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# Water soluble complexes of Fexofenadine Hydrochloride and α-cyclodextrins

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***ABSTRACT :****Fexofenadine hydrochloride(FFN),(±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzeneacetic acid hydrochloride, is a second generation antihistamine that is used to treat allergies. Molecule exists as zwitter ion in aqueous media at physiological pH. It belongs to the group of amine compounds and it is highly hydrophobic drug. Inclusion complexes of pharmaceutical compounds with cyclodextrins (CDs) have been extensively studied and utilized to improve the solubility, dissolution rate and bioavailability of poorly water-soluble drugs. In this work are investigated interactions of FFN with α- cyclodextin and it's derivarive by several techniques including phase solubility, UV/VIS and FTIR characterisation. Different concentrations of α-cyclodextrin and it's derivative 2-Hydroxypropyl-α-cyclodextrin in aqueous medium shows the positive effect on the phase solubility of fexofenadine hydrochloride. Also, inclusion complex is confirm by FTIR spectra of the obtained samples.*

***KEYWORDS -*** *Fexofenadine hydrochloride, solubility, complex, α-cyclodextrin*

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## I. Introduction

Fexofenadine Hydrochloride (Figure 1.) is an oral, second generation antihistamine that is used to treat the signs and symptoms of allergy. Fexofenadine blocks the H1 receptor for histamine and thus prevents activation of H1 receptor-containing cells by histamine.[1] Unlike the first generation antihistamines, fexofenadine and other second-generation antihistamines do not readily enter the brain from the blood, and, therefore, they cause less drowsiness. One of the disadvantages of the oral route of drug administration is low bioavailability, as most drugs have poor solubility in water. Fexofenadine hydrochloride is very slightly soluble in water, and poor aqueous solubility of a drug is the factor that limits its development into the desired formulation. The absorption of such drugs may be incomplete and variable, and hence there will be variations in the effectiveness.[2] Contribution of this work is improve the aqueous solubility of Fexofenadine Hydrochloride.

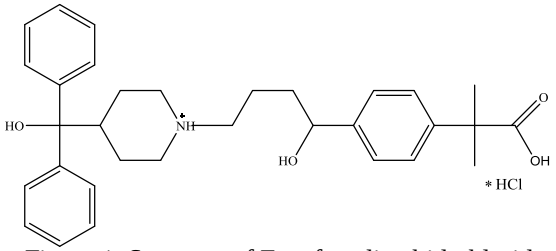


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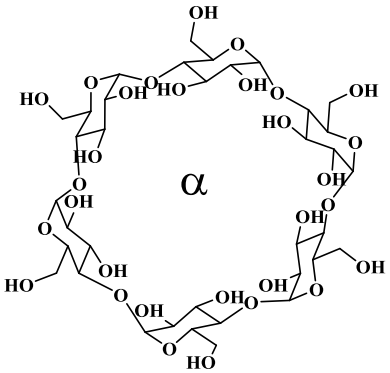
Figure 1. Structure of Fexofenadine hidrohloride

Cyclodextrins (CDs) are cyclic α-1,4 linked oligosaccharides of a-D-glucopyranose units that have relatively hydrophobic central cavity and hydrophilic outer surface. Cyclodextrins are classical examples of compounds that form inclusion complexes.[3] They are widely used for to improve the physicochemical and pharmaceutical properties such as solubility, stability, and bioavailability of poorly soluble drug molecules. They consists lipophilic inner cavity and hydrophilic outer surface, which are capable of interacting with a large variety of guest molecules by forming non-covalent inclusion complexes.[4]

Lipophilic drug molecules, as well as drug/cyclodextrin complexes are known to form aggregates in aqueous solutions, and common pharmaceutical excipients, such as water-soluble polymers and surface-active preservatives, are known to solubilize drugs in aqueous solutions.

Current stoichiometric models treat aqueous formulation as ideal solutions in which dissolved drug and cyclodextrin molecules, and individual complexes are independent of each other as well as of other excipients. CDs interact with poorly-water soluble compound to increase their apparent solubility.

Complexation- The central CD cavity provides a lipophilic microenvironment into which suitably sized drug molecules may enter and include. No covalent bonds are formed or broken during the drug/CD complex formation and in aqueous solutions, the complexes are readily dissociated. The rates for formation and dissociation of drug/CD complexes are very close to the diffusion controlled limits and drug/CD complexes are continuously being formed and broken apart. The value of $K_{1:1}$ is most often between 50 and 2000$M^{-1}$ with mean value of 130 $M^{-1}$ for α-CD. [5]




(a)

**α-Cyclodextrin**

(b)

| | |
|---|---|
| Number of glucose units | 6 |
| Molecular weight | 972 |
| Melting point (ºC) | 275 |
| Outer diameter (Å) | 14 |
| Large inside diameter (Å) | 6 |
| Small inside diameter (Å) | 5 |
| Cavity Height (depth) (Å) | 8 |
| Cavity Volume (Å) | 176 |

Figure 2. Structure (a) and structural characteristic (b) of α-cyclodextrin

1.1 Determination of drug solubility

The practical and phenomenological implications of phase-solubility analysis were developed by Higuchi and Connors. Phase-solubility analysis on the effect of complexing agents on the compound being solubilized is traditional approach to determine not only the value of the stability constant but also to give insight into the stoichiometry of the equilibrium. Experimentally, an excess of a poorly water-soluble drug is introduced into several vials to which a constant volume of an aqueous vehicle containing successively larger concentrations of the CD are added. The need for excess drug is based on the desired to maintain as high a thermodinamic activity of the drug as possible. The vials are shaken or otherwise agitated at constant temperature until equilibrium is established.

The suspensions are then filtered and the total concentration of the drug determined based on appropriate analitical techniques(UV/VIS soectrophotometry). The phase-solubility profile is then constructed by assessing the effect of the CD on the apparent solubility of the drug. [6]

Phase solubility diagrams fall into two major types: A and B. (Figure 3.)

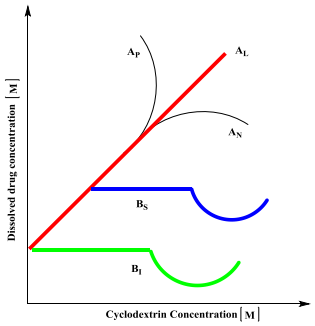



Figure 3. Phase solubility profiles and classification of complexes according to Higuchi and Connors

In A systems, the apparent solubility of the substrate increase as a function of CD concentration. Three subtypes have been defined:

- $A_L$ profiles indicate a linear increase in solubility as a function of solubilizer concentration. If the slope of the $A_L$ isotherm is greater than unity, higher order complexes are assumed to be involved in the solubilization. Although a slope of less than one does not exclude the occurrence of higher order complexes, a one to one complex is often assumed in the absence of other information
- $A_P$ systems indicate an isotherm wherein the curve deviates in a positive direction from linearity (i.e. the solubilizer is proportionally more effective at higher concentrations). $A_P$ systems suggest the formation of higher order complexes with respect to the CD at higher CD concentrations.
- $A_N$ relationships indicate a negative deviation from linearity (i.e. the CD is proportionally less effective at higher concentrations).

Drug/CD complexes, especially those of the natural CDs, have tendency to self-assemble in aqueous solutions to form aggregates. At elevated CD concentrations these aggregates can become large and precipitate as solid microparticles. In addition, the natural CDs and their complexes have limited solubility in aqueous solutions. These solubility limitations can give rise to characteristic B-type phase-solubility diagrams. [1]

The most common type of cyclodextrin complexes is the 1:1 drug/cyclodextrin complex (D/CD) where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD)

$$D + CD \underset{}{\overset{K_{1:1}}{\rightleftharpoons}} D/CD \qquad (1)$$

The value of the stability constant ($K_{1:1}$) is used to compare the affinity of drugs for different cyclodextrins of cyclodextrin derivatives. The total solubility of drug ($S_t$) in aqueoua cyclodextrin solution will then be:

$$S_t = S_0 + \frac{K_{1:1}S_0}{1 + K_{1:1}S_0}\left[CD\right]_t \qquad (2)$$

Where $S_0$ is the intrinsic solubility of the drug, i.e. the solubility when no cyclodextrin is present, and $[CD]_t$ is the total concentration of cyclodextrin in the aqueous medium. A plot of $S_t$ versus $[CD]_t$according to eq.(2) (i.e. a phase-solubility profile), will give a straight line with a slope $K_{1:1}S_0/(1+K_{1:1}S_0)$) less than unity and an intercept ($S_{int}$) equal to $S_0$: [5]

$$K_{1:1} = \frac{\text{Slope}}{S_0(1\text{-Slope})} \qquad (3)$$

If the slope of linear diagram is greater than unity, but less than 2, the complex formed is likely to be of second, or higher, order with respect to the drug, but first-order with respect to CD. For example, a $K_{2:1}$ value of drug/cd complex can be determined by: [7]

$$K_{2:1} = \frac{\text{Slope}}{(2\text{-Slope})S_0^2} \qquad (4)$$

## II. EXPERIMENTAL

### 2.1. Chemicals

In this study, the following chemicals were used for experimental work and all are of analytical grade of purity:

- Fexofenadine Hydrochloride, provided by "Bosnalijek" Sarajevo
- α-cyclodextrin, Sigma Aldrich
- Hydroxy- α-cyclodextrin, Sigma Aldrich
- Methanol, Merck
- Ethanol, Merck

The present work was designed to improve the aqueous solubility of FFN. Before proceeding with the formation of complexes, phase solubility analysis was carried out to determine the feasibility of complex formation between FFN and α-CD. After determining the stability constant value, the inclusion complexes of FFN were prepared using simple methods of inclusion complex formation like kneading and co-precipitation in different molar ratios. Physical mixtures of FFN and α-CD were also prepared for comparison purpose. The so

prepared complexes were then characterized using techniques like infrared-spectroscopy.

**2.2. Experimental procedure**

**2.2.1. Phase solubility studies**

Samples were prepared according to the method of Higuchi and Connors. A series of solutions of α-CD of concentrations ranging from 2mM-10mM in water were prepared. The solubility assay was performed in triplicate. Each of this solution (10ml) was added into a series of 50 ml stoppered conical flasks. A constant amount of pure fexofenadine hydrochloride (10mg) was accurately weighed and suspended into each of these solutions. The samples were left to stir continuously for 72 hours at room temperature (25°C) and then filtered through 0.45µm filter paper. Fresh samples were used to measure the phase solubility on a UV-spectrophotometer with a preliminary dilution corresponding to the interval of the calibration curve on the basis of which the concentration is measured. (Figure 4.)

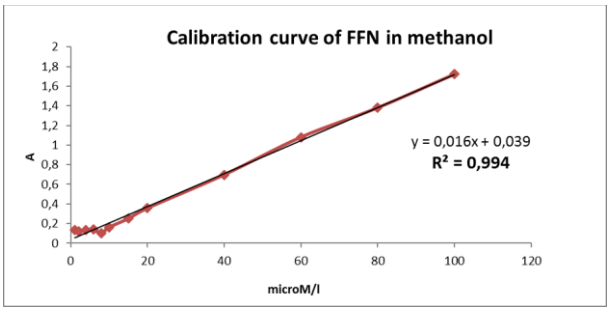



Figure 4. Calibration curve of Fexofenadine Hydrochloride in methanol

**2.2.2. Formulation of inclusion complexes by physical mixing method**

Fexofenadine Hydrochloride and α-CD's were blended in the mortar for 30 min in the molar ratios of 1:1, 1:2 and 2:1. The powder of the physical mixture was left in a desiccator containing anhydrous silica gel. After drying, a FTIR analysis of samples was performed.

**2.3. Apparatus**

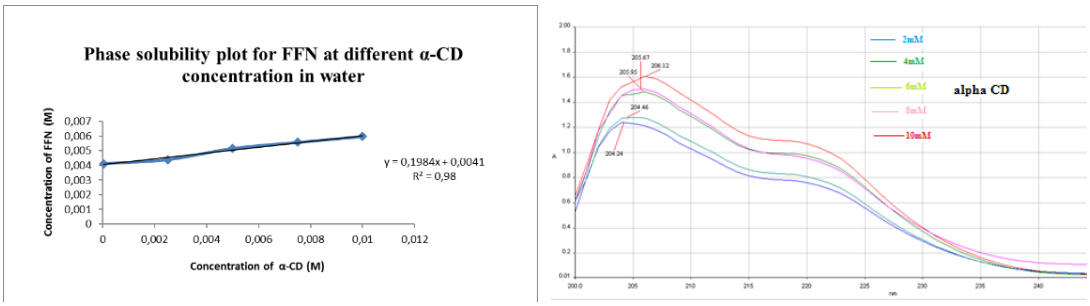
- Phase solubility measurements were done on a UV-spectrophotometer Perkin Elmer Lambda 25 based on a previously constructed calibration curve.
- Qualitative interpretation of the complex was performed with FTIR-spectrophotometer Perkin Elmer 1000; Infrared spectra of the samples were recorded at a resolution of 4 cm-1 and an interval of 4000-400 $cm^{-1}$. The sample is prepared by taking 10 mg of the sample, which is well powdered and homogenized, with about 90 mg of pure and well dried KBr. KBr must be dry during the preparation of the sample because otherwise, bands originating from water appear on the spectrum.

## III. RESULTS AND DISCUSSION

According to USP Solubility criteria [8] FFN is slightly soluble in water. It's aqueous solubility is 2,14 $mg/cm^3$. Therefore, it is of great importance to increase the aqueous solubility of the drug for better efficancy and chemical availability. The use of α-CD as a natural cyclodextrin and its synthetic derivatives, 2-hydroxypropyl-α-cyclodextrin, increases the aqueous solubility of fexofenadine hydrochloride.

Diagram in Figure 5. shows the effect of different concentrations of α-cyclodextrin on the phase solubility of fexofenadine hydrochloride in aqueous medium. According to Higuchi and Connors solubility profile, this belongs to A-type because the solubility of the substance increases with increasing concentration of cyclodextrin. Diagram in Figure 5a. shows $A_L$ type phase solubility and the possibility of forming a 1:1 stoichiometric complex because is slope lower than unity. The stability constant $K_{1:1}$ is calculated from Higuchi and Connors equation using parameters obtained from the phase solubility diagram. The stability constant for samples of fexofenadine hydrochloride-α-cyclodextrine prepared in aqueous solution is $K_{1:1}$=61.72 $M^{-1}$.

UV-VIS spectra of FFN-α-CD complexes is shown in Figure 5b. Spectrum shows batochromic and hyperchromic shift due to the presence of auxochromic groups such as cyclodextrin-derived hydroxyl groups. This indicate that a complex has formed between FFN and α-CD.




(a) (b)

Figure 5. (a) Phase solubility plot for FFN at different α-cyclodextrin concentration in water; (b) UV-VIS spectra of Fexofenadine Hydrochloride at different α-cyclodextrin concentration in water

The most important structural characteristic that determines the formation of a certain complex with certain molecules of a substance is the size of the cyclodextrin cavity. If the substance is too large to be incorporated into the cavity then it is not incorporated or it is partially incorporated into the cyclodextrin cavity. Maximum cavity size of α-cyclodextrin is about 6Å. Minimum transverse length of the benzene ring is 6.3 Å, the cyclohexane ring (7 Å) or the cyclopentane ring 5.8 Å. Thus, it is impossible for any six-membered ring to fully correspond to the α-cyclodextrin cavity.[9] Proof of this is value of a constant that is significantly lower than the stability constant of the complex formed between FFN and beta β-cyclodextrin which is $K_{1:1}$=114.96 $M^{-1}$. [2]

The use of alpha cyclodextrin derivatives achieves better solubility of substances because they are also more soluble in water. In this work, an α-cyclodextrin derivative was used, which is 2-hydroxypropyl-α-cyclodextrin. Prepared samples of FFN in different concentrations of 2-hydroxypropyl-α-cyclodextrin show an increase in the measured concentration with increasing concentration of cyclodextrin and according to the phase profile belongs to A-type phase solubility. Since the slope is less than one, it is an $A_L$ type of complex formation with the most probable 1:1 complexation ratio. (Fig 6.)

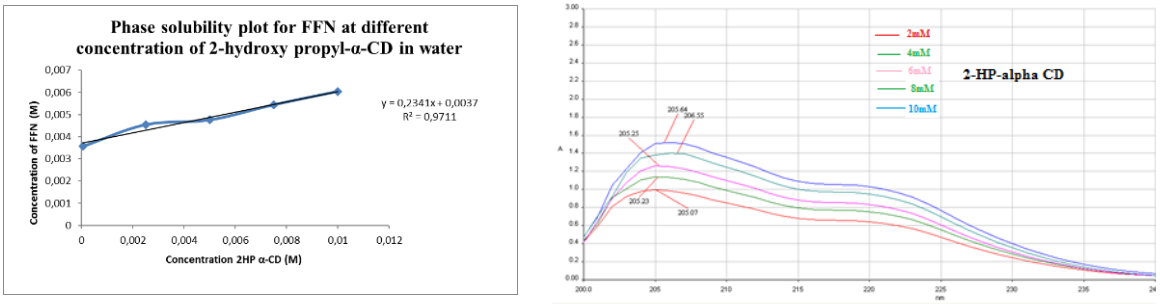



Figure 6. (a) Phase solubility plot for FFN at different 2-Hydroxi-propyl-α-cyclodextrin concentration in water; (b) UV-VIS spectra of FFN at different 2-Hydroxi-propyl-α-cyclodextrin concentration in water

Stability constants for samples prepared in aqueous solution were calculated to be $K_{1:1}$= 76.41$M^{-1}$ and has a slightly higher value of stability constant than samples prepared with α-cyclodextrin ($K_{1:1}$= 61,72$M^{-1}$). This means that there were significant interactions between FFN and alpha cyclodextrin derivatives. The reason for this may be the substitution of alpha cyclodextrin derivatives, which apparently increases the non-polar part of the cyclodextrin cavity and thus better solubilizes the FFN molecule. Comparing the values of the stability constant for FFN samples prepared in aqueous 2-hydroxypropyl-alpha cyclodextrin solution and samples prepared in aqueous 2-hydroxypropyl-beta cyclodextrin solution, it can be concluded that the ffn molecule is more favored by the beta cyclodextrin derivative. The reason for this may be in the fact that beta cyclodextrin has a larger diameter of the non-polar cavity and thus better incorporates the benzene ring of the ffn molecule.[2]

The values of the stabilization constants for α-cyclodextrin, β-cyclodextrin and their derivatives are shown in Table 1.

Table 1. Stability constant values for complexes formed between FFN and different cyclodextrins

| Cyclodextrin (water solution) | Stability constant value $K(M^{-1})$ |
|---|---|
| α-cyclodextrin | 61,72 |
| 2-hydroxypropyl-α-cyclodextrin | 76,41 |
| β-cyclodextrin | 114,96 |
| 2-hydroxypropyl-β-cyclodextrin | 7325,76 |
| Methyl-β-cyclodextrin | 2301 |

**Inclusion complexes of FFN/cyclodextrin by formation physical mixtures**- FFN and α-CD's were blended in the mortar for 30 min in the molar ratios of 1:1, 1:2 and 2:1. The powder of the physical mixture was left in a desiccator containing anhydrous silica gel. After drying, a FTIR analysis of samples was performed. Samples were interpreted using FTIR spectroscopy and the spectra of the samples were compared with the spectrum of pure CRS standard of FFN as well as the spectra of pure uncomplexed cyclodextrins. The FTIR spectra of pure FFN and of its binary mixtures are given in Figure 7. Pure FFN is showing peaks at 3298$cm^{-1}$ (hydroxyl groups), 2937$cm^{-1}$ (acid O-H), 1707$cm^{-1}$ (carboxylic group), 1655$cm^{-1}$ (C=C group), 1448$cm^{-1}$ (butyl chain), 1279$cm^{-1}$ and 702$cm^{-1}$ (aromatic rings).[10]

Characteristic changes in the formed complexes are visible on the IR spectrum. The peak originating from the hydroxyl group and located at about 3300 $cm^{-1}$ shows characteristic changes, is shifted towards larger wavelengths and the band is much less intense and much wider. This is especially pronounced in the molar ratio 2:1 where it is seen that the peak related to the presence of the hydroxyl group is almost completely lost, which is a confirmation that noncovalent interactions between FFN and cyclodextrin have occurred. Also, the peak at about 1700 $cm^{-1}$ originating from the carboxyl functional group is much lower in intensity and shifted towards smaller wavelengths, which is also evidence that there have been interactions between FFN and α-cyclodextrin.

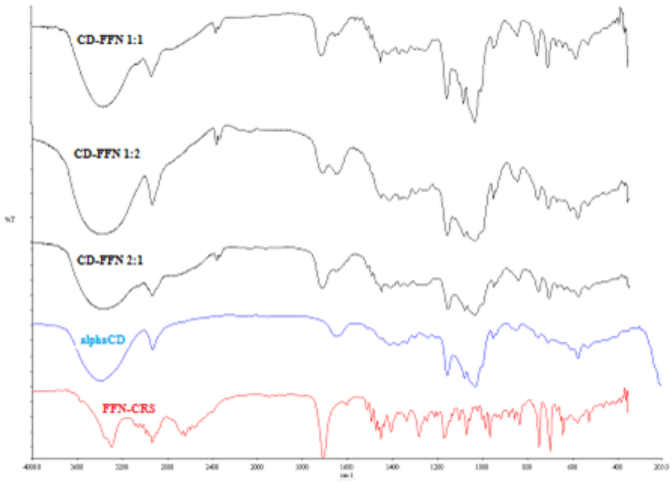



Figure 7. FTIR spectra of a physical mixture of fexofenadine hydrochloride and α-cyclodextrin in molar ratio 1:1, 1:2 and 2:1;

Changes in the IR spectrum are also visible in the formed complexes of the physical mixture FFN and 2-hydroxy propyl-α-cyclodextrin and it is shown in Figure 8. Also, similarly to α-cyclodextin, significant changes are at the peaks related to the hydroxyl and carboxyl functional groups, at about 3300 cm and at about 1700 cm, respectively. This is evidence that a complex has been formed between ffn and alpha cyclodextrin derivatives.

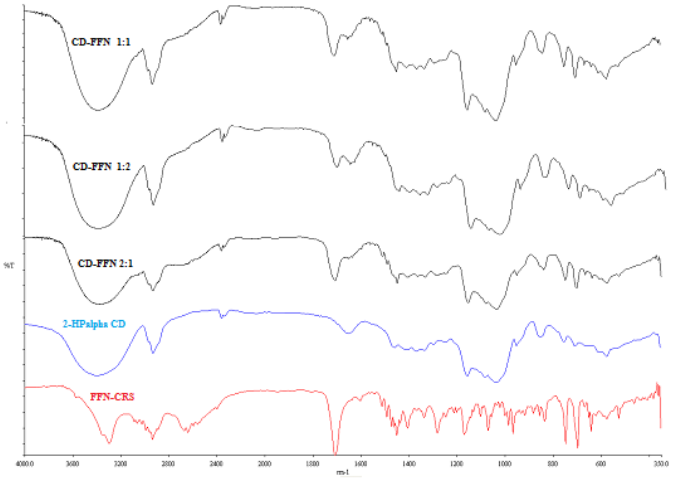



Figure 8. FTIR spectra of a physical mixture of fexofenadine hydrochloride and 2-hydroxipropyl-α-cyclodextrin in molar ratio 1:1, 1:2 and 2:1;

## IV. CONCLUSION

- The phase solubility study of Fexofenadine Hydrochloride showed $A_L$ type of graph using α-CD and 2HP-α-CD (2-10mM) in aqueous solutions;
- Solubility of FFN increases with host concentration in each case;
- In all phase solubility studies 2HP-α-CD showed greater solubility than α-CD;
- An inclusion complex of FFN with α-CD and 2HP-α-CD was found to be formed. UV VIS spectrophotometry was used as a method to confirm the complex;
- Using the FTIR method, the most significant interactions in the formation of inclusion complexes were observed in the complexation ratio 2:1;
- Possible use of inclusion complexes of FFN with α-CD and 2HP-α-CD can be further used in the development of modified release drug delivery system using various polymers.

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