Compression of Coated Drug Beads for Sustained Release Tablet of Glipizide: Formulation, and Dissolution

Compression of Coated Drug Beads for

Sustained Release Tablet of Glipizide:

Formulation, and Dissolution

Chien Nguyen [1], J. Mark Christensen [2, 3], and James W. Ayres[2], Ph.D.

[1]Chien Nguyen Ph.D., Industrial Department of Pharmacy, Hanoi University of Pharmacy, Hanoi, Vietnam, nguyenngocchien@yahoo.com

[2]J. Mark Christensen Ph.D., College of Pharmacy, Oregon State University, Corvallis, Oregon 97331. Jmark.christensen@oregonstate.edu, 541-737-5788.

[2]James W. Ayres Ph.D., College of Pharmacy, Oregon State University, Corvallis, Oregon, 97331, ayresa@onid.orst.edu.

[3] Author of Correspondence- College of Pharmacy, Oregon State University, 1601 SW Jefferson Avenue, Corvallis, Oregon 97331: Phone 541-737-5788; Fax 541-737-3999; Email:

jmark.christensen@oregonstate.edu

ABSTRACT

A promising formulation of glipizide comprising compression of four-layer coated beads into tablets which has advantages of providing a lag time (~ 2 hours) before drug release, retaining sustained-release characteristics, and providing approximately zero-order drug release, with drug release nearly independent of paddle speeds of 50 and 100 rpm during dissolution testing while keeping the benefits of mulitparticular dosage forms. The tablets contain beads with four layers: the drug layer of 71.25 g of sugar beads overcoated with 2.5 g of glipizide and 3.75 g of solid ethylcellulose (Surelease®); the hardening layer of 5 g of hypromellose (HPMC); the controlled release layer of 7.5 g of ratio solid content of Surelease®:lactose = 100:7; and outmost layer of 20 g of lactose:sodium starch glycolate (Explotab®) = 2:1. Then beads were compressed into tablets containing 11mg of glipizide with 1500 pounds of compression pressure.

Key words: glipizide, compressed-beads into tablets, sustained-release, Glucotrol® XL, zero-order release.

INTRODUCTION

Multiparticular dosage forms provide many benefits over the single unit dosage forms for the oral route such as uniformly distributing throughout the gastrointestinal tract, decreasing the risk of high local drug concentrations, dose dumping, and increasing drug bioavailability (Bodmeier, 1997; El-Gazayerly et al., 2004; and Vergote et al., 2002). Multiparticular dosage forms of orally sustained release drug delivery systems usually are ethyl cellulose (EC)-coated beads. Ethyl cellulose-coated beads can either be compressed into tablets or filled into gelatin capsules. Compression of ethyl cellulose-coated beads into tablets raises concerns regarding the loss of integrity of the polymer coat following compression. The pellets should not fuse into a non-disintegrating matrix during compaction. After compaction, disintegration of the tablet should release individual beads and drug release should not be affected by the compaction process (Dashevsky, et al, 2004). This has shown to be possible with reservoir type beads coated with acrylic coating that can deform but not rupture during compaction. Most studies on the compaction of beads coated with EC induced damage to the coating with loss of prolonged release properties (Bansal, et al., 1993; Bodmeier, 1997; Dashevsky et al., 2004).

Studies on compression of pellets coated with ethylcellulose (EC) revealed damage to the coating with a loss of sustained release properties and resulting in faster drug release because of weak mechanical properties (Bodmeier, 1997) of ethylcellulose regardless of particle size (Bechard and Leroux, 1992). Such partial loss of sustained release effect may be due to formation of cracks in the coat during compaction (Altaf et al., 1999; Bechard et al., 1992; El-Gazayerly et al., 2004; Maganti and Çelik, 1994). The

amount of polymer coating, compression pressure, bead size, number of layers, and type of binder/disintegrant excipient were important factors that affected drug release characteristics (Altaf et al., 1998). Films containing ethylcellulose plasticized with 24% dibutyl sebacate did not have the appropriate mechanical properties to withstand compaction stress without rupturing, regardless of the pellets particle size and excipients used (Bechard and Leroux, 1992). Controlled release properties of the pellets were therefore lost during compaction. To reduce damage to ethylcellulose coated pellets, one of the methods is to put compressed pellets in an oven at 70^0C for 24 h to obtain retardation in the drug release (Bodmeier, 1997).

Inclusion of binder/disintegrant agents, such as microcrystalline cellulose (MCC) powder or beads made from glyceryl palmitostearate and MCC between brittle MCC spheres, is an effective method of formulation modification which permits compaction without fracture, and provides satisfactory tablets having the same dissolution profile characteristics as the uncompacted beads (Mount et al., 1996). However, mixing the coated drug beads with a binder/disintegrant agent, in powder form, in the form of spheres, and as granules can lead to segregation issues during mixing and compaction.

Spray-layering of binder/disintegrant excipient onto beads can provide an effective way to circumvent segregation issues associated with mixing of the polymer-coated beads, and powdered or spherical/nonspherical binder/disintegrant excipients, providing excellent flow properties of the final formulation (Altaf et al., 1998), and also protect film coats from rupture during compaction.

Another way to protect film coats on beads is to use a sealant agent. A sealant layer consisting of a hydrophilic gel-forming agent is beneficial to help maintain sustained release properties of compacted beads by partially plugging cracks in a ruptured polymer coating. Upon contact with the dissolution medium, this gel-forming layer hydrates and swells, offering sufficient sealing to damaged areas in the sustained release polymer coating resulting from compaction (El-Gazayerly et al., 2004).

For development of a new beads-compressed tablet in the current research, glipizide was chosen as model drug. Glipizide is a second-generation sulfonylurea that acutely lowers blood glucose levels in humans by stimulating the release of insulin from the pancreas and is typically prescribed for patients with type II diabetes. Its short biological half-life (~3.4 $\pm$ 0.7 hours) necessitates administering 2-3 doses of 2.5-10 mg daily to achieve adequate blood glucose control (Patel et al 2005). A sustained release dosage form of glipizide clearly would have advantages in therapy. Several oral sustained release formulations of glipizide using various techniques have been tested (Gan et al. 2002; Defang et al. 2005a: Defang et al. 2005b: Patel et al. 2005: Jamzad and Fassihi 2006; Hsieh et al. 2006; Shivakumar et al. 2007; Ghosh et al. 2008).

The objective of this research was to delineate a promising formulation approach using ethylcellulose coated drug beads to produce "beads-compressed into tablets" that would provide nearly zero-order prolonged drug release, be relatively independent of dissolution media and stirring speeds (and gastrointestinal agitation and transit times).

MATERIALS AND METHODS

Chemicals

Active drug was glipizide from Teva Pharmaceuticals, USA (Sellersville, PA). Hydroxypropyl methylcellulose (Hypromellose, HPMC) type 2910 viscosity 15 (Methocel® E15 prem LV) was from Dow Chemical Company (Midland, MI), lactose monohydrate was a gift from Teva Pharmaceuticals, USA. Surelease® (ethylcellulose), formula No.: E-7-19010 with solids content of 25.0% was a gift from Colorcon (West Point, PA). Sodium starch glycolate low pH (Explotab®) was from Mendell, a Penwest company (Patterson, NY). White sugar spheres, mesh size 18-20, were a gift from Paulaur Corporation (Cranbury, NY). Glucotrol® XL, manufactured by Pfizer Corporation (New York, NY), was purchased from the Oregon State University campus pharmacy.

Method

Weight compositions of tablet formulations are shown in Table 1.

Bead -Coating procedure

Loaded drug coating with Surelease®: An amount of de-ionized (DI) water equal to the amount of Surelease® was added to a Surelease® dispersion in a beaker and mixed

well. Concentrated ammonium hydroxide, 0.2 to 0.5 ml, to adjust pH to 10-10.4, was added to the Surelease® dispersion. Glipizide in each formulation that would produce 2.3 to 2.5 g of glipizide in 110 g of final product (Table 1) was dissolved in the above Surelease® dispersion and mixed well for at least one hour. This dispersion was gently stirring during coating. The amount of sugar beads in each formulation (Table 1), mesh size 18-20, were placed into a laboratory Niro STREA spray coater, with the following parameters: Nozzle-needle 1.0 mm, drying temperature: 50^0C, outlet air temperature: 41^0C, pressure: 2-5 psi, flow: 1 ml/minute for coating.

HPMC hardening coating: HPMC (Table 1) was added to hot water (30% of total water in the formulation) at 80^0C in a beaker and stirred for 20 seconds. Then the rest of the water that was at room temperature was added producing a 5% solution of HPMC. This solution was stirred until HPMC was completely dissolved and the solution was gently stirring during coating. Drug loaded beads were put into the spray coater with the spraying parameters for coating: Nozzle-needle 1.0 mm, drying temperature: 50^0C, outlet air temperature: 41^0C, pressure: 10-12 psi, flow: 1.1 ml/minute.

Controlled release layer coating: An equal amount to Surelease® of DI water was added to a Surelease® dispersion in a beaker. Lactose monohydrate for each formulation respectively (Table 1) was dissolved in the above dispersion and mixed well for at least one hour and continuously gently stirring occurred during coating. The spraying parameters for coating were: Nozzle-needle 1.0 mm, drying temperature: 50^0C, outlet air temperature: 41^0C, pressure: 10-15 psi, flow: 1.1 ml/minute.

Binder/disintegrant layer coating: Lactose monohydrate was dissolved in water to produce an 8.2% (w/v) solution. Explotab® (equal to half of the amount of lactose, Table 1) was added to the above solution and mixed well for 30 minutes. The solution was kept gently stirring continuously during coating. The coating parameters during coating were: Nozzle-needle 1.0 mm, drying temperature: 30^0C, outlet air temperature: 28^0C, pressure: 10-12 psi, flow: 0.75 ml/minute for 45 grams of beads.

From inside to outside of each bead, is the sugar bead, a drug-Surelease® layer, a HPMC layer, a Surelease® controlled release layer, and finally a binder and disintegrant layer.

Bead Compaction

The beads were compressed into round tablets with diameter of 11.1 mm; thickness of 5.2 mm at the center and 3 mm at the edge using a Carver press fitted with a tablet punch and die. Separate tablets were made by applying 1000, 1500, 2000, or 3000 pounds (lbs) of pressure under a dwell time of 10 seconds after target pressures were reached. Each tablet contains 11 mg (110%) of glipizide based on drug content assay of the beads.

In Vitro Dissolution Testing of Formulations

Dissolution studies were performed according to the USP/NF apparatus 2. Test formulations were added to 700 ml of simulated gastric fluid without pepsin for the first 2 h, then 158 ml of 0.2 M Na_3PO_4 was added and the pH was adjusted to 7.4 ± 0.1 with 6N NaOH or concentrated hydrochloric acid, 12.1 M. The dissolution media was stirred at different rpm, and a constant temperature maintained at 37 ± 0.5^0C. 5-mL dissolution samples were filtered through flow filters (0.45 µm), and collected via an autosampler at predetermined time intervals for 24-h. Filtered solutions were centrifuged at 3000 rpm for 20 minutes; supernatants were measured to determine absorbance at 275 nm. Dissolution drug concentrations were determined via standard curves in each medium and converted to percentage glipizide released. Standard curves of observed absorbance versus glipizide concentration were constructed in simulated gastric fluid and pH 7.4 buffer at 275 nm in a UV spectrophotometer (Beckman, Model DU 640, Fullerton, CA). Three or six runs of each dissolution experiment were performed and the mean $\pm$ S.D. was calculated. Release of glipizide from tablets was compared to that obtained from Glucotrol®-XL osmotic pump reference tablets. Glipizide dissolution profiles are presented as percent drug release versus time curves.

Drug Content Assay

Tablet drug content assay was performed in duplicate. An amount of coated beads equivalent to 11mg of glipizide was weighed and compressed into a tablet at 1500 pounds pressure. Single tablets were transferred to 100-ml volumetric flasks. A pH 7.4 buffer solution was used to dissolve drug over a 24 hour period using a stirring bar to facilitate

the dissolution. Then the samples were centrifuged at 3000 rpm for 10 minutes. Supernatant was collected. Supernatant solutions were diluted 12.5 times with pH 7.4 buffer solution and filtered through a membrane of 0.45 µm diameter. The filtered solutions were measured by UV spectrophotometer at 275 nm in pH 7.4 buffer. The amount of glipizide contained in each formulation was determined using an appropriate standard curve.

pH 7.4 buffer preparation

To 400 ml of simulated gastric fluid pH 1.4 ± 0.1 was added 100 ml of 0.2M Na_3PO_4. The solution was mixed well and adjusted to pH 7.4 ± 0.1 with 6 N NaOH or concentrated hydrochloric acid (12.1M) as needed.

Statistical analysis

Statistical analyses such as multiple comparisons (Tukey method), multiple linear regression, and two-way ANOVA were carried out using S-plus 7.0 statistical software (TIBCO Software Inc, Palo Alto, CA 94304). Table 2 summarizes the factors and levels studied (i.e., paddle speed and compaction pressure). Every experiment was performed in triplicate. The significance level was set at $\alpha = 0.05$. Residual plots were used to check the assumption of constant variance and normal quantile quantile (QQ) plots were used to check the assumption of normality. The Tukey's assumptions are an ideal normal model with equal spreads and equal sample sizes in all groups. Since there are equal sample sizes in the treatments, the Tukey's method appears appropriate. The release rate over

time and the percentage of drug released at 16 hours (%release 16) were used as response variables. The release rate following the lag time is calculated as follows:

$$\text{Release rate} = \text{slope of dissolution curve} = \frac{\% \, release \, 16h - \% \, release \, 2h}{16 - 2}$$

RESULTS AND DISCUSSION

Effect of binder/disintegrant layer:

Based on preliminary formulation results, formulations started with a ratio of Surelease®:glipizide of 2:1, 10% weight gain of HPMC in the hardening layer, and then 10% weight gain of Surelease® to lactose = 100:5 in the controlled layer (compared to weight of sugar beads, glipizide and Surelease® solid content) to evaluate the appropriate amount of binder/disintegrant layer. The results are shown in Table 3 and Figure 1.

Table 3 presents the observed disintegration times of tablets during dissolution testing. For 11.11% weight gain of binder/disintegrant layer, F2 tablets did not disintegrate after 24 hours. In fact, the beads in F1 and F2 tablets were fused when compressed into a tablet to form a non-disintegrating matrix tablet. F1 tablets released little glipizide for 24h (not shown). For 16.67% weight gain of binder/disintegrant layer, disintegration of F3 tablets started at 3h and was complete before 20 h. For 22.22% weight gain of binder/disintegrant layer, F4 tablets disintegrated into individual beads within 3 hours and the four layer coated beads controlled drug release. Lactose in the 4th layer acts a binding agent, and sodium starch glycolate is a super disintegrant, which

causes the tablet to fall apart in the dissolution medium. Drug release depends on the disintegration time (or on the amount of disintegrant in the disintegrant layer) as seen in Figure 1. The greater the weight gain of disintegrating agents in beads the higher %release 16, and the faster the drug release as seen in Figure 1.

When the multilayered beads are compressed into tablets the outermost layers (the binder/disintegrant layer, the controlled-Surelease® layer, and HPMC) absorb the pressure, which can produce cracks in the Surelease®-controlled release membrane layer. The hardening-HPMC layer impedes drug from releasing from the Surelease®-drug layer and provides a lag time before drug is released and maintains sustained drug release. Tablets compacted from these coated drug beads were more cohesive and easily produced hard tablets with low compression pressures. Upon compaction, discrete beads could still be clearly distinguished on the surface of the tablet for all applied compression pressures. The 1500 lbs compaction pressure was chosen because beads compressed into tablets with this pressure passed friability testing. To evaluate the effect of amount of binder/disintegrant layer, %release 16 (percent of drug released after 16 hours of dissolution testing) was used as a response variable versus percent coating weight gain of binder/disintegrant layer. Table 4 shows results of the linear regression model with percentage of binder/disintegrant weight gain treated as a continuous variable, e.g. 11.11, 16.67 and 22.22 (% weight gain) when fitting models.

The result indicated that there is a strong relationship between the mean %release 16 and % weight gain of binder/disintegrant (P = 0.003, model 1 in the Table 4). The

relationship between the mean %release 16 discussed in model 1 and % weight gain of binder/disintegrant is as follows.

%release 16 = 26.164 + 2.381* (%weight gain of binder/disintegrant) (Eq. 1)
(8.969) (0.519)   (The numbers in parenthesis are the standard
error for each corresponding coefficient.)

An increase of 5% weight gain of binder/disintegrant layer is associated with an 11.903% increase (95% confidence interval is 6.820-16.990%) in %release 16 as seen in equation Eq. 1.

With 22.22% weight gain of binder/disintegrant layer, the drug release rate was higher than that of 11.11% and 16.67% weight gain of binder/disintegrant layer and closer to the drug release rate of the reference product Glucotrol® XL (Figure 1). More importantly, tablets having a 22.22% weight gain of binder/disintegrant ingredients disintegrated into individual beads within 3 hours during dissolution testing. Drug release from individual beads is preferable to a single tablet in controlling drug release. Thus, the 22.22% of weight gain of binder/disintegrant ingredients was chosen for the binder/disintegrant layer.

Effect of hardening and sealing agent, HPMC:

HPMC is a very good bead hardening agent, both for ease of use and to create durable beads. Figure 2 shows the effect of the inclusion of the coating layer with HPMC as the hardening agent applied at levels between 2.27% (F7) and 6.82% (F4) on the drug release from beads-compressed into tablets. Beads hardened with HPMC provided

excellent physical strength and stability during spray-coating with the sustained release membrane layer. The 6.82% (F4), 4.55% (F5), or 3.64% (F6) weight increase of HPMC to the total tablet composition showed little differences in effect on glipizide release from tablets; however 2.27% weight increase of HPMC (F7) to the total tablet composition reduced drug release from beads-compressed into tablets compared with 6.82%, 4.55%, or 3.64% of HPMC formulations (Figure 2). Statistical results also indicate that there were no statistically significant differences between F5 (4.55% of HPMC) and F6 (3.64% of HPMC) on % release at 16h. However, the differences of %release 16 between F7 (2.27% of HPMC) to F5 (4.55% of HPMC), and F4 (6.82% of HPMC) to F5 (4.55% of HPMC) were statistically significant (Tukey's method) Table 5. The % release at 16 hours from F5 (4.55% of HPMC) formulation was the highest and nearest to the reference standard Glucotrol® XL (Figure 2). In order to make strong beads that are resistant to compaction pressure, the more HPMC in the hardening layer the stronger the bead. However, increasing the amount of HPMC may increase labor time of coating and decrease % release at 16 hours. The 4.55% weight increase of HPMC used as the hardening layer appears an appropriate coating level in terms of producing a proper lag time and tensile strength for the sealing and hardening layer to produce the desired % release at 16 hours. Thus, 4.55% of HPMC in hardening layer was the adopted amount used for further study.

Effect of Surelease® on Glipizide release:

The influence of varying the amounts of Surelease® in the Surelease®-drug layer and the Surelease®-controlled release layer on drug release is presented in Figure 3.

As seen in Figure 3, as the amount of Surelease® increases in either the Surelease®-drug layer or the Surelease®-controlled release layer the more slowly drug is released. The inner amount of Surelease® in drug layer predominates over the controlled release layer when comparing F12 and F10 and comparing F9 and F10. Formulation F9 and formulation F10 show little differences with a 0.55% difference (compared with weight total) of Surelease® in controlled release layer. In contrast, with a similar difference in the amount of Surelease® in the drug layer (0.57% compared with weight total), F12 released drug much faster than F10. Also, when increasing the amount of Surelease® in the Surelease®-controlled release layer from 5.4 g in F12 to 7.5 g in F13 (~1.9%), F13 released drug more slowly than F12.

Statistical results in Table 6 also indicate that there were no statistically significant differences between F10 (Surelease®:lactose = 100:7) and F11 (Surelease®:lactose = 100:10) on % release at 16 hours. Therefore changing the ratio of Surelease®:lactose = 100:7 to 100:10 in the controlled release layer did not affect % release at 16 hours. There were also no statistically significant differences between F10 (5.4 g of Surelease®:lactose = 100:7) and F9 (6 g of Surelease®:lactose = 100:7) on % release at 16 hours. In other words, percent release at 16 hours did not differ when decreasing by the amount of 0.55% of Surelease®:lactose = 100:7 in the controlled release layer from F9 to F10. By decreasing the amount of Surelease®:lactose (0.62g of

Surelease®:lactose = 100:7) in the Surelease®-drug layer from F10 to F12, % release at 16 hours increased significantly after accounting for other factors. F8 was excluded from comparison because two factors were changed, while the other formulations only one factor changed. F8 was used to quickly check the effects of both amount of Surelease® (Surelease® in controlled release layer or in Surelease®-drug layer) and percent lactose in controlled release membrane on drug release. F8 tablets were also used to check the tablet hardness (Table 7). F8 Tablets produced with compression pressures from 1500 lbs to 3000 lbs passed the USP friability testing requirement. All tablets produced with compression pressures from 1000 to 3000 pounds had "tablet breaking forces" higher than 4 kg. This means that all tablets should be strong enough to resist chipping and breaking during coating and shipping process.

Formulation F12 released drug more rapidly than the reference Glucotrol® XL. To reduce the drug release rate from F12, 2.1 g (or 1.9%) of Surelease®:lactose = 100:7 was added to the controlled release layer (F13). The difference between F12 and F13 was significant. The dissolution profile of F13 matched Glucotrol® XL tablet up to 12 h. Thus, F13 was selected for further study.

Effect of compaction pressure on F4:

As shown in Figure 4, compression pressure from 1000 lbs to 2000 lbs had little effect on drug release from F4 at 100 rpm, paddle method. As known, reported effects of compaction pressure on drug release from EC coated beads was significant. Compaction pressure affected drug release from tablets compressed from EC coated beads (Maganti

and Celik, 1994; and Altaf et al., 1999). But, compression force is not a critical parameter in influencing drug release rate from Eudragit® RS 30D coated granules formulated into tablets. There are no significant differences between the dissolution profiles of the tablets compressed from Eudragit® RS 30D coated beads with hardness's 4, 8 or 12 kg/cm^2 (Palmieri et al., 1996), or Kollicoat SR 30 D coated beads (Dashevsky, 2004).

Effect of compression pressures and paddle speeds on drug release on F13

Figures 5, 6, and 7 shows the effect of paddle speeds and compression pressures on beads compressed into tablets, F13.

Dissolution curves of F13 tablets made under 1500 lbs compaction pressure were not different at 50 and 100 rpm paddle speeds and matched the reference Glucotrol® XL at 100 rpm up to 12 hours. At 150 and 200 rpm paddle speeds, the dissolution patterns of F13 tablets made under 1500 lbs were similar and significantly higher than that at 50 and 100 rpm paddle speeds but still close to reference Glucotrol® XL (Figure 5).

Formulation F13 at 2000 pounds compression pressure with 150 and 200 rpm paddle speeds gave the same drug release but higher than paddle speeds at 100 rpm and 50 rpm (Figure 6). For F13, 3000 lbs compaction pressure, the higher the paddle speed the faster the drug release (Figure 7). Interestingly, the glipizide dissolution patterns of F13 tablets made under 2000 lbs and 3000 lbs compaction pressure are close to those of Glucotrol® XL at 50 and 100 rpm paddle speeds, respectively.

Although compression pressures from 1500 lbs to 3000 lbs have little effect on drug release from F13 at 100 rpm paddle (Figures 5, 6, and 7), these compression pressures have more effect at paddle speeds of 50, 150, and 200 rpm (Figures 5, 6, and 7). At 50 rpm paddle speed, F13 with 2000 and 3000 lbs compression pressures had similar drug release that was a little lower than F13 compressed at 1500 lbs. At 150 rpm paddle speed, there was a little difference in drug release from F13 at 1500 and 3000 lbs compaction pressure. At 200 rpm paddle speed, F13 tablets compacted at 1500 and 2000 lbs gave similar dissolution profiles, but lower than 3000 lbs (Figures 5, 6, and 7).

As shown in Figure 6, paddle speeds at 100, 150 and 200 rpm did not affect drug release from Glucotrol® XL, but surprisingly paddle speed of 50 rpm slowed drug release from Glucotrol® XL significantly.

For 150 and 200 rpm paddle speeds all F13 tablets produced under all compression pressures have a higher variation from the reference Glucotrol® XL in the central part of the dissolution curves. This is due to an increased drug release at the beginning of the dissolution process, followed by a gradual slow decrease in the dissolution rate. While there is concave curvature for the F13 dissolution curves shown in Figures 5, 6, and 7 it should be noted that the amount of such curvature is far less than is typical for ethylcellulose coated drug beads and the slope is nearly linear in the 3 hour to 16 hour section for some curves (50 and 100 rpm), i.e., essentially zero-order drug release.

Even though glipizide was released faster from F13 tablets compacted at 1500 and 3000 lbs pressures at 150, and 200 rpm paddle speeds than that of reference Glucotrol[®] XL, the drug release in each interval from 3h to 16 h is close to release of reference Glucotrol[®] XL and this portion of the drug dissolution curve is most influential on the peak plasma concentration, Cmax.

Two-way ANOVA results of the influence of compression pressures and paddle speeds on release rate from F13 tablets are summarized in Tables 8. Results in Table 9 indicate that the effect of compression pressures on release rate strongly depends on the paddle speeds (P value = 0.006, model 2). Since model 2 developed for release rate included an interaction term, no general conclusion can be drawn across all pressures since the effect of compression pressures on release rate depends on paddle speed.

Two way ANOVA results for the comparisons of release rate between F13 tablets (1500 lbs) and Glucotrol[®] XL at different paddle speeds are summarized in Tables 8. Table 9 shows that the effect of dissolution paddle speeds on drug release rate is significant (P-value = 0.005, model 3). The drug release rate from F13 compacted with a force of 1500 pounds pressure does not significantly differ from that of Glucotrol[®] XL (P-value = 0.320, model 3).

Effect of exclusion of HPMC:

HPMC appears to have little effect on drug release, or decreases %release 16 h if amount of HPMC deviates from 4.55%. Another formulation, F14, was produced without HPMC, with other ingredients being the same as F13. Figure 8 shows the effect of exclusion of HPMC on drug release from beads only and beads-compressed into tablets. For beads only, exclusion of HPMC convincingly reduced extent and rate of drug release significantly from 2 to 24 hours. After 24 h, less than 5% of drug was released from F14-beads (without HPMC), compared with more than 78% from F13-beads (with HPMC). When F14 beads were compacted into tablets, the drug release was much faster than F14 beads, and lower than the dissolution profile of F13 tablets. Formulation F13, and F14 have the same % and % weight gain of Surelease® in the Surelease®-drug layer and controlled release layer, and lactose:Explotab® = 2:1 in the disintegrant layer. However, drug release was reduced due to the absence of HPMC in the formulation. It was also noted that compressed F14 tablets began disintegrating after 2 hours but was not complete until 5 hours, but for F13, tablets disintegrated within 3 hours during dissolution testing. It was concluded that the HPMC layer helps achieve the desired glipizide release profile. HPMC layer protects two Surelease® layers, Surelease® in drug-Surelease® layer and Surelease® in controlled release layer, from being fused into a matrix which can slow disintegration time and reduce drug release rate and extent.

Discussion

The lag time is created in part by the EC (ethylcellulose)/lactose-controlled release layer. With beads only, dissolution medium dissolves lactose and penetrates through lactose channels, reaching HPMC which hydrates and swells. When aqueous medium contacts drug in Surelease®-drug layer, drug dissolves and comes out through created channels. The time it takes from when a formulation is placed into a dissolution medium until drug release begins is "lag time".

With beads-compressed into tablets, all layers are deformed, sustained release layer is at least partially damaged, and lag time reduced. When tablets are put into a dissolution medium, the aqueous medium penetrates into binder/disintegrant layer between beads of tablet and then disintegrates tablet into individual beads. At the same time, the aqueous medium reaches into inner layers through lactose channels and any fractures created by compaction pressure. Dissolution medium still needs to hydrate and swell HPMC which cover the fractures, then dissolve drug and carry drug out through channels. Fissures created by compaction pressure shorten lag times. The Surelease®-drug layer plays a role in controlling drug release. It can control the rate of drug release from the core even when the Surelease®/lactose-controlled-layer is deformed severely. HPMC is not only a hardening agent but also helps protect two Surelease® layers from being fused into each other under the compression pressures. Surelease®- controlled release layer is adequately durable that hydrating HPMC does not swell sufficiently to rupture the Surelease®-controlled release layer. Release of drug occurs by diffusion through the EC coating and the channels produced as the lactose dissolves away. This release mechanism differs from time-controlled explosion systems (Ueda et al., 1994). In

this study, the statistical comparisons of the dissolution profiles are useful for product formulation optimization in order to reduce the number of experiments to delineate the roles of the four layers in the new formulation. To note that glipizide, a weak acid, is poorly soluble in acidic solution. To elucidate the behavior of glipizide tablets in simulated gastric and intestinal fluids, glipizide powder dissolution was tested. The result shows that in simulated gastric fluid only 2.5% of glipizide was dissolved for the first 2 hours. It can be a confounding factor when *in vitro* dissolution using simulated gastric fluid for the first 2 hours is tested for the lag time. Since little glipizide dissolves in an acidic medium, a formulation might be thought to have a lag time of two hours in simulated gastric fluid, but the real lag time can be shorter if the formulation was put directly into a medium with pH greater than 7. Thus, F13 tablets were tested in buffer medium pH 7.4 for 24 hours to check the lag time in this medium. The result shows that the lag time of F13 tablets in this testing condition was 1.5h. However, the *in vivo* times for 50% gastric emptying of pellets were 119 ± 15 minutes (light breakfast) and 285 ± 45 minutes (heavy breakfast) (Davis et al., 1984). Therefore, it is reasonable to test beads compressed into tablets for the first two hours in simulated gastric fluid and then buffer medium pH 7.4.

The new formulation system reported herein describes a method to produce a promising sustained-release tablet from coated-pellets. The process for producing the formulation uses traditional pharmaceutical processes and equipment opposed other techniques studied such as osmotic tablet (Gan et al., 2002) where the production process is complex. The glipizide release rate from the new dosage form (F13) is similar to

Glucotrol®XL. The predicted plasma concentrations from the glipizide release rate from the new dosage form (F13) are equivalent to Glucotrol®XL based upon convolution techniques yielding plasma concentration time curves, AUC $_{0\rightarrow24}$ and Peak Plasma Concentration (Cmax) values within five percent of each other (Cutler, 1978; Gillespie 1997; Veng-Petersen, 2001, and Watanalumlerd et al, 2007). The dosage forms robustness, reproducibility and reliability come from its unique features. These features start with Ethylcellulose being incorporated with drug to form a matrix drug release layer. Then this matrix is protected by HPMC-hardening layer, and overcoated by EC controlled release layer. Three coated layer pellets were then over coated with binder/disintegrant layer, which with HPMC and EC controlled release layers, reduced the effects problematic due to compression pressure. The particular structure of this formulation gives advantages of providing lag time, and approximately zero-order release that is nearly independent of paddle speeds at 50 and 100 rpm. Most importantly, the tablets retain the benefits of mulitparticular dosage forms since the tablet disintegrate into individual beads within hours and individual beads control the drug's release.

CONCLUSIONS

A promising formulation of glipizide was developed comprising four-layer coated beads compressed into tablets that keep the advantages of sustained-release characteristics with a proper lag time, and providing approximately zero-order drug release, and drug release that is nearly independent of paddle speeds 50 and 100 rpm. The amount of binding and disintegrate ingredients can be adjusted to produce an appropriate

disintegration time for the tablets. With 22.22% weight gain of binder:disintegrant (lactose:Explotab®) = 2:1, beads-compressed into tablets disintegrated within 3 hours during dissolution testing, and individual coated particulates controlled drug release. The inclusion of HPMC in the formulation as a bead hardening agent plays a role in manufacturing as well as keeping and facilitating desirable drug release with appropriate weight gain of 6.54%. There are two Surelease® layers and both are important for controlling release, with the predominate sensitivity being in a Surelease®-drug layer. This study shows that ethylcellulose coated beads can be compressed into tablets and after disintegration still provide excellent prolonged release of drug that closely simulates zero-order release.

Declaration of Interest

The authors report no declarations of interest.

REFERENCES

Altaf, S. A.; Hoag, S. W.; Ayres, J. W. (1999). Bead compacts. II. Evaluation of rapidly disintegrating nonsegregating compressed bead formulations. *Drug Dev Ind Pharm.*, 25(5):635-42.

Altaf, S. A.; Hoag, S. W.; Ayres, J. W. (1998). Bead compacts. I. Effect of compression on maintenance of polymer coat integrity in multilayered bead formulations. *Drug Dev Ind Pharm.*, 24(8):737-46.

Bansal, P., Vasireddy, S., Parikh, D. (1993) Effect of compression on the release properties of polymer coated niacin granules. *Journal of Controlled Release* 27:157-163.

Bechard, S.R. and Leroux, JC. (1992) Coated pelletized dosage form: Effect of compaction on drug release. *Drug Dev Ind Pharm.*, 18(18):1927-1944.

Bodmeier, Roland. (1997). Tableting of Coated pellets. *Eur J Pharm Biopharm.*, 43: 1-8.

Cutler, D. (1978). Linear systems analysis in Pharmaceutics, *Pharmacokin Biopharm.*, 6:227-241.

Dashevsky, A., Kolter, K., Bodmeier, R. (2004) Compression of pellets coated with various aqueous polymer dispersions. *International Journal of Pharmaceutics*. 279:19-26.

Davis, S. S.; Hardy, J. G.; Taylor [*], M. J.; Whalley, D. R. and Wilson, C. G. (1984). The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). *Int J Pharm.*, 21(3): 331-340.

Defang,O. Shufang, N. and Wei, L. (2005a), In Vitro and In Vivo Evaluation of Two Extended Release Preparations of Combination Metformin and Glipizide, *Drug Dev Ind Pharm,* 31:677–685.

Defang, O., Shufang, N., Wei, L., Hong, G., Hui, L. and Weisan, P. (2005b). Design and evaluation of compound metformin/glipizide elementary osmotic pump tablets. *J Pharm Pharmacol* 57: 817–820.

El-Gazayerly, O.N.; Vipaporn, R., and Ayres, J. W. (2004). Novel chewable sustained-release tablet containing Verapamil hydrochloride. *Pharm Dev Technol.*, 9(2):181-188.

Gan, Y.; Pan, W., Wei, M. and Zhang, R. (2002). Cyclodextrin Complex Osmotic Tablet for Glipizide Delivery. *Drug Dev Ind Pharm.*, 28 (8):1015–1021.

Ghosh, A.; Bhaumik, U.K.; Bose, A.; Mandal, U.; Gowda, V.; Chatterjee, B.; Chakrabarty, U.S.; and Pal., T.K. (2008), Extended Release Dosage Form of Glipizide:

Development and Validation of a Level A *in Vitro-in vivo* Correlation. *Biol. Pharm. Bull.*, 31(10):1946-1951.

Gillespie, W. R. (1997). Convolution-based approaches for in-vivo-in-vitro correlation modeling. *Adv. Exp. Med. Biol.* 423:53-65.

Hsieh, S.; Lin, J.; Chang, H.; Ho, C.; and Liou, M. (2006). Sustained-Release versus Immediate-Release Glipizide for Treatment of Type 2 Diabetes Mellitus in Chinese Patients: A Randomized, Double-Blind, Double-Dummy, Parallel-Group, 12-Week Clinical Study, *Clin Therap*, 28 (9):1318-1326.

Jamzad, S.; Fassihi, R. (2006). Development of a controlled release low dose class II drug-Glipizide. *Int J Pharm*, 32:24–32.

Maganti, L. and Çelik, M. (1994). Compaction studies on pellets: II. Coated pellets. *Int J Pharm.*, 20:55-67.

Mount, D.L.; Schwartz, J.B. (1996). Formulation and compaction of nonfracturing deformable coated beads. *Drug Dev Ind Pharm*, 22(7):609-621.

Palmieri, G. F.; Wehrle, P.; Martelli, S. (1996). Drug release from compressed Eudragit RS 30D coated beads. *Pharma Sciences*, 6(2):118-121.

Patel, J.K; Patel, R.P.; Amin, A.F.; and Patel, M.M. (2005). Formulation and Evaluation of Mucoadhesive Glipizide Microspheres. *AAPS PharmSciTech*, 6(1) Article 10.

Shivakumar, H.N; Patel, P.; Desai, B.; Ashok, P.; Arulmozhi, S. (2007). Design and statistical optimization of glipizide loaded lipospheres using response surface methodology. *Acta Pharm.*, 57:269–285.

Ueda, S.; Hata, T.; Asakura, S.; Yamaguchi, H.; Kotani, M.; and Ueda, Y. (1994). Development of a Novel Drug Release System, Time-Controlled Explosion System (TES). I. Concept and Design. *J Drug Target.*, 2 (1):35-44.

USP/NF 32/27, 2009, 263-270.

Veng-Petersen, P. (2001). Noncompartmentally-based pharmacokinetic modeling. *Adv. Drug Deliv. Rev.* 48:265-300.

Vergote, G. J.; Kiekens, F.; Vervaet, C.; Remon, J. P. (2002). Wax beads as binder/disintegrant agents during the compression of coated diltiazem pellets. *Eur J Pharm Sci*., 17(3):145-151.

Watnanalumlerd, P., Christensen, J. M. and Ayres, J. W. (2007). Pharmacokinetic modeling and simulation of gastrointestinal transit effects on plasma concentrations of drugs from mixed immediate-release and enteric coated formulations. *Pharm Dev Tech*. 12:193-202.