Research Article **CODEX: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

A REVIEW ON PHARMACEUTICAL EXCIPIENTS

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ABSTRACT

In addition to transporting the active drug to the site in the body where the drug is intended to exert its action, excipients play an important part in the manufacturing process. They may also be important for keeping the drug from being released too early in the assimilation process in places where it could damage tender tissue and create gastric irritation or stomach upset. In this review we discussed about all the excipients used in the pharmaceutical formulations.

KEYWORDS

Excipients, Active drug, Tissue, Gastric upset and Formulation.

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INTRODUCTION

Pharmaceutical excipient means any component other than the pharmacologically active drug which is included in the manufacturing process or is contained in a finished pharmaceutical product dosage form.

While selecting excipients for any formulation following things should be considered wherever possible: keep the excipients to a minimum in number minimize the quantity of each excipients and multifunctional excipients may be given preference over unifunctional excipients.

Fewer ingredients in the formulation are better for the following reasons.

1. Excipients are not completely inert. Even commonly used excipients that are deemed to be pharmaceutically inactive and nontoxic may cause adverse reactions
2. Less ingredient variability to influence process and product consistency
3. Better economic efficiency in product manufacturing
4. Less probability of chemical or physical interaction between API and excipients and among excipients.

Excipients play a crucial role in design of the delivery system, determining its quality and performance.

Excipients though usually regarded as nontoxic there are examples of known excipient induced toxicities which include renal failure and death from diethylene glycol, osmotic diarrhoea caused by ingested mannitol, hypersensitivity reactions from lanolin and cardiotoxicity induced by propylene glycol.

Excipients may also be important for keeping the drug from being released too early in the assimilation process in places where it could damage tender tissue and create gastric discomfort or stomach upset.

Excipient Grades[1,2]

Many excipients for pharmaceutical use are available in different grades. These grades are differentiated frequently by means of physical and chemical characteristics.

The reason for grades is to change the performance characteristics of excipients.

Excipients are chosen in tablet formulation to perform a variety of functions like

1. For providing essential manufacturing technology functions (binders, glidants, lubricants may be added)
2. For enhancing patient acceptance (flavors, colourants may be added)
3. For providing aid in product identification (colourants may be added)
4. For Optimizing or modifying drug release (disintegrants, hydrophilic polymers, wetting agents, biodegradable polymers may be added)
5. For enhancing stability (antioxidant, UV absorbers may be added). Table No.1: Provides different types of excipients used in pharmaceuticals[3-10].

Diluents (Fillers)

In order to facilitate tablet handling during manufacture and to achieve targeted content uniformity, the tablet size should be kept above 2-3 mm and weight of tablet above 50 mg. usually the range of diluent may vary from 5-80%.

Diluents are also synonymously known as fillers. Diluents are often added to tablet formulations for secondary reasons like to provide better tablet properties such as:

1. To provide improved cohesion
2. To allow direct compression manufacturing
3. To enhance flow
4. To adjust weight of tablet as per die capacity

Classification of diluents

Tablet diluents or fillers can be divided into following categories:

Organic materials

Carbohydrate and modified carbohydrates.

Examples

Powdered cellulose, Microcrystalline cellulose (MCC), Starch, Starch 1500 (Pregelatinized Starch), Lactose, Sucrose, Mannitol and Sorbitol.

Inorganic materials

Calcium phosphates and others.

Co-processed Diluents

Tablet diluent or filler may also be classified on the basis of their solubility in water as soluble and insoluble shown in Table No.2.

Selection of diluent

Should be done after considering properties of diluent such as:

Compactibility, Flowability, Solubility, Disintegration qualities, Hygroscopicity, Lubricity and Stab.

Co-processed diluents

Co-processing means combining two or more materials by an appropriate process. The products so formed are physically modified in such a special way that they do not loose their chemical structure and stability. Now a day's direct compression

technique has been one of the well-accepted methods of tablet manufacture.

Binders

Binders act as an adhesive to 'bind together' powders, granules and tablets to result in the necessary mechanical strength:

1. As a dry powder with other excipients in dry granulation (roller compaction, slugging) or as an extra-granular excipient in a wet granulation tablet formulation.
2. As a dry powder with other intra-granular excipients in wet granulation. When the granulating fluid is added, the binder may dissolve partially or completely to then exhibit adhesive binding properties in helping granules to form.
3. Most commonly in wet granulation, the binder is added already dissolved in the granulating fluid to enable a more effective and controllable granule formation.
4. Water is the most common granulating fluid, very occasionally in a co-solvent system with, e.g. ethanol.

Examples:

1. Dry binders: Pregelatinised starch, cross-linked PVP
2. Solution binders: HPMC, PVP
3. Soluble in water/ethanol mix: PVP.

Disintegrants

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet. Different types of disintegrants shown in Table No.3.

Superdisintegrants

As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs. Table No.4 contains different types of super disintegrants.

Antiadherents

Some material have strong adhesive properties towards the metal of punches and dies or the tablet formulation containing excessive moisture which has tendency to result in picking and sticking problem. Therefore, antiadherents or anti-sticking agents prevent adhesion of the tablet surface to the die walls and the punches. Talc, magnesium stearate and corn starch have excellent antiadherent properties. Vegan had suggested that silicon oil can be used as antiadherent. (Different types of antiadherents shown in Table No.5).

Glidants

Glidants are added to the formulation to improve the flow properties of the material which is to be fed into the die cavity and aid in particle rearrangement within the die during the early stages of compression. If the flow properties are extremely poor then glidants are ineffective and consideration of force free mechanisms may be necessary. The effect of glidants on the flow of the granules depends on the shape and size of the particle of the glidant and the the granule.

Examples:

The commonly used glidants are talcum, starch, colloidal silica silicates, stearates calcium phosphate, etc.

Wetting Agents

Wetting Agents in tablet formulation aid water uptake and thereby enhancing disintegration and assisting in drug dissolution.

Incorporation of anionic surfactant like Sodium Lauryl Sulphate (SLS) is known to enhance the dissolution. It has been established that SLS improves permeation of drug through biological membrane since it destroys the path through which drug has to pass and thus minimizing the path length for the drug to travel.

Wetting agents are mainly added when hydrophobic drug is to be formulated into tablet.

Examples:

SLS, Sodium diisobutyl sulfosuccinate are used as wetting agent in tablet formulation.

Dissolution Retardants

Dissolution Retardants are incorporated into tablet formulation only when controlled release of drug is required.

Examples:

Waxy materials like stearic acid and their esters can be used as dissolution retardants.

Dissolution Enhancers

They are the agents that alter the molecular forces between ingredients to enhance the dissolution of solute in the solvent.

Examples:

Fructose, Povidone, Surfactants are used as dissolution enhancer.

Adsorbents

Adsorbents are the agents that can retain large quantities of liquids. Therefore liquids like Vitamin E can be incorporated into tablets by addition of adsorbents.

Examples:

Most commonly used adsorbents in pharmaceuticals are anhydrous calcium phosphate, starch, magnesium carbonate, bentonite, kaolin, magnesium silicate, magnesium oxide and silicon dioxide.

Buffers

Buffers are added to maintain a required pH since a change in pH may cause significant alteration in stability.

Examples:

Most commonly used buffering agent in tablet formulation includes sodium bicarbonate, calcium carbonate, and sodium citrate.

Antioxidants

Antioxidants are added in tablet formulation to protect drug from undergoing oxidation. Antioxidants undergo oxidation in place of drug or they block the oxidation reaction or they act as synergists to other antioxidants. Chelators may also act as antioxidant.

Examples:

Most commonly used antioxidants include ascorbic acid and their esters, alpha-tocopherol, ethylene diamine tetra acetic acid, sodium metabisulfite, sodium bisulfite, Butylated Hydroxy Toluene (BHT), Butylated Hydroxy Anisole (BHA), citric acid and tartaric acid.

Chelating Agents

Chelating agents tend to form complexes with trace amount of heavy metal ions inactivating their catalytic activity in the oxidation of medicaments.

Examples:

Ethylenediamine tetracetic acid and its salts, Dihydroxy Ethyl Glycine, Citric Acid and Tartaric Acid are most commonly used chelators.

Preservatives

Preservatives may be a part of tablet formulation in order to prevent the growth of microorganisms in tablet formulation.

Examples:

Parabens like methyl, propyl, benzyl, butyl p-hydroxy benzoate are used as preservatives.

Colorants

Colorants neither contribute to therapeutic activity nor do they improve product bioavailability or stability but are incorporated into tablets for purposes like to facilitate identification of similar looking products with in a product line to avoid mix ups, to facilitate identification of products of similar appearance that exist in the lines of different manufacturers, to overcome colour change on aging, disguising of off-colour drugs, for brand image in the market, to enhance the aesthetic appearance of the product to have better patient acceptance. Some Commonly Used Pharmaceutical Colorants shown in Table No.6.

Flavours

Flavors are commonly used to improve the taste of chewable tablets as well as mouth dissolved tablets.

Flavors are incorporated either as solids (spray dried flavors) or oils or aqueous (water soluble) flavors.

Sweeteners

Sweeteners are added primarily to chewable tablets. Table No.7 shows different types of pharmaceutical sweeteners).

Table No.1: Excipients Used in Tablet Formulation

S.No	Excipients	Function
1	Diluents or Fillers	Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size.
2	Binders or Granulating agents or Adhesives	Binders add cohesiveness to powders, thus providing the necessary bonding to form granules, which under compaction form a cohesive mass or a compact which is referred to as a tablet.
3	Disintegrants	Disintegrant is added to facilitate a breakup or disintegration of the tablet when placed in an aqueous environment.
Antifrictional Agents		
4	Lubricants	Lubricants are intended to reduce the friction during tablet formation in a die and also during ejection from die cavity.
5	Antiadherents	Antiadherents reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.
6	Glidants	Glidants promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.
Miscellaneous		
7	Wetting agents	Wetting agents are added to tablet formulation to aid water uptake during disintegration and assist drug dissolution.
8	Dissolution retardants	Dissolution retardants as the name suggest, retards the dissolution of active pharmaceutical ingredient(s).
9	Dissolution enhancers	Dissolution enhancers as the name suggest, enhance the dissolution rate of active pharmaceutical ingredient(s).
10	Adsorbents	Adsorbents are capable of retaining large quantities of liquids without becoming wet; this property of absorbent allows many oils, fluid extracts and eutectic melts to be incorporated into tablets.
11	Buffers	Buffers are added to provide suitable micro environmental pH to get improved stability and / or bioavailability.
12	Antioxidants	Antioxidants are added to maintain product stability, they act by being preferentially oxidized and gradually consumed over shelf life of the product.
13	Chelating agents	Chelating agents are added to protect against autoxidation; they act by forming complexes with the heavy metal ions which are often required to initiate oxidative reactions.
14	Preservatives	Preservatives are added to tablet formulation in order to prevent the growth of micro-organisms.
15	Colours	Colours are added to tablet formulation for following purposes: to disguise off colour drugs, product identification and for production of more elegant product.
16	Flavours	Flavours are added to tablet formulation in order to make them palatable enough in case of chewable tablet by improving the taste.
17	Sweeteners	Sweeteners are added to tablet formulation to improve the taste of chewable tablets.

Table No.2: Types of Diluents

S.No	Insoluble Tablet Diluents	Soluble Tablet Diluents
1	Starch Powdered cellulose Microcrystalline cellulose Calcium phosphates etc.	Lactose Sucrose Mannitol Sorbitol etc.

Table No.3: List of Disintegrants

S.No	Disintegrants	Concentration in granules (%w/w)	Special comments
1	Starch USP	5-20	Higher amount is required, poorly compressible
2	Starch 1500	5-15	-
3	Avicel®(PH 101 & 102)	10-20	Lubricant properties and directly compressible
4	Solka floc®	5-15	Purified wood cellulose
5	Alginic acid	1-5	Acts by swelling
6	Na alginate	2.5-10	Acts by swelling
7	Explotab®	2-8	Sodium starch glycolate, superdisintegrant.
8	Polyplasdone®(XL)	0.5-5	Crosslinked PVP
9	Amberlite® (IPR 88)	0.5-5	Ion exchange resin
10	MC, Na-CMC & HPMC	5-10	-
11	AC-Di-Sol®	1-3	Direct compression
		2-4	Wet granulation
12	Carbon dioxide	_	Created insitu in effervescent tablet

Table No.4: List of Superdisintegrants

S.No	Superdisintegrants	Example of Superdisintegrants	Mechanism of action	Special Comment
1	Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol®	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	Swells in two dimensions. Direct compression or granulation. Starch free
2	Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Crosslinked PVP	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet
3	Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level serve as sustain release matrix
4	Alginic acid NF Satialgine®	Crosslinked alginic acid	Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
5	Soy polysaccharides Emcosoy®	Natural super disintegrant	---	Does not contain any starch or sugar. Used in nutritional products.

Table No.5: List of Antiadherents

S.No	Antiadherent	Concentration Range (%w/w)	Comments
1	Talc	1-5	Lubricant with excellent antiadherents properties
2	Corn starch	3-10	Lubricant with excellent antiadherents properties
3	Colloidal silica	0.1-0.5	Does not give satisfactory results due to small surface area. Cab-O-Sil® and Syloid®
4	DL-Leucine	3-10	Water soluble lubricant; excellent antiadherents properties
5	Sodium Lauryl Sulfate	less than 1	Antiadherents with water soluble lubricant
6	Stearates	less than 1	Antiadherents with water insoluble lubricant

Table No.6: Some Commonly Used Pharmaceutical Colorants (Synthetic)

S.No	FD & C Colour	Common Name
1	Red 3	Erythrosine
2	Red 40	Allura red AC
3	Yellow 5	Tartrazine
4	Yellow 6	Sunset Yellow
5	Blue 1	Brilliant Blue
6	Blue 2	Indigotine
7	Green 3	Fast Green

Table No.7: Some of the Sweeteners Used in Tablet Formulation

S.No	Natural Sweeteners	Artificial Sweeteners
1	Mannitol	Saccharin
2	Lactose	Cyclamate
3	Sucrose	Aspartame

CONCLUSION

Excipients are the most important field of pharmaceutical formulation which needs deep study to evaluate new formulation with different concentrations of different pharmaceutical aids.

ACKNOWLEDGEMENT

The authors are sincerely thanks to the Narasaraopet Institute of Pharmaceutical Sciences, Narasaraopet, Guntur, Andhra Pradesh, India for providing the facilities to complete this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Prasad Telaprolu. *et al*. A review on pharmaceutical excipients, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(4), 2013, 423-431.