FORMULATION AND QUALITY EVALUATION OF TWO CONVENTIONAL RELEASE TABLET FORMULATIONS

Kwabena Ofori-Kwakye*, Frederic Osei-Yeboah, Samuel Lugrie Kipo
Department of Pharmaceutics, College of Health Sciences, Faculty of Pharmacy & Pharmaceutical Sciences, Kwame Nkrumah University of Science & Technology, Kumasi, Ghana.
*Email: koforikwakye@yahoo.com; kokwakye.pharm@knust.edu.gh

ABSTRACT

The aim of this study was to formulate and evaluate the physical properties of two tablet formulations of metformin and paracetamol intended for fast disintegration and release in the gastrointestinal tract. The tablet formulations were prepared using similar excipients and manufacturing procedure in a local manufacturing site in Ghana over a ten (10) month period. The moisture content, angle of repose, bulk density, tapped density, hausner ratio, and Carr's index of granulates of the two formulations prepared by wet granulation was determined. The physical properties of the compressed tablets, namely; uniformity of weight, drug content, friability, disintegration time, crushing strength, tensile strength and dissolution were assessed. The tablet quality index of the formulations was evaluated using the crushing strength-friability/disintegration time (CSFR/DT) ratio. Granulates of both tablet formulations had good flow properties. The paracetamol tablets had lower crushing strength and disintegration time ($p < 0.05$) than metformin tablets. However, paracetamol tablets possessed higher friability and tensile strength ($p < 0.05$) than metformin tablets. The paracetamol tablets had higher tablet quality index (CSFR/DT) values than metformin tablets, indicating a better balance between the binding and disintegration properties of paracetamol tablets than metformin tablets. The variation in the physical properties of the two tablet formulations could be attributed to the differences in the physicochemical properties of the two drug substances.

Keywords: Flow properties of granulate, tensile strength of tablets, Paracetamol, Metformin, tablet quality index.

INTRODUCTION

Conventional-release tablets are expected to achieve fast tablet disintegration which would dissolve rapidly in the gastrointestinal tract for absorption into the bloodstream. The quality of a tablet affects its disintegration and dissolution in the gastrointestinal tract. Tablet quality is dependent on the physicochemical properties of the active pharmaceutical ingredients (API) and excipients used, as well as the manufacturing conditions employed during tablet compression.

The flow properties of granulates have a significant effect on the physical properties and ultimately on the quality of tablets produced. Powder flow from the hopper into the dies of a tabletting machine is a direct determinant of tablet weight, hardness and content uniformity of tablets [1]. Powder and granulate flow have been measured using parameters such as bulk or fluff density, tapped density, angle of repose, hausner ratio and Carr's index [2-4]. Various techniques are also available for the measurement of each of these parameters. Some of these techniques, however, suffer from lack of reproducibility and predictability, as a result, no single test is considered as a standard for measurement of powder flow[1].

The quality of compressed tablets is judged by parameters such as uniformity of weight, uniformity of content, drug content, hardness or crushing strength, disintegration time, friability, tensile strength and dissolution time. All these parameters are measured by a series of tests some of which are usually specified in accredited official compendia. A tablet is said to be of good quality if it conforms to all the specifications applicable to that tablet in the official compendia. Other parameters that have been used in tablet quality evaluation are crushing strength-friability ratio (CSFR) [5-6] and the crushing strength-friability/disintegration time ratio (CSFR/DT)[7-8]. In general, high CSFR values denote strong mechanical strength of tablets while high CSFR/DT values connote tablets of high quality and vice versa.

Paracetamol and metformin hydrochloride were chosen as model drugs for the study based on their poor compressibility, similar manufacturing formula and production process used in our local Ghanaian manufacturing company. Paracetamol is an antipyretic analgesic used in the treatment of headache and general body pain while metformin is a hypoglycemic agent used in the management of non-insulin dependent (type-2) diabetes mellitus and polycystic ovary syndrome. Granulates of the two formulations produced over a ten (10) month period were evaluated in terms of moisture content, angle of repose, bulk density, tapped density, hausner ratio and Carr's compressibility index. The physical parameters of the tablets manufactured over the same period, namely: weight variation, crushing strength, friability, tensile strength, disintegration time, dissolution and potency were also assessed.

MATERIALS AND METHODS

Materials

Paracetamol (Hebei Jiheng, Hebei, China), metformin hydrochloride (Aurobindo Pharma, Andhra Pradesh, India), maize starch (Maize Products-Kathwada, Ahmadabad, India), povidone [PVP k30] (Hellmuth-

Carroux, Hamburg, Germany), methyl hydroxybenzoate (Jiangxi, Taizhou, China), sorbtiol (Syral SAS, Mesnil St Nacaise, France), microcrystalline cellulose PH101 (Lavina, Mumbai-India), purified talc (Neelkanth Minechem, Raj, India), sodium starch glycollate (Cloonose Chemicals, UK), magnesium stearate (Unival, Shenshen, China), colloidal anhydrous silica (Degussa, Dusseldorf-Germany). All other chemicals used in this study were of analytical grade.

Preparation of granulates

The wet granulation technique was employed in the preparation of granulates of the two tablet formulations. Maize starch dispersed in cold water and gelled with heated water to form a paste (granulating paste) and povidone (PVP K30) dissolved in a 50:50 hydroalcoholic medium (granulating liquid) were used.

TABLE 1: Composition of paracetamol and metformin tablet formulations

Ingredient Name	Paracetamol Tablets	Metformin Tablets
	Quantity (% w/w)	
Paracetamol	87.1	-
Metformin	-	82.5
Maize starch	6.6*	4.8**
Povidone	2.1	4.5
Sorbitol	0.8	1.2
Purified talc	1.9	2.0
Sodium starch glycolate	0.4	0.5
Magnesium Stearate	0.9	0.7
Microcrystalline cellulose	-	3.0
Methyl hydroxybenzoate	0.2	0.2
Colloidal anhydrous silica	-	0.4

***** 3.6 % w/w used as paste in paracetamol granulate formation
******1.6 % w/w used as paste in metformin granulate formation

Table 1 shows the detail composition of the two tablet formulations. For paracetamol granulate, paracetamol, maize starch, sorbitol and methyl hydroxybenzoate powders [metformin granulate : metformin HCl, maize starch, sorbitol, microcrystalline cellulose and methyl hydroxybenzoate] were passed through mesh no. 18 on a Mechanical Sifter (Cadmach Machinery, Ahmedabad, India) and premixed in Rapid Mixer Granulator (Cadmach Machinery, Ahmedabad, India) at high impeller speed for 5 minutes. The granulating paste was added to the premix and the granulating liquid added sequentially at low impeller speed. Wet massing was done at high impeller and chopper speed for a set time and discharged for shredding through a 2.5 mm sieve in Multimill (Sams, Mumbai, India). The wet granulates were dried in a Fluid Bed Drier (Cadmach Machinery, Ahmedabad, India) and dry screened on the Mechanical Sifter using mesh no. 18. Purified talc and sodium starch glycolate [plus aerosil 200 for metformin] were sifted together but magnesium stearate, was sifted separately through mesh no. 18. The size reduced granulates were loaded with the sifted purified talc and sodium starch glycolate [plus aerosil 200 for metformin] into a V-blender (Cadmach Machinery, Ahmedabad, India) and blended for 20 minutes. Magnesium Stearate was finally added and blended for a further 10 minutes and discharged.

Properties of granulates

Granulates of the two tablet formulations were subjected to the following evaluation tests:

Moisture content

The moisture content of each batch of granulate was determined with a Halogen Moisture Analyzer (Metler Toledo, USA) immediately after blending and after exposure of the blended granulates to relative humidity (RH) of 65 % for 8 h. One (1) g sample of granulate was delivered into the sample tray of the apparatus and analyzed. The procedure was repeated twice and the results expressed as the average of three determinations.

Angle of repose

The angle of repose (ϑ) was determined using the funnel method [9]. A funnel was secured on a stand at a fixed height (h) above a graph paper placed on a horizontal surface. The sample was poured until the apex of the conical pile touched the tip of the funnel. The radius r of the conical pile was measured and the angle of repose calculated as follows:

$\vartheta = \tan^{-1} (h/r)$.

Bulk density

The bulk or fluff density (ρb) was determined by slowly pouring the granulate into a 10 ml graduated glass cylinder. The excess granulate was leveled off with a spatula. The bulk density was obtained by dividing the weight of granulate by the volume. The mean of three determinations was recorded.

Tapped density

The tapped density (ρt) was determined by tapping a graduated glass cylinder containing a known weight of granulates for a fixed time period. The tapped density was obtained by dividing the weight of granulate by the minimum volume of granulate attained after tapping. The mean of three determinations was recorded.

Hausner ratio

The Hausner ratio, which is an index which indirectly expresses the ease of flow of powder or granulates, was calculated as the ratio of the tapped density to the bulk density (ρt/ρb). Hausner ratio values ~ 1.2 portrays low interparticle friction and good granulate flowability while values >1.6 signifies cohesive properties and poor granulate flowability [9].

Carr's index

The Carr's index [9] (C) is used to predict the compressibility and ease of flow of granulate and was calculated as follows: $C = (\rho t - \rho b) / \rho t * 100$, where ρt is tapped density and ρb is bulk density.

Compression of tablets

Granulates of paracetamol and metformin hydrochloride produced by wet granulation were compressed into paracetamol tablets (target weight: 570 mg) and metformin tablets (target weight: 600 mg) on a 35-station Cadmach Tablet Press (Cadmach Machinery, Ahmedabad, India) at a speed of 16 rpm. The paracetamol tablets were compressed with 12.5 mm flat beveled edge punches whilst metformin tablets were compressed with 12.5 mm normal concave punches.

Evaluation of tablet properties

Metformin and paracetamol tablets were evaluated as per the following tests:

Assay of tablets

The paracetamol and metformin tablets were assayed using their respective British Pharmacopoeia (2007) assay methods[10].

Uniformity of weight

Twenty (20) randomly sampled tablets were weighed individually on a precision balance (Metler Toledo, USA) and the average determined.

Friability

The friability (FR) of the tablets was determined with a Scientific TF-2 Model Friability Test Apparatus (Veego, Mumbai, India). Twenty (20) tablets were collected, de-dusted and weighed on a precision balance (Metler Toledo, USA) and the weight recorded. The tablets were delivered into the transparent drums of the apparatus and set to rotate at 100 revolutions. The weight of de-dusted tablets after the test was taken and the difference in weight expressed as a percentage of the initial weight.

Crushing strength

Tablet crushing strength (CS) or hardness which is the force required to diametrically cause a tablet to fracture was determined using a Lab. Hosp. hardness tester (Mumbai, India). The test was repeated twice and the mean recorded.

Tensile strength

The tensile strength of paracetamol tablets (flat-faced beveled edged tablets) was calculated using the equation [11-13] $T_1 = 2P/\pi Dt$, while that of metformin tablets (convex-faced tablets) was calculated with the equation [14-15] $T_2 = 10P/ [\pi D^2 (2.84t/D - 0.126t/W + 3.15W/D + 0.01)^{-1}]$. Where, T_1 (or T_2) is tensile strength, P is the tablet crushing strength, D is diameter of tablet; t is the thickness of tablet and W is the width of the cylindrical region of the tablet. The diameter and thickness of the tablets was measured with a venier caliper.

Disintegration time

Disintegration test was carried out in distilled water using the BP Apparatus XIIG from Pharma Test (D-63512 Hamburg, Germany). Six tablets were placed in the cylindrical glass and the time taken for the tablets to disintegrate was recorded as disintegration time (DT).

In vitro drug dissolution studies

The dissolution of the compressed tablets was determined using a BP Paddle Dissolution Test Apparatus (G. B. Caleva Limited, Dorset, England). For paracetamol tablets, the test conditions were: 900 ml of phosphate buffer pH 5.8 at 37.0°C ± 0.5 and a paddle speed of 50 rpm. After 45 minutes, 20 ml samples were withdrawn and filtered into labeled conical flasks and diluted with 0.1 M NaoH to about 0.00075 % w/v. The absorbance of the resultant solution was determined spectrophotometrically (PerkinElmer spectrophotometer, Massachusetts, USA) at 257 nm, using 0.1 M NaoH as reference standard. The amount of paracetamol was calculated taking 715 as the value of A (1 %, 1 cm) at the maximum at 257 nm. For metformin tablets, 900 ml of 0.68 % w/v potassium dihydrogen phosphate orthophosphate adjusted to pH 6.8 by the addition of 1M sodium hydroxide at 37.0 ± 0.5°C was used. The paddle speed was 100 rpm. After 45 minutes, 10 ml samples were withdrawn and filtered into labeled conical flasks. The absorbance of the resultant solution was determined spectrophotometrically (PerkinElmer spectrophotometer, Massachusetts, USA) at 233 nm, using water as reference standard. The content of metformin was calculated taking 806 as the value of A (1 %, 1 cm) at the maximum at 233 nm.

RESULTS AND DISCUSSION

All the tablets used in this study were normal production batches, studied over a 10-month period. The formulations were designed using optimum quantities of carefully selected excipients based on experience and on information from literature [16-17]. Table 1 shows the detailed composition of the two tablet formulations. Metformin and paracetamol powder are both crystalline but poorly compressible materials [18-19]. Sorbitol was used for its humectant property. Microcrystalline cellulose (MCC) was added to the metformin formulation to improve its compactability and tabletability and to minimize its propensity to become over-wetted during granulate formation. Colloidal silica was used to reduce lump formation in metformin granulate [20]. Methyl hydroxybenzoate is a good preservative which was added to the tablet formulations to reduce microbial attack. Sodium starch glycollate (SSG) was used as a super-disintegrant, while purified talc and magnesium stearate were added for their anti-adherent and lubricant properties, respectively.

Table 2 shows the moisture content and flow properties of granulates of the two tablet formulations. The moisture content of the granulates was evaluated as a means of assessing their ability to absorb moisture during tablet compression as they flow through the hopper of a tableting machine. There was only a slight gain in moisture (< 0.1 %) when the granulates were exposed to

humidity conditions (RH 65 % for 8 h) comparable to that which pertains in tabletting cubicles. The paracetamol and metformin granulates could therefore be said to be non-hygroscopic, a feature which increases their flowability. Hausner ratio and Carr's index are indirect methods of assessing the flow properties of granulates [9]. For Hausner ratio, values > 1.6 is indicative of poor flowability while values ~ 1.25 show good flowability. In the case of Carr's index, values ≤ 16 % indicates good flowability while values > 23 % demonstrates poor flowability [9]. The values of the Hausner ratio and Carr's index obtained in this study showed that the metformin and paracetamol granulates possessed good flowability. Metformin granulates were generally denser than that of paracetamol granulates. However, angle of repose of 30.6° and 31.9° for metformin and paracetamol granulates, respectively, confirms the good flowability of the two granulates. The good flowability could be attributed to the increased particle size of the drug particles through the wet granulation technique. The particle size of a drug substance is known to affect the processing behavior of a formulation such as granule growth during wet granulation and the characteristics of the resulting granulate [21].

Table 2: Evaluation of paracetamol and metformin granulate

Property	Granulate	
	Paracetamol	Metformin
Moisture content (%)	*1.49 (0.26)	*1.50 (0.18)
	**1.52 (0.24)	**1.59 (0.21)
Angle of repose (°)	31.9	30.6
Bulk density (g/cm^3)	0.63	0.89
Tapped density (g/cm^3)	0.69	0.95
Hausner ratio	1.095	1.067
Carr's Index (%)	9.58	6.32
Flowability	Good	Good

*Readings taken immediately after blending of granulate
** Readings taken after exposing blended granulate to RH of 65 % for 8 hours

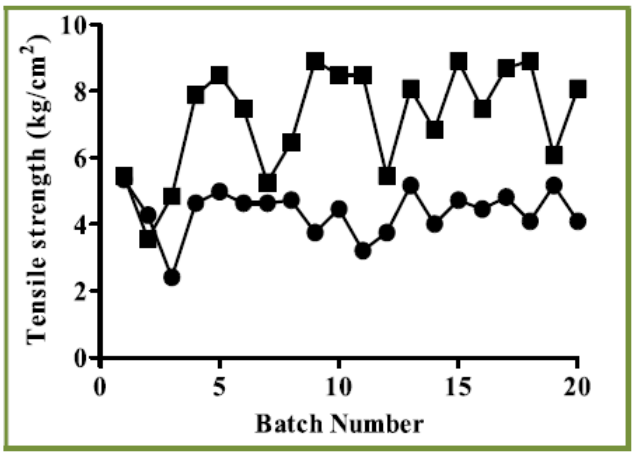
Table 3: Physical properties of paracetamol and metformin tablets (mean ± SD, n = 20)

Test parameter	Tablets	
	Paracetamol	Metformin
Average weight (mg)	570.44 ± 2.51	601.76 ± 4.19
Crushing strength, CS (kp)	5.63 ± 1.18*	8.04 ± 1.29
Friability, FR (%)	0.23 ± 0.09*	0.14 ± 0.12
Tensile strength (kg/cm^2)	7.19 ± 1.60*	4.37 ± 0.71
Disintegration time, DT (min)	0.81 ± 0.13*	7.93 ± 1.99
Assay (%)	100.32 ± 1.08	98.08 ± 1.59
Dissolution (%)	99.70 ± 0.01	98.38 ± 2.72

*P< 0.05 when compared to metformin tablets

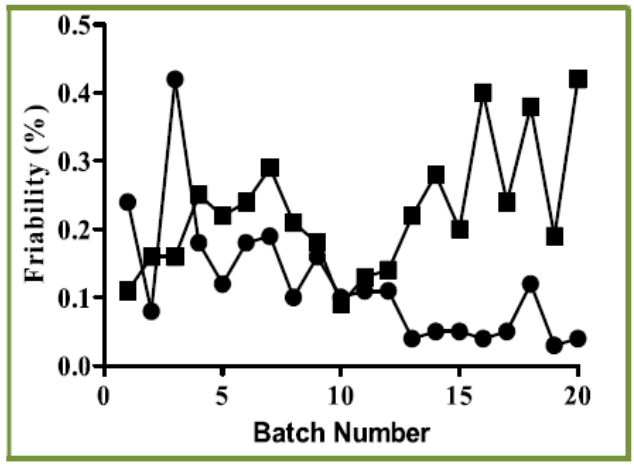
The competence of the compressed tablets from all the batches was evaluated using weight uniformity, crushing strength, tensile strength, friability, disintegration, assay and dissolution tests. Table 3 shows the aggregate physical properties of the different batches of the two tablet formulations. All the tablets had uniform tablet weight (metformin, 601.76 ± 4.19; paracetamol, 570.44 ± 2.51), and none of the individual tablet weights deviated by more than 5% and as such passed the BP uniformity of weight test. Metformin tablets were considerably harder ($p < 0.05$) than paracetamol tablets. However, the tensile strength of the different batches of paracetamol tablets was considerably higher ($p < 0.05$) than that of metformin tablets (Figure 1). Both tablet formulations showed very low levels of friability (< 0.3 %), even though paracetamol tablets were almost twice as friable as metformin tablets. Figure 2 shows that nearly all the batches of paracetamol tablets exhibited higher friability compared to metformin tablets.

Figure 1: Tensile strength of different batches of metformin and paracetamol tablets.



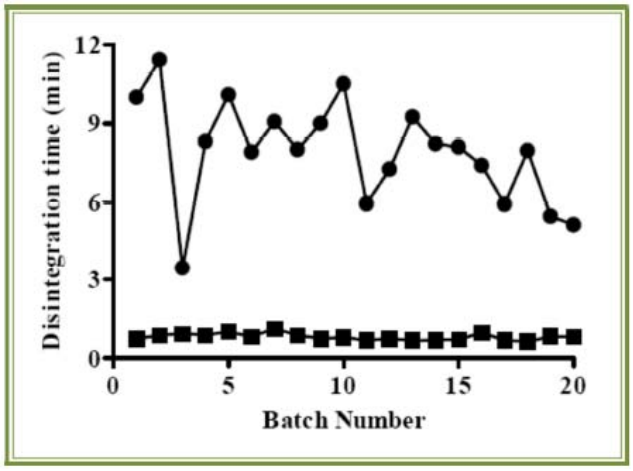
Formulation: ● = metformin tablets; ■ = paracetamol tablets

Figure 2: Friability of different batches of metformin and paracetamol tablets.



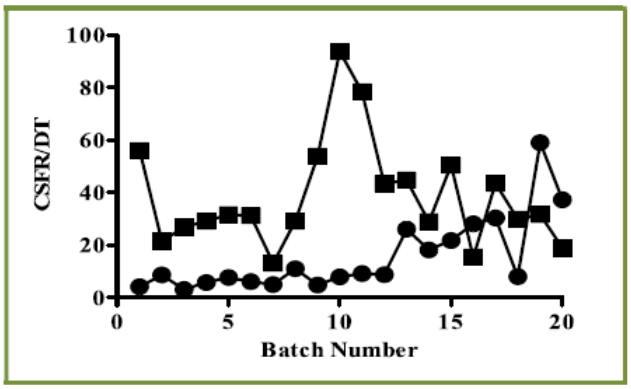
Formulation: ● = metformin tablets; ■ = paracetamol tablets

Figure 3: Disintegration time of different batches of metformin and paracetamol tablets in distilled water.



Formulation: ● = metformin tablets; ■ = paracetamol tablets

Figure 4: Comparison of tablet quality of different batches of metformin and paracetamol tablets based on the Crushing Strength-Friability/Disintegration time (CSFR/DT) index.



Formulation: ● = metformin tablets; ■ = paracetamol tablets

Figure 3 shows the variation of disintegration time for the different batches of the two tablet formulations. The paracetamol tablets disintegrated at a significantly shorter time ($p < 0.05$) in aqueous media than metformin tablets. Paracetamol tablets had disintegration times of ~ 1 min while that of metformin tablets was ~ 8 min. The disintegration time of tablets is dependent on factors such as the type and amount of drug and excipients used, as well as on tablet manufacturing conditions. Both formulations were designed as conventional tablets to be swallowed whole and must have the ability to break down into fragments for dissolution to take place when placed in the gastrointestinal tract. Even though about 2 % sodium starch glycolate (SSG) is considered sufficient for effective disintegration in pharmaceutical tablet formulations, in the current study, 0.4 % SSG was enough to achieve quick and effective disintegration of the various batches of paracetamol tablets. Metformin tablets, however, took a longer time to disintegrate than paracetamol tablets even though they contained a higher concentration (0.5 %) of SSG. This could be due to the fact that a relatively high amount of povidone, the binding agent, was used in the formulation of metformin tablets compared to the paracetamol tablets.

Tablets of the two formulations were assayed after compression and found to conform to the BP 2007 specification of containing not less than 95 % and not more than 105 % of drug content [10]. For the twenty (20) batches of tablets produced, the mean assay was 98.08 ± 1.59 % (range of 96.1 - 103.6 %) for metformin, and 100.32 ± 1.08 % (range of 98.5 - 102.6 %) for paracetamol tablets. The tablet dissolution test showed that at least 94 % of metformin (mean, 98.38 ± 2.72 %, n = 20) and at least 98 % of paracetamol (mean, 99.70 ± 0.01 %, n = 20) were dissolved in aqueous media in 45 minutes. The disintegration behavior of the tablets had a strong bearing on the dissolution rate of the different batches of tablets.

A good tablet is expected to possess sufficient mechanical strength to withstand fracture and erosion during handling while maintaining good disintegration and dissolution properties. The mechanical strength of a tablet is primarily due to inter-particulate bonding which could be van der waals forces, mechanical interlocking or formation of solid bridges [22]. Figure 4 compares the tablet quality of the different batches of metformin and paracetamol tablets based on the crushing strength-friability/disintegration time (CSFR/DT) index. The CSFR/DT ratio measures tablet strength (crushing strength) and tablet weakness (friability), as well as evaluate the negative effects of crushing strength and friability on the disintegration time of the tablets [7-8]. The CSFR/DT ratio thus offers a better index for tablet quality determination. On the whole, a high CSFR/DT ratio suggests a better balance between the binding and disintegrating properties of a tablet. Figure 4 shows that for all the batches tested, the CSFR/DT ratio for paracetamol tablets were generally higher than that of metformin tablets. This indicates a better balance between those two essential properties (binding and disintegrating) in paracetamol tablets than in metformin tablets. Even though the two tablet formulations contained similar excipients and the same manufacturing conditions were used, the differences in the physical properties of the tablets observed could be attributed to the nature of the two drug substances used. This is because the physicochemical properties of a drug substance, particularly the particle-related physical properties, are known to have a strong effect on the dosage form and the final drug product [23].

CONCLUSION

Granulates of paracetamol and metformin containing similar excipients had good flow properties as evidenced by their angle of repose, hausner ratio, and Carr's index values. Even though the tablets produced had good physical properties, there was a marked variation in the physical properties of the two tablet formulations with respect to crushing strength, friability, tensile strength and disintegration time. Paracetamol tablets appeared to

be of a higher quality than metformin tablets based on the quality assessment index CSFR/DT. Thus, there appeared to be a better balance between the binding and disintegration properties of paracetamol tablets than those produced from metformin tablets. The differences in tablet quality index and other physical parameters could be attributed to the differences in the physicochemical properties of the two drug substances used in producing the tablets.

REFERENCES

1. Kotadiya R, Patel V, Patel H, Comparative evaluation study of matrix properties of natural gums and semi-synthetic polymer, Journal of Pharmacy Research, 1 (2), 2008, 208 – 214.
2. Modasiya MK, Lala II, Prajapati BG, Patel VM, Shah DA, Design and characterization of fast disintegrating tablets of piroxicam, International Journal of PharmTech Research, 1 (2), 2009, 353 – 357.
3. Emeje M, Nwabunike P, Isimi C, Fortunak J, Mitchell JW, Byrn S, Isolation, characterization and formulation properties of a new plant gum obtained from Cissus refescence, International Journal of Green Pharmacy, January – March, 2009, 16 – 23.
4. Wagh MP, Yewale CP, Zate SU, Kothawade PI, Mahale GH, Formulation and evaluation of fast dispersible tablets of aceclofenac using different superdisintegrants, International Journal of Pharmacy and Pharmaceutical Sciences, 2 (1), 2010, 154 – 157.
5. Bakre LG, Jaiyeoba KT, Evaluation of a new tablet disintegrant from dried pods of Abelmuscus esculentus L (okra), Asian Journal of Pharmaceutical and Clinical Research, 2 (3), 2009, 82 – 91.
6. Odeku OA, Assessment of Albizia zygia gum as a binding agent in tablet formulations, Acta Pharm., 55, 2005, 263 – 276.
7. Alebiowu G, Itiola OA, Effects of starches on the mechanical properties of paracetamol tablet formulations. II. Sorghum and plantain starches as disintegrants, Acta Pharm., 53, 2003, 1 – 8.
8. Alebiowu G, Adeyemi AO, Influence of starch steeping period on dimensionless values of a paracetamol tablet formulation, Acta Poloniae Pharmaceutica – Drug Research, 66 (3), 2009, 311 – 320.
9. Staniforth J, Powder flow, In: Aulton ME. (ed.), Pharmaceutics – the science of dosage form design. 2nd Ed., Churchill Livingstone, London, 2002, p. 197 – 210.
10. British Pharmacopoeia, Her Majesty's Stationery Office, London, UK, 2007.
11. Billa N, Yuen K-H, Formulation variables affecting drug release from xanthan gum matrices at laboratory scale and pilot scale, AAPS PharmSciTech, 1(4), 2000, Article 30.
12. Sugimoto M, Matsubara K, Koida Y, Kobayashi M, The preparation of rapidly disintegrating tablets in the mouth, Pharm Dev Technol, 6 (4), 2001, 487 – 493.
13. Bi YX, Sunada H, Yonezawa Y, Danjo K, Evaluation of rapidly disintegrating tablets prepared by a direct compression method, Drug Dev Ind Pharm, 25 (5), 1999, 571 – 581.
14. Haririan I, Newton JM, Tensile strength of circular, flat and convex-faced Avicel PH102 tablets, Daru, 7 (3), 1999, 36 – 40.
15. Pitt KG, Newton JM, Richardson R, Stanley P, The material tensile strength of convex-faced aspirin tablets, J Pharm Pharmacol, 41, 1989, 289 – 292.
16. Rowe RC, Sheskey PJ, Quinn ME, Handbook of pharmaceutical excipients, 6th Ed., Pharmaceutical Press, London, 2009.
17. Niazi SK. (ed.), Handbook of pharmaceutical manufacturing formulations - Compressed solid products, 2nd Ed., Vol 1, CRC Press, Boca Raton, 2009.
18. Mohapatra A, Parikh RK, Gohel MC, Formulation, development and evaluation of patient friendly dosage forms of metformin. Part I: Orally disintegrating tablets, Asian Journal of Pharmaceutics, Jul – Sept, 2008, 167 – 171.
19. Alebiowu G, Itiola OA, The effects of starches on mechanical properties of paracetamol tablet formulations. I. Pregelatinization of starch binders, Acta Pharm, 53, 2003, 231 – 237.
20. Desai D, Li D, Evaluation of anti-caking agents for metformin hydrochloride and metformin-glipizide granulations, http://www.aapsj.org/abstracts/Am_2003/AAPS2003-002575.PDF.
21. Badawy SIF, Lee TJ, Menning MM, Effect of drug substance particle size on the characteristics of granulation manufactured in a high-shear mixer, AAPS PharmSciTech, 1 (4), 2000, Article 33.
22. Alderborn G, Nystrom C. (eds.), Pharmaceutical Powder Compaction Technology, Marcel Dekker Inc, New York, 1996.
23. Jurgens K, Influence of particle size and shape on the drug product – aspects of formulation and performance, American Pharmaceutical Review, May/June, 2006.

****