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SOLUBILITY EVALUATIONS OF OSIMERTINIB MESYLATE IN PHYSIOLOGICAL BUFFERS

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Abstract:

Limited water solubility of drugs is a prevailing problem to efficient drug delivery as a huge proportion of available drugs are poorly water soluble. Poorly soluble drugs suffer with low or incomplete oral absorptions leading to low or variable bioavalibilities. Osimertinib mesylate is a novel anticancer drug for the treatment of lung cancer. It is reported to have low absorption and exposure at therapeutic doses of 80 mg which could be due to low solubility in gastrointestinal tract. It is important to evaluate pH solubility profile of the drug over the gastrointestinal pH range in order to find the most suitable region of solubility and absorption. In this study, we are reporting saturated solubility of Osimertinib mesylate in different media with specific pH conditions including different physiological buffers such as simulated gastric fluid, simulated intestinal fluid, phosphate buffer saline. Solubility study was done by classical shake flask method and samples were analyzed by double beam UV spectrophotometer in triplicate. It was found to be very slightly soluble in water with an approximate value of 924 ± 6.06 µg/ml. Of all the tested buffer media, simulated gastric fluid pH 1.2, exhibited maximum solubility, which was approximately 2.3 folds of the solubility exhibited in distilled water. Solubility data over different pH conditions were statistically evaluated using one way ANOVA and post hoc Tukey test for valid conclusions. All media had significant effect on the solubility of the drug except sodium phosphate buffer, pH 3.2 and Acetate buffer pH 5.5 with respect to distilled water.

Keywords: *Osimertinib mesylate, absorption, Solubility, physiological buffers.*

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INTRODUCTION:

Solubility is defined as the maximum amount of a solute that passes in the solution to result in a saturated solution at a certain temperature. It depends on the physicochemical properties of the solute and the solvent. Based upon principles of like dissolves like, polar solutes have maximum solubility in polar solvents and vice-versa. Moreover, solubility of solutes in a particular solvent can be influenced by several other factors such as temperature, agitation, particle size of solute, and pH of the medium in which these are dissolved. Solubility of the drugs and dosage forms is known to play very critical role in the efficacy and performance of the oral therapy. [1] Thus low water solubility of drugs become one of the most critical challenges of the successful oral therapy. Low solubility causes low dissolution rate, low or inconsistent absorption and hence low or variable bioavailability [2]. Therefore enhancement of aqueous solubility and dissolution rate of drugs becomes important to improve bioavailability so as to achieve maximum therapeutic efficacy.

Osimertinib mesylate (OM) is a novel anticancer drug approved by USFDA for the treatment of lung cancer, one of the most common form of cancer leading to death worldwide [3]. Approximately, 80-90% of lung cancer comprise non-small cell lung cancer (NSCLC). [4]. Osimertinib is a third generation selective epidermal growth factor receptor (EGFR) inhibitor for NSCLC [5]. It's pharmacokinetics studies have reported low oral absorption and exposure. [6]. Solubility of Osimertinib is known to be affected by pH [7], however there no report available on the solubility of Osimertinib in physiological buffers such as simulated gastric fluid (SGF), simulated intestinal fluid (SIF). In this study, we have evaluated solubility of OM in different media including physiological pH conditions.

MATERIALS AND METHODS:

Chemicals

Osimertinib was purchased from Mesochem Technology Co., Ltd. Beijing, China. All other solvents and chemicals were of analytical grade and obtained from Sigma-Aldrich, USA.

Standard Plot of Osimertinib:

10 mg of OM was accurately weighed, dissolved in methanol and diluted with distilled water (DW) to get a concentration of about 1000 µg/ml. From this solution, suitable aliquots were transferred into 10 ml volumetric flask and diluted with DW to get concentrations 1, 2, 3, 4, 5, 10, 15, 20 and 25 µg/ml of OM which were then analyzed by double beam UV spectrophotometer (Jasco, V-630, Japan,) at 267 nm.

Saturated solubility studies:

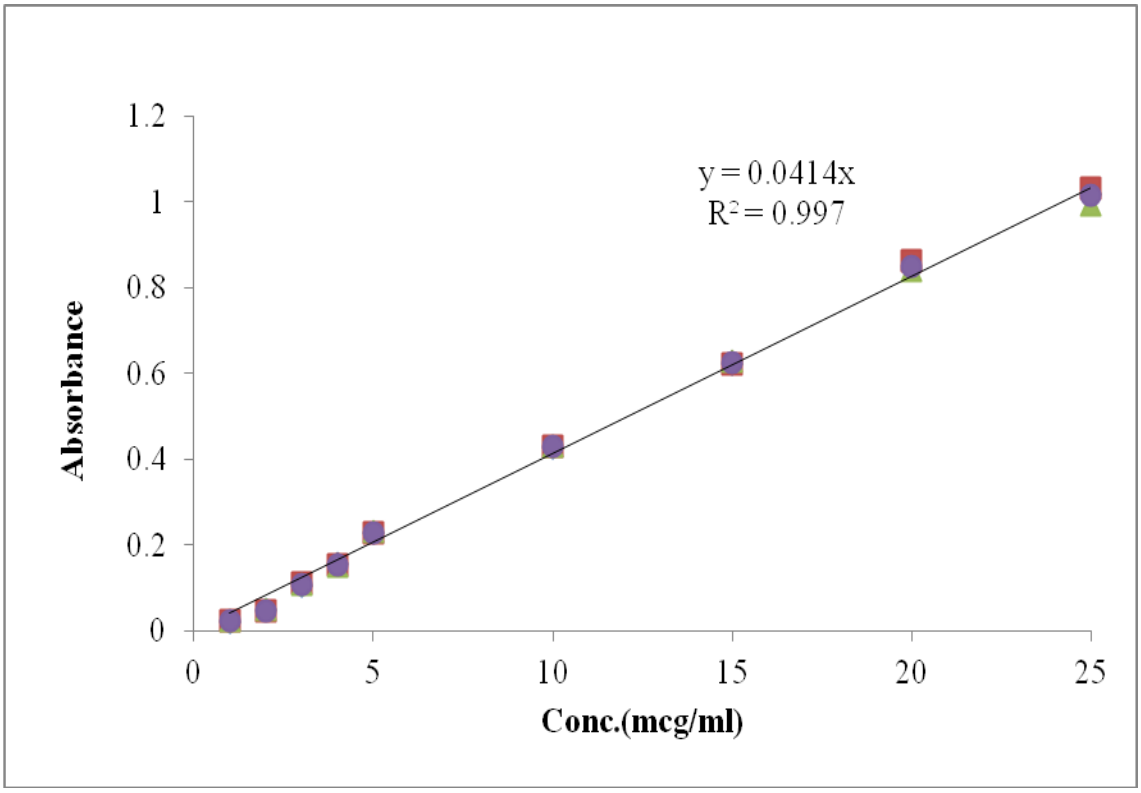
Saturated solubility studies of OM in water and different media with a pH range of 1-13, including physiological buffers such as simulated gastric fluid, simulated intestinal fluid, phosphate buffer saline etc. were carried out by classical shake flask method [8]. Excess amount of OM was incubated at 37°C and 100 RPM in biological shaker with 5 ml of distilled water or different media with specific pH conditions (Table 1) [9]. Suspensions were filtered using 0.45 micron membrane filter after 72 hours and amount of drug in solutions were analyzed by UV spectrophotometer after appropriate dilution in triplicate. To nullify the absorbance due to the presence of buffer components the UV spectrophotometer was calibrated with the corresponding blank in every measurement.

Statistical evaluations:

Solubility data were subjected to one way analysis of variance (one way ANOVA), to find out if the results are different and media has significant effect on solubility of drug using online statistical tool [10]. ANOVA results were further evaluated by post hoc Tukey test / Honest Significant Difference test to derive meaning inferences of effect of different media / different pH conditions on solubility of drug.

RESULTS AND DISCUSSION:

Standard solutions in a concentration range of 1-25 µg/ml of OM in methanol were prepared and evaluated by double beam spectrophotometer at 267 nm (Figure 1). Calibration plots were constructed in triplicate by plotting the concentration of drug on X axis and response (absorbance) on Y axis . The calibration curve constructed was evaluated by regression analysis. The simple linear calibration equation, $y = 0.0421x - 0.0121$, ($R^2 = 0.9975$), demonstrated good linearity of the method between the concentration range evaluated with a correlation coefficient of 0.998. LOD and LOQ values were determined to be 0.13 and 0.43 µg/ml, respectively.



1: Calibration plot of Osimertinib mesylate (N=3)

Saturated solubility study of OM in different media such as distilled water, simulated gastric fluid, simulated intestinal fluid, phosphate buffer saline pH 7.4, 0.1M NaOH, were carried out by classical shake flask method [8]. Equilibrium thermodynamic solubility of drug has been presented in Table 1, Fig. 2. Aqueous solubility was found to be approximately 0.1 mg/ml which is supposed to be very slightly soluble as per United State and British Pharmacopoeia definition of relative solubility [9]. As per US pharmacopoeia solubility of drug is defined as parts of solvent required to dissolve one part of drug thus every drug may fall in one of the seven category as listed in the Table 2.

Table 1: Saturated solubility of OM in different media

	Solubility Media	Absorbance @ 267 nm			Absorbance MEAN ± SD	Mean Solubility (µg/ml) ± SD
		N 1	N 2	N 3		
A	Distilled water pH 7	0.3802	0.3831	0.3852	0.3828 ± 0.0025	924.72 ± 6.06
B	Simulated gastric fluid pH 1.2	0.8948	0.8634	0.8941	0.8841 ± 0.0179	2135.51 ± 43.31
C	Sodium phosphate buffer pH 3.2	0.3996	0.3996	0.3994	0.3995 ± 0.0001	965.07 ± 0.29
D	Acetate buffer pH 5.5	0.3919	0.3960	0.4022	0.3967 ± 0.0052	958.21 ± 12.53
E	Phosphate buffer pH 5.8	0.4174	0.4211	0.4224	0.4203 ± 0.0026	1015.22 ± 6.27
F	Simulated intestinal buffer pH 6.8	0.5687	0.5689	0.5634	0.5670 ± 0.0031	1369.57 ± 7.53
G	Phosphate buffer saline pH 7.4	0.4489	0.4472	0.4466	0.4476 ± 0.0012	1081.08 ± 2.88
H	0.1M NaOH pH 13	0.4200	0.4199	0.4217	0.4205 ± 0.0010	1015.78 ± 2.44

Table 2: Relative solubility definition as per United State Pharmacopoeia

Solubility definition	Parts of solvent required for one part of solute	Solubility range (mg/mL)
Very soluble	< 1	> 1000
Freely soluble	from 1 to 10	100 – 1000
Soluble	from 10 to 30	33 – 100
Sparingly soluble	from 30 to 100	10 – 33
Slightly soluble	from 100 to 1000	1 – 10
Very slightly soluble	from 1000 to 10000	0.1 – 1
Practically insoluble	> 10000	< 0.1

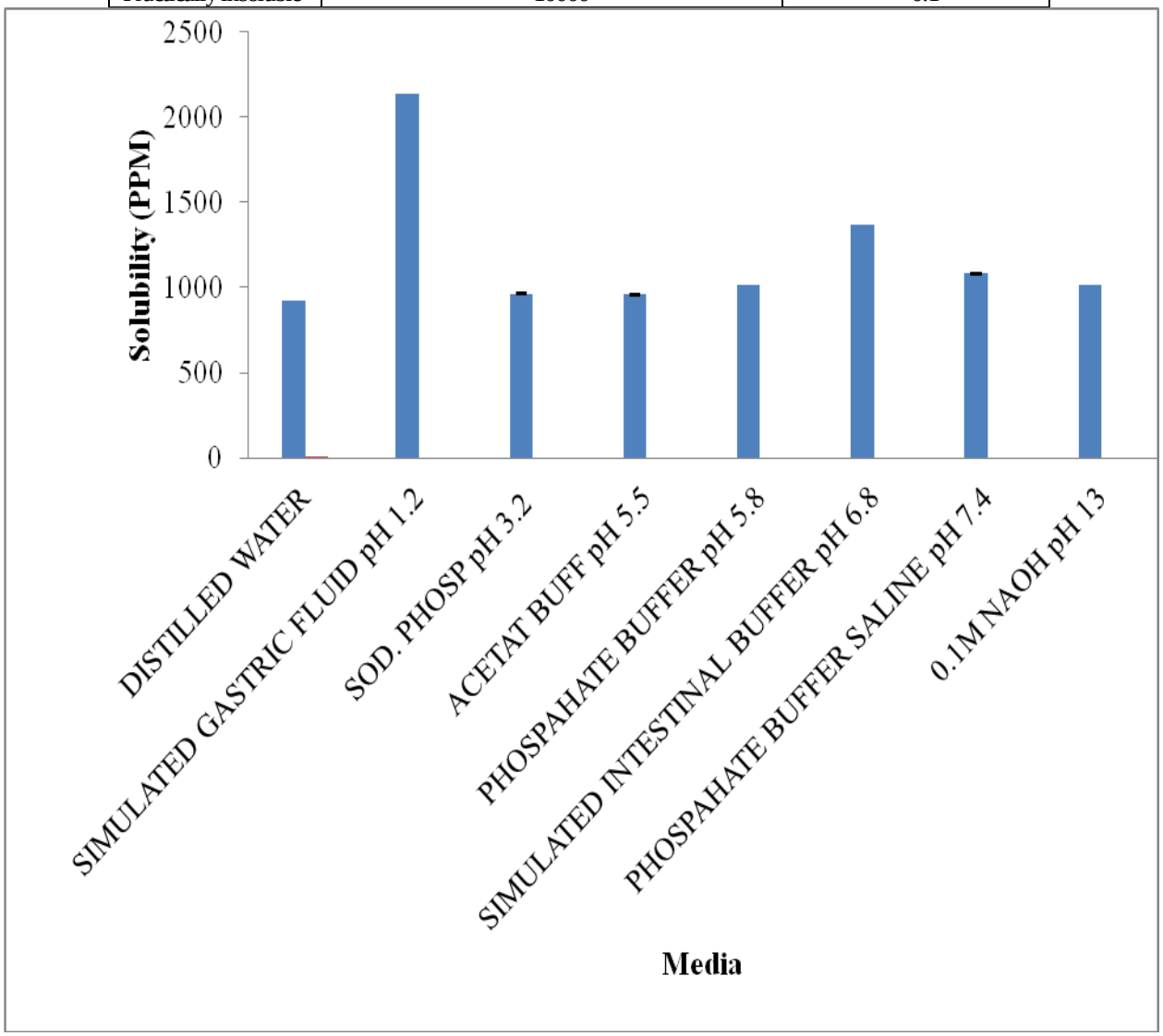


Fig 2: Saturated solubility of Osimertinib mesylate

Results of one way ANOVA of Solubility data depicted significant differences between the mean values of each media results as evident by very high F value, Fig. 3. Results of Post hoc Tukey test / Honest Significant Difference test to derive meaningful inferences of effect of each media with different pH conditions on solubility of drug, has presented in Fig. 4. All media had significant effect on the solubility of the drug except C (sodium phosphate buffer, pH 3.2) and D (Acetate buffer pH 5.5) with respect to A (distilled water, pH 7). Solubility was found maximum in simulated gastric fluid pH 1.2 with a value of 2135.51 ± 43.31 µg/ml which was approximately 2.3 fold higher that what was achieved in distilled water.

Treatment →	A	B	C	D	E	F	G	H
Input Data →	0.3802 0.3831 0.3852	0.8948 0.8634 0.8941	0.3996 0.3996 0.3994	0.3919 0.396 0.4022	0.4174 0.4211 0.4224	0.5687 0.5689 0.5634	0.4489 0.4472 0.4466	0.42 0.4199 0.4217

Descriptive statistics of your k=8 independent treatments:

Treatment →	A	B	C	D	E	F	G	H	Pooled Total
observations N	3	3	3	3	3	3	3	3	24
sum $\sum x_i$	1.1485	2.6523	1.1986	1.1901	1.2609	1.7010	1.3427	1.2616	11.7557
mean $\bar{x}$	0.3828	0.8841	0.3995	0.3967	0.4203	0.5670	0.4476	0.4205	0.4898
sum of squares $\sum x_i^2$	0.4397	2.3455	0.4789	0.4722	0.5300	0.9645	0.6010	0.5305	6.3622
sample variance s^2	0.0000	0.0003	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0263
sample std. dev. s	0.0025	0.0179	0.0001	0.0052	0.0026	0.0031	0.0012	0.0010	0.1621
std. dev. of mean $SE_{\bar{x}}$	0.0014	0.0104	0.0001	0.0030	0.0015	0.0018	0.0007	0.0006	0.0331

One-way ANOVA of your k=8 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	0.6033	7	0.0862	1,845.5172	1.1102e-16
error	0.0007	16	0.0000		
total	0.6041	23			

Fig 3: One Way ANOVA of solubility data

Tukey HSD results

treatments pair	Tukey HSD Q statistic	Tukey HSD p-value	Tukey HSD inferfence
A vs B	127.0484	0.0010053	** p<0.01
A vs C	4.2327	0.1173626	insignificant
A vs D	3.5146	0.2683443	insignificant
A vs E	9.4961	0.0010053	** p<0.01
A vs F	46.6779	0.0010053	** p<0.01
A vs G	16.4070	0.0010053	** p<0.01
A vs H	9.5552	0.0010053	** p<0.01
B vs C	122.8157	0.0010053	** p<0.01
B vs D	123.5338	0.0010053	** p<0.01
B vs E	117.5523	0.0010053	** p<0.01
B vs F	80.3705	0.0010053	** p<0.01
B vs G	110.6414	0.0010053	** p<0.01
C vs D	0.7181	0.8999947	insignificant
C vs E	5.2634	0.0305937	* p<0.05
C vs F	42.4452	0.0010053	** p<0.01
C vs G	12.1743	0.0010053	** p<0.01
C vs H	5.3225	0.0282360	* p<0.05
D vs E	5.9815	0.0114473	* p<0.05
D vs F	43.1633	0.0010053	** p<0.01
D vs G	12.8924	0.0010053	** p<0.01
D vs H	6.0407	0.0105525	* p<0.05
E vs F	37.1818	0.0010053	** p<0.01
E vs G	6.9109	0.0031852	** p<0.01
E vs H	0.0591	0.8999947	insignificant
F vs G	30.2709	0.0010053	** p<0.01
F vs H	37.1227	0.0010053	** p<0.01
G vs H	6.8517	0.0034548	** p<0.01

Fig 4: Post hoc Tukey test

CONCLUSION:

Osimertinib is reported to have low absorption and exposure at therapeutic doses of 80 mg which could be due to low solubility in gastrointestinal tract. Its solubility is known to be affected by pH conditions. In this study, we evaluated saturated solubility of Osimertinib in different media with specific pH conditions including different physiological buffers such as simulated gastric fluid, simulated intestinal fluid, phosphate buffer saline. Water solubility was found to be influenced significantly by different pH conditions. Of all the tested media, simulated gastric

fluid exhibited maximum solubility, which was approximately 2.3 folds of the solubility exhibited in distilled water. Based on this solubility data, we may suggest to develop gastroretentive dosage form in order to get better solubility and absorption of the Osimertinib mesylate.

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