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Impact of supply chain on some tablet properties of six brands of glibenclamide marketed in Jos metropolis

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Abstract

Drugs are important commodities that must be handled differently from other goods. Therefore, supply chain of drugs must be monitored until it gets to the patient to maintain therapeutic efficacy. Drug properties are compromised when stipulated storage conditions are not maintained over time, and this can result in a poor therapeutic outcome. This is more impactful for glibenclamide tablets, which many diabetic patients preferentially use because of its cost-effectiveness and availability. The aim of this study was to assess the impact of supply chain on tablet properties of six glibenclamide tablet brands marketed in Jos metropolis. Glibenclamide tablets obtained from hospital and community pharmacies, and patent medicine outlets, were subjected to quality control tests such as content uniformity, friability, crushing strength, disintegration time, and dissolution test. The results were analyzed using ANOVA, fit factors (f_1 and f_2) and dissolution efficiency (DE). The results showed that all the brands passed weight uniformity, friability and disintegration tests. The ANOVA showed significant difference between the release profiles of the brands. Brands from patent medicine outlet had lower content values compared to brands from pharmacies (A_1/A_3 - 102/98%; E_1/E_3 - 124/108%). Brands E_3 from patent vendor outlet failed f_1 and f_2 limits (15.3/47.9) while brands E_1 and F_1 from community pharmacies failed f_1, f_2 and DE limits (23.6/39.4/5.91 and 17.2/46.1/8.35) respectively. Brands from hospital pharmacies showed no adverse parameters. In conclusion, private commercial enterprises engaged in drug retail may have to be monitored closely to ensure drug quality and hence public health care.

Keywords: Tablet properties; Glibenclamide; Supply chain; Jos

INTRODUCTION

Pharmaceutical products are expected to be of good quality and without loss of potency on storage within their shelf life [1]. The primary interest of the manufacturers of pharmaceutical products and health authorities is to ensure drugs reach the patient without loss of therapeutic effect [2]. However, when poorly stored, tablets may absorb or loose moisture, which may influence hardness, disintegration time and the dissolution rate of the drugs, thereby altering the bioavailability and therapeutic efficacy, even when the drug potency and purity remain unchanged [3]. Hence, the impact of the supply chain on drug products from production site to the final consumer is a primary concern in patient care [4]. The longest resident time in drug movement from the manufacturer to the patient is in the retail outlets where they become exposed to varying temperature and humidity conditions in accordance with the prevailing conditions in such outlets [1,5]. Therefore, in order to

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maintain the potency and integrity of drugs throughout their shelf life, optimum storage condition is a necessity [1]. This necessitates *in vitro* quality control evaluations to determine the effect of supply chain on the quality of pharmaceutical products. Tablet properties are investigated to ascertain their continued conformity to the manufacturer's and official standard as at the time of production. An acceptable tablet must have good physico-mechanical properties and should remain intact during handling at all stages including production, packaging, warehousing, distribution, dispensing and administration by the patient [6].

Drug dissolution, a key factor in the success of therapeutic outcome of drug product, is a rate kinetic process that deals with how long it takes a solute to form a saturated solution. This is a crucial parameter to the overall therapeutic process, since the effectiveness of a tablet hinges on its rate of dissolution within the gastrointestinal tract (GIT) prior to absorption into the systemic circulation [6,7]. An *in vitro* dissolution test helps in formulation development, investigations for post-approval changes, quality control and post marketing surveillance [8]. When tablets are exposed to ageing conditions such as temperature and humidity on storage, their release profile may be reduced [3]. Due to adverse conditions prevalent in the retail outlets for pharmaceutical products, *in vitro* quality control tests are basic necessity to predict the bioavailability through the assessment of the tablet properties [9, 10].

Glibenclamide tablets is still a widely prescribed sulfonylurea antidiabetic drug in Jos metropolis due to its wide acceptance and relatively lower cost [6]. However, it belongs to class II in the Biopharmaceutical Classification System (BCS), which presents the drug as poorly soluble and highly permeable, making its bioavailability to be dissolution rate dependent [11].

This study is designed to investigate the impact of supply chain on the physico-mechanical properties and dissolution profile of some generic brands of glibenclamide tablets marketed in Jos metropolis.

EXPERIMENTAL

The materials used for the study were: pure glibenclamide powder (Batch Number 0000005638, CAS-10238-21-8 by Sigma-Aldrich Inc., USA), six brands of glibenclamide tablet (sourced from community Pharmacy, hospital Pharmacy and Patent medicine vendor outlets) as presented in Table 1. All the brands were within their expiry dates and the reagents were of analytical grade.

Standard solutions of glibenclamide powder were used for Beer-Lambert plots using pH 6.8 buffered media and by a method earlier reported [12]. The absorbance was taken to generate Beer-Lambert plot.

The physical evaluations were performed as described by USP 36 procedures and various authors [6,9]. Each brand of glibenclamide tablet was subjected to weight uniformity test (Gallenkamp Mettler Balance P165, England), friability test (ES eagle scientific Ltd. Nottingham, England), crushing strength test (Monsanto hardness tester), disintegration test (Eagle Scientific, England) and uniformity of content. Subsequently, *in vitro* dissolution studies was carried out using USP apparatus 2 (Hanson Research Corporation, Chatsworth, California) at pH 6.8 and 37°C. The dissolution media were replaced after each withdrawal for analysis, with exactly the same quantity withdrawn. The release profiles of the brands were determined from the graph and result reported.

The results of various evaluation studies were subjected to one way ANOVA to determine any significant difference between the innovator and the generic brands. The dissolution results were analysed with the fit

factors (f_1 difference factor, and f_2 similarity factor) and dissolution efficiency (DE).

The difference factor (f_1) shows the percentage error between the two curves at all time points. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared of errors calculated from the difference between the test and the standard samples at all time points.

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad \ldots 1$$

where n is the number of time points and R_j and T_j are the percentages of reference and test product respectively, released into the dissolution medium at time j (6, 13).

The dissolution efficiency (DE) of a pharmaceutical dosage form is the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the trapezium described by 100% dissolution in the same time (13).

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{j=1}^{n}\left(R_j - T_j\right)^2\right]^{-0.5} \times 100\right\} \quad \ldots 2$$

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\% \quad \ldots 3$$

where y is the drug percent dissolved at time t.

RESULTS

Table 1 shows the visual inspection of packaging and properties of glibenclamide tablets. The table shows that the brands were within their expiry dates, all were duly registered by regulatory authority (NAFDAC), and some were purchased from community pharmacies, others from hospital pharmacies and patent medicine vendor's outlets.

The results of the physico-mechanical properties of all the brands of glibenclamide tablet are displayed in Tables 2. It shows that all the brands passed uniformity of weight, friability, and disintegration time test but C_1, D_1, E_1 from community pharmacies failed uniformity of content test. The brands from patent medicine outlets are more friable and presents lower content than the ones sourced from pharmacies.

Dissolution profiles of glibenclamide tablet brands is presented in Figures 1 and 2. All the brands released more than 80% of their contents within 30 minutes and at 45 minutes all the brands has reached maximum release.

Table 3 shows the one way ANOVA of the dissolution profiles of six brands of glibenclamide tablet at 20 and 30 minutes. It shows a significant difference between the innovator and the other brands.

Table 4 shows the dissolution properties of all the brands of glibenclamide tablets. It shows that E_1 and F_1 from community pharmacies failed both f_1, f_2 and DE whereas E_3 from patent medicine failed f_1 and f_2. It also shows that all the brands have high dissolution efficiencies.

Table 5 shows the results of the one way ANOVA of the actual contents of brands E_1 and E_3. It shows a significant difference between the content of E_1 from pharmacy and E_3 from patent medicine.

DISCUSSION

The first step in quality assurance of pharmaceutical tablets is visual inspection, since any event of failure in meeting specifications for labeling, size uniformity, colour and tablet integrity nullifies further quality control tests [6]. As shown in Table 1, the brands complied with labeling information specifications, statutory demands, and there was no trace of imperfection.

Table 1: Visual inspection of packaging and properties of glibenclamide tablets.

Brand	Commercial name®	Expiry date	Source of purchase	Country of manufacture	NAFDAC number	Tablet shape	Tablet design	Tablet colour
A_1	Daonil	06/2018	CP	Nigeria	04-0744	Caplet	Scored	White
A_3	Daonil	02/2018	PV	Nigeria	04-0744	Caplet	Scored	White
B_1	Diatab	07/2018	CP	Nigeria	04-7873	Caplet	Scored	White
B_2	Diatab	02/2019	HP	Nigeria	04-7873	Caplet	Scored	White
C_1	Glemid-5	11/2018	CP	India	04-7261	Caplet	Scored	White
C_2	Glemid-5	10/2019	HP	India	04-7261	Caplet	Scored	White
D_1	NIDD	05/2019	CP	India	04-6679	Round	Unscored	White
E_1	Clezide	12/2019	CP	China	A4-2100	Caplet	Unscored	White
E_3	Clezide	12/2019	PV	China	A4-2100	Caplet	Unscored	White
F_1	Clamide	06/2019	CP	Malaysia	04-4015	Caplet	Scored	white

CP = community pharmacy; HP = hospital pharmacy; PV = patent vendors

Table 2: Physico-mechanical properties of brands of glibenclamide tablet.

Brand code	Uniformity of weight (mg) n = 20	Friability (%) n=3	Disintegration time (min) n=3	Crushing strength (N) n=10	Thickness (mm) n=10	Content (mg) n=3	Content (%)
A_1	153.9±3	0.06±0.03	3.23±0.03	58.9±4	2.76±0.06	5.1±0.15	102
A_3	154.9±4	0.10±0.04	3.40±0.09	60.1±1	2.82±0.07	4.9±0.20	98
B_1	161.0±3	0.14±0.04	1.46±0.05	22.9±3	3.14±0.02	4.8±0.31	96
B_2	166.5±1	0.19±0.01	0.53±0.06	20.4±3	3.10±0.02	5.1±0.15	102
C_1	198.5±6	0.16±0.03	2.59±0.30	31.0±2	3.05±0.02	5.6±0.60	112*
C_2	199.5±3	0.10±0.05	10.53±0.50	33.7±5	2.98±0.03	5.4±0.26	108
D_1	116.4±5	0.40±0.20	2.29±0.09	19.0±1	2.97±0.04	5.6±0.40	112*
E_1	223.2±4	0.20±0.03	2.57±0.54	64.7±5	3.93±0.02	6.3±0.25	124*
E_3	223.1±2	0.23±0.10	2.52±0.51	64.4±6	3.94±0.06	5.4±0.31	108
F_1	167.6±1	0.09±0.02	5.90±0.28	54.9±8	2.76±0.08	5.2±0.16	104

Content = Uniformity of content; *= Outside specified limits

Table 3: ANOVA of the dissolution profiles at two-time point dissolution using pH 6.8 buffer medium.

Time (min)	Source	df	Sum of squares	Mean square	f-value
20	Between groups	9	666.69	74.08	6.80*
	Within groups	20	217.80	10.90	
	Total	29	884.49		
30	Between groups	9	372.72	41.41	11.12*
	Within groups	20	74.48	3.7	
	Total	29	447.20		

*= Significant difference at P = 0.05; df = Degree of freedom; Table p-value = 2.39 at 95% confidence limit

Table 4: Dissolution properties of glibenclamide tablets.

Brand	DE	Difference with DE of innovator	f_1 Value	f_2 value
A_1 (Innovator)	77.55			
A_3	76.38	1.12	2.6	75.8
B_1	76.17	1.33	8.7	57.4
B_2	77.73	0.18	11.5	51.8
C_1	77.02	0.48	10.7	51.9
C_2	76.73	0.77	10.4	52.1
D_1	77.67	0.17	13.1	50.6
E_1	83.41	5.91	23.6*	39.4*
E_3	79.91	2.41	15.3*	47.9*
F_1	85.85	8.35	17.2*	46.1*

DE = Dissolution efficiency; * = failed specified limits

Table 5: ANOVA of the amount of glibenclamide in 5 mg tablet of brands A_1 versus A_3 and brands E_1 and E_3

Time (min)	Source	df	Sum of squares	Mean square	f-value
Brands A_1 and A_3	Between groups	1	0.060	0.60	1.13
	Within groups	4	0.217	0.053	
	Total	5	0.273		
Brands E_1 and E_3	Between groups	1	0.882	0.882	11.50*
	Within groups	4	0.307	0.077	
	Total	5	1.188		

F – Table value at 95% confidence (P<0.05) = 7.709; * = significant difference

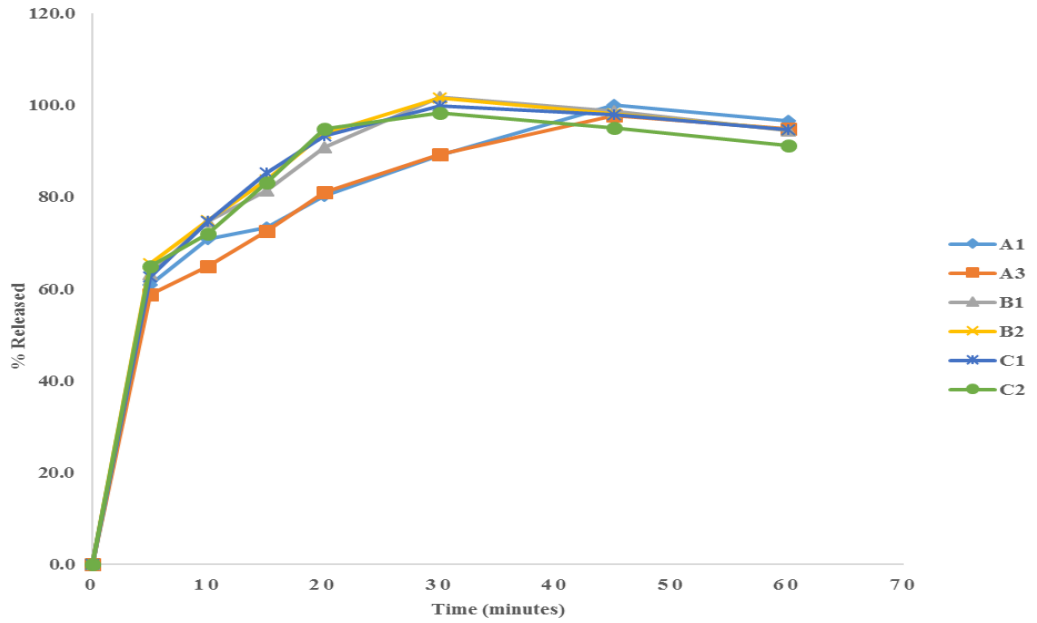

Figure 1: Dissolution profiles of Innovator (A_1 and A_3) with generic brands B_1, B_2, C_1, and C_2 in pH 6.8.medium.

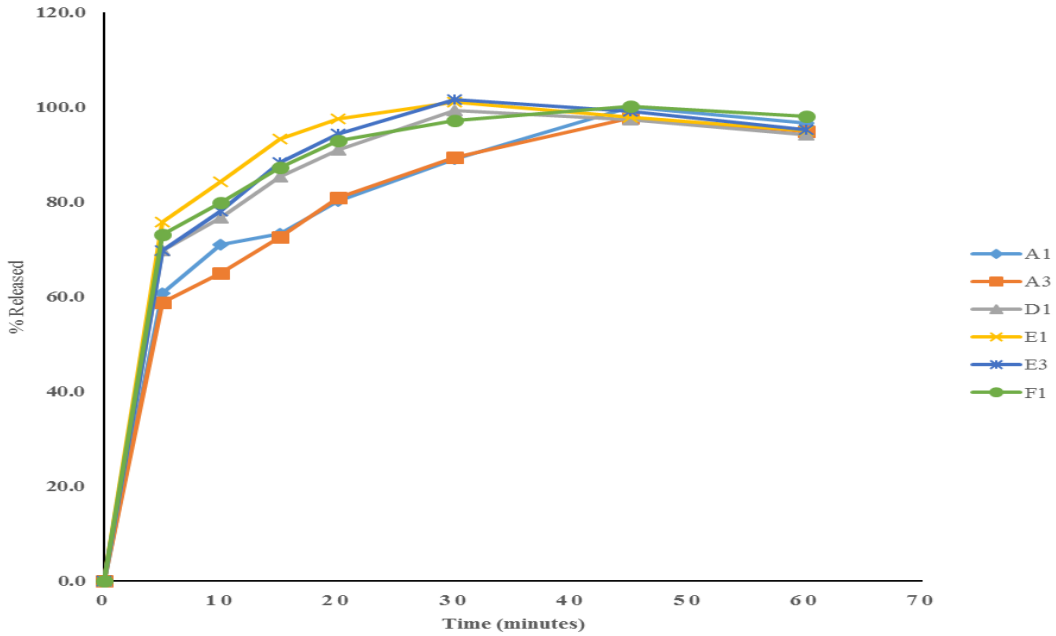

Figure 2: Dissolution profiles of Innovator (A_1 and A_3) with generic brands D_1, E_1, E_3, and F_1 in pH 6.8 medium

The results of the physico-mechanical properties of the brands in Table 2 showed that the weight variation for the six brands passed the official specified limits since the unit weights ranged from 116.4 mg – 223.2 mg. Uniformity of weight test is vital for uniformity of content and thus, the therapeutic outcome of a drug product [14]. The USP specified that for a tablet weight of 80 mg – 250 mg to pass uniformity of weight, out of 20 randomly selected tablets, not more than 2 tablets should deviate in weight up to 7.5% from the mean weight and no tablet should deviate up to 15% [6,14,15]. All the brands have their values for friability test, disintegration time and crushing strength fall within official limits.

From the results in Table 2, it is shown that brands from patent medicine outlets are more friable and generally presents lower content than the ones sourced from either community or hospital pharmacies. Brands E_1 (with 124% API content) and E_3 (with 108% API content) which are the same brand, having the same batch number and the same expiry date, but sourced from community pharmacy and patent vendor's outlets respectively, presented a significant difference in the amount of API content as presented in the one way ANOVA analysis in Table 5. This significantly lower content of glibenclamide from the patent vendor's outlet may be attributed to poor storage conditions such as adverse temperature [3, 16]. This implies that drugs hawked around under the sun in the markets and along streets, and those stored in hot premises without cooling facilities may have lost their potency before reaching the patients. Therefore, there is the need to enforce optimum storage conditions for dealers of pharmaceutical products. Pharmacists and regulatory authorities should closely monitor the storage conditions within the supply chain to avoid aging conditions such as temperature and humidity that may affect the release profiles of tablets [16].

The result of the dissolution profiles of the innovator brand and the other generic brands of glibenclamide tablet evaluated at pH 6.8 buffer medium was presented in Figures 1 and 2. At 30 minutes all the brands, irrespective of the outlet, have released up to 80% of their contents, passing this test [17]. However, from the results in Table 3 there was a significant difference between the dissolution profiles of the different brands of glibenclamide tablet at both 20 minutes and 30 minutes, because the calculated f-values (6.80 and 11.12 respectively) are higher than the table f-value (2.39) at 95% confidence limit. This means the dissolution profiles of these brands are significantly different from the innovator and among themselves. Center for Drug Evaluation and Research (CDER) recommends that, in order to characterize the quality of drug products through dissolution test, dissolution profiles at two or more points (rather than a single point) be used. This is believed to be better at reflecting the *in vivo* bioavailability of drugs, particularly for those drugs that are classified as Class II in the BCS of which glibenclamide belongs [18]. The 20 and 30 minutes were chosen because at these time intervals, all the brands had released 80% of their content and seven of them had reached their maximum API release [12, 19].

The data in Table 4 showed the dissolution properties of all the brands of glibenclamide tablets. It shows that brands E_1 (from community pharmacy), E_3 (from patent vendor) and F_1 (from community pharmacy) which have f_1/f_2 values as 23.6/39.4; 15.3/49.7 and 17.2/46.1 respectively, failed f_1 and f_2 limits for bioequivalence. Two dissolution profiles are considered similar and bioequivalent, if the f_1 value is between 0 and 15 and f_2 is between 50 and 100 [13]. The results in Table 4 also showed that all the brands have high values of DE (76.17 – 85.85) indicating high performance in dissolution. Dissolution efficiency is a measure of the performance of individual

brand, and it helps in assessing variation in batches [6]. However, the difference between the DE of innovator and the other brands ranged from 0.12 to 8.30. All the brands maintained close similarity to the innovator, except E_1, E_3 and F_1 that have difference in DE as 5.86, 2.36, and 8.3 respectively. The brand E_3 (from patent medicine vendor) which had borderline value for f_1 as 15.3, f_2 as 49.7 and then difference in DE as 2.36 is bioequivalent with the innovator. The magnitude of difference between a generic brand and the innovator signifies the degree of similarity with the innovator, and the closer to zero the greater the similarity [20]. Therefore, brands E_1 and F_1 (both from community Pharmacy outlet source) which failed the specified limits for fit factors and possess high value for difference in DE, are not bioequivalent with the innovator. Since brand E_3 from patent vendor's outlet failed f_1 and f_2 limits, and brands E_1 and F_1 from community pharmacies failed both f_1, f_2 and DE, they are not bioequivalent with the innovator brand. However, the dissolution data presented in Table 4 shows that the glibenclamide tablets sourced from hospital pharmacies did not show adverse parameters. It can be inferred that private commercial enterprises engaged in drug retail may have to be monitored closely to ensure drug quality and hence public health care. Poor storage conditions along the supply chain from the manufacturers through the various warehouses to the retailers can lead to deterioration before the drug products reach the patient [1].

Conclusion. All the brands passed the physico-mechanical assessments of tablets. However, the dissolution results revealed that two brands from community (commercial) pharmacies and one from patent vendors were not bioequivalent with the innovator and the brands from the patent vendor's outlets presented lower API content, which may be due to poor storage conditions. The drugs from the hospital premises showed no adversity. These infer that supply chain may impact negatively on pharmaceutical products before reaching the patients.

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