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Development of a robust once-a-day glipizide matrix system

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Abstract

The robustness of a new hydroxypropylmethylcellulose (HPMC) based modified release glipizide (10 mg) formulation was studied. The tablet formulations were prepared by dry blending the ingredients and direct compression, incorporating a range of release modifying agents up to ±20% w/w relative to an optimized formulation. The dissolution was assessed in 900 mL pH 6.8 buffer at 75 rev min^{-1} paddle speed. Calculated difference and similarity factors (f_1 and f_2) and results of analysis of variance suggest that the overall release profiles were similar. Compositional changes up to ±20% w/w and a reduction of drug dose to half did not change the general release pattern of this low dose/pH-dependent drug in a significant way. It is concluded that the drug release from the developed matrix systems is highly dependent on the kinetics of hydration and erosion, and that the proposed compositional changes within ±20% w/w did not alter this relationship. The particulate systems used were characterized by determining the Carr index, Hausner ratio and the rheological properties using a texture analyser. Results indicate that the release is reproducible and the system has potential for successful scale-up operation, while complying with recommended Food and Drug Administration guidelines "Scale Up and Post Approval Changes".

Introduction

A matrix system for glipizide, based on hydroxypropylmethylcellulose (HPMC), with release profiles similar to the Glucotrol XL push–pull osmotic pump was successfully developed (Jamzad & Fassihi 2006). A typical drug release profile for the developed formulation and Glucotrol XL is presented in Figure 1. It was further demonstrated that in the case of a low solubility/low dose drug, glipizide, synchronization of swelling and erosion fronts results in zero-order release kinetics (see Figure 1). The consistency and reproducibility of drug release from the developed formulation under various hydrodynamic conditions and pH environment, along with its desirable textural properties, led us to further exploit and evaluate the designed system for robustness, manufacturability and release stability upon storage.

During the past decade, the majority of product recalls from the market place by the Food and Drug Administration have been attributed to ageing effects and, consequently, unexpected dissolution rate alterations. It is required that solid dosage forms maintain their drug release properties during their shelf life. Therefore, evaluation of the release characteristics of the developed formulation after storage under different conditions for a certain period of time can provide valuable information about the reliability of the system.

Not every formulation developed in the laboratory is appropriate for scale-up production. In this respect, evaluation of formulation robustness is crucial. Limited changes during the scale-up operations, and formulation changes as described in "Scale Up and Post Approval Changes" guidelines (Food and Drug Administration 1997) should not significantly impact product properties, including its dissolution profile. To this end, determination of the impact of variations in formulation composition on dosage form performance, particularly with reference to the manufacturability and dissolution outcome, becomes important. Simple controlled release hydrophilic systems are generally more sensitive to changes in formulation composition and the dissolution media effect (Konard et al 1998; Kavanagh & Corrigan 2004), especially when the drug is either highly soluble or insoluble. A slight change in composition is likely to influence product characteristics and drug

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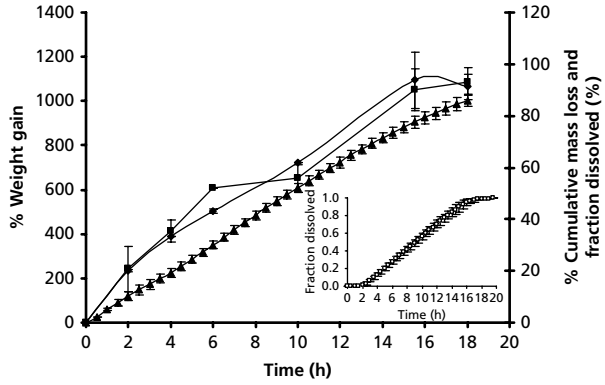

Figure 1 Synchronization of hydration (◆), erosion (■) and drug release (▲) from the optimized formulation (H4). Inset: release profile of 10 mg Glucotrol XL (□) in pH 6.8 phosphate buffer at 75 rev min^{-1} paddle rotation.

release profile. Therefore, it is necessary to study how the quality of a formulation is affected when certain changes are implemented into the system. For example, the influence of changes in the drug content, or the type and amount of release modifying excipients, on physical as well as release properties of a tablet formulation can be studied. In this work, a robust system is one that is not significantly influenced by these changes within a reasonable range. In addition, during preliminary tabletting, the powder flow and compression properties of a powder may not be evident when producing a tablet using a Carver press in small batches. In the scale-up procedure with a high-speed rotary press, however, both flow and compactibility behaviour are paramount. Too high weight variation is one problem arising from poor powder flow, while inappropriate compressibility may result in serious physical and functional defects of the tablets. Hence, evaluation of the developed formulations in terms of compressibility, powder cohesiveness, flow and lubrication efficiency is essential in foreseeing the quality of the final tablets to be produced on a larger scale.

The aims of this study were: (i) to evaluate the robustness of the model formulation with respect to changes in excipient composition and drug content; (ii) to measure the impact of changes in formulation compositions in terms of the type and/or amount of release modifying agents on dynamics of hydration, erosion and the resultant release; (iii) to study the dissolution stability of the developed formulation; and (iv) to determine the compressibility and flow properties of the developed formulation as a preliminary measure of manufacturability.

Materials and Methods

Materials

Glipizide was obtained from Sigma-Aldrich (St Louis, MO, USA). HPMC polymers (Methocel K100M, K15M, K100LV Premium CR) were obtained from Dow Chemicals Company (Midland, MI, USA), and spray-dried lactose monohydrate NF was from Foremost (Baraboo, WI, USA). Colloidal silicon dioxide (Syloid) was supplied by GraceDavison (Columbia, MD, USA), and magnesium stearate NF was supplied by Mallinckrodt (St Louis, MO, USA).

Preparation of the matrix tablets

The 10 mg glipizide tablets were prepared according to Table 1. In each case, all ingredients, except for magnesium stearate and colloidal silicon dioxide, were first passed through a 20-mesh stainless steel US standard screen (pore size 850 μm). Then, appropriate quantities of screened ingredients, enough to make 50 tablets, were weighed and manually mixed using a spatula for 3 min. Colloidal silicone dioxide was added, and the powder mix was blended for 2 min. Magnesium stearate, which was passed through a 60-mesh screen (pore size 250 μm), was added to the blend, and mixed for an additional 2 min. Tablets were compressed on a Carver press (Fred S. Carver Inc., IN, USA), using a 7-mm die and flat-faced punch assembly at a constant pressure.

Seven formulations were prepared in addition to the optimized model formulation described previously (Jamzad & Fassihi 2006). These were referred to as H5 to H11 (see Table 1). In formulations H5 to H10, the composition of excipients was changed, while in H11 the drug content was reduced to half that in the model formulation.

Table 1 Composition of formulations developed to study the robustness of formulation H4

Ingredients	Amount per tablet (mg)							
	H4	H5	H6	H7	H8	H9	H10	H11
Glipizide	10	10	10	10	10	10	10	5
HPMC K100M			30					
HPMC K15M	35	30		38.5	42	31.5	28	35
HPMC K100LV	55	60	60	60.5	66	49.5	44	55
Spray-dried lactose monohydrate	50	50	50	55	60	45	40	50
Magnesium stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Colloidal silicone dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total tablet weight (mg)	152.25	152.25	152.25	166.25	180.25	138.25	124.25	147.25
Hardness (kp)	8.1 ± 0.6	8.4 ± 1	8.6 ± 1	9.1 ± 1.4	8.7 ± 1	6.2 ± 1.5	7.2 ± 0.9	11 ± 1.2

Dissolution testing

Dissolution tests were conducted in 900 mL pH 6.8 phosphate buffer medium, maintained at 37°C, using USP 27 apparatus II, at 75 rev min^{-1} paddle rotation (VK 7000; Vankel, Cary, NC, USA). The method was modified by the insertion of a single mesh, in order to provide unconstrained hydration and swelling of the tablets (Durig & Fassihi 2000). Six tablets were tested per formulation, unless otherwise specified. Samples were taken automatically every 10 min, and were passed through a 35-μm filter. UV absorbance values at 276 nm (Cary-50 UV-Vis spectrophotometer) were compared with the calibration curve, and % dissolved versus time profiles were constructed.

Hydration and erosion studies

The capacity for hydration (buffer medium uptake) and the extent of erosion of formulations H4 to H10 were evaluated gravimetrically. In this study, for each time point, two tablets per formulation were weighed individually (original weight), and exposed to 900 mL pH 6.8 phosphate buffer medium under conditions similar to the dissolution test. At specific time points, tablets were removed from the medium, patted gently with a tissue paper, and weighed (wet weight). Hydrated tablets were dried at 60°C until constant weight was achieved (dry weight), and then were discarded. Equations 1 and 2 were used to calculate % weight gain and % mass loss for each formulation at each time point. H11 was not tested because of its similar composition to formulation H4. The reduction of drug content from 10 mg to 5 mg was not expected to change the degree of hydration and erosion.

$$\%\ \text{Weight gain} = 100 \times (\text{wet weight} - \text{dry weight})/\text{dry weight} \quad (1)$$

$$\%\ \text{Mass loss} = 100 \times (\text{original weight} - \text{remaining (dry) weight})/\text{original weight} \quad (2)$$

Compressibility and flow characterization by density measurement

Some 50 g of the powder mix of the H4 formulation was prepared according to Table 1, by blending HPMC K15M, K100LV and lactose, screened through a 20-mesh sieve, and glipizide in a laboratory scale V-shape blender (The Patterson-Kelly, East Stroudsburg, PA, USA) for 5 min. Then, colloidal silicon dioxide was added and mixed for 3 min. Magnesium stearate, which was screened through a 60-mesh sieve, was added to the powder for lubrication, and blended for an additional 3 min.

To measure the bulk density of this powder, 46.06 g of the powder was transferred into a 100-mL graduated cylinder. The volume was measured and recorded. Bulk density was calculated by dividing the weight by the volume. After tapping (1000 times; to constant volume) the volume was measured again, and the tapped density was calculated by dividing the weight by the tapped volume. The bulk density and tapped density values were used to calculate the Carr index or % compressibility (Carr 1965a) and the Hausner ratio (Hausner 1967) according to the following equations:

$$\text{Carr index (\% compressibility)} = ((\rho_t - \rho_0)/\rho_t) \times 100 \quad (3)$$

where ρ_0 is the bulk density and ρ_t is the tapped density

$$\text{Hausner ratio} = \rho_t/\rho_0 \quad (4)$$

Flow characterization by texture analyser

The H4 tablet powder flow, before and after lubrication with magnesium stearate, was characterized using a TA.XT2i Texture Analyzer (Texture Technologies Corp., Scarsdale, NY, USA), equipped with a ManUmit Powder Rheometer (Navaneethan et al 2005). Before the experiments, the instrument was calibrated for force, torque and distance. For each experiment, the powder sample was transferred into the graduated cylinder of the instrument, filling up to approximately 150–170 mL. A twisted paddle probe was used for the experiments. During a run, the probe rotates and moves vertically into the powder bed. The force applied by the blade is recorded against the distance of advancement into the powder from the original blade position. The probe then returns to its original position while rotating in the opposite direction. The data used for calculations and comparison were limited to an effective zone in the mid section of the powder bed, where the probe was completely located inside the powder bed and was able to interact with the powder. The effective zone was kept constant in all experiments to eliminate possible variations in results caused by testing samples at different heights in the powder bed. The following setting was used in these experiments: rotation angle of 45° and speed of 10 mm s^{-1} in compression mode (downward movement of probe), rotation angle of 175° and speed of 50 mm s^{-1} in lifting mode (return of probe to initial position), and effective zone between 20 and 70 mm within the powder bed. A conditioning (pre-run) experiment was performed on both non-lubricated and lubricated samples before the actual data collection with the same setting, to normalize the possible difference in powder filling procedure. Three runs were performed for each sample and the force–displacement profiles were achieved. The average force and area under the force–displacement profile in the effective zone, as a measure of work done by the probe on the powder, were calculated and used for evaluation of relative powder cohesiveness and flow properties.

Statistical analysis

The effect of change in the content of HPMC and lactose in the formulations (up to ±20% w/w) on the degree of matrix weight gain and mass loss, the rate of drug release at each time point up to 20 h, and the time to 25, 50 and 75% drug release were statistically analysed using one-way analysis of variance (JMP 6.0; SAS, NC, USA). Then, the post-hoc Tukey's test was performed to compare the means of individual groups of data. The effect of lubrication on the work and average force applied to the powder bed during the textural analysis experiments was statistically evaluated using analysis of variance and Student's *t*-test. The significance level was set at $P < 0.05$ for all tests.

Additionally, drug release profiles of all developed formulations were compared by calculating the difference factor (f_1) and similarity factor (f_2), using the H4 formulation as reference. Both factors are derived by applying statistical analysis (Moore & Flanner 1996). The fraction of drug released was used in calculations in order to normalize the % release values for the amount of glipizide actually present in each dosage form. The pull points at 30-min intervals, beginning from the first 30 min, up to one point above 85% release (for reference formulation, H4) were included in calculations.

Results and Discussion

Formulation robustness

The robustness of the H4 formulation was studied by changing the viscosity grade of the polymer (HPMC K100M instead of K15M in H6), and amount of release modifying ingredients, that is HPMC and lactose (in H5 and formulations H7–H10). The composition of the formulations is summarized in Table 1, and corresponding release profiles in pH 6.8 phosphate buffer at 75 rev min^{-1} are presented in Figure 2. The highest extent of dissolution variation related to H9 and H10, where the content of release modifying ingredients was reduced by 10% and 20%, respectively. This may suggest that matrix control over drug release can be impaired as a result of reducing the matrix weight below a certain level, particularly for relatively small matrix weights.

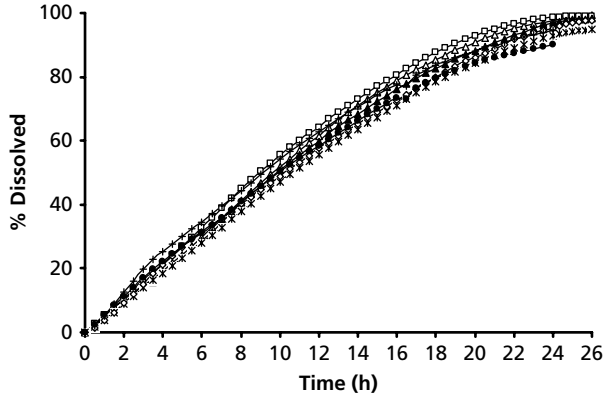

Figure 2 Comparison of dissolution profiles of formulations H4 (△), H5 (□), H6 (▲), H7 (∗), H8 (◇), H9 (●) and H10 (+) in pH 6.8 phosphate buffer at 75 rev min^{-1} paddle rotation (n = 6 for H4–H8; n = 3 for H9–H10). The highest s.d. values observed in the dissolution results were: 2.73, 4.22, 3.96, 3.46, 5.87, 8.5 and 8.8% for formulations H4 to H10, respectively.

Statistical analysis of dissolution data (shown in Figure 2) by one-way analysis of variance and Tukey's test demonstrated that only drug dissolution of formulations H5 and H7 after 8 h, and formulations H5 and H8 after 13 h, and the time to 50% and 75% release for formulations H5 and H7 were different ($P < 0.05$). However, as shown in Table 2, the calculated difference factor (f_1) and similarity factor (f_2) indicate the similarity of dissolution profiles of developed formulations when compared with the original formulation, H4.

To study the release mechanism in the developed formulations, the capacity of matrices for hydration and erosion were determined gravimetrically (Figure 3). The results revealed that the rate of hydration and erosion were comparable in developed formulations. Only formulations H5 and H7 at 10 h and later, also H5 and H8 at 15.5 h, showed a significantly different degree of weight gain and mass loss ($P < 0.05$). Changes in amount of release modifying agents within the studied range of ±20% w/w did not significantly impact the degree of hydration, swelling or the release mechanism and their interactive propensities in all formulations compared with H4, as shown in Figure 3. The observed difference between performance of H5 and H7, and H5 and H8, may be attributed to the highest difference in the concentration of the polymer among the formulations.

When the average values of weight gain or mass loss for formulations H4 to H10, at each time point, were plotted against the average fraction drug dissolved of all tablets, at the corresponding times, a linear relationship was clear between release and hydration ($R^2 = 0.9989$) as well as between release and erosion ($R^2 = 0.9854$). This demonstrates that the synchronization of swelling and erosion is the key phenomenon dictating zero-order release kinetics for this low solubility/low dose drug.

In the formulations studied, the amount and concentration of polymer was changed, while the ratio of lactose to total polymer remained constant at about 0.56. This ratio, within the context of other changes, appears to be the key parameter in controlling the rate of swelling and hydration behaviour of the matrix containing 10 mg glipizide. It was found that when the amount of water in the swollen matrix was normalized relative to the weight of the remaining matrix (see Equation 1), the net result indicated a similar hydration pattern for all formulations (Figure 3). This suggests that in a well designed hydrophilic system, containing low solubility/low dose drug, changes in the matrix components within the limits of ±20% w/w may not be a significant issue as far as the dissolution profile is concerned.

Table 2 Comparison of drug release in the developed formulations

Parameter	H4	H5	H6	H7	H8	H9	H10
f_1(%)	Reference	5.34	2.45	4.81	5.79	6.38	8.85
f_2	Reference	77.07	89.45	76.42	74	73.44	66.46
$t_{25\%}$ (h)	5.3 ± 0.3	4.6 ± 0.8	5.4 ± 0.3	5.4 ± 0.6	4.7 ± 1.0	4.9 ± 1.6	4.1 ± 1.0
$t_{50\%}$ (h)	9.7 ± 0.3	9.2 ± 0.4	9.8 ± 0.4	10.7 ± 0.4	10.3 ± 0.9	10.1 ± 1.7	9.4 ± 1.8
$t_{75\%}$ (h)	15.1 ± 0.5	14.5 ± 0.6	15.9 ± 0.9	17.0 ± 0.6	16.7 ± 1.1	16.7 ± 2.6	15.3 ± 2.5

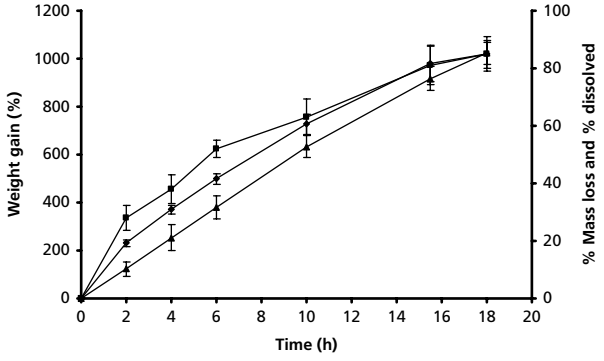

Figure 3 Average of % weight gain (◆, n = 14), % mass loss (■, n = 14), and % drug dissolved (▲, n = 35) in formulations H4 to H10.

In order to identify whether the matrix system developed for 10 mg glipizide could also be used for lower doses, a 5 mg glipizide tablet was developed according to the exact formulation and method used for the H4 formulation (Table 1) and dissolution profiles were determined (see Figure 4). The difference in dissolution results at all time points was not significant ($P > 0.05$). Also, the calculated similarity factor (f_2) for the two dissolution profiles, using H4 as a reference, was 75.71, which represents the sameness of drug release (Shah et al 1998).

Characterization of powder cohesiveness, compressibility and flow

The density of powder may influence the compressibility, flowability, tablet porosity and dissolution. Compressibility of a powder describes its ability to compress (decrease in volume), when pressure is applied; it is used as a measure to predict powder flowability. Powder density is widely measured to provide a foundation for compressibility and flow characterization (Abdullah & Geldart 1999). It is suggested that the relative change in density in response to changes during processing rather than the absolute density is more significant (Harnby et al 1987). Using the measured bulk and tapped densities for the H4 powder composition (0.49 g mL^{-1} and 0.583 g mL^{-1}, respectively), the calculated % compressibility or Carr index was 15.95%. This indicates good flowability as described by Carr (1965b). As the compressibility of a powder increases, the flow properties deteriorate. On the other hand, an appropriate compressibility is required to produce good quality tablets. Therefore, during the formulation development, a Carr index between 5% and 16% would be desirable.

Another measure to predict the flow property of a powder is the Hausner ratio (Hausner 1967). It provides insight into the extent of a powder's densification during tablet compression. Powders with greater propensity to densify have higher Hausner ratios. The Hausner ratio was calculated to be 1.19 for the H4 tablet powder, which corresponds to good flow (Wells 1988). Based on the calculated % compressibility and Hausner ratio, the developed formulation is likely to show good compressibility and flow properties during scale-up production.

In addition to the methods described above, several other approaches are used in order to predict or measure flowability of powders (Orband & Geldart 1997; Dyakowski et al 1999; Weth et al 2001; Lavoie et al 2002; Kachrimanis et al 2003; Freeman 2004). Recently, the use of a texture analyser/powder rheometer assembly in the evaluation of the rheological properties of powders and the lubrication efficacy has been reported (Navaneethan et al 2005).

The rheology of the H4 powder formulation before and after lubrication was studied using a texture analyser; the textural analysis profiles are shown in Figure 5. During a run, as a result of physical interaction between particles, powder resists the blade's rotation and movement. With free-flowing powders, this resistance is small. On the contrary, cohesive and non-flowing powders can produce physical bonds and bridges that increase a powder's resistance to flow, and hence require more force to be applied by the blade in order to maintain the predetermined speed. The peaks and troughs observed in the force–distance profiles of non-lubricated powder (Figure 5) represent the formation and breakage of these bonds and bridges. More pronounced fluctuations observed around the end of force–distance profiles (deeper

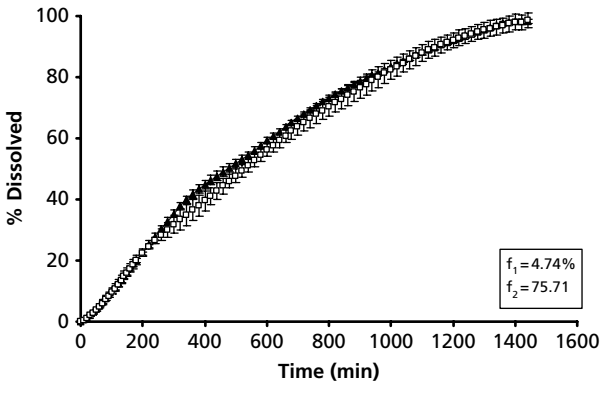

Figure 4 Effect of 50% reduction in drug content on release characteristics of formulation H4 (n = 3) in pH 6.8 phosphate buffer at 75 rev min^{-1} paddle rotation (▲, H11; □, H4).

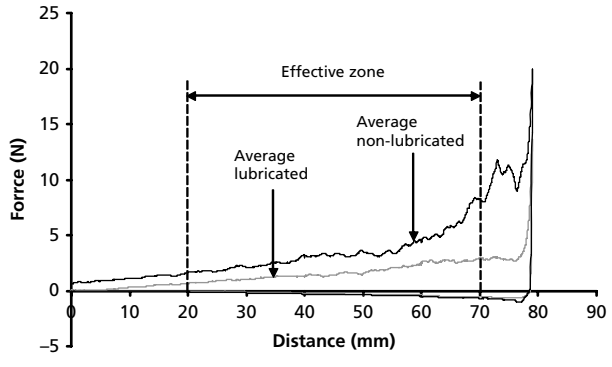

Figure 5 Comparison of average force–distance profiles of non-lubricated and lubricated H4 powder formulation (n = 3). Mean ± s.d. of work before and after lubrication: 0.1728 ± 0.0093 and 0.0763 ± 0.0017, respectively. Mean ± s.d. of force before and after lubrication: 3.46 ± 0.19 and 1.53 ± 0.03, respectively

than 65 mm) of non-lubricated powder (see Figure 5) may be attributed to some degree of powder compression happening in the lower portion of the powder bed, under the effect of blade movement.

When the powder was lubricated with magnesium stearate for 3 min in a V-blender, a decrease in frictional force and the work of the probe was obvious. Two typical characteristics of textural analysis profiles, that is the area under the curve within the effective zone (the area between the two vertical dashed lines shown in Figure 5) and the mean force recorded by the rotating probe inside the effective zone, were determined and are presented in Figure 5. The area under the curve or integrated force–distance profile in the effective zone represents the total work of the probe in order to overcome powder cohesiveness. The 56% reduction in force and work indicates the lubricating efficiency of magnesium stearate in reducing the physical interaction within the powder bed, which consequently weakens bond formation and improves powder flow properties. The observed reduction in the two measured parameters was highly significant ($P < 0.0001$). Since this method is new, with limited data available for powders with different cohesiveness and flow properties, the results should be analysed with caution until further experimentation. However, comparison of the measured parameters before and after lubrication is a useful approach in powder characterization during formulation development. Upon visual observation, the powder movement during experimentation appeared to take place smoothly, without bridging or caking.

Dissolution stability

The dissolution stability of the model formulation (H4) after storage of the tablets under ambient as well as stress conditions was evaluated. When tablets were stored in a well-closed glass container at ambient temperature for 9 months, the dissolution profile did not show significant differences compared with the dissolution at time 0 ($P > 0.05$ and $f_2 = 73.13$), as shown in Figure 6.

When the tablets were stored in a similar container at 40 °C/75% relative humidity for a 3-month period, the release rate was slower, the overall pattern was more linear, and the standard deviation of dissolution was significantly higher than the time 0 profile (Figure 7). The difference in drug release before and after storage was significantly different, with $P < 0.05$ and $f_2 = 41.91$. It is apparent that the combined effect of temperature and moisture, at the elevated levels during the storage period, is detrimental to the drug release kinetics from the H4 tablet formulation. Knowing that glipizide is not hygroscopic and shows good stability under similar conditions, the considerable change in release properties is most probably attributed to the matrix itself. The major components of the formulation, that is HPMC and lactose, are both hygroscopic and water soluble. It is likely that the polymers in the matrix are sensitive to changes in moisture-mediated glass transition temperatures via molecular mobility at the micro-scale, ageing effect. However, no weight gain was observed in the tablets, and no colour change was noticed. After 26 h of dissolution run, tablets were not fully dissolved and a portion was remaining in the form of a rod-shaped gel structure. Based on the above observations, it is suggested that glipizide matrix tablets should be packaged with desiccant in sealed containers to be completely protected from moisture.

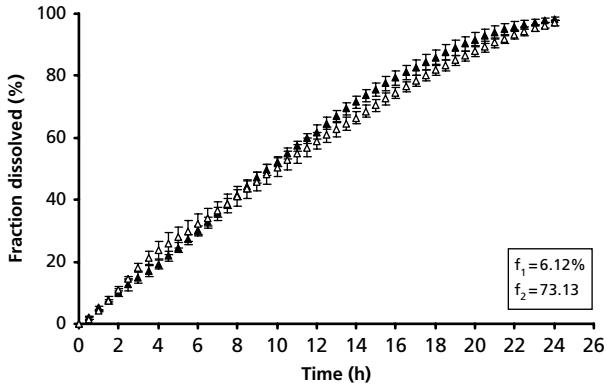

Figure 6 Comparison of drug release profiles of H4 tablets in pH 6.8 phosphate buffer at 75 rev min^{-1} paddle rotation before (▲, n = 6) and after (△, n = 3) 9 months storage in ambient conditions.

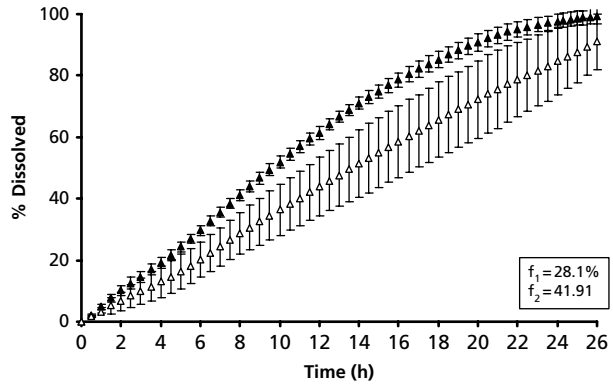

Figure 7 Comparison of drug release profiles of H4 tablets in pH 6.8 phosphate buffer at 75 rev min^{-1} paddle rotation before (▲, n = 6) and after (△, n = 3) 3 months storage in 40°C/75% relative humidity.

Conclusion

The designed matrix for glipizide, formulation H4, was shown to be insensitive to compositional changes within the studied ranges. It was demonstrated that drug release in all the developed formulations (H4–H10) is highly dependent on kinetics of hydration and erosion, suggesting that both swelling and consequent diffusion/erosion are the dominant mechanisms controlling the drug release. Based on the data presented here, for low solubility/low dose drug, matrix dynamics, and especially diffusion and erosion fronts, should work in concert if linear drug release is to be achieved. The formulation changes within ±20% w/w studied in this work did not significantly change the dynamics of hydration and erosion, and dissolution profiles remained within an acceptable range ($f_2 > 50$, with reference to the optimized formulation H4). Furthermore, reducing the dose to half did not change

the kinetics of drug release. It is concluded that in the developed formulations, the ratio of both excipients and release modifying polymers plays a fundamental role in controlling the matrix hydration/swelling and, by implication, the drug release kinetics.

The developed formulation showed appropriate compressibility and flow properties, implying the possibility of successful scale-up operation. Results also indicated that in order for tablets to maintain their release characteristics during the product shelf life, it is necessary to protect them from moisture and high temperatures. The developed formulations for glipizide can offer several advantages relative to the existing push–pull osmotic pump system: (i) simple formulation and use of well established ingredients; (ii) ease of manufacturing (no requirement for sophisticated processing or equipment); (iii) strong physical structure and complete matrix disintegration/dissolution; (iv) reproducible drug release and insensitivity to environmental pH, hydrodynamic conditions, and changes in excipients and drug content; (v) potential for matrix to be used as universal platform for other low solubility/low dose drugs for controlled drug delivery.

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