

Effect of Superdisintegrants on Some Physical Attributes and Release Profile of Paracetamol Immediate Release Tablets

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Abstract

The objective of this research was to formulate immediate release tablets of paracetamol for rapid action. Wet granulation method was adapted to formulate the tablets by using Maize Starch as diluent; Povidone k-30 as binder; Sodium starch glycolate, Kollidon CL, and Crosscarmellose sodium as superdisintegrants in different concentration (2-5%); Aerosil-200 to provide desirable flow characteristics and Magnesium stearate as lubricant. Total nine formulations were prepared and evaluated for hardness, thickness, friability, weight variation, disintegration time (DT) and *in vitro* drug release. Some pre-compression characteristics like bulk and tapped densities, compressional index, angle of repose, and hausner's ratio were also evaluated. The disintegration and dissolution were carried out in phosphate buffer at pH 5.8. It was found that disintegration time and dissolution were governed by superdisintegrants type and amount. Disintegration time was decreased with increase of superdisintegrants whereas % drug release rate and extent were increased with increase of superdisintegrants. So it can be concluded that the immediate release tablet of Paracetamol can be formulated for emergency treatment of pain and fever. All formulations were evaluated for pre-compression and post-compression parameters. The result obtained showed that the selected batch of tablet formulation containing sodium starch glycolate provides a short DT with sufficient crushing strength and acceptable friability.

Key words: Superdisintegrants, Paracetamol, Immediate release tablets

Introduction

Tablets for immediate release often consist of filler, a binder, lubricants and disintegrants (Fukami *et al.*, 2006). In many cases, the disintegration time of solid dosage forms is too long to provide appropriate therapeutic effect. To improve the disintegration time, so-called disintegrants are used. In the past, non-modified disintegrants such as alginates, starches, ambrelite resins, cellulosic materials, pectins etc. were used to accelerate disintegration. Today, fast working superdisintegrants are chemically modified polymeric molecules, typically by crosslinking the organic chains. Three classes of superdisintegrants are commonly used: modified cellulose (crosscarmellose sodium), crosslinked polyvinyl-pyrrolidone (Kollidon CL) and modified starch (Sodium Starch Glycolate). Superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction which causes the tablet to burst or the accelerated absorption of water leading to promote disintegration.

Proposed mechanism for the action of disintegrants include water uptake through wicking, swelling, deformation recovery and particle repulsion (Abu-lazza *et al.*, 2004) (Zhao and Augsburg, 2005b).

Paracetamol (acetaminophen) is one of the most widely used over the counter medication. It has analgesic and antipyretic properties, but low antiinflammatory activity (Ouellet and Percival, 2001). Paracetamol is usually formulated in tablets containing 300 to 500 mg of drug (Martinello *et al.*, 2006). As an analgesic we used paracetamol, which is classified in Class II, according to the Biopharmaceutical Classification System BCS (high permeability, low solubility) (FDA guidelines, 1995). For drugs in Class II, the principal limitation of its oral absorption is the dissolution rate. A tablet is considered to be rapidly dissolving when more than 85% of the labeled amount of drug substance (Q + 5%) dissolves within 30 min in a volume of < 900 ml buffer solution using USP Apparatus I or II (United States Pharmacopeia, 2007).

The basic objective of this study was to produce immediate release paracetamol tablets containing different types of superdisintegrants via wet granulation, to compare their properties, disintegration and dissolution profiles. To reach this goal, it was necessary to find a suitable superdisintegrants having excellent disintegrating properties. Furthermore, we studied how their characteristics influence the tablet manufacture and dissolution profiles.

Materials and Methods

Materials: Paracetamol, Na starch glycolate, Crosscarmellose Na, Kollidon CL, Povidon K-30, Starch, Aerosil 200 and Mg Stearate were obtained as gift samples from ACI Pharmaceutical Ltd, All chemicals used were of analytical grade.

Preparation of granules: The amounts of all ingredients are mentioned in Table 1. Firstly, the active drug (Paracetamol), diluent (Starch), and the 3/4 amount of superdisintegrants were passed through a 40 mesh sieve to obtain fine particles and mixed together for 10 mins with a mortar and pestle. The binding solution was prepared by dissolving Povidone k-30 in sufficient amount of water. This solution was then added drop by drop to the dry mixture in the mortar. During this addition, the mixture was continuously stirred in clockwise direction which was continued for a further 10 mins after all the binding solution had been added. At the end of this mixing, a uniformly mixed wet mass was obtained. The wet mass was dried in an oven for 30 mins at 60^o C. Again dry mass was passed through a 16 mesh sieve to obtain very fine particles. Finally, these fine particles were mixed with Aerosil-200, 1/4 superdisintegrant and Mg stearate to obtain granules with the pre-requisite flow properties. The powder blend was evaluated for flow properties such as bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and results are presented in Table 2 (Lachman *et al.*, 1987).

Compression of tablets: The ingredients depicted in Table 1 were compressed by using a Single punch tablet machine (Bangladesh) to produce round flat faced tablets weighing about 580 mg each with a diameter of 13mm, a minimum of 30 tablets were prepared for each batch, and results are given in Table 3.

Evaluation of tablets: The mechanical strength of tablets is often defined as the force required fracturing a

tablet across its diameter (Martinello *et al.*, 2006). Mechanical strength is directly related to porosity and disintegration time. The packaging process and transportation of the final product requires appropriate tablet strength. To ensure tablet strength the formulations were evaluated for hardness, weight variation, thickness, friability, disintegration time and *in vitro* dissolution study. (Yunaxia *et al.*, 1996)

Tablet hardness: Hardness is the crushing strength of tablet which determines the ease of handling and rigors of the transportation. For each formulation, 3 tablets were used for the study. The hardness of the tablet was determined and expressed in kg/cm².

Weight variation test: Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The data is presented in Table 3.

Thickness: The thickness of the tablets was measured using manual Vernier Caliper, and expressed in mm.

Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Friabilator (Veego, India) was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Prewighed sample of tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dedusted and reweighed. The percent friability was measured using the formula:

$$\%F = \{(W - W_0)/W_0\} \times 100$$

Where, %F = Friability in percent,

W = Initial weight of tablet.

W₀ = Weight of tablet after test.

Disintegration time: One tablet was placed in each of six tubes of disintegration test apparatus. Disintegration test was carried out in 800 ml of phosphate buffer of pH 5.8 at 37 ± 0.5^oC (European Pharmacopeia, 2008). Disintegration test apparatus without disc, time required for complete passage of tablet fragments through the sieve (#10) was considered as a disintegration time of a tablet.

In vitro Dissolution studies: The *in vitro* dissolution study was carried out in phosphate buffer of pH 5.8 with a USP dissolution test apparatus (USP XXII) Type 2

(paddle). In all cases the conditions were maintained to be exactly the same, i.e. the rpm was maintained at 100 while the temperature maintained always at $37 \pm 0.5^{\circ}\text{C}$. The dissolution machine that was used contained eight dissolution vessels. Each of the vessels contained 900 ml of the prepared buffer. The apparatus was then set up with paddles and the tablets directly placed in the dissolution vessels. 10 ml of samples were withdrawn at 5, 10, 15 min etc. intervals by replacing with the same fresh dissolution medium immediately to maintain the sink condition. The dissolution was carried out for 1 hr. This was done to get a simulated picture of drug release in the *in vivo* condition.

The sample that was collected was filtered first, and then diluted before being assayed at 258 nm using UV spectrophotometer (Shimadzu, Japan). The amount of drug release was calculated with the help of a straight line equation obtained from the standard curve of Paracetamol.

Results and Discussion

Nine formulations of Paracetamol were prepared with varying concentrations (2.59%, 3.45% and 4.31%) of three superdisintegrants: sodium starch glycolate, Kollidon CL, croscarmellose sodium and starch was used as diluent and providon K-30 as binder (Table 1).

Table 1. Formulations of Paracetamol immediate release tablets

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|--------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Paracetamol | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| Starch | 16 | 11 | 6 | 16 | 11 | 6 | 16 | 11 | 6 |
| Povidon K-30 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Sodium starch glycolate | 15 | 20 | 25 | - | - | - | - | - | - |
| Kollidon Cl | - | - | - | 15 | 20 | 25 | - | - | - |
| Croscarmallose-sodium | - | - | - | - | - | - | 15 | 20 | 25 |
| Aerosil 200 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Magnesium stearate | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Total weight (mg) | 580 |

Evaluation of pre-compression characteristics: Prior to compression of the tablets, the powder blends were subjected to various physical tests such as determination of angle of repose of the powder as well as the estimation of bulk, tapped density and compressibility index of the powder. The angle of repose was determined by fixed funnel and free standing cone method and the densities were measured by densiometer. Using bulk and tapped density data, Hausner's ratio and compressibility index were calculated.

Bulk density was found in the range of 0.277-0.424 g/ml and the tapped density between 0.374-0.533 g/ml. F8 gave the higher range of bulk density and F7 as well as F1 showed higher values of tapped densities while F6 revealed the lower range of bulk and tapped densities (Table 2). It can be seen from table 2 that all the values obtained were higher than 1.20 indicating better flow properties. The highest value (1.40) was given by F3 and lowest value was demonstrated by F8. A Compressibility Index of greater than 25% is considered to be an indication of poor flowability and below 15% an indication of good flowability of granules. As it can be observed from the table 2, the granules of almost all the formulations gave a compressibility index ranged from (17-29)%. Formulations F3 and F6 gave higher compressibility indices which were 28.60 and 25.94, respectively. This is indicated that these two formulations did not show satisfactory flow property and according to the comparison of bulk density and compressibility index, other formulations showed moderate flow property as none of the formulations have values less than 15%. The angle of repose of formulations ranged from (26-33) $^{\circ}$. This is indicated good flow properties of the granules for all the formulations. The highest values were given by F4, F5 and F6 in which, Kollidon CL was used as the superdisintegrants. It is advisable to increase the glidant and lubricant in cases of formulation F4, F5 and F6 to facilitate its passage through the hopper without any hindrance.

Table 2. Pre-compression blend characterization

| Parameters | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| Bulk density (g/ml) | 0.412 | 0.396 | 0.372 | 0.381 | 0.317 | 0.277 | 0.412 | 0.424 | 0.396 |
| Tapped density (g/ml) | 0.533 | 0.519 | 0.521 | 0.476 | 0.397 | 0.374 | 0.533 | 0.512 | 0.519 |
| Compressibility index (%) | 22.70 | 23.70 | 28.60 | 19.96 | 20.15 | 25.94 | 22.70 | 17.18 | 23.70 |
| Hausner's ratio | 1.29 | 1.31 | 1.40 | 1.25 | 1.25 | 1.35 | 1.29 | 1.20 | 1.31 |
| Angle of repose | 30.25 | 31.62 | 31.96 | 32.25 | 32.89 | 33.56 | 26.47 | 27.25 | 29.24 |

Evaluation of tablets: The powder blend was compressed using wet granulation technique. Various physical parameters like weight variation, thickness, friability and hardness were measured to evaluate tablets. Theoretically, the average weight of tablets of the different formulations should be 580 mg (Table 1). It was seen that the average weight of the tablets was particularly found to be remarkably consistent and somewhat uniform, which

was approximately 580 mg. From table 3, it is found that the average thickness of the tablets also ranged between 3.22-3.42 mm; however, the variations were not alarming and remained within the acceptable range. On the contrary, friability of the tablets of different formulations varied greatly range from 0.14-0.32%. The friability was found to be the greatest for formulation F8, which indicated maximum loss of tablets upon attrition.

Table 3. Paracetamol tablets characterization

| Evaluation | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|--------------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Weight variation (mg) | 581±1 | 579±1 | 580±2 | 578±2 | 581±1 | 580±.5 | 579±1 | 580±1 | 579±2 |
| Thickness (mm) | 3.22±0.08 | 3.30±0.04 | 3.35±0.03 | 3.37±0.04 | 3.42±0.02 | 3.40±0.05 | 3.36±0.04 | 3.41±0.06 | 3.38±0.03 |
| Friability (%) | 0.26 | 0.26 | 0.25 | 0.17 | 0.14 | 0.15 | 0.24 | 0.32 | 0.27 |
| Hardness (kg/cm ²) | 11.97±0.5 | 11.63±0.8 | 11.58±0.4 | 11.40±0.5 | 11.65±0.6 | 11.63±0.8 | 11.52±0.6 | 11.53±0.7 | 11.55±0.5 |
| Disintegration time (min.) | 2.4±0.1 | 2.2±0.1 | 2.1±0.2 | 2.8±0.2 | 2.5±0.1 | 2.4±0.1 | 3.0±0.2 | 2.8±0.2 | 2.7±0.1 |

Disintegration and dissolution profiles: The *in vitro* disintegration time (DT) of the tablets was found to be less than 3.0 mins. Tablets containing 4.31% sodium starch glycolate (F3) showed lowest disintegration time of 2.1 mins (Table 3). From table 1, it is seen that F1, F2 and F3 contain 2.59%, 3.45% and 4.31% of sodium starch glycolate respectively. After completion of disintegration it was found that with the increase of the amount of sodium starch glycolate, the disintegration time was decreased (Figure 1). Similar phenomenon was also observed when paracetamol was formulated with Kollidon CL and croscarmellose sodium keeping the above concentrations (Table 3). During the qualitative investigation among three superdisintegrants, F3, F6 and

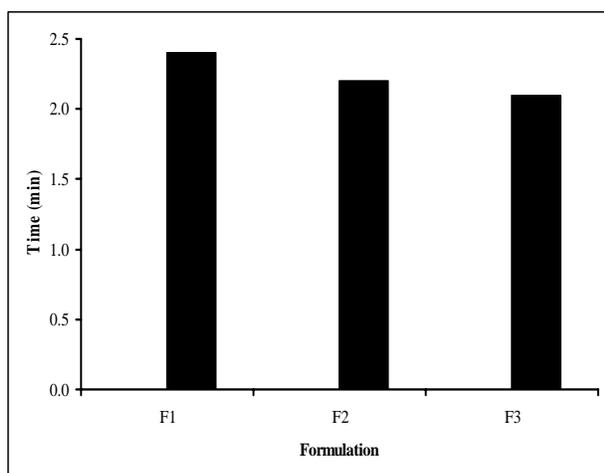


Figure 1. Disintegration time (min) of paracetamol from F1, F2 and F3 containing sodium starch glycolate as superdisintegrant.

According to some authentic references the maximum friability range should be in between 0.5-1%. As the friability values for none of the formulations exceed 1%, it does not pose any serious problems. Hardness of tablets of the different formulations varied widely ranging from 11.40-11.97 kg (Table 3). Since hardness greater than 5.10 kg is considered acceptable, all the formulations were therefore thought to show the desired hardness

F9 were compared (Figure 2). It was seen that the lowest disintegration time (2.10 mins) was found when sodium starch glycolate was used as disintegrant and the highest disintegration time (2.70 mins) was found with Crosscarmellose sodium. In all cases sodium starch glycolate decreased disintegration time than Kollidon CL and croscarmellose sodium (Table 3).

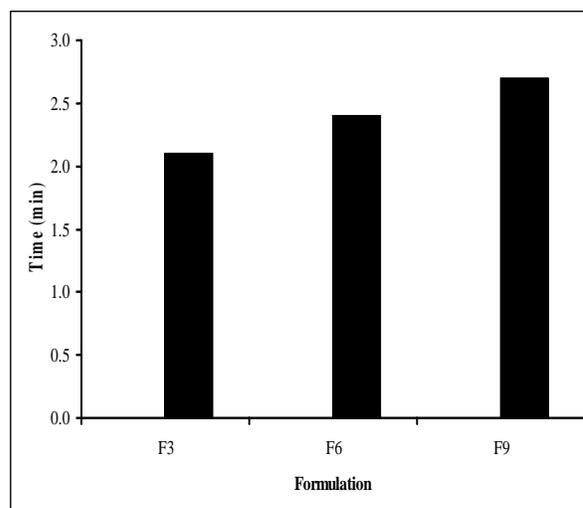


Figure 2. Disintegration time (min) of paracetamol from F3, F6 and F9 containing maximum amount of sodium starch glycolate, Kollidon k-30 and croscarmellose sodium respectively as superdisintegrant.

Effect of amount of superdisintegrants: Immediate release tablets were prepared according to the formulations stated in table 1 with Paracetamol as the active ingredient. The amount of drug in each formulation

was kept constant and the amount of superdisintegrants was increased gradually. Dissolution was carried out for 30 min using phosphate buffer pH 5.8 as dissolution medium. To explore the effect of amount of superdisintegrants, nine formulations in three groups were compared. In figure 3, F1, F2 and F3 were compared which contained 15, 20 and 25 mg of sodium starch glycolate as a super disintegrant, respectively. From the zero order release profile (Figure 3) it was observed that the total percent release of Paracetamol from F1, F2, and F3 were 57.4%, 63.8%, and 70.1%, respectively at the end of 30 minute. It is observed that with increasing the concentration of sodium starch glycolate, the rate and extent of drug release from the formulation was increased. This effect was due to the increase of concentration of superdisintegrants (sodium starch glycolate). Similar pattern of rate and extent of drug release were also found when we compared F4 to F6 and F7 to F9 which contained Kollidon CL and croscarmellose sodium respectively. At the end of 30 min F4 to F6 offered 55.3%, 61.5% and 65.4% whereas F7 to F9 showed 53.2%, 59.8% and 61.3% of drug release, respectively.

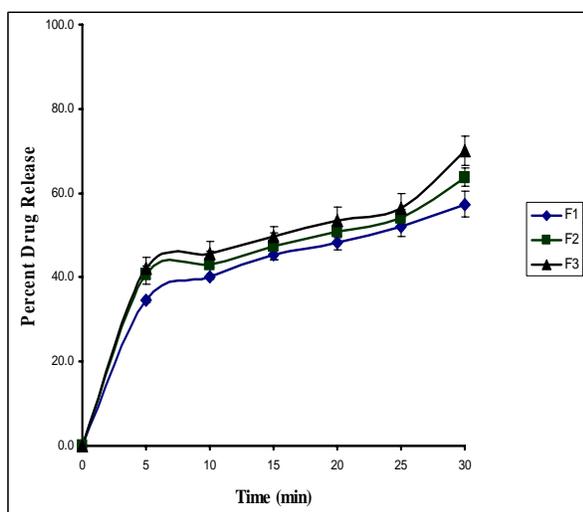


Figure 3. Zero order release of paracetamol from F1, F2 and F3 containing sodium starch glycolate as superdisintegrant.

Effect of superdisintegrants: To investigate the qualitative effect of superdisintegrants, F3, F6 and F9 were compared which contained 25 mg of sodium starch glycolate, Kollidon CL and croscarmellose sodium, respectively. It is observed from figure 4 that at the same level of superdisintegrants, sodium starch glycolate

offered maximum release of drug than others. The sequence of drug release from the tablets is given below:

Sodium starch glycolate > Kollidon CL > Croscarmellose sodium.

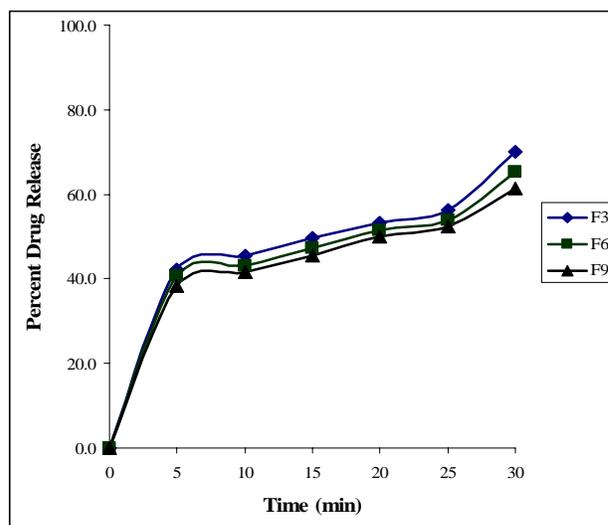


Figure 4. Zero order release of paracetamol from F3, F6 and F9 containing maximum amount of sodium starch glycolate, Kollidon k-30 and croscarmellose sodium respectively as superdisintegrant.

Conclusion

The *In vitro* drug release profile of all formulations was evaluated and the release studies demonstrated that the release of Paracetamol from all formulations was generally immediate. High concentration of superdisintegrants used in the formulations caused high percent release of drug, while lower concentration caused low release. Thus, the release characteristics were significantly influenced by the type and concentration of superdisintegrants used. Disintegration time was also governed by type and quantity of superdisintegrants. Disintegration time was decreased with the increase of superdisintegrants. Again, the various mechanical and physical parameters of granules and tablets such as the flow properties, hardness, friability etc. were seen to comply with the standards set by different international organizations e.g. pharmacopeias. Thus, the granules and tablets were found satisfactory in terms of physical parameters, disintegration time as well as the drug release profiles from the immediate release tablets.

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