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The *in vitro* study of interaction between antacids and anti-diabetic drug sitagliptin in the treatment of type II diabetes

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Abstract: Hyperglycemia is a long-lasting syndrome that occurs either when the pancreas cannot produce enough insulin, or the body cannot effectively utilize that insulin to regulate blood sugar levels. Non-insulin-dependent hyperglycemia, also known as type II diabetes, causes a common consequence of severe damage to many of the body's organs mainly the blood vessels and nerves. The majority of people around the world are suffering from non-insulin-dependent diabetes. The present work showed a great effort to investigate any possible interaction between antacids and sitagliptin (anti-diabetic drug) in the treatment of type II diabetes with gastrointestinal tract problems. The *in vitro* studies were carried out in simulated gastric juice pH 2.0 and intestinal pH 7.4 at 37°C. $MgCO_3$, $NaHCO_3$, $Mg(OH)_2$, $Al(OH)_3$ and $CaCO_3$ were used as antacids in these studies. It has been observed that % release of sitagliptin was significantly enhanced in the presence of calcium carbonate and magnesium carbonates.

Keywords: Sitagliptin, diabetes, hyperglycemia, anti-diabetic agent, antacid.

INTRODUCTION

Co-administration of more than one drug and drugs with other medications or supplements is frequent practice among patients suffering from multiple diseases (Marín-Peñalver *et al*., 2016). Such practice is most common among geriatric patients having co-morbidities including diabetes, cardiovascular diseases, hypertension, hyperlipidemia, gastric diseases, etc (Residori *et al*., 2003). One of the prevailing diseases among all kind of population including adults and children is diabetes mellitus type II. Blood glucose management is very crucial with medication and life style modification in order to reduce the risk of further health complications including cataract, kidney disorders, cardiovascular diseases, blood pressure, etc (AlShorman *et al*., 2021). However, the management of diabetes has become controversial and complex due to availability of variety of anti-diabetic medications (Babiker and Al Dubayee, 2017). Not only this, there are certain conditions where co-administration of drugs is necessary in order to reduce the side effects of other drugs that might lead to ineffectiveness (Bohm *et al*., 2021).

One of the preventable medication errors is interaction of drugs with other drugs upon their concomitant use (Ariff *et al*., 2022). The application of guidelines based on scientific proof and evidence can help to reduce such errors in order to improve patient safety, therapeutic efficacy and quality of care (Roghani *et al*., 2013). Medications errors are not only limited to the simultaneous use of drugs with other drugs, but these interactions can also be observed via taking drugs either with nutritional supplements, minerals, vitamins or antacids leading to futile therapeutic effect (Organization, 2021).

Patients suffering from diabetes mellitus normally require further pharmacological treatment due to the presence of several co-morbidities. One of such examples is the use of antacids for gastro-esophageal reflux diseases by the diabetic patients (Widyasari *et al*., 2021). Multiple pharmacological therapies, at one hand, decrease the risk of other disorders such as cardiovascular diseases, on other hand, increase the chances of interactions and adverse drug events. Therefore, it is necessary to consider gender and age of patients, use of herbal and nutritional supplements and absorption properties of drugs (May and Schindler, 2016).

In the light of above mentioned critical issue, this research aims to study the *in vitro* interaction studies of anti-diabetic agent with antacids. In this regard, *in vitro* release pattern of sitagliptin from tablet was observed in presence of selected antacids taking two different gastric conditions that include simulated gastric and simulated intestinal environment.

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MATERIALS AND METHODS

Drugs and chemicals

Sitagliptin standard was taken from Macter International Limited as a gift, while sitagliptin tablets (25mg) were purchased from local market. Hydrochloric acid (HCl), potassium chloride (KCl), potassium dihydrogen phosphate (KH_2PO_4), sodium dihydrogen phosphate (NaH_2PO_4), sodium chloride (NaCl), distilled water and antacids: Aluminum chloride ($AlCl_3$), magnesium carbonate ($MgCO_3$), sodium bicarbonate ($NaHCO_3$), magnesium hydroxide ($Mg(OH)_2$), calcium carbonate ($CaCO_3$) and aluminum hydroxide ($Al(OH)_3$) were purchased from Sigma-Aldrich (Japan) and Scharlau Chemie S.A. (Spain). All the reagents and chemicals were used of analytical grade. Deionized or distilled water was used in all experimental methods.

Instrumental analysis

Electronic weighing balance (No. D401401239, Type EB-3200H-A, capacity 3200 g, readability 0.01 g, Shimadzu Corporation, Japan) and analytical balance (AL-204/Mettler Toledo/12253004.120, max 210 g, e=1mg, min 0.01 g, d=0.1mg) were used for accurate measurement of weight of the samples. pH was determined by digital pH meter (Model No. pH 01/02, PCSIR Laboratories Complex, Karachi, Pakistan). Dissolution test was performed on dissolution apparatus (D-63512, Type PT-DT7, Serial No. 11661, Pharma Test, Hainburg, Austria). GENESYS 10S UV-Visible spectrophotometer (Model G10S UV-VIS, CAT 840-209700, SN 2L9P153006, Thermo Fisher Scientific, Madison WI.53711, USA) was used for observing absorption of the samples. Refrigerator (Model No. 9150, capacity 256/9 L/Cu.ft., Temperature range 2 to -25 ºC for freezer, Dawlance, Pakistan) was used for samples storage.

Preparation of buffer solution

In order to perform the *in vitro* interaction studies of sitagliptin with antacids, two pH buffer solutions were prepared having pH 2 considered as simulated gastric condition and pH 7.4 taken as simulated intestinal condition of gastrointestinal tract.

Hydrochloric acid-Potassium chloride buffer pH 2 (simulated gastric pH) was prepared by mixing 6.5 mL of 0.2M HCl and 25mL of 0.2M KCl in 100mL of distilled water.

Phosphate buffer pH 7.4 (simulated intestinal pH) was prepared *via* adding 0.585g NaCl, 0.64g Na_2HPO_4 and 0.06g KH_2PO_4 in 100mL of water. 0.1N HCl and 0.1N NaOH solutions were used to adjust the pH (BP, 208).

Following formulae were used for determining the required quantities of chemicals in making buffer solutions.

$$\text{Volume of HCl}=\frac{\text{Molecular weight}\times\text{Concentration required (M)}\times\text{Volume required (mL)}}{\%\text{Purity}\times\text{Specific gravity}\times 1000}$$

$$\text{Amount(g)}=\frac{\text{Molecular weight}\times\text{Concentration required(M)}\times\text{Volume required(mL)}}{1000}$$

Dissolution test

Dissolution tests, for evaluating the *in vitro* interaction of sitagliptin with antacids, were performed in two steps (Arayne *et al*., 2010). Initially, interaction was checked at simulated gastric pH condition; furthermore, at simulated intestinal pH condition. In this regard, sitagliptin standard and sitagliptin tablets were treated alone using dissolution apparatus type II that was considered as reference batch as no antacid was added. Following this, dissolution test of sitagliptin was performed in presence of five antacids. These batches of drug were considered as test batches.

At first, dissolution studies of sitagliptin tablet (n=6) and active ingredient (n=6) carried out individually in 900 mL of dissolution media having gastric simulated pH conditions with 50 rpm speed at 37±0.5ºC for 180 minutes. Following this with similar parameters, further dissolution studies of sitagliptin performed with five antacids including $Al(OH)_3$, $CaCO_3$, $Mg(OH)_2$, $MgCO_3$ and $NaHCO_3$ in simulated intestinal conditions.

- Sitagliptin tablet + 1 g $Al(OH)_3$ (n=6)
- Sitagliptin tablet + 1 g $CaCO_3$ (n=6)
- Sitagliptin tablet + 1 g $Mg(OH)_2$ (n=6)
- Sitagliptin tablet + 1 g $MgCO_3$ (n=6)
- Sitagliptin tablet + 1 g $NaHCO_3$ (n=6)

Sampling and measurements

At every 15 minutes interval, sample of 10 mL withdrawn from the dissolution medium and same volume of fresh medium added to conserve the volume constant. The samples were withdrawn at 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes time points. The withdrawal sample filtered and analyzed for quantification using UV-Visible spectrophotometer (Arayne *et al*., 2005).

STATISTICAL ANALYSIS

Data analysis was performed by calculating percent release of sitagliptin when treated alone and in presence of different antacids using following formula (Dey *et al*., 2015).

$$A_{\%}=\frac{A_t \times A_{std} \times V_d \times P \times 100}{A_s \times V_s \times A_{tab}}$$

In this equation,

$A_{\%}$=Percent amount of drug (mg) released in dissolution medium at time t (min)

A_t=Absorbance of test sample at time t (min)

A_s=Absorbance of standard

A_{std}=Amount of standard (mg)

V_s=Volume (mL) of solvent to dissolve A_{std}

V_d=Volume of dissolution medium i.e. 900mL

P=Purity of working standard

A_{tab}=Amount of drug (mg) present in one tablet i.e. 25mg

The calculated values are given in tables and dissolution profiles are compared by plotting release curves. The comparison of curves was further conducted *via* applying zero-order kinetics, first order kinetics and fit factors. Later, one-way ANOVA and Tukey`s test were also employed by using MS EXCEL 2013 to statistically analyzed collected data at significance level of 0.05. ANOVA showed in tables the overall difference among the reference and test batches of sitagliptin respecting both the gastrointestinal conditions (p<0.05). Whereas, Tukey's test highlighted the occurrence of difference concerning specific groups of data.

RESULTS

In vitro interaction studies of sitagliptin with five different antacids at gastric pH 2

The addition of $NaHCO_3$, $Mg(OH)_2$ and $CaCO_3$ did not show any change in total dissolution time and showed complete dissolution at the same time point of 120 minute. However, the addition of certain antacids including $MgCO_3$ and $Al(OH)_3$ altered the complete dissolution time for the sitagliptin tablet. The release of sitagliptin was completed 15 minutes before when $MgCO_3$ was added in the medium (fig. 1).

In vitro interaction studies of sitagliptin with five different antacids at intestinal pH 7.4

Respecting the simulated intestinal pH 7.4, the total dissolution of sitagliptin tablet was achieved in two hours (103.543±0.2213) as same as in case of pH 2. However, only one antacid $Al(OH)_3$ did not alter dissolution time while other antacids either decrease and increase the dissolution time. $NaHCO_3$ delayed the release by 15 minutes. Sitagliptin took three hours for complete release in presence of $Mg(OH)_2$ and it was released 15 minutes and 30 minutes before in presence of $MgCO_3$ and $CaCO_3$ respectively (fig. 2).

Mathematical and statistical tests

The collected data was further treated using mathematical and statistical tests in order to determine and verify the similarity and difference between dissolution profiles of sitagliptin with and without antacids mathematically and statistically.

Respecting the zero order kinetics studies, no substantial difference was observed in correlation coefficient R^2 values, close to 1, of sitagliptin release profiles following the addition of antacids in case of simulated gastric pH (table 1). However, the dissolution constant (k) value was fluctuated when different antacids were added. In case of $NaHCO_3$ and $Al(OH)_3$, k value is increased while it was decreased in presence of $MgCO_3$. $CaCO_3$ and $Mg(OH)_2$ did not affect the k value of sitagliptin release. The dissolution profiles obtained in simulated gastric pH, $NaHCO_3$ and $CaCO_3$ showed the highest values of R^2 in case of zero order model. In addition to this, R^2 values for dissolution profiles in simulated intestinal pH were found in range 0.969-0.995 having slight discrepancies.

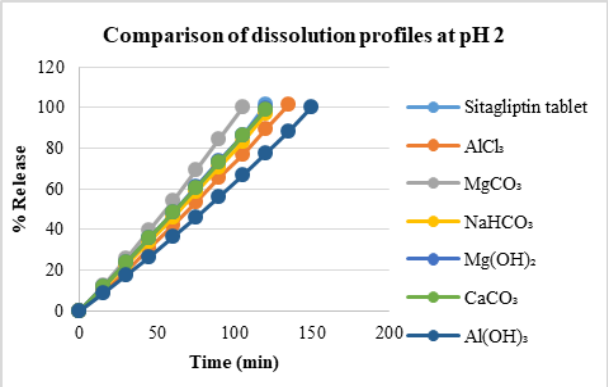

Fig. 1: Comparison of dissolution profiles of sitagliptin with five different antacids at pH 2.

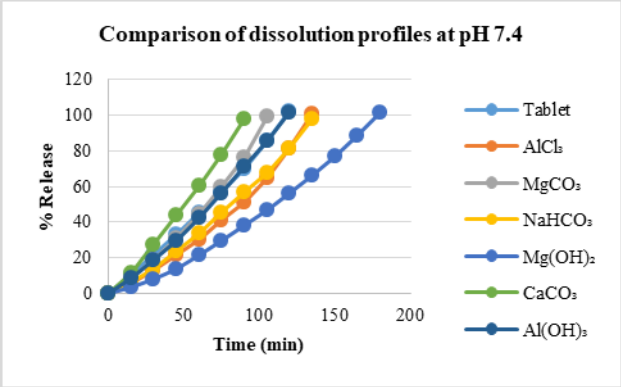

Fig. 2: Comparison of dissolution profiles of sitagliptin with five different antacids at pH 7.4.

In buffer pH 2 medium, dissolution profiles of sitagliptin are not found best fit with first order kinetics model as R^2 value is found less than 0.9 except in two cases where sitagliptin alone and in presence of $MgCO_3$ possessed R^2 =0.915. However, the presence of other antacids reduced the R^2 values of dissolution profiles (table 2).

Tables 3 and 4 exhibited the similar and dissimilar profiles on the basis of single value of *f1* and *f2* obtained for two profiles under comparison. At pH 2, the dissolution profiles of sitagliptin/sitagliptin+$NaHCO_3$, sitagliptin/ sitagliptin+Mg $(OH)_2$ and sitagliptin/sitagliptin + $CaCO_3$ showed the same release pattern having *f1* and *f2* values in defined limits of 0-15 and 50-100 respectively (table 3). Similarly, at pH 7.4, the profiles encompassing sitagliptin/sitagliptin+$MgCO_3$ and sitagliptin/ sitagliptin+ $Al(OH)_3$ were found equivalent (table 4).

ANOVA test showed that all the selected dissimilar dissolution profiles, of simulated gastric and intestinal pH, were same as $F<F_{crit}$ with p>0.05. However, Tukey`s

test was also applied on the results obtain from ANOVA. At pH 2, Tukey`s test confirmed the result for $MgCO_3$ and $Al(OH)_3$ as similar profiles to that of sitagliptin alone as calculated HSD<tabulated HSD (table 5). At pH 7, the selected profiles were also not found different using Tukey`s test at 0.05 level of significance (table 6).

DISCUSSION

In vitro interaction studies of sitagliptin with different antacids showed some changes in dissolution profiles at simulated gastric and intestinal pH. In the absence of antacids, sitagliptin tablet completely released in 2 hours at gastric pH 2. Also there was no significant changes observed in the dissolution profile of sitagliptin in the presence of $NaHCO_3$, $Mg(OH)_2$ and $CaCO_3$ (fig. 1). However, the addition of certain antacids including $MgCO_3$ and $Al(OH)_3$ triggered the dissolution time for the sitagliptin tablet (fig. 1), that might be due to various reasons leading to interaction. $Al(OH)_3$ delayed the dissolution time of sitagliptin by half an hour. The release of sitagliptin was completed in 15 minutes before when $MgCO_3$ was added in the medium (fig. 1).

Respecting the simulated intestinal pH 7.4 (fig. 2), the total dissolution of sitagliptin tablet was achieved in two hours as same as in case of pH 2 (fig. 1). However, only $Al(OH)_3$ did not alter dissolution time while other antacids either decrease and increase the dissolution time. $NaHCO_3$ delayed the release of tablet by 15 minutes. The complete dissolution of tablet sitagliptin took 3 hrs in presence of $Mg(OH)_2$ and it was released 15 minutes and 30 minutes before in presence of $MgCO_3$ and $CaCO_3$ respectively.

In order to determine and verify the similarity and difference between dissolution profiles of sitagliptin with/without antacids, the collected data was further treated with mathematical and statistical tests. In this regard, zero order kinetics, first order kinetics, fit factors, ANOVA and Tukey`s tests were applied. Zero order and first order kinetics model helped to evaluate the changes in dissolution mechanism of the tablet. This is useful to understand the interaction to some extent.

With zero order kinetics studies, there was no substantial difference observed in correlation coefficient R^2 values (close to 1) of sitagliptin release profiles following the addition of antacids at pH 2 (table 1). The same and close R^2 values indicate the strong linear relationship between the concentration releases against time. In this way, the release profiles are found best fit to zero order kinetic model. However, the dissolution constant (k) value was fluctuated when different antacids were added. In case of $NaHCO_3$ and $Al(OH)_3$, k value is increased while it was decreased in presence of $MgCO_3$. $CaCO_3$ and $Mg(OH)_2$ did not affect the k value of sitagliptin release.

The dissolution profiles obtained in simulated gastric pH 2, $NaHCO_3$ and $CaCO_3$ showed the highest values of R^2 in case of zero order model. It can be assumed that this model best explains the sitagliptin release from tablets in gastric pH. In addition to this, R^2 values for dissolution profiles in simulated intestinal pH were found in range 0.969-0.995 having slight discrepancies. However, the strong linear relationship was also found making the data of simulated intestinal pH best fit to the zero order kinetics. Zero order kinetics describes the disaggregation free slow release of sitagliptin from tablet dosage forms even in presence of antacids with slight change in R^2 values (table 2). Sitagliptin released in absence and presence of antacids independent of initial concentrations of tablet as well as antacids (table 3).

In buffer pH 2 medium, dissolution profiles of sitagliptin are not found best fit with first order kinetics model as R^2 value is found less than 0.9 except in two cases where sitagliptin alone and in presence of $MgCO_3$ possessed R^2=0.915. However, the presence of other antacids reduced the R^2 values of dissolution profiles (table 2). The result showed these profiles are not best fit to first order kinetics model and drug is not releasing with respect to the release principle of first order kinetics. Sitagliptin releases independently of concentration of reactants that is the addition of antacids did not affect the elimination of active ingredient from tablet dosage form (Dunnington *et al*., 2018). Moreover, first order kinetics model explains the drug release mechanism of poorly water soluble drugs having water soluble dosage form, while sitagliptin is water soluble and thus its dissolution profiles were not found best fit with this kinetics model (Wójcik-Pastuszka *et al*., 2019).

Tables 3 and 4 exhibited the similar and dissimilar profiles on the basis of single value of *f1* and *f2* obtained for two profiles under comparison. Respecting the determination of these factors, all the time points were selected to compute the value showing similarity and dissimilarity among the pairs of reference and test release profiles. At pH 2, the dissolution profiles of sitagliptin/sitagliptin+$NaHCO_3$, sitagliptin/ sitagliptin+ $Mg(OH)_2$ and sitagliptin/ sitagliptin+$CaCO_3$showed the same release pattern having *f1* and *f2* values in defined limits of 0-15 and 50-100 respectively (table 3). Similarly, at pH 7.4, the profiles encompassing sitagliptin/ sitagliptin+$MgCO_3$ and sitagliptin/ sitagliptin+ $Al(OH)_3$ were found equivalent (table 4). Similar release of sitagliptin from reference and test profiles proposes no interaction leading to affect the rate of drug elimination from tablet, while dissimilar release does. There might be any interaction due to antacid that has either decreased or increased rate of release (Boateng and Okeke, 2019). Such interaction causing specie can be studied at molecular level.

Table 1: Zero and first order kinetics parameters of dissolution curves at pH 2.

Kinetics		Sitagliptin tablet	Sitagliptin +$MgCO_3$	Sitagliptin +$NaHCO_3$	Sitagliptin +$Mg(OH)_2$	Sitagliptin +$CaCO_3$	Sitagliptin +$Al(OH)_3$
Zero order	K_0	0.032	-0.0007	0.0395	0.0326	0.034	0.079
	R^2	0.998	0.998	0.999	0.997	0.999	0.998
First order	K_0	-0.0003	0.0022	-0.0007	-0.0003	-0.0003	-0.0027
	R^2	0.915	0.915	0.776	0.682	0.704	0.559

Table 2: Zero and first order kinetics parameters of dissolution curves at pH 7.4.

Kinetics		Sitagliptin tablet	Sitagliptin +$MgCO_3$	Sitagliptin +$NaHCO_3$	Sitagliptin +$Mg(OH)_2$	Sitagliptin +$CaCO_3$	Sitagliptin +$Al(OH)_3$
Zero order	K_0	0.0809	0.0614	0.1180	0.1710	0.0003	0.0787
	R^2	0.994	0.98	0.987	0.98	0.995	0.991
First order	K_0	-0.0007	0.0006	-0.0026	-0.0044	0.02689	-0.0006
	R^2	0.893	0.638	0.558	0.834	0.582	0.878

Table 3: Difference (*f1*) and similarity (*f2*) factors for sitagliptin release in presence of antacids at pH 2.

Antacids	*f1*	*f2*	Dissolution profile
$MgCO_3$	33.58	36.7	Dissimilar
$NaHCO_3$	3.79	60.99	Similar
$Mg(OH)_2$	0.81	84.25	Similar
$CaCO_3$	0.89	81.65	Similar
$Al(OH)_3$	24.07	21.41	Dissimilar

Table 4: Difference (*f1*) and similarity (*f2*) factors for sitagliptin release in presence of antacids at pH 7.4.

Antacids	*f1*	*f2*	Dissolution profile
$MgCO_3$	7.34	61.59	Similar
$NaHCO_3$	22.23	24.41	Dissimilar
$Mg(OH)_2$	48.73	6.95	Dissimilar
$CaCO_3$	19.28	22.63	Dissimilar
$Al(OH)_3$	3.04	64.99	Similar

Table 5: Tukey`s test for dissimilar profiles at pH 2 taking α=0.05.

Antacids	Calculated HSD value	Tabulated HSD value	Dissolution profile
$MgCO_3$	0.03435	3.53	Similar
$Al(OH)_3$	0.07175	3.53	Similar

Table 6: Tukey`s test for dissimilar profiles at pH 7.4 taking α=0.05.

Antacids	Calculated HSD value	Tabulated HSD value	Dissolution profile
$MgCO_3$	0.18098	3.82	Similar
$Al(OH)_3$	0.23999	3.82	Similar
$CaCO_3$	0.09233	3.82	Similar

In addition, the release profiles which were found dissimilar using *f1* and *f2* tests were further subjected to ANOVA and Tukey`s tests in order to validate the results statistically. ANOVA test showed that all the selected dissimilar dissolution profiles, of simulated gastric and intestinal pH, were same as $F<F_{crit}$ with $p>0.05$. However, Tukey`s test was also applied on the results obtain from ANOVA. At pH 2, tukey`s test confirmed the result for $MgCO_3$ and $Al(OH)_3$ as similar profiles to that of sitagliptin alone as calculated HSD<tabulated HSD (table 5). At pH 7, the selected profiles were also not found different using Tukey`s test at 0.05 level of significance (table 6).

CONCLUSION

In vitro interaction studies of sitagliptin with five different antacids showed some changes in dissolution profiles obtained at simulated gastric and simulated intestinal pH at 37°C on the percent release time of the sitagliptin

tablet. Concomitant administration of drug with antacids may increase the percent release of drug in the case of magnesium marbonate at pH 2.0 and calcium carbonate at pH 7.4 in some extend and pointedly decrease in the case of aluminum hydroxide at pH 2.0, magnesium hydroxide and sodium bicarbonate at pH 7.4.

Overall, concomitant administration of drug with different antacids in simulated gastric and intestinal pH at 37^{o}C has not been significantly affected on the average release time of the tablet, so it can be co-prescribe for the better treatment of problems occurs in gastrointestinal tract as co-existing diseases of type II diabetes.

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