



# Overview of Hydrotrope Assisted Solubility Enhancement for Anticancer Oral Drug Delivery and Formulation Analysis

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## KEYWORDS

### Abstract

The management of cancer is till today remained a foremost challenge. But then remarkable advancement in the discovery of anticancer drugs and drug development has happened in the past few years. Nevertheless, this development has stemmed in a small number of efficacious oncological drug products owing to challenges connected with anticancer therapy and drug delivery. Although the most ideal route for anticancer drug therapy and delivery is oral administration, however the mainstream of anticancer agents at present in production channels and the most of them have been approved for commercial use have intrinsically poor aqueous solubility and without compromising with their potency and stability, this process cannot be improved. The poor aqueous solubility of anticancer drug substances in combination with other issues, heads to sub-optimal pharmacokinetic activity. As a result, these drug candidates have partial efficacy and safety parameters on oral administration. The hydrotropic solubilization is an encouraging formulation tools that predominantly improves the water solubility of poorly aqueous-soluble drug substances. In the present review, the challenges linked with the oral anticancer drug administration and the applications of hydrotropic solubilization technology in improving these types of challenges are discussed. We highlight the capacity of hydrotropic solubilizing agents not only to enhance the pharmacokinetic parameters of poorly aqueous-soluble anticancer drug substances, but furthermore their efficacy concerns and safety. The objective of this article is to account for the applicability of hydrotropic solubilization in formulating the anticancer drug substances, thus producing quality oncological formulations that head to better therapeutic products.

## Introduction:

Cancer is one of the major worldwide health problems. It is one among the prominent reasons of death globally. As per the American Cancer Society statistics of 2023, about 1,958,310 fresh cases of cancer and 609,820 cancer connected death cases are estimated to happen alone in the USA. As a result, the endlessly growing problem of cancer management not only demands the discovery and development of novel anticancer medications, on the other hand it furthermore sounds for the enhanced improvement of present anticancer therapy. In spite of the extremity of the explorative research in the field of anticancer therapy and drug discovery- development arena, the accomplishment level for anticancer medicines has persisted steadily poor for decades. It has been projected that, merely 1 of each 5,000–6,000 potential anticancer drug-candidate gets approval of FDA, and merely 5% of anticancer drug candidates arriving at

Phase-I of clinical trials are eventually get approved. In a latest research, the total possibility of novel anticancer drug candidates' fruitful promotion from Phase -I to final approval is generally unsatisfactorily low, about only 3.7%. One of the major reasons of such a high rate of unacceptability for novel anticancer medicines is because of their reduced process of pharmacokinetics, which mainly curtails from their poor aqueous solubility. It has been assessed that around 75% of novel drug-development stage contenders have poor aqueous solubility, and several of these drug candidates are anticancer-drugs.

Oral administration is one of the ultimate desired routes for drug-delivery of anticancer medicines. It has numerous benefits, like easiness of administration and economical cost of therapy. Oral route of administration lets achievable uninterrupted administration of drugs. One among the



preconditions for efficacious oral method of chemotherapy is attaining a dependable and reliable pharmacokinetic data profile for the drug substances, which facilitates fullest drug efficacy and least toxic effect. Conversely, quite a few challenges are connected with the physicochemical parameters of drugs and the physiological functioning of the GIT. All these challenges restrict the accomplishment of appropriate pharmacokinetics; hence they also restrict the pharmacodynamic properties of poorly aqueous soluble anticancer drugs administered by oral route.

The poor aqueous solubility of anticancer agents heads to sub-optimum preparations or needs the usage of excipients that possess harmful side effects. For instance, sorafenib tosylate, an anticancer drug administered by oral route is a kinase enzyme inhibitor used for the management of renal cell and hepatocellular carcinoma. As per the biopharmaceutical classification system (BCS), the drug sorafenib belongs to BCS: Class-II, which is categorized by its high permeability but low solubility. Thus, sorafenib has unsatisfactorily low and sluggish dissolution process in the GIT, which is a rate-limiting phase during its absorption process and, alongside its first-pass metabolic rate, resulting in orally low bioavailability and extensive intersubjective inconsistency. Accordingly, the poor aqueous solubility of sorafenib heads to either sub-therapeutic consequences or acute toxicity. Paclitaxel, a familiar anticancer drug, has poor aqueous solubility (less than 0.03 mg per mL). Hence, an injectable intravenous pharmaceutical preparation was formulated by means of Cremophor EL i.e. polyethoxylated castor oil and ethanol to make solubilize paclitaxel. The usage of Cremophor EL headed to acute allergic reactions in the patients. Despite the consumption of pre-medication, hypersensitive reactions still happened in and around about 45% of patient community, and strongly life-frightening side effects arose in round about 3% of patient groups. Therefore, the poor aqueous solubility of present antineoplastic drugs puts challenges not only for oral preparations but for intravenous formulations as well.

Quite a lot of efforts to solve the poor aqueous solubility of anti-cancer drugs already have been described, like the use of prodrugs, polymeric nanoparticles, lipid microspheres, solubilizers, and nano-colloids. However, these attempts are limited by quite a few challenges, for example, low drug-loading

capability, instability, potential material toxicity, composite physical structures, clearance and transformed drug distribution pattern.

The hydrotropic solubilization is a formulation skill where the drug, substance acknowledged as the active pharmaceutical ingredient i.e. API, is distributed in an amorphous carrier. Solubilizing agents help the dissolution of poorly aqueous-soluble drugs predominantly by offering the drug in an amorphous system, in that way decreasing the net energy essential for the improved solubilization of the crystalline drug-substance. Hydrotropic solubilization technology has offered remarkable advantages for therapeutically very potent, poorly aqueous-soluble anti-cancer drugs for example, vemurafenib, everolimus, venetoclax, olaparib and regorafenib.

### **Poor aqueous solubility of anticancer drugs:**

Poor aqueous solubility is an intrinsic property of several anti-cancer drugs for two chief reasons. First one, depending on the literature survey, there is rare emphasis is paid on the physicochemical characteristics of drug substances in the course of anti-cancer drug-discovery. Second, some particular crucial hydrophobic structural characteristic features are essential for anti-cancer drug activity, permeability and stability, which lend poor aqueous solubility to the drug substance.

One more contribution to the poor aqueous solubility of anti-cancer drug candidates is from the crystalline arrangement of the drug substance. Although the crystalline form of the drug has advantages such as higher purity and more stability, to make solubilize the crystalline form, its lattice-energy barrier needs to be overcome, which is not only challenging and heads to slower dissolution process. Conversely, the amorphous arrangement of an anti-cancer drug candidate has more aqueous solubility; however it is also characteristically substantially unstable, therefore practically all anti-cancer drugs are produced in crystalline formula. For example, bicalutamide is an anti-cancer drug employed in the management of prostate carcinoma, and it has very poor aqueous solubility. A number of findings have revealed that the amorphous system of bicalutamide has much more water solubility than its crystalline arrangement. Still, the amorphous system of bicalutamide is extremely unstable, leading to recrystallization of the drug substance. Therefore, bicalutamide is available



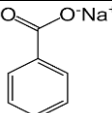
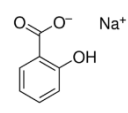
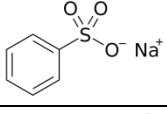
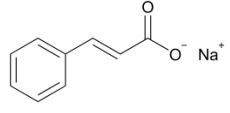
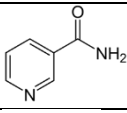
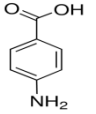
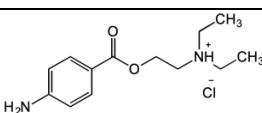
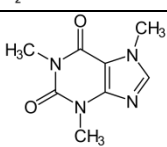
commercially in the poorly aqueous-soluble crystalline formula. Thus, poor aqueous solubility is an inherent physical property of a number of anti-cancer drugs [1].

#### Application of hydrotropic solubilization technique to anticancer drugs:

Almost a century before, in 1916, the word 'hydrotropy' was created by the researcher Carl A. Neuberg to mark some anionic organic salts, which substantially improved the water solubility of poorly soluble solute substances. Presently hydrotropic solutions hold a great demand in industry owing to their distinctive features like easy availability, higher separation factors without any solutes emulsification problem absence of fire hazards, good recovery, and eco-friendly nature.

Hydrotropic solubilizing agents are specified as ionic organic salts which facilitate increase or decrease in the solubility of a particular solute in a certain solvent through 'salt in' or 'salt out' phenomena, correspondingly. Salts which demonstrate 'salt in' effect of non-electrolyte substances are termed "hydrotropic salts" and the process is acknowledged as "hydrotropism". They do not possess any colloidal characteristics but they increase solubility by providing weak interaction by means of certain solute fragments. A hydrotropic substance interacts by a less aqueous-soluble particle through weaker Van der Waal's interaction like attracting dipole-dipole interaction or  $\pi$ - $\pi$  interactions. Some examples of such substances are given in Table 1.

**Table 1: Substances commonly used as Hydrotropic Agents**

Sl.	Substance	Type	Structure
1.	Sodim Benzoate	Aromatic Anionic	
2.	Sodium Salicylate	Aromatic Anionic	
3.	Sodium Benzene Sulphonate	Aromatic Anionic	
4.	Sodium Cinnamate	Aromatic Anionic	
5.	Nicotinamide	Aromatic Anionic	
6.	Para-amino Benzoic Acid	Aromatic Cationic	
7.	Procaine	Aromatic Cationic	
8.	Caffeine		



9.	Sodium Alkanoate	Aliphatic Linear	$\text{CH}_3(\text{CH}_2)_n\text{C}(=\text{O})\text{O}^-\text{Na}^+$
10.	Urea	Aliphatic Linear	$\text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}_2$

Apart from the above examples, some structurally modified analogues of these prototype compounds are also widely used as hydrotropic agents, for example Sodium benzene di-sulphonate, Sodium-3-hydroxy-2-naphthoate, Sodium para toluene sulphonate, Sodium cumene sulphonate, N, N-diethyl nicotinamide, N, N-dimethyl benzamide and N, N-dimethyl urea [2].

#### Hydrotrope Substances as anticancer drug carriers:

Hydrotrope agents possess unique ability to function as carriers intended for active bulk drugs. These agents have capability to produce dynamic and non-covalent assemblages, i.e. cluster forms in presence of water. If the hydrophobic substances are present, such cluster formations are stabilized by forming prolonged, extremely stable mesoscopic size droplets owing to a phenomenon termed as ‘mesoscale hydrotropic solubilization’. Such types of constituents assist in processing several products including pharmaceuticals,

agrochemicals and cosmetics. Delicate modification in surfactant particle geometry leads to a noticeable effect on the macroscopic rheological properties of the system. All these micellar solutions behave as a pattern for tissue-engineering and as a transformer of the drug-delivery. Furthermore, hydrotrope agents perform different roles such as oil in water (o/w) micro-emulsion stabilizing agents, solubilizers, cleaning agents, viscosity modifiers, in pre-formulation and development. As their action is on the molecular levels, hydrotrope agents produce better efficiency in bottom-side-up (overturned) methods than top-side-down (stratified) methods. On considering all these capabilities, formulation researchers are producing a number of drug- delivery methods centered on hydrotropic solubilization methodology to improve the therapeutic efficiency of crucial drug candidates including anticancer agents. Examples are stated in Table 2.

**Table 2: Hydrotropic agents used for the solubilization of some Anticancer Drugs**

Sl.	Drug	Hydrotropic Agents	Methodology	Reference
1.	Etoposide	Sodium Benzoate, Sodium ortho hydroxyl benzoate, Sodium gentisate and sodium salts of 2,4-dihydroxy- and 2,6-dihydroxybenzoic acid and 2,4,6-trihydroxybenzoic acid	Hydrotropic Solubilization	[3]
2.	Paclitaxel	Poly(4-(2-vinylbenzyloxy-N-picolynicotinamide)) (P(2-VBOPNA))	Co-polymer micelle system	[4]
3.	Paclitaxel	2-(4-(vinylbenzyloxy)-N,N-diethylnicotinamide) (VBODENA-COOH)	Oligomer nanoparticles	[5]
4.	Paclitaxel	Polyglycol Dendrimers	Hydrogels	[6]
5.	Paclitaxel	Nicotinamide	Nanocarriers	[7]
6.	Paclitaxel	N,N-diethylniacinamide (DENA),	Nano Drug Delivery System (NDDS)	[8]
7.	Paclitaxel	Sodium Salicylate	Hydrotropic Solubilization	[9]



8.	Curcumin	Sodium Salicylate	Transdermal	[10]
9.	9-Nitro Camptothecin	Cyclodextrins	Liposomes, Niosomes, Nanoparticles, Micelles	[11]
10.	Bicalutamide	Cyclodextrins	Inclusion Complex	[12]
11.	Paclitaxel and Docetaxel	PEG-Valine citrulline	Hydrotropic Solubilization	[13]
12.	Clofazimine	Mesoporous Silica Nanoparticles	Hydrotropic Solubilization	[14]

#### Transdermal formulations:

Transdermal route of drug administration affords the benefits of accomplishing a curative result deprived of the dangers of possible toxic side effects those can occur following oral therapy. The choice of a proper drug-carrier in transdermal preparation is very essential since it may affect the percutaneous (skin) absorption.

For instance, a transdermal 5-Fluoro Uracil (anticancer agent) formulation was produced by means of polyglycerol fatty acid mono-esters (PGMC) as hydrotropic agents. Average particle size of the solution comprising of PGMC was around 14 nm. Transdermal hydrotropic formulation improved skin permeability of 5-Fluoro Uracil owing its capability of hydrotropic nature to form composite aggregates [15]. In specific, in the topical formulations, the distribution coefficient i.e. Log D value of a substance plays a significant role in the process of solubilization. It indicated decisive influence on solubility enhancement factor (SEF). SEF is the ratio of solubility of material in ternary combination mixture to its solubility in a blank pure

solvent under same conditions of temperatures. All mixtures with log *D* values amid 2 and 4.5 indicated a SEF more than 5 in a 40% aqueous urea solution whereas with a log *D* value less than 2 or above 5, SEF was less than 5. In some other cases for example, diclofenac and prednicarbate, SEF attained was more than 5 at 5% urea and less than 250 at 20% urea [16].

#### Spectrophotometric estimations:

The analysis of poorly water soluble drugs is usually performed by UV-Visible spectrophotometric techniques. It generally involves using various organic solvents like dimethyl formamide, acetone, benzene, Chloroform, acetonitrile, carbon tetrachloride, ethanol, diethyl ether, toluene and methanol for recording spectrum. A main disadvantage associated with these different organic solvents is their toxicity, cost, volatile nature and flammability. To avoid such complications, hydrotropic solubilizing agents are now being employed. Hydrotropic agents used for the spectrophotometric determinations are listed in Table 3.

**Table 3: Application of Hydrotropic in Spectrophotometric Quantifications**

Sl.	Drug	Hydrotropic Agent	Molar Concentration	Improvement in solubility (Folds)	Reference
1.	Amplodipine	Sodium Acetate	2M	75	[17]
2.	Aceclofenac	Sodium Acetate	2.5M	400	[18]
3.	Cefadroxil	Urea	6M	10	[19]
4.	Diclofenac	N,N-Dimethyl Urea	7.5M	11	[20]
5.	Fuazolidine	2 M sodium acetate, 8 M urea, 2 M niacinamide and 2 M sodium benzoate (25:25:25:25% V/V)	Mixed	32	[21]
6.	Hydrochlorthiazide	Nicotinamide	2M	43	[22]
7.	Ketoprofen	Potassium Acetate	2M	210	[23]
8.	Losartan	Sodium Chloride	2M	63	[24]
9.	Metronidazole and Furazolidine	Sodium acetate and 8 M urea solution	Mixed	28	[25]





		(50:50% V/V)			
10.	Naproxen	Ibuprofen Sodium	0.5M	350	[26]
11.	Nalidixic Acid	Sodium Benzoate	2M	98	[27]
12.	Ornidazole	Ibuprofen Sodium	0.5M	10	[28]
13.	Rosiglitazone	Urea	6M	14	[29]
14.	Simvastatin	Sodium Chloride	2M	90	[30]
15.	Tenofovir	Sodium Benzoate	2M	120	[31]

### Green synthesis:

Hydrotropic agents offer an efficient, simple and green medium for numerous industrialized organic conversions. Furthermore, being cost-effective, eco-friendly, non-toxic and non-flammable, hydrotropic substances hold additional physicochemical parameters necessary as substitute green solvents for organic reaction processes. Within the definition and framework of green chemistry, aqueous hydrotropic technique provides a number of benefits like trouble-free handling, cleaner reaction profile, short reaction time and high rate of conversions thus rendering it beneficial choice for the speedy organic synthesis. One more main characteristic property of hydrotropic solubilization medium is its very simple recovery after the completion of reaction from its reaction mixture and its recyclability makes these conventions more catchy green chemistry methodology [32].

### Conclusion:

Hydrotropic solubilization is a proven and well established approach to boost the water solubility of hydrophobic drug substances, enabling their oral formulations as well as dermal drug delivery, also for analytical method development. Nevertheless, maximum number of hydrotropic substances studied so far possesses harmful toxicity concerns and are still incompetent, owing to the large quantities being necessary to accomplish substantial solubility enhancements thus further researches like mixed hydrotropy are required with respect to address these issues.

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