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A Study of in-vitro interaction of Ketotifen Fumarate with Desloratadine at different gastric and intestinal pH

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Abstract: *The prime object of this project was to elucidate the possible importance of drug-drug interactions (DDIs) as a contributing factor towards drug safety.The main focus of the project was to identify whether there is any interaction between Ketotifen fumerate (antihistamine) and Desloratadine (antihistamine) present or not at different pH. From Job's continuous-variation analysis we found the view of drug-drug interaction at different concentration ratio atl pH (0.4, 1.2, 2.0,6.0) except 2.8, 6.8.7.4 . If both Ketotifen and Desloratadine will be administered concurrently, complex will be formed after reaction, which will reduce the pharmacological activities of both drugs in short grade.*

Key words: *Drug interaction, Desloratadine, job's plot, Ketotifen, pH, Spectral pattern.*

I. INTRODUCTION

A drug interaction is a situation in which a substance (usually another drug) affects the activity of a drug when both are administered together. This action can be synergistic (when the drug's effect is increased) or antagonistic (when the drug's effect is decreased) or a new effect can be produced that neither produces on its own. Typically, interactions between drugs come to mind (drug-drug interaction). However, interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and medicinal plants or herbs (drug-plant interactions). People taking antidepressant drugs such as monoamine oxidase inhibitors should not take food containing tyramine as hypertensive crisis may occur (an example of a drug-food interaction). These interactions may occur out of accidental misuse or due to lack of knowledge about theactive ingredients involved in the relevant substances.[1]It is therefore easy to see the importance of these pharmacological interactions in the practice of medicine. If a patient is taking two drugs and one of them increases the effect of the other it is possible that an overdose may occur. The interaction of the two drugs may also increase the risk that side effects will occur. On the other hand, if the action of a drug is reduced it may cease to have any therapeutic use because of under dosage. Notwithstanding the above, on occasion these interactions may be sought in order to obtain an improved therapeutic effect.[2]

1.1 Drug Interaction Influenced by pH;

Drugs can be present in either ionised or non-ionised form, depending on their pKa (pH at which the drug reaches equilibrium between its ionised and non-ionised form).[3] The non-ionized forms of drugs are usually easier to absorb, because they will not be repelled by the lipidic bylayer of the cell, most of them can be absorbed by passive diffusion, unless they are too big or too polarized (like glucose or vancomicyn), in which case they may have or not specific and non specific transporters distributed on the entire intestine internal surface, that carries drugs inside the body. Obviously increasing the absorption of a drug will increase its bioavailability, so, changing the drug's state between ionized or not, can be useful or not for certain drugs.Certain drugs require an acid stomach pH for absorption. Others require the basic pH of the intestines. Any modification in the pH could change this absorption. In the case of the antacids, an increase in pH can inhibit the absorption of other drugs such as zalcitabine(absorption can be decreased by 25%), tipranavir (25%) and amprenavir (up to 35%). However, this occurs less often than an increase in pH causes an increase in absorption. Such as occurs when cimetidine is taken with didanosine. In this case a gap of two to four hours between taking the two drugs is usually sufficient to avoid the interaction.[4]

1.2 Ketotifen Fumarate:

Ketotifen is a second-generation noncompetitive H1-antihistamine and mast cell stabilizer. It is most commonly sold as a salt of fumaric acid, ketotifen fumarate, and is available in two forms. In its ophthalmic form, it is used to treat allergic conjunctivitis,[5] or the itchy red eyes caused by allergies. In its oral form, it is used to prevent asthmaattacks. Side effects include drowsiness, weight gain, dry mouth, irritability, and increased nosebleeds.The drug is marketed as ophthalmic solutions under the brand names Zaditor/Zaditen(Novartis),[6] Alaway (Bausch and Lomb), Zyrtec Itchy-Eye Drops, and Claritin Eye.Ketotifen fumarate is a second-generation H1-antihistamine/mast cell stabilizer available in two forms. In

its ophthalmic form, it is used to treat allergic conjunctivitis or the itchy red eyes caused by allergies. In its oral form, it is used to prevent asthma attacks.

1.4 Desloratadine

Desloratadine belongs to a group of medications known as antihistamines, specifically the class known as H1-receptor antagonists. During an allergic reaction, the body produces a chemical called histamine, which causes allergy symptoms such as hives, runny nose, sneezing, itchy throat, congestion, and itchy watery eyes. Desloratadine works by blocking the action of histamine in the body.

1.5 Job's plot

A Job plot (also known as the method of continuous variation or Job's method; named after P. Job) is used to determine thestoichiometry of a binding event. This method is widely used in analytical chemistry, instrumental analysis, and advanced chemical equilibrium texts and research articles. In solutions where two species are present (i.e. species A and species B), one species (A) may bind to the other species (B). In some cases, more than one A will bind with a single B. One way to determine the amount of A binding to B is by using a Job plot.In this method, the total molar concentration of the two binding partners (e.g. a protein and ligand or a metal and a ligand) are held constant, but their mole fractions are varied. An observable that is proportional to complex formation (such as absorption signal or enzymatic activity) is plotted against the mole fractions of these two components. The maximum (or minimum) on the plot corresponds to the stoichiometry of the two species[7] if sufficiently high concentrations are used. This method is named after P. Job, who introduced this methodology in 1928.[8] An early work of I. Ostromisslensky describes essentially the same approach [9].

II. Mathods And Materials

2.1 Materials

All the chemicals and reagents used in this study were of analytical grade and were stored under optimum storage conditions. The experimental mixtures and solutions were prepared in standard volumetric flasks about one hour prior to recording the data.

2.2 Drugs Used in the Study

Ketotifen Fumarate & Desloratadine

2.3 The λ_{max} value of drug used in the study

300nm (The λ_{max} Ketotifen Fumarate)

2.4 Instrument Used:

Name	Source
pH Meter	Cyberscan 500, Hanna, Portugal
UV/VIS Spectrophotometer	UV mini-1240, Shimadzu, Japan
Electronic balance	Shimadzu Corporation, Japan
Water bath	Memmert, Germany

Table 1: Instruments used in the study

2.5 Solvents

i) Distilled water ii) Hydrochloric acid iii) Ethanol

2.6 Name and Source of Buffer ingredients

Ingredients of Buffers	Source
Sodium hydroxide	Reagent grade, Merck, India
Potassium dihydrogen phosphate (KH_2PO_4)	Reagent grade, Merck, India
Hydrochloric acid	Reagent grade, Merck, India
Potassium Chloride	Reagent grade, Merck, India
Sodium Chloride	Reagent grade, Merck, India

Table 2: Name and Source of Buffer ingredients

2.7 Preparation of Hydrochloric acid

In order to prepare Hydrochloride acid of 0.1 M concentration, 9.1 ml of hydrochloric acid (Molecular weight 36.5 gm/mol, 37% concentrated) was taken in a liter volumetric flask and the volume made up with distilled water to the mark. Similarly 18.18 ml of HCl acid was diluted in a liter volumetric flask up to the mark with distilled water to make the solution of 0.2 M concentration.

2.8 Preparation of potassium chloride

In order to prepare Potassium chloride of 0.2 M concentration, Potassium chloride (14.9 gm), (Molecular weight 74.55 gm/mol) was dissolved in distilled water in a liter flask and the volume made up to the mark with same solvent.

2.9 Preparation of potassium dihydrogen phosphate

In order to prepare potassium dihydrogen phosphate of 0.1 M concentration, Potassium chloride (13.609 gm), (Molecular weight 136.09 gm/mol) was dissolved in distilled water in a liter flask and the volume made up to the mark with same solvent.

2.10 Preparation of Sodium hydroxide

In order to prepare of 0.1 M concentration, sodium hydroxide pellets (20 gms), (Molecular weight 40 gm/mol) were taken in a 500 ml volumetric flask, dissolved in little distilled water and volume was made up to the mark with the same solvent. 100 ml of this solution (1 M concentration) was further diluted in 500 ml volumetric flusk with distilled water, resulting concentration was 0.2 M.

2.11 Preparation of buffers solutions

2.11.1 Preparation of acidic buffer (pH 0.4, 1.2, 2.0, &2.8):

These buffers are prepared by using sodium chloride, potassium chloride, sodium hydroxide and hydrochloric acid with the help of pH meter

2.11.2 Preparation of Basic buffer (pH 6.0, 6.8, &7.4):

These buffers are prepared by using Potassium dihydrogen phosphate (KH_2PO_4), potassium chloride, sodium hydroxide and hydrochloric acid with the help of pH meter

2.12 Preparation of Ketotifen Fumarate solution

100 ml of 1×10^{-3} M solution of Ketotifen Fumarate was prepared as the stock solution by dissolving 0.425 gm of Ketotifen Fumarate in 100ml of distilled water in a 100 ml Volumetric flask. To prepare 1×10^{-5} M solution of Ketotifen Fumarate, 1ml of 1×10^{-3} M solution was taken in another 100 ml volumetric flask and the volume was adjusted by distilled water up to the mark.

2.13 Preparation of Desloratadine solution

100 ml of 1×10^{-4} M solution of Desloratadine was prepared as the stock solution by dissolving 0.425 gm of Desloratadine in 100ml of distilled water in a 100 ml Volumetric flask. To prepare 1×10^{-5} M solution of Desloratadine, 1ml of 1×10^{-4} M solution was taken in another 10 ml volumetric flask and the volume was adjusted by distilled water up to the mark.

2.14 Method Used:

Job plot ,also known as the method of continuous variation or Job's method

III. RESULTS AND DISCUSSION

In the present investigation, the interaction of Ketotifen Fumarate and Desloratadine has been studied by different methods of analysis under different pH (0.4, 1.2, 2.0, 2.8, 6.0, 6.8 & 7.4) at different concentrations. The spectral characteristics and spectrophotometric analysis of the complexation process have been evaluated. The results obtained from various methods are discussed below.

3.2 Effect of Ketotifen Fumarate on Desloratadine by Job's method of continuous variation at Different pH

The molar ratios of the complexes of Ketotifen Fumarate with **Desloratadine** were estimated by Job's spectrophotometric method of continuous variation. The observed absorbance values measured in pH 0.4,1.2,2.0,2.8,6.0,6.8 and 7.4 at various concentrations 1 X 10^{-5} M to 9 X 10^{-5} M Ketotifen Fumarate with

Desloratadine at 300nm is given **in tables 03-12 and.** In this method, solutions of different concentrations of Ketotifen Fumarate and Desloratadine were prepared by plotting corrected absorbance against the volume fraction of one reactant. It may be mentioned that drug solutions with identical analytical concentrations are mixed in such a way that total volume and the total moles of reactant in each mixture is constant but the mole ratio of the reactants varies systematically.

At pH 0.4,1.2,2.0,2.8,6.0,6.8 and 7.4 forms strong 1:1 complex Ketotifen Fumarate with Desloratadine

Table:03: Values of job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 0.4

Conc. Of Kitotifen	Absorb. of Kitotifen	Conc. Of Desloratadine	Absorb. Of Desloratadine	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.16	9	0.541	0.305	0.396
2	0.268	8	0.479	0.315	0.432
3	0.419	7	0.426	0.363	0.482
4	0.543	6	0.361	0.375	0.529
5	0.687	5	0.306	0.432	0.561
6	0.826	4	0.211	0.529	0.508
7	0.971	3	0.157	0.677	0.451
8	1.129	2	0.102	0.86	0.371
9	1.229	1	0.059	1.087	0.201

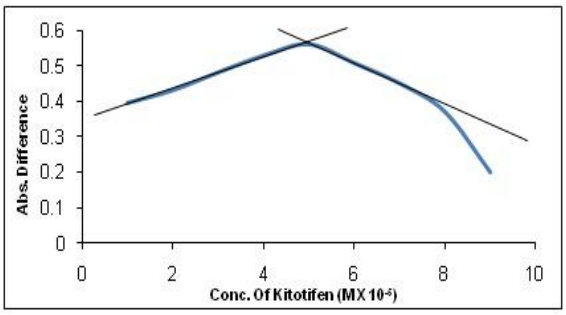

Fig.01: Job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 0.4

Discussion: At pH 0,4 various concentrations comprising 1 X 10^{-5} M to 9 X 10^{-5} M of ketotifen were interacted with Desloratadine. The breakdown in the curve at a concentration of ketotifen 5 X $10^{-}5$ indicates the presence of drug interaction

Table 04: Values of job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 1.2

Conc. Of Kitotifen	Absorb. of Kitotifen	Conc. of Desloratadine	Absorb. Of Desloratadine	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.127	9	0.634	0.352	0.409
2	0.265	8	0.55	0.367	0.448
3	0.365	7	0.495	0.372	0.488
4	0.54	6	0.392	0.407	0.525
5	0.669	5	0.321	0.439	0.551
6	0.795	4	0.273	0.484	0.584
7	1.065	3	0.22	0.843	0.442
8	1.126	2	0.136	0.962	0.3
9	1.201	1	0.084	1.071	0.214

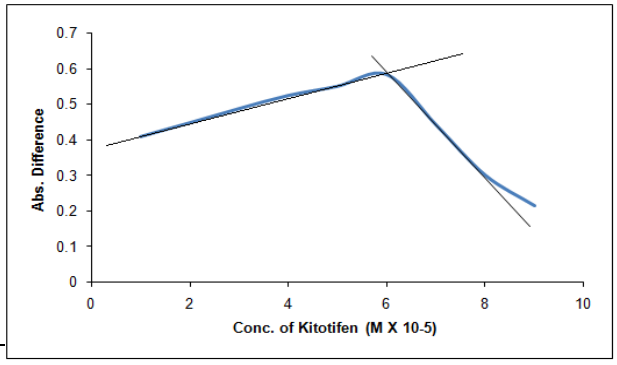

Fig.02: Job's plot for complexation of Ketotifen Fumarate With Desloratadine at pH 1.2

Discussion: At pH 1.2 various concentrations comprising 1 X 10^{-5} M to 9 X 10^{-5} M of ketotifen were interacted with Desloratadine. The breakdown in the curve at a concentration of ketotifen 6 X $10^{-}5$ indicates the presence of drug interaction.

Table :05: Values of job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 2.0

Conc. Of Kitotifen	Absorb. of Kitotifen	Conc. of Desloratadine	Absorb. Of Desloratadine	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.167	9	0.509	0.246	0.43
2	0.318	8	0.444	0.296	0.466
3	0.42	7	0.389	0.301	0.508
4	0.608	6	0.336	0.382	0.562
5	0.773	5	0.295	0.485	0.583
6	0.895	4	0.227	0.602	0.52
7	1.059	3	0.172	0.806	0.425
8	1.218	2	0.115	0.994	0.339
9	1.349	1	0.073	1.227	0.195

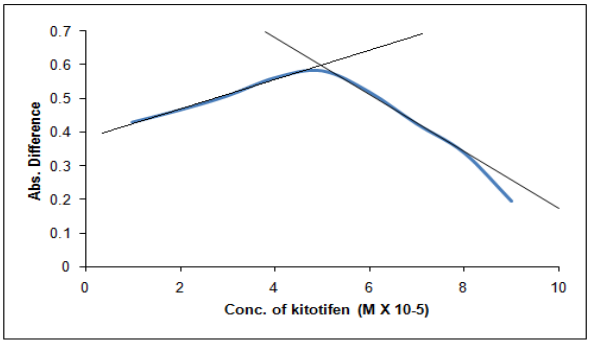

Fig. 03: Job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 2.0

Discussion: At pH 2.0 various concentrations comprising 1 X 10^{-5} M to 9 X 10^{-5} M of ketotifen were interacted with Desloratadine. The breakdown in the curve at a concentration of ketotifen 5 X $10^{-}5$ indicates the presence of drug interaction.

Table: 06: Values of job's plot for complexation of Ketotifen Fumarate With Desloratadine at pH 2.8

Conc. Of Kitotifen	Absorb. of Kitotifen	Conc. of Desloratadine	Absob. of Desloratadine	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.137	9	1.15	0.207	1.08
2	0.275	8	1.001	0.238	1.038
3	0.426	7	0.835	0.285	0.976
4	0.588	6	0.707	0.37	0.925
5	0.722	5	0.563	0.449	0.836
6	0.868	4	0.444	0.552	0.76
7	0.993	3	0.333	0.704	0.622
8	1.126	2	0.208	0.824	0.51
9	1.271	1	0.096	1.082	0.285

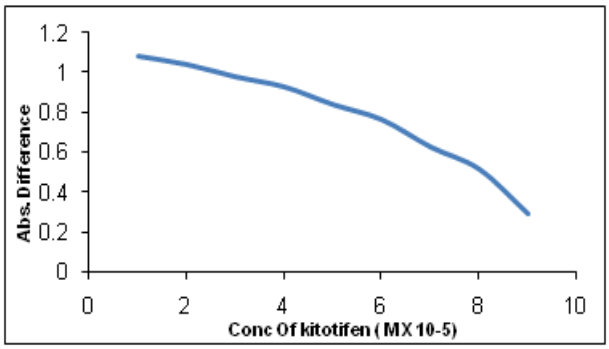

Fig.04: Job's plot for complexation of Ketotifen Fumarate With Desloratadine at pH 2.8

Discussion: At figure 04; as there is no breakdown of straight line, we can assume that there no drug drug interaction at pH 2.8

Table 07: Values of job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 6.0

Conc. Of Kitotifen	Absorb. of Kitotifen	Conc. of Desloratadine	Absorb. Of Desloratadine	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.115	9	1.19	0.075	1.23
2	0.295	8	1.17	0.12	1.345
3	0.471	7	1.1	0.135	1.436
4	0.623	6	0.88	0.215	1.288
5	0.702	5	0.702	0.261	1.143
6	0.88	4	0.623	0.52	0.983
7	0.973	3	0.471	0.662	0.782
8	1.19	2	0.34	0.99	0.54
9	1.271	1	0.161	1.123	0.309

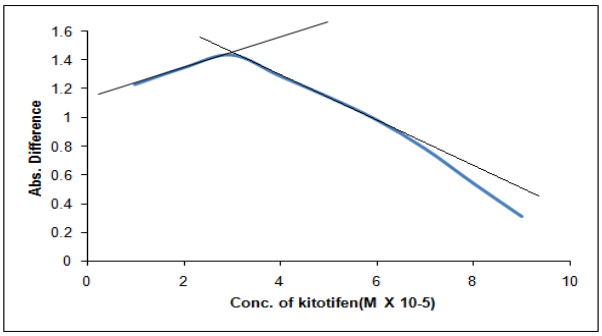

Fig.05: Job's plot for complexation of Ketotifen Fumarate With Desloratadine at pH 6.0

Discussion: At pH 6.0 various concentrations comprising 1 X 10^{-5} M to 9 X 10^{-5} M of ketotifen were interacted with Desloratadine. The breakdown in the curve at a concentration of ketotifen 3 X $10^{-}5$ indicates the presence of drug interaction

Table 08: Values of job's plot for complexation of Ketotifen Fumarate With Desloratadine at pH 6.8

Conc. Of Kitotifen	Absorb. of Kitotifen	Conc. of Desloratadine	Absorb. Of Desloratadine	Absorb. of mixture	Absorb. difference
M × 10^{-5}	A	M × 10^{-5}	B	C	D=(A+B)-C
1	0.123	9	1.198	0.03	1.291
2	0.259	8	1.061	0.069	1.251
3	0.42	7	0.824	0.127	1.117
4	0.528	6	0.745	0.215	1.058
5	0.676	5	0.595	0.323	0.948
6	0.811	4	0.464	0.451	0.824
7	0.931	3	0.353	0.636	0.648
8	1.076	2	0.23	0.806	0.5
9	1.174	1	0.112	1.01	0.276

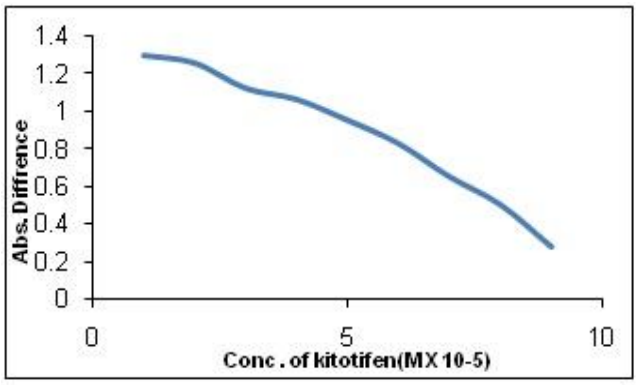

Fig.06: Job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 6.8

Discussion: At figure 06; as there is no breakdown of straight line, we can assume that there no drug drug interaction at pH 2.8.

Table 09: Values of job's plot for complexation of complexation of Ketotifen Fumarate With Desloratadine at pH 7.4

Conc. Of Kitotifen	Absorb. of Kitotifen	Conc. of Desloratadine	Absorb. Of Desloratadine	Absorb. of mixture	Absorb. difference
$M \times 10^{-5}$	A	$M \times 10^{-5}$	B	C	D=(A+B)-C
1	0.125	9	1.088	0.026	1.187
2	0.254	8	0.969	0.062	1.161
3	0.38	7	0.854	0.129	1.105
4	0.527	6	0.759	0.258	1.028
5	0.661	5	0.627	0.391	0.897
6	0.782	4	0.48	0.474	0.788
7	0.902	3	0.371	0.625	0.648
8	1.031	2	0.243	0.826	0.448
9	1.132	1	0.14	0.998	0.274

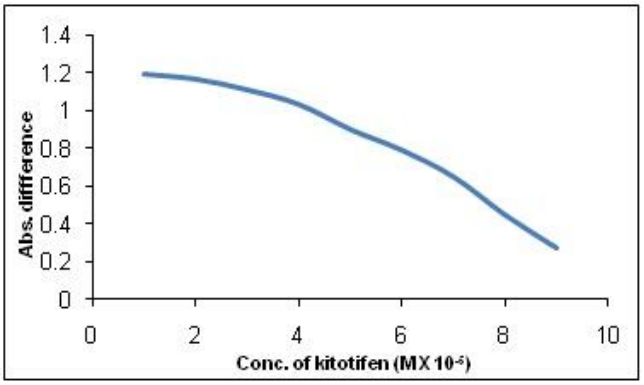

Fig.07: Job's plot for complexation of Ketotifen Fumarate with Desloratadine at pH 7.4

Discussion: At figure 07; as there is no breakdown of straight line, we can assume that there no drug drug interaction at pH 7.4.

IV. CONCLUSION

The experimental results indicates that at pH 0.4,1.2,2.0,6.0 interaction of ketotifen Fumarate with Desloratadine decrease the free drug concentration of both drugs which results in decrease affinity towards the receptors. Ultimately one or both drugs may show diminished pharmacological activity.

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