041 | 0.844 |
| F7A | 8719 | 1.40 | 0.772 | 0.377 | 0.395 | 22.22 | 0.177 | 0.045 | 0.823 |
| F7B | 8008 | 1.42 | 0.788 | 0.386 | 0.402 | 33.33 | 0.156 | 0.030 | 0.844 |
| F7C | 9846 | 1.50 | 0.833 | 0.415 | 0.418 | 22.52 | 0.115 | 0.045 | 0.885 |
| F7D | 8467 | 1.82 | 0.812 | 0.399 | 0.413 | 29.40 | 0.145 | 0.034 | 0.850 |

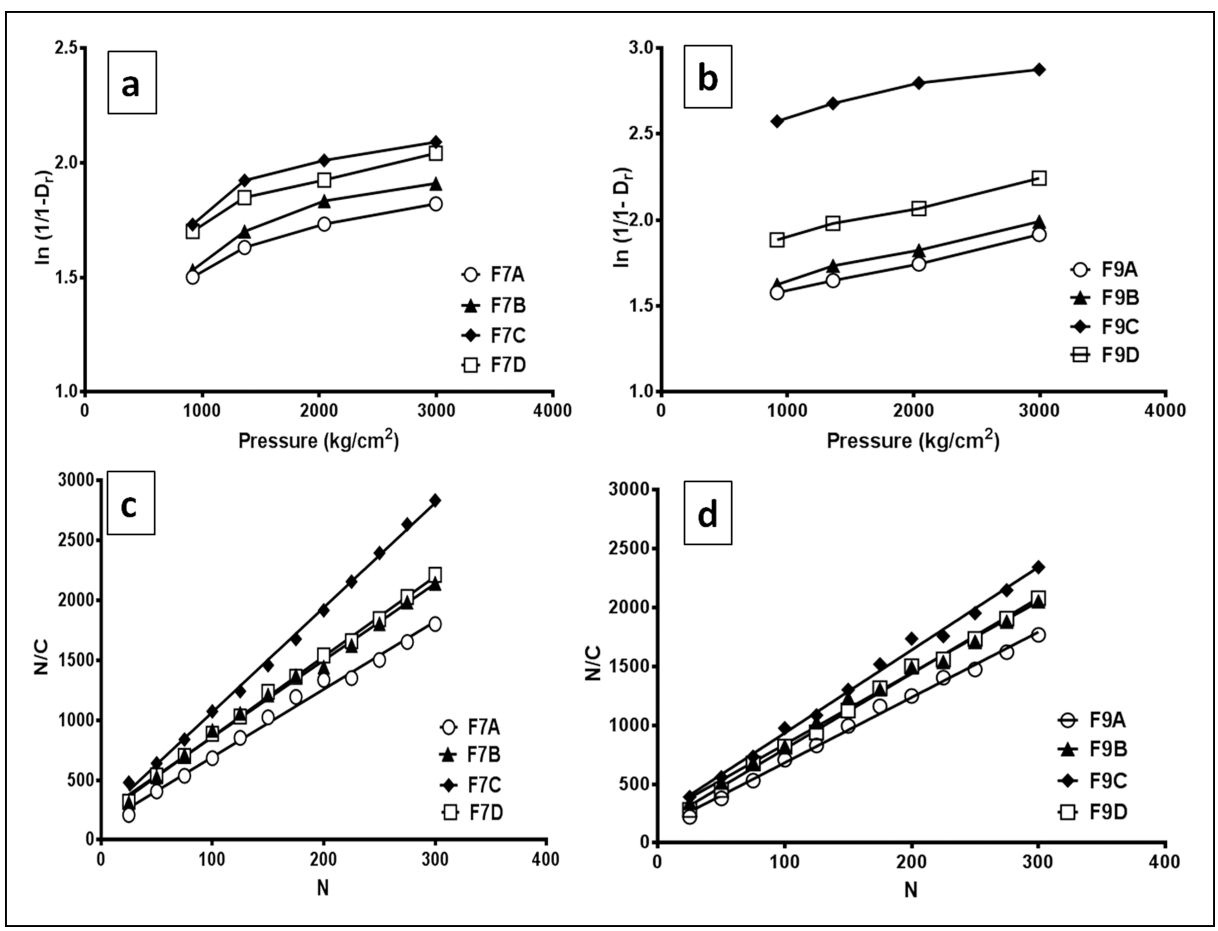


Fig. 1: Heckel plots for F7 (a) and F9 (b) tablet formulations, and Kawakita plots for F7 (c) and F9 (d) tablet formulations containing diclofenac sodium.

**Table 3: Physicochemical properties of cellulose acetate butyrate (CAB) and cellulose acetate propionate (CAP) polymers employed in this study**

| Material | Particle size, (μm) * | Viscosity, (sec.) ** | MWt (Mn) ** | % Butyryl /Propionyl content ** |
|---|---|---|---|---|
| CAP75000 | 152.0 ± 72.5 | 16–31 | 75000 | 45–49 |
| CAP15000 | 604.2 ± 430.5 | 0.10–0.20 | 15000 | 40–45 |
| CAB50-54 | 664.7 ± 207.3 | 0.01–0.03 | 16000 | 50–54 |
| CAB35-39 | 245.2 ± 112.9 | 17–28 | 70000 | 35–39 |

* Measured using a (Microtrac S3500, USA). ** Obtained from Acros Organics (http://www.acros.com)

and true densities of the formulations. The $D_o$ values for F7 tablet formulation were generally higher than the $D_o$ values of F9 formulations which was attributed to the presence of the drug and the diluent with (especially the diluent) large $D_o$ values. The calculated $D_o$ values for both tablet formulations were in the decreasing order FC > FD > FB > FA which are also apparent from Figs. 1a and 1b.

The $D_B$ values, which represent particle rearrangement phase in the early compression stages, were generally higher for F9 tablet formulations, thus exhibiting more particle/granule rearrangement at low compression pressure compared to F7 formulations. Furthermore, in all tablet formulations, except F3 and F8, $D_B$ values were higher than the corresponding $D_o$ indicating that the total degree of densification, $D_A$, was mostly due to particle rearrangement at low compression pressures.

In both F7 and F9 tablet formulations, $D_A$ values were in the decreasing order FC > FD > FB > FA as shown in Table 2 and in Figs. 1a and 1b. It was apparent that F9 tablet formulations showed larger $D_A$ values than the corresponding F7 tablet formulations. It was also evident that tablets containing CAB polymers (FC and FD tablets) showed larger values than those tablets containing CAP polymers (FB followed by FA tablets) which could be due to larger $D_o$ values of CAB-containing formulations. In addition, it was found that in each polymer group, smaller particle size polymers yielded larger $D_A$ values.

Figures 1c and 1d show representative Kawakita plots of tapping experiments for F7 and F9 formulations. In both formulations, a linear relationship was obtained with correlation coefficient, $R^2$ ranging from 0.9917–0.9984. Table 2 shows values of $a$ which represents compressibility or the amount of densification due to tapping, $b$ which represents cohesiveness or how fast or easily the final packing state was achieved, and $D_I$ where $D_I = 1 - a$, thus representing the initial relative density with the application of small pressures or tapping. Values of $a$ were highest for FA formulations containing the finest particle size polymers indicating a maximum amount of volume reduction or densification due to tapping, and lowest for FC formulations indicating minimum densification, while formulations FB and FD exhibited moderate values. Values of $D_I$ were in the decreasing order FC > FD > FB > FA and were in agreement with the order of $D_A$ values (densification due to filling and at low pressures) obtained from Heckel plots and expected to be due to the same reasons discussed earlier.

In both F7 and F9 formulations, the $P_k$ values, which are an inverse measurement of the extent of plastic deformation, were in the decreasing order of FA≥ FC > FD > FB. Therefore, it can be understood from $P_y$ and $P_k$ values that formulations FA and FC exhibited the highest extents, but lowest onsets or rates of plastic deformation, while formulation FB followed by FD exhibited the lowest extents, but highest rates of plastic deformation. Thus, for compression operation purposes, formulation FB and FD will be more useful than FA and FC in a high-speed tablet machine with a short dwell time.

### *2.2. Drug release studies, crushing strengths, flow properties and compactability*

Since drug and diluents were kept the same at constant concentrations in all tablet formulations, the drug release behaviour was dependent on the type and the concentration of the polymers as matrix formers as well as on the mechanical properties of the compact.

Dissolution profiles in 0.1N HCl (pH 1.2 ± 0.2) for F7 tablet formulations (F7A, F7B, F7C, F7D) compressed at 6000 lb is shown in Fig. 2d where it is apparent that a cumulative drug release of less that 10% was experienced by all tablet formulations. This behaviour was attributed to the low solubility of diclofenac sodium in the acidic medium since it is a weak acid (pka 4.0) and shows pH dependent solubility. Therefore, the low solubility of diclofenac sodium in acidic media limits its initial release from the surface and as well as the formation of channels within the matrix. In addition, the hydrophobic properties of CAP and CAB polymers prohibited to great extents water hydration and tablet wetting.

Dissolution profiles in phosphate buffer (pH 6.8 ± 0.2) for F7 formulations compressed at 2700, 4000 and 6000 lb are shown in Figs. 2a, 2b and 2c, respectively. Among CAP- containing tablets, F7B tablets containing CAP1500 exhibited faster drug release than the F7A tablet containing CAP75000. This behaviour can be understood based on larger molecular weight, in addition to the larger crushing strength of F7A tablets as shown in Table 4. For CAB-containing tablets, F7D tablets containing CAB35-39 polymer released the drug less rapidly compared to F7C tablets which contains CAB50-54 polymer. This again can be explained based on the larger molecular

**Table 4: Crushing strengths in kilopounds (Kp) for F7 tablet formulations at different compression pressures**

| Crushing strength (Kp) Pressure kg/cm2 | F7A | SD | F7B | SD | F7C | SD | F7D | SD |
|---|---|---|---|---|---|---|---|---|
| 919.4976881 | 15 | 0.8 | 11.6 | 1.7 | 12.6 | 1.1 | 13.8 | 0.3 |
| 1362.218881 | 18.1 | 0.1 | 14.9 | 0.6 | 15.5 | 0.2 | 16.1 | 0.3 |
| 2043.328696 | 20 | 0.1 | 16.9 | 0.8 | 17.3 | 0.8 | 18.5 | 0.8 |
| 2996.882438 | > 20 | – | 18.3 | 2.2 | > 20 | – | > 20 | – |

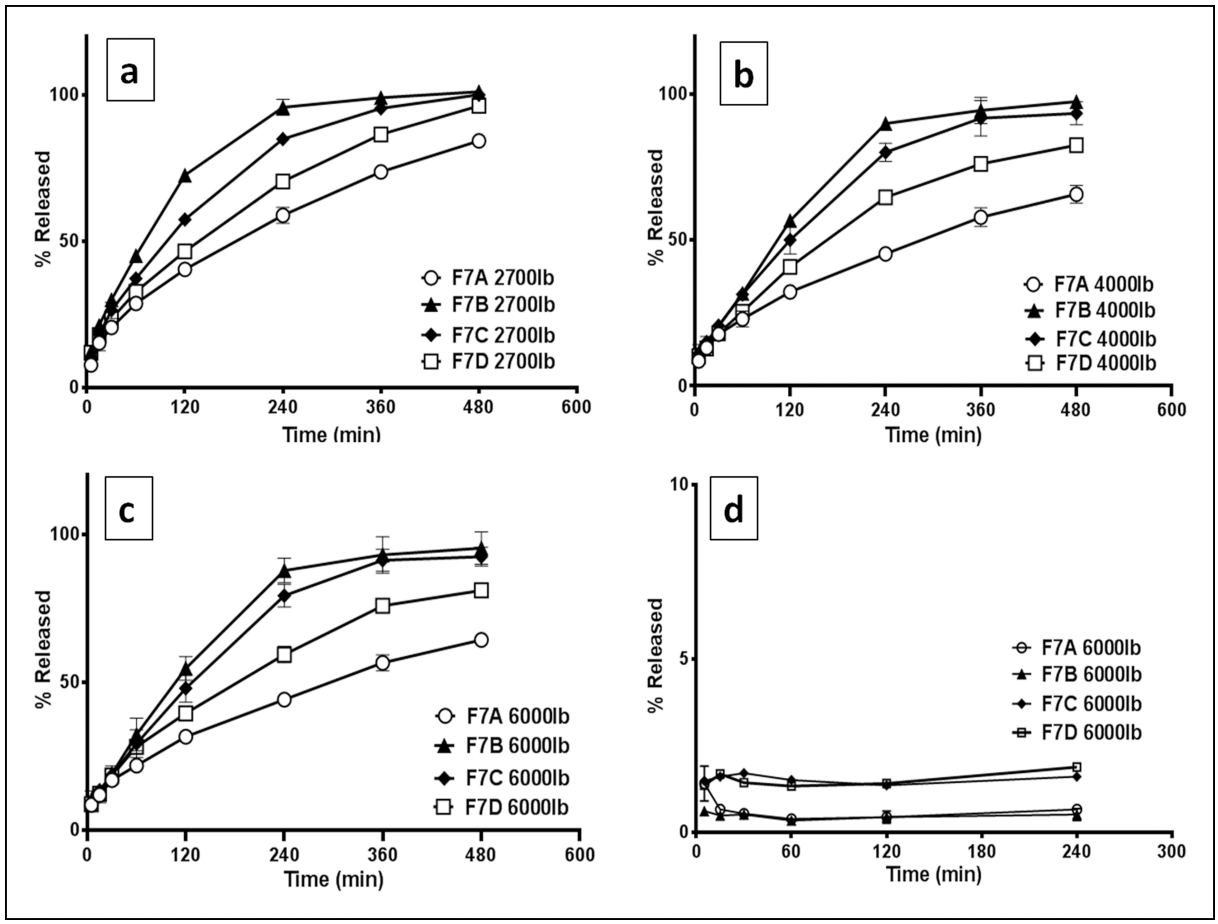


Fig. 2: Release profiles for F7 tablet formulations compressed at different forces in phosphate buffer of pH 6.8 ± 0.2 (a, b and c) and 0.1N HCl of pH 1.2 ± 0.2 (d).

weight of CAB35-39. This behaviour can also be explained by larger crushing strengths of F7D tablets compared to F7C tablets at all compression forces which can be attributed to the smaller particle size of CAB35-39 polymer since particle size is claimed to play an important role on final formulation properties (Mallipeddi 2009). Hence, results of the current study were in agreement with results obtained by Katikaneni et al. (1995) and Crowley et al. (2004) using ethyl cellulose. Overall, as shown in Figs. 2a, 2b and 2c, the drug release rates were in the decreasing order F7B > F7C > F7D > F7A. For example, at compression force of 4000 lb (1362.22 kg/cm$^2$) approximate T50% values were 105, 128, 188, 310 min for F7B, F7C, F7D, and F7A, respectively. Similar pattern was noticed at 2700 lb and 6000 lb. Drug release from tablets containing polymers belonging to different groups but of similar particle sizes were found to depend mainly on polymer molecular weight and viscosity. For example, F7B tablets showed faster release than F7D, and F7C tablets released the drug more rapidly than F7A tablets.

A correlation between compression pressures or crushing strengths and the T50% (time required for 50% of the total drug to be released) for F7 formulations was constructed as shown in Figs. 3a and 3b, respectively. A curvilinear relationship was observed in both situations suggesting that except for F7A formulation, the increase in compression pressure or crushing strength resulted in little increment in T50%. Beyond certain compression pressure or crushing strength values, the T50% for all formulations including F7A apparently reached a constant value despite the linear increase of tablet crushing strength as the compression force increased over the entire range of forces studies as shown in Fig. 4a. Such a behaviour could be attributed to the mechanism of drug release from hydrophobic matrices containing water-soluble drugs and/or diluents (Gurny et al. 1982) where drugs and/or diluents dissolution created water-filled channels that facilitate further drug release.

Compactability is the ability to form a strong coherent compact from powdered material during densification. It reflects the two most important effects of applied pressure: tablet strength and solid fraction. The solid fraction increases with decrease in porosity. The compactability profile for F7 tablet formulations is represented by plotting tensile strength *versus* porosity as shown in Fig. 4b. All plots showed good linearity with high correlation coefficients and all tablet porosities were within the reported range for most materials (Mattsson 2000). It was shown that porosities of F7 formulations were in the decreasing order F7A > F7B > F7C > F7D. Therefore tablet formulation F7A which possessed the highest porosity (or the lowest solid fraction) showed the lowest drug release rates (Figs. 2a, 2b, and 2c) indicating that polymer type (CAP75000) was the main factor in controlling drug release. As mentioned earlier, tablet formulation F7D was shown to release the drug at lower rates compared to that of F7C tablets. In addition to the effects of larger molecular weight, and higher crushing strengths of F7D tablets, the plots of tensile strength *versus* porosity (Fig. 4b) showed that F7C tablets possessed higher porosity values than F7D, thus facilitating easier and faster water penetration accompanied with drug and diluents dissolutions. This is in contradiction to previously published work (Katikaneni et al. 1995) where faster release rates were associated with higher polymer viscosity grade. This can be attributed to the finer particle size of CAB35-39 polymer in F7D tablet formulation compared to CAB50-54 polymer in F7C formulation and thus is expected to facilitate less the penetration of water into F7D matrices (Dabbagh 1996). Overall, it seems that the combined effects of finer particle size and larger molecular weight of CAB35-39 polymer

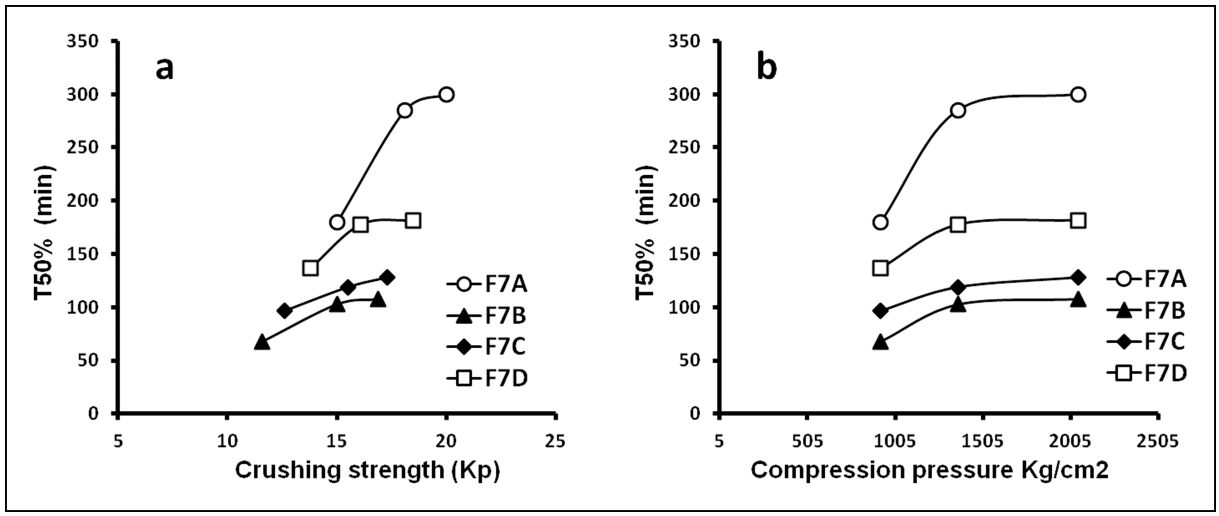


Fig. 3: T50% against crushing strengths (a) and against compression pressure (b) for F7 tablet formulations

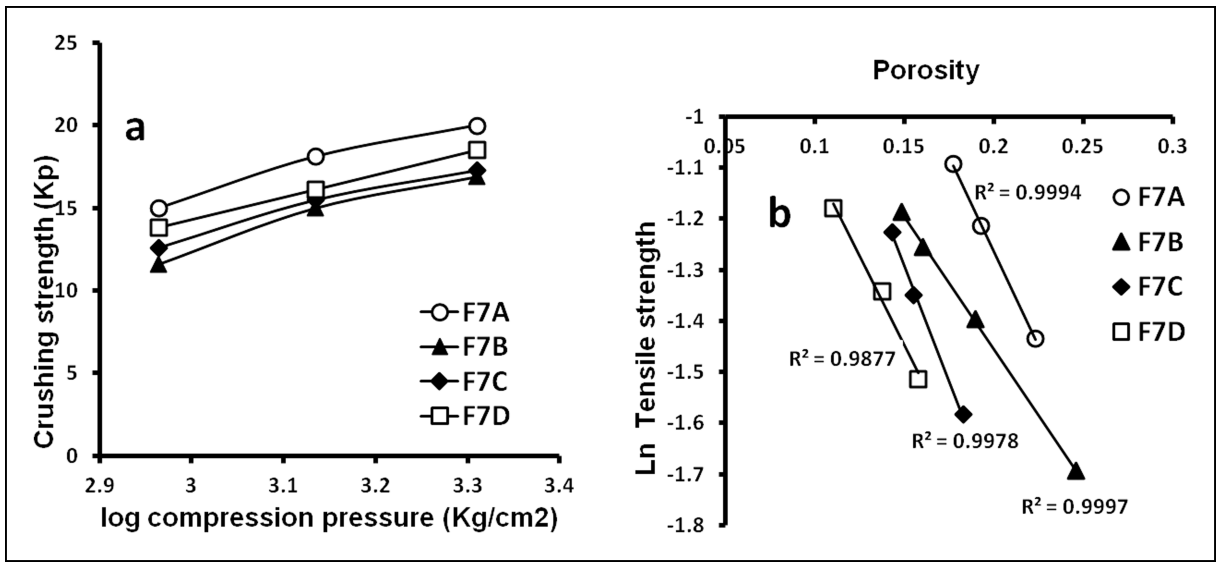


Fig. 4: Crushing strength against compression pressure (a) and porosity against tensile strength (b) for F7 tablet formulations.

and higher crushing strengths of the corresponding F7D tablets might offset the effect of viscosity grades on tablet porosity and drug release rates.

The packing and cohesive properties of powders are very important in production of tablets. This is of particular relevance during powder filling of dies during tabletting process (Podczeck and Sharma 1996). In this study, F7A, F7B and F7D powders exhibited low Hausner ratios (Hausner 1967) (< 1.25) and low Carr′s Index (Carr 1965) (< 25%) as shown in Table 5, indicating fair to excellent flowability, packing and cohesive properties. In fact, F7D formulation exhibited excellent flow properties which may be attributed to its unique composition since the particle size of corresponding polymer in this formulation (CAB35-39) is close or equivalent to the particle sizes of the drug (diclofenac sodium) and the diluents (lactose) used in the formulation. It was apparent in this study that as the difference between the particles sizes of the components of the formulation increased, the powder flowability worsens. Therefore, particle size and particle size distribution of the components of the powder formulations influences the flow properties (Odeniyi et al. 2008).

**Table 5: Hausner's ratios and compressibility Carr′s indices for F7 tablet formulations**

| Formulation | Hausner ratio | Carr′s Index (%) |
|---|---|---|
| F7A | 1.23 | 19.03 |
| F7B | 1.21 | 17.40 |
| F7C | 1.36 | 26.67 |
| F7D | 1.18 | 15.68 |

It is interesting to note that the $P_y$ values obtained from Heckel plots were found to relate well to flow properties of F7 formulations. Formulations having fair to excellent flowabilities (F7A, F7B and F7D) were found to have the lowest $P_y$ values (Table 2), while F7C tablet formulation exhibited the highest $P_y$ value (lowest rate or onset of deformation), which may be attributed to its poor flowability.

Tablet formulations F7A, F7D and F7C showed promising extended release of diclofenac sodium to various extents. However, optimization of the compression force might be needed to tailor both the release rates to acceptable levels. Although, there are no official specifications for the crushing strength of tablets, compression forces can be also tailored to the acceptable crushing strengths (Banker and Anderson 1986) since resistance to crushing of the tablets is included as a tablet evaluation test in the British Pharmacopoeia (British Pharmacopoeia 2002) and will depend on the end use of the tablet (Odeniyi and Jaiyeoba 2007).

In conclusion; the release rate of water-soluble drug diclofenac sodium from directly compressed tablets containing hydropho-

bic cellulose esters; cellulose acetate butyrate (CAB) and cellulose acetate butyrate (CAP) could be optimized by adjusting compression force and by changing polymer type and its molecular weight, particle size, and viscosity grade since all these factors were found to affect tablet mechanical and dissolution properties. Particle fragmentation and plastic deformation are believed to be the predominant consolidation mechanism for F7 tablet formulations made of a mixture of CAB or CAP polymers, diclofenac sodium and α-lactose. However, plastic deformation was the main mechanism of densification for F9 tablet formulations composed almost entirely of CAB or CAP polymers. All F7 tablet formulations showed good compactabilites. Tablet formulation F7D containing CAB35-39 polymer was considered the optimum formulation owing to optimum mechanical as well as dissolution properties.

## 3. Experimental

### 3.1. Materials

Cellulose acetate propionates (CAP75000 and CAP1500), Cellulose acetate butyrates (CAB50-54 and CAB35-39) were obtained from ACROS Organics, NJ, USA. Diclofenac Na, Lactose monohydrate and Methocel E5, were generously provided by TQ Pharma (Amman, Jordan), Mg stearate was obtained from (Fizmerk India chemicals, India) and Talc from (Riedel-De Haen AG, Seelze-Hannover, Germany)

### 3.2. Powder evaluation

Bulk density, which is the ratio of the sample weight to the volume of the powdered sample, was determined by placing 50 g of powder into a 100 ml glass cylinder. For the tap density, the powder was tapped until a constant volume was reached using an automated tap density tester (Jotling Volumeter, Copley, UK) for 1000 taps. True density was determined using a gas pycnometer (Ultrapycnometer 1000, Quantachorome Instruments, Fl, USA).
The mean particle sizes of the polymers, the drug and the diluent employed in this study were measured using dynamic light scattering (DLS), also known as photon correlation spectroscopy (PCS), using a (Microtrac S3500, USA).

### 3.3. Tablet compression and evaluation

A 13.02 mm cylindrical-uniaxial-stainless steel die equipped with flat-faced punches (Carver press, WABASH, Indiana, USA) was used to compress powdered formulations into compacts. For the different tablet formulations, the following procedure was followed: diclofenac sodium was mixed with all excipients except the lubricant/glidant (Mg stearate and Talc) in a V-shape blender at 35 rpm 9 min. Then, Mg stearate and Talc were added and mixed for 1 min. Mixed powders were manually placed into the die and were directly compressed for 30 s at different forces (from 2700 lb to 8800 lb) to quantify the effect of applied force/pressure on tablet properties. The tablets were produced at room temperature between 23 °C and 26 °C with an humidity between 37 and 42% RH. Approximately 25 tablets were prepared at each level of compression and tablets were stored in airtight containers in the same room of production for at least 24 h after compression to allow for consistent stress relaxation and hardening among tablets. For each formula, the average tablet weight was 500 ± 10 mg and the average amount of active ingredient per tablet was 100 ± 3 mg.

### 3.4. Characterization of tablets

#### 3.4.1. Determination of tablet weight, thickness, diameter, geometric volume, true density and relative density

Six tablets (n = 6) from each batch were selected randomly and the weight, thickness, diameter of each individual tablet was measured using digital slide calliper ($6^{//}$ Digital Caliber, China). The geometric volume of each tablet was calculated and the average was calculated using the following formula:

$$\text{geometric volume} = \pi(\text{Diameter}/2)^2 . \text{Thickness}$$

The true density of each of the six tablets was measured using a gas pycnometer (Ultrapycnometer 1000, Quantachorome Instruments, Fl, USA).
The apparent density of the six tablets was calculated (= weight of the tablet/ its geometric volume) and the relative density ($D_r$) was calculated as the ratio of apparent density $A$ of the compact to its true density.

#### 3.4.2. Determination of tablet crushing strength

Tablets crushing strengths (n = 6) were measured by a hardness tester (Copley, Mod. 2E/205/ Switzerland) in terms of kilopound (Kp).

#### 3.4.3. Moisture contents

Moisture content for all prepared tablets were measured while stored at room temperature between 23 °C and 26 °C with an humidity between 37 and 42% RH using volumetric Karl Fischer titration method (AF8 KF Titrator, Thermo Fisher Scientific, USA).

#### 3.4.4. Heckel analysis

The volume reduction mechanism under the compression force was determined using the Heckel model for relating the relative density of the powder bed during compression to theapplied pressure (Heckel 1961a, b). Heckel equation (Eq. 1) is used with the assumption that powder compression follows a first order kinetics with the interparticulate pores as the reactants and densification of the powder as the product.

$$\ln\left[\frac{1}{1-D_r}\right] = KP + A \tag{1}$$

where $D_r$ is the relative density of the powder bed at compression pressure, $P$ The slope of the straight line portion in Heckel equation is the reciprocal of the material's mean yield pressure, $P_y$. From the value of the intercept, $A$, the relative density can be calculated using Eq. (2) (Humbert-Drozet et al. 1983)

$$D_a = 1 - e^{-A} \tag{2}$$

The powder's relative density when applied pressure equals zero ($D_0$) describes the initial rearrangement phase of densification due to die filling. The relative density, $D_B$, given in equation 3, describes the phase of rearrangement at low pressures.

$$D_B = D_A - D_0 \tag{3}$$

#### 3.4.5. Kawakita analysis

The Kawakita and Lüdde (Kawakita and Lüdde 1970/1971) equation relates compression pressure and the degree of volume reduction ($C$) of powders. A version of Kawakita Eq. (4) can be used for a tapping experiment to assess the flow properties of powders (Lin and Cham 1995, Yamashiro et al. (1983):

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab} \tag{4}$$

where $N$ is the number of taps, constant $a$ is indicative of total or maximum volume reduction for the powder bed and describes its compressibility, and constant $b$ is inversely related to material's plasticity, $P_k$ (Zhang et al. 2003) which is also the pressure required to reduce the powder bed by 50% (Shivanand and Sprockel 1992). The constants ($a$ and $b$) can be evaluated from a plot of $\frac{N}{C}$ versus $N$, where $C$ is the degree of volume reduction and can be determined using the following formula:

$$C = \frac{V_0 - V_P}{V_0} \tag{5}$$

where $V_0$ is the initial volume of the powder bed and $V_P$ is the powder volume after compression (or volume of the tablet).

#### 3.4.6. Dissolution tests

Three tablets of approximately similar weights from F7 formulations were tested for the release of the drug (diclofenac sodium) using USP XX Π rotating paddle apparatus at 100 rpm in 900 ml of phosphate buffer (pH 6.8 ± 0.2) and in 900 ml of 0.1 N HCl (pH 1.2 ± 0.2) at 37 °C. Samples were taken at predetermined intervals for 8 h then filtered through a 0.45 μm Millipore filter and the concentration of the drug was measured spectrophotometrically at 274 nm. The sample taken was replaced by same volume of fresh medium. The percentage released was calculated and the average values were plotted against time to obtain the release profiles of the different tablet formulations.

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