INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY
Review Article

Pharmaceutical Excipients: A review

Shilpa P Chaudhari* and Pradeep S Patil

Marathwada Mitra Mandal's College of Pharmacy, Thergaon, Pune, Maharashtra, India.

ABSTRACT

Excipients play an important role in formulating a dosage form. These are the ingredients which along with Active Pharmaceutical Ingredients make up the dosage forms. Excipients act as protective agents, bulking agents and can also be used to improve bioavailability of drugs in some instances, the following review discusses the various types and sources of excipients along with their uses, and these can be used for different activities. Specific excipients are best suited for a particular dosage form; the selection criterion for excipients and various interactions that an excipient can undergo during its course of stay in formulation has been discussed in this review. Some excipient interactions can be detrimental and need to be avoided. This has been detailed out in the interaction section. Excipients as like other active pharmaceutical ingredients need to be stabilized and standardized; the following review gives brief information about standardization and stabilization process alongwith the safety evaluation parameters of the excipients.

Keywords: excipient, Interactions, co-processed excipients, Standardization.

INTRODUCTION[1-5]

Many dosage forms formulated today are complex system containing many other components along with the active pharmaceutical ingredient (API); these compounds are generally added along with the active pharmaceutical ingredients in order to

- **Protect, support or enhance stability of the formulation**:- Most of the times it is observed that the active pharmaceutical ingredient in its pure form does not retain its stability for long which results in its denaturation, or sticking to the container wall thus rendering it unfit, hence in order to stabilize the API excipients are added which aid in maintaining the stability of the product and ensures that API retains its stability for a considerable period of time thus improving the shelf life of dosage formulation.
- Bulk up the formulation in case of potent drug for assisting in formulation of an accurate dosage form.
- Improve patient acceptance.
- **Help improve bioavailability of active drug**: - Excipients usually help in improving the bioavailability of the active pharmaceutical ingredient for e.g. In many cases an active substance (such as aspirin) is not absorbed easily by human body in such cases the active ingredient is dissolved in or mixed with an excipient which may either act as solvent or assist in absorption of the drug in human body.
- Enhance overall safety and effectiveness of the formulation during its storage and use.

These components are generally termed as excipients and according to the international pharmaceutical excipient council, Excipient is defined as "Any substance other than active drug or pro-drug that is included in the manufacturing process or is contained in finished pharmaceutical dosage forms".

The US pharmacopoeia-National formulary (USP-NF) categorizes excipients according to the functions they perform in the formulations e.g. Binders, disintegrants etc.

Excipients can be classified on the basis of their origin, use in dosage form, and functions they perform as follows

1. **Excipient based on their origin**[5]

Animal source: - Lactose, Gelatin, Stearic acid, Bees wax, Honey, Musk, Lanolin etc.

Vegetable source: - Starch, Peppermint, Turmeric, Guar gum, Arginates, Acacia etc.

Mineral source: - Calcium phosphate, Silica, Talc, Calamine, Asbestos, Kaolin, Paraffin, etc.

Synthetic: - Boric acid, Saccharin, Lactic acid, Polyethylene glycols, Polysorbates, Povidone etc.

2. The following tables gives a classification of various excipients used in pharmaceutical dosage forms: (*table no 1,2,3)*

3. **Classification of excipients based on their functions** [10-13]:-

Excipients are classified on the basis of the functions they perform such as:-

Various excipients used in solid dosage forms perform various functions like:-

Binders, diluents, lubricants, disintegrating agent's plasticizers etc, e.g.: when 5% starch is used in formulation it acts as a binder for tablet formulations where as when it is used in dry form it can perform the function of a disintegrant.

Excipients that are used in liquid dosage forms are:-

Solvents co- solvents, buffers anti-microbial agents emulsifying agents sweetening agents, flavors, etc

Some excipients have therapeutic values which are classified as under:-

Anesthetics [10]:- chloroform, etc

Laxatives: - bentonite, psyllium, xanthan gum[11], guar- gum etc.

Ph modifiers: - citric acid.

Astringent: - cinnamon, alum, zinc sulphate.

Carminative: - cinnamon[13], dill water, anise water.

Nutrient sources: - agar[12], lactose, etc.

Excipient selection [14]:-

Excipients can be considered as indispensible component of medicinal products and in most of the formulations they are present in greater proportion with regards to active pharmaceutical ingredient, as it forms the bulk of the formulation it is always necessary to select an excipient which satisfies the ideal properties for a particular excipient. Excipient selection generally focuses on the desirable characteristics of excipients such as functionality, material consistency, regulatory acceptance, cost, availability, and sources. Material properties like micromeritics, chemical thermal rheological, mechanical etc also play an important role in development of drug formulation.

Formulators must also consider physicochemical properties, stability and compatibility issue, pharmacokinetic attributes, permeation characteristics, segmental absorption behavior, drug delivery platform, intellectual property issues etc while selecting an excipient for formulation development, this may help in determining the absorption challenges and desired delivery platform for active pharmaceutical ingredients.

The concept of quality by design (QbD) helps in understanding excipients normal variability and its potential impact on the processes of formulation development can be achieved. Excipient compatibility tests allows us to determine drug excipient interactions which can be either avoided or can be modified to utilize in an efficient manner which helps in minimizing the risk associated with the excipients. Excipient selection also depends on various routes of administrations. Excipient selection must be done on the basis of characteristics an excipient offers.

The ideal characteristics of an excipient are given as under:-

An excipient must be:-

- Chemically stable
- Non reactive
- Low equipment and process sensitive
- Inert to human body
- Non toxic
- Acceptable with regards to organoleptic characteristics
- Economical
- Having efficiency in regards with the intended use.

Excipients even though considered inert substance, have the tendency to react with drug components, other excipients, and also the packaging system. Excipients may also contain various impurities which may result in decomposition of the active pharmaceutical ingredients in the formulation thus altering the shelf life of the formulation.

The various type of interactions that an excipient can undergo are termed as

- Drug-Excipient interactions
- Excipient-Excipient interactions
- Package-Excipient interactions

These interactions are discussed in detail as follows:-

- **Drug – Excipient interaction**[15-19]

In pharmaceutical dosage forms the active pharmaceutical ingredients are in intimate contact with the excipients which are in greater quantity. Excipients and drugs may have certain incompatibilities which lead to drug –excipient interaction.

Excipients affect the physicochemical characters of the active pharmaceutical ingredient which may lead to formation of molecular complexes, increase in rate of chemical degradation etc.

Drug excipient interactions are further classified as

- Physical interactions
- Chemical interactions
- Biopharmaceutical interactions

a. **Physical interactions**: - physical interactions alter the rate of dissolution, dosage uniformity, etc. physical interactions do not involve chemical changes thus permitting the components in the formulation to retain their molecular structure. Physical interactions are difficult to detect. Physical interactions can be either beneficial or detrimental to the product performance which is dependent on its application.

Various types of physical interactions are listed as in table no 4.

b. **Chemical interactions**: - active pharmaceutical ingredients and excipients react with each other to form unstable compounds. Several chemical drugs –excipient interactions have been reported in literature. Generally chemical interactions have a deleterious effect on the formulation hence such kind of interactions must be usually avoided, various examples of chemical interactions have been listed in table no - 5.

c. **Biopharmaceutical interactions**: - these are the interactions which are observed after administration of the medication. Interaction within the body is between medicine and body fluids which influence the rate of absorption. All excipients interacts in physiological way when they are administered along with active pharmaceutical ingredients, various examples of biopharmaceutical interactions are stated as follows:-

1) P**remature breakdown of enteric coat**:- the enteric coating polymers like cellulose acetate phthalate and hydroxyl propyl cellulose acetate phthalate, are soluble more at basic pH, but antacids raise pH of stomach resulting in breakdown of the enteric coat in stomach and release of active pharmaceutical ingredient in stomach itself, which results in degradation of drug in stomach. In case of NSAID's premature breakdown of enteric coat may cause side effects like gastric bleeding.

2) **Interactions due to adjunct therapy**: - Tetracycline antibiotics form complexes with calcium and magnesium ions which are quite common excipients in various formulations which may be administered along with tetracycline as adjunct therapy the complex so formed is not absorbed from the G.I.T.

3) **Increase in gastrointestinal motility:** - many of the excipients like sorbital, xylitol, have tendency to increase the gastrointestinal motility thus reducing the time available for absorption of drugs like metoprolol.
Polyethylene glycol 400 also has influence on the absorption of Ranitidine.

d. **Excipient –Excipient interactions** [19, 20, 21, 22, 23, 24, 25, and 26]:- Excipient-Excipient interactions though observed very rarely, these are of prime importance in determining the stability of the dosage forms. Excipient –Excipient interactions can be undesirable as well as some interactions are used in the formulations to get the desired product attributes. Various excipients undergo such kind of interactions.

Examples of undesirable Excipient-Excipient interactions are listed in table 6 [15].

Some excipients are formulated as mixture in order to obtain desired effect in the product; such Excipient- Excipient interactions are beneficial for improving functional performances in the formulation. Such type of excipients can be considered as co-processed excipients.

Co processed excipients: - Tablets are generally considered as a dosage form of choice when oral route is preferred, because of accurate dosing, better patient compliance. Excipients such as binders, disintegrants, diluents, glidants, lubricants

etc are used along with the active pharmaceutical ingredient in the tablet manufacturing, These excipient offer in enhancing various properties like dissolution, absorption etc of active pharmaceutical ingredient when in tablet. Some excipients fail to give the desired output; hence the need for modified excipients with enhanced properties is developed.

Co processing is a novel concept that has been introduced, which alters excipient functionality by retaining favorable attributes and supplementing with newer ones, by processing parent excipient with another excipient. The high functionality excipients so formed help improve process ability such as flow properties, compressibility, and improved disintegration and dissolution profiles.

Introduction of high speed tablet machines and direct compression techniques pose several problems with the tablet manufacturing. Co processed excipients aid in solving such problems with their multifunctional properties. Co processing provides a synergy of functionality improvement, as well as masking the undesirable properties of individual excipients. Co processing is aimed at improving flow properties, compressibility, disintegration potential and development of filler binder combination.

Many bulk excipients that are used for conventional tablets are unsuitable for orally disintegrating tablets which necessities the use of specific excipients and technology to mask drugs unacceptable taste and improve the orally disintegrating tablet properties. The quick effect of dispersion is due to the excipients ability to absorb water quickly. Tablets rapid dispersion on surface of tongue is also facilitated by use of superdisintegrants like crosspovidone sodium, starch glycolate, crosscarmellose.

e. **Added functionality mannitol for orally disintegrating tablets**: - directly compressible mannitol is generally used because of its property to prepare robust tablets, spray dried or directly compressible mannitol are highly porous and friable which upon compression fill the interstitial spaces between larger porous particles. The disadvantage of orally disintegrating tablets is that they are very friable, co processing of mannitol with some polyols offer similar flowability and compressibility with addition of low friability as compared to direct compressed mannitol.

f. **Added functionality partially pregelatinized starches**:- partially pregelatinized starches are used as filers in hard gelatin capsules (5-75%) binders in wet granulation tabletting (5-20%), disintegrants in tablet formulation(5-10%) and also in direct compression tablets which also provide better particle size control, decreased friability, narrow particle size distribution, and reduced levels of fines. Partially pregelatinized starch particles having compact, embedded matrix are significantly less friable than those made of loosely associated ones. Such type of compact matrix partially pregelatinized starches help in rapid dissolution of drugs e.g. acetaminophen.

Some examples of such excipients are given in table no 7

g. **Package –Excipient interactions[28-31]:-** Packaging of pharmaceuticals is a vital part of the processing steps of product formulation, hence in pharmaceutical industry its essential that package selected adequately preserves the integrity of products, the selection of package therefore begins with a determination of products physical and chemical characteristics, its protective needs, and its marketing requirements.

The package thus selected should be inert in nature, should protect the product from external environmental conditions, etc.

Usually the packaging material used is glass; plastic, metal, rubber closures etc, these containers and closures react to certain extent with the drug product as well as with the excipient and give deleterious effects thus altering the product stability. Such interactions generally cause loss of product quality. These interactions are listed in the following table no 8:-

Standardization of excipients [32]

Excipient quality plays a vital role in assuring safety, quality and efficacy of dosage forms. Standardization of excipient usually assures the customers and manufacturers that the excipient quality will meet the international market, therefore the rules for regulation of bulk excipients are stringent and whenever a new excipient is to be introduced it is necessary for the applicant to submit safety and quality data and for an approved excipient the applicant has to provide literature reference data.

The various reasons for which excipients must be standardized are:-To assure the customer that the excipients used are safe and will not alter the formulation and cause undesirable effects.

- To assure the manufacture that he is using a standard quality material for formulating his dosage form and
- To reduce resources to host frequent customer audits and assure excipient GMP audit is conducted against appropriate GMP conformance expectations.

The standard chosen as framework for quality management system is ISO 9001. The Iso certification has the advantage of assuring the customers that excipient manufactueres quality management system has been verified independently.

GMPpractise for excipients assures product integrity, avoid product contamination etc.

IPEC is an international industry association which is formed with the main objective of development and harmonization of international excipient standard and development of newer excipients. It deals with three kinds of stakeholder groups viz; suppliers, users and regulatory authorities. It is necessary to obtain sufficient data about the excipient and the manufacturer or distributer, usually to get such information and information of the excipient in detail the users and customers send questionnaires to the supplier, the questionnaire consists of large amount of queries which becomes very difficult to resolve and address every individual as lot of time and money is wasted during this process, hence in order to minimize this stressful process IPEC has put forward an standardized excipient package that comprises of

- Product regulatory database
- Site quality overview and
- Site and supply chain security overview.

This information is useful in responding to the questionnaires and other requests in a simplified and standard process which is very effective in saving time. This information helps both users and suppliers to manage the information in a systematic and efficient manner.

- **Product regulatory database:** - this document has been formed with the main objective of providing information about important physical properties, manufacturing and regulatory information specific to excipients to the user which facilitates the use of excipients in drug formulations. The various sections included are

– **General product information:-** this includes information like product identification , product code/name, scope of document, and any other information that is necessary,

– **Manufacturing, packaging, release and supplier information:-** this section describes the information regarding excipient manufacturing site and the information related with it, for e.g.:- manufacturing processing, packaging, product release warehousing, laboratory site etc, distribution channels, GMP or GDP compliance statements, equipment information etc.

– **Physicochemical information:**- this section deals with the information related to the physical and chemical characteristics of the product for e.g.:- CAS number, information about the origin of excipients, their synonyms, its morphological characteristics, processes applied during manufacturing, mixed excipient information and the country of its origin if applicable.

– **Regulatory information:-** this section describes the regulatory status of an excipient, it includes information like compendia compliance (e.g. USP-NF, Food chemicals codex, BP etc) drug master file, or European Directorate for the Quality of Medicines and healthcare (EDQM) certificate of suitability, viral safety, allergens, hypersensitivity information, residual solvent information, metal catalyst and metal reagent residue information. Kosher/Halal status, bioburden/ pyrogen (optional) information etc.

– **Miscellaneous product information:**- this section includes information like lot/batch number, expiry date, use, nutritional information (if applicable) packaging information etc.

- **Revision:**- this section provides information regarding version control for document.
- **Contact information:**- this section includes the contact details of the supplier.

- **Site quality overview**:- this document gives information regarding the site of manufacturing, and any other areas related to the excipient processing or testing, there are various sections that are included in this document which are as follows:-
  - **Site overview**:- it describes supplier's organization and production capabilities, topics included in this section are site name, address, corporate ownership, customers audit policy (optional) site details etc.
  - **Compliance evidence**:- this section describes information of facilities being provided e.g. ISO certification, GMP inspection by competent authority, GMP statements, external audit programs like International Pharmaceutical Excipients Auditing(IPEA),AIB international, GMA-SAFE, etc.
  - **IPEC-PQG GMP compliance**:- this section deals with information about how the suppliers comply with the applicable elements of IPEC-PQG-GMP guide.
  - **Miscellaneous site information**:- this includes any additional information provided(optional).
  - Other information includes the contact details etc.
- **Site and supply chain security overview:-**

This document deals with information regarding protection of product and continuity of supply as assured by supplier, this document includes information about site name, address, evaluation of carrier, tamper evident packaging, qualification of distributer, broker, intermediate storage location, repackaging, relabeling activities, FDA registration information , security, safety and environmental considerations etc.

Thus these documents help in assuring the user, customer and supplier about the quality of excipient and may also give assurance that this process will continue to provide excipients of good and standard quality.

Excipient stability testing[33]

The main objective behind the compatibility testing is to find out most appropriate Excipients(s) for the particular API in dosage form under consideration and also those Excipients(s) that should be avoided for particular API . Excipients are derived from various sources such as natural and synthetic origins. Natural sources of excipients are usually contaminated with microorganisms and certain impurities that may render the formulation incompatible and cannot be used, thus in order to avoid any incompatibilities in formulation the excipients must be tested for their stability.

IPEC with an objective to contribute to the development and harmonization of international excipient standards has laid certain guidelines for the stability testing of excipients. These guidelines provide an approach for excipient manufacturer to establish a stability study program for excipients, which will help in defining revalidation intervals or expiration date.

The primary purpose of excipient stability study serves the purpose to retain its stability throught the manufacturing process, packaging upto the point at which the package is opened. The stability studies are designed on the basis of following factors like 1) utilization of historical data about a particular excipient and drawing conclusions about excipient stability.

2) Conducting stability studies using excipients packed in commercial packaging placed in different warehouses where the temperature is monitored.

3) Conducting studies using conditions and recommendations as in ICHQ 1A (R2):-

These guidelines serve the purpose of stability testing which provides the evidence of the quality of drug products under influence of various climatic conditions. Choice of test conditions are based on the analytic effects of climatic conditions in three regions namely Europe, Japan and United states.

Following procedures are followed in accordance to the guidelines:-

1) **Stress testing**: - it helps to identify the degradation products within the formulations. Such testing's are carried in single batch where the effect of temperature is tested where the temperature is kept in increments of 10^0c for e.g. 50^0c, 60^0c etc above which accelerated stability testing is performed. Humidity is maintained at around 75% RH or greater for the testing procedure. Photo stability testing forms an integral part of stress testing where the excipients are exposed to conditions as mentioned in ICHQ 1B.

2) **Specifications**:- specifications to analytical procedures are followed as per the guidelines

mentioned in ICHQ 6A[9] and ICHQ 6B, and for degradation products as in ICHQ 3A.

3) **Testing frequency**:- for long term storage conditions testing is carried out every three months over first year, every six months over second year, and annually thereafter.

For accelerated stability studies testing carried out at 0 month, 3 month, and 6 month. Testing over period of 6 months is generally recommended.

1) **Storage conditions**:- excipients are tested for the storage conditions for its thermal stability, moisture sensitivity or solvent loss. The specifications for storage testing are given as under: (Table no 9)

Stability indicating test methods: - Excipients should be tested for their stability using stability indicating assay methods, microbiological, physical and chemical tests,

Chemical stability can be measured by chromatographic techniques, physical stability by microscopy, particle size analysis, in vitro dissolution tests etc.

Various analytical tools such as thermal analysis, chromatographic techniques, diffuse reflectance spectroscopy, etc are used in detection and characterization of the excipient compatibility.

Stability considerations should also be given to comparison of composition profile of excipient at the limit of its retest/ revaluation intervals if appropriate to that of excipients at time zero, the composition should remain unchanged within the recommended storage conditions.

Excipient safety evaluation[34]

In 2007, the IPEC-Americas Safety Committee developed the IPEC New Excipient Safety Evaluation Procedure, which is an independent excipient review procedure. The procedure is intended to reduce costs stemming from unnecessary testing and the uncertainty related to using new excipients, thereby encouraging their use in drug development and boosting innovation in formulating drug products. In this procedure Excipients are evaluated for their safety using various in-vitro assay methods to screen for potential toxicity in this process the undesired toxicity producing material can be eliminated, this program is developed in different tiers of testing, where in first tier the compound is tested for its genotoxicity, cytotoxicity, metabolism and ability of compound to cross the biological membrane. This step may also include development of QSAR studies which can help predict the toxicity of compounds. In later cases the other steps can be followed, for eg testing for immunotoxicity studies, repeat dose toxicity testing and safety pharmacology studies etc.The documentation procedure begins with submission of the excipient safety dossier (in Common Technical Document format) to Product Development Group,which sends it to the NEEC(New excipient evaluation committee) chairperson, who distributes it to other committee members. It is recommended that Excipient dossiers be prepared according to IPEC's Master File Guide. The file guide comprises two parts. The first is the administrative section, which is region-specific based on submission specifics and local requirements. The second is the core technical document (CTD) that includes all technical details and summaries needed for Excipient acceptance in most regions, including CTD P4 requirements. Reviews are expected to last 1 to 3 months, depending on the quantity of information within (or absent from) the dossiers. In most cases, the cost will be based on not more than 50 hours of review time plus administrative overhead. The chairperson or a designee collates the comments of the committee members and drafts a report that is sent to each member for concurrence or further discussion. Once agreement is reached, the final report is sent to the excipient sponsor for review and comment. If the expert committee cannot agree on one or more points in the final report, the sponsor is told of the disagreements and the reasons for them. The sponsor may discuss the final report with the expert committee and request clarifications or explanations. Once everyone is satisfied, the chairperson signs the final report and sends it to the sponsor, who becomes its sole owner. The report will contain, at a minimum:

1. Discussion of chemical and toxicological data and human safety concerns based on intended use of the excipient;
2. Opinions on conformance with data needs according to the CDER Guidance; and
3. Identification of data gaps, if any, and points of reviewer disagreement that were not resolved and the reasons for them.

The IPEC New Excipient Safety Evaluation Procedure provides an excellent method for independently evaluating the safety of new excipients, including co-processed mixtures of existing excipients, physical and chemical modification of existing excipients, higher use levels of existing excipients, and NCEs. The Excipient sponsor can use the NEEC's report to support the use of a new excipient in a drug development approval process. As new excipients emerge, it's important to recognize their potential

use in various complex delivery systems, and the IPEC procedure helps do that.[35].

Table 1: Excipients used in solid dosage forms[6,7]

Excipient category	Function in formulation	Working principle	Examples
Diluents	Fillers	Make up the bulk of solid unit dosage forms when drug itself is inadequate to produce the bulk.	Lactose, Directly compressible Starches, Dextrose, Sorbitol, Microcrystalline cellulose, Dibasic Calcium phosphate dehydrate.
Binders and Adhesives	Impart cohesive qualities to powdered material.	Improves free flow qualities by formulation of granules to desired hardness and size.	Acacia, Gelatin, Starch paste, Polyvinyl pyrrolidone, Glucose, Carboxymethyl cellulose, Povidone.
Lubricants	Reduce inter-particular friction, prevent adhesion of tablet material to the surface of dies and punches facilitate easy ejection of tablet from die cavity and improve the rate of flow tablet granulation	Interpose a film of low shear strength that interface between the tabletting mass and die wall	Talc, Stearic acid, Magnesium stearate, Calcium stearate, Polyethylene glycol, Surfactants, vegetable oil.
Glidants	Improve flow characteristics of powder mixture.	Added in dry state prior compression, it reduces friction between particles.	Colloidal Silicone dioxide (Carbosil), Asbestos free starch, Corn starch.
Disintegrants Superdisintegrants	Facilitate breakup or disintegration after administration Improved disintegrant efficacy resulting in decreased use levels when compared to traditional disintegrants	Function by drawing water into the tablet, swelling it and causing the tablet to burst apart.	Starches, Clays, Cellulose, Cross linked polymers, Modified starches such as Primogel and Explotab, Veegum HV. Crosscarmalose, Cross Povidone, Sodium starch glycolate.
Coloring agents (these must be approved and certified by F.D.A)	Impart aesthetic appearance to dosage form, disguising off color drugs, product identification.		FD and C, D and C dyes and lakes.
Flavors	Limited to chewable tablets/ tablets intended to dissolve in mouth.	Mask unpleasant taste	Spray dried and other flavors, syrups etc.
Sweeteners	Impart sweet taste to the formulation; use is limited to chewable tablets.		Mannitol, Saccharin.etc
Sorbents	Moisture proofing	Limits the fluid sorbing, taking up of liquid or gas either by adsorption or absorption in dry state.	Silica gel, activated carbon, clay etc
Coating materials	Protect tablet ingredients from detoriation by moisture, help swallowing unpleasant tasting tablets		Hydroxypropylmethyl cellulose (HPMC), Synthetic polymers, Shellac, Corn protein Zein, Polysaccharides, Capslues coated by Gelatin, Povidone, Ethyl cellulose.
Plasticizers	For soft gelatin capsule preparation, gelatin based suppositories, film coated tablets etc.	Produce elasticity and flexibility to the coating materials in case of tablets, determine hardness of capsule shell in case of soft gelatin capsule and impart softness and resilience to suppositories.	Castor oil, Diacetylated Monoglycerides, Polyethylene glycol, Polypropylene glycol, Triacetin.

Table 2: Excipients used in liquid dosage forms[8]

Excipient category	Function in formulation	Working principle	Examples
Solvents.	Dissolving solute/Active pharmaceutical ingredient.	Breaking of bonds and reducing effective charge on ions thus increasing Solute-Solvent forces of attraction which are eventually greater than Solute-Solute and Solvent-Solvent forces of attraction.	Water, alcohol, acetic acid, acetone, ethyl acetates, syrups, etc.
Co solvents	Increase the solubility of solute in solvents.	Co-solvent system works by reducing the interfacial tension between predominantly aqueous solutions and hydrophobic solutes.	Ethanol, Sorbitol, Glycerin, Propylene glycol etc.
Buffers	Maintain pH of the formulation.	Act by binding hydrogen ions in acids and donating hydrogen ions in bases	Phosphate buffers, Acetate buffers, Citric acid Phosphate buffers etc
Antimicrobial preservatives.	Prevent microbial growth in formulations.	Bacteriostatic action	Benzyl alcohol, Butyl paraben, Phenol, Thiomersal etc.
Antioxidants	Control oxidation.	Act by getting preferentially oxidized or by blocking an oxidative chain reaction.	Ascorbic acid, Sodium bisulphate, Thiourea, Butyl Hydroxy Toluene (BHT), Tocopherols.etc
Wetting agents	Aid wetting and dispersion of hydrophobic active pharmaceutical ingredients.	Act by reducing interfacial tension between solids and liquids in suspensions.	Sodium Lauryl Sulphate (SLS), Tween 80, Spans, Lecithins etc.
Antifoaming agents	Discourage formation of stable foam.	Lowers surface tension and cohesive binding of liquid phase.	Simethicone, Organic phosphates, Alcohols, Paraffin oils, Sterates and glycols.
Thickening agents.	Prevent settling/sedime-ntation, modify viscosity.	Work by entrapment of solid particles.	Methyl cellulose, Hydroxyethyl cellulose, Microcrystallince cellulose etc.
Humectants	Retard evaporation of aqueous vehicles from dosage forms	They are hygroscopic in nature which helps in preventing evaporation of solvent.	Propylene glycols, Glycerol, Polyethylene glycol etc.
Chelating agents.	Protect drug from catalysts that accelerate the oxidative reaction.	Chelating agents form complexes with metal ions inactivating their catalytic activity in oxidation of medicaments.	Disodium EDTA, Dihydroxy ethyl glycine, Citric acid and Tartaric acid.
Emulsifying agents	Prevent coalescence of the dispersed globules.	Forms barriers at interface, and reduces interfacial tension.	Sodium Lauryl Sulphate, Cetrimide, Macrogol esters, Sorbitan esters etc.
Flocculating agents.	Prevent caking	Addition of an electrolyte reduces the magnitude of zeta potential of dispersed particles.	Starch, Sodium alginate, Carbomer.etc.
Sweetening agents	Impart sweetness		Sucrose, Sorbitol, Saccharin, Aspartame, Sucralase
Colors.	Impart color		Amaranth, Erythrosin, Eosin, Tartarazine etc.
Flavors	Impart flavor		Aromatic waters, Syrup etc
Excipient used in aerosol Propellant	Developing pressure in container which expels the product		Trichloromonofluoromethane, Dichlorodifluoromethane, Etc.

Table 3: Excipients used in semisolid dosage forms[9]

Excipient category	Function in formulation	Examples
1. Structure forming excipients	Form gel like structure	Cetosterly alcohol, sorbiton and other hydrophilic surfactants , fluid hydrocarbons like mineral oils etc
2. Preservatives	For preserving the formulation	Benzyl alcohol, proply paraben, methyl paraben, chlorocresol, imidazolidinyl urea, sodium benzoate etc
3. Antioxidants	Prevent oxidation	Butyl hydroxy toulne , butyl hydroxy anisole, ascorbic acid etc
4. Solubilizers	Enhance solubility of the active	Lanolin, cholesterol or cholesterol esters

	ingredient in ointments	
5. Gelling agents	Form gels	Carbomer934, pemulen®, carboxy methyl cellulose, hydroxy propyl cellulose, xanthan gum etc
6. Emollients	Modify vehicle/skin characteristics to assist penetration of active ingredient through skin	Glycerin, mineral oil, petrolatum, isopropyl palmitate etc
7. suppository bases	Used to form base for dissolving active ingredient	Cocoa butter, glycerin, coconut oil, gelatin, hydrogenated vegetable oil, polyethylene glycol etc

Table 4: Physical interactions

Interaction	Beneficial effect examples	Detrimental effect examples
Complexation:- Usually binds reversibly with drugs to form complex, sometimes insoluble complexes are formed which lead to slower dissolution and decreased absorption of drug. Result observed in such cases is detrimental	Cyclodextrin is often used to improve bioavailability of poorly water soluble drugs. This increases bioavailability and increases rate and extent of drug dissolution by increasing mucosal permeability or increasing stability of drug.	Tetracycline formed insoluble complex with calcium carbonate leading to slower dissolution and decreased absorption.
Complexing agents can also be used to increase bioavailability of poorly water soluble drugs Result observed in such case is beneficial	Complexation of Cyclodextrin with ursodeoxycholic acid increased bioavailability caused by increased dissolution.	Formulation of chlorpromazine with polysorbate 80 and sodium lauryl sulphate decreased membrane permeability of drug.
Adsorption:- Adsorption of drug by excipient can lead to reduced bioavailability as the drug is not available for dissolution. Adsorption of drug on excipient surface can assist in increasing surface area of drug available for dissolution which eventually increases bioavailability.	Formulation of Indomethacin (NSAID) using kaolin as adsorbent increased its dissolution rate which leads to increase in bioavailability of drug.	1) Cetyl Pyridinium chloride cations get adsorbed on the surface of magnesium stearate which acts as a lubricant in tablet containing Cetyl Pyridini8um chloride. This leads to marked reduction in the antibacterial activity of the drug. 2) Decrease in absorption of dicumarol in the formulations containing excipients like Aluminum hydroxide, Starch, Talc, owing to the adsorbing properties of excipients
Solid dispersion:- This kind of interactions improves the dissolution and bioavailability of hydrophobic drugs. Sometimes solid dispersion interactions can result in slow dissolution of drugs.	Improved dissolution rates of drugs like Piroxicam, Norfloxacin, Nifedipine and Ibuprofen were observed when these drugs were formulated into solid dispersions using Polyethylene glycol of different molecular weights.	Solid dispersion product formed due to interaction between Povidone and Stearic acid in a capsule showed slow dissolution of drugs.

Table 5: Chemical interactions

teraction	fect observed	amples of drugs undergoing such interactions
Hydrolysis	ugs with functional groups like esters, amides, lactones, undergo hydrolysis, in presence of water, low or high pH, in presence of alkaline metals, acids, acids i.e. anion and hydrogen ion, alkali etc.	esthetics , antibiotics, vitamins, and barbiturates,
Oxidation	idative reactions are catalyzed by oxygen, light, heavy metal ions, fumed metal oxides, fumed silica, fumed, zirconia etc. idation process involves removal of an electropositive atom or electron or radical, or addition of oxygen atom, generally the interactions of the active pharmaceutical ingredients are with oxidizing impurities in excipients or oxidative degradation products of excipients.	eroids, Vitamins, Antibiotics, Epinephrine, Aldehydes, Alcohols, Phenols.

	ugs with substructures like Benzilic carbons, Allylic carbons, Tertiary carbons, and α position of heteroatoms undergo oxidation.	
Racemization	nversion of a chemical into its optical or geometric isomer, having different pharmacological or toxicological activity.(here optically active substance looses its optical activity without change in chemical composition) .biological activity of the formulations is hampered as for e.g. biological effect of a drug in dextro form can be less than that in laevo form.	Adrenaline has optical 15-20 times greater biological activity then D –Adrenaline.
Polymerization	e polymorphic forms possess higher potential energy with respect to the thermodynamically stable or lowest energy forms. This potential energy is given out during mixing with the solvent, in some cases potential energy of compound is sufficient to exhibit an apparent solubility greater than more stable form which may eventually result into reversion of drug into less soluble form	norphous forms of sodium and potassium Penicillin-G were unstable to dry heat, whereas crystalline forms were stable for several hours.
Maillard reactions	rbonyl group of sugar reacts with amino acid, producing N-substituted Glycosylamine and water, unstable Glycosylamine undergoes amidroid rearrangement forming ketosamine which reacts to produce water and reductones or produce short chain hydrolytic fission products etc, rate of Maillard reactions increases as the water activity increases.	mary amines undergo maillard reactions, causes yellow brown coloration of drugs like chlorpromazine, etc. illard reaction products found in capsule containing lactose and antidepressant Fluoxetine.
Photolysis	composition resulting from absorption of radiant energy in the form of light. Reactions like ring alterations, oxidation-reduction, polymerization etc are catalyzed or accelerated by exposure to sunlight. Exposure to light may lead to discoloration or even decomposition of product	ch interactions are observed in Riboflavin, Folic acids, Nifedipine, containing formulations. Prednisolone and Methyl-prednisolone degradation is observed in alcoholic preparations.

Table 6: Excipient –Excipient Interactions

cipient	**compatible with excipients like,**	**fect observed**
acia.	Ethanol (95%) Ferric and other salts Trivalent salts Aqueous solutions (having negative charge) react with gelatin. Soaps in case of emulsions and suspensions.	Precipitate organic salts of Acacia Mucilage of acacia becomes gelatinous. initiate coagulation Form coacervates
cohol.	Acidic solution. Alkali mixtures	React vigorously with oxidizing agents. Darken color of preparation owing to reaction with residual amount of aldehyde.
ntonite	Acids. Alcohol. Cationic antimicrobial preservatives	Aqueous suspensions precipitated, acid washed bentonite does not have suspending properties. Precipitation of bentonite primarily due to dehydration by lattic structure. Antimicrobial efficacy reduced.
tylated Hydroxy Toluene (BHT)	Oxidizing agents like Peroxides and Permanganates. Ion salts Acids	Cause spontaneous combustion. Discoloration with loss of activity. Heating with catalytic amount of acids causes rapid decomposition with release of flammable gas Isobutane
osscarmellose Sodium	ygroscopic excipients like Sorbitol	ficacy as disintegrant reduced.
latin	Aldehyde. Cationic and anionic polymers.	Gelatin film hardens resulting in hard gelatin capsule shell. Viscosity is altered.
propyl Myristicate.	rd paraffin	oduces granular mixture.

Table 7: Co-processed excipients

o-processed Excipient	**mbination of**	**e**
dipress	ctose, Povidone and Crosspovidone.	ed for direct compression process in tablet manufacturing.
osolv	crocrystalline cellulose and fumed silica.	ally disintegrating excipient matrix

ırlac	ırch and Lactose	ed for orodispersible tablets and chewable tablets where palatability is of prime importance.
crocellac	crocrystalline cellulose and Lactose	r improving flow property.
llactose	wdered cellulose and Lactose.	tter flow property
adryl and Opadry	PMC, Titanium dioxide, PEG.	rmulation of easily dispersible film coating system.
cipient	eraction with	nefit gained
nthum gum	ratonia	scosity increased.
PMC and hydroxypropyl ethyl cellulose.	dium Lauryl Sulphate	scosity increased.
latin	ısticizer	oduced Soft gelatin capsule.

Table 8: Package- excipient interactions

Materials	Interactions observed	Effect observed
2) Glass	1) leaching of alkali	Change in pH of the formulation
	2) adsorption/absorption of excipients:-	Inactivation of formulation resulting in instability.
	3) Glass containers possess oxides of Boron, Sodium, Potassium, Calcium, Iron and Magnesium which interact with formulation.	lter physical and chemical stability of the formulation. E.g.:- sulphate salts react with barium and calcium to form inorganic insoluble salts.
	4) Oxidative reactions.	ron and Manganese oxide cations catalyze oxidative reactions, these ions are extracted from glass and cause decomposition.
2) Plastic	1) Moisture uptake	) Moisture uptake associated with disintegrants in tablet form micro-cracks due to disintegrant swelling.) Capsule becomes soft and sticky and undergoes chemical reactions that affect dissolution behavior. 3) Change in the hardness of tablets is observed. 4) Strength change in lactose-corn starch tablets' observed in strip packaging. 5) Discoloration of sugar coated tablets of Ascorbic acid.
	2) Migration.	) Water in oil type of emulsions have tendency to migrate and diffuse into hydrophobic plastic containers. 2) Tocopherols may be absorbed into plastic.
	3) Leaching.	1) Dyes migrate into parentrals and cause toxic effects. 2) Release of a constituent from plastic results in contamination.) Leaching of antioxidants from polyolefinic plastics into oleginious containers anti-oxidants like Pentaerythrityl tetrakis (3, 5-di-tert-butyl-4-hydroxyphenyl) propionate (Irganox) and tris (2, 4- di-tert-butylphenyl) phosphate (Igrafos) showed release into oily vehicles which affects content quality.
	4) sorption	Preservatives are sorbed into the containers leading to the loss of preservative activity.
3) metals	1) corrosion	1) Tin tubes can be corroded by chlorides or acidic conditions.)Sodium lauryl suphates are mildly corrosive to steel, copper, brass, bronze, and aluminium
	2) reactivity	Aluminium reacts with fatty alcohol emulsions to form a white encrustation, unstable for mercury containing compounds.
4) rubber	1) sorption	ntimicrobial preservatives like phenyl mercuric acetate are known to partition into rubber during storage reducing formulation concentration below effective antimicrobial levels
	2 Water permeability	Permeation of water through closures affects the overall stability of formulation.
	3) Leaching	resence of rubber closure extractives in the vial solutions could affect toxicity pyrogeneticity of injectable preparations, interaction with preservatives to cause inactivation or loss of stability and causes physical instability of preparation.
	4) dissolution	1) Ethyl oleate dissolves certain types of rubber and causes others to swell. 2) When Isopropyl myristicate comes in contact with rubber there is drop in viscosity with concomitant swelling and partial dissolution of the rubber.

Table 9: Storage conditions

In general case		
Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH. or 30°C ± 2°C/65% RH ± 5% RH.	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH.	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH.	6 months
Drug substances intended for storage in a refrigerator		
Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months
Drug substances intended for storage in a freezer		
Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

CONCLUSION

Excipients being an indispensible component of medicinal products, must be evaluated for their safety and stability. The various excipent interactions like drug- excipient interactions, excipient-excipient interactions and package- excipient interactions may render the excipient harmful for use in formulation. In order to avoid the use of incompatible excipients and to assure that that the excipients are safe and stable for use in the designing of the formulation, various stability testing procedures are carried out where the excipients are subjected to extreme conditions of temperature ,humidity etc. if the stability testing data is in favor of the use of excipient in formulation the excipients are further tested for assuring safety, which is the most important feature of any formulation intended to be used in humans or animals. As new excipients emerge, it's important to recognize their potential use in various complex delivery systems, and the IPEC procedure subjects new excipients for potential use in humans to a thorough safety assessment.

The safety assurance of excipients helps the formulator to design an effective and safe dosage form with the use of efficient and safe excipients.

Thus for an excipient to be in a formulation it must be highly stable, safe and efficacious, and above all it must comply with the expected performance in the formulation.

REFERENCES

1. Dorothy Chang, Ron Kun Chang" review of current issue in pharmaceutical excipients" may 2 2007, available on www.pharmtech findpedia.com.
2. Lakshmana Pramod et.al" globalregulatory perspective of bulk pharmaceutical excipients" available on www.pharmainfo.net/ review/global-regulatory perspective-bulk-pharmaceutical – excipients.
3. Patrick J Crowley, Luigi G Martini " excipients for pharmaceutical dosage forms" Encyclopedia of pharmaceutical technology 02 oct 2006. Available at www.informaworld.com.
4. Lokesh Bhattacharyya, Stefan Schuber, Catherine Sheehan, and Roger William "Excipients: background/introduction" Excipient development for pharmaceutical biotechnology and drug delivery systems; Ashok Katdare , Mahesh V. Chaubal (ed) ©by Informa Healthcare USA, Inc, 2006;1-2.
5. Giorgio Pifferi, Patrizia Restani" the safety of pharmaceutical excipients" farmaco 58 (8) 541-550 (2003).
6. Herbert A Liberman, Leon Lachman, and Joseph B Schwart, Pharmaceutical dosage forms- tablets, Informa Healthcare vol –I, second edition, pg -88-120.
7. http://www.pharmpedia.com/Tablet.
8. Leon Lachman, Herbert A Lieberman, Joseph .L.Kanig, "the theory and practice of industrial pharmacy", , Varghese publishing house, third edtion 1990; 457-471.
9. Prashant Srivastava "Excipients for Semisolid Formulations"excipient development for pharmaceutical biotechnology and drug delivery systems; Ashok Katdare , Mahesh V. Chaubal (ed) ©by Informa Healthcare USA, Inc, 2006;197-207.
10. www.inchem.org/document/pims/chemical/pim121.htm (chloroform)

11. www.webmd.com/vitamins-supplements/ingredients.mono-340-xanthan
12. www.sciencebuddies.shtml.org/microbio agar.
13. www.herbco.com/p-785-cinnamon chips.
14. Sari Airaksinen et.al" excipient selection can significantly affect solid state phase transformation in formulation during wet granulation" apps pharmscitech, 2005, 6(2), E 311-E 322, DOI10.12081 pt 060241
15. Md Zaki Ahmad, et. al" drug excipient interactions and compatibility study; a review" J Pharm Res 2010, 3 (9), 2092-2095.
16. Patrik Crowley, Dr Luigi G Martini "drug excipient interactions" www.callumconsultancy.com/article/drug excipient interaction.pdf
17. D.D Wireth et.al" maillard reaction of lactose and fluoxetime hydrochloride, a secondary amine" J Pharm Sci, 87, 31-39 (1998).
18. www.informahealthcare .com "excipient development for pharmaceutical biotechnology and drug delivery systems" page 93-124
19. Fenghe Qiu" identification of drug excipient interaction products using stress testing assisted approach" boehringer Ingelhein pharmaceuticals INC. available on www.americanpharmaceutical review.com.
20. Raymond C Rowe, Paul J Sheskey and Paul J Weller; Handbook of Pharmaceutical Excipients, Pharmaceutical press, American Pharmaceutical Association, 4th ed, 2003
21. M.C Gohel "a review of coprocessed directly compressible excipients", j.pharm pharmaceut sci (www.cspscanada.org) 8(1) 26-93, 2005
22. Ashish A Joshi and Sergio Neves" from commodities to specialized excipients" available on www.pharmquality.com
23. Minakshi Marwaha et.al" co processing of excipients; a review on excipient development for tableting performance" Int j app pharmceut, 2010;2 (3), 41-47.
24. Mahesh Kreer et.al" application of novel excipients in the allopathic and herbal formulations" j.chem.pharm.res, 2010, 2(4), 851-860.
25. Hans Leuenberger " from functionality excipients towards drug carrier system"Chimi Caoggi. Chemistry today. Vol 24 nr5, sept/Oct 2006, page 64-66.
26. Ashish A Joshi and Xavier Duriez "added functionality excipients; an answer to challenging formulations" pharmaceutical technology excipients, solid dosage forms 2004, www.pharmtech.com
27. Md Zaki Ahmad, et. al" drug excipient interactions and compatibility study; a review" j pharm res; 2010, 3 (9), 2092-2095.
28. Kenneth C Waterman, Bruce C Macdonald "package selection for moisture protection for solid oral drug product" J Pharm Sci, 2010;99(11):4437-4452.
29. Dennis Jenke" evaluation of chemical compatibility of plastic contact material and pharmaceutical products; safety and considerations related to extractable and leachable" J Pharm Sci, 2007;96(10): 2566-2581.
30. B Marcato, S Guerra, et.al" migration of antioxidant additives from various polyolefinic plastics into oleaginous vehicles" Int j Pharmceut, 2003;257(1-2):217-225.
31. Thomas Gonyon et.al "container effects on the physicochemical properties of parentral lipid emulsions" Int j app basic nutri sci, 2008;24, (11) :1182-1188.
32. The IPEC excipient information package (EIP) template and user guide 2009. www.ipec-europe.org/UPLOADS/Excipients_Insight_nov09_final(1).pdf
33. EMEA, ICH Topic Q1 A (R2) , stability testing of new drug substance and products. Aug 2003, CPMP/ICH/2736/99. Available at www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002651.pdf
34. Christopher DeMerlis, Jay Goldring, Ranga Velagaleti, William Brock, and Robert Osterberg, regulatory update; the IPEC novel excipient safety evaluation procedure, Nov 2009, Volume 33, Number 11.
35. Christopher DeMerlis ;Elaine V. Knight ;R. Christian Moreton ;Robert E. Osterberg, "Eye on Excipients", Tablets and capsules -formulation production and packaging vol 9, number 3, april 2011, 33-41.