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Review article

COSMO models for the pharmaceutical development of parenteral drug formulations

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ABSTRACT

The aqueous solubility of active pharmaceutical ingredients is one of the most important features to be considered during the development of parenteral formulations in the pharmaceutical industry. Computational modelling has become in the last years an integral part of pharmaceutical development. In this context, *ab initio* computational models, such as COnductor-like Screening MOdel (COSMO), have been proposed as promising tools for the prediction of results without the effective use of resources. Nevertheless, despite the clear evaluation of computational resources, some authors had not achieved satisfying results and new calculations and algorithms have been proposed over the years to improve the outcomes. In the development and production of aqueous parenteral formulations, the solubility of Active Pharmaceutical Ingredients (APIs) in an aqueous and biocompatible vehicle is a decisive step. This work aims to study the hypothesis that COSMO models could be useful in the development of new parenteral formulations, mainly aqueous ones.

1. Introduction

The poor solubility of Active Pharmaceutical Ingredients (APIs) can be a relevant obstacle in the development of new parenteral products [1,2]. The solubility profile of APIs can impact deeply the medicine's life cycle since it can set and limit several product characteristics in terms of pharmaceutical properties and thus, impact undoubtedly the formulation and subsequent development processes [3-7].

In the development of parenteral products, the aqueous solubility of APIs is naturally a crucial property that deserves to be well-studied. The poor aqueous solubility can, in the worst cases, hinder the development of parenteral formulations calling into question the quality of these products attending to their safety (biocompatibility), efficacy (bioavailability), and stability [8,9]. Due to this fact, studies about solubility should be performed carefully during the molecular design and pharmaceutical formulation to ensure commercial viability [8-10]. Unfortunately, around 70 % of APIs and new chemical entities are poor water-soluble molecules belonging to the Biopharmaceutical Classification System (BCS) classes II and IV [11,12].

The selection of excipients is another very important step during the development of parenteral formulations. Negative interactions with the APIs, other excipients and with packaging components can result in loss of drug solubility, activity, stability and, biocompatibility [13,14]. Since the excipients is commonly the major components in a parenteral formulation its selection must be careful assessed to achieve an effective, safe and stable product [13].

Abbreviations: API, Active Pharmaceutical Ingredient; ANN-QSPR, Artificial Neural Networks/Quantitative Structure-to-Property Relationship; BCS, Biopharmaceutical Classification System; COSMO, Conductor-like screening model; COSMO-RS, Conductor-like Screening Model for Realistic Solvents; COSMO-SAC, Conductor-like Screening Model – Segment Activity Coefficient; COSMO-RS-DARE, COSMO-RS with Dimerization, Aggregation, and Reaction Extension; DES, Deep eutectic solvent; HSP, Hansen Solubility Parameter; IL, Ionic liquid; NRTL-SAC, Non-random two-liquid- Segment Activity Coefficient model; PC SAFT EOS, Perturbed chain-statistical associating fluid theory equation of state; RMSE, Root mean squared error; UNIFAC, Universal Quasichemical Functional-group Activity Coefficients; PCM, Polarizable continuum model; WFI, Water for injection.

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Advances in the field of computation during the 70 s and 80 s allowed the accelerated progress of quantum chemistry, resulting consequently in the fast development of optimized solvation models [5,15-18]. Taking into account that solubility is a complex phenomenon, their simulation is a challenging task [5-7,19,20]. It is dependent on various molecular attributes in addiction to solute–solvent interactions and solute/solvent interactions themselves [5]. With this, an *in silico* approach in the early research steps can results in effective cost and time savings during the development of pharmaceutical molecules and products [20].

The conductor-like Screening model (COSMO) belongs to the class of Continuum solvation models [21], however, it is specifically characterized by its low computational costs and the simplistic approach concerning quantum mechanical and statistical calculations [22]. With these evident advantages, the COSMO models have demonstrated applicability in some modern scientific areas for the development of new technological products such as lithium-based batteries [23], high-performance supercapacitors [24], new refrigeration systems [25] and strategies for the removal of organic pollutants from the environment [26-37].

This work aims to study the applicability of COSMO models in the formulation of parenteral pharmaceutical products during the development process, mainly the aqueous ones. For this, the theoretical and practical concepts around COSMO models were briefly explored. Also, works available in the literature about their ability to predict and contribute to the improvement of the solubility of pharmaceutical compounds in aqueous media were considered and reviewed.

2. COSMO models

Theoretical and computational models have been demonstrated to be important supplements to the exploration of new solutes and solvents [38]. In general, there are three types of thermodynamic models: (1) theoretical models, (2) semi-theoretical (or semi-empirical) models, and (3) empiric models [39,40]. Each one has different accuracies and reliable ranges in the results [40]. While the empirical and semi-empirical models are developed using correlations obtained by experimental data, but without theoretical meaning, theoretical models, like COSMO, estimate entirely the desired properties based only on the molecular structure and without the further requirement of experimental data (*ab initio* approach) [39,40].

Previously, before the development of COSMO, some models such as Universal Quasichemical Functional-group Activity Coefficients (UNIFAC) were proposed [41,42]. These models were commonly based on the free energy of molecules in solution revealing some clear disadvantages, mainly the requirement of large sets of experimental data. Thus, considering these models only achieved good in the interpolations of the experimentally derived data, the enormous evolution of computation power allowed the emergence of *ab initio* approaches, such as the COSMO model, to simulate the solvation phenomena [41].

The COSMO model was conceptually proposed for the first time in 1993 by Klamt and Schüürmann [21]. In this approach, geometry optimization of a solute within a realistic dielectric continuum model becomes practicable due to the relevant advances in the field of computation and emerged as the simplest way to calculate the screening energy of a molecule in a dielectric medium [21]. The COSMO model is based on computational quantum mechanics by knowing the molecular structure and requiring the calibration of a small set of universal parameters [40,43].

Briefly, in the COSMO model, the dielectric constant of the medium ($\varepsilon \geq 1$) is changed from the characteristic of each solvent (a finite value) to infinite ($\varepsilon=\infty$). This change converts the medium into a perfect conductor and modifies the boundary conditions of the electrostatic problem [17,21,41,44,45]. The essential difference between COSMO and other dielectric continuum models is the usage of a scaled conductor boundary condition instead of the exact dielectric boundary condition [46]. With this approach, COSMO models promote an alternative definition of Polarizable continuum model (PCM) charge distribution [21].

After that, in 1995, Klamt et al. [41] introduced the Conductor-like Screening Model for Realistic Solvents (COSMO-RS) as "a totally new approach for the calculation of solvation phenomena" [21,41]. Based on the previous works, Klamt presented the theoretical basis of COSMO-RS, introducing at the same time, a new and instructive view of solvation phenomena [44]. For this, Klamt and co-workers [38] successively combined the COSMO calculations with a statistical thermodynamics treatment of interacting surfaces. In COSMO-RS, molecules are treated as a collection of surface segments. An expression for the chemical potential of segments in the condensed phase was derived in which needed interaction energies between segments were determined from COSMO calculations [46]. This model was originally applied to the prediction of vapor pressures and partition coefficients, with an average accuracy of within a factor of 2 [47]. The COSMO-RS can be recognized as "a theory of interacting surfaces" [48] and is based on the principle that "if a solvent calculation of the ideal surface charge densities for all faces of a solute molecule, then it is able to screen the solute as a good as a conductor.".

Meanwhile, the Conductor-like Screening Model - Segment Activity Coefficient (COSMO-SAC) was proposed formerly by Lin and Sandler [47] in 2002. In the original work, these authors, proposed the calculation of an activity coefficient model using molecular solvation based on the COSMO-RS however this work resulted in the development of an alternative version of the COSMO-RS model with their own designation, COSMO-SAC [47]. In this model, as is performed in the COSMO-RS, the quantum mechanical COSMO calculations are performed to obtain the screening charges for molecules in a perfect conductor. Nevertheless, another statistical mechanical model is proposed, considering the molecules as a collection of surface segments for the calculation of segment activity coefficients [47]. One of the most advantageous features of this model is that it requires only a single radius for each atom in the COSMO solvation calculations, one universal parameter to discern hydrogen-bond acceptors and donors, and two universal parameters to determine segment interactions [47]. Additionally, Lin and Sandler [47] argued that despite the COSMO-RS method has provided promising results, the equation for the segment chemical potential used in COSMO-RS does not correctly converge to certain boundary conditions, and due to this fact, the final expression for the activity coefficient fails to satisfy thermodynamic consistency relations [47].

Nowadays, besides COSMO-RS and COSMO-SAC, other alternative COSMO-RS models have been proposed (Table 1 and Fig. 1).

In the table I are presented the main COSMO-RS models proposed in the literature. There, the proposes and main advantages (highlights) of each model are described.

According to the table I, each COSMO-RS extension was proposed to simplify the calculations, improve the results, or adapt the COSMO calculations to specific applications:

- COSMOfrag was developed to optimize the COSMO-RS calculations reducing the computation efforts.
- COSMO-RS-DARE was proposed to improve the COSMO-RS results in mixtures containing carboxylic acid and nonpolar components.
- COSMOsim and COSMOsim-3D adapted the COSMO-RS results for the detection of new bioisosteric drug candidates based on the degree of similarity to the σ profiles.
- COSMOmic, COSMOplex and COSMOperm adapt the COSMO-RS calculations to self-organizing molecular systems.

Despite clear differences exist concerning the proposes of each COSMO-RS extension, the conceptual basis is shared between them.

After the introduction of the COSMO-RS Klamt in 1995, Hornig and Klamt[49] proposed COSMOfrag as a COSMO-RS simplification [49]. In contrast with COSMO-RS, the COSMOfrag allow the application of COSMO calculations to complex molecules reducing the computation

Table 1
Main COSMO models developed and proposed.

Author(s)	COSMO model	Year	Proposes	Highlights
Klamt A. and Schüürmann G. [18]	COSMO	1993	• Proposed as a new dielectric continuum model with some simplistic algorithms. • It allowed the calculation of the dielectric screening energy of real-shape molecules in a dielectric medium. • At the same time, it proposed a new strategy for the analytic calculation of screening energy gradients within real-shape cavities.	• Simplified and explicit calculation of the screening energy of a molecule in a dielectric medium. • The geometry optimization of a solute within a realistic dielectric continuum model becomes practicable. • Compared with other dielectric continuum models, one of the greatest advantages of COSMO is its essential robustness concerning artifacts generated from the outlying charges.
Klamt. A. [38]	COSMO-RS	1995	• Presented as a new approach to the quantitative calculation of solvation-related properties (vapor pressures, surface tensions, and octanol/water partition coefficients). • COSMO-RS is a combination of COSMO with a statistical thermodynamics' treatment of molecular interacting surfaces (chemical potential segments).	• The starting point of the COSMO-RS theory is the calculation of the dielectric screening charges and the ideal screening energy through the application of COSMO algorithms. • COSMO-RS presents the ability to distinguish between two solvents with identical dielectric constants but different molecular properties. • COSMO-RS intrinsically treats solute and solvent in the same way, rather than considering the solvent as just a dielectric field.
Lin S. and Sandler S. [44]	COSMO- SAC	2002	• The molecules are treated as a collection coefficient of activity segments and not as a collection of chemical potential of segments. • COSMO-SAC model uses an improved and exact statistical mechanical model for the determination of the segment activity coefficients.	• The COSMO-SAC model was based on the COSMO-RS. • COSMO-SAC resolves some inconsistencies observed in the results obtained from the COSMO-RS model. Mainly in the cases where the final expression for the activity coefficient of COSMO-RS fails to satisfy the consistency of some thermodynamic relations and does not correctly converge to certain boundary conditions.
Hornig M. and Klamt A. [46]	COSMOfrag	2005	• COSMOfrag was developed to avoid the time-consuming calculation of the screening charge densities (σ profiles). • For each molecule, this model searches in a database for identical fragments from other molecules and constructs the σ profile.	• Compose the σ profile of new molecules from preexisting σ profiles of other molecules, reducing the time-consuming calculation. • Makes viable the obtention of results for larger and more complex molecules, since the COSMO − RS calculations were unavoidably restricted to small- to medium-sized molecules. • A database with 40 000 molecules allows the reliable calculation of properties for almost any class of compound in life science or drug design.
Thormann M. et al. [47]	COSMOsim	2006	• COSMOsim was presented as a novel approach for the similarity quantification of drugs' effect based on the similarity of the σ-profiles. • Allows the detection of new bioisosteric drug candidates based on the degree of similarity to the σ profiles.	• The obtained results reveal clearly that COSMOsim perceives molecular similarity in the same manner that medicinal chemists do. • The similarity of σ profiles appears to be a necessary condition for drugs with similar physiological action.
Klamt A. et al. [48]	COSMOmic	2008	• COSMOmic extended the application of COSMO-RS to the simulation of solutes in micellar systems. • It is presented as a new approach for the modeling of molecules in micellar systems, mainly in biomembranes.	• COSMOmic allows the efficient prediction of the distribution of molecules in micellar systems • COSMOmic is essentially free of additional adjustable parameters. • COSMOmic is equally well applicable to any micellar systems composed of nonionic or ionic surfactants. • It is not necessary to calculate a whole membrane system but only to calculate COSMO values for each element composing the micellar system.
Thormann M. et al. [51]	COSMOsim 3D	2012	• COSMOsim3D is an extended version of the COSMOsim • It was developed to overcome the neglected 3D distribution of molecular polarities, which is crucially determining for all ligand–receptor binding. • It is used to measure intermolecular similarities based on the 3D representation of the surface polarization charge densities.	• The analysis of 3D alignment and 3D similarity allows a very good separation of true bioisosteric pairs from random pairs. • Detection of physiological similarity of chemically very different structures and hence for scaffold hopping.
Sachsenhauser T. et al. [52]	COSMO-RS-DARE	2014	• COSMO-RS-DARE is an extension of COSMO-RS where the dimerization of carboxylic acids and nonpolar components are considered.	• With COSMO-RS-DARE is achieved a better description of mixtures containing carboxylic acid and a nonpolar component. • COSMO-RS-DARE has higher accuracy than activity coefficients calculated with COSMO-RS.
Klamt A. et al. [49]	COSMOplex	2019	• COSMOplex approach is based on the COSMOmic model. • COSMOplex allows the self-consistent simulation of a wide range of self-organizing molecular systems at significantly lower computational costs.	• This method extends the application range to many new areas, such as the prediction of micellar structures and critical micelle concentrations, finite loading effects in micelles and biomembranes, the free energies and structure of liquid interfaces, and microemulsions. • No additional adjustment of empirical parameters was required.
Schwöbel J. and Klamt A. [50]	COSMOperm	2019	• COSMOperm is an adaptation of COSMOplex model but focused on the study of Skin penetration. • Simulates the composition of human skin, including short- and long-chain ceramides, cholesterol, and fatty acids in the stratum corneum.	• This approach allows the generation of membrane systems on a very detailed molecular level. • The individual membrane systems can be modified easily to identify local effects and pathways, which are responsible for either retaining or impairing the skin barrier function.

Abbreviatures: COSMO- Conductor-like Screening Model, COSMO-RS- COSMO for Realistic Solvents, COSMO-SAC- COSMO- Segment Activity Coefficient, COSMO-RS-DARE- COSMO-RS with Dimerization, Aggregation, and Reaction Extension.

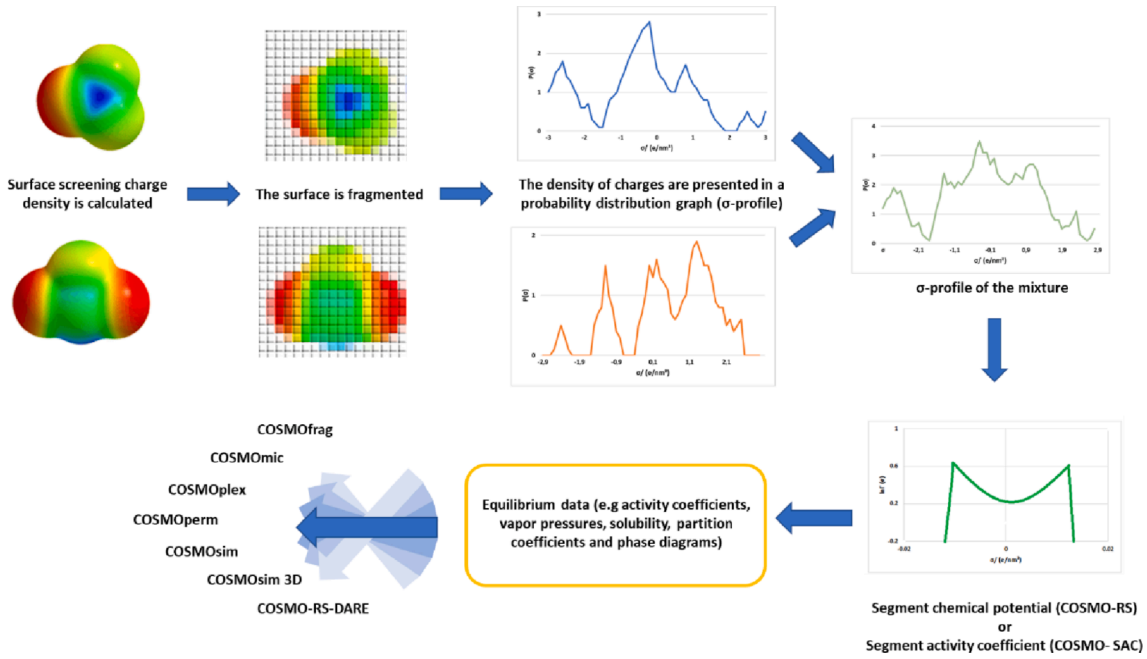

Fig. 1. Brief schematic illustration of the COSMO principles.

time by several orders of magnitude. After that, the same work group proposed the COSMOsim. This model is based on the quantification of σ-profile similarity between molecules. The authors suggested that since this similarity is a necessary condition for drugs of similar physiological action for the detection of new bioisosteric drug candidates [50]. In 2008, the COSMOmic was proposed as a new approach for the modelling of molecules in micellar systems and in biomembranes [51]. COSMOmic is an adaptation of COSMO-RS for anisotropic solvents such as micelles or bilayers [51]. Meanwhile, was proposed COSMOsim-3D to overcome a relevant disadvantage related to COSMOsim. Indeed, COSMOsim introduced a global measure of molecular similarity, but did it by neglecting the 3D distribution of molecular polarities. COSMOsim-3D showed to be able of measure intermolecular similarities based on the 3D representation of the surface polarization charge densities σ and thus allowing to determine all ligand–receptor binding [52]. In 2014 was proposed COSMO-RS-DARE to overcome a COSMO-RS limitation [53]. COSMO-RS-DARE was presented as better COSMO model to the study of mixtures containing a dimerizing carboxylic acid and nonpolar components since in the COSMO-RS, all spatial information is neglected turning impossible the consideration of molecular dimerization in COSMO simulations [53]. More recently was proposed the COSMOplex to overcome the inability of COSMOmic to consider the hard-core repulsion of molecules. To this, this new approach introduced a system pressure in each of the layers, similar to molecular dynamics or dissipative particle dynamics simulations [54]. At the same time was proposed the COSMOperm as a computational human skin model. This model is an extension of COSMOperm but representing specifically the composition of a human skin [55].

3. Solvation and its impact on the pharmaceutical development

This section explored how the COSMO models have been used for pharmaceutical proposes (sections 3.1 and 3.2) and how they could be valuable allies for the development of new parenteral products (sections 3.3 and 3.4).

To this, an in-depth literature search was performed mainly in Pubmed, Web of Knowledge, and Google scholar. Terms such as COSMO* PHARMA*, PHARMACEUTICAL, DRUG, API, COMPOUND, SOLUB*, SOLUBILITY, DISSO*, DISSOLUTION, COSMO-RS, COSMO-SAC, PARENT*, PARENTERAL, INJECT*, INJECTABLE was used and combined between them. Since the goal of this work is to equate the application of COSMO models for a new proposal but based on already published works, the cited works were selected subjectively, according to their quality, and clarity, to explain our point of view.

3.1. Pharmaceutical applications of COSMO models

Solid drug formulations, such as tablets and capsules, can provide an effective and safe therapeutic program cost-effectively. However, in several cases, it is not possible to prescribe solid formulations or orally administrated medicines [8,9,56].

Compounds in the liquid state either in pure form or in solution, are extraordinarily complex systems to describe theoretically [38]. Indeed, the properties of molecules in liquid systems are influenced by interactions with all neighbouring molecules in a dynamic form and the calculation of these properties requires an efficient sampling and thermodynamic averaging of all the possible arrangements of solute and solvent molecules [38].

For Chemistry, and naturally, for pharmaceutical proposes, COSMO models have been revealed to be useful in the determination of several compounds' characteristics such as Pka [57-63], partition coefficient [64-66], and Melting point[67]. Also, COSMO has been able to help in the study of molecular co-crystallization, solvation/desolvation [68-70] and chemical stability [71-74]. Additionally, some works demonstrated that COSMO could be applied in the screening of pharmacologic analogues [74-76], in the determination of solvation-free energies[77,78], in the study of conformational states of molecules [59,79] and in the study of biological processes [80-85].

Regarding the pharmaceutical formulation, COSMO models have been used in the study of the solubility of APIs in several media, such as aqueous [61,86,87], lipidic [88,89], ionic liquids [90,91] and deep eutectic liquids [92-94]. Additionally, some studies about the solubility and stability of drugs in complex formulations, mainly micellar and liposome systems, have been published [95-98]. In Pfizer, COSMO-RS has been successfully used in the solvent selection for early polymorph and re-crystallization screens [99].

3.2. Solvents and co-solvents applied for the formulation of parenteral formulations

The solvents are a crucial part of parenteral pharmaceutical products since they are not only solubilizing agents but they are also the administration vehicles of parenteral formulations [9,100].

Water for injection (WFI) is the most common solvent, however other organic solvents and co-solvents have been used to improve the solubility, stability, and tolerability of the APIs and the respective formulations [9,100]. Indeed, for more than 50 % of parenteral formulations, organic solvents/co-solvents such as propylene glycol, polyethylene glycols, and ethanol are used either alone or in combination with other solvents to allow a satisfactory solubility of poor soluble drugs [9,100,101]. Additionally, tonicity adjusting agents and buffering components are elements that need to be considered when we are talking about the solubility of pharmaceutical molecules since they can change the dielectric constant and pH of the solutions [9,87,100,102].

In the market, parenteral products are mainly available in solutions, suspensions, and emulsions. From all, the solutions are the simplest and most convenient form of presentation of an injectable product since the parenteral suspensions and emulsions present some constraints [8]. Indeed, when administrated intravenously, the suspensions present an increased risk of venous embolism [103] and the emulsions present an increased risk of liver, immunologic dysfunctions, and fat embolism [8,56,104]. To this, the development of parenteral formulations in aqueous solutions is always the best result to be achieved and all efforts must be performed to achieve such products. Some strategies to solubilize poor water-soluble molecules exist before proceeding to more complex strategies. The use of co-solubilization of salts, co-solvents, surfactants, complexing/dispersing agents, or the development of water-soluble crystals of the API could avoid the development of more complex products. For these strategies, some studies using COSMO approaches are available in the literature [105-107].

3.3. Predicting the aqueous solubility of APIs using COSMO models

The determination of solubility parameters is fundamental for the pharmaceutical sciences. Due to this fact, *in silico* methods have been proposed as a promising way to predict the solubility behaviour of chemical substances before the execution of experimental studies [107]. As written above, the solubility of APIs in water is an important characteristic of pharmaceutical compounds to understand and predict their physicochemical properties. Indeed, the solubility profile of the APIs defines how the compound can be formulated and thus impact for example the choice of the via of administration and their pharmacologic properties (i.e pharmacokinetics and pharmacodynamics) [8,9].

In the literature, some authors studied the predictive power of COSMO models for the aqueous solubility of APIs. Several works have been reported to demonstrate the predictive capability of API solubility not only in water but also in organic [88,108] and ionic liquids (ILs) [90,91]. Since the formulation of parenteral products in ionic liquids is not desirable due to their high toxicity [84] and the use of organic solvents has some constraints as described previously, this subchapter will be focused on some works where the aqueous solubility of pharmacological substances was studied.

In 2001, Klamt et al. [86] demonstrated how the COSMO-RS method, originally developed for the prediction of liquid–liquid and liquid–vapor equilibrium constants based on quantum chemical calculations, is capable to predict aqueous solubilities of a wide range of typical neutral drug and pesticide compounds. In this work, the COSMO-RS method has been introduced as a novel predictive method for the aqueous solubility of solid and liquid drug-like compounds. After that, Ikeda et al. [109] demonstrated that COSMO-RS can reproduce reasonably experimental data about the solubility of drugs [109]. For this, this work employed COSMO-RS calculation in predicting the solubility of drugs and drug-like compounds in various solvent systems. Additionally, the authors evaluated the salt effect on the solubility of caffeine [109]. Yet, concerning the direct solubility prediction by the COSMO models, Pozarska et al. [99] proposed the application of COSMO-RS to help with the selection of excipients for formulation development in early discovery to preview their solubility [99]. In the conclusion, the authors reported that COSMO-RS was able to reasonably predict excipients with the best solubilizing power for the set of compounds used as an example [99]. Meanwhile, Palmelund et al. [92] compared the solvation capacities of six deep eutectic solvents (DESs) compared to water and three conventional pharmaceutical solvents (PEG 300, ethanol, and glycerol) for 11 APIs. Additionally, the authors compared the experimentally determined solubilities with the computational solubilities predicted by the COSMO-RS. They concluded that some APIs poorly soluble in water may be soluble in DESs and reinforced the concept that COSMO-RS can be used to reduce the need for experimental data to screen potential DESs solvents for a given API.

To evaluate the solubility models, some authors published works comparing different models or different COSMO algorithms. Tung et al. [110] estimated the solubility of Lovastatin, Simvastatin, Rofecoxib, and Etoricoxib by COSMO-SAC and Non-random two-liquid- Segment Activity Coefficient model (NRTL-SAC) solubility screening protocol for the development of crystallization processes. The authors concluded that NRTL-SAC model offered superior performance over the ab initio COSMO-SAC model. However, they advised that no additional optimization was performed on the COSMO parameters over that performed by Lin and Sandler [47]. In other work, Hahnenkamp et al. [108] determined the solubility of Aspirin, Paracetamol, and ibuprofen in a few organic solvents using COSMO-RS, UNIFAC, and a modified model UNIFAC. The authors compared the results with experimental results and concluded that modified UNIFAC and UNIFAC achieved the best-predicted results compared with COSMO-RS. Also, Moodley et al. [111] compared computational results obtained through original UNIFAC, modified UNIFAC (Dortmund), COSMO-RS, and COSMO-SAC for some polycyclic steroidal and triterpene solutes and concluded that the modified UNIFAC (Dortmund) model provided a superior solubility prediction when benzene as a solvent was considered, but UNIFAC model provided a superior solubility prediction in aqueous systems [111]. Recently, Mahmoudabadi and Pazuki [40] investigated the solid/liquid equilibria of a vast list of pharmaceutical compounds in water and in some non-aqueous solvents. In this work, the authors compared the results obtained by the original COSMO- SAC model (COSMO-SAC (2002)) with a semi-predictive model named Flory–Huggins model and a revised version of the COSMO-SAC (COSMO-SAC (2010)). They concluded that the original COSMO–SAC model (COSMO-SAC (2002)) presents an acceptable accuracy except for more complex molecules, where the presence of groups such as COO and COOH or electronegative atoms require more modifications in the COSMO-SAC model. After that, the same authors developed a predictive perturbed chain-statistical associating fluid theory equation of state (PC–SAFT EOS) based on COSMO for pharmaceutical compounds [112]. The obtained RMSE based on the logarithmic scale for the predictive PC-SAFT EOS was a lower value than root mean squared error (RMSE) for the COSMO-SAC model but is the same as that for RMSE for COSMO-RS model. Thus, the predictive PC-SAFT EOS and COSMO-RS models demonstrated the same accuracies [112].

Unfortunately, in some cases, the COSMO approach has not achieved satisfactory results. Cysewski et al. [4] were not able to applicate the model COMSO-RS to predict the solubility of Theophylline in several solvents, achieving percentage errors above 103 % by adopting an alternative predictive approach based on a machine learning protocol. The authors reported that the error introduced by COSMO-RS was a not-systematic type and had not a linear relationship [4]. After this work, Cysewski et al. [3] used the same machine learning to predict the solubility of sulfamethizole, however, in this work, the authors used a simpler and more intuitive set of molecular descriptors [3]. Despite the authors concluded that the efficient utilization of the machine learning

protocol requires an adequate pool of experimental data, it is important to highlight that the inclusion of COSMO theory data was important for the development of an accurate predictive model. To evaluate the accuracy of the COSMO-RS model, Duanmu et al. [22] tested the validity and performance of the COSMO-RS model in predicting aqueous solubility of 1852 small organic molecules. However, in this work, COSMO-RS failed dramatically in molecules with larger dipole moments and with electronegative atoms [22]. In conclusion, the authors stated that the presence of uneven charges in the σ-profiles induced by electronegative atoms leads to strong hydrogen bond corrections which in turn results in the overestimation of aqueous solubilities [22].

Despite COSMO-RS and COSMO-SAC were proposed almost 30 years ago, they continue to be widely used and referred in the literature. Nevertheless, as described previously, alternative COSMO models have been proposed to improve the obtained results or to adapt the model to more specific applications. Concerning the pharmaceutical proposes, Thormann et al. [50] developed in 2006 a new COSMO model for the quantification of drug similarity. With this method, the authors proposed a σ-profile-based drug similarity measure COSMOsim for the detection of new bioisosteric drug candidates. After that, the same work group [52] developed and validated with about 600 pharmacological entities their new COSMOsim approach named COSMOsim3D. According to the authors, this model overcomes one of the most relevant disadvantages of the COSMOsim, since the COSMOsim method ignores the 3D distribution of molecular polarities, which determines crucially all ligand-receptor bindings [52]. Other notable example was the development of the COSMOquick method proposed in 2012 by Loschen and Klamt [113]. According to the authors, this graphical user-interface which internally calls COSMOfrag for the generation of σ-profiles, can achieve higher accuracy results using multiple experimental reference solubilities. Indeed, Mohammady et al. [114] and Wyttenbach et al. [67] achieved interesting results using the COSMOquick software in the determination of the optimum conformer for co-crystallization and to estimate some thermodynamic values, respectively. Recently, Cysewski et al. [115] studied the temperature-dependent solubility of nicotinamide (niacin) in six pure solvents (including water) and five aqueous-organic binary mixtures (methanol, 1,4-dioxane, acetonitrile, DMSO, and DMF). In this work, the authors successfully determined the niacin solubility using the COSMO-RS-DARE model, known to offer more accurate results for systems containing carboxylic acid groups and nonpolar components [115]. Simultaneously the same group published another work where the solubility of Theobromine was determined experimentally, by COSMO-RS, and COSMO-RS-DARE. The authors achieved a poor correlation between experimental solubility values and the ones computed using COSMO-RS but improved results using COSMO-RS-DARE [116].

Alternatively, some authors are developing new models but using COSMO's sigma profiles as molecular descriptors [117]. It is very interesting to note that regardless of the original thermodynamic formulas developed for COSMO models, COSMO σ-profiles have become precious tools in de development of models that are not related directly to the original COSMO-RS [118]. As an example, today some models are the mixing of energy of solutions using COSMO molecular descriptors linked with a semi-empirical model using a combined Artificial Neural Networks/Quantitative Structure-to-Property Relationship (ANN-QSPR) methodology [118,119]. In two works, Panayiotou and co-workers [120,121] developed a new Hansen Solubility Parameters (HSP) approach, where the splitting of acidic and proton donor groups is based on the sigma profiles of the quantum-mechanics obtained through COSMO-RS theory. They tested some pharmaceutical compounds in some solvents and compared experimental data with their new approach [120,121].

3.4. COSMO models applied for the development of parenteral formulations

Despite the clear advantages of the use of computational models for pharmaceutical development, the number of published works is scarce. During the literature review, only one work reporting the use of COSMO models for the development of parenteral formulations was found [114]. In this work, M. Mohammady et al. [114] successfully developed a novel solubilization strategy for Carvedilol by efficiently integrating current techniques of cocrystal forming and nanoprecipitation. To find the most promising Carvedilol coformers, the authors used the COSMOquick to rank a large number of common Carvedilol coformers based on the reduction of free energy (ΔG) of complex formation. After that, using the same software, the most appropriate solvent was chosen evaluating the solubility of carvedilol and the previously selected coformers in different organic solvents. With this, the optimum coformer (tartaric acid) was selected based on its rank, safety, injectability, and availability, and the most appropriate organic solvent (acetone) was chosen considering high solubility, low toxicity, and water miscibility.

In conclusion, the authors reported the successful development of a novel solubilization strategy for Carvedilol resulting in the synthesis of ultra-fine carvedilol nanocrystals able to be used in parenteral formulations. Concerning the COSMO model, the authors concluded that the *in silico* approach based on COSMOquick software revealed the capability to find the best solvents and coformers for the co-crystallization process [114].

During the literature research, was not found any work reporting the use of COSMO models for the selection of excipients and vehicles in the development of aqueous parenteral products. Some studies trying to predict the dissolution of APIs and excipients in aqueous media were found; however, none of these works aimed to predict the dissolution of pharmaceutical substances in parenteral vehicles. The work performed by Pozarska et al. [99] is an excellent example of how COSMO models could be useful in the selection of excipients during the pre-formulation of parenteral products. In this very interesting work, COSMO-RS was applied as an excipient ranking tool in the early formulation development of pharmaceutical products in general. The authors reported that the COSMO models were able to predict reasonably the solubilising power of certain excipients over a list of 6 unidentified pharmaceutical compounds. Interestingly, this work was performed and supported by Pfizer which concluded that the performed strategy can help the formulators to "*quickly narrow down the number of excipients used for solubility screening and formulation development in the lab without requiring any of Physico-chemical information on the compound*" [99]. This work has demonstrated that COSMO-RS could be able to predict reasonably the excipients with the most promising solubilizing power for a set list of compounds. In the future, an identical approach but specifically focused on parenteral products could result in a more efficient pre-formulation process of parenteral products.

3.5. Future perspectives on the use of COSMO models for the development of parenteral formulations

As cited previously, the COSMO models have shown to be extremely useful in the *in silico* study of several physicochemical properties related to pharmaceutical ingredients. According to all the reviewed studies, the COSMO models have been used to study the solubility of pharmaceutical substances but only to demonstrate the predictive capability of the COSMO models. Due this fact, there are in the literature several works reporting the use of COSMO models for the prediction of API's solubility however as described in the previous topic the availability of published works proposing practical applications is scare.

In the future and concerning parenteral aqueous solutions, we propose a planned and structured use of COSMO models in the pre-formulation of new products. To this, should be used the same strategies presented by many authors to others proposes but with an extreme

interest in the pharmaceutical development of new parenteral products.

Through this work, we cited some works where the COSMO models have demonstrated the ability to predict experimental results without any experimental data previously obtained. The works cited previously, performed by M. Mohammady et al. [114] and Pozarska et al. [99] sum up very well how COSMO models could be a very important tool during the early development of parenteral products mainly the aqueous ones. In other words, COSMO models could be an important tool in the screening of improved API forms, and in the selection of the best excipients able to improve the dissolution of already available APIs and thus turning possible the development of parenteral products with optimized bioavailability and stability (Fig. 2).

4. Discussion

Nowadays, the continuum solvation models are commonly recognized as powerful tools to describe solute–solvent systems. The conjugation of the electrostatic and quantum mechanical principles allowed the development of models able to simulate many molecular properties without the obtention of experimental data. The use of computational models, such as COSMO, might contribute to the development of more efficient pharmaceutical processes since predictive results could guide the research strategies for promising solutions and products.

The COSMO models become very popular due to their conceptual and algorithmic simplicity. Indeed, COSMO-based models have been demonstrated to be very useful in wide areas of physics, chemistry, and health sciences.

Drugs' solubility is a crucial property for all the pharmaceutical sciences since several APIs are poor-soluble or even extremely low-soluble in water. This fact turns the development of aqueous parenteral products into a challenging task. In the literature, many authors reported successful results in the utilization of COSMO-based models to predict the solubility of pharmaceutical compounds in aqueous media. Unfortunately, there are also cases where the lack of refinements/parametrizations and the presence in the molecule of electronegative atoms and carboxylic functional groups caused biased results. Due to this, and to improve the accuracy of results, new extensions based on the COSMO approach have been proposed with very promising results.

During the literature research, only one work reported the use of the COSMO approach for the development of a parenteral product. This study reported the synthesis of optimized cocrystals of Carvedilol with better bioavailability, safety, and stability features. This work demonstrated it be possible to optimize the development of parenteral formulations using the COSMO approach however in this work the COSMO models were used for the development of new API forms and not to predict the best excipients to develop and produce a new finished product. Nevertheless, according to our literature research, the selection of excipients using COSMO models could be also possible. With this research, we conclude that despite COSMO models have been widely used in the study of pharmaceutical substances, the obtained results are not usually used for practical and specific purposes.

Based on research we propose two main strategies where COSMO models could be an important tool in the development of parenteral products, mainly the aqueous ones where the solubility of the APIs is a critical step. According to this, the COSMO approach could be useful to the early development of parenteral products for the development of

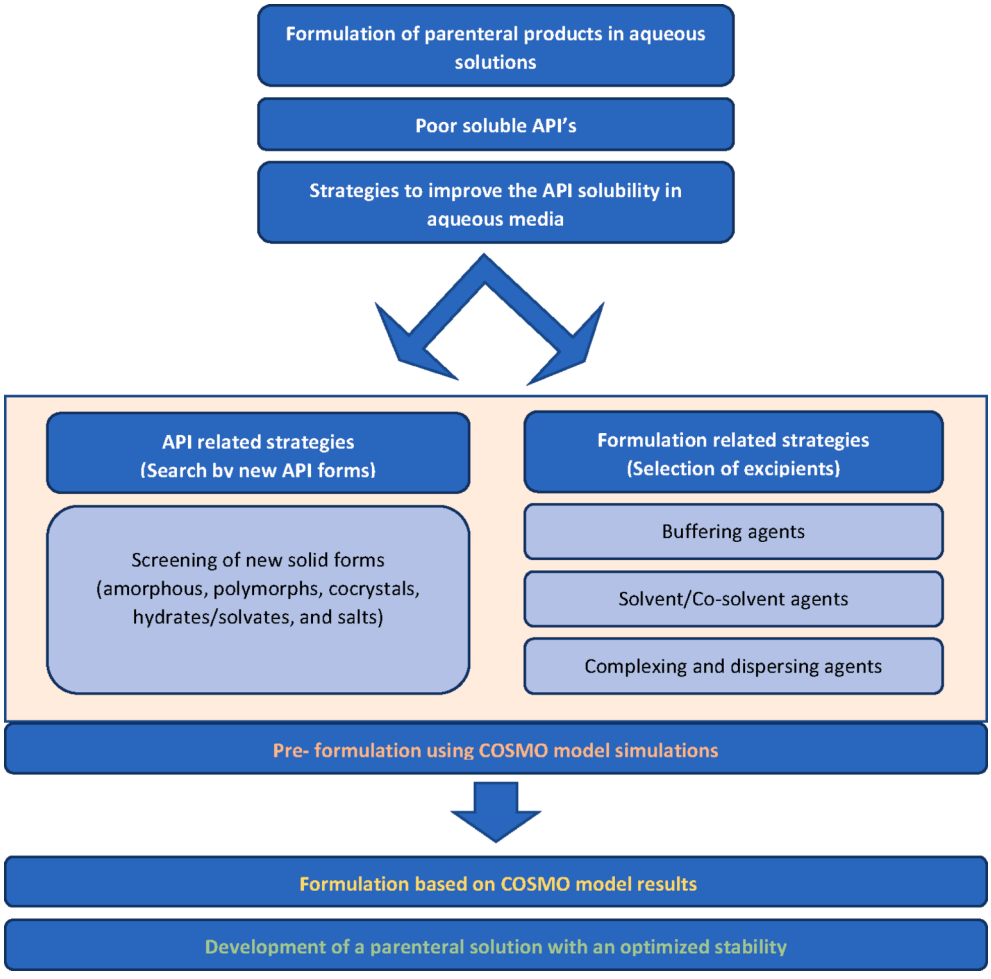

Fig. 2. COSMO model as a screening tool in the development of new parenteral formulations.

new API forms with the best physicochemical properties and for the selection of the excipients that could result in the formulation of parenteral products with better bioavailability and stability features. In the future, taking into account the very limited number of published works where the COSMO models are used for practical purposes in the pharmaceutical field, we suggest their inclusion in the formulation step of new pharmaceutical products, such as parenteral formulations.

5. Conclusion

Despite there is in the literature many works where COSMO models are used to predict the solubility of pharmaceutical substances in aqueous media, this approach seems to be not yet extensively explored in the design of most promising API forms nor in the optimized selection of excipients for the development of new aqueous parenteral formulations. According to our literature research, computational models such as COSMO could be powerful tools during the development of new aqueous parenteral products reducing the effective costs related to research and development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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