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HUMIC ACID AS NOVEL EXCIPIENT IN BOON OF DRUG DELIVERY

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ABSTRACT

This review examined naturally occurring humic compounds, such as fulvic acid, humus, and humic acid, which vary in composition depending on where they are found and the extraction method employed. They have various groups in their molecular structures, such as phenols and carboxylic acids. In this setting, humic substances—such as inclusion complexes like cyclodextrin with hydrophobic drugs—have emerged as essential excipients for the future. It is subsequently utilized in medication delivery systems, medicines, and nutraceuticals. Despite the fact that humic acid has several therapeutic uses, not much is known about its worldwide market, solubility, pH, etc. The potential of pharmaceutical excipients, which are based on the idea that they can improve the solubility and bioavailability of biopharmaceutical medications, is also examined in this review.

Keywords: Humic acid, Cyclodextrin, Carboxylic acids, enhance solubility

INTRODUCTION

Natural resources of humic substances are substances that are abundantly prevalent in nature and can be produced from both marine and terrestrial sources. These are produced by microbial degradation [1].

Humic compounds, such as fulvic acid (FA) & humic acid (HA), have been used in a variety of industries, from farming to biomedicine, but unfortunately, their use as pharmaceutical excipients is still in its

beginning stages [2]. Romans are the first people to use the word "humus," which was then habituated to refer to the entire soil. The macromolecules called as humic acids (HAs) constitute humic substances (HS), which are natural sources that exist in different sources such as water, soil etc. that have formed as a result of the decomposition of plant and animal remnants [3, 4]. The empty fruit bunch (EFB) of palm trees, a

natural and renewable resource, has recently been demonstrated as a suitable substrate for the fermentation of HAs. Furthermore, polymerization/condensation reactions in chemical synthesis can be used to synthesize Has [5, 6]. It is obvious that, depending on specific geographic, climatic, physical, and biological factors, the mechanisms of humic substance synthesis might differ slightly [7, 8].

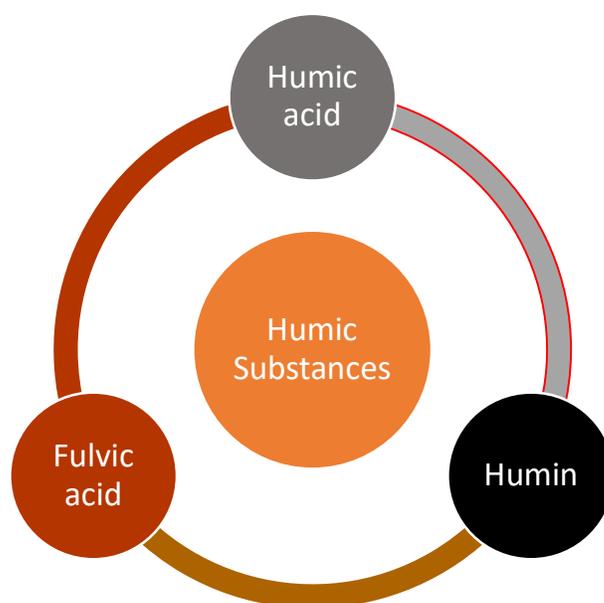


Figure 1: Different types of humic substances with colors

The three parts of humic materials are humin, humic & fulvic acids. In reality, any novel excipient is only considered for incorporation if it has the ability to overcome challenges that arise during the drug development process. In aquatic environments, HS can make up to 95% of the total dissolved organic matter and is often equal to or higher than the concentrations of inorganic ions.

In the humification process, a variety of components, include sugar moieties, fatty acids, aliphatic and aromatic chains combine to produce humic acids (HAs), which are macromolecules associated by hydrogen bonds and hydrophobic interactions [7]. The choice of drug delivery system natural materials is more biocompatible, accessible, and modifiable than artificial materials, frequently have

minimal toxicity, and they might have favorable pharmacokinetics, they also typically have these characteristics in greater supply. In recent years, the pharmaceutical industry has also found use for this unique biopolymer. The development of systems for the controlled release of drug compounds in the body may advantage from the manufacturing of polymer-drug complexes [13].

The enormous potential of biopolymers as drug carriers, though, is still underused and requires more emphasis [9, 10]. The chemical composition of humic acids is difficult to accurately characterize because of their complex; at this point it is generally accepted that these carbon-containing molecules are flexible linear polymers with carboxylic and phenolic groups functioning as the primary functional groups. Humic acid substances are known to form groupings stabilized by intermolecular hydrogen bonds and the hydrophobic effect at neutral pH [11].

The possibility of both natural and synthetic chemicals arranged in a clathrate-like manner within the border openings of HA polymers is recognized. In regard to biomaterials like, various drug combinations can enhance a drug's solubility, permeability, and dissolution. The potential for developing novel drug delivery systems, the enhancement of the manufacturing process, and most significantly, there is

abundant evidence for the various pharmacological potentials of HA, including its anti-oxidant, anti-inflammatory, and gut-health enhancing characteristics. Depending on the sources, HA may be employed in everything from nutritional supplements to pharmaceuticals [1].

A widely used technique for enhancing solubility is the complexing of pharmaceuticals with hydrophilic molecules [1]. Additionally, there is a persistent lack of effective excipients for enhancing formulation properties. While extremely acceptable, synthetic excipients can occasionally not be used because to their excessive costs and other limitations. Researchers have already looked into natural ingredients like fulvic acid (FA) and humic acid (HA) in extensive detail as possible beneficial excipients [2].

FA is a low-molecular-weight substance that has a high permeability to cell membranes and, if combined with water, becomes completely absorbable by living cells. These features not only boost the water solubility of poorly soluble drugs, but also help improve their permeability [2]. In the majority of the studies which have been reported, humic compounds are used as one of the FA, HA, and Humin's earliest known sources in Indian traditional medicine. While a consistent and affordable supply of raw materials is a key necessity, the percentage yield of humic compounds from

shilajit is quite low, which is regarded a barrier to commercial product development. So, it is wise to just rely on shilajit as a source for pharmaceuticals which use Humic acid. The parts of HS known as HAs are soluble in alkaline conditions, partially soluble in water, and insoluble in acidic environment. Because of their amphiphilic nature, HA's form pseudo-micelle-like structures in neutral to acidic environments. Hydrophobic drugs' water solubility has been enhanced by the exploitation of this feature, as well as being explored for application in the remediation of pollution. The quantity of the various functional categories that constitute HAs is determined by their origin, age, climate, and environmental circumstances throughout extraction and manufacture. The number of the various functional categories that compose HAs varies depending on the HA's place of origin, age, climate, and other environmental factors. The functional groups of phenol and carboxylic acid, which enable the deprotonation of OH/OOH, are mainly responsible for the many actions of HAs. The studies demonstrated that humic acids had substantially higher activity than fulvic acids: HA > HMA > FA, and that humic acid release was dependent on coal, peloid, or peat [4-6]. As per chemical analyses, it was mainly composed of humus (60–80%), as well as other substances such benzoic acid, hippuric acid, fatty acids,

ichthyol, ellagic acid, resin, triterpenes, sterol, aromatic carboxylic acids, 3,4-benzocoumarins, amino acids, and phenolic lipids. According to studies, humic and fulvic acid, which functioned as a carrier molecule for the active ingredients, as well as the availability of bioactive dibenzo- α -pyrones are also what provide shilajit its major physiological effects.

Global market on Humic acid: Soil, humus, peat, and coal are examples of organic materials that biodegrade to produce humic acid. It is a complex blend of several acids containing phenolate and carboxyl groups that is frequently utilized to give crops and plants, as well as people, the necessary nutrition. As a result, the agricultural and pharmaceutical industries make extensive use of humic acid for a range of purposes. With a compound annual growth rate (CAGR) of 7.7% from 2023 to 2030, the global humic acid market was estimated to be worth US\$ 1,144.3 billion in sales in 2023.

The current COVID-19 epidemic has affected the humic acid market globally. In an effort to stop the virus's spread, a number of governments throughout the world have implemented nationwide lockdowns, which have caused businesses to close and other economic activity to stop. For example, the 2020 report from the International Monetary Fund states that the world economy shrank by 3.0% in 2020, a significant contraction

that was worse than the financial crisis of 2008–2009. In addition, the agricultural sector as a whole saw a decline in demand for the humic sector due to the decreased need for pesticides and fertilizers. However, it is anticipated that the need for humic acid

in the pharmaceutical industry would rise due to the growing need for medications as well as a range of acids and chemicals to carry out vaccine trials [47].

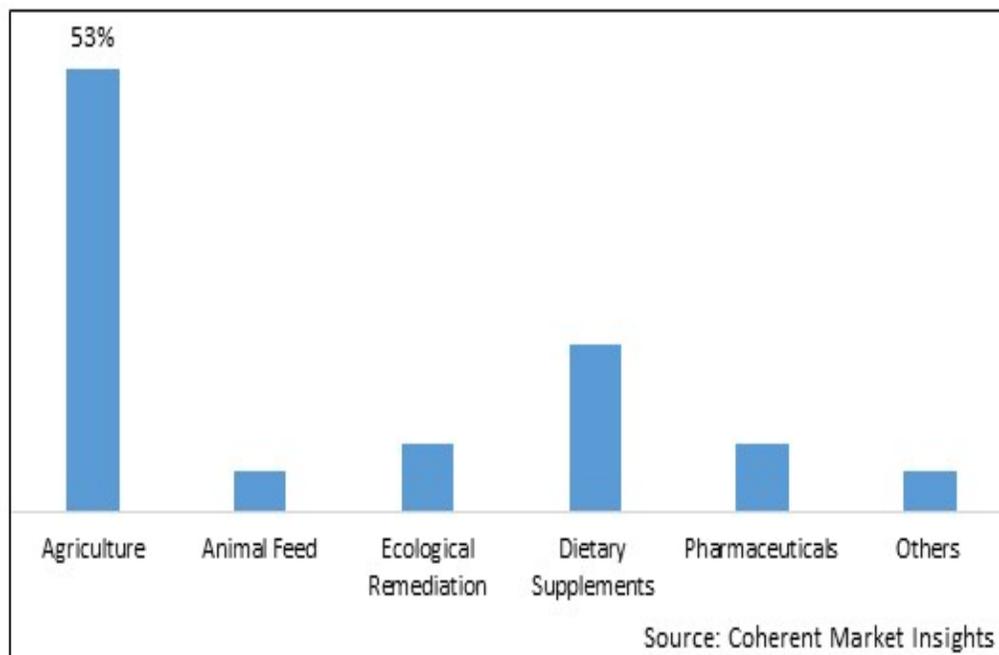


Figure:2 Humic acid global market

HA Properties: The key characteristics of HAs, including solubility, reliance on pH, interaction with hydrophobic groups, and metal chelation, are linked to their structure, namely their amphiphilicity and the variety of functional groups that compose each molecule.

Physicochemical properties of Humic substances:

Solubility & pH:

Developing a successful drug delivery system requires the consideration of the solubility of the drugs. An established method for enhancing solubility of drugs is complexation with hydrophilic molecules. By lowering the pH to near 1 with HCl solution, fulvic acids are maintained in solution whereas humic acids precipitate into the solution. Between humic & fulvic acids, there is this functional difference.

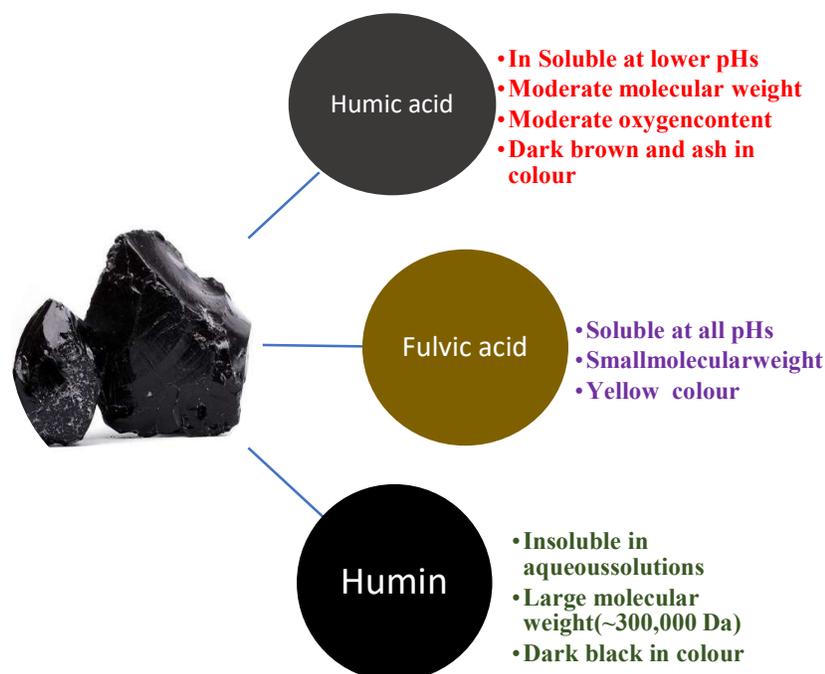


Figure 3: Different types of humic substances with pHs

Diluted alkali cannot dissolve humin. The alcohol-soluble part of the humic fraction is commonly referred to as humic acid. According to, "gray humic acids" (GHA) are soluble in alkaline media with low ionic strength, "brown humic acids" (BHA) are soluble in alkaline circumstances regardless of ionic strength, and fulvic acids (FA) are soluble in alkaline media regardless of pH and ionic strength. Humic acid is a complicated mixture of several distinct acids that includes phenolic and carboxylic groups rather than a single acid. Consequently, the mixture reacts functionally as a tribasic acid or, less frequently, as a dibasic acid. For producing humic acid for soil correction, the same well-known processes are used. When ions that are often found in the environment combine with humic acids, humic colloids

are formed. Humic acids are insoluble in water at acid pH values, in contrast to fulvic acids, which are also derived from humic substances and are soluble in water across the pH range [23].

Role of excipient in drug development:

The majority of HA's functional groups are carboxylic, hydroxylic, phenolic, carbonylic, and aminic, all of which are amorphous or colloidal in nature and have a high molecular weight. HA is a good choice for pharmacological research because of its chemical flexibility and lack of toxicity. Saluja and Agarwal's patent application number 814/Del/2001 claims Indian patents and that piroxicam has a better bioavailability when it is complexed with HA. Similar patents also explained the materials of Shilajit have a bio-enhancement

potential in depth. The patent application number 531/Del/20054 explained detailed separation and characterisation of HA and fulvic acid from Shilajit. HA has recently been looked into as a solubilizing agent for drugs that are weakly water soluble (BCS II and IV, respectively). When compared with their hydrophilic exterior, the hydrophobic centre of HA macromolecules is huge. Anticonvulsant carbamazepine was coupled with HA to make complexes that may entrap the anticonvulsant and had more effectively solubility, wettability, dissolution, and permeability properties. They discovered that complexation improved the pharmacokinetics and absorption of carbamazepine. investigated a number of b-carotene-HA complex ratios and reported that the complexation enhanced b-carotene's water solubility as well as its photostability. This research also described the use of HAs produced from biomass as natural surfactants in industrial settings. HA complexed with furosemide enhanced solubility and diuresis [1].

The FA-based products have also undergone a few clinical trials. Conversely, because FA (obtained from Shilajit) is considered to form inclusion complexes with hydrophobic drugs, the majority of research to date in the field of exploring the potential of pharmaceutical excipients is founded on the theory that it can increase the solubility and bioavailability of Biopharmaceutical

classification class of II and IV drugs [1]. Furthermore, mucoadhesion, acid buffering, and modified drug-releasing properties of Fulvic acid have also been reported. So, there is enough PoC (Proof of Concept) to investigate it as a beneficial excipient in commercial drug formulations.

But there could be a variety of explanations why it has not been done thus far.

1. Shilajit has one of the sources for FA in the vast majority of studies based on pharmaceutical excipients. The high price and limited availability of Shilajit are the main obstacles to the investigation of this type of FA in commercial drug products.

2. Humic substances (HS), also known as fulvic acid, are not easy to handle. Several molecules of various sizes are typically present in a sample. Variations in chemical composition and structural characteristics are always possible with different sources. The amount, kind, and size of functional groups, as well as other characteristics, can vary between molecules. One unique quality of HS is its ability to exhibit spontaneous changes in their conformation and aggregation state in response to factors in the solution, such as pH and ionic strength. No matter how modest the modification to the chemical composition is, it is thought that every change in an excipient's chemical composition results in a new excipient, and this may cause the developmental pathway

of a drug product to take a completely different course.

Moreover, if an excipient is not listed, it is new or novel (this also applies to FA).

i. The FDA's database of inactive ingredients, accessible at

<https://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm>.

ii. The U.S. Pharmacopeia (USPNF), the European Pharmacopeia (Ph. Eur.), or the Japanese Pharmacopeia are the three main compendia (JP).

iii. Other well-known compendia like "Fiedler: Lexikon der Hilfsstoffe for Pharmazie, Kosmetik and angrenzende Gebiete" or An Encyclopedia of Pharmaceutical, Cosmetic, and Associated Uses of Excipients, "Manual of Pharmaceutical Excipients").

The excipient producer's ability to supply ingredients with consistent chemical and physical qualities is crucial to the final product maker. When bioequivalence (BE) comparisons between essential, clinical trial batch ("bio-batch") and commercial scale-up lots are made as part of the pharmaceutical product approval process, this is very important. To ensure proper assurance of the performance of the completed product, the excipient utilized to create commercial quantities should not change greatly from those used in bio-batches. Minimizing variation between the various excipient batches is crucial, for this

reason. To determine the BE of the drug product, additional testing by the manufacturer of the final product may be necessary if there are appreciable changes between the excipient lots used in clinical and commercial drug product lots. Therefore, it was deemed important to investigate its physicochemical composition, microbiological count, functional characteristics, compatibility with other excipients, as well as the toxicological profile of FA.

Humic substance on drug delivery system:

In drug delivery system shows humic compounds serve as a carrier to increase bioavailability. Contrarily, the well-noted anticonvulsant drug carbamazepine (CBZ) has restricted access to the brain. Complex formation with humic compounds has increased the bioavailability and pharmacokinetic characteristics of CBZ. Humic acid and fulvic acid have been compared on a number of parameters, including their capacity to produce complexes and improve solubility, permeability, and dissolution. After oral delivery of complexes, this study also examined pharmacodynamic and biochemical characteristics [25, 26].

Several pharmaceutical techniques, including solvent evaporation, physical mixing, freeze drying, and kneading, were typically chosen for complex production and

conformational characterization (molecular modeling). CBZ-humic acid and CBZ-fulvic acid preclinical studies on rodents produced notable results in terms of their anticonvulsant and antioxidant activities.

Sachin D. Rede, Rupal K. Jani. *et al* explains a potent anticancer drug, paclitaxel (PTX) has poor tissue localization, low water solubility, and restricted bioavailability after oral treatment. Improved solubility and bioavailability of PTX can be achieved by complexing it with HA.

Fulvic acids are too small to go through a similar process, thus they remain in solution. Humic acids, on the other hand, are large enough to allow macromolecules to "roll" up to create micro clusters or rings that, at a particular pH (acidic), will precipitate.

Humic and fulvic acids can form complexes with ions like Mg^{2+} , Ca^{2+} , Fe^{2+} , and Fe^{3+} due to the presence of functional groups like carboxylic and phenol groups. The presence and arrangement of functional groups in humic substances facilitate the formation of chelate complexes. In order to control the bioavailability of metal ions, humic acids have a biological role in the production of humic chelate complexes.

In order to increase furosemide's aqueous solubility, dissolution rate, and permeability, complex formation with fulvic and humic acid was necessary to improve the drug's low aqueous solubility rate. This, along with an improved understanding of

structure-behavior relationships, increased the drug's in-vivo diuretic effects on male wistar rats.

Humic compounds isolated from shilajit have the potential to increase bioavailability. This capability was demonstrated in a study using the antifungal ketoconazole, whose solubility rate was greatly increased when combined with fulvic and humic acid because of its micellization properties. The use of fulvic acid as a water-soluble carrier has been strongly suggested by in vitro and in vivo studies using silymarin which is not particularly water-soluble.

The solubility of the drug linearly increased with carrier concentration in a binary system between silymarin and fulvic acid. Aspirin's stability and bioavailability issues are solved by a fulvic acid and aspirin formulation. As compared to the original drug, aspirin formulations with fulvic acid enhance the antiulcerogenic activity of aspirin by tackling its stability and bioavailability limitations. A highly promising topical treatment for MRSA and *P. aeruginosa*-infected wounds is carbohydrate-FA.

Antipyretic, anti-inflammatory, analgesic, and anti-aggregatory properties are all present in aspirin. At the current work, solid complexes between aspirin and humic were prepared using the lyophilization and solvent evaporation techniques at molar ratios of 1:1 and 1:2. DSC, XRD, FT-IR, and

SEM were used to examine the molecular interactions between aspirin and humic acid. The existence of solid inclusion complex development was amply demonstrated by this technique. The aspirin dissolving rates and stability were dramatically increased by the lyophilized compound in a molar ratio of 1:2. The optimized freeze-dried (1:2) aspirin complex therapy with humic acid showed a highly significant ($p < 0.05$) anti-inflammatory activity when it came to inhibiting rat paw edema. When compared to aspirin, the anti-ulcerogenic action was demonstrated by a considerable decrease in ulceration, as indicated by the lowest score of 0.63 ± 0.10 [44].

Vucskits AV *et al.*, Two experiments were conducted to examine the effects of fulvic acid (FA) and humic acid (HA) on the thyroid function, immunological response, and production parameters in rats. Strong humoral immune activation was the outcome of supplementing with humic acid and FA. According to our results, humic compounds' minor hypothyroid effect can be ascribed to their FA content [45].

In early research, we demonstrate that HAs interact with Pluronic F127 (PF127) to produce stable nanoparticles, that may be employed in pharmaceutical formulations as-is or after entrapping nonpolar drugs. Despite their great potential, the application of HAs in the cosmetic and pharmaceutical fields has not been well explored, such as in

the solubilization of hydrophobic drugs, in UV-visible absorption and as an antioxidant.

Nutraceutical applications of Humic substances:

Fulvic acid and humic acid are excellent choices for use in nutraceuticals because of their many amazing health benefits for humans. According to research, fulvic acid is a critical element of nutraceutical beverages. Fulvic acid serves as an electrolyte, balancing the ionic concentration of physiological fluids, and may serve as an electron acceptor or donor depending on the needs of the cells. Moreover, it interacts freely with a variety of other ions to boost their bioavailability.

Fulvic acid forms substances with low molecular weights. They can therefore easily penetrate through the plasma membrane. It is also known to boost enzyme activity, particularly that of respiratory enzymes. Alkaline phosphates, transaminase, and invertase are a few of the enzymes that fulvic acid affects. It serves as the body's free radical scavenger because of its antioxidant properties. It enhances RNA synthesis and DNA content in the cell. By the formation of a compound with vitamin and metal ions, it also functions as a catalyst. The ionic balance in physiological fluids is maintained by fulvic acid, an organic natural electrolyte.

Dai C, Xiao X, *et al.*, Fulvic acid (FA), a humic compound, has numerous

nutraceutical benefits, including anti-inflammatory, antibacterial, and immune-regulating capabilities. However, systematic evaluations of safety remain insufficient. In the current investigation, a battery of toxicological experiments was undertaken in accordance with internationally established standards to explore FA's genotoxicity and repeated-dose oral toxicity. Sprague-Dawley (SD) rats and ICR mice were used. FA is the primary active element in HA, and it has been employed in human medicine or as animal feed additives in animal production due to its diverse pharmacological qualities and relative safety compared to the direct usage of antibiotics, such as colistin sulfate [46].

Hajdrik, P. Pályi, B *et al.*, The antiviral activity of a humic compound comprising Zn^{2+} , Se^{-} , and ascorbic acid was studied against the SARS-CoV-2 virus B1.1.7 Variant of Concern, or "Alpha Variant," in a VeroE6 cell line. The substance was designed as a nutritional supplement material. The combination, at relatively low concentrations of its intended active components, has a strong antiviral effect in vitro, according to the results. In the applicable SARS-CoV-2 virus inhibition test, even picomolar concentration ranges of humic compounds, vitamin C, and Zn^{2+}/Se^{-} ions in the provided composition were sufficient to achieve 50% viral replication suppression. The antioxidant

effect, decrease in viral multiplication, enhancement of cell membrane resistance, decrease in inflammatory mediator cytokine release, and other synergistic effects on a cell-virus system may all contribute to this antiviral effect. Additionally, employing suitably constructed humic substance containing candidate formulations, in vivo challenge experiments and clinical intervention studies are essential [47].

Future prospect on Humic substances:

Research on humic substances is still very significant to pharmaceutical formulation and drug delivery systems. Humic substances may be strong candidates for a wide range of diseases based on the cumulative evidence of their biochemical and molecular effects. However, while experimental research will always be crucial, molecular simulations of HS are expected to become more useful in the years to come. This is particularly true for providing a greater level of understanding of experimental data, for advising the development of novel experiments, and for predicting characteristics and phenomena at the molecular scale.

The potential for humic acid compounds to be a candidate for enhancing solubility exists even though the supporting literature is limited. This bodes well because of the way we now handle these kinds of problems. It's vital to remember that research on humic compounds might be inconsistent at times.

This is due to differences in dosage, parent material, and isolation techniques, among other factors. Furthermore, opinions on parent material, a typical isolation, and the structure of humic components are divided. Combining all of these factors and determining dosage for various age groups and humic conditions is therefore crucial. In terms of humic acid function and its impact on solubility-related problems, this will assist in reaching definitive conclusions.

CONCLUSION:

Humic acid complexation can lead to expected improvements in stability and dissolution. However, it appears that this novel approach can help solve the problem of poor solubility and bioavailability. It serves as a novel excipient and offers the potential to boost BCS Class II and IV drugs in the future, expanding in the global market for nutraceutical and pharmaceuticals industry.

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Conflicts of Interest

The authors declare no conflict of interest.

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