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INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

EFFECT OF SOLUBILITY ENHANCERS ON THE SOLUBILITY OF PARACETAMOL

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ARTICLE INFO

Received 10 October 2012
Received in revised 21 October 2012
Accepted 3 November 2012
Available online 26 November 2012

Keywords
Solubility, Paracetamol, Cyclodextrin

ABSTRACT

Solubility plays an important role in dissolution and absorption of drug. Paracetamol has less solubility in aqueous media and belongs to class IV drug according to biopharmaceutical classification system.The aim of present study was to study the effect of different solubility enhancing agents at room temperature on the solubility of paracetamol. Different solubility enhancing agents like β-cyclodextrin, Hydroxypropyl-β- cyclodextrin, mannitol, urea and Sodium Lauryl Sulphate (SLS) in various concentrations like 0.25 % w/v, 0.5 % w/v, 0.75 % w/v and 1.0 % w/v were used to study the solubility of paracetamol in water as well as phosphate buffer pH 7.4 system.

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Please cite this article in press as Joshi HA et.al. Effect Of Solubility Enhancers On The Solubility Of Paracetamol. Indo American Journal of Pharm Research.2012:2(11).

INTRODUCTION

The oral rout of drug administration is most common and popular rout as it confers convenience, easy ingestion and patient compliance.[1] The term solubility is defined as the maximum amount of the solute that can dissolve in given amount of solvent. It can also be defined qualitatively as well as quantitavely. Quantitatively it is defined as concentration of solute in a saturated solution at certain temperature and qualitative terms; it is defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent Poorly aqueous soluble drugs are usually characterized by low bioavailability due to less absorption which is a major concern of pharmaceutical industries worldwide. Studies to improve the solubility of these drug candidates have been carried out with various techniques like micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization and hydrotrophy. [2, 3]

Paracetamol is a nonsteroidal analgesic and antipyretic drug with minimal side effects. It is freely soluble in ethanol (95%) and acetone; sparingly soluble in water, very slightly soluble in dichloromethane and ether. The drug suffers from poor bioavailability because of its poor aqueous solubility. According to biopharmaceutical classification system (BCS) it belongs to class IV drug. Present study is carried out to investigate the carrier that improves the solubility of paracetamol and thus bioavailability.[4,5]

MATERIALS AND METHODS

Materials

Paracetamol, Urea, Mannitol and Sodium Lauryl Sulphate (Research Lab, Pune) procured from our institute,β-cyclodextrin (β-CD), hydroxyl propyl-β-cyclodextrin HP-β-CD) purchased from S.D. Fine chemicals, Potassium di-hydrogen phosphate (AR Grade), Sodium hydroxidepurchased from Loba Chemi Pune, Double distilled water freshly prepared and used.

Methods

Preparation of Standard Curve of Paracetamol Phosphate Buffer

Standard curve of Paracetamol was plotted by dissolving 100 mg of drug in 100 ml phosphate buffer pH 7.4. 1ml of the above solution was pipette out in 100 ml volumetric flask and diluted upto 100 ml. This solution served as the stock solution. From the stock solution 1ml, 2ml, 3ml, 4 ml upto 9 ml were transferred to 10 ml volumetric flask and diluted with phosphate buffer pH 7.4 upto mark to obtain the solution of concentration 1 µg/ml, 2 µg/ml, 3 µg/ml,4 µg/ml upto 9 µg/ml respectively. The dilutions were sonicated for 10 minutes to remove air entrapped if any and analyzed for absorbance at 257 nm using UV- Spectrophotometer(Schimadzu UV 1700). [4]

Phase Solubility Study

The phase solubility studies were carried out according to Higuchi and Connors. Briefly, an excess amount of paracetamol was added to the aqueous solutions (10 ml) of mannitol, urea, sodium lauryl sulphate (SLS),β-cyclodextrin (β-CD) and hydroxyl propyl-β-cyclodextrin HP-β-CD) of varying concentrations (0.25 %w/v to 1.0%w/v). The flasks were sealed and kept for 72 hours with constant shaking. After the equilibrium reached the samples of each flask was filtered through Whatman filter paper no 40. The filtered solution was diluted with phosphate buffer pH 7.4 and analyzed by U.V. Spectrophometer (Schimadzu UV 1700). The work study was carried out at room temperature.[6]

RESULT AND DISCUSSION

Standard Curve for Paracetamol

A Standard plot of paracetamol was plotted in the concentration range of 1 µg/ml to 10 µg/ml in phosphate buffer pH 7.4 with the absorbance measured at 257 nm. The calibration equation for the standard graph was found to be y=0.068x and the regression coefficient (R^2 =0.947) wasused in all calculations. The standard plot of paracetamol shown in figure1

Table 1: Standard Curve For Paracetamol at pH 7.4

Serial Number	Concentration in [mcg/ml]	Absorbance at 257 nm
1	0	0
2	1	0.158
3	2	0.188
4	3	0.261
5	4	0.295
6	5	0.396
7	6	0.401
8	7	0.48
9	8	0.532
10	9	0.626
11	10	0.625

Table 2: Solubility of Paracetamol in Distilled Water

Concentration of Solubility Enhancing Agent (% w/v)	Solubility of Paracetamol in Distilled Water (mg/ml) in presence of				
	Mannitol	Urea	Sodium Lauryl Sulphate	β-Cyclodextrin (β-CD)	Hydroxyl Propyl-β-Cyclodextrin HP-β-CD)
0	12.693	12.693	12.693	12.693	12.693
0.25	12.2628	13.6642	19.9124	14.5401	25.5182
0.5	17.6934	16.8759	20.9051	14.5985	26.2190
0.75	17.8102	21.9562	21.1971	14.9489	26.5109
1	18.6277	53.3139	21.8978	15.9416	29.8978

Table 3: Solubility of Paracetamol in Phosphate Buffer pH 7.4

Concentration of Solubility Enhancing Agent (% w/v)	Solubility of Paracetamol in Phosphate Buffer pH 7.4 (mg/ml) in presence of				
	Mannitol	Urea	Sodium Lauryl Sulphate	β-Cyclodextrin (β-CD)	Hydroxyl Propyl-β-Cyclodextrin HP-β-CD)
0	13.69	13.69	13.69	13.69	13.69
0.25	15.3577	14.1898	18.2190	11.1533	27.5036
0.5	16.2336	15.2409	20.9051	13.7226	28.6131
0.75	18.3942	16.8759	23.0657	14.1314	29.0803
1	22.2482	17.5182	24.0584	15.0657	30.4818

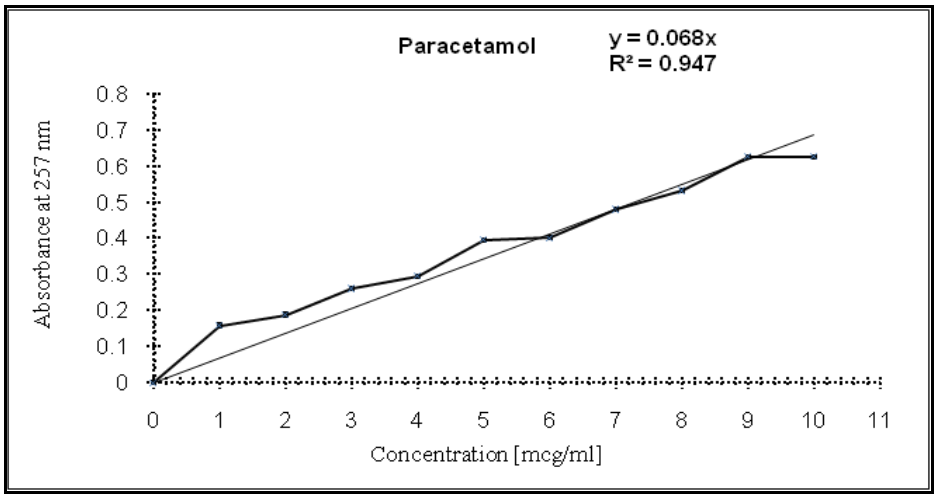

Figure 1: Standard Curve for Paracetamol at pH 7.4

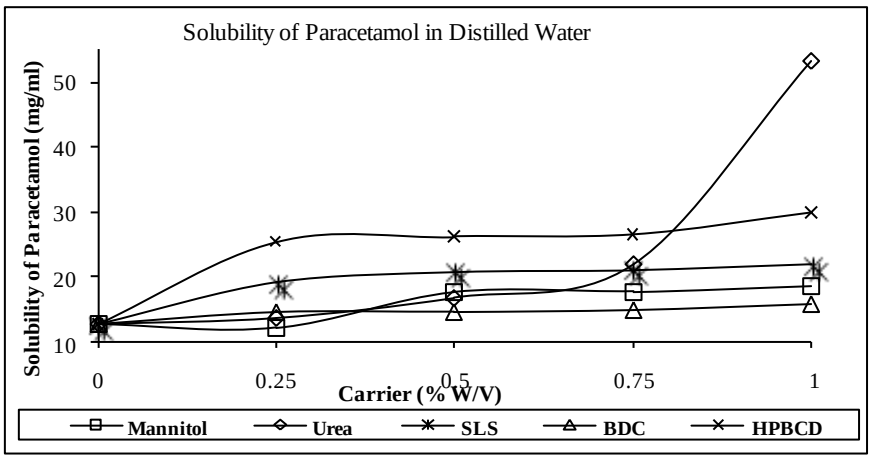

Figure 2: Standard Curve for Paracetamol in Distilled Water

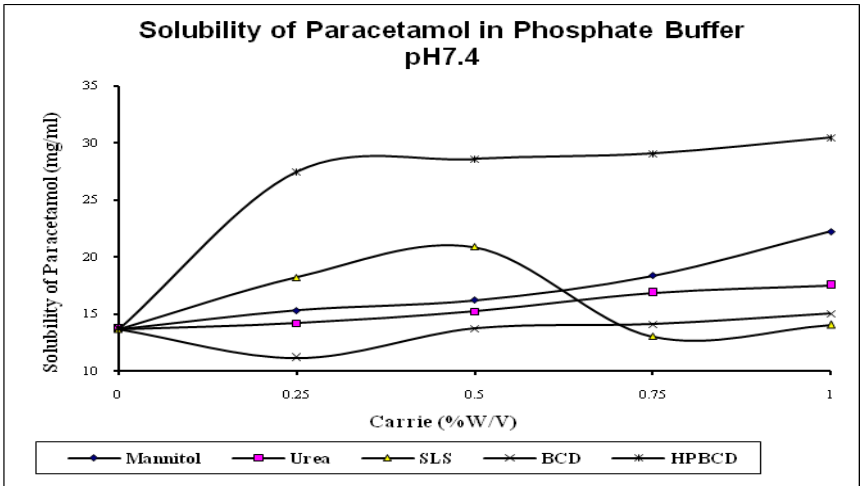

Figure 3: Standard Curve for Paracetamol in Phosphate Buffer pH 7.4

Phase Solubility Study

The introduction of Biopharmaceutical Classification (BCS) in 1995 was the result of continuous efforts on mathematical analysis for the elucidation of the kinetic and dynamics of the drug process in gastrointestinal tract (GI). The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. It allows for the prediction of *in-vivo* pharmacokinetics of oral immediate release (IR) drug products by classifying the drug entity either if four class. [7] According to the BCS system paracetamol belongs to class IV category indicating poor solubility and poor permeability.[5] In the present study the solubility of paracetamol was found to be 12.963 mg/mlin distilled water and 13.786 mg/ml in phosphate buffer pH 7.4. The solubility data from literature survey was 13.69 mg/ml [6], 14.7 mg/ml at 20^0 C, 14.3 mg/ml at 25^0 C and 23.7mg/ml at 37^0 C.[8]The phase solubility study of paracetamol was carried out in presence of hydrophilic carriers like mannitol and urea, Complexing agents like β-cyclodextrin (β-CD) and hydroxyl propyl-β-cyclodextrin (HP-β-CD) and surfactant SLS at different concentrations. The solubility in distilled water and phosphate buffer pH 7.4 increases gradually with increase in concentrations of mannitol, urea, SLS, β-CD, Hp-β-CD. The maximum solubility in distilled water at 1%w/v of mannitol, urea, SLS, β-CD and Hp-β-CD was 18.6277 mg/ml (1.46 fold), 53.3139mg/ml (4.2 fold), 21.8978 mg/ml (1.725 fold), 15.9416 mg/ml (1.25 fold) and 29.8978 mg/ml (2.35 fold) respectively. The maximum solubility inphosphate buffer pH 7.4 at 1%w/v of mannitol, urea, SLS, β-CD and Hp-β-CD was 22.2482 mg/ml (1.625 fold), 17.5182 mg/ml (1.27 fold), 24.0584 mg/ml (1.75 fold), 15..657 mg/ml (1.1 fold) and 30.4818 mg/ml (2.22 fold) respectively. The results are presented Table 2 and 3

CONCLUSION

Amongst the various carriers used to improve the solubility of paracetamol, hydroxylpropyl-β-cyclodextrin (HP-β-CD) yielded most favorable results in terms of consistency and can be suitably used in immediate release (IR) and sustained release (SR) drug dosage forms of paracetamol.

ACKNOWLEDGEMENT Authors are thankful to management of Shivnagar Vidya Prasarak Mandals College of Pharmacy for providing infrastructural facilities for the studies. The Authors are also thankful to D.J.Taur, Faculty Shivnagar Vidya Prasarak Mandals College of Pharmacy.

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