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# *In vitro* Study on Interaction of Ketotifen Fumerate with Paracetamol

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***Abstract:*** *Interaction of ketotifen fumerate and paracetamol was studied in aqueous media. The ability of interaction of ketotifen with paracetamol is dependent on pH of the solution and it has been found that ketotifen forms 1:1 complexes at different pH. The stability constants have been calculated from the Ardon's spectrophotomeric measurements of the reaction systems. When ketotifen was interacted with paracetamol and the absorbance was determined at 300 nm the stability constants were found of -7.32 and -7.84 at pH 1.6 and 7.4 respectively.*

**Key words**: Stability constant, Job's method, Ardon's mehod, ketotifen and paracetamol.

## Introduction

Ketotifen is a 4-(1-methyl-4-piperidylidene) -4H-benzo {4,5} cyclohepta {1,2-b} thiophen-10(9H) -one hydrogen fumerate. Ketotifen has been shown to inhibit the release of histamine and leukotriene from basophil and lung tissue, to antagonize histamine at $H_1$ receptors, to inhibit calcium uptake, to block the passive anaphylactic reaction, to reverse isoprenaline induced beta adrenoceptor tachyphylaxis, and to inhibit both allergen induced and drug induced asthma[1]. Most double blind placebo controlled clinical trials on ketotifen have shown it to have a beneficial effect in the treatment of asthma [2,3] equivalent to that of disodium cromoglycate [4,5]. Paracetamol is a widely used over-the-counter analgesic and

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antipyretic. It is commonly used for the relief of fever, headache, and other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. In combination with non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics, paracetamol is used also in the management of more severe pain such as postoperative pain .While generally safe for human use at recommended doses (1000 mg per single dose and up to 4000 mg per day for adults, up to 2000 mg per day if drinking alcohol)[6], but unlike phenacetin and its combinations, paracetamol is not considered to be carcinogenic at therapeutic doses[7]. Paracetamol is available as tablet, capsule, suspension, suppository and injectables. In recommended doses, paracetamol generally is safe for children and infants, as well as for adults[8]. Paracetamol is commonly used in multi-ingredient preparations for migraine headache, typically including butalbital and paracetamol with or without caffeine, and sometimes containing codeine [9]. The mechanism of action of paracetamol is the inhibition of cyclooxygenase (COX), an enzyme responsible for the production of prostaglandins, which are important mediators of inflammation, pain and fever. However, the mechanism by which paracetamol reduces fever and pain is still debated largely because paracetamol reduces the production of prostaglandins [10].

## Methods:

### Job's Spectrophotometric method[11]

Absorbance of series of ketotifen fumerate and paracetamol with molar ratios 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 were measured by keeping the total mole constant. The observed absorbance of the mixtures at various mole fractions was subtracted from sum of the values for free drugs (ketotifen fumerate and paracetamol). The absorbance difference (D) was then plotted against the mole fractions of the drug in the mixtures. A curve thus obtained showed a maximum at a point, which indicated the molar ratios of drug drug interaction.

### Ardon's spectrophotometric method[12]

The paracetamol concentration was kept fixed ($2X10^{-4}$) while the ketotifen concentrations were varied. The absorbance of free drug solutions and those of mixtures were measured at 300nm. The *in vitro* interaction studies were perfomed by observing Ardond's spectrophotometric curves. The absorbance of ketotifen was measured at 300 nm using the Ardon's equation $1/[D-\varepsilon_{AC}]=1/KC(\varepsilon_{com}-\varepsilon_A)[B]+1/C(\varepsilon_{com}-\varepsilon_A)$. The values of stability constants (K) were calculated from

the [intercept] / [slope] of the straight lines obtained. In the above equation D is the absorbance of the mixture, C is the molar concentration of the interacting molecules, [B] is the molar concentration of the drug, $\varepsilon_{com}$ is the molar extinction co-efficient of the complex and $\varepsilon_A$ is the molar extinction co-efficient of the interacting molecules. The values of $1/( D-C\varepsilon_A)$ versus 1/Drug was plotted and the values of stability constants were calculated from intercept/slope of the straight lines obtained.

**Results and discussions:**

| Conc. of Ketotifen(M) | Absorbance ( D Value) | |
|---|---|---|
| | pH= 1.6 | pH= 7.4 |
| $1 X 10^{-5}$ | 0.739 | 0.747 |
| $2 X 10^{-5}$ | 0.792 | 0.796 |
| $3 X 10^{-5}$ | 0.826 | 0.799 |
| $4 X 10^{-5}$ | 0.799 | 0.757 |
| $5 X 10^{-5}$ | 0.759 | 0.750 |
| $6 X 10^{-5}$ | 0.715 | 0.675 |
| $7 X 10^{-5}$ | 0.650 | 0.562 |
| $8 X 10^{-5}$ | 0.477 | 0.434 |
| $9 X 10^{-5}$ | 0.344 | 0.229 |

**Table-1:** *Absorbance of ketotifen at different pHs (using Job's method).*

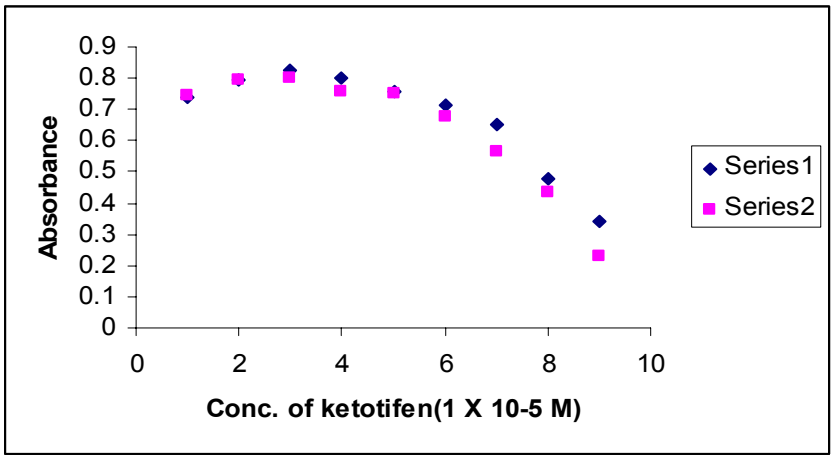


**Figure 1***: Job's plot for complexation of ketotifen with paracetamol at 300nm*

These curves obtained by the job's methods show breaks at different molar concentrations of both drugs. It is found that the curve obtained

at pH 1.6 is some what flat related to at pH 7.4. On the other hand, slow kinetics of interaction occurs between ketotifen fumerate and paracetamol at pH 1.6. Continuous variation plot gives information on the relative affinities of the complexes and it also depends on the intrinsic spectral characteristics of each complex.

| $1/D \times 10^{-5}$ | $1/(D-C\epsilon_A)$ | |
|---|---|---|
| | pH= 1.6 | pH= 7.4 |
| 0.33 | 14.71 | 10.99 |
| 0.25 | 6.21 | 4.98 |
| 0.2 | 3.48 | 3.16 |
| 0.167 | 2.39 | 2.13 |
| 0.143 | 1.58 | 1.50 |

**Table-2:** *Absorbance of ketotifen at different pHs (using Ardon's method, when conc. of paracetamol is constant)*

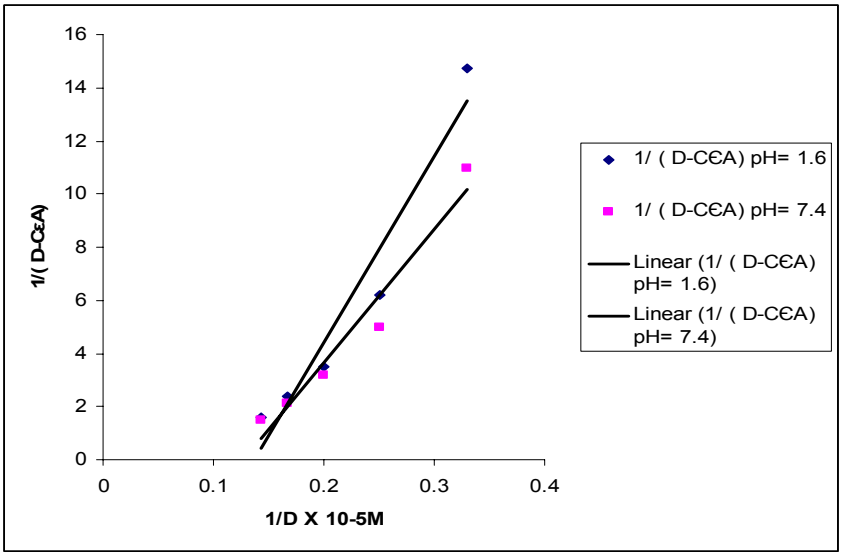


**Figure 2:** *Ardon's plot for complexation of ketotifen with paracetamol at 300nm.*

The Ardon's plots have been used to evaluate the stability constants and it has been seen that when values of $1/(D-C\varepsilon_A)$ are plotted against 1/ Drug , straight lines are obtained obeying the Ardon's equation. The values of stability constants at different pHs are shown in Table 3. Very low values of stability constant (between negative values and 1) mean that the formation of complex is readily dissociated, yielding

essentially all drugs in ionic form at pH as low as stomach pH (about pH 2 to 3) to as high as physiologic pH 7.4 [13].

| System | pH | Stability constants |
|---|---|---|
| Interaction of ketotifen with paracetamol | 1.6 | -7.32 |
| | 7.4 | -7.84 |

**Table-3:** *Stability constants values of ketotifen with paracetamol at different pH.*

It is observed that, the resulting values of stability constant are negative. These negative values are the sign of low interaction between ketotifen with paracetamol. It can conclude that these two drugs cannot safely be administered orally at a time.

**Conclusion**

The experimental result indicates that interaction of ketotifen with paracetamol slightly decrease the free drug concentration of both drugs. Ultimately one or both drugs may show diminished pharmacologic activity. Although a detailed *invivo* experiment would be necessary to get a clear idea about the therapeutic properties of both drugs.

**References:**

1. CRAPS, L.P. and NEY, U.M., ( 1984), *Ketotifen: Current views on its mechanism of action and their therapeutic implications*. *Respiration* v.45, pp. 411-421.
2. BROBERGER, U. et al, ( 1986), *Ketotifen in pollen induced asthma: A double blind placebo controlled study. Clin allergy* v.16, pp. 119-127.
3. TINKELMAN, D.G. et al, (1985), *A multicenter trial of the prophylactic effect of ketoifen, theophylline and placebo in atopic asthma. J. Allergy Clin Immunol* v.76, n.3, p.487-497.
4. CRAPS, L. et al, (1978), *Clinical investigaton of agents with prophylactic allergic effect in bronchial asthma. Clin allergy* v.8, pp. 373-382.
5. STANGL, B. et al, (1980), *The protective effec of ketotifen in bronchial asthma. Respiration* 39 : pp12-15.

6. http://www.drugs.com/acetaminophen.html.

7. BERGMAN, K. et al , (1996), *The genotoxicity and carcinogenicity of paracetamol: a regulatory (re)view". Mutat Res* v.349, n.2, pp. 263-88.

8. Acetaminophen, (2009), *Physicians' Desk Reference, 63rd ed. Montvale, NJ: Thomson PDR :* 1915-1916.

9. Reader's Digest Guide to Drugs and Supplements,(2002), *Pleasantville, New York; Montreal: Reader's Digest Association, Inc. ISBN 0-7621-0366-3:* pp.18-20.

10. ROSSI, S., (2008). *Australian Medicines Handbook. Adelaide: Australian Medicines Handbook. ISBN 0-9757919-6-7. http://www.amh.net.au.*

11. JOB, P., (1971), *Ann. Chim.*v.9, pp. 113.

12. ARDON, M., (1971), *Oxidation of ethanol by ceric perchlorate, J. Chem. Soc.* pp.1811-1815.

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