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Studies of Interactions of Valsartan, Glimepiride and Ciprofloxacin HCl by DSC and HPLC

Mohammad Farhadur Rahman[1], Md. Abdus Salam[1], Asma Rahman[2] and Md. Zakir Sultan[2]

[1]Department of Chemistry, University of Dhaka, Dhaka-1000, Bangladesh
[2]Centre for Advanced Research in Sciences, University of Dhaka, Dhaka-1000, Bangladesh

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Abstract

This article deals with the results of *in vitro* interactions among glimepiride, ciprofloxacin HCl and valsartan at the molar ratio of 1:1:1 by DSC and HPLC method. The DSC thermogram of the mixture (glimepiride, ciprofloxacin HCl and valsartan) showed different melting endotherm than the melting endotherm for standard valsartan, ciprofloxacin HCl and glimepiride. Since the melting endotherms of mixture and individual drugs were not identical, it demonstrated the presence of interactions among the drugs. This result was further verified by HPLC to observe their recovery range. The % recovery ranges were found as 25.33, 23.49 and 135.82% for glimepiride, ciprofloxacin HCl and valsartan, respectively. The abnormal percentage recovery range and peak areas fluctuation further indicated the interactions among glimepiride, ciprofloxacin HCl and valsartan.

Key words: Drug-Drug Interaction, Glimepiride, Ciprofloxacin HCl, Valsartan, DSC, HPLC.

Introduction

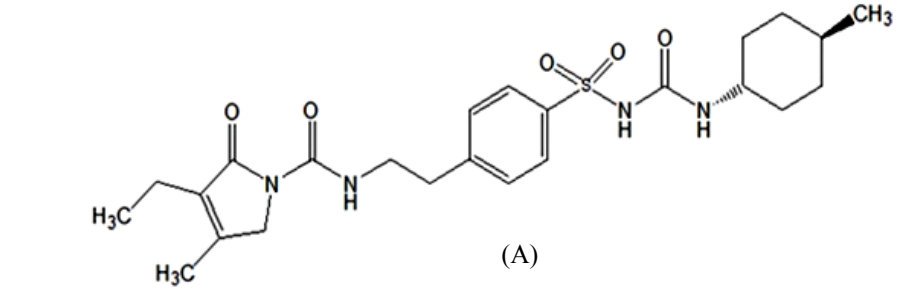
Concurrent administration of more than one drug is a common practice in medical science, although one drug may interact with another. This interaction may be either synergistic or antagonistic or may lead to toxic effects. However, interactions may also exist between drugs and foods (drug-food interactions). These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances (National Prescribing Service, 2009; Kristensen, 1976). Patients with diseases like kidney/heart transplantation or failure, diabetes mellitus and hypertension, anemia, bone and lipid disorders and so on are frequently prescribed numerous medications. Concomitant use of a large number of medications may have increased risks for drug-drug interactions. The effects of a moderate interaction may cause deterioration in the patient's clinical status, resulting in additional treatment, hospitalization, and/or an extended hospital stay or life-threatening or permanent damage (Brouwers, 1992; Hansten and Horn, 1989).

Knowledge of drug interactions may allow early recognition and prevention of adverse consequences. However, to take any step to manage the problems of informations the nature of interaction should be known (Ahsan *et al.*, 2011). For the drugs which are being used conventionally, interaction studies are also very important to detect the problems yet to be known.

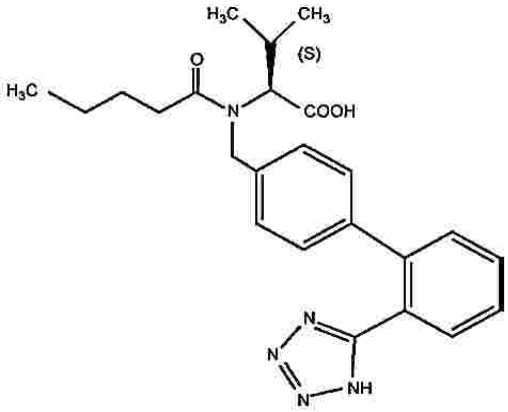
Now-a-days, it is common phenomenon that most of the patients are affected by hypertension, diabetic and infection at the same period of time. Glimepiride is frequently prescribed with ciprofloxacin HCl and valsartan for concomitant use in patients suffering from diabetes, infections and hypertension in Bangladesh. These drugs may exhibit effects independently or may interfere or interact with each other. Valsartan is widely used in treatment

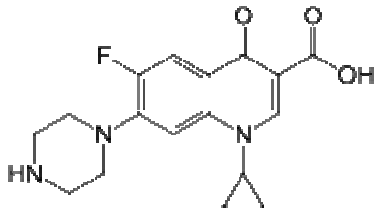
Correspondence to: Md. Zakir Sultan; Tel.: +880-2-9661900; extn-4722; E-mail: zakir.sultan@du.ac.bd
[Ψ]Present address: Department of Chemistry, Bangladesh University of Textiles, Dhaka-1208, Bangladesh

of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy (Criscione *et al.*, 1995; Psaty *et al.*, 1997; Cohn and Tognoni, 2001). Ciprofloxacin HCl is used to fight bacterial infections in the body. It is also used for the treatment of infections caused by specific pathogens known to be sensitive (Ahsan *et al.*, 2012). In 2010 over 20 million outpatient prescriptions were written for ciprofloxacin, making it as the 35th most commonly prescribed drug, and the 5th most commonly prescribed antibacterial, in USA (Müller *et al.*, 1995; Langtry and Balfour, 1998). The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. The structures of the drugs are shown in figure 1.



(A)





(B) (C)

Figure 1. Structure of glimepiride (A), valsartan (B) and ciprofloxacin HCl (C).

In his article, we report the drug-drug interactions of some commonly used drugs that are frequently prescribed in Bangladesh for the benefits of the patients by using DSC and HPLC, which are most commonly used to determine the drug-drug interactions (Pignatello and Francesco, 2011; Serafini *et al.*, 2012; Arayne *et al*., 2010).

Materials and Methods

Drugs and reagents: Working standards glimepiride (potency: 95.41%), ciprofloxacin HCl (potency: 94.23%) and valsartan (potency: 99.9%) were collected. HPLC grade acetonitrile, methanol and glacial acetic acid were purchased from Active Fine Chemicals Ltd., Dhaka, Bangladesh.

Instrumentation: Differential Scanning Calorimeter (DSC) (Model: DSC-60 WS, Shimadzu

Corporation, Japan) was used for recording DSC thermograms. HPLC (model: UFLC Prominence, Shimadzu Corporation, Japan) on Phenomenex C-18 (4.6 × 250 mm, 5 µm) column equipped with an auto sampler (Model-SIL 20AC HT) and UV-Visible detector (Model-SPD 20A) was used for the analyses. The data was recorded using LC-solutions software.

Experiment

DSC method: Five mg drug mixture (mixture of valsartan, glimepiride and ciprofloxacin HCl at a molar ratio of 1:1:1) was weighed and mixed properly to make a solid homogeneous mixture in a watch glass. From this mixture 2.70 mg was taken into aluminum pan and sealed properly, and the thermogram was taken from DSC 60, Shimadju, Japan. The temperature range of DSC runs for mixture and standards were 30 °C to 350 °C. Experiment was performed under nitrogen gas at a flow rate of 20 ml/ min and increase in temperature by 10°C/ min.

HPLC method: Twenty ml of acetic acid was taken and added into distilled water, and the solution was made up to 1000 ml to get the solution of 2% acetic acid. Then it was sonicated for 10 minutes. The chromatographic conditions was developed by using a C-18 bonded silica column (250 x 4.60 mm, 5µ, Phenomenex, Inc) with a mobile phase comprising of 2% acetic acid and acetonitrile (40:60, v/v) with flow rate 0.70 ml/min at wavelength of 240 nm.

Preparation of standard and sample solutions: Thirty mg of each drug was weighed and taken in a 100 mL volumetric flask. At first the drugs were dissolved separately in 50 ml mixture of acetonitrile and distilled water (50:50) and the volume was adjusted to 100 ml with the same solvent. The concentration of the each solution was 100 µg/ml. The stock solutions were diluted by serial dilution procedure to get the concentrations in the range of 80% - 120%. Five mg from the solid homogeneous mixture was taken into a test tube and dissolved in methanol. The sample mixture was filtered using 0.45 µm syringe filter. In the similar way the standard solutions were also prepared.

Calibration curve: To get the individual calibration curve of each drug, five different concentration levels (40, 45, 50, 55 and 60 µg/ml) were prepared from standard solution by 50% distilled water and 50% acetonitrile. Then 20µL from each solution was injected into the HPLC using autosampler and the analyses were monitored at 240 nm and repeated three times. The average peak areas were plotted against concentrations.

Results and Discussion

DSC method for drug-drug interaction analysis: The DSC is a reliable method for the study and detection of drug-drug interactions. The DSC thermograms of the mixture (glimepiride, ciprofloxacin HCl and valsartan) and individual drugs were carried out at the temperature range of 30°C to 350°C. The DSC thermograms of the mixture showed sharp melting endotherm at 104.13°C, 154.89°C and 290.07°C which corresponded to its melting with normalized energy of -1.14 mW/mg, -1.34 mW/mg and -2.26 mW/mg, respectively (Figure 2). The individual melting endotherms for valsartan, ciprofloxacin HCl and glimepiride were found at 117°C, 152.65°C and 213.85°C, respectively. The melting endotherms of the physical mixture and individual drugs were not identical which represented the identity of a different product. That means bond breaking and forming to yield a new product indicated the presence of strong drug interactions among the drugs.

HPLC method for drug-drug interaction analysis: The HPLC analytical condition for mixture and the individual drugs (glimepiride, valsartan and ciprofloxacin HCl) was developed by using the mobile phase (2% acetic acid and acetonitrile, 40:60 v/v) at a flow rate of 0.7 mL/min. The injection volume was 20 µL for standards and sample. Before analysis, every standard and sample was filtered through 0.45 µm filter tips. The mobile phase was also filtered, sonicated and degassed before use. The column eluate was monitored with a UV detector at 240 nm. All analyses were done at ambient temperature under isocratic conditions. The retention

times found for standard ciprofloxacin HCl, valsartan and glimepiride were at 2.77 ± 0.1 min, 8.58 ± 0.1 min and 13.81 ± 0.1 min, respectively.

Calculation of percentage (%) recovery: Linearity: The linearity of each drug was evaluated by using calibration curves to calculate the coefficient of correlation and intercept values. The calculated value for linearity from the calibration curve of ciprofloxacin HCl, valsartan and glimepiride were 0.9991, 0.9993 and 0.9981, respectively (Table 1, Figure 3).

The presence of interaction might be clear from the percentage recovery range of those drugs in the mixture. The % recovery ranges were found as 23.49%, 25.33% and 135.82% for ciprofloxacin HCl, glimepiride and valsartan, respectively. The abnormal recovery range might be due to chemical bonds broken in liquid stage of mixture drugs. This indicated interaction among the drugs.

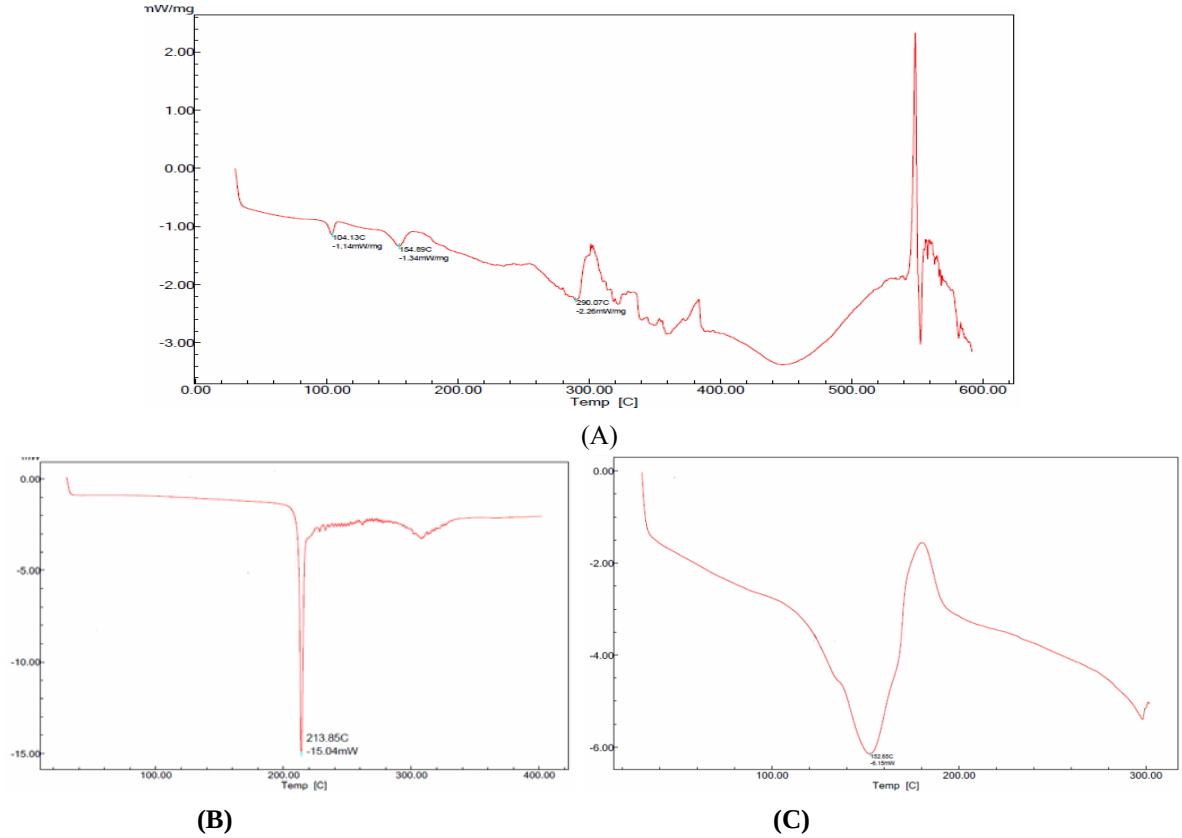
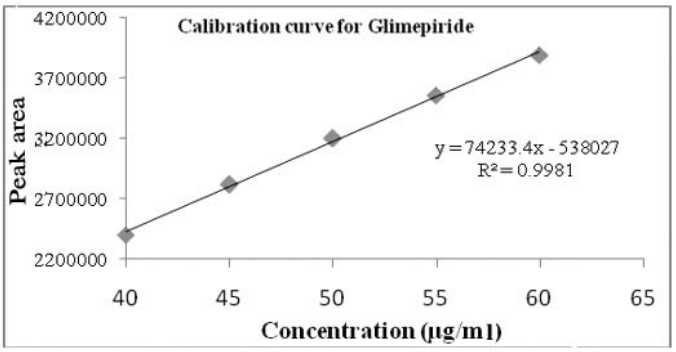


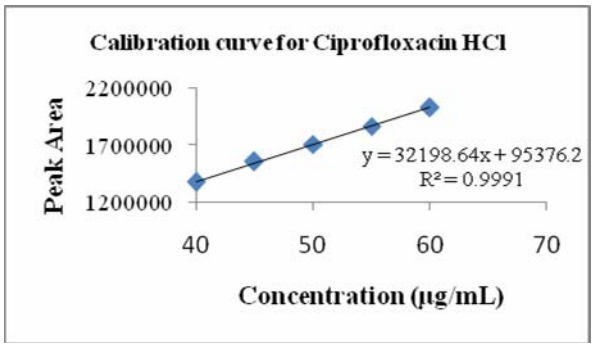
Figure 2**.** The DSC thermogram of the mixture (A), glimepiride (B) and ciprofloxacin HCl (C).

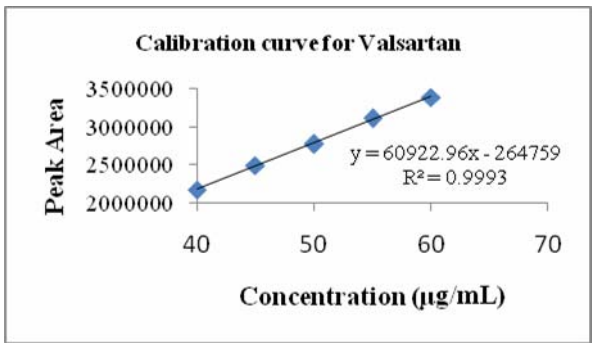
Table 1. Peak area at various concentrations for ciprofloxacin HCl, valsartan and glimepiride.

Concentration µg/ml	Peak area		
	Ciprofloxacin HCl	Valsartan	Glimepiride
40	1373846	2168012	2403059
45	1555455	2486791	2819468
50	1708820	2766916	3197840
55	1863761	3101487	3558440
60	2024659	3383738	3889408



(A)





(B) (C)

Figure 4. Calibration curve and linearity of glimepiride (A), ciprofloxacin HCl (B) and valsartan (C).

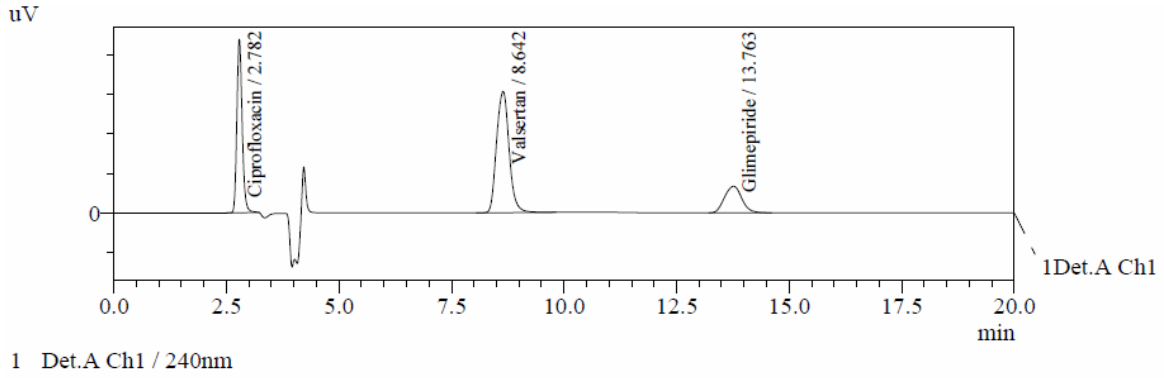


Figure 3. Chromatogram for mixture at 240 nm.

Conclusion

Knowledge of drug-drug interactions may allow early recognition and prevention of adverse consequences. The most comprehensive understanding of clinically significant drug interaction can be achieved by combining knowledge of the mechanism of drug interaction with recognition of the high-risk patients and the identification of drug with a narrow therapeutic index. Problems arising from the interaction of drugs may be overcome by partial changes in the molecular pattern, by blocking the reactive site in the molecule, by changing the dosage regimen or by avoiding the combined application of the interacting drugs. However, to take any step to manage the interaction problems, the nature of interaction should be known.

It is important to know the possible interactions of a new drug prior to use clinically. For drugs which are being used conventionally, interaction studies are also very important to detect the problems yet to be known.

In course of research works, the antidiabetic, antiinflammatory and antihypertensive drugs were used to study the interactions among the drugs. For detection of drug- drug interactions, reliable DSC and HPLC methods were used. The present study revealed a clear indication of interaction among glimepiride, valsartan and ciprofloxacin HCl in both DSC and HPLC method. However, this was a preliminary study and more extensive investigations should be conducted to have conclusive remarks.

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