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In Vitro Drug-Drug Interaction of Metformin HCl with Omeprazole and Lansoprazole

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Abstract: Metformin HCl is an effective oral hypoglycemic agent for glycemic control in diabetes mellitus type 2 patients. Metformin HCl with omeprazole and lansoprazole is often required to control glycemia and cure GERD simultaneously. This raised the probability of drug-drug interactions of metformin HCl with omeprazole and lansoprazole. This study evaluated the in vitro drug-drug interaction between metformin HCl with omeprazole and lansoprazole by applying a dissolution test followed by UPLC analysis. The dissolution test of metformin HCl was conducted both independently and in conjunction with omeprazole and lansoprazole under two gastrointestinal conditions. The study then assessed the quantitative impact of omeprazole and lansoprazole on a single dose of metformin HCl using UPLC analysis. The study results demonstrated that the availability and release percentage of metformin HCl in vitro increased in simulated gastrointestinal conditions when administered with lansoprazole and omeprazole. The dissolution profiles of metformin HCl reference and test batches in the simulated gastrointestinal fluid showed dissimilarity according to the fit factors *(f2* and *f1*). The ANOVA revealed significant results at a 95% CI ($P<0.05$) when comparing the mean percent release of metformin HCl. This confirms notable differences in the dissolution profiles between the reference and test batches in simulated gastrointestinal fluid. This in vitro metformin HCl, omeprazole, and lansoprazole drug-drug interaction study concluded that metformin HCl in vitro availability increases, which consequently affects bioavailability and could enhance the therapeutic efficacy of metformin HCl. Additional in vivo research is necessary to fully understand the clinical implications of this drug-drug interaction. It is recommended that the co-administration of metformin HCl with omeprazole and lansoprazole be closely monitored, and simultaneous intake of metformin HCl with omeprazole and lansoprazole be avoided.

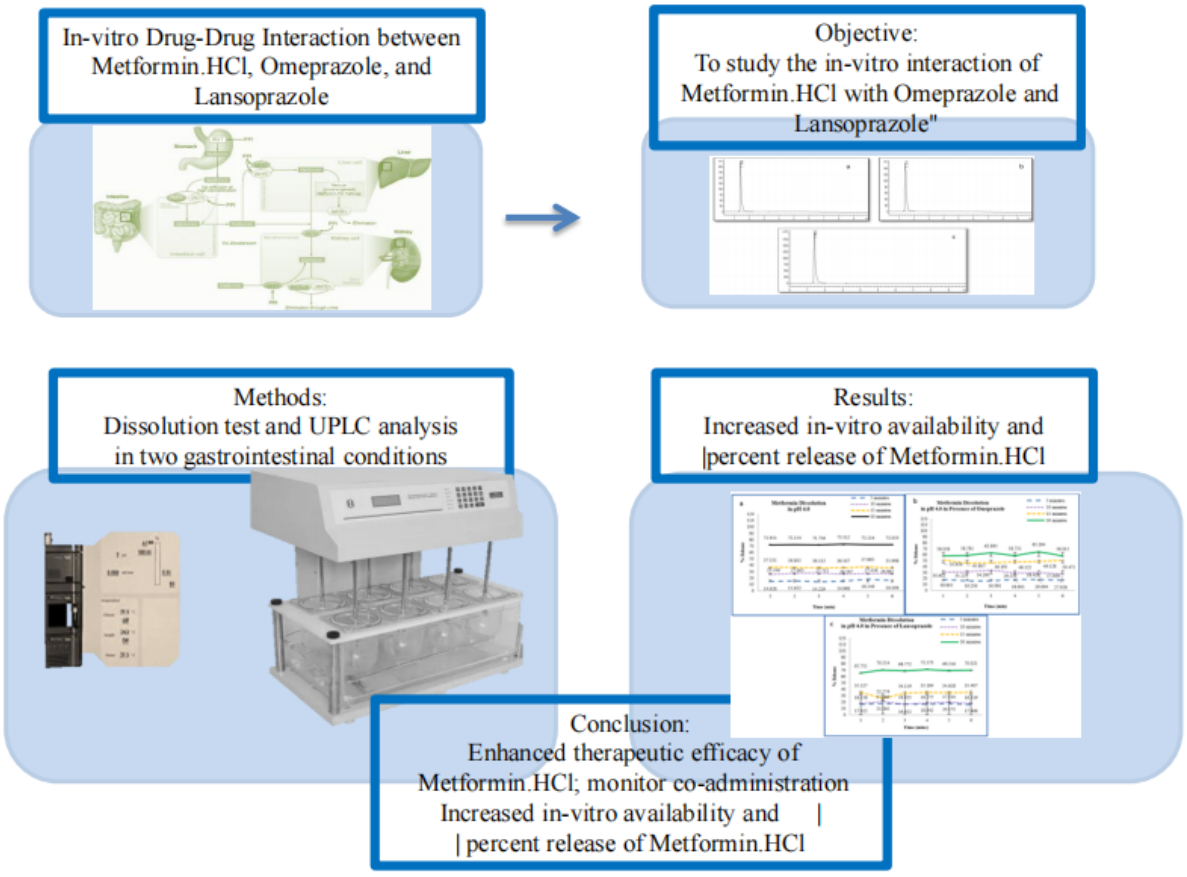
Keywords: metformin HCl, omeprazole, lansoprazole, UPLC.

盐酸二甲双胍与奥美拉唑和兰索拉唑的体外药物相互作用

摘要：盐酸二甲双胍是一种有效的口服降糖药，可用于控制2型糖尿病患者的血糖。通常需要将盐酸二甲双胍与奥美拉唑和兰索拉唑同时使用，以控制血糖并治疗胃食管反流病。这增加了盐酸二甲双胍与奥美拉唑和兰索拉唑发生药物相互作用的可能性。本研究通过溶出试

验和随后的超高效液相色谱分析评估了盐酸二甲双胍与奥美拉唑和兰索拉唑之间的体外药物相互作用。在两种胃肠道条件下，分别进行了盐酸二甲双胍的溶出试验以及与奥美拉唑和兰索拉唑联合进行的溶出试验。然后，该研究使用超高效液相色谱分析评估了奥美拉唑和兰索拉唑对单剂量盐酸二甲双胍的定量影响。研究结果表明，当与兰索拉唑和奥美拉唑一起服用时，在模拟胃肠道条件下盐酸二甲双胍的体外利用度和释放百分比增加。根据拟合因子（f2和f1），盐酸二甲双胍参考批次和测试批次在模拟胃肠液中的溶出曲线显示出差异。方差分析显示，在比较盐酸二甲双胍的平均释放百分比时，95%
CI（磷<0.05）的结果显著。这证实了盐酸二甲双胍参考批次和测试批次在模拟胃肠液中的溶出曲线存在显著差异。这项体外盐酸二甲双胍、奥美拉唑和兰索拉唑药物相互作用研究得出结论，盐酸二甲双胍体外可用性增加，从而影响生物利用度并可能增强盐酸二甲双胍的治疗效果。需要进行额外的体内研究才能充分了解这种药物相互作用的临床意义。建议密切监测盐酸二甲双胍与奥美拉唑和兰索拉唑的共同给药，并避免同时服用盐酸二甲双胍和奥美拉唑和兰索拉唑。

关键词：盐酸二甲双胍、奥美拉唑、兰索拉唑、超高效液相色谱。



Graphical Abstract. In vitro drug-drug interaction of metformin HCl with omeprazole and lansoprazole

1. Introduction

Metformin HCl (1,1-Dimethylbiguanide monohydrochloride) is an oral biguanide hypoglycemic drug mostly prescribed for diabetes mellitus type 2 patients [1]. It can be used as a single pharmacological agent or in combination with other antidiabetic drugs [2]. Metformin HCl is also commonly used for treating polycystic ovary syndrome, gestational diabetes, overweight, and cancer [3]. Generally, it works in the

gastrointestinal tract and minimizes glucose uptake and reduces gluconeogenesis in the liver simultaneously by increasing insulin reactivity, which enhances peripheral glucose uptake [2]. In the treatment of type 2 diabetes, many other medications are prescribed to address dyslipidemia, blood glucose control, hypertension, antiplatelet therapy, and GERD [4]. The issues surrounding drug-drug interactions and pharmacological treatment in clinical assessment are of particular concern when it comes to managing diabetes mellitus type 2 [5]. Patients with diabetes mellitus type 2 are at a higher risk of experiencing drug-drug interactions and drug-food interactions [6]. For the treatment of GERD, cisapride is given to patients with diabetes mellitus type 2, which has been removed from clinical use specifically for drug-drug interactions because it develops life-threatening drug-induced ventricular arrhythmia (torsades de pointes) with QT prolongation [4].

For the treatment of overweight type 2 diabetes mellitus patients, metformin HCl is generally prescribed as a first-line agent [7, 8]. Organic cation transporter 1 (OCT1) in the liver plays a crucial role in the metabolism of metformin HCl, leading to significant changes in its effects, and organic cation transporter 2 (OCT2) is found in the kidney, where it controls the renal elimination of metformin HCl [9]. GERD is common in diabetes mellitus type 2 patients [10]. In addition, gastrointestinal syndromes are associated with diabetes mellitus. As time progresses, the likelihood of developing gastrointestinal syndromes increases. At the same time, poor glycemic control is unconventionally related to gastrointestinal syndromes [11].

Consequently, concomitant intake of metformin HCl with omeprazole and lansoprazole is essentially needed to control blood glucose levels and treat gastrointestinal syndromes [12]. Co-administration of metformin HCl with omeprazole and lansoprazole should influence the essential therapeutic action of these agents [11, 13, 14]. On the other hand, omeprazole and lansoprazole are administered to reduce stomach acid. Omeprazole and lansoprazole are recommended and drugs of choice in GERD incidents [15]. Omeprazole and lansoprazole are commonly prescribed for GI diseases [16]. These medications inhibit OCT 1, which reduces the uptake of metformin HCl in the liver [9, 17]. The absorption of several drugs from the gastrointestinal tract is influenced by omeprazole and lansoprazole due to their impact on gastric pH [18].

It is recommended that the concurrent use of omeprazole and lansoprazole may alter the pharmacological action of each other. The objective of this study was to evaluate the potential quantitative impact of co-administering metformin HCl with omeprazole and lansoprazole, which may lead to undesirable drug-drug interactions. We analyzed the drug-drug interaction between metformin HCl and omeprazole and lansoprazole in simulated gastrointestinal fluid at different pH levels. This was achieved through the use of chromatographic techniques.

2. Materials and Methods

2.1. Reagents and Materials

KH_2PO_4 (potassium dihydrogen phosphate), NaOH (sodium hydroxide), KOH (potassium hydroxide), H_3PO_4 (orthophosphoric acid), ACN (acetonitrile), distilled water, metformin tablets (500 mg), lansoprazole capsules (30 mg), and omeprazole capsules (40 mg).

2.2. Procedure

Metformin HCl dissolution test was conducted in 1000 ml of dissolution medium under the condition of simulated gastric pH (buffer pH 4.0) with 50 RPM at 37±0.5°C for 60 min. From the dissolution medium at different times, the sample of 10 ml was withdrawn, and a similar fresh medium volume was replaced for sink condition retention at a similar temperature. The samples were withdrawn at 0-, 5-, 10-, 15-, 30-, 45-, and 60-min intervals. The withdrawn samples underwent filtration before being analyzed using UPLC. The mobile phase used for analysis consisted of 65 volumes of acetonitrile and 35 volumes of phosphate buffer (pH 5.75 was then adjusted with the use of 10% orthophosphoric acid) [19]. The UPLC analysis was performed utilizing a C-8 XDB column (150 mm × 4.6 mm, 5-µm particle size), with an injection volume of 5 µL, a flow rate of 1 mL/min, and a run time of 10 minutes. The chromatograms were obtained at 218 nm. The study involved conducting in vitro drug-drug interaction dissolution tests for Metformin HCl:

1. Dissolution test for the reference batch of Metformin HCl tablets (500 mg) with a sample size of n=6;
2. Dissolution test for the test batch of Metformin HCl tablets (500 mg) in combination with omeprazole with a sample size of n=6;
3. Dissolution test for the test batch of Metformin HCl tablets (500 mg) in combination with lansoprazole with a sample size of n=6.

A similar method with similar factors was conducted under simulated conditions of an intestine with 6.8 and 9.0 pH. In the UPLC studies, the following formula was used for the quantitative estimation of metformin HCl under varying conditions:

$$A_d = \frac{PA_t \times C_s \times V_D \times P}{PA_s \times V_s}$$

The amount of Metformin HCl (mg) released in the dissolution medium at time t (min) is A_d, the standard

amount of Metformin (mg) is A_s, the potency of the working standard is P, and the volume of the dissolution medium (1000 ml) is V_D. At time t, the test peak area (mAu) is represented as PA_t, while the standard peak area (mAu) is denoted as PA_s. The volume of solvent in ml required for dissolving the standard amount is V_s.

2.3. Dissolution Profile Comparison

Dissolution profiles of the test and control batches of metformin HCl were evaluated with the use of fit factors (*f1* and *f2* factors). The experimental data in the fit factors were analyzed by fitting difference factors (*f1*) and similarity factors (*f2*) [20]. The use of *f2* and *f1* factors for dissolution profile comparison is recognized and widespread by the FDA [21]. It is a simple way to comprehend accurate results [22]. Generally, *f2* is presented as the logarithmic reciprocal square root transformation of the sum of square errors. It indicates the sameness among the dissolution curves by evaluating the similarity in their percentage dissolution, while *f1* indicates the relative error between two curves.

$$f_1 = \left\{\left[\sum_{n=1}^{n} |R_t - T_t|\right] \Big/ \left[\sum_{n=1}^{n} R_t\right]\right\} * 100$$

where:

n - number of time points

R_t - percent release of reference batch at time t in dissolution test

T_t - percent release of test batch at time t in dissolution test

$$f2 = 50 \times \log\left(\frac{100}{\sqrt{1 + \frac{\sum(R_t - T_t)^2}{N}}}\right)$$

where:

T_t - percent release of test batch at time i in dissolution studies

R_t - percent release of the reference batch at the time of dissolution studies

N - number of time points

When selecting test and reference samples for comparison, it is crucial to ensure that they have the same time points. The required percent release is measured at three time points at minimum. The value of zero should be excluded when calculating the *f1* and *f2* factors [23]. The similarity between reference and test dissolution profiles can be determined by calculating the *f2* value, with values falling between 50 and 100 indicating identical profiles. Conversely, if the *f2* value is less than 50 and the *f1* value falls between 0 and 15, the dissolution curves are considered non-identical. In this case, the test and reference dissolution profiles are equivalent. However, if the *f1* value exceeds 15, the release from the sample batch should be rejected as the dissolution profiles will not be considered identical [21].

All statistical analyses were performed using SPSS Version 21. A comparison was conducted between a simulated gastric fluid with a pH of 4.0 and simulated intestinal fluids with pH levels of 6.8 and 9.0. At 95% C.I, the percent release mean value was calculated and then assessed using ANOVA [24]. Furthermore, after conducting an ANOVA, Tukey's and the Games-Howell post-hoc tests were utilized to determine the appropriate groups for evaluating the specific differences in concrete.

3. Results and Discussion

Metformin HCl standards were analyzed using ultra-performance liquid chromatography, with elution at 218 nm. Peaks were observed for metformin HCl in the simulated gastrofluid and intestinal fluid (Fig. 2).

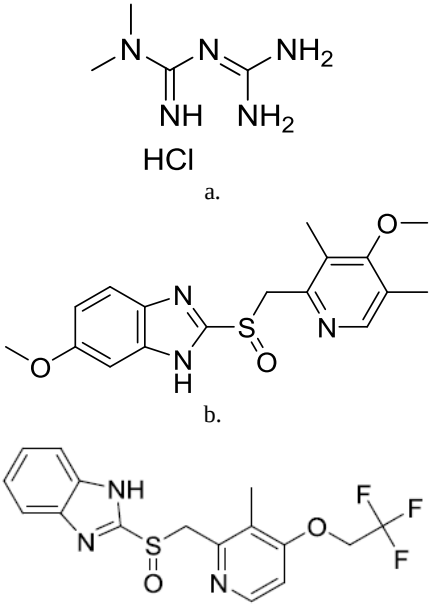


Fig. 1 a. Structure of metformin HCl, b. structure of omeprazole, c. structure of lansoprazole (The authors)

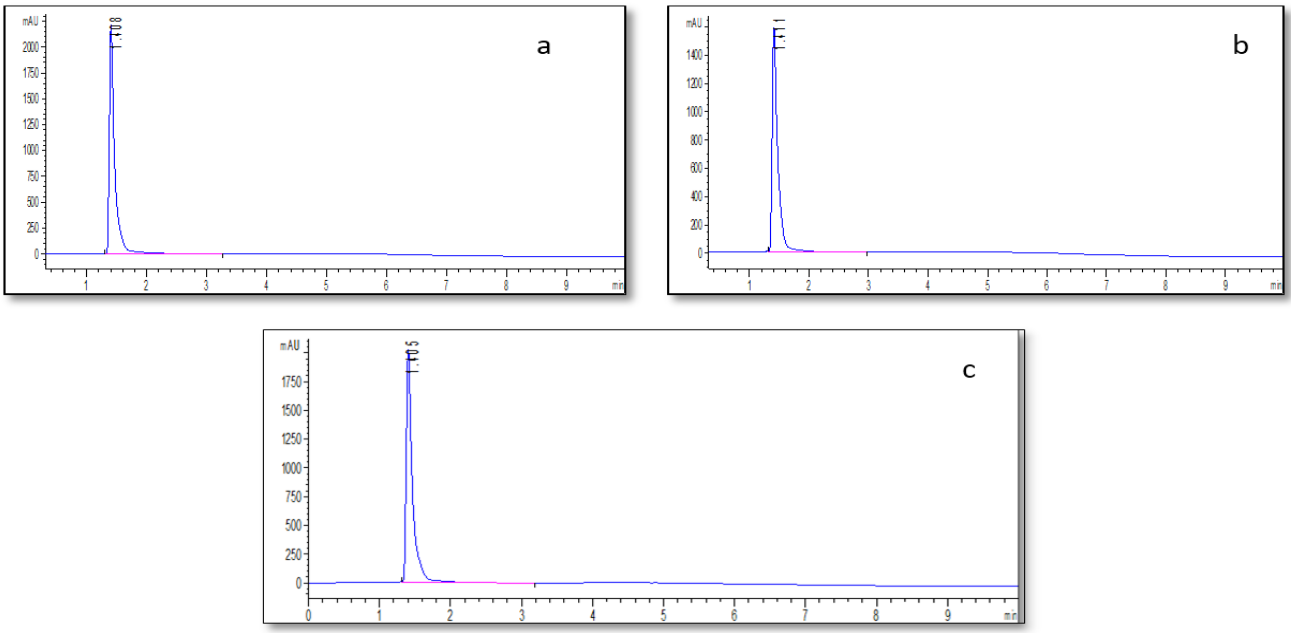


Fig. 2 UPLC chromatogram of Metformin HCl in various simulated fluids: (a) in simulated gastric fluid with a pH of 4.0, Metformin HCl has a retention time of 1.408 minutes; (b) in simulated intestinal fluid with a pH of 6.8, the retention time is 1.411 minutes; (c) in simulated intestinal fluid with a pH of 9.0, the retention time is 1.405 minutes (The authors)

The presence of lansoprazole and omeprazole significantly enhanced the release of metformin HCl in simulated intestinal fluid, as opposed to the release of metformin HCl alone in simulated gastric fluid. The study examined the release of Metformin HCl both alone and in combination with omeprazole and lansoprazole in simulated gastric fluid at a pH of 4.0. Results showed that Metformin HCl took 60 minutes for complete release in the simulated gastric fluid. The presence of omeprazole and lansoprazole did not affect the release of Metformin HCl in the same conditions (Table 1). The complete release of metformin HCl + omeprazole and metformin HCl + lansoprazole was observed within 30 minutes in simulated intestinal fluid with pH levels of 6.8 and 9.0. In contrast, the reference batch required 60 minutes for complete release; thus, the dissolution time of metformin HCl is reduced by one hour compared with the reference batch in intestinal fluid with a pH of 6.8 (Table 2). Furthermore, the dissolution time of metformin HCl was found to be comparable in both pH 9.0 and pH 6.8 dissolution mediums, with half an hour remaining before reaching complete release when compared to the reference batch of metformin HCl (Table 3). At pH 4.0, similarities were observed in the *f2* values of the release profiles of the test and reference batches. The *f1* value provides the equivalence between dissolution curves of the release profiles of the test and reference batches in the simulated gastric fluid. In pH 6.8 and 9.0 (i.e., simulated intestinal fluid), the *f2* values show dissimilarities in the release profiles of the test and reference batches. The *f1* value confirms the distinction between the release profiles of the reference and test batch dissolution curves (Table 4). For statistical calculations, SPSS (Version 21) was used. The tests used for one-way analysis of variance included post hoc Tukey's and the Games-Howell tests to assess the significance among means. At a 95% CI (P<0.05), there were significant differences between the release profiles of the reference and test batches (Table 5).

Table 1 Release percentage of metformin HCl in simulated gastric fluid at pH 4.0 (The authors)

Simulated gastric fluid (pH 4.0)			
Min	**Release Percentage of MET**	**Release Percentage of MET with OMZ**	**Release Percentage of MET with LNZ**
0	0	0	0
5	15.602±1.405	17.527±1.231	16.758±0.441
10	26.876±0.934	30.497±2.181	18.714±1.721
15	36.675±0.749	48.447±2.145	33.373±3.751
30	72.193±0.534	60.286±3.050	69.201±1.906
45	94.362±1.963	88.240±1.589	85.310±0.831
60	103.025±2.371	101.689±0.639	9.9.679±1.822

Table 2 Release percentage of metformin HCl in simulated intestinal fluid at pH 6.8 (The authors)

Simulated Intestinal Fluid (pH 6.8)			
Min	**Release Percentage of MET**	**Release Percentage of MET with OMZ**	**Release Percentage of MET with LNZ**
0	0	0	0
5	26.608±0.786	27.573±0.974	26.745±1.089
10	46.468±1.364	51.005±0.574	48.756±1.491

15	54.138±1.648	91.489±0.507	84.227±1.294
30	75.179±1.164	105.022±1.492	101.267±5.148
45	94.767±1.132	-	-
60	103.257±1.927	-	-

Table 3 Release Percentage of metformin HCl in simulated intestinal fluid at pH 9.0 (The authors)

Simulated Intestinal Fluid (pH 9.0)			
Min	**Release Percentage of MET**	**Release Percentage of MET with OMZ**	**Release Percentage of MET with LNZ**
0	0	0	0
5	26.929±0.609	27.573±0.974	27.898±0.657
10	47.200±0.675	51.005±0.574	47.492±0.608
15	65.508±0.306	91.489±0.507	87.103±0.259
30	88.113±1.496	105.022±1.492	101.417±1.195
45	92.038±0.953	-	-
60	103.061±1.130	-	-

Table 4 *f1* (difference factor) and *f2* (similarity factor) (The authors)

	Simulated gastric fluid (pH 4.0)		**Simulated intestinal fluid (pH of 6.8)**		**Simulated intestinal fluid (pH of 9.0)**	
	MET+OMZ	**MET+LNZ**	**MET+OMZ**	**MET+LNZ**	**MET+OMZ**	**MET+LNZ**
f2	55.464	68.283	37.348	37.397	42.684	20.785
f1	19.313	10.317	28.183	28.955	47.162	15.876

Table 5 The different superscripts in a row indicate significance variations in the mean values, which are presented as triplicate mean ± SD (The authors)

Simulated gastric fluid (pH 4.0)			
Min	**Release Percentage of MET**	**Release Percentage of MET with OMZ**	**Release Percentage of MET with LNZ**
0	0	0	0
5	15.602^{a}±1.405	17.527^{b}±1.231	$16.758^{a,b}$±0.441
10	26.876^{a}±0.934	30.497^{a}±2.181	18.714^{b}±1.721
15	36.675^{a}±0.749	48.447^{b}±2.145	33.373^{a}±3.751
30	72.193^{a}±0.534	60.286^{b}±3.050	69.201^{a}±1.906
45	94.362^{a}±1.963	88.240^{b}±1.589	85.310^{c}±0.831
60	103.025^{a}±2.371	101.689^{a}±0.639	99.679^{a}±1.822
Simulated intestinal fluid (pH 6.8)			
0	0	0	0
5	26.608^{a}±0.786	27.573^{a}±0.974	26.745^{a}±1.089
10	46.468^{a}±1.364	$51.005^{a,b}$±0.574	48.756^{b}±1.491
15	54.138^{a}±1.648	91.489^{b}±0.507	84.227^{b}±1.294
30	75.179^{a}±1.164	105.022^{b}±1.492	101.267^{b}±5.148
45	94.767±1.132		
60	103.257±1.927		
Simulated intestinal fluid (pH 9.0)			
0	0	0	0
5	26.929^{a}±0.609	27.573^{a}±0.974	27.898^{a}±0.657
10	47.200^{a}±0.675	51.005^{b}±0.574	47.492^{a}±0.608
15	65.508^{a}±0.306	91.489^{b}±0.507	87.103^{c}±0.259
30	88.113^{a}±1.496	105.022^{b}±1.492	101.417^{c}±1.195
45	92.038±0.953	-	-
60	103.061±1.130	-	-

This in vitro study suggests that the combination of metformin HCl with omeprazole and lansoprazole has a significant impact on in vitro availability due to fluctuations in dissolution time, ultimately affecting the therapeutic efficacy of metformin HCl. In simulated gastric fluid at pH 4.0, metformin HCl and metformin HCl + omeprazole were completely released within 60 minutes, indicating a similar in vitro release rate of metformin HCl in both reference and test batches. However, the percentage release of metformin HCl varied over time. Table 1 and Fig. 3 and 4 illustrate the differences in percent release between reference and test batches. Additionally, the presence of lansoprazole also impacted the in vitro availability of the reference at each time interval (Table 1). Omeprazole and lansoprazole are acid-labile drugs. When exposed to gastric fluid with a pH of 4.0, neither omeprazole nor lansoprazole stimulated the release rate of metformin HCl [25]. The test batches' *f2* values, as presented in Table 4, indicate that they are greater than 50. This suggests that the reference and test batches exhibit similar release profiles. However, the *f1* value for metformin HCl + omeprazole, also shown in Table 4, is not close to 0. This proves that the dissolution curves of the reference and test batches are dissimilar. On the other hand, in the simulated gastric fluid from Table 4, the *f1* value for metformin HCl + lansoprazole is 10.317, which is near 0. This result demonstrates the equality in release profiles and dissolution profiles of the reference and test batches.

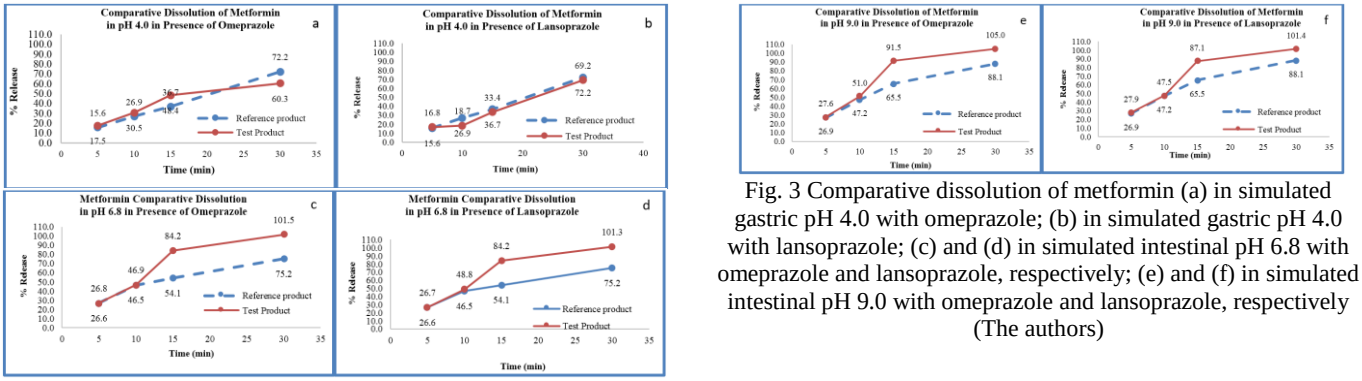


Fig. 3 Comparative dissolution of metformin (a) in simulated gastric pH 4.0 with omeprazole; (b) in simulated gastric pH 4.0 with lansoprazole; (c) and (d) in simulated intestinal pH 6.8 with omeprazole and lansoprazole, respectively; (e) and (f) in simulated intestinal pH 9.0 with omeprazole and lansoprazole, respectively (The authors)

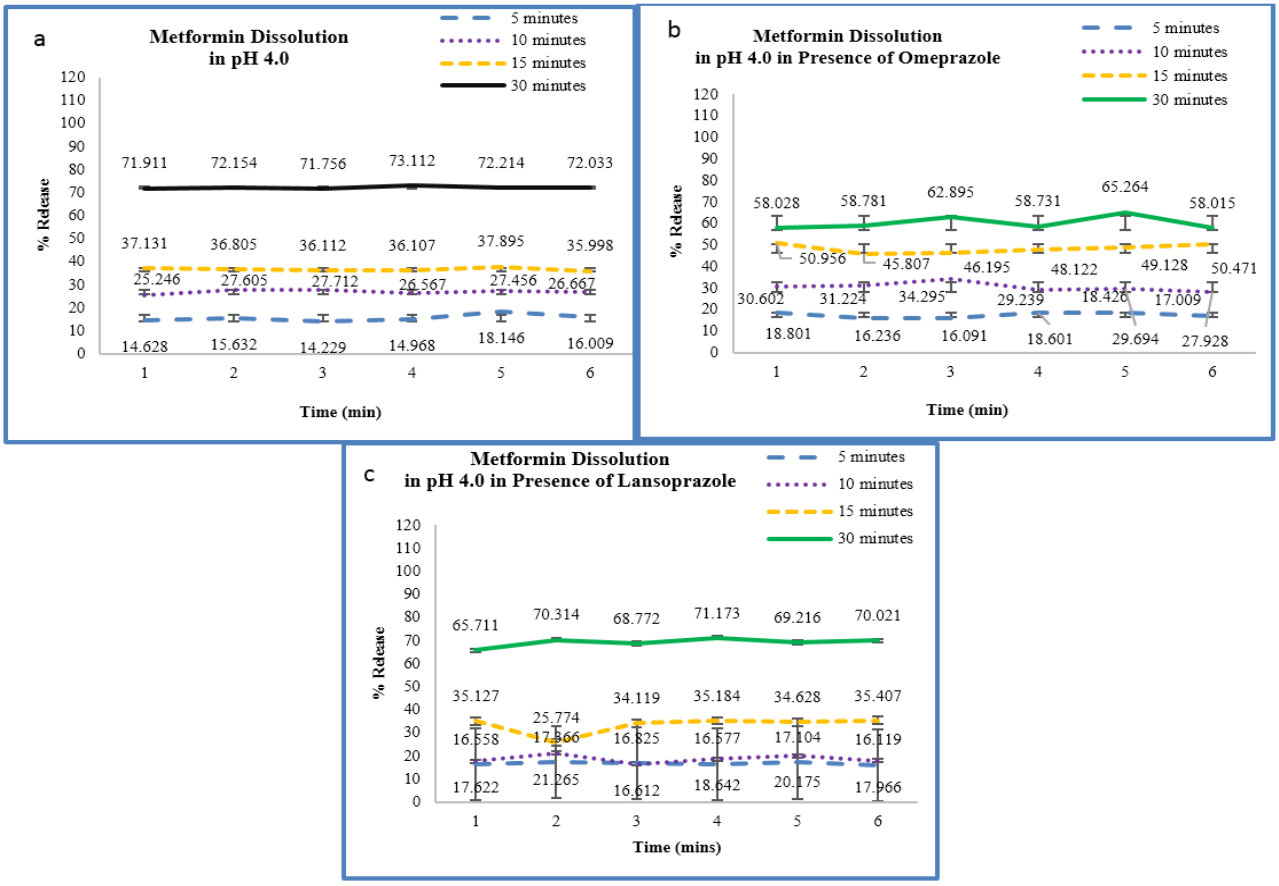


Fig. 4 Dissolution profiles of metformin in simulated gastric fluid at pH 4.0: (a) metformin alone; (b) metformin in the presence of omeprazole; (c) metformin in the presence of lansoprazole (The authors)

In simulated intestinal fluid with a pH of 6.8, it was observed that metformin HCl, when combined with omeprazole, was completely released within 30 minutes. This is in contrast to the reference batch of Metformin HCl, which took 60 minutes to be completely released in the same medium. The dissolution period decreased to 30 minutes when metformin HCl was combined with omeprazole, as compared to metformin HCl alone. Table 1 and Fig. 3 and 4 illustrate the changes in the percentage release of metformin HCl with omeprazole and metformin HCl alone. At 10 minutes, a similar dissolution time for metformin HCl release was observed in the presence of omeprazole in a dissolution medium with an intestinal pH of 6.8. However, at 15 minutes, differences in the percentage release of metformin HCl were noted. Specifically, 91.489%±0.507% of the test batch was released, while only 54.138%±1.648% of the reference batch metformin HCl was released. According to Table 2, the percentage release of metformin HCl in the reference batch at 30 minutes was 88.113%±1.496%. The complete release of metformin HCl in the test batch was 105.022%±1.492%. The research findings indicate that metformin HCl is released more rapidly in combination with omeprazole. Specifically, metformin HCl in a pH 6.8 solution (simulated intestinal fluid) was completely released earlier than the reference batch.

Fig. 3 and 5 and Table 2 demonstrate that omeprazole and lansoprazole have a significant impact on the in vitro release of metformin HCl. The percentage of release within 30 minutes in a dissolution medium with a pH of 6.8 is increased. Additionally, there is a considerable variance observed in the in vitro dissolution profiles of metformin HCl at each time interval. As indicated in Table 4, the *f2* values for

metformin HCl + omeprazole and metformin HCl + lansoprazole are below 50, specifically 37.348 and 37.397, respectively. This demonstrates that the reference and test batches exhibit distinct dissolution release profiles [26]. Furthermore, the *f1* values in Table 4 are not close to 0 for the test batches, supporting the conclusion drawn from the *f2* factor and confirming the differing dissolution release profiles [26].

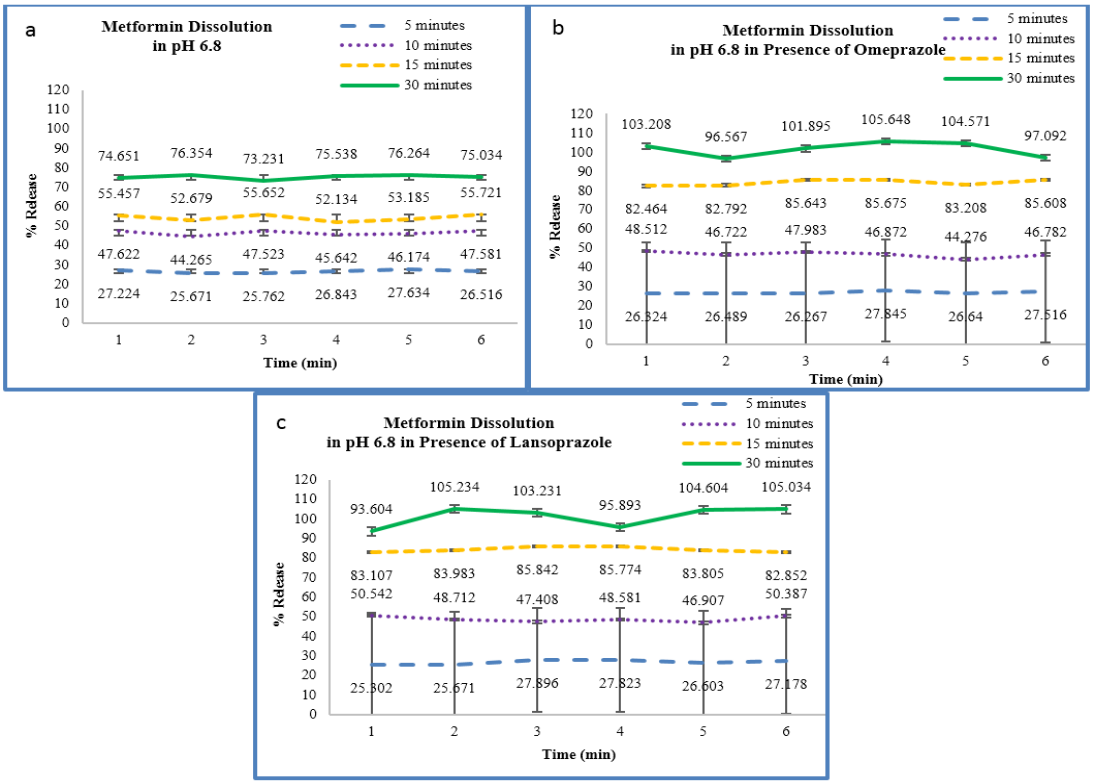


Fig. 5 Dissolution profiles of metformin in simulated intestinal fluid at pH 6.8: (a) metformin alone; (b) and (c) metformin in the presence of omeprazole and lansoprazole, respectively (The authors)

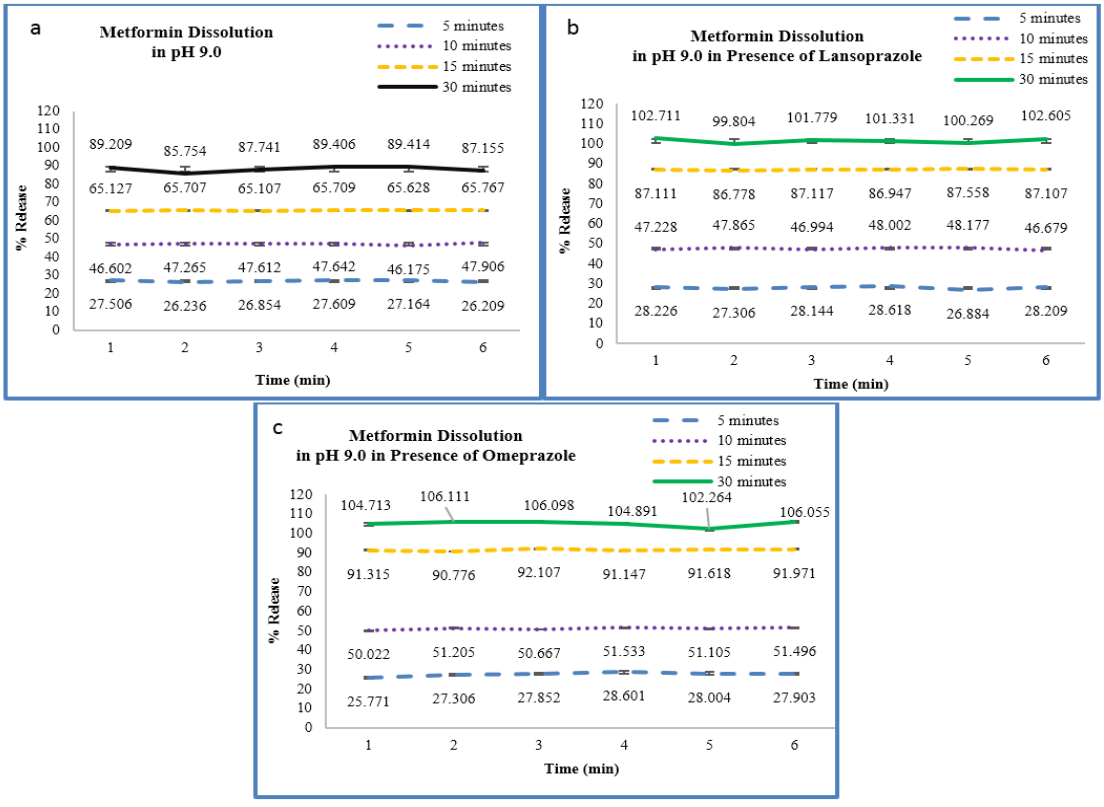


Fig. 6 Dissolution profiles of metformin in simulated intestinal fluid at pH 9.0: (a) metformin alone; (b) and (c) metformin in the presence of lansoprazole and omeprazole, respectively (The authors)

The release of metformin HCl was significantly increased in the presence of omeprazole and

lansoprazole in a simulated pH of 9.0, as compared to the reference batch. Table 4 illustrates the difference in the release profile of metformin HCl between the reference batch and when combined with lansoprazole and omeprazole.

SPSS (Version 21) was utilized for statistical calculations. A statistical analysis of variance was conducted at a significance level of 0.05 to assess the significance of the mean values of Metformin HCl dissolution results. This evaluation was performed on the reference batch and in the presence of omeprazole and lansoprazole in pH 4.0 simulated gastric fluid at various time intervals (Table 5). The results of the ANOVA at 5 minutes indicated significant variations among the mean values of release profiles of the reference and test batches containing metformin HCl + omeprazole. Conversely, at 5 minutes, the test batch containing metformin HCl + lansoprazole demonstrated substantial similarities with the reference batch and the batch containing metformin HCl + lansoprazole. Although the analysis of variance test did not yield specific proposals for group sets with differences, Tukey's test was employed to identify significant differences between the group sets. This test was applied to the set of groups with considerable variations in mean values [27]. At a 10-minute interval, Tukey's test at a significance level of 0.05 revealed significant variations in the mean values of the release profiles between the reference and test batches containing metformin HCl + lansoprazole. However, at the same interval, the reference and test batches containing metformin HCl + omeprazole showed significant similarities. At 15 minutes, Tukey's test at a significance level of 0.05 indicated significant dissimilarities between the mean values of the release profiles of the reference and test batches containing metformin HCl + omeprazole, while showing significant similarities between the reference and test batches containing metformin HCl + lansoprazole. At a 30-minute interval, Tukey's test at a significance level of 0.05 demonstrated considerable variation in the average mean values of the release profiles between the reference and test batches containing metformin HCl + omeprazole, with significant similarities observed between the reference and test batches containing metformin HCl + lansoprazole. At a 45-minute interval, Tukey's test at a significance level of 0.05 showed significant variation in the average mean values of the release profiles between the reference and test batches. At 60-minute intervals, implementing the Games-Howell test at a significance level of 0.05 revealed remarkable similarities between mean values of the release profiles of the reference and test batches.

Furthermore, Tukey's test was conducted at a significance level of 0.05 to assess the similarities in the mean values of metformin HCl release profiles between the test and reference batches in intestinal fluid with a pH of 6.8 at various time intervals. The results of Tukey's test at 5 minutes indicated significant similarities between the release profiles of the reference and test batches. However, at 10 minutes, significant variations were observed among the mean values of the release profiles of metformin HCl in the test batches containing lansoprazole and omeprazole, compared to the reference batch. At 15 minutes, both test batches exhibited significant similarities in their mean release profile values. The Games-Howell test at 30 minutes and a significance level of 0.05 revealed notable differences in the mean values of release profiles between the test and reference batches. At 30 minutes, the mean release profiles of metformin HCl combined with omeprazole and lansoprazole showed significant similarities to the reference batch.

Tukey's test was conducted at the 0.05 significance level to assess the similarity of metformin HCl release profiles at different time intervals in simulated intestinal fluid at pH 9.0. At 5 minutes, the test revealed significant similarities between the release profiles of the reference and test batches. However, at 10 minutes, notable differences were observed between the average mean values of the reference and test batches containing metformin HCl and omeprazole, while significant similarities were found between the reference and test batches containing metformin HCl and lansoprazole. Further analysis at 15 and 30 minutes showed significant differences among the mean values of the release profiles of the reference and test batches. Both test batches exhibited significant differences in the mean value of release profiles at 15 minutes.

The current in vitro studies on drug-drug interaction recommend prohibiting concomitant intake of metformin with omeprazole and lansoprazole.

4. Conclusion

This study determined in vitro drug-drug interaction between metformin HCl with omeprazole and lansoprazole by applying a dissolution test followed by UPLC analysis. Drug-drug interaction studies confirmed a reduction in dissolution time and considerable dissimilarity in the in vitro release profiles of metformin HCl at every time interval. This drug-drug interaction may lead to the development of severe ADRs. Prior research has shown that taking metformin HCl together with omeprazole and lansoprazole can impact the effectiveness of these medications. However, to confirm and approve the presence of in vivo drug-drug interactions between metformin and selected PPIs (omeprazole and lansoprazole), it is recommended that future research be conducted on in vivo drug-drug interactions.

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