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Solubility and Dissolution Rate Determination of Different Antiretroviral Drugs in Different pH Media Using UV Visible Spectrophotometer

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Abstract: Solubility and dissolution rate of three antiretroviral drugs such as lamivudine, zidovudine and stavudine was studied in four media having different pH. The samples were analyzed by using UV Visible spectrophotometer. lamivudine shows more solubility that is 276.08 mg/mL in 0.01 N HCl. Stavudine showing highest solubility that is 101.23 mg/mL in pH 4.5 acetate buffer. Zidovudine showing highest solubility that is 28.90 mg/mL in both water and 0.01 N HCl. All three drugs showing lower solubility in pH 6.8 phosphate buffer. Lamivudine and stavudine showing good dissolution rate in all media and showing similar release profiles and good correlation, whereas in zidovudine it was clearly observed a slower release at initial time points and then faster release profiles. The solubility and dissolution data in various media is helpful in predicting the bioavailability and also in dissolution method development.

Keywords: Solubility, GIT, Dissolution, Antiretroviral drugs.

Introduction

The oral bioavailability of a drug is a highly complicated property. It is mainly depends on the drug's solubility in the gastrointestinal tract and its absorption into the blood stream[1, 2]. Aqueous solubility of a chemical is defined as the amount of solute dissolved in a saturated

aqueous solution under equilibrium conditions. Solubility is not only a property of interest to many areas of academic research, but also a key parameter when it comes to drug design and formulation development in the pharmaceutical industry[3]. The solubility of active ingredient(s) is one of the key aspects in screening of possible dissolution media[4] for the oral dosage forms. The dissolution of formulations in different media is a regulatory requirement[5] and is directly useful in predicting the drug absorption throughout the gastro intestinal tract. However, the solubility of drug molecules varies considerably with the pH, and as the pH takes different values throughout the gastrointestinal tract. pH-dependent solubility would significantly assists in improving the modeling of oral bioavailability of drugs. In pre-formulation drug solubility in different pH media is important aspect because it directly simulate the drug absorption through out the GI tract[6-8]. Hence solubility and dissolution rate are interrelated because the dissolution rate is mainly depends on the drug solubility in the dissolution medium. In the present research work we have studied the solubility and dissolution rate of three anti retroviral drugs such as lamivudine, zidovudine and stavudine. These dugs are official in the United States Pharmacopoeia (USP)[9].

Experimental

Instruments

All the absorbance values were measured on UV- visible spectrophotometer Schimadzu, UV-1700 E 23. Mechanical shaker, ORBITEX, Scigenics biotech was used for shaking of volumetric flasks. The in vitro dissolution studies were performed using USP type I dissolution apparatus LABINDIA, DISSO-2000, Mumbai, India.

Materials

Lamivudine, zidovudine, and stavudine were obtained as a gift sample from Alkem laboratories Ltd (Mumbai, India). The tablets for dissolution rate determination were purchased form commercial market. All other chemicals and reagents used in the study were of analytical grade.

Construction of standard calibration curves for lamivudine, zidovudine and stavudine

Accurately weighed quantity of lamivudine was transferred in to the volumetric flask. Required quantity of water was added to the above volumetric flask. Shake the volumetric flask until the complete solubility of the drug and make up the volume with remaining quantity of water. This is stock solution for the construction of lamivudine standard calibration curve. Similarly stock solutions for lamivudine were prepared in the following media such as 0.01 N HCL, USP acetate buffer pH 4.5 and USP phosphate buffer pH 6.8. Standard calibration curves for lamivudine were constructed using above stock solutions. Similarly above mention procedure was applied to zidovudine and stavudine for the construction of standard calibration curves.

Determination of solubility for lamivudine zidovudine and stavudine in various pH media

Required quantity of water was transferred in to volumetric flask. The water was heated up to 37 ± 0.5^{0}C using magnetic stirrer provided with heat. Previously weighed quantity of lamivudine was added to the above volumetric flask until the saturation point occurs. The total quantity of lamivudine added was recorded. Stirring was continued up to 5 hours at 37 ± 0.5^{O}C. The sample was filtered through 0.45 µm membrane filter (MILLIPORE). A measured

quantity of filtered sample was transferred in to another volumetric flask and made further dilutions. The absorbance was measured using UV visible spectrophometer. Repeat the same process mentioned above using 0.01 N HCL, USP acetate buffer pH 4.5 and USP phosphate buffer pH 6.8. Similarly the above process was applied to zidovudine and stavudine for the determination of solubility. The results were graphically represented in Figure 1. The solubility in different media was summarized in Table 1.

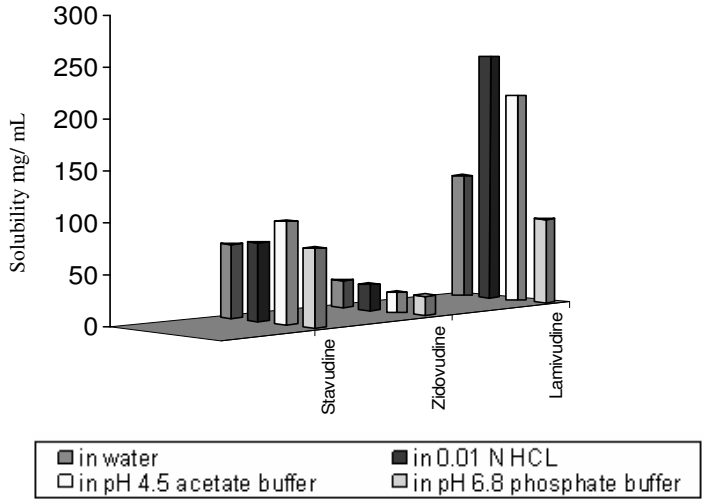

Figure 1. Solubility data of lamivudine, zidovudine and stavudine in various pH media

Table 1. Solubility of lamivudine, zidovudine and stavudine in various pH media

	Water	0.01 N HCl	pH 4.5 Acetate buffer	pH 6.8 phosphate buffer
LAMI , mg/mL	140.01	276.08	230.50	92.76
ZIDO, mg/mL	28.90	27.36	21.36	20.10
STAV, mg/mL	75.36	78.19	101.23	76.13

Key: LAMI-Lamivudine, ZIDO-Zidovudine, STAV-Stavudine.

Determination of dissolution rate for lamivudine zidovudine and stavudine in various pH media

The drug release rate form stavudine capsules was characterized using USP type 1 at 75 rpm, 900 mL of dissolution medium at 37 $\pm$ 0.5^{O}C. The dissolution media used in the study were water, 0.01 N HCL, USP acetate buffer pH 4.5 and USP phosphate buffer pH 6.8. A sample of 5 mL of sample was withdrawn form the dissolution medium and replaced with 5 mL of blank media. The samples were withdrawn at 5, 10, 15, 30 and 45 minutes and analyzed using UV visible spectrophometer. The results of dissolution rate were summarized in Table 2 and Figure 4.

The drug release rate form lamivudine and zidovudine form tablets were characterized using USP type 2 at 50 rpm, 900 mL of dissolution medium at 37$\pm$0.5^{O}C. The various dissolution media used in the study were water, 0.01 N HCL, USP acetate buffer pH 4.5 and USP phosphate buffer pH 6.8. A sample of 5 mL of sample was withdrawn form the dissolution medium and replaced with 5 mL of blank media. The samples were withdrawn at

5, 10, 15, 30 and 45 minutes and analyzed using UV visible spectrophometer. The results of dissolution rate were summarized in the Table 2, Figures 2 and 3.

Table 2. In-vitro dissolution rate of lamivudine tablets 150 mg, zidovudine tablets 300 mg and stavudine capsules 30 mg in various pH media

	Water			0.01 N HCl			pH 4.5 Acetate buffer			pH 6.8 phosphate buffer		
Time min	Cumulative % released											
	LAMI	ZIDO	STAV	LAMI	ZIDO	STAV	LAMI	ZIDO	STAV	LAMI	ZIDO	STAV
5	95	76	86	91	53	88	94	55	92	89	62	87
10	95	88	92	93	88	99	95	73	99	92	76	96
15	96	92	100	93	93	100	95	86	100	96	88	100
30	96	96	100	95	95	100	96	91	100	99	91	100
45	97	99	100	96	99	100	99	97	100	99	96	100

Key: LAMI-Lamivudine tablets 150 mg tablets, ZIDO-Zidovudine 300 mg tablets, STAV-Stavudine 30 mg capsules.

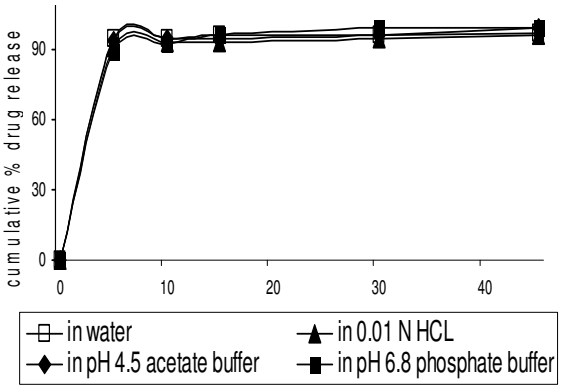

Figure 2. Drug release rate of Lamivudine tablets 150 mg in various pH media

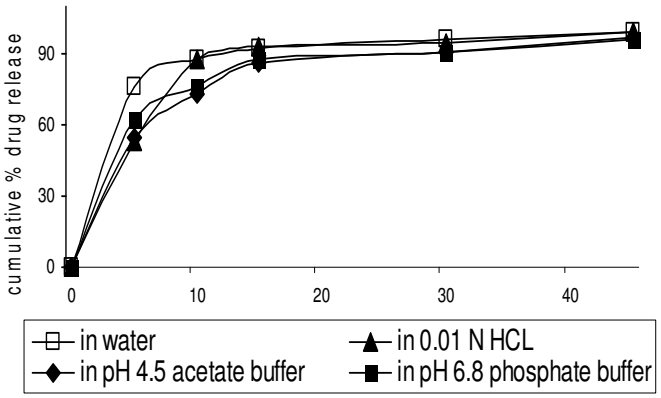

Figure 3. Drug release rate of Zidovudine tablets 300 mg in various pH media

Results and Discussion

All three drugs lamivudine, zidovudine and stvudine showing good solubility profile in all pH media. Lamivudine shows highest solubility in 0.01 N HCl where as stavudine showing highest solubility in pH 4.5 acetate buffer. Zidovudine showing highest solubility in both water and 0.01 N HCl. All three drugs showing lowest solubility in pH 6.8 phosphate buffer, however it is negligible when compared with the dosage wise solubility as defined in bio pharmaceutical system (BCS) of solubility classification. Figure 1 is the graphical representation of solubility data of all the drugs.

The dissolution of lamivudine and stavudine in all pH media showing similar release profile and showing good correlation (Figure 2 and Figure 4), whereas in case of zidovudine it was clearly observed a slower release at initial time points (Figure 3) and then showing faster release profiles. The overall dissolution rate of all these three drugs showing more than 86 % of drug release form their dosage forms is clearly indicating the availability of drug at the site of absorption.

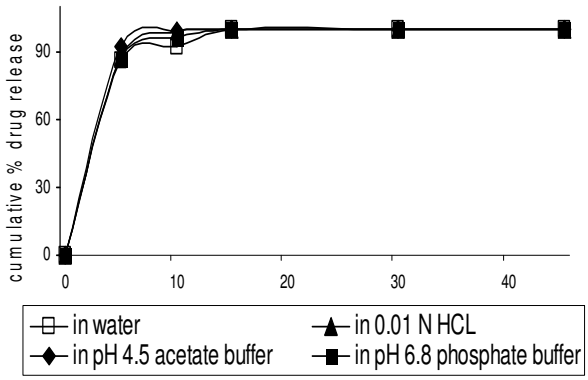

Figure 4. Drug release rate of stavudine capsules 30 mg in various pH media

Conclusion

Solubility determination in various pH media is a prerequisite in drug development because it gives the complete idea of drug behavior in various pH media. With the solubility data we can predict the drug absorption. Based on the solubility data we can develop a good dissolution medium which is essential for absorbable drugs. Based on the above solubility data we can conclude that all the drugs are high soluble. The dissolution data in various pH media is helpful in predicting the bioavailability and also in dissolution method development when we prepare a combination of drug product.

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