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Future of Humic substances as Pharmaceutical Excipient

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Abstract

Humic Substances (HS) occur naturally in our environment and are the remains of a process called humification, which is the biodegradation of biomass that then recombines and converts into dark colored complex compounds with no definite chemical structure. These are the end result of microbial degradation but resistant to further microbial degradation. It has a strong global presence as a dietary supplement and cosmetics applications for different beneficial uses. Till date its exploration as a pharmaceutical excipient has been limited to academic research only but the data being presented augurs a good commercial success.

Keywords: Humic Acid; Fulvic Acid; Solubility Enhancer; Bioavailability Enhancer; Supramolecular Structures; Biodegradation.

Abbreviations: HA: Humic Acid; FA: Fulvic Acid; PoC: Proof of Concept; BE: Bio Equivalence ; USFDA: United States Food and Drug Administration; ICH: International Conference on Harmonization; BCS: Biopharmaceutics Classification System; FDA: Food and Drug Administration; JP: Japanese Pharmacopoeia; USP: United States Pharmacopeia; NF: National Formulary; Eur Ph: European Pharmacopoeia; BP: British Pharmacopoeia; CHD-FA: Carbohydrate Derived Fulvic Acid

HS constitutes as much as 95% of the total dissolved organic matter in aquatic systems and often equal to or greater than the concentrations of inorganic ions present. Solid sources of HS are soil, peat and coal. From chemistry point of view these are supramolecular structures of heterogenous molecules comprising of sugar, fatty acids, polypeptides, aliphatic chains, and aromatic rings, held together by hydrophobic interactions (such as van der Waals forces, π-π interaction, ion-dipole moment interactions) and hydrogen bonds [1,2].

HS are classified into following components, based on solubility at different pH ranges.

a. **Humic acids** (HA): It is the fraction of HS which is soluble in water under alkaline pH but insoluble in acidic pH. It has high molecular weight and brown to black in color.
b. **Fulvic acids** (FA): It is the fraction of HS which is soluble in water under all pH conditions, golden to yellow-orange in color. Comparative to HA, it is more bioactive and lower molecular weight.
c. **Humin**: It is the fraction of humic substances that is not soluble in water at any pH value. Humins are black in color.

The most common applications of HS include agriculture, as soil amendments and fertilizer additives, landscape and

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turf construction and maintenance, water and soil remediation, dietary/food supplements, livestock feeds and drilling mud additives. There are also few reports that establish the PoC (Proof of Concept) to explore HS in different potentials as pharmaceutical excipient [3-12]. Solubility/Bioavailability enhancement potential of BCS class II and IV drugs is the most widely reported property in the category of pharmaceutical excipient. A summary of few of the reports have been given in Table 1. FA has also been reported for acid buffering and mucoadhesive properties [11]. Based on aqueous solubility profile it can be construed that FA has the highest potential as compared to other HS to be explored as a commercial excipient. On the other hand HA (alone or in combination with other pH sensitive polymers) can be used in enteric coated drug delivery systems.

Drugs	Type of HS (Source)	Max solubility enhancement	Reference
Furosemide (BCS Class II)	Humic acid (Shilajit)	Better dissolution profile	[3]
Furosemide (BCS Class II)	Fulvic acid (Shilajit)	23 times	[4]
Ketoconazole	Fulvic acid (Shilajit)	Better dissolution profile	[5]
Aspirin	Humic acid (Shilajit)	Better dissolution profile	[6]
Carbamazepine (BCS Class II)	Fulvic acid (Shilajit)	2268.75%	[7]
Carbamazepine (BCS Class II)	Humic acid (Shilajit)	1742%	[8]
Itraconazole (BCS Class II)	Fulvic acid (Shilajit)	23.92 times	[9]
Celecoxib (BCS Class II)	Fulvic acid (Shilajit)	11.46 times	[10]
	Humic acid (Shilajit)	9.62 times	
Itraconazole (BCS Class II)	Fulvic acid (Shilajit)	363.84 times	[11]
Silymarin	Fulvic acid (Shilajit)	20 times	[12]

Table 1: Humic substances have been studied as solubility enhancing excipient for different drugs.
Different drug: HS ratios were studied but only the best performing ratio have been tabulated. Pharmacodynamic parameters were also evaluated in few of the studies.

As there is no precedence of use of HS in a commercial drug product, it will be considered a new (novel) excipient. An excipient being used for the first time in a drug product or by a new route of administration is classified as new (novel) pharmaceutical excipient. In general an excipient is new (novel), if it is not listed in:

i. The FDA Inactive Ingredient database (https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm).
ii. Any of the 3 major compendia, U.S. Pharmacopeia (*USP-NF*), European Pharmacopoeia (Ph. Eur.), or Japanese Pharmacopoeia (JP).
iii. Other widely known compendia such as the "Handbook of Pharmaceutical Excipients" or "Fiedler: Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete" (Encyclopedia of excipients for pharmaceutical, cosmetic and related use).

The HS are not a simple substance to deal with. A sample would typically contain a range of different size of molecules. With the change of source, chances of variation in chemical composition and structures are always there. The molecules may vary with respect to both number and type of functional groups and also with respect to size. A special characteristic of HS is its capacity to show spontaneous changes in their conformation and aggregation state as a function of solution conditions like pH and ionic strength [13]. It is assumed that any change in the chemical composition of an excipient produces a new excipient, no matter how minor the modification to the chemical composition is. From regulatory point of view even the mixtures of excipient ingredients can be treated as a novel excipient when the subject mixture is to be used in a dosage form for which its constituent excipients have not already independently been used in that intended route of administration. So, the finished product manufacturer is highly dependent on the excipient manufacturer to provide materials that are uniform in chemical and physical characteristics. This is particularly important in the context of the pharmaceutical product approval process where bioequivalence (BE) comparisons are made between pivotal, clinical trial batch ("biobatch") and commercial scale-up lots.

The excipient used to manufacture commercial lots should not differ significantly from those used in bio-batches to provide adequate assurance of finished product performance. Therefore, it is important to minimize variation between the different batches of excipient. However if significant differences do occur between excipient lots used in clinical and commercial drug product lots, additional testing by the finished product manufacturer may be required to establish the BE of the drug product [14]. Although the excipient

qualification does not directly involve the regulatory authorities, they set many of the conditions that have to be satisfied if a user is to employ an excipient in their product. A standard requirement of non clinical data has been suggested by FDA [15], considering that relevant prior human use has not been adequately documented. The actual data requirement for a particular excipient depends upon different factors like,

i. Route of administrations (Oral, Topical, Injectable or Pulmonary)
ii. Duration of use of drug product (short term, intermediate and long term use)
iii. Fate of excipient in human body (e.g., PK data is required if an excipient is extensively absorbed and biotransformed)
iv. Population to be used (e.g., pediatric)
v. If there is any pharmacological potential. If the excipient is found to be pharmacologically active, the subsequent development requires evaluation of pharmacological activity using a battery of standard tests (see ICH guidance S7A). It is better to obtain these data at an early point of development.

The variability in HS is not unique to it. With variable magnitude it has been a common challenge with naturally occurring substances. But the natural substances have an advantage of history of consumption in different categories of products like food, dietary supplements, indigenous drugs etc. There are a few examples of natural substances which also have similar challenges but are being successfully used as excipient in drug products (Table 2).

Name/Mol wt/Mol structure	Pharmaceutical Excipient status			Dietary Supplement Dietary	Drug status Ayurveda	Food Status
	USFDA_IIG*	Pharmacopoeia	Textbook of PE**	Supplement	/ Unani	
Acacia Complex, loose aggregate of carbohydrate. Mol wt- 240 000 – 580 000.	√ (oral, topical)	USP-NF, BP, PhEur, JP	√	√	√	Food additive-EU, FSSAI
Almond oil Not defined, Mix of different compounds.	√ (topical)	USP-NF, BP, PhEur	√	√	√	Food and Chemical codex-US, FSSAI
Guar Gum $(C_6H_{12}O_6)n \approx 220\,000$	√ (oral, topical)	USP-NF, BP, PhEur	√	√	√	Food additive-EU & FSSAI
Olive oil Not defined, Mixture of acids	√ (oral, topical)	USP-NF, BP, PhEur, JP	√	√	√	Well accepted

Table 2: Different uses of naturally occurring ingredients have been tabulated. Chemical structures of these substances are complex and not well defined. √ sign indicates that the particular ingredient is being used in this category.
*USFDA, Inactive Ingredient Database
** Text book of Pharmaceutical Excipients

Similarly, HS based dietary supplements and cosmetic products are available all across the globe. These are being recommended to children also. HS based product (e.g. Carbohydrate Derived Fulvic Acid (CHD-FA)) is also being investigated as a therapeutic agent with potentials like anti-viral, anti-bacterial, anti-fungal and anti-inflammatory properties (including the drug resistant forms) (http://www.fulholdpharma.com/). These are also available as medicine in natural medicine comprehensive database http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&s=ND]. USFDA also suggests that existing human data for some excipients can substitute for certain nonclinical safety data and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies. So, it doesn't seem that there should be a major safety concern if the HS (either FA or HA) are developed as pharmaceutical excipient so far the quality standards are maintained.

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