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Article

Quality control and drug–drug interactions between commercially available Metoprolol and Glimepiride tablets

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Quality is paramount and needs to be maintained throughout the shelf life of pharmaceuticals. The current study aimed to evaluate the quality, potency, and drug–drug interaction in an *in vivo* animal model by using two drugs, namely, metoprolol and glimepiride. Tablets were selected for their physical characteristics, such as shape, size, and color. Quality control tests, such as weight variation, hardness, friability, and disintegration tests, and *invitro* drug release studies were performed as per USP. Drug–drug interaction and *in vivo* studies were carried out according to the standard protocol of the animal ethics committee. Quality control tests of both the tablets were within the specified range. The cumulative release percentages of the drugs were 81.12% and 85.36% for Metoprolol Tartrate and Glimepiride, respectively, in a physiological buffer solution within 1 h. The combination of metoprolol and Glimepiride also significantly decreased the blood glucose level in diabetic animals. However, the blood glucose level increased in the group receiving metoprolol only, but the difference was not significant. The result suggested that the formulations are safe. However, the chronic use of this combination requires frequent monitoring of blood glucose level to improve its efficacy and for the patient's safety.

Keywords: Quality control test of tablets. *In vitro* drug release study. Drug drug interaction study. Metoprolol Tartrate and Glimepiride.

INTRODUCTION

Poor-quality medicines and medical products are causing significant public health concerns (Geyer, Sousa, Silveira, 2018). Even though medicinal product regulatory agencies and systems are active and reliable, low-quality formulations are still in the market (Abrantes, Duarte, Reis, 2016). The decrease in quality could be due to many reasons, e.g., intentional or unintentional falsification and substandard or degraded ingredients, but the outcomes are always unpredictable and disastrous (Sakuda *et al*., 2020). The low active pharmaceutical ingredient (API) content in the dosage forms, interactions between API and excipients, interactions among excipients, and interactions between environmental factors and API (Fathima *et al*., 2011) or with excipient results in the poor disintegration and dissolution properties of the tablets; other intended standard sets for the formulations could be compromised with the expected role in the enduser (Szakonyi, Zelkó, 2012). Moreover, a degraded API might result in severe outcomes in sensitive populations, such as pediatric and geriatric patients (Dixit, Puthli, 2009). Hence, both downsized and metabolized APIs are cause for concern, because they escalate the individual and societal healthcare costs and reduce health related quality of life (HRQoL) (Cunningham, Binks, Olson, 2009). According to a study

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conducted in sub-Saharan African countries, 16.3% of the cardiovascular medicines sampled and studied had poor quality (Nduka *et al*., 2016). The prevalence of low-quality antidiabetic drugs in the market will take its toll on human health globally (Saraswati *et al*., 2018). Recently, WHO revealed 11 substandard and falsified antidiabetic formulations between 2013 and 2017 (WHO, 2019). As diabetes and hypertension are health issues related to older population, a global and regional understanding of the epidemiology of poor quality medicinal products is essential (De Boer *et al*., 2017).

Pharmaceutical products are required to conform to standards in terms of safety, efficacy, and quality before being released to the market for public use; these products are expected to maintain such standards until their specified expiry dates (Zilker, Sörgel, Holzgrabe, 2019). Stability of the pharmaceutical formulations is an essential quality (Kumar, Bhatia, Rawal, 2018). Thus, the formulator considers all factors, such as chemical, physical, therapeutic, microbiological, and toxicological parameters, in formulation design, manufacture, packaging, transport, and storage until the product finally reaches the user (Amarji *et al*., 2018; Bajaj, Singla, Sakhuja, 2012). However, product variation is inevitably introduced during packaging, long-haul transportation, storage at the distributor's warehouse, and handling at the retail pharmacy center; such variation significantly affects the desired performance of the formulations (de Oliveira Melo *et al*., 2014; Zhou, 2009). Accelerated stability studies were designed and conducted before the release of the formulations to the market. Stability data were subsequently obtained from the pilot batches stored under standard conditions at the manufacturing site but not for the dosage forms that are subjected to various environments, handling techniques, and storage conditions. These factors can influence the stability of a pharmaceutical product (Bajaj, Singla, Sakhuja, 2012). They might promote physical and chemical interactions between the active ingredients and the excipients, container, or closure system used for packaging (Bharate, Bharate, Bajaj, 2016). The light, heat, and moisture conditions encountered during shipment, storage, and handling accelerate degradation reactions, such as oxidation, reduction, hydrolysis, or racemization (Blessy *et al.,* 2014.). The other contributing factors for degradation reactions are pH, radiation, API concentration, the quality of the raw materials used, and the length of time between formulation and usage of the product (Shukla *et al*., 2016). Consequently, the dosage form may change in appearance, consistency, content uniformity, and moisture content (Bhuyian *et al*., 2015). The chemical reaction that occurs with API may lead to the loss of potency. Such reaction could happen with any dosage form that meets with such circumstances (Alsante *et al*., 2007). If such changes happen for antihypertensive and antidiabetic agents, which are used most commonly by the aged population, critical health issues may occur, thereby negatively affecting their life. In reality, no mechanisms are available to test the stability, potency, and safety of the pharmaceutical formulations from the retail centers. Therefore, conducting quality control studies that cover the chemical, physical, and biological attributes according to pharmacopeial standards would be appropriate.

As few pharmaceutical industries exist in Saudi Arabia, the bulk of the pharmaceutical requirements are being imported from other countries. Even though the quality of care is paramount to the Ministry of Health in Saudi Arabia, the various extreme environmental parameters and the unmeasured human negligence at different points of transporting, handling, and storage might significantly impact and compromise the quality of pharmaceutical products. No study has evaluated the quality and potency of a dosage form that was selected from the point of dispensing. Therefore, we conducted this study by selecting two categories of drugs that are widely used, namely, popular brands of antihypertensives and antidiabetics, to evaluate the quality, potency, and drug–drug interaction (DDI) parameters in *in vitro* models.

MATERIAL AND METHODS

Material

Sodium hydroxide and tribasic sodium phosphate were purchased from Merck Laboratory in Stockholm, Sweden. Hydrochloric acid (37% pure) was procured from Sigma-Aldrich, Saudi Arabia. The innovator of

Metoprolol Tartrate tablet (code: MT-BP) at 100 mg and Glimepiride tablet (code: GP-DM) at 1 mg was purchased from a local community pharmacy, Jazan, KSA. All other purchased chemicals were of analytical grade.

Equipment

The following test equipment was used for this study: a double beam UV-visible spectrometer (UV mini-1700, Labomed, USA with 1 cm quartz cells), a Martini pH meter MI-150, a Copley tablet dissolution tester, an electronic digital balance (Adam PW124), a Copley friability tester FR-200, and a Monsanto hardness tester.

Preparation of 0.1 N HCL

To prepare 500 mL of 0.1 N HCL, 4.20 mL of concentrated HCL (37%) was diluted with 500.0 mL of distilled water (Gohel, Patel, Bariya, 2003).

Preparation of simulated buffer solution medium

Phosphate buffer solution (pH 6.8) was prepared as follows: 11.45 g of NaH_2PO_4 and 28.8 g of Na_2HPO_4 were dissolved in water. The volume was adjusted to 1000 mL. Tribasic sodium phosphate (0.20 M) was also prepared (de Carvalho Mendes *et al*., 2019).

Determination of λ_{max} in pH 6.8 phosphate buffer solution for Metoprolol Tartrate and Glimepiride

A pure drug solution was prepared and scanned using a UV spectrophotometer from Labomed, model UVD-3200, from 200 to 400 nm to determine the λ_{max}.

Preparation of calibration curve of Metoprolol Tartrate and Glimepiride in pH 6.8 buffer solution

Pure metoprolol (99.94% pure) at 100 mg was dissolved in 2 mL of methanol to obtain a clear solution. Then, pH 6.8 buffer was added to the 10 mL mark in a volumetric flask. From the solution, 1 ml was taken and mixed with the pH 6.8 buffer solution, which was added up to the 100 mL mark in a volumetric flask. From this solution, 1–6 mL was removed and placed in a 10 mL volumetric flask, to which the pH 6.8 buffer solution was added up to the 10 mL mark in each volumetric flask. The achieved concentration range of this solution was 10–60 µg/mL. Pure Glimepiride (99.96% pure) at 1 mg was dissolved in 2 mL of methanol to obtain a clear solution. Then, pH 6.8 buffer was added up to the 10 mL mark in a volumetric flask. From the solution, 0.2 mL to 1.2 mL was removed and placed in a 10 mL volumetric flask. The pH 6.8 buffer was added up to the 10 mL mark into each volumetric flask. The achieved concentration range of this solution was 2–12 µg/mL (Altinöz, Tekeli, 2001).

Evaluation of tablet

The physical appearance of the tablet:

The shape, size, and color of Lopressor and Amaryl tablets were examined visually (Gupta, Dubey, 2019).

Weight Variation Test of tablets as per USP

The weight variation test confirmed the accurate dose of the drug. According to the USP guidelines weight variation test of tablets, 20 tablets were weighed individually. The average weight was calculated, and the individual tablet weights were compared with the range obtained from the percentage limit allowance as per USP. The tablets passed the USP test if not more than two tablets are outside the range, which was calculated as mention above, and if no tablet differs by more than two times its percentage limit (Uddin *et al*., 2017).

Hardness test of tablets

This test was performed to ensure that tablets were sufficiently hard and would not break during handling. However, they should break into small pieces as soon as they reach the stomach to facilitate absorption. The unit was expressed in kg. The hardness range for oral tablets was usually 4 to 8 or 10 kg of pressure applied, but for hypodermic and chewable tablets, this value was 3 kg. In some sustained release tablets, a higher hardness value can be achieved (in the range 10–20 kg).

The tablet was placed diagonally on the Monsanto tester, and then, the screw was tightened until it touched the tablet's edge. When the scale read zero, the initial reading was recorded. The screw was tightened until the tablet broke. The final reading on the scale was recorded, and the actual hardness was calculated by subtracting the initial value (Blanco *et al*., 2006; Karmoker *et al*., 2016).

Friability test of tablets as per USP

Friability test was performed to check for loss of medicament during transportation, packaging, and other means of handling. Roche friability tester was used to estimate the loss of weight of six tablets after 100 rotations at the rate of 25 rpm. Tablets were allowed to fall from a height of six inches. Six tablets were weighed. Six tablets were kept together in a disc, in one partition of the two chambers. They were revolved for 4 min at a speed of 25 rpm. Then, the same six tablets were weighed together again. The percentage loss of weight was calculated (Osei-Yeboah, Sun, 2015), as well as percentage friability, as follows:

$$\frac{\text{Initial weight of 6 tablets} - \text{final weight of 6 tablets after rotation}}{\text{Initial weight of 6 tablets}} \times 100$$

Disintegration Test for Tablets as per USP

Disintegration test was performed to ensure that the tablet would break into small pieces up to the granular level to liberate the drug to the surrounding medium at a specified time and under a given condition. The disintegration test for tablets was performed according to USP using a Copley disintegration tester. Initially, six tablets were taken for the disintegration test, and each tablet was tested. Only one tablet was kept in each of the six tubes of the basket assembly. Then, the apparatus was operated using 0.1 N HCL maintained at 37± 2 °C for 1 h. If 1 or 2 tablets failed to disintegrate within a specified time and under a given condition, then the test will be repeated on 12 more tablets. Out of 18 tablets, no less than 16 should disintegrate to pass the disintegration test (Bandari, Mittapalli, Gannu, 2014).

***In vitro* drug release studies of Metoprolol Tartrate and Glimepiride innovator tablet**

In vitro drug dissolution studies are vital and are used as a quality control tool to monitor the batch-to-batch consistency of the drug released in dosage form (Bodea, Tomuţă, Leucuţa, 2010). In *in vitro* dissolution testing, the dissolution process is the rate-limiting step. USP dissolution apparatus Type-I (basket) is the most widely used dissolution test for different types of tablet evaluation at a stirring rate of 50 rpm. *In vitro* dissolution was performed for brands coded as MT-BP and GP-DM, according to the USP dissolution apparatus. An *in vitro* dissolution study was carried out in pH 6.8 phosphate buffer solution for both tablets. A UV-visible spectrophotometer was used to measure the amount of drug released from each tablet in the dissolution samples (Verma, Chattopadhyay, 2012).

Animals and treatment Plan:

Mice weighing approximately 30–45 g were randomly divided into five groups, and each group had six mice, as follows: Group–I: Control (received only vehicle); Group – II: Diabetic control (treated with streptozotocin, STZ); Group – III: treated with STZ + MT-BP; Group – IV: treated with STZ + GP-DM; Group –V: treated with STZ + MT-BP + GLIM GP-DM. The control group was fed commercial feed (Labina). The high fat (HF) diet with 66.5% commercial feed, 13.5% lard, and 20% sugar was given to all groups that received STZ. The HF diet has more calories from lipids (22%) and less carbohydrate (10%) and protein (12%) compared with the diet fed to the control. Each group was housed individually in metabolic cages in an environmentally controlled room and had free access to food and water. The body weight, water intake, and food intake of each rat were recorded daily. Glycemia was measured every 3 days using test strips (Accu-Chek). The control animals received only vehicle (0.01 M citrate buffer, pH 4.5). The animals received their respective diets for 12 days, and on the 13th day, a single dose of STZ was administered intraperitoneally (60 mg/ kg body weight) to animals fasted for 12 h in the HF-STZ group. GP-DM and MT-BP

were given 10 mg/kg, P.O. to the respective group. After 3 days of induction with STZ (on the 7th day of treatment), blood glucose was measured to confirm the establishment of diabetes. Animals were considered diabetic if they had postprandial glycemia values greater than or equal to 400 mg/dL (Cefalu, 2006; Zhang *et al*., 2003). The animals were maintained according to the College of Animal Experimentation, and the study was approved by the Ethics Committee of the Jazan University, KSA (Letter No.- 803/1208/1441).

In vivo DDI studies:

The effect of GP-DM and MT-BP individually and in combination were tested on five groups. Each group had six mice. The change in blood glucose levels was observed during the investigation by collecting the blood samples from the tail vein at different time intervals (0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, and 7.0 h) after drug administration, and glucose levels were estimated by using a glucometer. The individual and combined effects of GP-DM and MT-BP on blood sugar levels were tested after the administration of a single dose to the animals.

Statistical Data Analysis

The data were analyzed by inStat software, one-way ANOVA with post-test, and Tukey-Kramer Multiple comparisons. The P-value of <0.05 was considered significant. Variation among the column means was significantly greater than that expected by chance.

RESULT

Determination of λ_{max} in pH 6.8 phosphate buffer solution for Metoprolol Tartrate and Glimepiride

By the UV method, λ *max* was determined to be 224 and 227 nm for Metoprolol Tartrate and Glimepiride, respectively, at pH 6.8 (Figures 1 and 2). It was used to prepare a calibration curve.

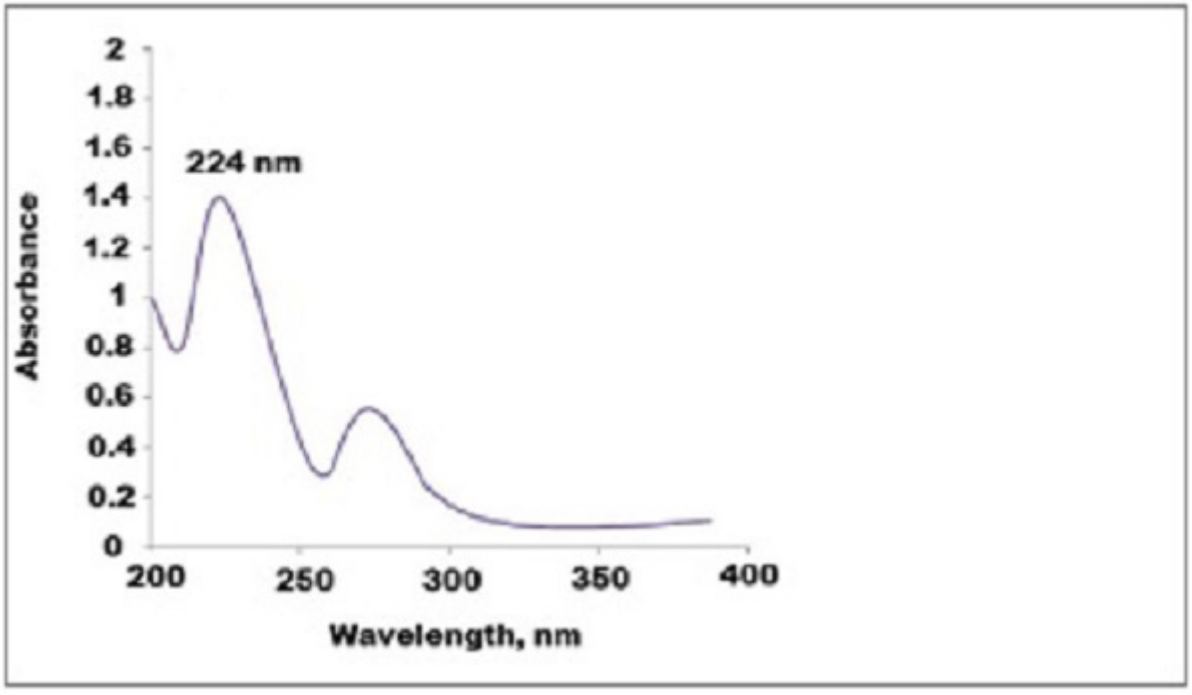

FIGURE 1 - λ_{max} of Metoprolol Tartrate in pH 6.8 buffer solution at 224 nm.

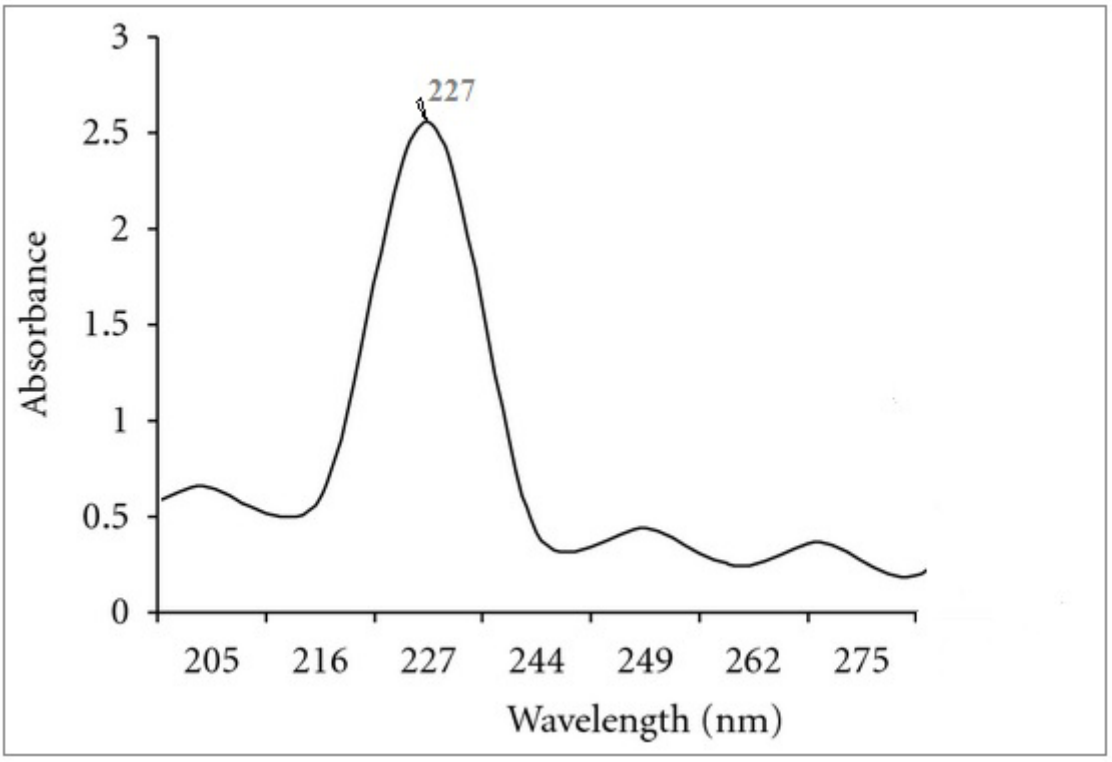

FIGURE 2 - λ_{max} of Glimepiride in pH 6.8 buffer solution at 227 nm.

Preparation of the calibration curve of Metoprolol Tartrate and Glimepiride in pH 6.8 buffer solution

The calibration curves of Metoprolol Tartrate and Glimepiride were developed using the pH 6.8 buffer solutions, as shown in Figures 3 and 4, respectively, to determine the drug content released during different stages of the dissolution study.

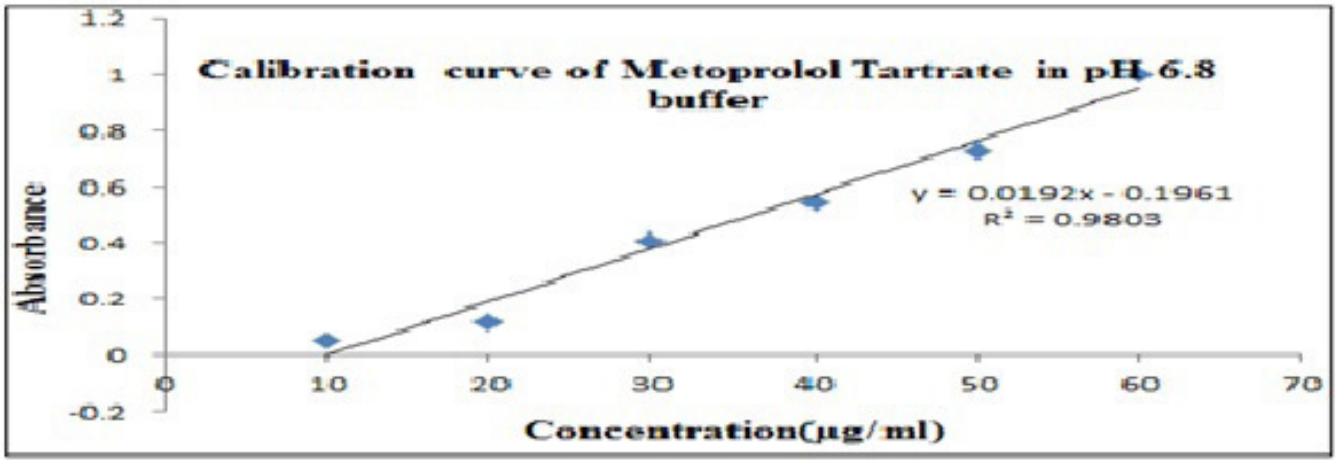

FIGURE 3 - Calibration curve of Metoprolol Tartrate in pH 6.8 buffer solution.

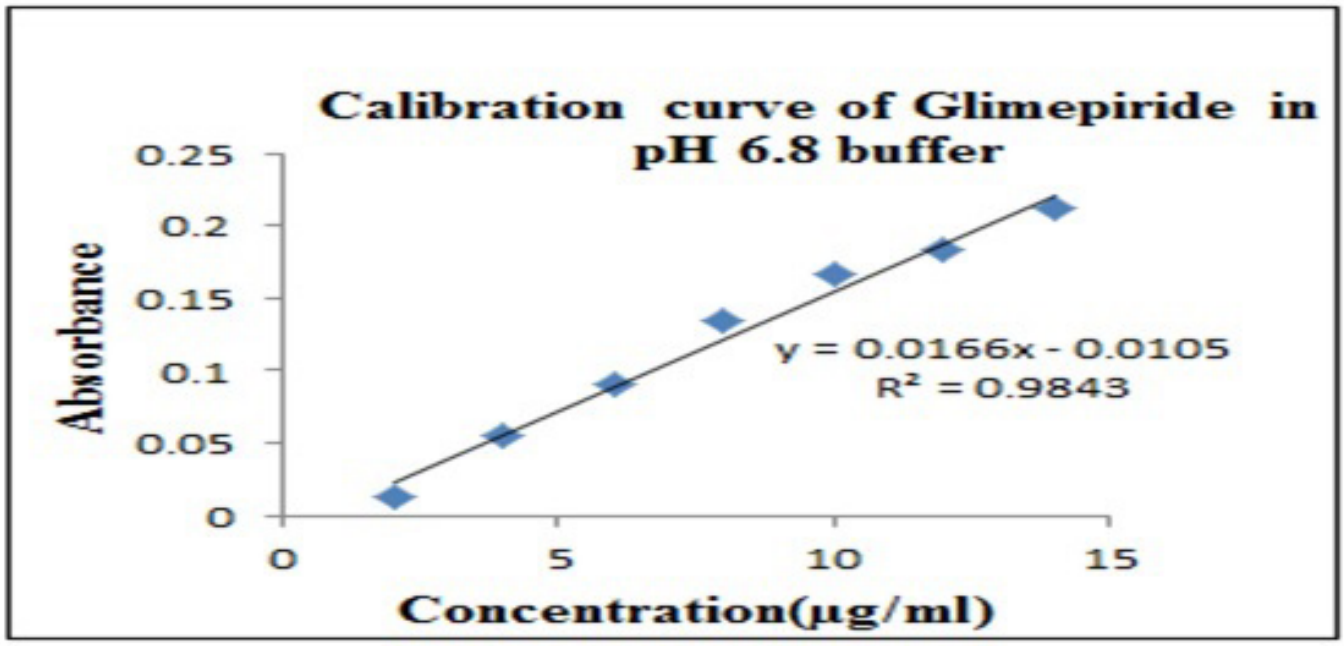

FIGURE 4 - Calibration curve of Glimepiride in pH 6.8 buffer solution.

The physical appearance of the tablet

Metoprolol Tartrate innovator tablets are white, smooth, slippery, round in shape, and film coated. Glimepiride innovator tablets are sunset color, smooth, slippery, flat dumbbell in shape, and film coated, as described in Table I.

TABLE I - Physical appearance of Metoprolol Tartrate and Glimepiride Innovator tablet

Brand Name	Color	Surface	Shape	Coated/ Uncoated
Metoprolol Tartrate (100mg)	white	Smooth and slippery	Round	Film-coated
Glimepiride (1mg)	Sunset	Smooth and slippery	Flat and dumbbell	Film-coated

Weight Variation Test

Weight variation test of Metoprolol Tartrate and Glimepiride were carried out as per USP specifications. All brands, as well as the standard, passed the test. This type of testing confirms that tablet weight is within the range and that therapeutic effects will not vary after consumption by patients, as shown in Table II.

TABLE II - Quality control test results of Metoprolol Succinate (100mg) and Glimepiride (1mg)

Drug Name	Tablet Evaluation Test			
	Weight variation test	Hardness Test (Kg)	Friability Test	Disintegration Time (Mins.)
Metoprolol Succinate (100mg)	Out of 20 tablets, no one fails	4.166±0.408	0.054% loss of weight	All six tablets disintegrate within 6.04 mins.
Glimepiride (1mg)	Out of 20 tablets, no one fails	2.91±0.671	0.245 % loss of weight	All six tablets disintegrate within 3.53 mins.

Hardness Test

Tablet hardness tests of Metoprolol Succinate and Glimepiride were carried out as per specifications, as shown in Table II. All tablets broke within the 4–6 kg weight. The hardness test results confirmed that the tablet was hard enough to not break during handling and transportation or before ingestion by patients. Six tablets from each group were tested.

Friability Test

The disintegration test of Metoprolol Tartrate and Glimepiride was carried out as per USP specifications. The percentage of weight losses of the different tablet was calculated in all cases, as illustrated in Table II. As a result, all tablets successfully passed the friability test. This test confirmed that no further loss of weight of a tablet occurred during packaging, handling, or transportation.

Disintegration Test

The disintegration test of the tablets of Metoprolol Tartrate and Glimepiride was conducted as per USP specifications. All tablets were disintegrated in an acidic medium within 30 mins. Results confirmed that a tablet disintegrated within the specified time and that all granules passed through sieve number 10 in the disintegration apparatus, as outlined in Table II.

In vitro drug release studies of Metoprolol Tartrate and Glimepiride innovator tablet

In vitro drug dissolution studies are a vital part and are used as a quality control tool to monitor batch-to-batch consistency of the drug release from a dosage form. [25] Dissolution testing is the rate-limiting step in *in vitro* testing and determines the reliability and discriminatory capabilities of dissolution tests for Metoprolol Tartrate and Glimepiride innovator tablets. USP dissolution apparatus Type-I (basket) is the most widely used dissolution tests for most of the film-coated tablets at stirring rates of 100 or 50 rpm. [26] The release profiles were estimated for both types of tablets at a stirring rate of 50 rpm using the basket method. An *in vitro* dissolution study was conducted in a phosphate buffer pH 6.8. A UV-visible spectrophotometer determined the amount of drug released from each tablet in the dissolution samples. The release of drugs from an oral solid dosage form is an essential aspect of drug bio-availability. Accordingly, dissolution testing of solid oral drug products is one of the essential control tests for assuring product uniformity and batch-to-batch equivalence. *In vitro* dissolution methods are developed to assess the potential *in vitro* performance of a solid oral dosage form. The cumulative release percentages of Metoprolol Tartrate and Glimepiride were 81.12% and 85.36%, respectively, as described in Figure 5.

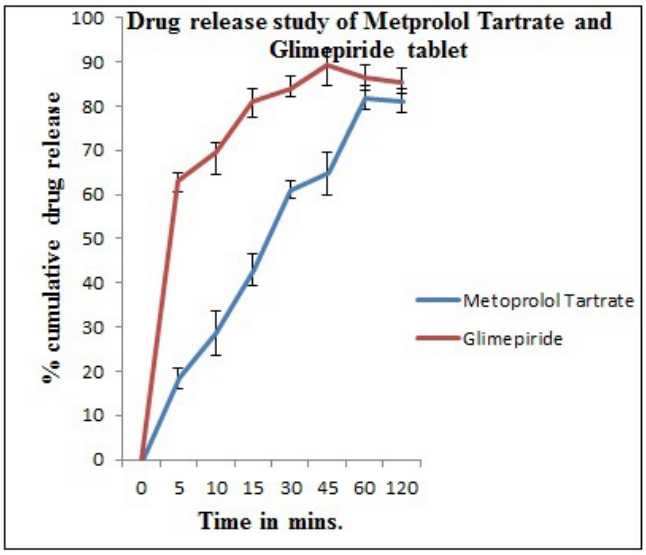

FIGURE 5 - percentage cumulative drug release of Metoprolol Tartrate and Glimepiride.

In vivo drug-interaction studies

Table III depicts the blood glucose levels at different time intervals in different groups of treatment. In the control group treated with vehicle, we did not find any variation throughout the study. The diabetic type-2 condition was confirmed in all the STZ-treated groups as the blood glucose increased beyond 400 mg/dl. The average blood glucose level was 424 mg/dl. In group III, in which the animals were treated with Metoprolol, the blood glucose reduced from 426.71 mg/dl to 337.71 mg/dl, and a difference of 89 mg/dl (20.85%) blood glucose was found in 7 h. In group IV, in which mice were treated with Glimepiride, a significant fall in blood glucose level from 418.57 mg/dl to 88.17 mg/dl was observed, which resulted in a difference of 330.4 mg/dl (78.94%). In Group V, animals were treated with both drugs, and showed a reduction in blood glucose from 420.71 mg/dl to 72.14 mg/dl, which resulted in a statistically significant difference ($P<0.05$) of 348.57 mg/dl (82.85%) in 7 h, as shown in Figures 6 and 7. The difference in blood glucose among the differentially treated groups and their statistical significance are provided in Table IV. The maximum difference was found between STZ-induced group vs. Glimepiride-treated group (220.64 mg/dL, $P<0.001$), followed by STD-induced group vs. the combination of metoprolol and glimepiride (206.16 mg/dL, $P<0.001$).

TABLE III - Blood glucose at different time intervals in the individual animal

Group-1 (Control)	**Blood glucose mg/dl/animal**							
Time point (hrs)	1	2	3	4	5	6	**Average**	**±SD**
0.00	93	99	102	107	98	97	99.33	4.760952286
0.50	99	107	105	104	96	103	102.33	4.082482905
1.00	97	103	95	96	90	95	96.00	4.195235393
1.50	99	100	101	91	100	104	99.17	4.355073669
2.00	108	108	102	109	105	109	106.83	2.786873995
3.00	105	94	99	105	101	94	99.67	4.966554809
5.00	101	90	100	90	94	96	95.17	4.750438576
7.00	98	89	91	93	92	96	93.17	3.311595789
Group-II - Diabetic control (standard treated)								
Time point(hrs)	**1**	**2**	**3**	**4**	**5**	**6**	**Average**	
0.00	488	490	495	498	480	493	420.57	6.314005596
0.50	492	499	480	505	490	500	423.79	8.914407814

TABLE III - Blood glucose at different time intervals in the individual animal

1.00	498	500	510	515	490	505	431.29	8.94427191
1.50	500	505	515	520	500	508	435.64	8.124038405
2.00	502	508	520	515	495	510	436.00	8.959166628
3.00	490	499	500	500	490	500	426.00	5.049752469
5.00	495	498	499	498	483	495	424.71	5.955389716
7.00	483	499	495	490	480	498	421.71	7.935153853
Group-III (STZ induced+METO)								
Time point(hrs)	**1**	**2**	**3**	**4**	**5**	**6**	**Average**	
0.00	490	495	498	499	500	505	426.71	5.036533199
0.50	445	448	446	442	445	440	380.93	2.875181154
1.00	400	410	405	408	407	400	347.29	4.195235393
1.50	395	400	398	390	385	399	338.36	5.89067059
2.00	390	395	388	392	394	395	336.57	2.875181154
3.00	380	375	373	378	382	387	325.43	5.036533199
5.00	375	373	370	365	368	372	318.29	3.619392214
7.00	395	390	389	395	388	400	337.71	4.622409184
Group-IV (STZ+GLIME)								
Time point(hrs)	**1**	**2**	**3**	**4**	**5**	**6**	**Average**	
0.00	485	490	488	482	495	490	418.57	4.501851471
0.50	400	405	403	402	408	410	346.93	3.777124126
1.00	345	348	340	335	360	350	297.00	8.640987598
1.50	300	290	295	305	310	291	256.07	7.968688725
2.00	210	205	215	203	202	204	177.29	5.00999002
3.00	140	145	137	135	135	130	117.86	5.099019514
5.00	78	80	85	75	78	79	68.57	3.311595789
7.00	100	90	105	110	103	102	88.14	6.653319973
Group-V (STZ+METO+GLIME)								
Time point(hrs)	**1**	**2**	**3**	**4**	**5**	**6**	**Average**	
0.00	500	495	490	480	485	495	420.71	7.359800722
0.50	380	385	383	378	380	390	328.07	4.366539438
1.00	320	305	308	310	315	318	268.14	5.921711464
1.50	290	280	285	285	300	305	249.50	9.703951085

TABLE III - Blood glucose at different time intervals in the individual animal

2.00	180	175	165	160	168	171	145.86	7.139094247
3.00	140	135	130	132	138	131	115.57	4.03319559
5.00	65	63	68	63	55	63	54.57	4.308905507
7.00	87	84	87	86	79	75	72.14	4.939635614

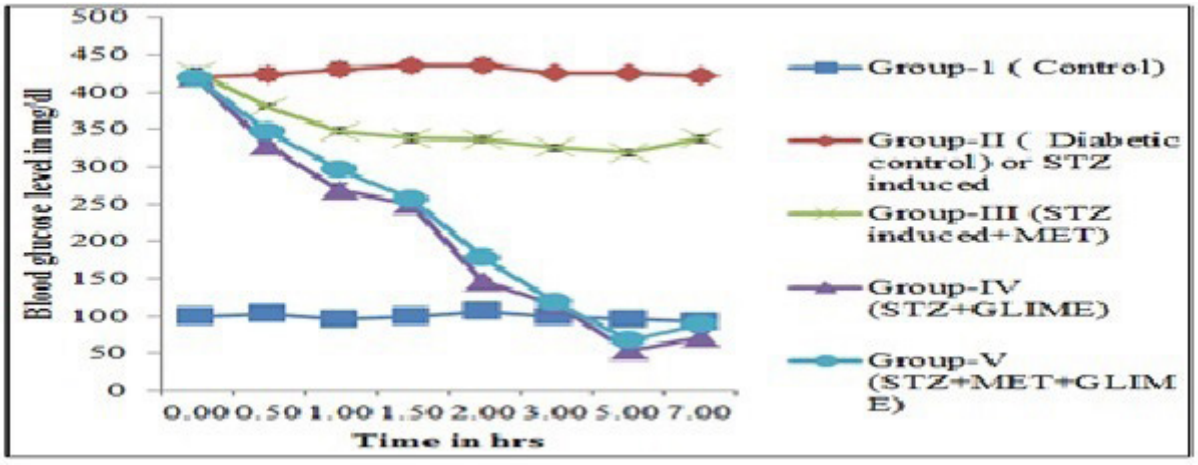

FIGURE 6 - Blood glucose level of the differentially treated groups.

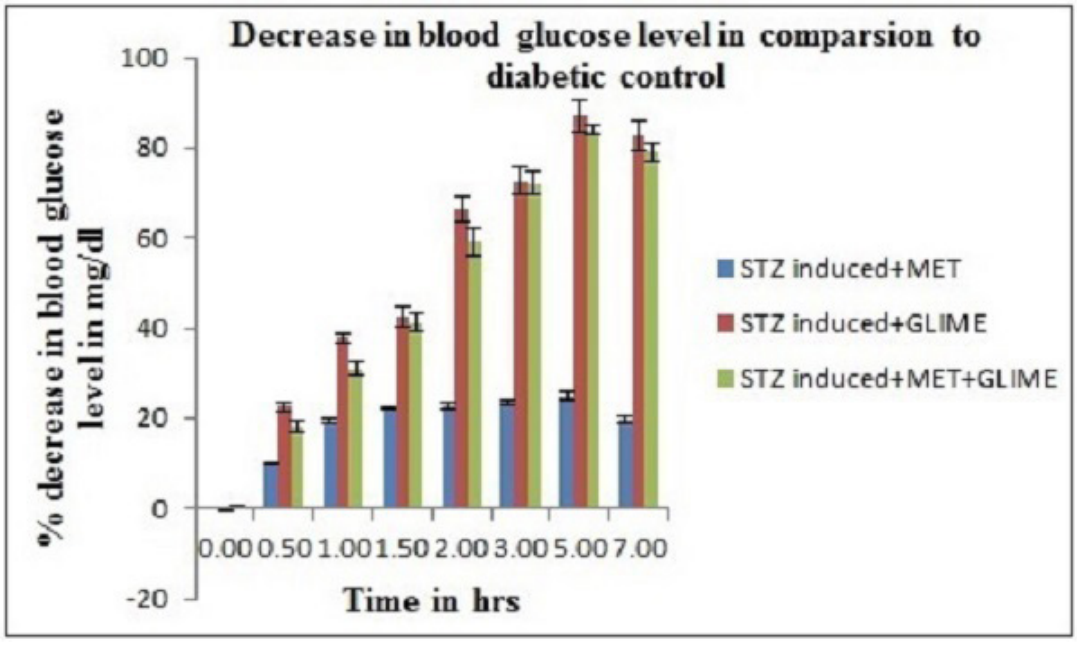

FIGURE 7 - Percentage decrease in blood glucose level in different treatment plans compared with the diabetic control.

TABLE IV - Statistical analysis among different treated animal groups

Sl. No.	Comparison	Mean Difference	95 % CI (Confidence interval)	P-Value
1	STZ induced Vs Metoprolol	76.053	-51.437-203.54	ns P>0.05
2	STZ induced Vs Glimepiride	220.64	93.154-348.13	***P<0.001
3	STZ induced Vs Metoprolol +Glimepiride	206.16	78.670-333.65	***P<0.001
4	Metoprolol Vs Glimepiride	144.59	17.101-272.08	*P<0.05
5	Metoprolol Vs Metoprolol +Glimepiride	130.11	2.618-257.60	*P<0.05
6	Glimepiride Vs Metoprolol +Glimepiride	-14.484	141.97-113.01	ns P>0.05

DISCUSSION

The ministry of health is the largest healthcare provider in the kingdom along with the other two sectors, namely, the government institutions and the private sector, which cover 62%, 20%, and 17% of health care, respectively. The government provides free health care to pilgrims as well, thereby covering another 3.4 million annually. However, the kingdom is not well equipped to manufacture the required pharmaceuticals and depends on other countries for its daily drug requirements (Walston, Al-Harbi, Al-Omar, 2008). The kingdom massively imports pharmaceuticals from different countries, and considerable facilities are required to carry out quality testing. Studies of this nature are being reported for the first time in the kingdom, and they have essential relevance.

This study was undertaken to assess the quality parameters of the two widely used formulations at the point of dispensing and also to evaluate the DDI between them. We used all the tests to ensure the quality, efficacy, and safety of the tablets by adopting physical, chemical, and biological procedures. The outcomes of the study are essential in assessing the impact of the packaging, handling, and transportation under different environmental conditions on the consumers. The formulations selected were within the shelf life period.

The physical appearance of Metoprolol and Glimepiride tablets was smooth and slippery, film-coated, and intact. There was no distortion of the size and shape of the tablets, which indicated that these tablets withstood the wear and tear of handling and transporting, and it reflected that packing of the material was perfect. The distortion in the physical appearance of the formulation was the measure of the efficiency of the packing materials used. If the packing materials are not of good quality, then they may leak, and the medicines will be exposed to the environment. The tablets would absorb moisture and swell. Chemical interactions between the drug molecule and the excipients or with the environmental constituents may occur. Moreover, the hardness test conducted on these tablets indicated that they were strong enough to withstand the rough handling and transportation process. Similarly, all the tablets have passed the friability test performed as per USP, thereby confirming that no further loss of weight occurred during transportation.

All the tablets of both drugs were picked for the tests from community centers and did not shown much weight variation among themselves, indicating that therapeutic benefit may not vary after consumption by the patients. The disintegration study revealed that the formulation maintained the pharmacopeial standard of breaking up to the granular level, which helps release the drug into the stomach. All tablets fragmented under acidic conditions within 30 min. The drug release profile of the tablets was also within the conformity of the pharmacopeial standards. These disintegration and dissolution studies indicated that the formulations were in uniformity and

conformation with the set standards and might provide the expected bioavailability. The selected formulations have passed all the qualitative and quantitative tests. The specification limits of these products established as per the standard protocols will remain for the entire duration of the shelf life.

After concomitant administration of Metoprolol, a marginal decrease in the blood glucose level was observed in diabetic mice, whereas the administration of Glimepiride significantly decreased the blood glucose level. However, the combination of the two drugs significantly decreased the blood glucose level of diabetic animals. Comorbidities are associated with patients who are suffering from type 2 diabetes mellitus. However, blood glucose level increased in non-diabetic hypertensive patients who are taking metoprolol (Groop *et al.*, 1983). Hypertension and high blood lipid-related microvascular and macrovascular complications usually occur in patients with diabetes (Hermans, Ahn, Rousseau, 2012). Multidrug pharmacotherapy is needed to treat such conditions, which often leads to a higher risk of adverse reactions and interactions. Drugs exposed to environmental factors may undergo decomposition, even if the user is unaware of it. The metabolite formed due to decomposition might have different pharmacological responses compared with the original drug. It might also initiate DDIs. Alteration of metabolism by enzymes is the most complicated process by which these metabolites induce DDIs. The clinical consequences of enzyme induction or inhibition depend on the pharmacological and toxic effects of both the parent and its toxic metabolite(s). Our study revealed that the level of blood glucose in mice treated with both Metoprolol and Glimepiride showed variation. The co-prescription of these drugs might have precipitated a decrease in blood glucose levels. However, the mechanism underlying these changes needs to be investigated.

In many cases, the combination of Metoprolol and Glimepiride could have been intentionally prescribed. In some cases, it might have been consumed by mistake. In both cases, the drugs interact with each other to produce a more harmful effect on individuals. There are several possible reasons for the variation in the blood sugar levels after the concomitant administration of these drugs, such as the induction or suppression of several enzymes related to metabolism, the multiplicity of enzymes and transporters involved in the disposition of these two drugs, intricacies or overlapping in the pathways and interactions, and the perplexing pharmacokinetic interactions with the administered drugs in animals. The production of metabolic-intermediate complexes in the body might be an unusual form of the inhibition of the enzyme–substrate complex, which causes variation in blood glucose level. However, we found no deformities in the packaging system of these tablets. Hence, they were not exposed to environmental conditions, and no interaction occurred among them at all. Recommending a combination of these two medications, especially in elderly patients, requires much vigilance and constant monitoring of their blood glucose levels.

CONCLUSION

The tablets of Metoprolol and Glimepiride have passed all the quality tests performed and met the standards of pharmacopeias. Taking both drugs in combination is most common among patients with type-2 diabetes and hypertensive disease. Therefore, monitoring DDI effects on blood glucose level is required. Our study's results suggested that the difference between the blood glucose levels of the diabetic control and Metoprolol-treated animal was non-significant (p). In contrast, the difference in blood glucose levels of the diabetic control and Glimepiride-treated animals was significant (p). The results suggested that the chronic use of this combination requires the consistent monitoring of blood glucose level. People with diabetes may need to take extra care to monitor their blood sugar level while using Metoprolol medication along with Glimepiride.

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