IJPSR (2017), Vol. 8, Issue 6 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 December, 2016; received in revised form, 18 January, 2017; accepted, 17 February, 2017; published 01 June, 2017

EFFECT OF ACIDIC, NEUTRAL AND BASIC pH ON SOLUBILITY AND PARTITION-COEFFICIENT OF BENZOIC ACID BETWEEN WATER-BENZENE SYSTEM

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Keywords:

Solubility, Partition coefficient, Effect of pH, Factors affecting solubility, Nernst distribution coefficient

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ABSTRACT: Solubilization is depends on solute-solvent interaction, dissociation of solute in solvent into ionic form, temperature, pressure, hydrogen bonding, dielectric constant, polarity and non-polarity of substance, pH, etc. Partition coefficient was determined in two immiscible solvents in aqueous and organic layer. Benzoic acid was selected for present study for its solubilization in different pH buffer solutions (acidic, neutral and basic) and for partition coefficient study at room temperature. Solubility of benzoic acid in different pH buffer solutions was analyzed by titration method. Most common two immiscible solvent such as water as hydrophilic solvent and benzene as hydrophobic solvent were selected for partition coefficient study. The drug benzoic acid was partitioned between these solvent by shake-flask method and analyzed the concentration of drug in both solvents by acid-base titration method. Solubility and distribution of benzoic acid between benzene-buffer solution of pH 4.0, 7.0, 9.0 and distilled water have been determined. It was observed that the benzoic acid remains un-dissociated monomer molecular form in aqueous layer and as dimer associated form in organic layer. Solubility of benzoic acid in distilled water was found to be 0.142 $\pm$ 0.033 g/100 g of water and at different pH 4.0, pH 7.0 and pH 9.0 was found to be 0.153$\pm$0.01, 0.148$\pm$0.708 and 0.186 $\pm$0.145 respectively. Graphically it was observed that solubility in pH buffer solutions in acidic medium was slightly higher than basic pH. The partition coefficient of benzoic acid in benzene-water system was found to be 0.636 and in buffer solutions of pH 4.0, pH 7.0 and pH 9.0 were 0.841, 0.624 and 0.589 respectively. Graphically it was observed that partition coefficient of benzoic acid in acidic pH was higher than neutral and basic medium.

INTRODUCTION: Quantitatively solubility is defined as the concentration of solute in a saturated solution at a certain temperature and qualitatively it may define as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. It is expressed as the number of milliliters of solvents in which one gram of solute will dissolve. In the chemical and pharmaceutical sciences.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(6).2637-40

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (6).2637-40

Partition coefficients are useful in estimating the distribution of drugs within the body. Hydrophobic drugs with high octanol/water partition coefficients are mainly distributed to hydrophobic areas such as lipid bilayers of cells and blood. Conversely hydrophilic drugs (low octanol/water partition coefficients) are found primarily in aqueous regions such as blood serum. [1] If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each become saturated. If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio. If C_1 and C_2 are equilibrium concentration of substance in solvent$_1$

and $solvent_2$, the equilibrium expression becomes $C_1/C_2 = K$. This K is known as the 'partition-coefficient or distribution-coefficient or distribution ratio or Nernst distribution law equation'. [2] If one of the solvents is a gas and the other a liquid, a gas/liquid partition coefficient can be determined. For example, the blood/gas partition coefficient of a general anesthetic measures how easily the anesthetic passes from gas to blood. [3] Partition coefficients can also be defined when one of the phases is solid, for instance, when one phase is a molten metal and the second is a solid metal, [4] or when both phases are solids. [5]

The partitioning of a substance into a solid results in a solution. Partition coefficients can be measured experimentally in various ways (by shake-flask, HPLC, etc.) or estimated via calculation based on a variety of methods (fragment-based, atom-based, etc.). Colorless crystalline solid benzoic acid having faint pleasant odor is selected for present work due to its solubility in acetone, benzene, CCl_4, $CHCl_3$, alcohol, ethyl ether, hexane, phenyls, liquid ammonia, acetates etc. Therapeutically Benzoic acid helps prevent infection caused by bacteria. Benzoic acid and salicylic acid topical (for the skin) is a combination medicine used to treat skin irritation and inflammation caused by burns, insect bites, fungal infections, or eczema.

Salts of benzoic acid are used as food preservatives and as an important precursor for the industrial synthesis of many other organic substances. Typical levels of use for benzoic acid as a preservative in food are between 0.05– 0.1%. Foods in which benzoic acid may be used and maximum levels for its application are controlled by international food law. [6, 7] It was used as an expectorant, analgesic, and antiseptic in the early 20^{th} century. [8] In teaching laboratories it is a common standard for calibrating a bomb calorimeter. [9] Benzoic acid was selected for present study for its solubilization in different pH buffer solutions (acidic, neutral and basic) and for partition coefficient study at room temperature. Solubility of benzoic acid in different pH buffer solutions was analyzed by titration method. Most common two immiscible solvent such as water as hydrophilic solvent and benzene as hydrophobic solvent were selected for partition coefficient study. The drug benzoic acid was partitioned between these solvent by shake-flask method and analyzed the concentration of drug in both solvents by acid-base titration method.

MATERIALS AND METHODS:

Materials: The drug Benzoic acid provided by Research lab fine chem. Industries, Mumbai and Buffer solutions of different pH (4.0, 7.0 and 9.0) were provided by Merck specialties Private Ltd., Mumbai. All chemicals and solvents were used of analytical reagent grade and freshly prepared distilled water was used throughout the work.

Methods:

Determination of solubility: Solubility of Benzoic acid (S) in different pH buffer solution was estimated by acid-base titration method at room temperature (25 ^{0}C). In present work 100 ml of buffer solution of different pH (4.0, 7.0 and 9.0) were taken in different beakers and in each beaker about 200 mg of benzoic acid was added, stirred well with glass rod to produced saturated solutions (some solid must be left undissolved). These solutions were heated if required. Prepared solutions were cooled at room temperature and 5 ml of these solutions were withdrawn into previously weight dry conical flask (W_1). Conical flasks with 5 ml were weight again (W_2) and these solutions were titrated against 0.05 N NaOH solutions (freshly prepared) using phenolphthalein as an indicator. End point was pink color and these readings were recorded (V). Solubility of benzoic acid in g/100 g of solvent was determined by formula as described below and compared the solubility against distilled water as blank. The graph was plotted between solubility in g/100 g of solvent and buffer solutions of different pH. The effect of pH on solubility of benzoic acid was studied graphically.

If W_1= Weight of empty conical flask
W_2= Weight of conical flask with 5 ml solution
W_3 = Weight of solution = ($W_2 – W_1$) gram
W_4= Weight of solute (benzoic acid) = 0.122 x 0.05 x burette reading (V)
W_5 = = Weight of solvent = ($W_3 – W_4$)

S = Solubility of benzoic acid in g/100 g of solvent

$$= \frac{\text{Weight of solute } (W_4) \times 100}{\text{Weight of solvent } (W_5)}$$

Determination of partition coefficient: Partition coefficient at different pH was estimated by shake-flask acid-base titration method. A 10 % solution of benzoic acid in benzene (bb solution) was prepared in a beaker. In four different separating funnel prepared the four different solutions as follows-

1. 40 ml of buffer solution pH 4.0 + 40 ml bb solution.
2. 40 ml of buffer solution pH 4.0 + 30 ml bb solution + 10 ml benzene.
3. 40 ml of buffer solution PH 4.0 + 25 ml bb solution + 15 ml benzene.
4. 40 ml of buffer solution pH 4.0 + 20 ml bb solution + 20 ml benzene.

These flasks were shaked on water-bath incubator shaker for 24 hours at room temperature (25 ^{0}C). All solutions were allowed to stand for 30 minutes on a stand to achieve equilibrium. It contained lower aqueous layer and upper benzene layer. The lower aqueous layers of each flask were removed in dry beaker by retaining benzene layer in separating flask. Pipetted out 10 ml of aqueous layer into a dry conical flask and titrated against 0.01 N NaOH using phenolphthalein as an indicator. End point was pink color and this reading was recorded. In another dry conical flask pipette out 5 ml of benzene layer and 10 ml of distilled water was added. The solution was titrated against 0.1 N NaOH solution using phenolphthalein as an indicator. End point was pink color and this reading was recorded. Same procedure was followed with buffer solution pH 7.0 and pH 9.0 and with distilled water as blank sample. Estimation of partition coefficient (K) was calculated for such system by formula as follows-

a) For aqueous layer concentration of benzoic acid in moles/litre is calculated by normality determination as eq. 1, 2 and 3.

$N_1V_1 = N_2V_2$ ………………(1)

Where N_1= Normality of aqueous layer = Naq

Naq = 0.01 V_2 / 10 ……(2)

N_2= Normality of NaOH for titration = N org = 0.01 N

Naq = Caq ………………(3)

V_1 = Volume of aqueous layer taken = 10 ml
V_2 = Volume of NaOH consumed (burette reading)

a) For organic layer concentration of benzoic acid in moles/litre is calculated by normality determination as eq. 4, 5 and 6.

b) $N_3V_3 = N_4V_4$ ………..(4)
Where N_3 = Normality of organic layer = Norg

Norg = 0.1 V_4 / 5 ………(5)

N_4 = Normality of NaOH for titration = 0.1 N

N org = C org …… (6)

V_3 = Volume of organic layer taken = 5ml

V_4 = Volume of NaOH consumed (burette reading)

c) Partition coefficient for benzene-water system was determined by equation 7 as follows-

$$K = \text{Caq} / \text{Corg}^{1/2} \quad \text{…..(7)}$$

$$K = \frac{\text{Concentration in aqueous layer } (C_W)}{\{\text{Concentration in organic layer } (C_O)\}^{1/2}}$$

The graph was plotted between partition coefficient (k) and buffer solutions of different pH. The effect of pH on K of benzoic acid was studied in benzene-water system.[10]

RESULT AND DICUSSION: Solubilization is depends on solute-solvent interaction, dissociation of solute in solvent into ionic form, temperature, pressure, hydrogen bonding, dielectric constant, polarity and non-polarity of substance *etc.* **Table 1** shows analyses of solubility of benzoic acid at 25 ^{0}C. It was observed that solubility of Benzoic acid (S) in distilled water was found to be 0.142 $\pm$ 0.033 g/100 g of water at room temperature (25 ^{0}C) and it was maximum in neutral pH buffer solution 7.0.

TABLE 1: ANALYSES OF SOLUBILITY AT 25 °C

Sno.	Solvents	Solubility*(S) (g/100 g of solvent) (Mean±SD)
1	Distilled water	0.142 ± 0.033
2	Benzene-buffer solution pH 4.0	0.153 ± 0.012
3	Benzene-buffer solution pH 7.0	0.186 ± 0.145
4	Benzene-buffer solution pH 9.0	0.148 ± 0.708

* Result expressed as (Mean ± SD) (n = 3) at 25 ^{0}C

Graphically in **Fig. 1** it was concluded that solubility in pH buffer solutions in acidic medium was slightly higher than basic pH due to ionic dissociation.

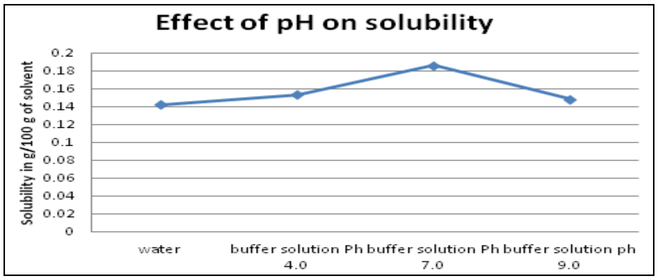

FIG.1: EFFECT OF pH ON SOLUBILITY

The distribution of benzoic acid between water and benzene when studied shows that the ratio C_{W}/C_{O} does not remain constant, but the ratio $C_W/C_O^{1/n}$ remains constant. This was because of two molecule association (dimerization|) by hydrogen bonding between benzoic acid molecules in benzene layer and remain as monomer molecule in aqueous layer. [11] **Table 2** shows effect of pH on Partition coefficient and it was analyzed that partition coefficient of benzoic acid in benzene-water system was found to be 0.636 and in buffer solutions of pH 4.0, pH 7.0 and pH 9.0 were 0.841, 0.624 and 0.589 respectively.

TABLE 2: ANALYSES OF pH ON PARTITION COEFFICIENT

S no.	Solvents	Partition coefficient (K)
1	Benzene-water system	0.636
2	Benzene-buffer solution pH 4.0	0.841
3	Benzene-buffer solution pH 7.0	0.624
4	Benzene-buffer solution pH9.0	0.589

Graphically it was observed that partition coefficient of benzoic acid in acidic pH was higher than neutral and basic medium (**Fig. 2**).

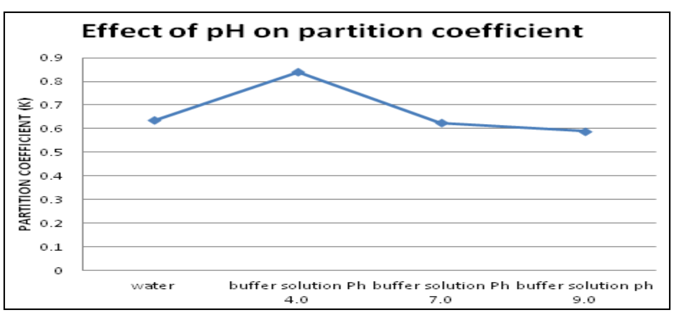

FIG. 2: EFFECT OF pH ON PARTITION COEFFICIENT

CONCLUSION: It was concluded that study of solubilization and partition coefficient of benzoic acid in different solvents have greater value in preformulation design of any dosage form. The study of solute dissociation or association in particular solvent, the quantity of solute extracted from its solution, formula determination of complexes, spreading coefficient determination for topical preparation, amount of drug distributed into blood and other body fluids etc are estimated by these methods.

ACKNOWLEDGEMENTS: The author thanks to pharmaceutics department and library of Siddhant College of Pharmacy, Sudumbare, Pune for providing help and valuable data.

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How to cite this article:
Chaurasia G: Effect of acidic, neutral and basic pH on solubility and partition-coefficient of benzoic acid between water-benzene system. Int J Pharm Sci Res 2017; 8(6): 2637-40.doi: 10.13040/IJPSR.0975-8232.8(6).2637-40.