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A Recent Advancement in Approaches used for Estimation of Drug Solubility: A Review

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ABSTRACT

Background: *Solubility assessment of a new chemical entity during preformulation is found to be the most essential and crucial stride during the drug origination that involves various drug physicochemical properties. More deliberation has been made towards the drug aqueous solubility. Since water is the unique solvent of the biological system and it is well known that drugs should be reached to its receptor site in the body through the aqueous and non-aqueous solvent. Therefore, measuring and assessing the solubility of new chemical entities in various solvents is one of the foremost elements of compound characterization during the drug development process.*

Objective: *This review article tries to sum up the current experimental approaches and directed the recent advances in the experimental approaches to assess the quantitative estimation of solubility of a new drug entity during preformulation. A review includes the high throughput methods that are intended to determine the thermodynamic solubility of drug as well as also reporting some traditional methods that have been utilized for such studies. Advanced and modified methodology has been discovered by many researchers from the last five years and has been used to estimate the solubility of a new drug candidate.*

Conclusion: *Thus, this review aims to represent various Preformulatory approaches that forecast by various researchers from last five years (2015-2019) for the quantitative estimation of solubility of new drug candidate*

which can replace the reported traditional methods and targeting as well as representing some new modified approaches which are exclusively reducing the time and providing appropriate results for such studies.

Keywords: Solubility, Aqueous solubility, Quantitative estimation, Thermodynamic equilibrium preformulation, High throughput

Abbreviations: DMSO: Dimethyl sulfoxide; IND: Indomethacin; HPLC: High-performance liquid chromatography; EtoH: Ethanol; DFP: Deferiprone; NMP: N-methyl-2-pyrrolidone; Prx: Piroxicam; PAMAM: Poly (amidoamine); CC: Candesartan cilexetil; RTV: Ritonavir; UPLC: Ultra performance liquid chromatography; GCZ-CAT: Gliclazide-Catechol; GCZ-RES: Gliclazide- Resorcinol; GCZ-PTSA: Gliclazide-p (toluenesulfonic); GCZ-PPZ: Gliclazide-Piperazine; TOL-PPZ: Tolbultamide- Piperazine; GPZ: Glipizide; Bex-HCL: Benexate Hydrochloride; IPA: Isopropanol; EG: 1,2-ethanediol; PG: 1,2-propanediol; EA: Ethyl ethanoate; MPM: Mycophenolatemofetil; PBS: Phosphate buffer saline; MEOH: Methanol; 2-BUOH: 2-Butanol; THP: Transcutol; GEM: Gemfibrozil

INTRODUCTION

Pre-formulation studies have been inaugurated that aids in the dosage form design of new chemical entities, imposed the scientific principles and rationale for formulation development by lowering trail-and-error efforts and also impacted drug quality and efficacy [1]. Such a study raised the knowledge of the physical and chemical pharmacy of pharmaceutical science and bio-pharmaceutics, influencing the therapeutics availability of drug products [2]. The reason for the study is to understand the various approaches of solubility assessment and their nature which are most widely involved in the characterization of the drug candidate and their utilization in optimizing the conditions in the formulation of dosage forms [3,4]. Preformulatory Solubility assessment is an important activity during drug research origination as it reflects the necessary information that assisted in numerous and diverse research activities which can further relate with drugs biological activity, its structure optimization, various pharmacokinetics screening, dosage form selection for animal dosing for checking their efficacy, and also help to derive pharmacokinetics (PK) and toxicity data [5,6]. Its determination is simple which requires a well-developed and carefully performed method. The solutes physical state and the solution's physical and chemical conditions necessitate the concentration of compound that dissolves and the amount that precipitates always impacted on solubility measurements [7]. The solubility of one substance in another is a measure of the degree of molecular mixing between the two pure substances at thermodynamic equilibrium. The composition of a saturated solution, expressed as a proportion of a designated solute in a designated solvent, represents this thermodynamic limit of solubility [8,9]. Accurate determination of the aqueous solubility of pharmaceutical materials is important for understanding both quality control, and drug delivery issues for pharmaceutical formulations [10,11]. Poorly-water soluble drug substances represent a significant percentage of the molecular entities in the industry's drug development pipeline and are a growing percentage of that commercially available 40 % of the currently marketed products are poorly soluble based on the biopharmaceutical classification system (BCS) [12,13].

Aqueous solubility of the drug is one of the most condemning Physico-chemical properties for drug absorption and bio-availability. Poorly soluble drug shows inappropriate pharmacokinetic properties, and precisely, increasing the solubility of a

drug improves formulation development. Hence, screening and determining aqueous solubility is one of the most essential steps in drug discovery and development [14,15]. As per FDA guidelines, drugs that a had low solubility if their solubility in 250 ml of aqueous solution at pH 1–7. 5 is less than the amount contained in a tablet or capsule with the highest dosage [16]. Thermodynamic solubility is measured at equilibrium as a solid compound is in excess to the solvent, and this value is a function of only the medium and temperature. In contrast, kinetic solubility is a dynamic property measured on a non-equilibrium state and depends not only on medium and temperature but also on time and concentration [17]. In the early stages of lead optimization and candidate selection, large numbers of compounds are generated in small quantities and, therefore, high throughput and low compound consumption during solubility screening/measurement are very important. For this reason, kinetic solubility assays are preferred. In contrast, during pharmaceutical development, since compounds are available in large quantities, thermodynamic solubility assays are often used [18]. Drug solubility greatly impacted the oral administration of the drugs which is the most important rate-limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response [19]. Formulation experts often deal with this problem, the estimation of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of the drug development process, especially for the oral-drug delivery system. Keeping all these, different approaches were developed and performed as well as for the solubility quantification of orally administered drugs [20]. Numerous experimental methods have been involved to measure the solubility of the solid drug. Despite this, High throughput assay has lately been available, whereas, the use of accurate solubility method is somewhat expensive and time taking process [21]. This review aims to represent various Preformulatory approaches envisaged by various researchers from last five years (2015-2019) in solubility determination studies which can replace traditional oldest shake flask method described by the Speairs which, however, a time taking method and is most frequently used for quantitative estimation of thermodynamic solubility of drugs [22,23].

LITERATURE REVEW

Preformulatory Approaches for Solubility Estimation of Drugs by Thesaurus Envisaged in the Year 2015

Chen et al. Solid dispersion method: High throughput method for Solubility determination of crystalline drug Telaprevir was investigated by Chen et al. for the study of Bile Salts as Crystallization Inhibitors of Supersaturated Solutions of Poorly Water-Soluble Compounds in various media with or without 0. 1% surfactant by adding an excess amount of the drug in 15 ml of solution. The mixture was then followed by stirring and equilibration for 48 h 37°C in a water bath. Separation of solution from excess solid was then done by ultracentrifugation at 35,000 rpm for 20 minutes at 25°C, using Optima L-100 XP ultracentrifuge equipped with a swinging-bucket rotor SW 41 Ti. Telaprevir concentration in the supernatant was then estimated using an SI Photonics UV/vis spectrometer, which was coupled with a dip probe, dependent on the drug [24].

Shakeel et al. isothermal method: Quantification of crystallineVanillin in various Carbitol-water mixtures at a different temperature and atmospheric pressure was investigated by Shakeel et al. during the study. The solubility of Vanillin in Carbitol- water mixtures has been done at temperature T = 298. 15-318. 15 K and pressure p = 0. 1 MPa. The value of m was varied from 1. 0 analyzed by reversed-phase high-performance liquid chromatography at 220 nm. All studies were performed in triplicates [25].

Kumar et al. solvent-anti-solvent interaction method: Evaporation assisted Solvent–Ant-isolvent interaction method was used for the solubility estimation of Griseofulvin (Anti-cancer Drug) researched by Kumar et al. Acetone was used as solvent and water as an anti-solvent. The solubility of the Griseofulvin quantified by formulating its nanoparticles and the concentration

of drug was measured using a UV– Visible spectrophotometer. For this, a known quantity of each sample (20 mg) was weighed and added to a 100 ml conical flask containing 5 ml of water. The prepared aqueous suspension was placed on a magnetic stirrer for uniform mixing equipped with a thermostatic water bath at 37 ± 1°C for 24 h at 100 rpm. After 24 h, a solution was then centrifuged and filtered using WhatmanAnodisc 25 filter of pore size 20 nm to remove undissolvedparticles. Necessarydilution (with water) was performed to maintain the concentration using optical density at a wavelength of 296 nm [26].

Mohammadzad et al. Jouyban-Acree and Vanthoff-Abraham method: Aqueous solubility of Naproxen (NSAIDs) was successfully computed in mixed solvents using a combined Mathematical model described by Jouyban- Acree, and Vanthoff-Abraham. The solubility of Naproxen was determined by the shake flask method by preparing binary mixtures of solvents2-propanol + water in volume fractions varying by 0. 10 intervals. Approaches were followed by adding excess amount of Naproxen to each flask and placing in an incubator shaker at temperature 298. 2 to 313. 2 K. Solutions were then shaken until the solubility equilibrium was reached, and was verified by the undissolved drug which was filtered using cellulose membrane filters 0. 45 μm and analyzed by UV/Vis spectrophotometer, followed by required dilutions by distilled water-ethanol 50: 50mixture. The absorbance of the diluted solutions was recorded at 262 nm and the molar concentrations were determined using UV absorbance calibration curve [27].

Barate et al. 96-Well plate method: Thermodynamic equilibrium solubility of five model drugs, i. e. Ibuprofen, Budesonide, Carbamazepine, Chlorzoxazone, and Valsartan was measured in simulated fluids by 96 well plates through Estimation method. Methanol was used as a solvent as it was compatible with 96-well plates. Each experiment was performed in triplicate. Varying amounts of the drug have been loaded in wells. The amount of drug loading required was 0. 76–1200 mg sample for 4 test media (in triplicate). The solubility was then determined using a calibration curve method. A graph of concentration (μg/ml) versus absorbance (average of 3 determinations) was plotted to find out the saturation point of a compound. Hence, the obtained solubility values using established 96-well plate protocol was well following literature values (r=2 >0. 84) [28].

Schonherr et al. Chasing Equilibrium Solubility (CheqSol) and Curve Fitting Solubility method: The solubility of 34 active agents (Including ACE-inhibitors, b-blockers, Anti-diabetic and lipid-lowering substances) was determined using the SiriusT3 apparatus based on pka values, solubility, and concentration and pH profile. Intrinsic solubility of drugs was quantified by this Potentiometric Chasing Equilibrium Solubility method (CheqSol) and Curve Fitting Solubility method. CheqSol is generally applicable for ionizable compounds, insolubility was determined by dissolving and titrating the substance until a precipitate of neutral species was formed. The solution was then back titrated until the substance started dissolving again to achieve sub-saturation. To determine the substance intrinsic solubility, this change between the sub-saturated and supersaturated state was repeated several times. Whereas, Curve-Fitting method was used for highly soluble and rapidly precipitating compounds. Titration of the dissolved substance with acid or base could be done until precipitation occurred and equilibrium was established. The resulting curve was used to determine the shift between the theoretical aqueous pKa titration curve and the experimental precipitation titration curve. Solubility values could be calculated by observing the distance of the shift that depends on the known amount of the compound [29].

Laura I. Mosquera-Giraldo et al. Gas-Liquid phase separation method: Characterization of the phase behavior of supersaturated aqueous solutions of a high Tg drug, Telaprevir (used in hepatitis C infections) was reported by Laura I. Mosquera-Giraldo et al. In their study, highly supersaturated aqueous solutions of Telaprevir were produced by adding to 20 ml of 100 mM sodium phosphate buffer pH 6. 8 with and without 5μg/ml HPMCASMF using the solvent exchange method and

characterized using a variety of analytical techniques, i. e. nuclear magnetic resonance (NMR), fluorescence and ultraviolet spectroscopes, as well as dynamic light scattering (DLS). The samples mixing was done at 300 rpm, 37°C for 48 h followed by separation of solutions was from the excess solid by ultra-centrifugation at 40 000 rpm for 20 minutes, using Optima L-100 XP ultracentrifuge equipped with Swinging-Bucket Rotor SW 41 Ti. The supernatant concentration was determined using a SI Photonics UV spectrometer which was coupled to a fiber optic probe about path length of 10 mm at a wavelength of 270 nm was analyzed in triplicate [30].

Table 1: Briefing reported solubility estimation methods in the year 2015.

Method Name	Chemical Entity	Solvent Used	Authors
Solid Dispersion method	Celecoxib, Griseofulvin, Felodipine, Tadalafil, Telaprevir, Warfarin, Naproxen,Indomethacin, Bifonazole, Nevirapine	Sodium Taurocholate, Sodium glycocholate,Sodiumglycodeoxycholate, SDS	Chen et al.
Isothermal method	Vanillin	Carbitol- water	Shakeel et al.
Solvent- Antisolvent method	Griseofulvin	Ultrapure water, ethanol, acetone	Kumar et al.
Jouban- Acree and Abraham method Fitting Solubility method	Naproxen	2-propanol, water	Mohamadzedet al.
Estimation method	Ibuprofen, Budesonide, Carbamazepine, Chlorzoxazone, Valsartan	Water, Methanol	Barate et al.
Chasing Equilibrium Solubility method (CheqSol) and Curve	ACE-inhibitors, b-blockers, Anti-diabetic and lipid-lowering substances	Acetonitrile, dioxane, DMSO, Isopropanol, methanol and potassium hydroxide	Schonherr et al.
Gas-liquid phase method	Telaprevir	Water	Mosquera et al.

Year 2016

Prasad et al. Ternary solid dispersion method: Higher apparent solubility of Indomethacin was achieved by precipitation inhibition mechanism to maintain supersaturation by utilizing very low polymer concentrations. The solubility of IND in 0. 01 N Hydrochloric acid at pH = 2 in precipitation media 0. 01 N HCl and methanol mixture was carried out. 50 mg of Indomethacin was added to a 20 ml vial containing 10 ml of either 0. 01 N HCl or precipitation media followed by shaking for 24 h at 25°C. The sample was then subjected to centrifugation and filtration through 0. 22 μm filters and was analyzed by HPLC [31].

Fathi- Azarbayjani et al. Higuchi and Connors shake-flask method: Solubility parameters for Deferipronewere determined based on Higuchi and Connors's shake-flask method in binary mixture compositions. The total solubility parameter of DFP was calculated by Fedor's group contribution method and compared to the solubility parameter of various solvent mixtures to estimate maximum solubility in a specific co-solvent ratio. Initially in Higuchi and Connors's shake-flask method, an excess amount of drug was introduced into screw-capped bottles containing solvent and placed on a shaker-incubator at 25 ± 0. 1°C of

specified temperatures and allowed to equilibrate for 48 h. Pure solvents and binary solvent mixtures of water and co-solvent were prepared by mixing ethanol and N-methyl-2-pyrrolidone with water. The ratio of the co-solvents was prepared in the desired combination and was kept measuring the equilibrium solubility of the drug. Then, samples were filtered and analyzed spectrophotometrically at 273. 5 nm for drug contents [32].

Erturk et al. Higuchi and Connors method: Higuchi and Connors method was used effectively in the investigation of aqueous solubility of the poorly soluble drug Candesartan Cilexetil in the presence of poly (amidoamine) (PAMAM) dendrimers. The procedure followed as such, an excess amount of drug was added to 5 ml amber colored vials containing increasing concentrations of PAMAMs (0. 125 to 2. 00 mM) and then the vials were sealed. The resulting suspensions were shaken with an orbital shaker at 200 rpm while maintained at 37 ± 0. 1°C in an incubator for 24 h. The obtained mixtures were centrifuged at 6000 rpm for five minutes, and the insoluble excess drug was removed by filtering through 0. 45 μmcellulose acetate filters. The concentration of the drug was determined spectroscopically by using UV-Vis spectrophotometer in the wavelength ranges of 230-400 nm. UV-spectrum was taken at 254 nm for three repeated measurements. The absorbance was correlated with the calibration curve and the amounts of drugs were determined [33].

Charumanee et al. Phase- Solubility method: Phase solubility method was used for the study of the solubility of Piroxicam (Prx) depending on the inclusion complexation with various cyclodextrins (CDs) and on ethanol as a co-solvent by Charumanee et al. The method was applied for the estimation of drug solubility in binary and ternary systems. The procedure included the weighing of excess amount of drug, and placing into the glass screwed cap bottle and followed by addition of the appropriate volume of ethanol and water to obtain varying percentages of ethanol i. e. 1%, 3%, 5%, 7%, 10%, and 20% respectively. Homogeneity of the mixtures was then ensured by Sonication using an ultrasonic cleaner of 50 kHz for a certain minute and then placed on the magnetic plate. The mixture was stirred using a small magnetic bar at 150 rpm for 48 h in a thermostatic incubator with temperature-controlled at 25 ± 0. 1°C. The mixture was then filtered a through 0. 45 μmmembranetoobtain a clear filtrate which was diluted, and the absorbance was measured at 359 nm using a UV-spectrophotometer. The influence of ethanol on Prx solubility was assessed by plotting the concentration of Prx against the percentage of ethanol. The results were correlatedusingYalkowsky and Roseman's logarithmic—linear model [34].

Yousaf et al. Solvent Evaporation method: For the study of the influence of Polypyrrolidone quantity on the solubility, crystallinity and oral bioavailability of the Fenofibrate micro-sphere was explored through the Solvent evaporation method. In this, an excess amount of prepared microsphere was added to about 1 ml distilled water which was then vortex-mixed for 1 minute followed by agitation at 100 rpm in a water-bath at 25°C for 5 h and centrifuged at 10000 × g for 10 minutes. The supernatant (500 μl) was diluted with acetonitrile (500 μl) and filtered and analyzed by HPLC for estimating the drug concentration. The concentration of Fenofibrate in the eluent was detected at 286 nm [35].

Fujimori et al. HPLC method: Through the HPLC method, Fujimori et al. investigated the solubility and bio-availability Spray- dried powder of Ipriflavone (hydrophobic flavone), with trans-glycosylated rutin (Rutin-G), trans-glycosylated stevia (Stevia-G) and hesperidin (Hesperidin-G). For their study, they have successfully utilized the principle of the HPLC method for solubility estimation of prepared samples. In this, the samples were dispersed into 30 ml of distilled water and thereafter incubated at 37 C with shaking at 100 strokes per minute. The dissolved amount of Ipriflanone was determined by high-performance liquid chromatography with a detection wavelength of 254 nm. The injection volume of 10 lL and a flow rate of 1. 0 ml/min. The mobile phase was 0. 1 wt% phosphoric acid/acetonitrile (30/70) [36].

Wei et al. reported the novel inclusion complex of Glabridin and hydroxyl propyl β-cyclodextrin (HP-β-CD) to enhance solubility and bio-activity of GlabridinthroughHiguchi and Connors method. methods include the quantification of solubility of the drug by the addition of an excess amount of Glabridin 65 mg or Glabridin-HP-β-CD complexes 100 mg into 1 ml of water, prepared suspension then stirred at 25°C for 72 h. Samples were filtered through a 0. 22 μm membrane filter to remove excess insoluble substances and 25 μl of the filtrate was properly diluted with 25 ml ethanol. The amount of Glabridin dissolved was calculated using the absorbance at 282 nm. The solubility of Glabridin or Glabridin-HP-β-CD in water was then deduced according to the dilution proportion [37].

Table 2: Briefing reported solubility estimation methods in the year 2016.

Method Name	Chemical Entity	Solvent Used	Authors
Ternary solid dispersion	Indomethacin	Water, Methanol, Acetonitrile	Prasad et al.
Higuchi and Connors shake-flask method	Deferiprone	Water, Ethanol, NMP	Fathi Azarbayjaniet al.
Higuchi and Connors method	Candesartan Cilexetil	Deionized water	Erturk et al.
Phase- solubility method	Piroxicam	Ethanol	Charumanee et al.
Solvent evaporation method	Fenofibrate	Distilled water, Ethanol, Acetonitrile	Yousaf et al.
HPLC method	Ipriflavone	Distilled water, Acetonitrile	Fujimori et al.
Phase Solubility method	Glabridin	Ethanol, water	Wei et al.

Year 2017

Beig et al. Ultra Performance Liquid Chromatography method: The apparent solubility of Carbamazepine as a function of the PEG-400 level was estimated through the UPLC. Carbamazepine content in the different samples was analyzed on a WatersAcquity UPLC H-Class system equipped with PDA detector and controlled by Empower software. For this, Carbamazepine solubility in three solubility-enabling formulations (20%, 60%, and 100% w/w PEG-400/MES buffer) was measured at 37°C. PEG-400 solutions were added to glass vials containing excess amounts of drugs. Tightly closed vials were then placed in a shaking water bath at 37°C and 100 rpm. The establishment of equilibrium was assured by a comparison of samples after 24 and 48 h. Before sampling, the vials were centrifuged at 10,000 rpm for 10 minutes. The supernatant was carefully withdrawn and immediately assayed for drug content by UPLC [38].

Samie et al. Shake flask method**:** Utilization of principles of well-versed shake flask method was seen in the study by Samie et al. for the estimation of solubility and dissolution of the new multi-component systems of three Antidiabetic drugs Gliclazide, Tolbutamide and Glipizide (GCZ, TOL, and GPZ) and comparison with the parent API. To carry out such study solubility of each drug was measured at 1 h and 24 h at room temperature 27 ± 2°C. The absorption coefficient of each solid phase was measured by the slope of the absorbance versus concentration curve of at least five known concentrated solutions in a pH 7. 4 of phosphate buffer medium and measured at different λmax of UV-Vis spectrometer [39].

Enright et al. Standard Shake flask method**:** The standard shake flask method was explored for the investigation of the impact of gut microbiota- mediated bile acid to enhance the solubility of poorly soluble drugs. In this method, an excess of the drug added to 3 ml of phosphate buffer at pH 6. 8 containing either 20 mM bile salt alone with combination with 5 mM sodium oleate. A concentration of 20 mM was selected to ensure all bile salts were utilized at levels exceeding their reported critical micelle concentration (CMC) ranges. Sample vials were screw-capped vortexes to aid dispersion and subjected to

standard shake flask conditions at 37°C. 1 ml volumes were withdrawn at 24 hr intervals and transferred to 1. 5 ml Eppendorf tubes. Samples were subsequently centrifuged at 13000 rpm for 13 minutes, and the clear supernatant was then pipetted into clean tubes, and the centrifugation cycle was repeated to ensure separation from any residual solid phase drug. The resulting secondary supernatant, deemed clear of a precipitate, was subject to HPLC analysis [40].

Kong et al. Mechano-chemical method: Estimation of solubility ofSimavastainwas done through the Mechano-chemical method by Kong et al. In the method of solubility estimation, mechanical treated products, which were withdrawn from different milling times, were separately put into a 50 ml flat-bottomed flask with 10 ml of distilled water. Then the flasks containing the mixture were kept in a shaking incubator for 1, 2, 3, 6, 16 h with 200 rpm at +37°C. Noted time (3 h) was used in further experiments as this was the time at which constant concentration of SIM in solution was reached and doesn't change till at least 16 h. Centrifugation was performed for resulting suspensions were at 12,000 rpm for 5 minutes. The samples were then filtered using a paper filter and analyzed by HPLC method [41].

Table 3: Briefing reported solubility estimation methods in the year 2017.

method Name	Chemical Entity	Solvent Used	Authors
Ultra-Performance Liquid Chromatography method	Carbamazepine	PEG400	Being et al.
Shake flask method	Gliclazide, Tolbultamide	Distilled water	Samie et al.
Standard Shake flask method	Celecoxib, Danazole, Fenofibrate, Felodipine, Ketoconazole, Nifedipine, Phenytoin	Acetonitrile, Methanol and Dichloromethane	Enright et al.
Mechano-chemical method	Simvastatin	Distilled water	Kong et al.

Year 2018

Colombo et al. in-situ solubility method: *In-situ* solubility method was employed while carrying out the studies of preparation of amorphous Indomethacin nanoparticles by aqueous wet bread milled by Colombo et al. In this, sample was dissolved in 40 mL of water at 25°C by setting the paddle stirring rate to 300 rpm to prevent the floating of the powder, and their absorbance was recorded by *in situ* UV/VIS spectroscopy from 200 to 700 nm at interval of 4 s. Hence, the short interval was used to detect the re-crystallization of materials. Here, two different cell path lengths were used: 5 mm for the freeze-dried powders, 20 mm for original Indomethacin powder and amorphous Indomethacin powder and performed in triplicates under drug excess conditions. The drug concentration was 7 times higher than the drug solubility in the case of amorphous nanoparticles and nanocrystals (approx. 2 mg drug in 40 ml). The calculation of the amount of drug dissolved in the media was made by the software provided with the equipment, determined through the UV-metric MEC/pKa-assay of Sirius® in Form [42].

Fornells et al. CheqSol method: Selected 16 drugs of different chemical natures were analyzed using the CheqSol method (Stuart and Box, 2005) for their solubility estimation. The method followed as such, 10 ml of ISA solution are added to an accurately weighed amount of drug. The pH was then immediately adjusted to a value where the compound exists predominantly in its ionized form. Titration was initiated by adding KOH or HCl (depends on to nature of the compound), and solubility was appreciably reduced by increasing the concentration of the neutral species. At supersaturation, precipitation gets started. At this point, small amounts of acidic and basic titrant were alternately added, creating a subsequent positive and negative pH gradient, which in turn makes the drug solution go alternately from sub-saturated to supersaturate. The solubility of the

neutral species was estimated from the point at which the pH gradient becomes zero, i. e. where no net dissolution or precipitation of the compound occurs, through mass, and charge balances and the pKa of the compound. All measurements were performed successfully in triplicates to get the mean values [43].

Jouyban et al. saturation shake flask method: The solubility of Celecoxib (NSAIDs) in binary solvent mixtures (2-propanol and water) at different temperatures was investigated at 293. 3 K- 313. 2 K through the saturation Shake flask method of Higuchi and Connors. The method was followed by adding an excess amount of drug to the solvent medium, placed into the stoppered flask. Then, samples were placed on a shaker, which was placed in an incubator equipped with a temperature-controlling system. A period of 2 days (48 hours) was needed for saturation solutions to achieve equilibrium at the deliberated temperature where the number of aliquots was filtered using hydrophobic Durapore filters (0. 45 μm), then diluted by ethanol (96 %v/v or 0. 935 in mass fraction). Hence, the absorbance was recorded at 254. 5 nm using a UV-Vis spectrophotometer, and the molar concentrations of diluted solutions were calculated using a UV absorbance calibration curves [44].

Kalam et al. Isothermal method: Mycophenolatemofetil (Anti-rheumatic) drug solubility in different at temperature and pressure, T = 298. 2 Kto 318. 2 K″ and p = 0. 1 MPa through Isothermal method. 10 different solvents including water, ethanol, IPA, EG, PG, n-butanol, EA, DMSO, PEG-400 and Transcutolwasused for the study. The solute-solvent mixture was vortexes and transferred to the "Biological Shaker" at 100 rpm for 72 h. After 72 h, each solute-solvent mixture was taken out from the shaker and allowed to settle solid particles for 24 h. After 24 h settling of Drug particles, diluted suitably with mobile phase and subjected for the analysis of MPM content by the proposed UPLC method at 214 nm. The concentration of MPM (μg g−1) insolubility samples was determined from the calibration curve of MPM [45].

Perrier et al. Design of experiment equilibrium solubility method: The equilibrium solubility of BCS class II drugs in simulated media spanning the full range of both fasted and fed intestinal states in a single experiment was successfully explored through Design of experiment equilibrium solubility method in which a powdered drug (10 mg) was added to a centrifuge tube (15 ml Corning®). The required volume of each stock solution (section above) and water were added to provide a final volume of 4 ml in every tube. pH was then adjusted to 5 or 7 using 0. 1 M HCL or 0. 1 M KOH. Tubes were shaken for 1 h at room temperature and then pH adjusted again as before. Tubes are then placed in an orbital shaker and incubated for 24 h at 37°C and 240 rpm. Following incubation, the tubes were checked for the presence of the solid drug, then centrifuged (13,000 rpm, 5 min) and the supernatant (500μl) was sampled to determine the solubilized drug concentration by HPLC [46].

Table 4: Briefing reported solubility estimation methods in the year 2018.

Method Name	Chemical Entity	Solvent Used	Authors
In-situ solubility method	Indomethacin	Water	Colombo et al.
CheqSol method	Papaverine HCl, Dibucaine HCl, Cyproheptadine HCl, BendroflumethiazideBupivacaine HCl, Isoxicam, Propranolol HCl, Warfarin, Ketoprofen, Diclofenac sodium, Benzthiazide, Haloperidol, Maprotiline HCl, Olanzapine, Pindolol, Tetracaine	Water, DMSO	Fornells et al.
Saturation Shake flask method	Celecoxib	2-propanol, water	Jouyban et al.

Isothermal method	Mycophenolatemofetil	Water, Ethanol, IPA, EG, PG, n-Butanol, EA, DMSO, PEG-400, Transcutol	Kalam et al.
Design of experiment equilibrium solubility method	Fenofibrate, Indomethacin, Phenytoin, Gradients Felodipine, Probucol, Aprepitant, Tadalafil, Carvedilol, Zafirlukast	Methanol, Acetonitrile, Water	Perrier et al.

Year 2019

Sree Harsha et al. solvent evaporation method: The solubility of Tamoxifen citrate (as in physical mixtures) was estimated by utilizing the principles of the Solvent evaporation method. The procedure followed as such, an excess of Tamoxifen citrate (50 mg), dissolved in 25 ml of water and phosphate-buffered saline (pH 6. 8, 7. 4 PBS), with and without the inclusion of carriers. Physical mixtures solutions were vortexes for 5 minutes and placed in a benchtop water bath shaker at an angular acceleration of 100 rpm for 24 h at 37 ± 1°C. After an incubation of 24 hrs, the samples were vortexes for 5 minutes and centrifuged at 10,000 rpm at 37 ± 1°C and diluted with the different solvent systems, and samples were analyzed using high-performance liquid chromatography (HPLC). The above procedure was repeated in triplicate to determine the solubility of TC [47].

Li et al. saturation shake-flask method: The concept of the Saturation shake-flask method (Jouyban et al. 2018) was well utilized in the study of solubility determination of compound 2-amino6-chloropurine in water and 11 other organics. High-performance liquid chromatography was used for the determination of 2-amino-6-chloropurine equilibrium solubility at T = 278. 15−333. 15 K at intervals of 5 K and ambient pressure p = 101. 2 kPa. The experimental procedure followed as such, the excess 2-amino-6-chloropurine was added into a given amount of pure solvent in triplicates. Each 2- amino-6-chloropurine mixture was mixed completely and then transferred to a thermostatic shaker. The mixture was shaken by using a shaker at a speed of 100 rpm. To acquire the equilibrated time, 0. 5 ml of liquid phase was withdrawn by using a 2 ml syringe at intervals of 1 h and tested with the Agilent 1260 high-performance liquid-phase chromatography. The analysis results showed that 19 h was enough for all the solutions to arrive at equilibrium. Then, the solution was removed from the shaker and permitted to precipitate all the 2-amino-6-chloropurine particles, which would take an additional 3 h. The upper liquor was taken out carefully, diluted, and tested by using high-performance liquid-phase chromatography [47].

Kalam et al. also explored the equilibrium/saturated solubility values of solid Gemfibrozil in twelve, different solvents, i. e., H_2O, MeOH, EtOH, IPA, 1-BuOH, 2-BuOH, EG, PG, PEG-400, EA, DMSO, and THP through saturation shake flask technique at T = 298. 2 K to 318. 2 K" and "p = 0. 1 MPa"21. Similarly, excess amount of solid GEM (g) in known amounts (g) was dissolved in a given solvent. Every GEM- solvent/solute-solvent binary system was mixed properly and placed in a "Biological Shaker". The speed and equilibrium time of the biological shaker was set at 100 rpm and 72 h, respectively. At the end of the experiment, the sample vial was removed from the biological shaker and allowed to settle the undissolved GEM particles for about 24 h. After complete the settling of undissolved solid particles of GEM, the sample was carefully taken, diluted and utilized for the quantification of GEM contents by the UPLC-UV method at λmax of 254 nm [49].

Wang et al. Isothermic static technique: The solubility Artesunate in four, mixed solvents composed of water and several organic solvents were measured by the isothermal static technique. The supernatant solution of the equilibrium solution was taken and analyzed by HPLC. In this, a relatively large amount of Artesunate powder was added to the jacketed beaker and

mixes with the prepared mixed solvents. Continuous stirring was performed to ensure that the solution and the drug can be thoroughly mixed at a certain temperature by placing on a magnetic rotor controlled by a micromagnetic stirrer equipped with the thermostatic bath which was able to control the temperature of the circulating fluid, and thus maintained the mixed solution under a suitable temperature condition. Thus, approximately 0. 5 ml of the supernatant was removed from the mixed solution by a preheated syringe (2 ml) equipped with a pore syringe filter (PTFE 0. 2 μm) about 2 h; afterward diluted by a volumetric flask according to a certain ratio, and then analyzed by HPLC [50].

Table 5: Briefing reported solubility estimation methods in the year 2018.

Method Name	Chemical entity	Solvent Used	Authors
Solvent evaporation method	Tamoxifen citrate	Water	Sree Harsha et al.
Saturation shake-flask method	2-amino-6-chloropurine	Water	Li et al.
Saturation shake-flask method	Gemfibrozil	Water	Kalam et al.
Isothermic static technique	Artesunate	Water	Wang et al.

DISCUSSION

Overall, this review attaching the pre-formulation approaches for quantitative estimation of solubility of new drug candidates considering as one of the foremost physio-chemical properties that relate to drug absorption and bio-availability. Most of the chemical entities show poor solubility that leads to the inappropriate pharmacokinetic property that crimps formulation development. Thus, numerous experimental methods have been developed for arbitrating the solubility of solid drugs. Despite, high-throughput assay have lately been available, whereas, the use of accurate solubility method is somewhat expensive and time taking process. Therefore, new and improved approaches have been discovered by many researchers for assessing the solubility of the drug. Stacking all the recent and transmitted approaches for preformulatory solubility estimation since the last five years is translated in this review article. Likely, reported in 2015 by Chen et al. that utilized solid dispersion method for solubility determination of crystalline Telaprevir in various media for study the bile salt as a crystallization inhibitors show increase concentration of a drug. Similarly, Shakeel et al. investigated the solubility of Vanillin in the carbitol-water mixture at different temperatures and pressure using the isothermal method and analyzed by reversed-phase high-performance liquid chromatography. Kumar et al. estimate the solubility of Griseofulvin through Solvent- Anti-solvent interaction method and determine their concentration by dilution with water. Whereas, Mohammadzad et al. enhances the solubility of Naproxen in two solvent i.e. 2-propanol and water through jouybanacree and vanthoff- Abraham method Similarly, in 2016 Prased et al. utilizes ternary solid dispersion method by enhancing the solubility of Indomethacin through precipitation inhibition mechanism with the use of low polymer concentration. Fathi-Azarhayjani et al. enhances the solubility of Deferiprone through the utilization of Higuchi and Connors shake flask method in the various solvent mixture. Charumanee et al. studied the solubility of Piroxicam through phase solubility method with the complexation of cyclodextrin in two solvent i.e. ethanol and water. Hence, Yousaf et al. utilized the solvent evaporation method for enhancing solubility of Fenofibrate with the influence of polyprrrolidone to estimate their concentration. In the year 2017, Beig et al. through ultra-performance liquid chromatography methods were used to determine the solubility of Carbamazepine in PEG-400/MES buffer on water Acquity UPLC H-class system. Samie et al. also estimated the solubility of three antidiabetic drug-like Gliclazide, Tolbutamide, and Glipizide through well-versed shake flask method. Kong et al. investigates the solubility of Simavastain through the mechano-chemical method and analyzed by HPLC. Latterly, in 2018 and 2019, Colombo et al. employed a unique *In-situ* solubility method for the preparation of amorphous Indomethacin by Wet bread milled and determine their solubility and Sree Harshe et al. estimated the solubility of Tamoxifen

citrate by utilization of Solvent evaporation method and determine the concentration in HPLC respectively. On that account, several ways have been used by different researchers for measuring solubility drugs. Supplementarily, the more studies are still demanded to scrutinize the approaches that must be convenient and competitive.

CONCLUSION

As translating solubility, a phenomenon of dissolving the drug in a specified solvent to give homogeneous mixture is an essential parameter to attain the desired concentration of drug in a solvent. Low aqueous solubility is a crucial problem encountered with the formulation of origination. Attempting this, various approaches were experimentally proved to attain the solubility of the drug candidate. The use of classic method i.e. Shake flask method was however widely recommended by researchers but moderately a time-consuming process. Hence, to cop off the oldest method, new and improved methods have translated for figuring the solubility of the drug. These methods generally abating time and claiming convenient results. Achieving current methodologies used for assessing the solubility study probing by researchers for the last five years (2015-2019). Currently, medium to high thorough put methodologies for determining solubility related parameters such as dissolution, supersaturation, and precipitation have been developed. Hence, the rapid elevated computational methods are driving the development of various modeling and simulations approaches seemly predicting solubility from molecular structure.

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