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A DETAILED REVIEW ON THE ROLE OF EXCIPIENTS IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT
Excipients play important role in formulating dosage form. These are ingredients added with various active pharmaceutical ingredients make up the dosage form. Pharmaceutical excipients having the backbone of an Pharmaceutical formulations. Excipients act as protective, as a bulking agent and increase bioavailability of Drugs. In this review we discuss about the sources of various types of excipients they occur along with uses, their selection criteria and various interaction that an excipients during it course stay in formulations has be discussed in this review. Some excipients interaction can be toxic and need to be avoided. The following review gives brief information about the stability study , drug excipients compatibility and along with their various safety evaluation parameters of the excipients.

KEYWORDS: excipients, Interaction, drug excipients compatibility, stability.

INTRODUCTION

Pharmaceutical formulations composed many components including active pharmaceutical ingredients along with other excipients such as diluent, binders, disintegrant, lubricating agent etc. these ingredients contribute a key role in maintaining quality, safety, and efficacy of formulation to protect human health[1] these are inert substance added to contribute physicochemical stability of in vitro as well as in vivo active pharmaceutical ingredients during formulation development. Excipient significantly affected quality of finished product[2] todays commercially available excipients provide required functions, from processing aids that's increase lubricity, enhance flow ability, and improve compressibility and compatibility to agents that impact specific functional property to the final product (e.g. modifying drug release). The international pharmaceutical excipients council (IPEC) defines an excipients as any substance other than active drug and prodrug that is included in manufacturing process or is contained in a finished pharmaceutical dosage form. Nonactive pharmaceutical excipients are chemicals with wide range of molecular sizes, from small molecules to large polymer, and large variety of unique physicochemical characteristics. Therefore pharmaceutical excipients offers a wide range properties to influence many characteristics of pharmaceutical product, thereby achieving optimal therapeutic efficacy. In which the excipients overall contribution of excipients in dosage form that more than 70% of formulation contain excipients concentration than drug.

The Role Of Excipients In Pharmaceutical Formulations

The role of excipients varies substantially depending on the individual dosage form. These include (1) modulating solubility and bioavailability of drug (2) enhancing stability of the drug in dosage form (3 helping drug to maintain suitable polymorphic form, (4) maintaining pH and osmolarity of liquid products (5) acting as antioxidant, suspending agent, emulsifier, aerosol propellant, base, tablet diluents (6) preventing aggregation and dissociation and (7) modulating immunogenic response of drug (eg adjuvants) and others in these various context , excipients and issues associated with them can be considered following different areas. "Functionality''. A excipients interacts with the drug in the dosage form and/or provides a matrix that affect the critical quality attributes of the drug. Including solubility, stability and bioavailability. Limited understanding of excipients functionality can compromise product quality and process control. "Safety and Efficacy": Excipients can be associated with adverse events either by direct action or formation of undesirable adducts. Excipients can improve immunogenic properties of vaccines by acting as adjuvants. By modifying pharmacokinetic parameters such as absorption and distribution, excipients can change exposure pattern and thus influence both safety and efficacy outcomes. "Processability'': good understanding of characteristics and functional contribution of excipients aid in day- to-day manufacture of dosage. Form. In addition to their functional performance, ideally excipients should be chemically stable, nonreactive with drug and other

excipients inert in human body, have low equipment and process sensitivity, have pleasing organoleptic properties and well are charterized and well accepted by industry and regulatory agencies. Approximately 800 excipients are currently used in marketed pharmaceutical products and this number is expected to grow with new therapeutic categories such as gene therapy cell therapy and new drug delivery technologies of drug.

Classification of Excipients

Excipients can be classified according to the dosage form, they are solid, liquid or semisolid to perform various functions. Solubility, stability, and affordability are among the criteria used to select the excipients/additives. These components can be broadly categorized into the following categories

- Depending on the source natural, semisynthetic or synthetic
- Depending on the application: anti adhesive, glidants, filer and so on;
- Depending on the types od degradable materials: biodegradable and non-biodegradable.

Excipients used in the solid dosage forms

The solid dosage forms are the most commonly used dosage form because of the stability and ease of mass production "the solid dosage form, which are solid in nature contain one or more drugs for therapeutic effects and" example of solid dosage forms include pills, capsule, tablet, granules sachets, powders, dry powder inhalers chewable, and others. Additives are utilized in solid dosage forms for a variety of applications including.[3]

- To aid in formulation
- To sustain the drug
- To improve patient acceptability
- To improve visual attractiveness
- To enhances storage period
- To avoid contamination and invasion of bacteria
- To give unique size and form of dosage form

Table 1: Excipients used in solid dosage forms.

Excipients	Uses/ function	Example
Diluents	Act as a filler	Lactose, dextrose, sorbitol, starch, MCC, dibasic calcium phosphate dehydrate
Binders/Adhesives	Enhance cohesiveness of the powdered material	Acacia, gelatin, Starch paste, glucose, polyvinyl pyrrolidine, povidone
Lubricants	Minimize interparticular friction, avoid adhesion of tablet material to surface of dies and punches, insure easy ejection of tablet from die cavity, improve rate of flow of tablet granulation	Talc, surfactant, magnesium stearate, polyethylene glycol, steric acid vegetable oil calcium stearate
Disintegrant	For breakdown of tablets into small particles when comes in contact with gastrointestinal fluid	Modified starches, like primogel and exploitable, Veegum HV starches, cellulose, clays, cross linked polymers
Coloring agents (Must be approved and certified by F.D.A)	Impart aesthetic appearance to dosage forms, and identification of products	FD and C, D and C lakes and dyes.
Glidants	Enhance flow characteristics of powder mixture	Asbestos, free starch, colloidal silicone dioxide (carbosil), corn starch
Sorbents	Moisture proofing	Activated carbon, clay, silica gel
Plasticizer	Used for preparation of soft gelatin capsule, film coated tablet and gelatin based suppositories	Polyethylene glycol, polypropylene glycol, castor oil, Triacentin, a acetylated mono glycerides
Sweeteners	Improve sweetening ability of formulations	Saccharin and mannitol
Flavours	Masking bitter and unpleasant taste of API	Syrup, spray dried other flavours,
Coating materials	Protect tablet ingredients from deterioration by avoiding moisture	Corn, protein, zein, synthetic polymer, ethyl cellulose, HPMC, povidone, shelac

Excipients used in liquid dosage forms

Liquid dosage form are chemical compound used as drug or medication intended for administration or consumption, they may administered systemically by mouth or injected, by using different techniques, into the skin, muscles, or veins. The selection of excipients for liquid formulation depends on the products chemical and physical stability and compatibility and maintenance of appropriate organoleptic product such as textures, taste , consistency, colors and so on.[4] Several excipients used for this (table 2)

Excipients	Uses/functions	Example
Solvents	For dissolving API/solute	Water, ethyl acetate, acetic acid, syrups, alcohol
Cosolvents	Increase the solubility of solute in solvents	Propylene glycol, sorbitol, ethanol
Buffers	Maintain pH of solution	Acetate buffer, phosphate buffer, etc.
Antioxidant	It control oxidation of formulation	Butyl hydroxyl Toluene, sodium bisulphate, thiourea,

		ascorbic acid
Preservatives	Prevent microbial growth in formulation	Butyl parabens benzyl alcohol, phenol, and thiomersal
Antifoaming agent	To reduce foam formation during formulation	Paraffin oil, organic phosphate, stearate and glycols, alcohols,
Thickening agent	Prevent sedimentation and modify the viscosity of products	Methyl cellulose, microcrystalline cellulose, hydroxyl ethyl cellulose etc.
Wetting agent	Reduce surface tension of liquid and act as surfactant	Spans, tween80, sodium lauryl sulphates(SLS), lesithin
Chelating agent	Protect the drug from catalyst and accelerate the oxidation reaction	Disodium EDTA, tartaric acid, and citric acid
Flocculating agent	Prevent caking	Carbomer, starch, sodium alginate, etc.
Humectant	Increase solubility of active ingredient and elevate hydration of skin	Polyethylene glycol, propylene glycol, glycerol
Sweetening agent	Impart sweetness	Sucrose, saccharin, sucralase, sorbitol, aspartane
Flavors	Impart flavors	Syrup, aromatic water, etc
Colors	Impart color	Amaranth, Erythrosi, Eosin, Tartarazine etc.
Emulsifying agent	Prevent coalescence of the dispersed globules.	Sodium Lauryl Sulphate, Cetrimide, Macrogol esters, Sorbitan esters etc.
Excipient used in aerosol Propellant	Developing pressure in container which expels the product	Trichloromonofluoromethane, Dichlorodifluoromethane, Etc.

Excipients used in semi solid dosage forms

Semisolid are the topical dosage form used for the therapeutic, protective, cosmetic functions. They may be applied to the skin, or used nasally, vaginally, or rectally. In which Excipients used in semisolid dosage forms. Semisolids may be topical or sterile dosage forms. The uniform distribution of the base, drug and excipients is required for good extrudability and spreadability. Their viscosity and morphological features become crucial in such cases.[3] Excipients used in semisolid dosage forms are specified in table 3

Table 3: Excipients used in semi solid dosage forms.

Excipients	Uses/functions	Example
Structure forming excipients	Forming gel like structure	Cetosterly alcohol, sorbiton and other hydrophilic surfactants , fluid hydrocarbons like mineral oils etc
Solubilizers	Enhance the solubility of active ingredient in formulation	Lanolin, cholesterol or cholesterol esters.
Antioxidant	Prevent oxidation of reaction	Butyl hydroxy toulne , butyl hydroxy anisole, ascorbic acid etc
Preservatives	Prevent the growth of microbes in pharmaceutical formulations	Benzyl alcohol, proply paraben, methyl paraben, chlorocresol, imidazolidinyl urea, sodium and benzoate
Gelling agent	Forming gels	Carbomer934, pemulen®, carboxy methyl cellulose, hydroxy propyl cellulose, xanthan gum etc
Emollients	Should be able to skin is moist	Glycerin, mineral oil, petrolatum, isopropyl palmitate etc
Suppository bases	Used to form base for dissolving active ingredient	Cocoa butter, glycerin, coconut oil, gelatin, hydrogenated vegetable oil, polyethylene glycol etc

Types of Excipients: Excipients are classified on the basis of number and nature of the components used**.**

Single entity single-entity excipients These are excipients that contain only one component that is the integral part. Examples: cellulose, gelatin, starch

Combination/blend of multiple excipients combinations of multiple excipients containing a minimum of two pharmacopoeial/non pharmacopoeial additives using the different parts are combined as one with no significant artificial modifications for strong blend/mixes during which the specific ingredient remains actually distinct to a particulate level. Microcrystalline cellulose (MCC) and lactose are the examples.

Innovative excipients or chemical entities This is characterised as additives that have altered in order to produce unique excipients that are typically not documented by the US Food and Drug Administration (FDA). A novel excipient is any pharmacologically inactive material that is purposely added to the dosage form. According to the FDA, These compounds do not appear on the list of inactive components. Gelatinized maize starch with sodium carboxyl methyl cellulose and MCC are example of innovative excipients

Co-processed additives these are the combinations minimum two excipients that develop to change their properties. In which they improve their qualities of particular excipients. Various methods are used in co-processing such as gelatinization, FBD granulator, Hot melt extrusion Roller compaction, wet granulation, spray drying, co-precipitation, milling, solvent evaporation. This are method used in case of co-processing.[4]

Selection criteria of excipient

Pharmaceutical excipients are the substance that are added to medicine to fulfill various functions, such as improving stability, improving appearance, improving bioavailability, improving solubility of co-processing Excipients they do not have pharmacological activity but used as a vehicle to deliver the active ingredient of medicine[4]

When choosing right excipients , there are several factors are considered as they directly affect properties of medicine.

1 Efficacy: pharmaceutical excipients can affect the bioavailability: the rate and extent to which medicine and active ingredient is absorbed into the bloodstream and becomes available to act in the body at the site of action.

2 Safety: some excipients may cause side effects that's can be harmful to patients health.

3 Stability: excipients can affect stability of the medicine, so excipients should selected as to they does not interact with other components of medicine, affecting its potency, and quality during its shelf life.

4 Manufacturing process: excipients can affect the manufacturing process of medicine including the compatibility with the manufacturing processes and equipment used. Choosing the right excipients can help improve the efficacy of manufacturing process.

5 Addmistration: excipients can affect form and ease of administration of medicine, so it is important to choose excipients that are the compatible with the intended form of administration (e.g. tablets, capsules, solutions, orals, solutions etc.)

6 Function: choosing the pharmaceutical excipients depends mostly on function they will be perform in the medicine. There are several types of excipients, each of which has role in the functioning of the medicine.

Stability and compatibility studies of excipients with drug molecules

The stability of excipients directly dependent on type of excipients, its chemical and physical property and it is used alone or simultaneously with other excipients , a classification of excipients according to degree of stability was made excipients are distinguished from very stable ,stable , or limited stability these classification depends on the period of times for which the excipients proved always stable when packed in specific container. The stability evaluation includes both physical and chemical, evaluation where excipients can be classified as very stable when there are no changes during production and excipients remain unchanged With the same property for atleast 60 months at particular package meanwhile stable excipients are stable in range between 24 and 60 months for reassessment and impurities are easily detected.[5]

Incompatibility:- inactivation of drug activity through decomposition , when we mix with two or more API and excipient with each other then they antagonist the action and affect adversely on safety, therapeutic uses, and appearance[6], pharmaceutical incompatibilities generally due to changes in physical and chemical or therapeutic properties resulting from interaction of API and excipients or other products in which various factors influence the nature of drug excipients interaction such as a) physicochemical properties of drug and excipient, b) processing conditions, c) environmental factors, d) impurities present on excipients etc.[7]

A) Physical interaction:- physical interaction is common it us very difficult to detect physical interaction does not required any chemical changes is frequently used in manufacturing the dosage forms. Physical interaction are unintended which usually cause problems. Can either beneficial and detrimental in performance.

Example of physical interaction between API and excipients in this primary amine drug and microcrystalline cellulose. When dissociation is carried out in water small percentage of drug may be bound to the microcrystalline cellulose and are not release, for high dose drug, this not produce major issues , and but low dose drug can lead dissolution failure. This has caused problems in the past . But nowadays dissolution is carried out using weak electrolyte solution for the dissolution medium . Under this revised dissolution test , absorption of microcrystalline cellulose us reduced and 100% dissolution may achieved for low dose APIs[8]

B) Chemical interaction:- susceptibility of API toward the excipients is dependent on the possible chemical reaction pathway and upon the energy of the associated transition state which act as a energy barrier for the reaction depending on the electronic structure of the API molecule and the reaction mechanism, the height of this energy barrier can vary widely ,and thus influence the how fast API degrade. Five modes of API degradation upon interaction with or their impurities, these node are hydrolysis, oxidation and physical transformation and Other such as polymerization and isomerization, its include conversion of chemical into its optical isomer isomers have different pharmacological and toxicological activity , example levo (L) form of adrenaline 15-20 times greater than dextro form.[9]

C) Physiological and biopharmaceutical interaction these are the interaction generally observed after administration of medication. In which interaction of medicine with body fluids which influence the Absorption. All excipients interact in physiological way when they are administered along with pharmaceutical ingredients or API[7] various example are listed –

- Premature breakdown of enteric coat
- Interaction due to adjuvant therapy
- Increase in gastrointestinal motility

CONCLUSION

Excipients play the crucial role in the manufacturing of various dosage forms, it is an essential elements they having various kind of functional properties, in which these review explore the various types, selection criteria, stability, compatibility and various interaction associated with them. When choosing the right excipients is crucial for ensuring medicines are safe stable and help understand the excipients interact with each other and active ingredient helps create better formulations. When any pharmaceutical company having appreciate knowledge about excipients they create better medicines, improving patient outcomes public health.

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