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Research Article

Determination of Saturated Solubility of Mirtazapine Using UV Visible Spectrophotometer

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Abstract

Solubility is an important parameter for designing new drug formulations. Many drugs possess poor aqueous solubility hence, poor bioavailability. Many pharmaceutical industries face these issues while designing new drug entities. A new assessment revealed that about 70–90% of drug candidates are in the development stage, while up to 40% of the marketed products are water-insoluble which leads to low bioavailability, reduced therapeutic effects, and increased dose. Poor solubility is one of the major driving forces behind the development of numerous new drugs. There are various techniques to enhance the drug solubility such as particle size reduction, Nano-suspension, use of surfactants, salt formation, solid dispersion, etc. Mirtazapine (BCS Class II) has poor water solubility; to test an optimum pH for its solubility saturated solubility method was applied. Saturated solubility is a method in which drugs with poor solubility are dissolved in different acidic, basic media, and in distilled water. This study suggests proper dissolution media improves the solubility of water-insoluble drugs. UV-spectroscopy is a method to determine the solubility of drugs in various media and through this method, maximum absorption at a particular wavelength is determined for drug solution. Afterward, this solution of the drug, in various media, is studied to decipher the unknown concentration of the drug in a given solution by the Beer-Lambert law. With the aid of UV-spectroscopy, it was determined that the solubility of mirtazapine increases with increasing pH of mediums.

Keywords: Dissolution medium, mirtazapine drug, poor water solubility, saturated solubility, UV spectrophotometer.

1. Introduction

A homogenous solution of solute i.e., a solid, liquid, or gaseous chemical substance is formed by dissolving it in a solid, liquid, or gaseous solvent. The solubility of a substance essentially depends upon the solvent as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not lead to any increase in its concentration in the solution. In quantitative terms, solubility refers to the maximum amount of a solute in a solvent at a specific temperature. Whereas, qualitatively solubility means that when a solute (solid, liquid, or gaseous) is dissolved in a solvent (solid, liquid, or gaseous) it forms a homogeneous solution. Moreover, a saturated solution is the one in which the solute is in equilibrium with the solvent. (Lipinski 2002, Stegemann et al. 2007). Drug solubility is the maximum concentration of the drug (solute) dissolved in the solvent under specific conditions of temperature, pH, and pressure. (Khuwijitjaru, Adachi, and Matsuno 2002). The drug solubility in saturated solution is a static property, whereas the drug dissolution rate is a dynamic property that relates more

Table 1. Descriptive terms of drug dissolved in a solvent.

Descriptive Terms	Approximate volume of solvent in milliliters per gram of solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very Slightly Soluble	From 1000 to 10,000
Insoluble	More than 10,000

closely to the bioavailability rate (Kumar and Singh 2016). Furthermore, the solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction. The solubility of a drug is described in various descriptive terms in Table 1 which is based on the amount of drug dissolved in milliliters of solvent.

The main purpose of mirtazapine, an atypical antidepressant, is to treat major depressive disorder (MDD). In 1989, researchers synthesized this drug (Ottman, Warner, and Brown 2018). In 1994, the Netherlands approved the use of mirtazapine to treat MDD (Watanabe et al. 2011, De Boer 1996). In 1996, the FDA in the US finally authorized it for the treatment of moderate to severe depression. Tetracyclic antidepressants, or TeCAs, include mirtazapine. Mirtazapine acts by increasing the release of serotonin and norepinephrine the central presynaptic alpha-2-adrenergic receptors inhibition. Another name for mirtazapine is a noradrenergic and selective serotonergic antidepressant (Nutt 2002, Schwasinger-Schmidt and Macaluso 2019).

Moreover, it has a strong sedative and soothing effect, exerted through H_1 histamine receptors as well as 5-HT2A, 5-HT2C, and 5-HT_3 serotonin receptors (Ezealisiji, Mbah, and Osadebe 2015, Shafiq et al. 2007). Mirtazipine at the dose of 15 mg, 30 mg, and 45 mg is available commercially. With a logarithm partition coefficient (octanol-water) of 2.9, mirtazapine is very hydrophobic and almost insoluble in water.

The pharmacokinetic profile of mirtazapine shows that it has a longer half-life (20–40 hours), strong protein binding (85%), and an average bioavailability (50%). Therefore, it was presumed that improving mirtazapine's water solubility would in turn increase its bioavailability, decrease protein binding as well as half-life, inevitably lessening its adverse symptoms (Lee, Langer, and Shastri 2003). Another study aimed to know the saturated solubility of the drug in different solutions at various pH (Yıldız et al. 2018).

Drug absorption from the gastrointestinal tract (GIT) can be limited by a variety of factors most significant contributor being poor aqueous solubility and limited membrane permeability of the drug molecule. When administered orally, an active agent must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach the systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing of solubility, and dissolution rate of poorly water-soluble drugs (Patel et al. 2007). The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs, the rate-limiting step is drug release from the dosage form and solubility in gastric fluid and not the absorption. The BCS classification system is given in Table 2. Therefore, increasing the solubility in turn increases the bioavailability for BCS class II & IV drugs (Patil, Pawar, and Sahoo 2012).

Novel molecules with less aqueous solubility encounter various problems during generic drug

Table 2. Biopharmaceutics Classification System.

BCS Class	Solubility And Permeability	Examples Of Drugs	Solubility in water
BCS Class I	High Solubility High Permeability	B-Blockers i.e., Propranolol	29mg/ml
BCS Class II	Low Solubility High Permeability	Anti-psychotics i.e., Mirtazapine	0.09mg/ml
BCS Class III	High Solubility Low Permeability	H2 Blockers i.e., Ranitidine	660mg/ml
BCS Class IV	Low Solubility Low Permeability	Diuretics i.e., furosemide.	0.0182mg/ml

development as well as formulation development. Many drugs are either weak acids or weak bases and are poorly water-soluble. The reduced solubility of the drug results in poor absorption, and variable bioavailability and is harmful to GIT mucosa. Dealing with drug dissolution is a big challenge for formulation scientist (Kumar and Singh 2016).

2. Materials and Methods

2.1 Materials

The model drug mirtazapine (Organon and CO Pharmaceutical Company in New Jersey USA; having 100.09% purity with standard drug) was gifted by Wilshire Pharmaceutical Company Lahore, Punjab, Pakistan. All chemicals for manufacturing buffer solutions were purchased from a local market in Khyber Pakhtunkhwa, Pakistan. Some organic solvents i.e. methanol, acetonitrile, and reagent i.e. HCl of analytical grade were also purchased.

2.2 Methods

2.2.1 Scanning of λ_{max} of the Drug in Different Dissolution Media

Scanning of λ_{max} of mirtazapine was done using a UV-visible spectrophotometer. Scanning in diverse dissolution medium (e.g. distilled water, acetate buffer pH 3.6, acetate buffer pH 4.5, acetate buffer pH 5.6, phosphate buffer pH 6.8, phosphate buffer pH 7.5) was completed.

A stock solution of mirtazapine was prepared in each medium. The stock solution was prepared by dissolving 100mg drug per ml methanol and making up the volume to 100 ml in a volumetric flask. Then dilutions were done till the mark using a particular solution of given media. Moreover, the λ_{max} of mirtazapine in all solutions was scanned under spectrum mode in the wavelength range from 200 – 400 nm, and peaks were recorded (Larsson 2009).

2.2.2 Determining Standard Curve in Different Media

Standard curves of mirtazapine were observed in different dissolution media, such as distilled water, acetate buffer pH 3.6, acetate buffer pH 4.5, acetate buffer pH 5.6, phosphate buffer pH 6.8, and phosphate buffer pH 7.5). The stock solution of the drug was prepared in every medium. For its preparation, 100 mg of the drug was taken in a volumetric flask and dissolved in 1 mL of methanol. After that, dilution was done till the mark using a particular solvent. Further, the dilutions were made using the same dissolution medium to make different concentration solutions for the standard curve. The λ_{max} of the drug in each medium was scanned using a UV Visible Spectrophotometer. The temperature of the media was maintained at 35^0C (Galande et al. 2012).

2.2.3 Saturated Solubility

Saturated solubility of the drug was determined in distilled water, and various buffers from pH 1.2 to pH 7.5 mL medium. The required pH media was taken in 5 mL amber-colored glass vials. An excess amount of drug was added to each vial and then it was closed with a stopper. Those glass vials were attached to an orbital-shaking water bath. The

Table 3. The scanned drug λ_{max} values in different dissolution media

Dissolution medium used for the drug	Scanned drug λmax (nm)
Distilled water	292
0.1 N HCl (pH 1.2)	292
Acetate Buffer pH 3.6	292
Acetate Buffer pH 4.5	292
Acetate Buffer pH 5.6	292
Phosphate Buffer pH 6.8	292
Phosphate Buffer pH 7.5	292

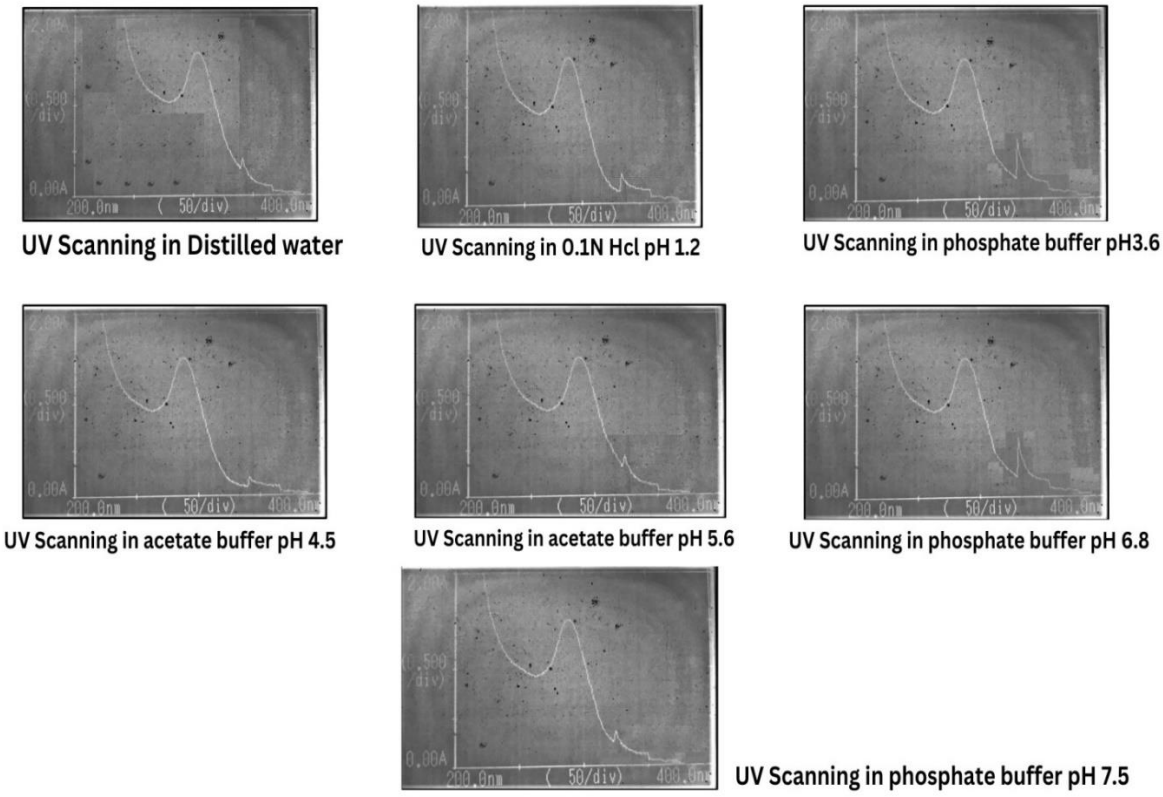

Figure 1. UV Scanning of mirtazapine in various pH solutions.

shaking was done for 48 hours at a speed of 50 rpm and the temperature maintenance was done at around 37 ± 0.5 °C. The resulting test samples were filtered using syringe filters with 0.22 μm pore size. The filtrate was collected and after suitable dilutions with the same solvent, the absorbance of the drug was taken with a UV-visible spectrophotometer (UV – 1601PC, Shimadzu Corporation, Japan) at the pre-scanned λ_{max} in a particular solvent. Then the absorbance was converted into concentration by using a standard curve of a drug in the respective solvent (Wahbi et al. 2002).

3. Results

3.1 Scanning λ_{max} of Drug in Dissolution Media with Different PH

Scanning of wavelengths (λ_{max}) of drug in diverse dissolution medium is given in Figure 1. It was found that the wavelength of the drug was the same in all dissolution media. This shows that the

Table 4. Linear equation and correlation coefficient values in different dissolution media

Solvent used for study	Linear equation (y=mx+c)	Correlation Coefficient (r2)
Distilled Water	y = 0.0067x+0.2206	0.9201
0.1 Hcl (pH 1.2)	y = 0.0143x+0.2484	0.9261
Acetate Buffer pH 3.6	y = 0.0233x+0.2258	0.9532
Acetate Buffer pH 4.5	y = 0.0236x+0.3029	0.9688
Acetate Buffer pH 5.6	y = 0.0204x+0.4483	0.9888
Phosphate Buffer pH 6.8	y = 0.031x+0.1451	0.9937
Phosphate Buffer pH 7.5	y = 0.0202x+0.2627	0.9891

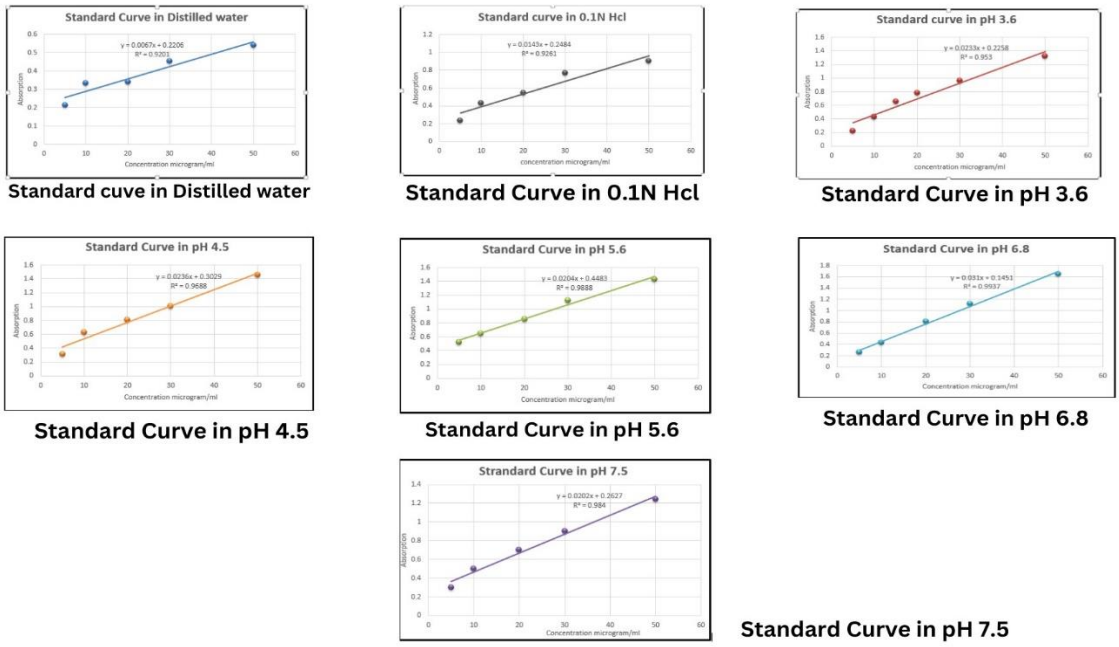

Figure 2: Standard curve mirtazapine in different pH.

wavelength of the drug is not affected by the pH of the dissolution medium.

3.2 Standard Curve in Various Dissolution Media

The standard curve of the drug in different aqueous media was established, as shown in Figure 2. The linear equation and co-efficient correlation (r^2) values of the standard curves in various media are presented in Table 4. The results showed excellent correlation coefficients for drugs in different dissolution media. A significant correlation between the analyte concentration and absorbance was found, which proved the method to be appropriate for analysis.

3.3 Saturated Solubility Study

Saturated solubility of mirtazapine in various dissolution media was studied. Data is given in Figure 3. It was demonstrated that the solubility of the drug varies with the variation of pH of different dissolution media.

4. Discussion

Due to the poor aqueous solubility of mirtazapine, this study was designed to know its solubility at different pH levels. For this purpose, the saturated

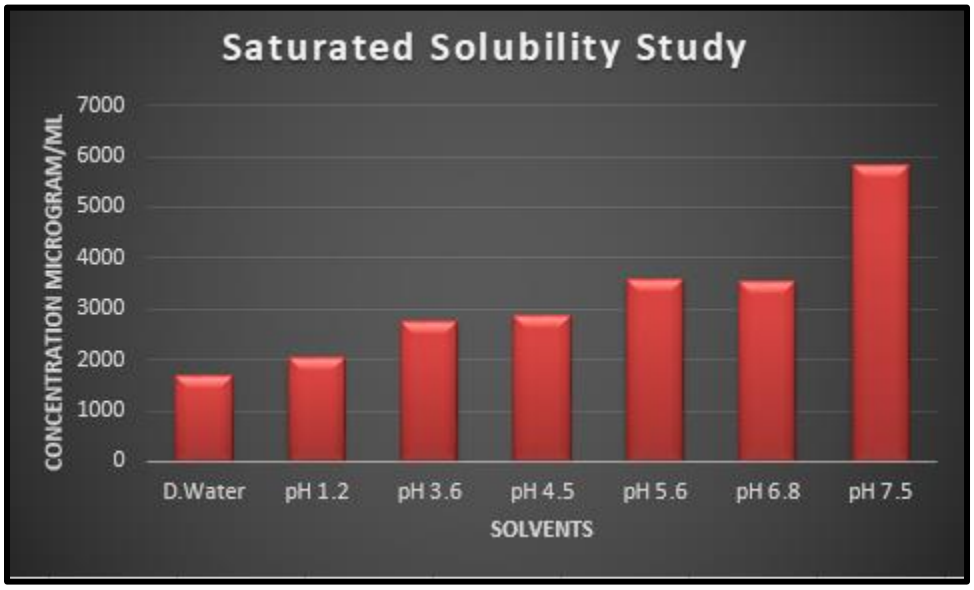

Figure 3: Saturated solubility study for mirtazapine.

solubility of the drug was expressed and analyzed with the help of a UV spectrophotometer (Larsson 2009). Analysis showed that scanning of the drug was not different at the maximum wavelength of the drug at the UV spectrophotometer. That demonstrated that every medium contained the drug but in a specific amount.

A saturated solubility study was done to determine if there was a correlation between the absorbance of the drug at maximum wavelength and concentration of the drug at different pH levels of dissolution medium (Patel et al. 2007). The correlation coefficient equation was obtained with the help of a standard curve that was drawn between the concentration and absorbance of the drug at the maximum wavelength of the drug. The correlation coefficient equation showed that as the pH of the dissolution medium was increased the high concentration of the drug was solubilized and the absorbance value correspondingly increased at the spectrophotometer. This study showed that the solubility of mirtazapine is dependent on pH.

In Figure 3 the data for the saturated solubility study is given. This study shows that the solubility of mirtazapine is minimal in distilled water because of the unionization of the drug. The unionization of a drug increases its permeability, but solubility becomes limited in a particular medium. At pH 7.5 the drug was completely ionized, and its solubility was optimal. Analysis of mirtazapine revealed that the solubility of a poorly water-soluble drug could be increased if the pH of a dissolution medium was enhanced (Kumar and Singh 2016).

5. Conclusion

The current study was designed to determine the saturated solubility of mirtazapine. This study revealed that mirtazapine exhibits pH-dependent solubility. Its solubility is least at the acidic pH of 1.2, which is the pH of gastric acid. The lowered solubility begets limited bioavailability of the drug from the stomach. While solubility profile of the drug improved as the pH of the dissolution media was increased. Essentially, the study concluded that mirtazapine's solubility could be enhanced by increasing the pH of the dissolution media.

Conflict of Interest

The authors declare that they have no conflicts of

interest to disclose.

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Study Approval
There are no animal/human subjects involved so, this study requires no institutional or ethical review board approval.

Consent Forms
NA.

Authors Contributions
YS conceptualized the study and wrote the final manuscript, FA and S helped with the experimentation, literature search analysis, and writing the first draft, FK and S did the literature search and review of the studies, and YS supervised the whole project and wrote the final manuscript.

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