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Review on Pharmaceutical Excipients

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ABSTRACT

Excipients are components of a finished drug product other than the active pharmaceutical ingredient (API) and are added during formulation for a specific purpose. In contrast to active ingredients, minor components of an excipient may have significant impact on its pharmaceutical performance. They are included in dosage forms to aid manufacture, administration or absorption. Excipients as like other active pharmaceutical ingredients need to be stabilized and standardized. They act as protective agents, bulking agents and can also be used to improve bioavailability of drugs in some instances. 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.

Keywords: Excipients, Direct compressible diluents, Fillers and binders.

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INTRODUCTION

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[1-5]

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 inhuman body.

Enhance overall safety and effectiveness

It enhances safety and effectiveness of the formulation during its storage and use. These components are generally termed as excipient sand 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 (USPNF) 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 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. Excipients based on their functions [9-12]

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 [9]:- chloroform, etc

Laxatives: - bentonite, psyllium, xanthan gum[10],guar- gum etc.

Ph modifiers: - citric acid.

Astringent: - cinnamon, alum, zinc sulphate.

Carminative: - cinnamon[12], dill water, anise water.

Nutrient sources: - agar[11], lactose, etc.

SELECTION OF EXCIPIENT [13]

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.

NEW PHARMACEUTICAL EXCIPIENTS

1) Direct compressible diluents

a. Crystalline lactose 100% monohydrate (Brand name: Tablettose® 80)

It is an agglomerate crystalline lactose 100% monohydrated (USP/NF-Ph.Eur. – JP) that was designed in the Seventies for direct compression. It combines the good fluidity of heavy particle lactose and the good compressibility of a fine worn out lactose. It is white, smooth to tact, very stable and non hygroscopic dust. Its great specific area facilitates a fast dissolution. The irregular surface of the agglomerate one is structured so that it facilitates a good adhesion of the assets providing stable uniformity of assets and mixtures.

Applications

1. Conventional Tablets
2. Effervescence Tablets

Property

Fluidity: It demonstrates very good properties of flow, even mixing it with active principles of bad fluidity[15.]

b. Crystalline lactose monohydrate & amorphous lactose (Brand name: FlowLac® 100)

Spray is a monohydrated lactose dried (USP/NF - Ph. Eur. – JP) designed for direct compression. It is compound of a 85% of crystalline lactose monohydrated and a 15% of amorphous lactose that confers very good properties to him of compressibility. Due to the process of spray dried, the grains are spherical which confers excellent properties of fluidity. They are recommended for tablets of low doses, masticables tablets, effervescence tablets and filling of capsules.

Applications

1. Formulations of with low doses of assets

2. Masticable tablets

3. Effervescences Tablets

4. Filling of capsules

Property

1) Fluidity: it demonstrates very good properties of flow, even mixing it with active principles of bad fluidity.

2) Compressibility: FlowLac-100 does provide equivalent or better.

c. Spray dried maltose powder (Brand name: Advantose™ 100)

Advantose™ 100 maltose powder is a spray dried disaccharide carbohydrate. The safety and mouth feel qualities of maltose are well known. Now, by spray drying, the flow and tableting properties are greatly improved. It could be said that maltose has the flow properties of Dicalcium phosphate, the compressibility of MCC, and a better solubility than lactose. As can be seen in the microphotographs below of Advantose™ 100 maltose powder, these spray dried particles are

spherical and the combination of fine and coarse particles contribute to superior flow.

Applications

1. It can be used with low bulk density materials.

2. It tolerates variability in lubricant levels.

3. It produces stable tablets.

4. It has low hygroscopicity.

5. It is stable at various mix times.

6. It has good dilution potential.

d. Silicified microcrystalline cellulose (Brand name: PROSOLV SMCC®)

PROSOLV® is a high functionality ingredient that offers significant benefits in terms of tablet size, production yield and overall cost. Early use in formulation development can result in early market entry, direct compression formulas, and smaller tablets that consumers prefer.

Property

1. High Compatibility

2. High Intrinsic Flow

3. Enhanced Lubrication Efficiency

4. Improved Blending Properties

Applications

It provides tremendous benefits throughout the product lifecycle in:

1. Formulation

2. Manufacturing

3. Marketing

e. Silicified Microcrystalline Cellulose

(Microcrystalline Cellulose, Ph.Eur., NF, JP & Silica, Colloidal Anhydrous, Ph.Eur. & Colloidal Silicon Dioxide NF & Light Anhydrous Silicic Acid JP)

Property

1. They are multifunctional. They contribute two or more functions to a formulation through a single ingredient.

2. They have high inherent functional performance, even at low use levels, allowing for increased batch sizes and higher drug loading.

3. They require no complex processing, making them ideal for cost effective direct compression processes.

4. They impart their high inherent functional performance to the overall formulation. This last criterion is critical since it separates high functionality excipients from other multi-functional excipients or conventional specialty grade excipients. Binders are ingredients that can be used in a wet or dry state and help to bind all of the ingredients in a formulation together to achieve a robust dosage form. Microcrystalline cellulose is one example that enables formulators to develop effective direct compression and wet granulation processes[16.]

f. Poly Vinyl Pyrrolidone + Vinyl acetate(Brand name: PLASDONE S-630)

Physical & chemical properties

Hydrophilicity/ hydrophobicity

Addition of vinyl acetate groups to the vinyl pyrrolidone polymer chain reduces its hydrophilicity relative to PVP homopolymer.

Compressibility

It has higher compressibility making it an excellent choice as a tablet binder aid for direct compression and dry granulation.

Compatibility

PLASDONE S-630 polymer is compatible with a wide range of active and in active ingredients used in pharmaceutical products.

Solubility

It is soluble in water and a wide variety of pharmaceutically acceptable solvents, including alcohols, esters and ketones.

Viscosity

It is good viscous enough to be used as a wet granulating binder. In tablet coating, the low solution viscosity of PLASDONE S-630 copolymer results in higher solids coating formulations which can reduce application time and increase productivity[17.]

2) Fillers and binders property together

a. Functional Filler (ARBOCEL®)

Powdered Cellulose, Ph.Eur., NF, JP Powdered cellulose is used as an economic and inert diluent in tableting and capsule filling. Especially in wet granulation it works synergistically with other economic excipients such as starch or lactose. Combined with these, ARBOCEL® improves tablet hardness and disintegration time.

b. Cellulose + lactose (Brand name: CELLACTOSE 80)

Cellactose 80 is spray-dried compound consisting of 75% alpha-lactose monohydrate (Ph. Eur./USP-NF/JP) and 25% cellulose powder (Ph.Eur.) dry matter. Cellactose 80 , designed especially for direct tableting, combines filling & binding properties of two excipients which have been synergistically combined to an one-body excipients providing better tableting performance at lower cost.

<32micro<=20%	Angle of repose: 32-35º
<160micro 35-65%	Density poured :380(g/l)
<200micro>=80%	Density tapped : 500(g/l)
(Air jet sieve)	Hausner ratio : 1.2

Applications

1. Herbal extract tablets
2. Chewable tablets
3. Mineral salt tablets
4. Cores for coating
5. Oblong tablets4

c. Microcrystalline cellulose+lactose (Brand name: MICROCELAC 100)

Particle size distribution

MICROCELAC 100 is spray dried compound consisting of 75% alpha-lactose monohydrate & 25% Microcrystalline cellulose DRY MATTER. Both filling & binding properties of two excipients which have been synergistically combined to an one-body excipients providing better tableting performance at lower cost.

<32micro<=15%	Angle of repose: 34º

<160micro 70% Density poured :500(g/l)

<250micro>=90% Density tapped : 610(g/l)

(Air jet sieve) Hausner ratio : 1.16

d. EMDEX®

Dextrates, NF

Ideal for chewable and soluble tablets, EMDEX® is the only compendial (NF) dextrate that delivers the required flow, compaction, taste masking and flavor carrying capacity. It is highly water-soluble and gives a cool smooth mouth feel. EMDEX® is also available GMO free.

3) Disintegrants

a. Starch + Lactose (Brand Name: StarLac)

It is directly compressible grade material. It is made of crystalline lactose monohydrate & maize starch in a portion of 85:15 respectively. It has good fluidity & in their main application the tablet with low doses ,elobration of nuclei of coverings[15.]

Property

(a) Disintegrantion: use as additional super disintegrant can be reduced or avoided.

(b) Compressibility: it is used as direct compression & offer excellent compressibility.

(c) Fluidity: it ensure uniformity of weight ,greater capacity of pick particle ,greater rank of speed of compression[15.]

b. Soy Polysaccharide(Brand name: emcosoy)

Soy polysaccarides, is an all-natural, soft while to light-tan power, which Dose not contain starch or sugar. It is derived from dehulled and defatted soybean fiakes by a special process. Emcosoy is a kosher product and is manufacture without the use of bleaching agents. Emcosoy typically has 75% dietary fiber with the main components including five type of higher polysaccarides: cellulose, hemicellulose, protein, gum and mucilage. It is ideally suited for low calorie (2kcal/g) and diabetic applications. Emcosoy sts ip excellent disintegration and improved dissolution characteristics when tablets are prepared by direct compression. Its use in soluble system has evidenced fast and efficient disintion of tablets prepared with a broad range of hardness values.

Superdisintegrants

Despite a rising interest in controlled –release drugs delivery system, the most common tablets are those intended to be swallowed whole, disintegrating and releasing their medicaments rapidly in the gastrointestinal tract. A Disintegrant is substance in a tablet formulation that enables the tablets to break up into smaller fragments upon contact with gastrointestinal fluids .Such a rapid rupture of tablet matrix increase the surface area of the tablet particles, there by increasing the

rate of absorption of the active ingredient and producing the desired therapeutic action. The proper choice of disintegration and its consistency of performance are critical to formulation development of such tablets. In the past starch was one of the most widely used inexpensive and effective tablets disintegrants. A high concentration of starch is required to bring about effective disintegration. Examples of Superdisintegrants are crosscarmelose, crospovidone and sodium glycolate which are cross linked cellulose crosslinked polymer and a crosslinked starch, respectively. Viscous grades which form a gel in water and chloride reduced types (PCF) complying with Japanes food regulations are available on request.

a. Sodium Starch Glycolate(Brand name: VIVASTAR)

Super Disintegrant having great disintergration power and cost savings. VIVASTAR PSF (Pharmaceutical Solven Free) is innovative in that it can improve stability of certain drugs by removing residual solvents. Viscous grades which form a gel in water and chloride reduced types (PCF) complying with Japanes food regulations are available on request.

4) Lubricants & plasticizers

a. Lubricant + Modified release

Sodium Stearyl Fumarate, (Ph.Eur., NF, JPE**)(Brand name: PRUV®)**

PRUV® is a hydrophilic lubricant**.** It avoids many problems associated with magnesium stearate including active incompatibility*, over lubrication, and film formation in effervescent tablets. Product development time and bioavailability of certain actives can be improved e.g. Azathioprin, Cefaclor, Cilazapril, Clarithromycin, Clopidogrelacetate, Diclofenac, Fosinopril, Ibuprofen, Ketorolac, Levofloxacin, Nifedipin, Omeprazol, Ramipril, Trandolapril.

Change Notification PRUV

Change Notification for PRUV Sodium Stearyl Fumarate, Ph.Eur., NF, JPE

b. Hydrogenated Refined Vegetable oil (Brand name: Lubritab)

Lubritab is made from fully hydrogenated refined vegetable oil that is sprayed into a dry, fine powder. Lubritab has been specifically created for application in the production of pharmaceutical tablets. An edible product of vegetable origin, Lubritab is low in ash content with practically no trace of heavy metals. The low iodine value and low acid value indicate that Lubritab is less chemically reactive than other commonly used lubricants, thus assuring excellent formulation compatibility. While Lubritab is generally used as a lubricant in a range of 0.5 4.0%, it is also employed as an auxillary dry binder when tablets and capsules tend to cap or laminate. In such cases, the addition of up to 5% could eliminate these problems and aid in producing satisfactory tablets. It is most effective when added in the dry state in the last blending operation

before compression and blended for 10-15 minutes. When using Lubritab it is recommended that an anti-adherent also be considered[18.]

Plasticizer

a. Dibutyl Sebacate.

Formula: [(CH2)4CO2(CH2)3CH3]2

Mol Wt.-314.46

Synonyms:-Sebacic acid **,** Dibutyl Ester, Bis(Nbutyl) Sebacate; Butyl Sebacate; Decanedioic acid, Dibutyl Ester; Di-n-butyl Sebacate.

General description and applications

Dibutyl Sebacate is a plasticizer permitted in the field of food contact material, medical and pharmaceutical. It is used as a plasticizer for polymers and synthetic rubbers. There are almost infinite esters obtained from thousands of potential starting materials. Esters are formed by removal of water from an acid and an alcohol,e.g.,carboxylic acid esters, phosphoric acid esters, and sulfonic acid esters. They are also used as intermediates for the manufacture of a variety of target compounds. The almost infinite esters provide a wide range of viscosity , specific gravity, vapor pressure, boiling point, and other physical and chemical properties for the proper application selections[22.]

b. Glyceryl behenate(Brand name:-COMPRITOL 888ATO)

Description: Off white powder. Tasteless, non-reactive with other formulation Ingredients.

Physical Characteristics

Water content:-NMT 0.5%

Particle size Distribution Through US 250 mesh: 85%

Applications

1. Lubricant

Decreases ejection force and improves compressibility. Not sensitive to over blending Does not interfere with tablet disintegration or drug release rate.

a. Pellets

Can be incorporated into pellets via extrusion/ spheronization. Microcrystalline cellulose pellets containing Compritol® 888 ATO, can be compressed into tablets[20.]

b.Guar gum powder(Brand name: Ultra Guar™)

A pure, rapidly hydrating guar gum powder. Produced under the strictest raw material selection and hygienic conditions, UltraGuar™ does things conventional guar gum powders cannot. This all natural polymer produces exceptionally high viscosity, achieving 5600+ cps in about two

minutes. Due to its ultra power less is needed. Its rapid hydration dramatically speeds up processing times at a fraction of the cost of CMC. Ultra Guar™ hydrates quickly in both hot and cold aqueous solutions making it ideal for instant beverages, sauces, dressings, soups, gravies and more[10.]

5) Glidants

Attapulgite

Attapulgite is a kind of crystalloid hydrous magnesium-aluminium silicate mineral, having a special laminated chain structure in which there is a crystalline lattice displacement existed. Thus it makes the crystals contain uncertain quantities of Na+, Ca+,Fe3+ and Al, and present in the shape of needles , fibers or fibrous clusters. Attapulgite has very good colloidal properties such as :specific features in dispersion , high temperature endurance. Furthermore, attapulgite has certain plastic and adhesive characters. Its ideal molecular formula is: Mg5Si8O20(HO)2(OH2)4.4H2O.Attapulgite clay mineral have the following special features: geological conditions under which Chinese attapulgite was deposited are different from that of the USA attapulgite deposits , our attapulgite products have very low grit (percentage retained on a 325 mesh wet screen),low free silica content, and low carbonate content.

6) Thickener

Dextrin

Dextrin are a group of low-molecular-weight carbohydrates produced by the hydrolysis of starch. Dextrin are mixtures of linear α-(1,4)-linked D-glucose polymers. They have the same general formula as carbohydrates but are of shorter chain length. Industrial production is generally preformed by acidic hydrolysis of potato starch. Dextrin are water soluble, white to slightly yellow solids which are optically active. Analytically, dextrin can be detected with iodine solution, giving a red coloration with green spots. The cyclical dextrins are known as cyclodextrins. They are formed by enzymatic degradation of starch by certain bacteria, for example Bacillus macerans. Cyclodextrins have toroidal structures formed by 6-8 glucose residues. For example, maltodextrin is a moderately sweet polysaccharide used as a food additive, unrelated to barley malt. Foods containing Maltodextrin may contain traces of amino acids, including glutamic acid as a by-product of the manufacturing process. However, the amount of amino acids would not be high enough to have any dietary significance[19.]

7) Thickener and Stabilizers

a. VIVAPUR® MCG :(Microcrystalline cellulose and Carboxy methyl cellulose sodium)

An excellent thixotropic gelling agent to stabilize suspensions and emulsions. It is pH stable and

could be used in hot and cold medium[7].

8) Colours

Titanium Dioxide and Iron oxide(Brand name: CANDURIN)

CANDURIN® range includes Silver Colours

Silver pearl effects based on titanium dioxide.

Interference colours

Interference pearl color effects (gold, blue, red and green) based on titanium dioxide.

Golden Colours

Golden pearl effects based on titanium dioxide and iron oxide.

Iron Oxide Colours

Bronze-deep red pearl color effects based on iron oxide

Influence of light

Light must reach the CANDURIN® particles as directly as possible otherwise the desired resources distribution only several countries in the world at the present. Attapulgite reserve capacity of Xuyi contains the 70% in China, and 35% in the world. Compared to the largest commercial attapulgite de pearl effect will be reduced or not visible at all.

CANDURIN® particle size

Small particle-sized pigments (sheen range, 5 - 25µm) result in an increased hiding power in combination with satiny pearl effect. The largest particle sizes (sparkle range, 10 - 150µm) exhibit eye-catching glitter effects, whereas medium sized pigments (luster range, 10 - 60µm) provide both, exquisite pearl luster combined with a medium hiding power resulting in uniform luster effects.

9) Sweeteners

a. Enzymatically treated Sucrose (Brand name: Galen IQ)

Manufacturing process

Galen IQ™ qualities are derived from sucrose in a two stage production process. First sucrose is converted to the disaccharide 6-0—D-glucopyranosyl fructose (isomaltose), a significantly more stable reducing compound, in an enzymatic transglucosidation process. In the second step, the hydrogenation of isomaltose leads to ht estearoisomer disaccharide alcohol 1-O-D-glucopyranosyl D-mannitol dehydrate(1,1 GPM dihydrate) and 6-O-Dglucopyranosyl- D-sorbitol (1,6-GPS) in an approximate equimolecular mixture. The ratio between the main components can be varied with the an additional special crystallization process. As a result, specific GalenIQ™ qualities are obtained, e.g. enriched in 6-O-Dglucopyranosyl-D-sorbitol (1,6

GPS) Providing Higher Solubility. Depending on the quality, the mixture contains approximately 3-5% crystal water, which is strongly bound to the GPM crystal. In its final state, GalenIQ™ is a white, odorless, water soluble, crystalline substamce[22.]

c. Isomalt (Brand name: CARGILL)

Isomalt is a sugar substitute consisting of disaccharide alcohols. It is derived exclusively from sugar by enzymatic conversion into isomaltose, which is then hydrogenated to obtain the two components mixture of GPS and GPM.

d. Xylitol

Description: white to off-white free flowing powder, with excellent compressibility. Xylitol is a sweet sugar, but is non-carcinogenic, and suitable for diabetics[19.]

e. Erythriol

Erythriol (butane-1, 2, 3, 4-tetraol) is a natural sugar alcohol (a type of sugar substitute) which has been approved for use in the United States and throughout much of the world. It is 70% as sweet as table sugar yet it is virtually non-caloric, does not affect blood sugar, does not cause tooth decay, and is absorbed by the body, therefore unlikely to cause gastric side effects unlike other sugar alcohols. Under U.S. Food and Drugposits in the United States, Xuyi attapulgite products. Administration (FDA) labeling requirements, it has a caloric value of 0.2 calories per gram (95% less than sugar and other carbohydrates), but other countries such as Japan label it at 0 calories.

e. Sucralose or Splenda(Brand Name: - D-et)

Discovered in 1976, sucrose is 600 times sweeter than sugar and does not metabolize to produce energy, thus it does not contain calories. It is the only low calorie sweetener that is made from sugar, which has been changed so passes through the body unchanged and unmetabolized. Substituting for three alcohol groups on the sugar molecule with three chlorine atoms creates sucralose. It is heat stable and can be used in cooking and baking or anywhere on would use sugar without losing its sweetness. Sucralose is currently used in more than 30 countries and the FDA approved it in 1998 as a table top sweetener. It has been studied for more than 20 years, and 110 published animal and human safety studies have concluded that sucralose is safe for everyone to consume. Since, chlorine is something we consume every day in our water and other foods we eat, it is safe in this formulation. As a result, sucralose does not require any warning labels.

Sweetness Receptor Site

The drastically increased sweetness of sucralose is due to the structure of molecule. In the case

of sucralose, the two chlorine atoms present in the fructose portion of the molecule lead to more hydrophobic properties on the opposite side of the molecule (upper left), which extends over the entire outer region of the fructose portion o the sucralose molecule.

Area (AH+): This area has hydrogen available to hydrogen bond to chlorine attached to the glucose bottom portion of the molecule.

Area (B-): This area has a partially negative oxugen available to hydrogen bond to the partially positive hydrogen of an alcohol group.

Area (X): This area is more or less perpendicular to the other two ares interacts through hydrophobic or non-polar properties to the fructose portion of the as previously noted molecule[19.]

f. Acesulfame potassium(Brand Name: Sunett)

Chemical Structure of Acesulfame Potassium

Acesulfame K is 180-200 times sweeter than sucrose (table sugar), as sweet as aspartame, about half as sweet as saccharin, and one-quarter the sweetness of sucralose. Like saccharin. It has a slightly bitter aftertaste, especially at high concentrations. Kraft Foods has patented the use of sodium ferulate to mask acesulfame's aftertaste. Alternatively, acesulfame K is often blended with aspartame or other sweeteners. These blens are reputed to give a more sugar-like taste where each sweetener masks the other's aftertaste, and to exhibit a synergistic effect wherein the blend is sweeter than its components. Popular products containing acesulfame K include Diet Rite Cola, Fruit Shoot, Pepsi Max, Coca-Cola Zero, Fresca, Diet Coke with Slenda, Sprite Zero, Powerade, Trident gum, Wrigley's Spearmint gum, some SoBe products, XS Energy Drink, Propel Fitness Water, Sugarfree Red Bull, Diet Lipton Green Tea with Citrus, Diet Arizona Energy Drinks, Danone Silhouette spring water-based beverages, Presidents Choice "PC 0 Cola", Nestle Natural Fruit Flavored Water Beverags, Sugarfree sugarfree Jell-O, Monster Energy low carb, and Equal table sweetener. In carbonated drinks it is almost always used in conjuction with another sweetener, such as aspartame or sucralose[19.]

g. Alitame(Brand name: Aclame)

Alimate is an artificial sweetener developed by Pfizer in early 1980s and currently marketed in somecountries under the brand name Aclame. Like aspartame, alitame is an aspartic acid-containig are not sweet, but the unexpected discovery of aspartame in 1965 led toa search for similar compounds that shared its sweetness. Alitame is one such second- generation dipeptide sweetener. Neotame, developed by the owners of the Nutrasweet brand, is another. Alitame is an intense sweetener, with sweetness potency 2000 times greater than that of sucrose. It is a dipeptide of Laspartic acid and D-alanine, with a terminal Nsubstituted tetramethylthietanyl-

amine moiety.

Description: Discovered by Pfizer, Inc., alitame (brand name AclameTM) is a sweetener formed from the amino acids L-aspartic acid and D-alanine, and a novel amine.

Relative Sweetness: 2,000 times sweeter than sucrose.

Metabolism: The aspartic acid component is metabolized normally. The alanine amide passes through the body with minimal metabolic changes. Alitame is such an intense sweetener: its caloric contribution to the diet is insignificant.

Limitations: Though alitame has excellent shelf life, prolonged storage in some standard acidic solutions at elevated temperatures may result in off-flavors.

Application: Alitame has the potential to be used in almost all ares where sweeteners are presently used e.g., baked goods and baking mixes, hot and cold beverages, dry beverage mixes, milk products, frozen desserts and mixes, toiletries and pharmaceuticals.

Safety: Extensive animal and human studies have been conducted to support the safety of alitame. The petition for regulatory approval demonstrates its safety for human consumption.

Status: A petition for alitame's use in a broad range of foods and beverages has been foled in the U.S. Alitame is approved for use in a variety of food and beverage products in Australia, New Zealand, Mexico and the people's republic of China. Approval also is being sought worldwide[19.]

h. Thaumatin

Thaumatin is a low-calorie (virtually calorie-free) protein sweetener and flavours modifier. The substance is often used primarily for its flavors modifying properties and not exclusively as a sweetner. Totally natural, thaumatin is metabolized by the body as any other dietary protein. Within West Africa, the katemfe fruit has been locallycultivated and used to flavor foods and beverages for some time. The fruit's seeds are encased in a membranous sac, or aril, that is the source of thaumatin. In the 1970s, the Talin Food Company of Merseyside, in the United Kingdom, began extracting thaumatin from the fruit and selling it under the trade name Talin. In 1990, researchers at Unilever reported the isolation and sequencing of the two principal proteins found in thaumatin, which they dubbed thaumatin in genetically engineered bacteria[19.]

10) Flavorant & act as antioxidant

Citrus Bioflavonoids

Water–soluble citrus bioflavonoid can be readily added to beverages, candies, and chewing gum to enhance the beneficial effect of bioflavonoid. Bioflavonoid save well-documented anti-oxidant effect and are widely used to enhance vascular system health. The bulk of this important class of nutrients is lost when citrus fruit is made into juice-but now you can enhance your

product and restore some of those precious nutrients[23.]

Carob powder

Carob powder comes in light , medium and dark roast and can be tailored to match cocoa powder particle size and flavor thus facilitating ease of application and compatibility. Carob powders are low in fat, absent in cholesterol, high in dietary fiber and contain beneficial anti oxidants. Carob is also theobromine and caffine free.

Curcumin

This GRAS ingredients use dates back to ancient times. Its anti-inflammatory and anti antioxidant properties have been the focus of many studies. Curcumin standardize to 95% curcuminoids in power & granular forms.

Neohesperidin

This GRAS citrus bio flavonoid is a grate flavor modifier and enhancer, particularly for fruit flavors. It enhances the fruiter notes and some of the more subtle flavors, while subduing the more dominant acid notes . it is use in beverages, dairy product, confections, table top sweeteners, snacks, and most fruit based products, it also masks the off tastes of synthetic sweeteners[23.]

INTERACTIONS

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:

1. Drug – Excipient interaction[24-28]

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 N chemical degradation etc.

Drug excipient interactions are further classified as

- Physical interactions
- Chemical interactions
- Biopharmaceutical interactions

2. 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.

3. 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.

4. 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.

5. Excipient Excipient interactions [28, 29, 30, 31, 32, 33, 34, 35]

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. 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 coprocessed 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.

a. 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.

b. 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.

6. Package –Excipient interactions[36-39]

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.

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