Republic of Iraq

Ministry of Higher Education

And Scientific Research

University of AL-Qadisiyah

College of Pharmacy

A Research Submitted To The College Of Pharmacy For The Requirement Of B.Sc Degree

Preparation of Solid Dispersion For Solubility Enhancement

Done By: Ali Ayed & Abeer Jodah

Supervised By: Dr. Basam Al Zayady

2017 A.D.

1438 A.H.

Dedication

This Research is dedicated to my father, who taught me that the best kind of knowledge to have is that which is learned for its own sake , It's also dedicated to my mother, who taught me that even the largest task can be accomplished if it's done one step at a time.

Thanks to Dr. Bassam who has been the ideal supervisor. His sage advice, insightful criticisms, and patient encouragement aided the writing of this research in innumerable ways, I would also like to thank all of the doctors for the steadfast support for this project , A special thanks to Dr. Bassim Irheim the dean on the college.

(وانزل الله عليك الكتاب والحكمة وعلمك ما لم

تكن تعلم وكان فضل الله عليك عظيماً)

Chapter one

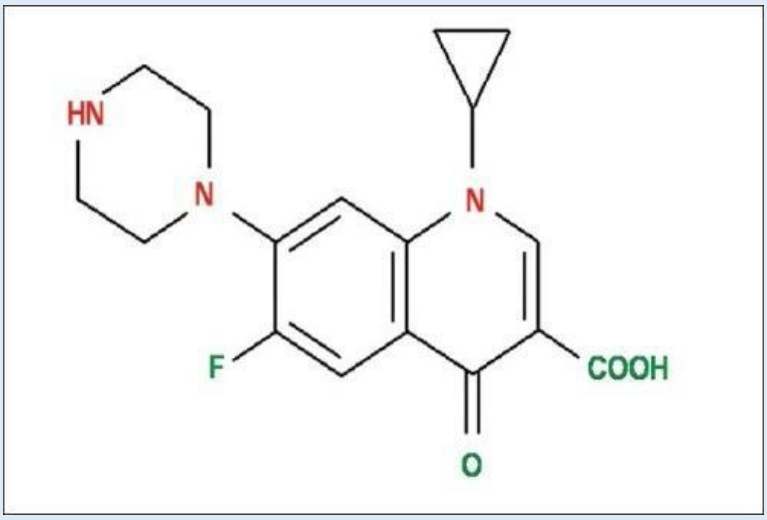
Introduction

1. Introduction

1.1. Ciprofloxacin

Ciprofloxacin is a second-generation fluoroquinolone antibiotic with a broad spectrum of activity that usually results in the death of the bacteria.[1]

Systematic (IUPAC) Name:- 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-quinoline-3-carboxylic acid [2]



It is used to treat a number of bacterial infections such as bone and joint infections, intra-abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections, among

others. For some infections it is used in addition to other antibiotics. It can be taken by mouth or used intravenously.

There are many bacterial infections for which ciprofloxacin can be used for example Shigella, E. Coli, Campylobacter, Pneumonia, H. Influenza, Catarrhalis, Pseudomonas Aeruginosa, Bacteroides Bacteria.[3]

The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for bacterial DNA replication, transcription, repair, and recombination.[6]

Common side effects include nausea, vomiting, diarrhea, and rash. It increases the risk of tendon rupture and worsening muscle weakness in people with the neurological disorder myasthenia gravis.[3]

Rates of side effects appear to be higher than some groups of antibiotics such as cephalosporins but lower than others such as clindamycin.[4] Studies in other animals raise concerns regarding use in pregnancy .[5]

The solubility of ciprofloxacin extremely depends on the pH value. It is almost insoluble in water and alcohol. At pH 4 - 5 it shows the highest solubility (>40 mg/ml).

This corresponds to the hydrochloride form of ciprofloxacin, if the pH value is adjusted with hydrochloric acid. Ciprofloxacin is almost insoluble in the neutral pH range, while solubility increases with increasing pH value (approx. 30 mg/ml at pH 11).

The solubility's of ciprofloxacin in methanol, ethanol, 1-propanol, acetone, and chloroform have been determined with temperatures from 293.15 to 333.15 K by a static equilibrium method.[10]

The stability of the dry substance of ciprofloxacin is very high at room temperature. Solutions in dialysis fluid (25 mg/L) are stable even after 42 days when stored at 37°C [1].

1.2. Solid dispersion (SD)

Oral bioavailability of a drug depends on its solubility and/ or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed.

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carriers or matrix at solid state prepared by melting , solvent evaporation or other technique.[7]

The basic mechanisms responsible for increasing solubility of drugs are: [8]

-Wetting

-Reduced particle size or particle agglomeration

-Soluble complex formation.

- **Techniques of SD**
  - Melting (Fusion) method
  - Solvent Evaporation method
  - Kneading method
  - Spray Drying method
  - Hot Melt Extrusion method.

- **Advantages of SD**: [9]

  Generally, solid dispersion is mainly used

  - To reduce particle size.
  - To improve wet ability.
  - To improve porosity of drug.
  - To decrease the crystalline structure of drug in to amorphous form.
  - To improve dissolvability in water of a poorly water-soluble drug in pharmaceutical.

- **Disadvantages of SD:**

The major disadvantages of SDs are related to their instability, several systems have shown changes in crystalline and a decrease in dissolution rate on ageing.

By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility.

Moisture and temperature have more of deteriorating effect on SD than on physical mixtures [10].

1.3. Polyethylene Glycol 6000

It is a mixture of the polycondensation products of ethylene oxide and water obtained under controlled conditions. It is represented by the formula $HOCH_2\ [CH_2OCH_2]_nCH_2OH$, where n is between 112 and 158.

Description: A creamy white, wax-like solid, powder or flakes; odor, faint and characteristic. Freezing point 53^0 to 56^0.[11] Store protected from moisture [12]

Chapter two

materials and methods

2. materials and methods

2.1. materials used:

- Ciprofloxacin HCl (Lap.medico,India)
- polyethylene glycol 6000
- phosphate buffer (Sodium phosphate monobasic and sodium phosphate dibasic) (Qualikems)
- methanol

2.2 Instruments used in this study :

- sensitive balance
- UV – visible spectrophotometer
- Oven
- Electrical melting point apparatus
- pH meter
- Water bath with shaker

2.3 Methods

2.3.1 *Characterization of Ciprofloxacin HCl*

2.3.1.1 *Determination of Ciprofloxacin HCl Melting Point*

The melting point of Ciprofloxacin HCl was determined according to the method stated by the USP [13]. One side sealed capillary glass tube was dipped in a small amount of Ciprofloxacin HCl . The tube was gently tapped on a solid surface to form a column of powder in the bottom of the tube and then placed in the electrical melting point apparatus, the temperature at which complete melting of powder occurs was recorded as the melting point.

2.3.1.2 *Determination of λ_{max}*

Fifty milligrams of Ciprofloxacin HCl powder was dissolved in 100 ml of phosphate buffer (pH 6.8) to prepare 0.5 mg/ml stock solution. From this stock solution, a dilute (0.01 mg/ml) solution was prepared and scanned by UV spectrophotometer at the range of 200-400 nm, in order to determine the wave length of maximum absorbance (λ max).

2.3.1.3 *Determination of Calibration Curve*

Calibration curve of Ciprofloxacin HCl in phosphate buffer solution (pH 6.8) was constructed by preparing serial dilutions of the drug from 0.5 mg/ml stock solution.

These serial dilutions included the following concentrations: (0.002, 0.004, 0.008, 0.012, 0.016, and 0.02) mg/ml

The absorbance of each solution were obtained by spectrophoto-metrical analysis at the wave length of maximum absorbance and plotted against concentration to obtain the calibration curve.

2.3.1.4 *Determination of Ciprofloxacin HCl Solubility*

An equilibrium solubility determination of Ciprofloxacin HCl was carried out using the shake flask method [14] in phosphate buffer solution (pH 6.8) media.

An excess amount of the drug was added to 20mL of phosphate buffer solution in a 50mL stoppered glass bottle, and stirred in a water bath with shaker at 37±2°C. Sample was taken after 48 hours, filtered, diluted with test medium, and then the UV absorbance of the drug was determined spectrophotometrically

at its λ max, and from this absorbance the concentration of that saturated solution was determine which represents the solubility of Ciprofloxacin HCl in phosphate buffer solution.

2.3.2 *Preparation of Ciprofloxacin solid dispersion by* **Solvent evaporation method**

Different formulas of Ciprofloxacin solid dispersion were prepared as shown bellow using solvent evaporation method.

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight.

The first step in the solvent method is the preparation of a solution containing both matrix material and drug.

The second step involves the removal of solvent resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties [15]

Different formulation patches were prepared as bellow:

F1 : drug 1 : 1 polymer polyethylene glycol 6000

F2: drug 1 : 2 polymer polyethylene glycol 6000

Solvent evaporation method: Required amount of drug is accurately weighed and transfer in to mortar. The drug and the polymer were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 70 c temperature with continuous stirring to obtain dry granules.

F3: Physical Mixture: Accurately weighed required amount of Ciprofloxacin and polyethylene glycol 1:1 drug-to-carrier weight ratio were mixing thoroughly in a mortar until a homogeneous mixture was obtained for 3 min.

The product was kept in desiccators at room temperature until for further study or investigation.

Chapter four

Results and discussion

3. Results and discussion

3.1. Characterization of ciprofloxacin HCl

3.1.1. *Determination of ciprofloxacin HCl Melting Point*

The melting point of ciprofloxacin HCl was found to be 232 °C. This result is the same as reported in the British Pharmacopoeia [16] which indicates the purity of the drug powder.

3.1.2. *Determination of λ_{max}*

Scanning the solution which contains (10) µg/ml of ciprofloxacin HCl in phosphate buffer solution (pH 6.8) by UV spectro-photometer at 200-400 nm, gave the spectrum with a maximum absorbance peak at 276 nm. These results are in agreement with the reported one.[16]

3.1.3. *Construction of Calibration Curve*

Calibration curve of ciprofloxacin HCl in phosphate buffer (pH6.8) was constructed and represented in figure bellow which was obtained by plotting the absorbance versus concentration. The straight line indicates that calibration curve obeys Beer's law within the range of concentration used.

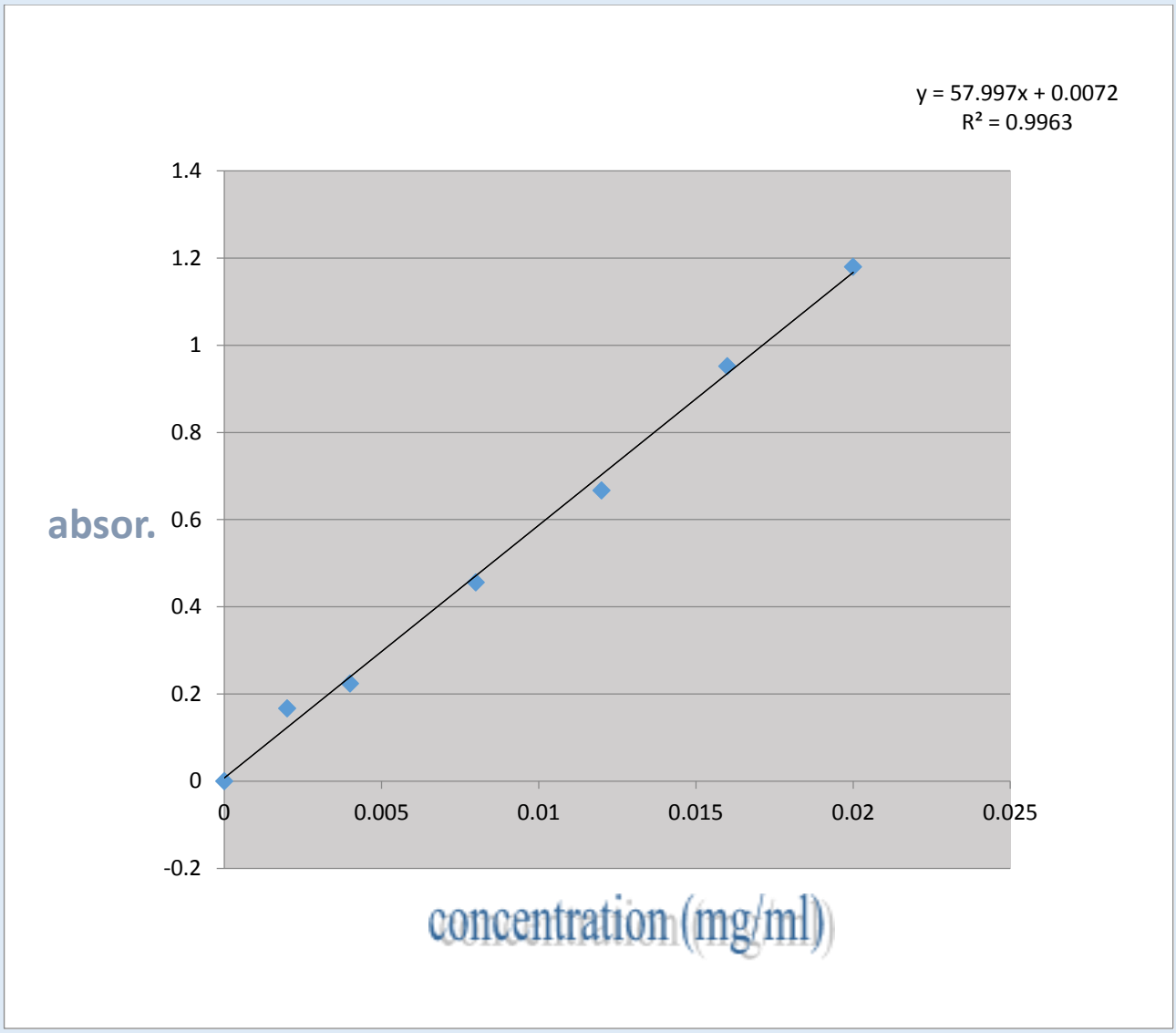


Figure : Calibration curve of ciprofloxacin HCl in phosphate buffer *(PH 6.8 at 37° C)*

3.1.4. *Determination of ciprofloxacin HCl Solubility*

3.1.4.1. pure drug

After 48 hours in the water bath with shaking, solubility in phosphate buffer (pH 6.8) was measured spectrophotometrically, it was **91 mg/ml**.

3.1.4.2. SD preparations

a- F1 formula

The solubility of ciprofloxacin HCl in F1 solid dispersion preparation was found (**144 mg /ml**) in the phosphate buffer

b- F2 formula

The solubility of ciprofloxacin HCl in F2 solid dispersion preparation was found (**119.3 mg /ml**) in the phosphate buffer .

3.1.4.3. physical mixture

The solubility of ciprofloxacin HCl in F3 physical mixture preparation was found (**110 mg /ml**) in the phosphate buffer .

Discussion

The first trail was done by using pure drug; it has shown poor dissolution property because of less solubility of drug in the dissolution medium. Improvisation: As pure drug has shown poor dissolution property, in order to enhance the dissolution rate we used different methods for preparing solid dispersions.[17]

In solid dispersion F2 formula the drug was prepared by using polyethylene glycol 6000 as a disintegrant in the ratio of 1:2 and by using Solvent evaporation method, the solubility was increased from 91 to 119.3 mg/ml.

Nearly the same result was obtained in the F3 formula in which the drug was mixed physically with the polyethylene glycol 6000 and the solubility obtained was 110 mg/ml.

The best result was obtained with the formula F1, in this trail solid dispersion of drug was prepared by using polyethylene glycol as a disintegrant in the ratio of 1:1 and by using Solvent evaporation method and the solubility was increased to 144 mg /ml .

SUMMARY AND CONCLUSION:

This study was undertaken with an aim to formulate an Anti-Biotic drug in the form solid dispersion to overcome the poor solubility drawback of the drug. [18]

The selected Antibiotic agent was Ciprofloxacin. The drug Ciprofloxacin is having poor solubility in the water.

Solid dispersions were prepared by using the polyethylene glycol as a disintegrant in 1:1 and 1:2 ratios.

Among the different techniques used for preparation of solid dispersions solvent evaporation technique has been used shown the increase in dissolution rate that is the F1 was found to has a faster solubility and dissolution property which was prepared by using polyethylene glycol as a disintegrant in the ratio of 1:1. Hence finally it was concluded that F1 as an optimized formula with an increased rate of dissolution rate and solubility.

Chapter five

References

References

1. Ball, P. (2000). **"Quinolone generations: Natural history or natural selection?".** Journal of Antimicrobial Chemotherapy. 46: 17–24
2. https://en.wikipedia.org/wiki/Ciprofloxacin.
3. ciprofloxacin hydrochloride. **The American Society of Health-System Pharmacists**. Retrieved Aug 23, 2015.
4. Heidelbaugh, J. J.; Holmstrom, H (2013). **"The perils of prescribing fluoroquinolones**". The Journal of family practice. 62 (4): 191–7
5. **"Prescribing medicines in pregnancy database"** Australian Government. 23 Aug 2015.
6. San Diego, C. **Ciprofloxacin: In Vitro Activity, Mechanism of Action, and Resistance**. Rev Infect Dis 1988; 10 (3): 516-527.
7. Chiou WL, Riegelman S. **Pharmaceutical applications of solid dispersion systems**. J Pharm Sci. 1971;60(9):1281-1302.
8. Amidon, G. L.; Lennernas, H.; Shah, V. P.; Crison, J. R. Theoretical basis for a biopharmaceutical drug

classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995; 12 (3), 413-420.

9. Lachman L, Lieberman HA, Kanig JL eds**. The theory and practice of industrial pharmacy**. 3rd ed. Bombay, Varghese Publishing house; 1987;p 61-69.
10. Butler, MJ**. Method of producing a solid dispersion of a poorly water-soluble drug**. US Patent No. 5 1999;985:326.
11. Mogal S., Gurjar P.,Yamgar D. and Kamod A.C. **Solid dispersion technique for improving solubility of some poorly soluble drugs.** Der Pharmacia Lettre, 2012, 4 (5):1574-1586
12. **Indian Pharmacopoeia 2007 volume First** ,Government of India , Minstery of health & family welfair, New Delhi.
13. **United States Pharmacopoeia XXX**. The USP Convention. 2007
14. Wei-Qin (Tony) Tong. **Practical aspects of solubility determination in pharmaceutical preformulation** In: Augustijns P, Brewster ME, editors: **Solvent systems and**

their selection in pharmaceutics and biopharmaceutics. New York : Springer, 2007, p 138-140.

15. Okonogi S, Puttipipatkhachorn S. AAPS PharmSciTech. 2006:7(2): E1-E6.

16. **British Pharmacopeia (BP)**, 2010.

17. Kameswararao Sankula , Saieswar Kota, Srinath Nissankarrao. **Enhancement of Dissolution rate of Ciprofloxacin by using various Solid Dispersion Techniques.** International Journal of Pharma Research and Health Sciences2014;2(1):80-86

18. Brahmaiah Bonthagarala*, Leela Madhuri Pola and Sreekanth Nama. **ENHANCEMENT OF DISSOLUTION RATE OF CIPROFLOXACIN BY USING VARIOUS SOLID DISPERSION TECHNIQUES**. International Journal of Pharma Research and Health Sciences 2013;4(11):4376-4383