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REVIEW PAPER

Pharmaceutical Aids: Classification and their importance

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ABSTRACT

The pharmaceutical aids are either drugs or substances which have low or no pharmacological effect/therapeutic value but they are essentially used in the preparations of pharmaceutical dosage forms such as ointments, tablets, injections or emulsions. Various inorganic and organic chemicals are known which have extensive application in the processing of pharmaceuticals. In this review we will get to know what pharmaceutical aids, their classification, different categories are and what is their significance in the preparation, preservation and storage of pharmaceutical products. These pharmaceutical aids are required for purposes such as preservations, acidification, alkalization, adsorption, filtration, prevention of oxidation, stabilization and complexion.

Keywords: - *Pharmaceutical ids, classification, pharmocognosy, Indian pharmacopoeia, excipients, ingredients, ointments, dosage, binders, natural colourants*.

INTRODUCTION

There are various organic and inorganic substances which have wide-ranging application in processing of pharmaceuticals drugs and these substances have very little or no therapeutic value but are important in the manufacturing of various pharmaceutical formulations such as tablets, liquids, ointments, and injectable. These pharmaceutical aids remain in the final product and they do not exert any specific action on the body. Many times these pharmaceutical aids are referred to as "pharmaceutical necessities". The pharmaceutical aids should be of the same quality as the therapeutic agent and they should be subjected to the similar quality controls. The objective of these pharmaceutical aids is to deliver the drug to the patient in the required amount, at the required rate, in batches and has a shelf life. This is most commonly used because of ease in manufacturing, accurate dosage and convenience in administration. It is crucial that pharmaceutical aids are to be of the same quality as that of the therapeutic agent and should be subjected to similar quality controls.

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Classification of pharmaceutical aids

These pharmaceutical aids are classified into various categories such as:

- Acidifiers and alkalizers

- Antioxidants and preservatives
- Absorbents and adsorbents
- Excipients
- Colorants
- Diluents, binders and lubricants
- Filter aids
- Buffers

Acidifiers and alkalising agents

These are substances which are mainly used to change the reaction of the liquid product or to maintain the pH of the product. These agents should not exert any kind of harmful effects on the body. One example of acidifying agents is Sulphuric acid (H_2SO_4) which is one of the important mineral acids and is industrially obtained by lead chamber process and the contact's process. Recently it is being prepared by first oxidizing sulphur dioxide to sulphur trioxide in presences of vanadium pentaoxide as catalyst. Sulphur trioxide is then dissolved to pyrosulphuric acid which with reaction with carefully calculated amounts of water yields high concentrated sulphuric acid.

Antioxidants and preservatives

Antioxidants are currently used as pharmaceutical excipients which can delay or inhibit the process of oxidation. [2] Substances are added to the pharmaceutical dosage form for preventing microbial growth and spoilage of the preparation is known as preservatives. Both preservatives and antioxidants are widely being used in the preparation of emulsions, mucilages, ointments and sterile preparations. [1] Some typical preservatives used in pharmaceutical formulations are: anti-oxidants like vitamin A, vitamin E, vitamin C, selenium and retinyl palmitate; amino acids like cysteine and methionine and synthetic preservatives like parabens and propyl parabens. [4] Only a few compounds are added as preservatives in preparations of pharmaceutical drug products. A generic method is developed for all the preservatives which are most commonly used. One example is of Butylated hydroxytoluene (BHT) which is an antioxidant and is most commonly used in preparations of solid dosage formulations to retard oxidative degradation of the excipients. For preparing liquid or semi-solid pharmaceutical dosage form, including the preservatives is very crucial and examples are EDTA, sorbic acid, sodium benzoate and parabens. [3] **Diluents, binders, lubricants and disintegrating agents**

Diluents are inert substances which are added to the active ingredient when it is given in small amounts, to increase the bulk of the product. Binders are substances which are used to impart cohesive properties to powdered materials and are also used for granulation. They also add mechanical strength to the tablets or any such formulations. Examples of binders are gelatin, polyethylene glycol, starch, cellulose and starch coil. Lubricants are substances which are added as a pharmaceutical aid to improve the rate of flow of granules and thus prevent cohesion and

adhesion of other substances while the manufacturing of tablets. [1]

TABLE-1 PRESERVATIVES

SUBSTANCES	PROPORTIONS USED	USES
Benzoic acid	0.1%	Used as an antibacterial preservative ingredient of camphor tincture IP.
Ethyl paraben	0.5% in water 0.15% in oils and creams	Used as an antifungal preservative.
Sodium benzoate	0.1%	Antifungal preservative.
Glycerol	50% in formulations	Common preservative
Benzyl alcohol	0.9%	Common preservative

Absorbents and adsorbents

Absorbent is process wherein a material absorbs some amount of liquid or gas into it and adsorbent is a process by which the liquid or gas gets accumulated on the surface of a solid material. One the most common example which is used as a pharmaceutical aid is **Diatomite or diatomaceous earth.** Diatomaceous earth consists of silicon dioxide along with alumina and ferrous oxide in significant quantities**.** It has specific properties like porous structure, high silica content, low density and low conductivity coefficient which make it a suitable aid in the pharmaceutical applications. It has excellent absorption power because of its macro-porous structure. [5] Diatomite is used as an absorbent with adsorbent properties to regulate the release of cationic drugs in pharmaceutical industry. Recent inventions related to solid pharmaceutical formulations have shown that it contains diatomite or natural mineral mixture containing diatomaceous earth as filler besides the active ingredient and option other auxiliary agents. [6]

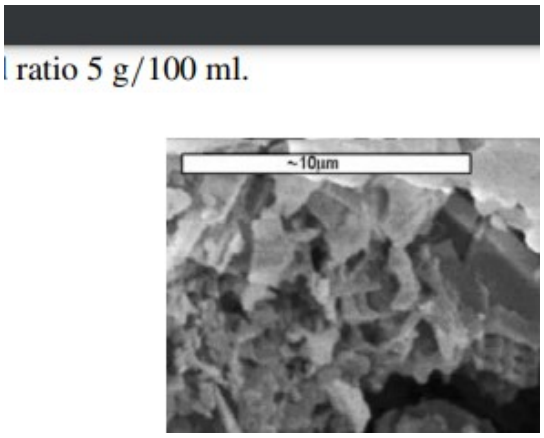


Figure 1- SEM Photograph of diatomaceous earth [6]

Excipients

Substances which are formulated alongside the active pharmaceutical ingredient of a medication, included for the purpose of long-term stabilization, bulking up solid formulations that contain potent active ingredients in small amounts or to confer therapeutic enhancement on active ingredient in final dosage are known as excipients. Pharmaceutical regulations and

standards require that all ingredients in drugs and their chemical composition are identified and shown to be safe. Excipients were assumed to be the "inactive" ingredient in the formulations but are sometimes thought to be "a key determinant of dosage form performance" and have its effects on the pharmacodynamics and pharmacokinetics. The types of excipients include anti-adherents, binders, coatings, colours, disintegrants and preservatives.

Based on their origin excipients are classified as:

Animal source: Gelatin, lactose, bees wax, honey, musk, lanolin and stearic acid.

Vegetable source: starch, turmeric, guar gum, peppermint, acacia and arginates.

Mineral source: Calcium phosphates, Silica, talc, Calamine, kaolin, paraffin and bentonite.

Synthetic: polyethylene glycols, povidone, polysorbates, boric acid and lactic acid. [7]

Talc

Talc is a mineral compound which has a significant commercial importance and is used in consumer products and has a proven history of safe use. It has direct consumer application in body powders, formulations and pharmaceutical tableting. Talc is used for various purposes like processing aids in the tablet formulations and in over-the-counter (OTC) products. It is used a glidant and helps as a flow agent for other active ingredients. The quantity of talc used in tablet formulations may range from 0.5% to 2.0% by weight of the tablet. As a lubricant it is helps to ensure that as the tablet is released from the die wall in the tablet press, hence it will not crack and remain smooth. Talc also prevents the tablet from sticking to surfaces when it is used as a dusting agent. In pharmaceuticals, it is particularly used as an excipient and a coating aid. Coating with talc makes it easier for the consumer to swallow the tablet and helps disguise the unpleasant taste. This is used as pharmaceutical aid to ensure that the coating or film will remain affixed to the tablet without showing cracks or ridges. Using talc in pharmaceutical formulations also adds to strength and helps brighten the pigments or colorants used for coating. [8]

Kaolin

Kaolinite that is $Al_2Si_2O_5(OH)_4$, is an abundant geomaterial regarded as one of the most common clay materials in earth's crust and is widespread among other kaolin polymorphs like halloysite, nacrite and dickite. This substance exhibits excellent physical, chemicals and surface physicochemical properties and that is why it has been used in many pharmaceutical applications as excipient or active ingredient. Apart from its application in classic pharmaceutical use, recent research has shown that its derivatives are considered as a promising material in many biomedical innovations areas also for example- in drugs, protein and gene delivery, based on high interaction capacities

with organic and biochemical molecules, bioadhesion and cellular uptake.

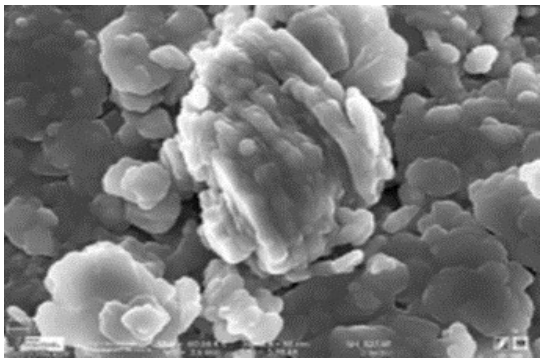


Figure-2 SEM photograph of Kaolin

Pharmaceutical kaolin grades are in high demand for usage as excipients in solid and semi-solid dosage formulations and the most important functionalities of kaolin used as an excipient are reported as diluent, binder, disintegrant, pelletizing and granulating, amorphizing, particle film coating, suspending and emulsifying agent. It is also used as an active agent for treatment of some common diseases because of its uninjured bioactivity. Kaolin can also be topically administered as haemostatic agent, anti-inflammatory agent, dermatological protector and antibacterial, antiviral, detoxification or anti-diarrhoeal agent. Kaolin has also been used as a haemostatic wound dressing agent. Wounds are caused by various reasons and causes vascular damages and skin breakdown, which facilitate toxicity and microbial invasion which may produce uncontrolled massive bleeding causing haemorrhagic shock leading to death. Kaolin is considered as a potent activator of substantial clotting pathway as it helps on accelerating clot formation within wounds. The blood-clotting potential is directly influenced by negative charged surface of kaolin at the pH of blood and human plasma. Once kaolin comes in contact with blood, it immediately begins the clotting process by transforming and enhancing the blood coagulation factor XII to its active form which activates the factor XI which is plasma thromboplastin antecedent and pre-kallikrien, which are directly responsible for bleeding prevention and wound dressing. Therefore kaolin has been used and applied as a topical haemostatic agent in the common wound dressing and other commercial products. It is also being used as a dermatological protector, anti-inflammatory and topical analgesic agent, and antibacterial agent and as a gastrointestinal protector agent. Kaolin also interacts with other drugs types such as digoxin for treatment of heart diseases, pseudoephedrine as a nasal/sinus decongestant and stimulant, oral hypoglycaemia agents for treatment of diabetes mellitus, flurazepam for treating insomnia and cimetidine for treatment of heartburn and peptic ulcers. [9]

Bentonite

Montmorillonite is a major component of bentonite and is a multifunctional clay mineral aid. It has unique characteristics and which is why it has applications in various industrial and pharmaceutical fields, including swelling and adsorption. The high adsorption capacity of bentonite contributes to increase in drug

entrapment and sustained release of drugs. [10] It is also used in cosmetics and medical markets. Bentonite is used a filler in pharmaceutical drugs and due to its absorption/adsorption capacities, it allows paste formation. Such formulations include industrial protective creams, anti-irritants for eczema, calamine lotion and wet compresses. In medicine, bentonite is used as an antidote in heavy metal poisoning. It also has applications in personal care products such as baby and face powders, sunburn paint, mud packs and face creams. [11] Change of pharmacokinetics properties takes place when adsorption is carried out using bentonite/ montmorillonite. For example, encapsulating glutathione into montmorillonite increases its oral bioavailability. Glutathione and montmorillonite are hybridized in this case, protected the glutathione from being hydrolysed in the intestines, enhanced bioavailability and elevated liver concentration of glutathione. This substance also enhances the cellular uptake of drugs. A research reported that paclitaxel-loaded montmorillonite/poly (lactic-co-glycolic acid) nanoparticles increased the drug uptake in two human colon derived cell lines compared to that of montmorillonite-free nanoparticles. Incorporation of montmorillonites in the formulation of pharmaceutics strengthened the interactions with cells via increasing the van der Waals forces and hydrogen bonding which suggests that the drug-loaded nanoparticles with bentonite may strongly interact with epithelial surface of gastrointestinal tract and enhance cellular affinity. Bentonite also modifies excretion of drugs. An example of this is montmorillonites-adsorbed amphetamine formulation, where amphetamine is a cationic drug which strongly intercalates with montmorillonite, which will slow down the release of the drug and decreases absorption and excretion. [10]

Gelatin

Pharmaceutical use of gelatin has a number of advantages over the other drugs which don't use gelatin as ingredient. It is used as an excipient in the production of hard capsules and soft gels. The advantages of gelatin are that it has lower production costs, fewer manufacturing complexities and secures excellent active pharmaceutical ingredient dissolution rates. It also protects the sensitive ingredients of the drug from light, oxygen, microbial growth and other forms of contamination. [13] Gelatin capsules are most popular dosage forms for drugs, over-the-counter products and food supplements. Gelatine coating makes the tablets easy to swallow and is preferred by consumers due to its smooth surface. It is highly compatible with the ingredients, is non-allergic and comprises proteins that get easily digested in the gastrointestinal tract, which facilitates the release and adsorption of active ingredients. Soft capsules are the preferred dosage form for any liquid, paste-like or oil-based fills. Soft gelatine versions of the pharmaceutical drug are hermetically sealed and airtight, thereby

masking any unpleasant odour or taste of the fills. One of the most recognized benefits of using gelatine is the enhanced bioavailability of the nutrient. Soft gel capsules provide opportunity to improve the absorption of poorly soluble drugs by encapsulating liquid and paste-fill formulations with very low particle sizes. Soft gel capsules are also versatile in nature, they start releasing the contents in 5-15 minutes. The time duration and specific effect can be modified and adapted as per the consumer needs by just altering the formulation of gelatine capsule shell. Gelatine capsules have endless varieties in terms of colour, shape and size, allowing unique presentations and customized products. [12] There are two types gelatine commonly used as binder in tablets- gelling and non-gelling. Gelling gelatin has high gel strength that gives cohesiveness, resistance and hardness to the tablets. These have longer disintegration rates since it has high gel strength. Non-gelling gelatin is used in direct compression. It has comparatively low binding power which makes the tablets weaker. It has fast disintegration rate which means that the drug would start showing its effects a lot sooner. For gelatin to be considered and accepted as a pharmaceutical aid it needs to meet certain standards such as quality control and traceability, technical specifications like gel strength, pH range, conductivity, microbiological limits, loss on drying and zinc and chromium contents, GMP compliant that is it needs to be produced in alignment with good manufacturing practices which is suitable for tis intended application. [13]

Natural colours

Formulations of pharmaceuticals like tablets, coatings, capsules, liquid orals, toothpaste and ointments are generally coloured to enhance the aesthetic appearance, prolong the stability, produce standard preparations or it can be for identification purposes. The colourants or the constituents in the natural pigments are utilized to meet the demand needed in the medicine. For examples, bixin is applied as one of the natural colouring agents for ointments and plasters and film coating for tablets employed chlorophyll and carotenoids are used as vitamin supplements. [14] Some advantages of natural colourants are that they are eco-friendly, biodegradable, non-carcinogenic, easy to dispose, generate less pollution, non-toxic and non-allergic. [15] Natural pigments are in wide use not only because of their high availability as a colouring agent, but they also exhibit abundance of health-promoting values such as antioxidant and antimicrobial activity which has various applications in pharmaceutical industry. **Curcumin,** found in henna, turmeric ad other such natural sources are widely use in cosmetics and pharmaceutical/medicinal purposes. Henna has hundreds of phytoconstituents and prevalent in the extracts are coumarins, flavonoids and naphthoquinones. They yield red-orange pigment from the extract of leaves. It has

antibacterial, antifungal, hypotensive ability and wound healing abilities. [14]

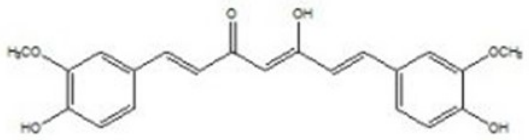
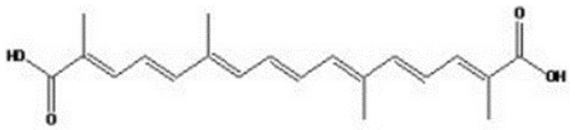
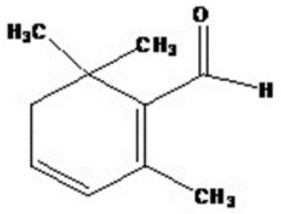


Figure-3 Chemical structure of Curcumin [14]

Yellow-orange colour from **Saffron stigma** is contributed by crocin along with other constituents such as crocetin, picocrocin and safranal. These have therapeutic values which are being used anti-depressant, anti-tumour, antioxidant agents and also help in improving memory.



(A)



(B)

Figure-4 A: Chemical structure of Crocetin; **B**: Chemical structure of Safranal [14]

Classification of natural colorants is on the basis of their origin:

Plant/vegetable origin: These colours are derived from leaves, roots, bark, fruits and flowers in dried or wet forms. Examples are curcumin (yellow) from turmeric, red pigment from madder roots and blue from water lily.

Insect/animal origin: These colourants are obtained from secretion and dried bodies of insects or animals. Deep violet colour is obtained from secretin of sea mollusc. Murex is one of the oldest known animal dyes. Other examples are from lac insect secretion, urine of cow and from shellfish.

Mineral origin: These colorants are obtained from oxides and minerals from the earth's crust. Oxides and hydrated oxides of manganese and iron, orchers, titanium dioxide, umbers are examples of mineral origin colourants.

Microbial/fungal origin: Colourants can be produced from bacteria, algae, fungi and yeast and these have anticancer and antioxidants properties. They are used in baby foods, energy drinks, capsules of drugs and tablets. Examples are brown pigment from *Bacillus spp.,* red from *Serratia marscenes* (bacteria) and yellow from *Ashbya gossypii* (fungus). [15]

Table 2- Classes of Chemical Structures Basis for Natural Pigments

NAME	PROPERTIES	EXAMPLES
Indigoid dyes	Basic structure is indigotin and it is the source of primary colour blue.	Anthocyanins
Pyridine dyes	It is an isoquinoline alkaloid with a bright yellow colour.	Barberine
Carotenoid dyes	Polymer of 8 isoprene monomers which give the colour yellow, orange and red.	Bixin Lycopene Carotene
Quinonoid dyes	Quinine functional groups are found in the structure. The colour ranging from yellow to red.	Benzoquinones Naphthiquinones Anthroquinones
Flavonoid dyes	It is a hydroxyl or methoxy substituted flavone existing in the structure. Includes pigments like pale yellow, deep yellow, orange, red and blue.	Isoflavones (pale yellow) Flavones and aurones (deep yellow) Aurones (orange) Anthocyanins (red and blue)
Betalain dyes	It consists of water soluble nitrogen in the structure which comprises yellow and violet pigments.	Betaxathins (yellow) Betacyanins (violet)
Dihydropyran based dyes	The structure is closely related to flavones.	Brazilin Haematoxylin

CONCLUSION

There are various substances used as pharmaceutical aids and these substances are being different in terms of their properties and functions. These functions include excipients, binders, coating agents, antioxidant agents, preservatives, colouring agents and filter aids. These components are evaluated for their safety and stability to be used as medicinal products or as an aid in pharmaceutical formulations. The safety assurance of these pharmaceutical aids helps the formulator to further design an effective and safe dosage form with the use of efficient ingredients.

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