

Determination of Release Mechanism from Multiple Coefficients & *in vitro* Release Kinetics of Metformin Hydrochloride alone and along with Herbal Sex Stimulants – Trends for Herb-Drug Interactions

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Abstract: Type-2 diabetes patients suffer from decreased libido in their early life; these patients take the oral hypoglycemic drug and herbal sex stimulant to control the diabetes as well as to increase the libido. The combined use of herbs and drugs has increased the possibility of herb-drug interactions. The study was undertaken to explore the herb-drug interactions. The investigation was done by *in vitro* dissolution test of Metformin HCl in absence or presence of herbal sex stimulants available in local market. Different mathematical models were adopted to explore the release kinetics. In this study higher percent release of Metformin HCl observed in presence of herbal sex stimulants, but the increase was not significant. The highest percentage of release was found at simulated intestinal medium pH 6.8 and at pH 4.5 in compared to simulated gastric medium pH 1.2 for Metformin HCl alone and Metformin HCl in presence of herbal sex stimulants. From the multiple coefficients determination data of Metformin HCl and Metformin HCl in presence Herbal Sex Stimulants it was observed that the Higuchi release kinetics was predominated at pH 1.2, but in case of pH 4.5 and 6.8, the first order release kinetics was predominated. Increased release pattern of Metformin HCl by administration of herbal sex stimulants gives better absorption, which gives us an idea that if we take these two drugs concurrently there will be no hazardous effect from each other.

Keywords: Metformin HCl; Herbal Sex Stimulants; multiple coefficients (r²); Release kinetics, herb-drug interactions.

1. Introduction

A drug interaction is a situation in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own. These may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances (Bushra R, Aslam N, Khan AY; 2011). Typically, interaction between drugs comes to mind (drug-drug interaction). However, interactions may also exist between drugs & foods (drug-food interactions), as well as drugs & herbs (drug-herb interactions). The mechanisms for drug interaction can be divided into several general categories: pharmacokinetics (absorption, distribution, metabolism, and excretion of a drug) and pharmacodynamic interactions (Barbara, 2006). In this research work Drug-herb interaction is concerned. Herbal medicines follow modern pharmacological principles. Drug-herbal interactions can occur at the pharmaceutical, pharmacodynamic or pharmacokinetic (PK) levels (Beijnen and Schellens, 2004) but most of the interactions occur at PK level (Brazier and Levine, 2003) that involves changes in absorption, distribution, metabolism and excretion of the conventional drug, which in turn determine the bioavailability of the drug. Conventional synthetic pharmaceuticals such as synthetic

corticosteroids, nonsteroidal anti-inflammatory drugs and other prescription drugs, potent drugs such as phenylbutazone, in fact examples of almost every therapeutic drug class have been found in certain herbal remedies as contaminants. A recent study by Ramsay et al. found that potent corticosteroids had been deliberately added to herbal creams in order increase their efficacy (Ramsay et al, 2003). This problem is widespread, and occurs in both Oriental and European countries (Segasothy and Samad, 1991; Chan et al., 1993; Anonymous, 1978, 1989, 1993) These “adulterated” herbal medicines sometimes result in serious ailments such as acute renal failure (De Smet, 1995; Abt et al., 1995; Nelson et al., 1995; Gertner et al., 1995; Van et al., 1994). This type of herb-drug interaction help us to see look forward regarding any type interaction at pharmacokinetics level when Metformin HCl given with herbal sex stimulants.

Metformin hydrochloride is 1,1-dimethyl-biguanide hydrochloride. Metformin hydrochloride is an oral anti-diabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function (Clinical Guidelines Task Force, 2005; National Collaborating Centre for Chronic Conditions, 2008.; American Diabetes Association, 2009). The medication

works in several ways. It reduces the amount of sugar made by the liver, limits the amount of sugar absorbed into the body from the diet, and makes insulin receptors more sensitive (helping the body respond better to its own insulin). All of these effects cause a decrease in blood sugar levels. Metformin HCl is typically taken one to three times a day and comes in several forms and strengths. It comes in tablet form, two different long-acting forms, and a liquid version. Herbal sex stimulants for Men contains a selection of herbs (John, 2007) from around the world and which are traditionally identified as having aphrodisiac properties and are safe and non-addictive. They are known for their supportive function in maintaining sexual health and well-being. Herbal sex stimulants for men is used for strong erections without risk of side effects, maintain sexual arousal, drive and desire, promotes systemic and hormonal balance. In this study we have observed release kinetics of Metformin HCl alone and along with Herbal Sex Stimulants with response to their multiple coefficients (r^2) to understand Herb-Drug interactions.

2. Materials, Methods and Equipments

2.1 Materials

Metformin HCl (designated as MH) tablets of one brand and the innovator brand with labeled contents of 500 mg and six different herbal sex stimulants (designated as H1, H2, H3, H4, H5, and H6) for men according to Bangladesh National Formulary of Unani Medicine were obtained from local market of Bangladesh. All the drugs were checked for their production and expiry dates. Double distilled water was used throughout the research. Other materials used for analysis were also purchased from local market and these were all analytical grade.

2.2 List of Equipments

Table 1

Sr. No	Name of Equipment
1	Electronic balance
2	USPDissolution apparatus - II
3	UVVisible spectrometer

2.3 Methods

a) Preparation of dissolution medium

Simulated gastric medium of pH 1.2 (0.1 N HCl), acetate buffer pH 4.5(0.1 M Acetic acid solution + 0.1 M Sodium acetate solution) and simulated intestinal medium pH 6.8 (Sodium hydroxide + potassium dihydrogen phosphate + 10% w/v solution of phosphoric acid) were prepared.

b) *In vitro* Dissolution studies of Metformin HCl alone and in presence of herbal sex stimulants

Dissolution studies were conducted according to USP method (USP XXII) using apparatus II paddle at a speed of 50 rpm and the temperature was maintained at $37 \pm 0.50^\circ\text{C}$. The total duration of dissolution was 6 hours in which the tablets were subjected to simulated gastric media (pH 1.2), acetate buffer media (pH 4.5), and simulated intestinal media (Buffer pH 6.8) in every separate experiment. After the medium was placed in the vessels, paddle rotation was

started and the system was allowed to equilibrate for 15 min. Each vessel, vessel position, and corresponding tablet result were assigned the same number. Thus, each sub sample of two tablets tested simultaneously, every individual tablet result was identified with a particular vessel and position. From the prepared medium, 900 ml of simulated gastric medium (0.1 N HCl pH 1.2) was placed in each vessel ($n=6$) and the apparatus was assembled. 500 mg Metformin HCl tablets were weighted and placed in the baskets as one tablet in each vessel. Five different Herbal sex stimulants were also weighted and placed in five different vessels with the metformin HCl tablet of 500 mg in such a way that the first vessel contain only Metformin HCl tablet of 500 mg. So one vessel contains only Metformin HCl tablet of 500 mg and other five vessels contain Metformin HCl tablet of 500 mg with one Herbal sex stimulant. (So one vessel contains the drug and the other five vessels contain the drug with herbal drug). Than the dissolution tester switched on, the temperature was $37 \pm 0.50^\circ\text{C}$ with rpm 50. The total dissolution time was 360 minutes. 5 ml sample were collected at 0min, 10min, 20 min, 30min, 40min, 50 min, 60min, 90min, 120min, 150 min, 180 min, 210 min, 240 min, 270 min, 300 min, 330 min, and 360 min and at the same time 5 ml of fresh dissolution medium were added to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at a wavelength of 233 nm for Metformin HCl by spectrophotometer (Shimadzu UV/Vis spectrophotometer 1700, Tokyo, Japan). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time (minutes) curve. By the above same method for simulated gastric medium (0.1 N pH 1.2), the dissolution test for acetate buffer (pH 4.5) and simulated intestinal medium (Buffer pH 6.8) were also performed.

2.4 Kinetics modeling of drug release

In vitro drug release data obtained from the dissolution studies of Metformin HCl tablets alone and in presence of Herbal sex stimulants were fitted to zero order, first order and Higuchi equation to ascertain the kinetic modeling of drug release. The multiple coefficients (r^2) were also determined for the best fit release kinetics.

2.4.1 Zero Order Kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disintegrate and release the active pharmaceuticals ingredients (API) slowly according to time and this can be represented by the following zero order rate kinetics (Wagner, 1969) :

$$Q_t = Q_0 + k_0 t$$

Where,

Q_t = amount of drug released in time 't',

Q_0 = initial amount of drug in the solution,

k_0 = zero order release constant

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used

to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs, coated form, osmotic systems, etc.

2.4.2 First Order Kinetics

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman. The following relation can express this model:

$$\text{Log } Q_t = \text{Log } Q_0 + kt/2.303$$

Where, Q_0 = initial amount of drug in the solution,

kt = first order release constant

Q_t = amount of drug released in time ' t ',

The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amounts of drug released by unit of time diminish.

2.4.3 Higuchi Model

Higuchi (Higuchi, 1963) developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$$f_t = kH \sqrt{t}$$

Where, kH = Higuchi diffusion constant,

f_t = fraction of drug dissolved in time ' t '.

Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

3. Results and Discussion

To investigate the release kinetics mechanism of Metformin HCl alone and Metformin HCl with herbal sex stimulants we performed dissolution study, which is an in vitro test to forecast the in vivo release phenomenon of Metformin HCl and Metformin HCl with herbal sex stimulants. From multiple coefficients we determined the release mechanism of Metformin HCl alone and Metformin HCl with herbal sex stimulants. Oral administration of Metformin HCl alone and concomitant administration of herbal sex stimulants might bring some relative change in release kinetics of Metformin HCl.

Release kinetics (Zero Order, First Order & Higuchi release kinetics) of Metformin HCl and Metformin HCl with herbal sex stimulants

In case of Zero order rate kinetics (cumulative amount of drug released versus time; Fig.-1) it was observed that the percent release of metformin HCl and metformin HCl in presence of herbal sex stimulants increased with time (minutes) and maximum percent release was found after 360

minutes (6 hours) at different simulated pH medium (pH 1.2; pH 4.5; and pH 6.8). Higher percent release of metformin HCl observed in presence of herbal sex stimulants.

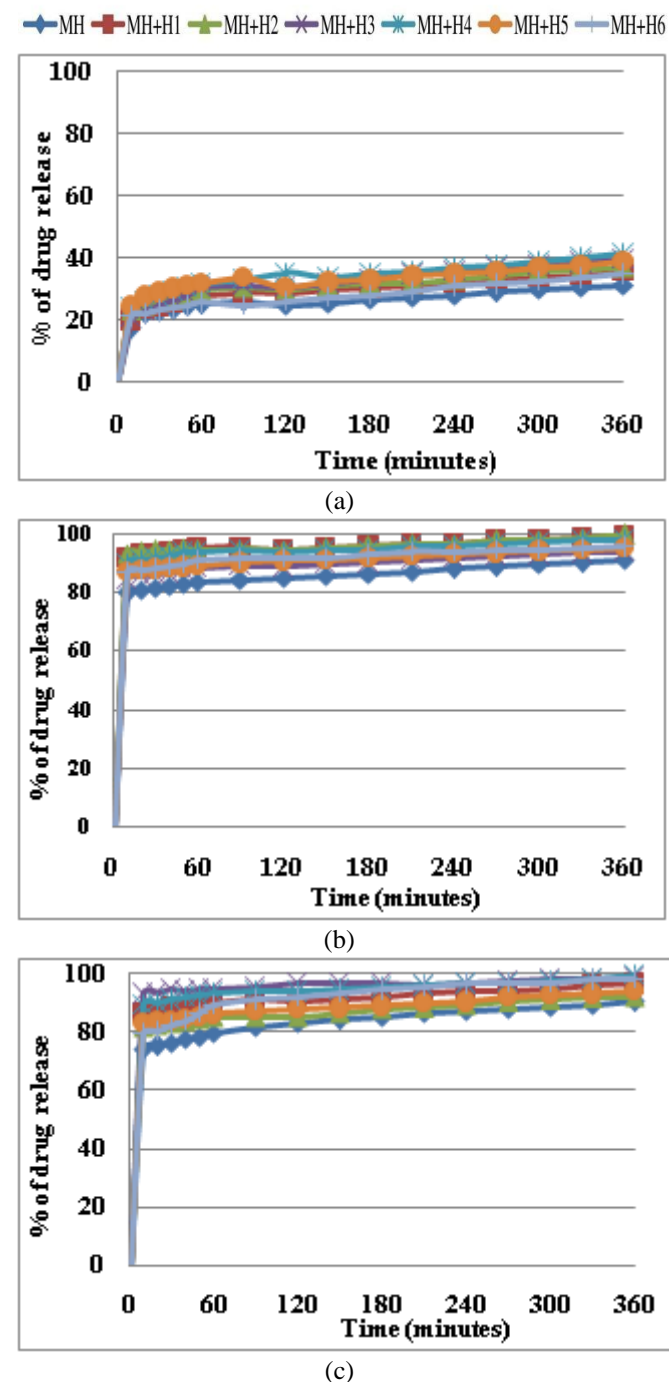


Figure 1: Zero order rate kinetics profiles of Metformin HCl (blue line) and Metformin HCl in presence of six Herbal Sex Stimulants (other six lines except the blue line) at pH 1.2 (a), pH 4.5 (b) and pH 6.8 (c) at the end of 360 minutes. Here the blue line slightly below the others six lines. Thus the percent release of Metformin HCl in presence of Herbal sex stimulants increased slightly at different pH (1.2, 4.5, & 6.8).

In case of First order rate kinetics (log cumulative percentage of drug remaining versus time; Fig.-2) it was observed that the log of percent remaining of Metformin HCl decreased more in presence of herbal sex stimulants and minimum value was found after 360minutes (6 hours) at different simulated pH medium (pH 1.2; pH 4.5; and pH 6.8). It was also observed the log of percent remaining of Metformin

HCl in presence of six Herbal Sex Stimulants lower than of Metformin HCl alone.

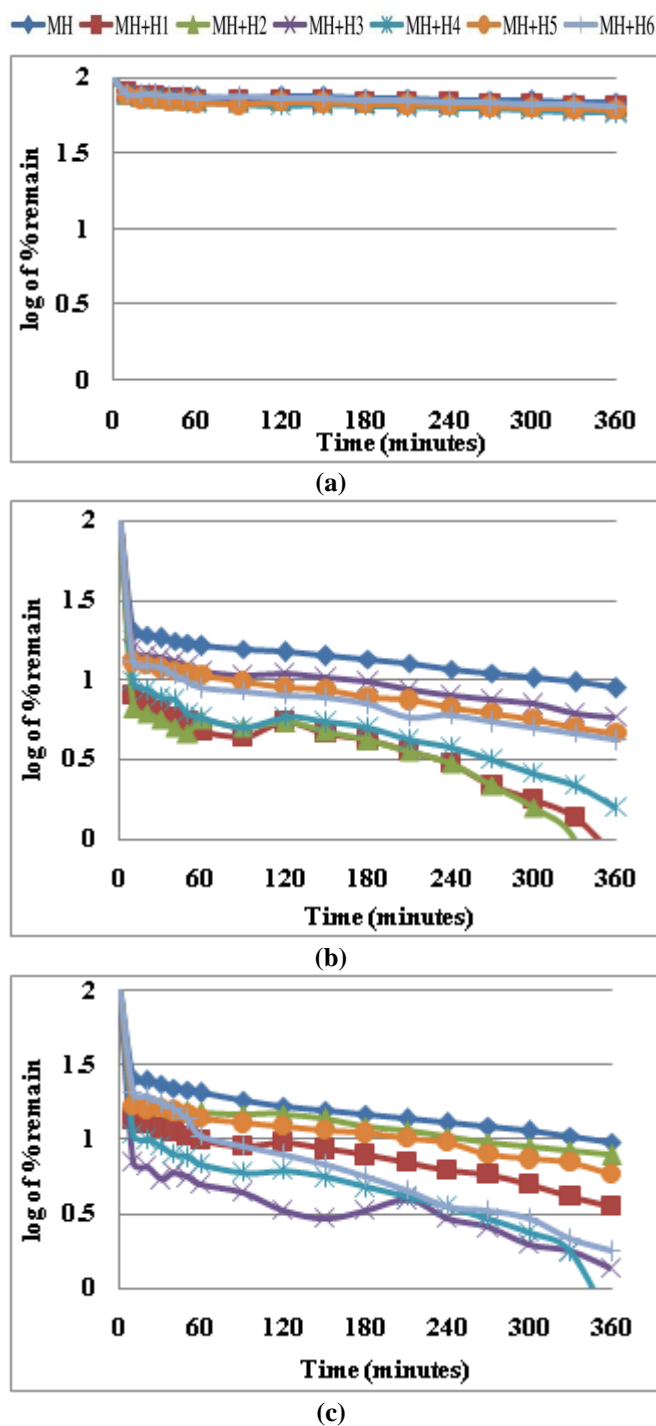


Figure-2: First order rate kinetics profiles of Metformin HCl (blue line) and Metformin HCl in presence of six Herbal Sex Stimulants (other six lines except the blue line) at pH 1.2 (a), pH 4.5 (b) and pH6.8 (c). There is slight difference in log of percent (%) remaining in presence of herbal sex stimulants with Metformin HCl.

In case of Higuchi release kinetics (cumulative percentage of drug released versus square root of time; Fig.-3) it was observed that the percent release of metformin HCl and metformin HCl in presence of herbal sex stimulants increased with square root of time (minutes) and maximum percent release was found after 360 minutes (6 hours) at

different simulated pH medium (pH 1.2; pH 4.5; and pH 6.8). Higher percent release of metformin HCl observed in presence of herbal sex stimulants than that of metformin HCl alone.

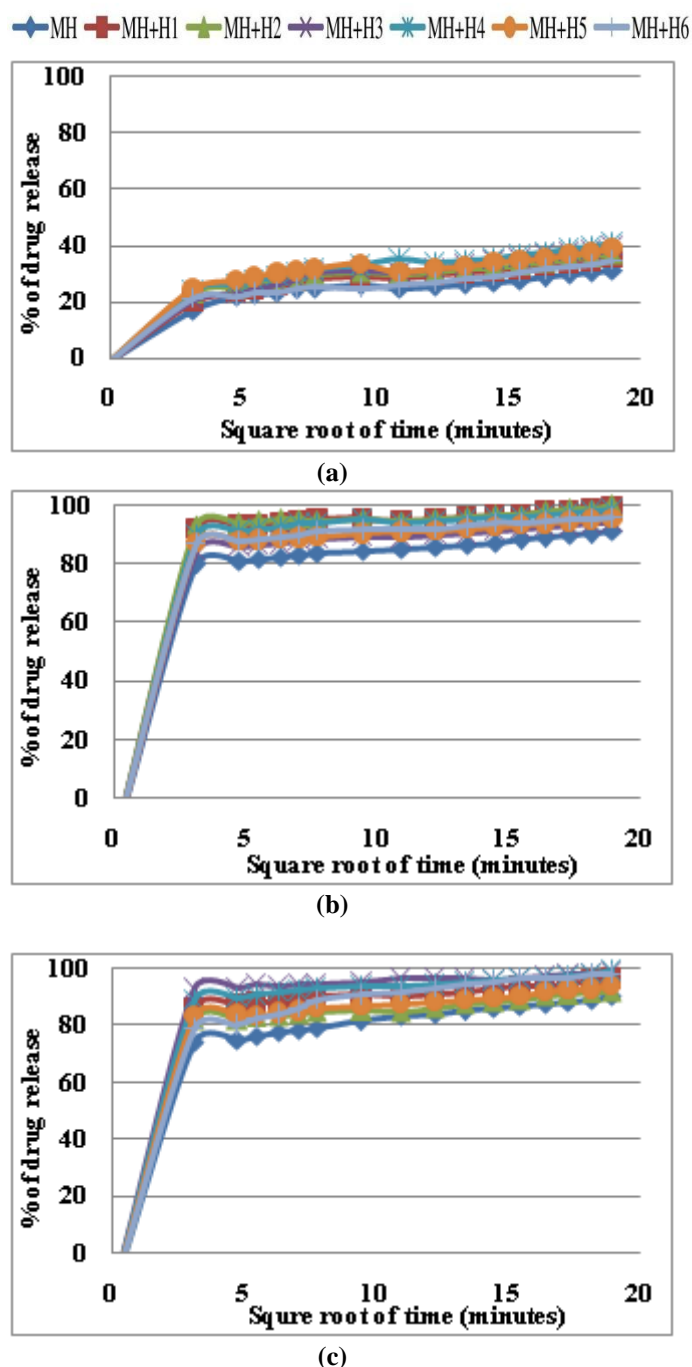


Figure-3: Higuchi release kinetics profiles of Metformin HCl (blue line) and Metformin HCl in presence of six Herbal Sex Stimulants (other six lines except the blue line) at pH 1.2 (a), pH 4.5 (b) and pH6.8 (c) at the end of 360 minutes. Here the blue line slightly below the others six lines. Thus the percent release of Metformin HCl in presence of Herbal sex stimulants increased slightly in case of Higuchi release kinetics at different pH (1.2, 4.5, & 6.8).

■ MH ■ MH+H1 ■ MH+H2 ■ MH+H3 ■ MH+H4 ■ MH+H5 ■ MH+H6

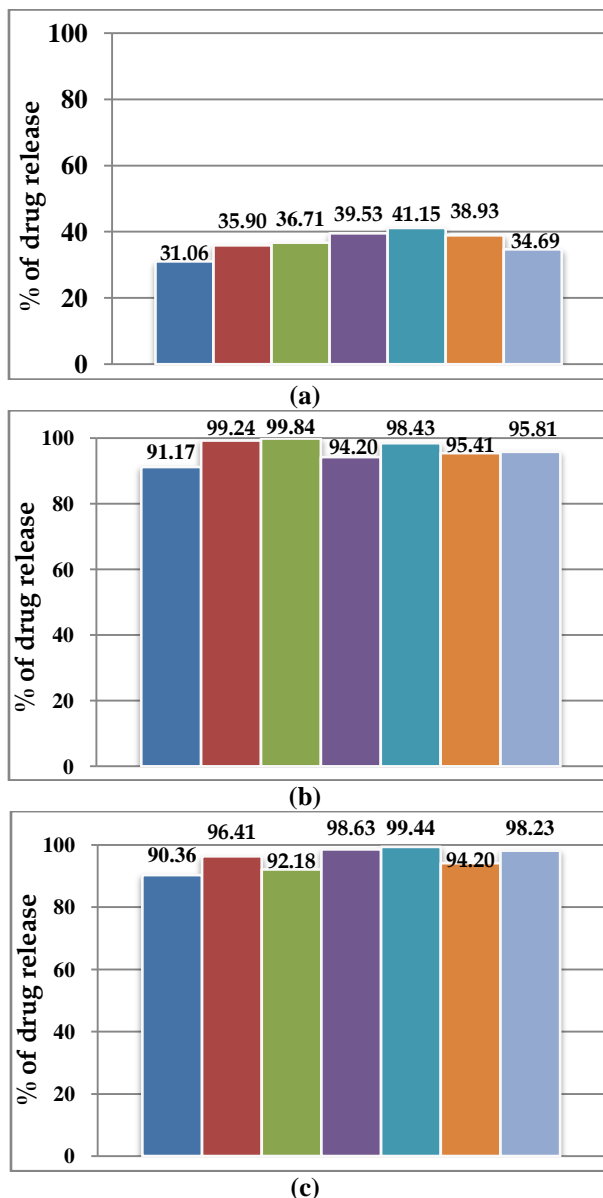


Figure-4: Bar diagram showing the comparison among the percent (%) release of Metformin HCl (blue bar) and Metformin HCl in presence of six Herbal Sex Stimulants (other six bars except the blue bar) at simulated gastric medium of pH 1.2 (a), pH 4.5 (b) and pH6.8 (c) at the end of 360 minutes. Here the blue bar slightly below the others six bars. Thus the percent release of Metformin HCl in presence of Herbal sex stimulants is slightly more at different pH (1.2, 4.5, & 6.8).

The release kinetics (Zero Order, First Order & Higuchi release kinetics) of Metformin HCl and Metformin HCl with herbal sex stimulants shows significant change with the change of pH, the percent release (%) of Metformin HCl alone and Metformin HCl with herbal sex stimulants increases with the increase of pH from 1.2 to 6.8. But the release kinetics between Metformin HCl alone and Metformin HCl with herbal sex stimulants shows no significant change at individual pH; these are summarized in Figure- 1, 2, 3 and 4. Similarly, same thing was happened while we have seen the Log of % remaining of drug versus time. Here at the beginning the Log of % remaining of drug was the most, but it was the lowest after 360 minutes (6 hours). Again same thing occurred while Metformin HCl

dissolved with herbal sex stimulants at different simulated pH medium. Since the percent (%) release of Metformin HCl was not significantly changed in presence of herbal sex stimulants comparing to Metformin HCl alone, which gives us an idea that if we takes this two drug concurrently there will be no hazardous effect from each other.

Determination of release mechanism from multiple coefficients

From the drug release data of Metformin HCl, and Metformin HCl in presence of six different Herbal Sex Stimulants were treated in different kinetics orders such as Zero Order Plot, First Order Plot and Higuchi Plot (Figure-1, 2 and 3), and their correlation coefficients (r^2) (Table-1) were determined for pH 1.2, pH4.5, and pH 6.8 to identify their release mechanism. It was observed from the multiple coefficients determination data (Table-1) of Metformin HCl and Metformin HCl in presence Herbal Sex Stimulants (designated as H1, H2, H3, H4, H5, and H6) that the release kinetics was close to 1 in case of Higuchi plot than First order and Zero order kinetics at pH-1.2 (Table-1) where at pH-4.5 (Table-1) and at pH-6.8 (Table-1) the release kinetics was close to 1 in case of First order plot than Higuchi and Zero order kinetics.

Table-1: Multiple coefficients determination data of Metformin HCl and Metformin HCl in presence of six different Herbal Sex Stimulants in simulated gastrointestinal and intestinal medium. It was observed that the release kinetics was close to 1 in case of Higuchi plot at pH-1.2 where at pH-4.5 and at pH-6.8 the release kinetics was close to 1 in case of First order plot.

Sample	Multiple coefficients determination (r^2) at pH-1.2			Multiple coefficients determination (r^2) at pH-4.5			Multiple coefficients determination (r^2) at pH-6.8		
	Zero order	First order	Higuchi	Zero order	First order	Higuchi	Zero order	First order	Higuchi
MH	0.463	0.522	0.660	0.189	0.475	0.356	0.249	0.602	0.432
MH+H1	0.512	0.586	0.709	0.142	0.620	0.295	0.171	0.561	0.334
MH+H2	0.483	0.560	0.677	0.138	0.623	0.287	0.186	0.490	0.350
MH+H3	0.600	0.684	0.791	0.169	0.479	0.331	0.133	0.516	0.285
MH+H4	0.518	0.607	0.717	0.148	0.571	0.304	0.166	0.695	0.328
MH+H5	0.418	0.493	0.609	0.162	0.497	0.322	0.189	0.541	0.355
MH+H6	0.561	0.637	0.732	0.162	0.506	0.324	0.258	0.833	0.448

From multiple coefficients (r^2) it is suggested that with increase of pH of the simulated media for Metformin HCl and Metformin HCl in presence of Herbal Sex Stimulants followed First Order Kinetics.

From the above results it is clearly demonstrated that the percent (%) release Metformin HCl increased more in presence of herbal sex stimulants as well as with the increase of pH which indicated that the increase in absorption of Metformin HCl in presence of Herbal Sex stimulants. But the significant percent release (%) of Metformin HCl not observed at the present study.

4. Conclusion

Infer from dissolution study it is clearly demonstrated that the percent release (%) of Metformin HCl alone and Metformin HCl in presence sex stimulants increases with the increase of pH and higher percent (%) release observed at simulated pH medium of 6.8 than pH 4.5 and 1.2, so the absorption of the Metformin HCl alone and Metformin HCl in presence sex stimulants will be increased from intestinal pH rather than gastric pH. From the percent (%) data it is also suggested that at different simulated pH medium of 1.2, 4.5 and 6.8 the percent (%) release of Metformin HCl not increased significantly in presence of herbal sex stimulants. Hence, we can say that on the basis of our present study if patient takes Metformin HCl and herbal sex stimulants concomitantly no harmful effect will occur.

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