

**New pharmaceutical excipients in solid dosage forms – A review**

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Abstract

The objective of a medicinal formulation development project is to deliver drug to the patient in the required amount, at the required rate, consistently within a batch, from batch to batch, and over the product's shelf life. To produce a drug substance in a final dosage form requires pharmaceutical ingredients. In selecting excipients for pharmaceutical; dosage forms and drug products the development pharmacist should be certain that standards exist and are available to assure the consistent quality and functioning of the excipient from lot to lot. The development of new materials for use as pharmaceutical excipients requires the demonstration of the absence of toxicity and freedom from adverse reactions. The selection and testing of nonactive ingredients or excipient in the design of drug dosage form present to the formulator the challenge of predictive foresight. While the ability to solve problems when they occur is a valuable attribute, the ability to prevent the problem through adequate experimental design is a virtue. Newer excipients provide the means for simplifying formulation development, and improving overall operational costs while preserving the quality that is expected by the industry. The present review focus on such newer Excipients which have proved their potential in developing efficient solid dosage forms.

Key-Words: Pharmaceutical excipients, Nonactive ingredients, Solid dosage form

Introduction¹⁻²

Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form.^{1, 2} Excipients play a wide variety of functional roles in pharmaceutical dosage form, including:

- Modulating solubility & bioavailability of APIs,
- Increasing the stability of active ingredients in dosage forms,
- Helping active ingredients maintains preferred polymorphic forms or conformations,
- Maintaining the pH and /or osmolarity of the liquid formulations,
- Acting as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and tablet disintegrants,
- Preventing aggregation or dissociation (e.g. of protein and polysaccharide actives),
- Modulating immunogenic responses of active ingredients (e.g. adjuvants), and more.²

Approval of excipients

Under U.S. law, an experiment, unlike an active drug substance, has no regulatory status and may not be sold for use in food or approved drugs unless it can be qualified through one or more of the three U.S. Food and Drug administration (FDA) approval mechanisms that are available for components used in food and/or finished new drug dosage forms. These mechanisms are:

- Determination by FDA that the substance is "generally recognized as safe" (GRAS) pursuant to Title 21, U.S. Code of federal regulation, parts 182, 184 or 186 (21 CFR182, 184 & 186) ;
- Approval of food additive petition as set forth in 21 CFR 171; or
- The excipient is referenced in, and part of, an approved new drug application (NDA) for a particular function in that specific drug product.

Excipients contained in over-the-counter (OTC) drug products subject to FDA monographs referenced in 21CFR parts 331-358 must comply with the requirements in 21CFR 330.1 (e) which reads as for "The product contains only suitable inactive ingredients which are safe in the amounts administered & do not interfere with the effectiveness of the preparation or with suitable test or assays to determine if the product meets its professed standards of identity, strength, quality, & purity. Color additives may be used

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only in accordance with section 721 of the act & subchapter A of this chapter.²

Functionality and performance of excipients

The objective of a medicinal formulation development project is to deliver drug to the patient in the required amount, at the required rate, consistently within a batch, from batch to batch, and over the product's shelf life.

The US Food & Drug administration's Quality in the 21st century initiative, which includes the quality by design (QbD) & process analytical technologies (PAT) initiatives, requires that the pharmaceutical industry better understand its product formulations & manufacturing unit processes. In addition, ICH Q8-Pharmaceutical Development (also issued by FDA as Guidance for Industry), links in to the common documents (CTD) & suggest the need for greater understanding in the design & development of pharmaceutical formulation of formulation & processes. Consequently, industry is expected to demonstrate that it understands its formulations & process & can define the appropriate design space that will allow the routine manufacture of pharmaceutical products that deliver the correct amount of drug to the patient, at the required rate, consistently from dose to dose & from lot to lot, over the shelf-life of the product (i.e., "a robust formulation").

A robust formulation may be defined as: A formulation that is able to accommodate the typical variability seen in the API, excipients, & process without the manufacture, stability, or performance of the product being compromised. The larger the design space, the more likely we will produce a robust formulation.

Most formulations have three components: the active pharmaceutical ingredient drug (API), the excipients (s), & the manufacturing process (es). In some instances, there is the fourth component: the primary packaging. To understand product variability we must understand input variability. The variability of API, excipients & process parameters are obvious components of the overall variability. Nonetheless, other factors could affect the manufacture, stability, or performance of the product. For example, how materials are fed into the unit process, how materials interact together during processing, & how an operator carries out the operations can all affect the final product attributes.

Thus, for a given formulation & process, we must understand variability in the raw materials & their interactions to define the process & then demonstrate sufficient understanding of the process to define the design space for the product.

Two main approaches can be used to achieve consistent products. The traditional approach is to specify the input parameters more tightly, particularly the excipients & process (but also the API), & to limit the product variability by limiting the input variability. This approach does not address the variability in interactions. This interaction factor, the sum of all the interactions, also can cause problems. A second, more modern approach is to accept that there will be input variability & work to gain a sufficient understanding of the process to define an appropriate process end-point. A particular unit process is thus continued until the end-point is achieved. This second approach seems better matched to the intent of the QbD initiative, & also is likely to give a larger design space, & thus, a more flexible formulation & process.

Functionality,functionality-related characteristics, and excipients performance

Functionality applies equally to APIs & excipients.

Functionality has been defined as: a desirable property of a [material] that aids manufacturing & improves the manufacture, quality or performance of the drug product. In the context of the pharmaceutical formulation & products, each formulation will have its own peculiar requirements for functionality. Thus, functionality can only be properly tested by the manufacture & subsequent testing of a batch of product. This process is less than desirable.

An approach currently in vogue is to identify a surrogate test, usually a physical test, that bears some relations to the required functionality. The European pharmacopoeia defines such properties as they relate to pharmacopoeia materials as follows: physical &/or physicochemical characteristics those are critical to the typical uses of an excipients. Most excipients are included in many different products & may impart several different types of functionality depending on a particular type of application.

In some instances, product manufacturers have established a correlation between a product &/or manufacturing performance & some physicochemical property of a key ingredient. In such circumstances, the product manufacture may request an additional test to be included in its specification for that ingredient.

The perils of excipient lot selection

As a short-term fix for existing formulations or, in some cases, as a longer-term strategy, excipient companies are frequently approached by customers to supply material to a tighter specification than regular material. It is important to remember that many excipients are not produced using simple batch processing, most of the large use excipients are produced using some form of continuous

processing(24-7 operation). For such manufacture, the lot number refers to define time in the plant, & the lot size is governed by the risk to the manufacturer of a recall. The capacity of such manufacturing plants is rated in thousands of tone per annum. The plants are operated to produce material that passes specification, but there is an inherent variability in the output that cannot be avoided. In addition, the pharmaceutical usage of many excipients is small in comparison with the overall output.

If the excipient manufacturer is approached to undertake extra testing to select the lot(s) to be delivered to a customer, they assumed that & upper & lower limits exist for the “functionality” parameter (performance parameter or functionality-related characteristic). In cases for which there is only an upper or a lower limit, the following discussion may be amended appropriately. The effect of the variability is small in relation to the relation specification. In this situation, there a negligible effect for either the excipient manufacturer or the user beyond the cost of the extra testing. Nonetheless, this is frequently not the case. The alternative scenario whereby only a proportion of batches meet the criteria. For example approximately 50% of batches meet the criteria. The schematics are idealized & show a very regular cyclical variation. Reality is not as regular, & the issue of how many lots must be tested to identify one lot that meets criteria is economically important. In this example, three or four lots may need to be tested for each order.

In the required specification is at one or other extreme of the observed variability. In these examples, about 10% of excipients lots would meet specification, and 10 or more lots may need to be tested for each other. In addition, the continuity of supply is an issue when lot selection is used. The excipients manufacturer may be forced to set aside particular lots for the particular customer to maintain supply continuity, which adds to the costs associated with the order. The excipient user has two options: to change to a new supplier of the NF material or continue to purchase the material from the original supplier & do the necessary testing in- house & undertake the necessary auditing of the excipient manufacturing site on a regular basis. A major supplier of corn syrup NF cased supplying material with the NF designation although it continued to manufacture to the same specification, in the same plant, & under the same quality management system. NF-quality propylene glycol stearate is no longer available. Propylene glycol stearate may not be a large volume excipient but it was a major headache for companies using it in either investigational medicinal or commercial products. The corn syrup issue had wider ramifications because many

oral solution & suspension products are formulated using corn syrup. In the U.S., FDA’s remit is to safeguard the public health. The USP-NF supports this effort through the development of official standards for pharmaceutical materials & products. The pharmacopoeia is concerned with the purity, safety, & efficacy of drugs & medicines. For excipients, the issues are really safety & adulteration. Excipients are seldom “pure” materials. Most excipients, with the exceptions of those intended for parenteral or other similar products are mixtures of materials. Their functionality arises from the presence of other components that are crucial to the performance of the excipient. These other components have been variously termed “essential minor components” or “functional components”. In the USP-NF, they are referred to as “concomitant components.” We must continue to develop our understanding of both material and unit processes, & how they interact. Some recent initiatives such as the National Institute of Pharmaceutical Technology and Education may help. The pharmacopoeias can also help by providing the necessary standardized method for performance tests.

There appears to be broad agreement that such tests should not be mandatory & should not have limit imposed by the pharmacopoeias. Nonetheless, there seems to be disagreement on how to incorporate such tests in to the pharmacopoeias. The European pharmacopoeia appears to favor designating the appropriate tests in the individual monographs but including the list in a nonmandatory section of the monograph. The USP favors a nonmandatory general information chapter approach based on what types of tests might be applicable for specific application rather than a specific excipients. TriPEC’s (an umbrella international organization comprising the three regional excipients council: the international pharmaceutical excipients council of the America, the international pharmaceutical excipients council of Europe, & the Japanese Pharmaceutical Excipients Council). Position is straightforward. A harmonized approach is needed. Whether all these different views can be resolved easily remains to be seen.

Performance tests (functionality related characteristic) will be an issue for the foreseeable future. We must establish a harmonized approach to how they are incorporated into the pharmacopoeias & what tests are appropriate for which applications. There probably will not be any broad “fixes”, & we must continue to develop our knowledge & understanding of the materials & processes & how they interact to produce medicines that consistently meet the public’s expectations.

Economic issues must also be addressed. There is no advantage in having the best monograph possible if we cannot get material that conforms to it. Robust formulation and processes will also be a critical issue moving forward, particularly in the context of QbD & the trend toward less-soluble drugs for which formulation robustness is more critical. Although it is outside the scope of this article, the issue of how we will train our future formulation & development scientists also must be addressed.³

Drug-excipient compatibility studies

In the solid dosage form the drug is in intimate contact with one or more excipient; the latter could affect stability of drug. Knowledge of drug excipient interaction is therefore very useful to the formulator in selecting appropriate excipients. These information may already being existence for known drug. For new drug or excipients the preformulation scientist must generate needed information.

A typical tablet contains binders, lubricants, disintegrate, fillers etc. compatibility screening for a new drug must consider two or more excipients for each class. The ratio of drug to excipients use in these tests is very much subject to the discretion of the preformulation scientist. It should be consistent with the ratio most likely to be encountered in the final tablet and will depend on the nature of the excipient and the size and the potency of the tablet. Often the interaction is accentuated for easier detection by compressing or granulating the drug-excipient mixture with water or other solvents. The three techniques commonly employed in drug-excipient compatibility screening are chromatographic technique using either HPLC or TLC, differential thermal analysis, and diffused reflectance spectroscopy.

1. Chromatography in drug-excipients compatibility study
2. Differential thermal analysis in drug-excipient compatibility study
3. Diffused reflectance spectroscopy¹

An **excipient** is an inactive substance used as a carrier for the active ingredients of a medication. In many cases, an "active" substance (such as aspirin) may not be easily administered and absorbed by the human body; in such cases the substance in question may be dissolved into or mixed with an excipient. Excipients are also sometimes used to bulk up formulations with very potent active ingredients, to allow for convenient and accurate dosage. In addition to their use in the single-dosage quantity, excipients can be used in the manufacturing process to aid in the handling of the active substance concerned. Depending on the route of administration, and form of medication, different

excipients may be used. For oral administration tablets and capsules are used. Suppositories are used for rectal administration. Often, once an active ingredient has been purified, it cannot stay in purified form for long. In many cases it will denature, fall out of solution, or stick to the sides of the container. To stabilize the active ingredient, excipients are added, ensuring that the active ingredient stays "active", and, just as importantly, stable for a sufficiently long period of time that the shelf-life of the product makes it competitive with other products. Thus, the formulation of excipients in many cases is considered a trade secret. Pharmaceutical codes require that all ingredients in drugs, as well as their chemical decomposition products are identified and guaranteed to be safe. For this reason, excipients are only used when absolutely necessary and in the smallest amounts possible.⁹

Classification of excipients in solid dosage forms

Additives are usually classified according to some primary function they perform in the pharmaceutical dosage form. Many additives will also often have secondary functions, which may not be of a beneficial nature in good, solid design of beneficial, while others may impair dissolution. The most effective lubricants are water repellent by their nature, which may retard both disintegration and dissolution.¹ The two major classifications of additives by function include those which affect the compressional characteristics of the pharmaceutical dosage form:

- ▶ Fillers and Diluents
- ▶ Binders and Adhesives
- ▶ Glidants
- ▶ Lubricants
- ▶ Antiadherents

And those which affect the biopharmaceutics, chemical and physical stability, and marketing consideration of the pharmaceutical dosage form:

- ▶ Disintegrants
- ▶ Coatings

Changing the dissolution rates of active species

- ▶ Colours
- ▶ Flavours
- ▶ Sweeteners
- ▶ Preservatives
- ▶ Sorbents¹

Fillers and diluents

Fillers fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the fillers make it possible for the final product to have the proper volume for patient handling. A good filler must be inert, compatible with the other components of the formulation, non-hygroscopic, soluble, relatively

cheap, compactable, and preferably tasteless or pleasant tasting. Plant cellulose (pure plant filler) is a popular filler in tablets or hard gelatin capsules. Dibasic calcium phosphate is another popular tablet filler. A range of vegetable fats and oils can be used in soft gelatin capsules. Other examples of fillers include: lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate.

Binders

Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets. Binders are usually starches, sugars, cellulose or modified cellulose such as microcrystalline cellulose, hydroxypropyl cellulose, lactose, or sugar alcohols like xylitol, sorbitol or maltitol. Binders are classified according to their application:

- Solution binders are dissolved in a solvent (for example water or alcohol) and used in wet granulation processes. Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, starch, sucrose and polyethylene glycol.
- Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples include cellulose, methyl cellulose, polyvinylpyrrolidone, and polyethylene glycol.

Glidants

Glidants are used to promote powder flow by reducing interparticle friction and cohesion. These are used in combination with lubricants as they have no ability to reduce die wall friction. Examples include colloidal silicon dioxide, talc, and etc.

Lubricants

Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall. Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

Antiadherents

Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches.

Disintegrants

Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing

the active ingredients for absorption. Disintegrant types include:

- Water uptake facilitators
- Tablet rupture promoters

They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, thereby facilitating dissolution. Examples of disintegrants include: cross linked polyvinyl pyrrolidone, sodium starch glycolate, cross linked sodium carboxymethyl cellulose (crosscarmellose).

Coatings

Tablet coatings protect tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow. For most coated tablets, a cellulose (plant fiber) film coating is used which is free of sugar and potential allergens. Occasionally, other coating materials are used, for example synthetic polymers, shellac, corn protein zein or other polysaccharides. Capsules are coated with gelatin.

Colours

Colours are added to improve the appearance of a formulation. Colour consistency is important as it allows easy identification of a medication.

Flavours

Flavours can be used to mask unpleasant tasting active ingredients and improve the likelihood that the patient will complete a course of medication. Flavourings may be natural (e.g. fruit extract) or artificial. -a bitter product may use mint, cherry or anise

-a salty product may use peach, apricot or liquorice

-a sour product may use raspberry or liquorice

-an excessively sweet product may use vanilla

Preservatives

Some typical preservatives used in pharmaceutical formulations are

- antioxidants like vitamin A, vitamin E, vitamin C, retinyl palmitate, and selenium
- the amino acids cysteine and methionine
- citric acid and sodium citrate
- synthetic preservatives like methyl paraben and propyl paraben.

Sorbents

Sorbents are used for tablet/capsule moisture-proofing by limited fluid sorbing (taking up of a liquid or a gas either by adsorption or by absorption) in a dry state.

Sweeteners

Sweeteners are added to make the ingredients more palatable, especially in chewable tablets such as antacid or liquids like cough syrup. Therefore, tooth decay is sometimes associated with cough syrup abuse. Sugar can be used to disguise unpleasant tastes or smells.

New pharmaceutical excipients**Direct compressible diluents****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 nonhygroscopic 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.⁴

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.

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.

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.

PROSOLV® Characteristics

- High Compactibility
- High Intrinsic Flow
- Enhanced Lubrication Efficiency
- Improved Blending Properties

PROSOLV® Benefits

PROSOLV® provides tremendous benefits throughout the product lifecycle in:

- Formulation
- Manufacturing
- Marketing

Silicified Microcrystalline

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

High functionality excipients are inactive ingredients that meet four criteria:

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.⁸

Poly Vinyl Pyrrolidone + Vinyl acetate

Brand name: PLASDONE S-630

Physical & chemical properties

Hydrophilicity/ hydrophobicity

Addition of vinyl acetate groups to the vinylpyrrolidone 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.⁶

Fillers and binders property together

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.

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: 32-35°
<160micro 35-65% Density poured :380(g/l)

<200micro>=80% Density tapped : 500(g/l)
(Air jet sieve) Hausner ratio : 1.2

Applicatons

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

Microcrystalline cellulose+lactose

Brand name: MICROCELAC 100

Particle size distributon

MICROCELAC 100 is spray dried compound consisting of 75% alpha-lactose monohydrate & 25% Microcrystalline cellulose DRY MATTER. Both filling & binding propertties 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: 34°
<160micro 70% Density poured :500(g/l)
<250micro>=90% Density tapped : 610(g/l)
(Air jet sieve) Hausner ratio : 1.16

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.

Disintegrants

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.⁴

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.⁴

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 flakes 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 polysaccharides: cellulose, hemicellulose, protein, gum and mucilage. It is ideally suited for low calorie(2 kcal/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 absorpion 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

Sodium Starch Glycolate

Brand name: VIVASTAR

VIVASTAR (Sodium Starch Glycolate)-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.

Lubricants & plasticizers

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

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.⁷

Dibutyl Sebacate.

Formula: $[(CH_2)_4CO_2(CH_2)_3CH_3]_2$

Mol Wt.-314.46

Synonyms:-Sebacic acid , Dibutyl Ester, Bis(N-butyl)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 selections⁹.

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

Lubricant

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

Pellets

Can be incorporated into pellets via extrusion/spheronization. Microcrystalline cellulose pellets containing Compritol® 888 ATO, can be compressed into tablets¹⁰.

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 sexceptionally 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.¹¹

Glidants

Attapulgit

Attapulgit 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. Attapulgit has very good colloidal properties such as :specific features in dispersion, high temperature endurance. Furthermore, attapulgit has certain plastic and adhesive characters. Its ideal molecular formula is :Mg₅Si₈O₂₀(HO)₂(OH)₄.4H₂O. Attapulgit clay mineral resources distributin only several countries in the world at the present. Attapulgit reserve capacity of Xuyi contains the 70% in China, and 35% in the world. Compared to the largest commercial attapulgit deposits in the United States, Xuyi attapulgit products

have the following special features: Because the geological conditions under which Chinese attapulgit was deposited are different from that of the USA attapulgit deposits, our attapulgit products have very low grit (percentage retained on a 325 mesh wet screen), low free silica content, and low carbonate content.

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 dextrans are known as cyclodextrans. They are formed by enzymatic degradation of starch by certain bacteria, for example Bacillus macerans. Cyclodextrans 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.⁹

Microcrystalline cellulose and Carboxy methyl cellulose sodium

Brand name: VIVAPUR® MCG

Thickener and Stabilizer for Pharmaceutical and Food Products

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.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

pearl effect will be reduced or not visible at all. **CANDURIN® particle size:** Small particle-sized pigments (sheen range, 5 - 25 μm) result in an increased hiding power in combination with satiny pearl effect. The largest particle sizes (sparkle range, 10 - 150 μm) exhibit eye-catching glitter effects, whereas medium sized pigments (luster range, 10 - 60 μm) provide both, exquisite pearl luster combined with a medium hiding power resulting in uniform luster effects.

Sweetners

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-O-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 the ester isomer disaccharide alcohol 1-O-D-glucopyranosyl D-mannitol dehydrate (1,1 GPM dihydrate) and 6-O-D-glucopyranosyl-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 substance.¹³

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.

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.⁹

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 Drug

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.

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 one 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 of 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 oxygen 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 areas and interacts through hydrophobic or non-polar properties to the fructose portion of the as previously noted molecule.⁹

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 blends 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 Beverages, Sugarfree sugarfree Jell-O, Monster Energy low carb, and Equal table sweetener. In carbonated drinks it is almost always used in conjunction with another sweetener, such as aspartame or sucralose.⁹

Alitame

Brand name: Aclame

Alitame is an artificial sweetener developed by Pfizer in early 1980s and currently marketed in some countries under the brand name Aclame. Like aspartame, alitame is an aspartic acid-containing and is not sweet, but the unexpected discovery of aspartame in 1965 led to a 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 L-aspartic acid and D-alanine, with a terminal N-substituted tetramethylthietanyl-amine moiety.

Description: Discovered by Pfizer, Inc., alitame (brand name Aclame™) 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 areas 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 filed 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.⁹

Thaumatococcus

Thaumatococcus is a low-calorie (virtually calorie-free) protein sweetener and flavors modifier. The substance is often used primarily for its flavor-modifying properties and not exclusively as a sweetener. Totally natural, thaumatococcus is metabolized by the body as any other dietary protein.

Within West Africa, the katemfe fruit has been locally cultivated 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 thaumatococcus. In the 1970s, the Talin Food Company of Merseyside, in the United Kingdom, began extracting thaumatococcus 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 thaumatococcus, which they dubbed thaumatococcus in genetically engineered bacteria.⁹

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 have 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.¹⁶

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 caffeine free.

Curcumin

This GRAS ingredient uses dates back to ancient times. Its anti-inflammatory and anti-oxidant properties have been the focus of many studies. Curcumin standardize to 95% curcuminoids in powder & granular forms

Neohesperidin

This GRAS citrus bioflavonoid is a great flavor modifier and enhancer, particularly for fruit flavors. It enhances the fruitier notes and some of the more subtle flavors, while subduing the more dominant acid notes.

it is used in beverages, dairy products, confections, table top sweeteners, snacks, and most fruit based products, it also masks the off tastes of synthetic sweeteners.¹⁶

Use as cores in sustained release formulation

Non-pareil seeds are specially designed spherical particles of uniform granules that are practically inert, odorless and tasteless. Non-pareil seeds are available in the following U.S. standard sieve sizes:

14-18 mesh sieve (1000-1400µm), 35-40 mesh sieve (425-500)

16-18 mesh sieve (1000-1180), 18-20 mesh sieve (850-1000)

30-35 mesh sieve (500-600), 40-60 mesh sieve (250-425)

20-25 mesh sieve (710-850), 25-30 mesh sieve (600-710) 16-20 mesh sieve (850-1180)

Non-pareil seeds are intended for use as cores in sustained release formulations. In this process, non-pareil seeds are the bases upon which drugs are coated and then given a protective barrier. A drug must then either diffuse through this barrier coat or the barrier layer must be dissolved away to release the drug.⁷

Stability enhancer in capsule

Super refined PEG 300, 400 & 600 are highly purified polyethylene glycols. Super refining is a technique that removes polar impurities, such as peroxide species, aldehyde and ketones. Removal of these polar impurities eliminates their adverse interaction with active pharmaceutical ingredients (APIs), thereby enhancing the stability of the drug and or the vehicle itself. In accelerated stability trials (50°C), Super Refined PEG 400 NF demonstrated a peroxide value at least 50% lower than a standard pharmaceutical grade both initially and after four weeks. Formaldehyde value after four weeks were at least 60% lower. Super Refining of PEGs also minimizes the potential for gelatin cross-linking. Impurities found in some standard pharmaceutical grades of PEGs can lead to stability problems in gelatin capsules due to the impurities cross-linking with the gelatin. Super Refining removes the impurities that cause this problem. Polyethylene glycols are widely used as excipients in a variety of pharmaceutical products, including topical, oral and parenteral preparations.¹⁴

Absorption enhancer

Super Refined Oleic Acid NF is a high purity lipid designed to aid drug delivery. Oleic acid can enhance transdermal drug transportation and is also employed in pulmonary and nasal delivery systems. By removing polar impurities including primary and secondary oxidation products, Super Refining of oleic acid ensures formulations have greater stability and reduced potential for cellular (skin) irritation, the company

claims. In vitro testing with Super Refined Oleic Acid NF, as compared with a standard, has shown a clear reduction in intercellular leakage – an indicator of skin irritation potential. This benefit offers the formulator the option of reduced skin damage for an equivalent formulation. Super Refined Oleic Acid NF is recommended as an absorption enhancer in topical, transdermal and oral dosages, an excipient in nasal and pulmonary metered dose inhalers (MDIs) and as a component of self-emulsifying drug delivery systems (SEDDS).²⁶

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Table 1: Description of Arbocel as a filler

Functional Filler: ARBOCEL© Newsletter (November 2006)

Grade	Average Particle Size by laser Diffraction (µm)	Bulk Density (typical)(g/cm ³)	Main Application
ARBOCEL®M80	60	0.22	Fine, fibrous grade of powdered cellulose, suitable for wet granulation.
ARBOCEL®P290	80	0.30	Fine grade with increased density and improved flow. Suitable for wet granulation and direct compression, especially in combination with MCC.
ARBOCEL®A300	250	0.35	Coarse grade with excellent flow properties used in direct compression and for capsule fillings.

Table 2: Me-OH based and Et-OH based Superdisintegrants

Me-OH based	Et-OH based	pH Value	Main Application
VIVASTAR®P		5.5 - 7.5	Superdisintegrant with a rapid and high degree of swelling for capsule formulations. Especially for poor water soluble actives and tablet matrices with lower pH values.
	EXPLOTAB®	5.5 - 7.5	Superdisintegrant with a rapid and high degree of swelling for capsule formulations. Especially for poor water soluble actives and tablet matrices with higher pH values.
VIVASTAR®PSF		5.5 - 7.5	Special grade with very low methanol content. Especially suited for alcohol and moisture sensitive actives.
	EXPLOTAB®CLV	5.5 - 7.5	Special grade with increased number of crosslinkings. Especially suited for wet granulation applications.
VIVASTAR® Low PH		3.0 - 5.0	Special grade with low pH value. Complies with Typ (B) Ph. Eur, NF.
	EXPLOTAB® Low PH	3.0 - 5.0	Special grade with low pH value. Complies with Typ (B) Ph. Eur, NF.

Table 3: Applications of CANDURIN®

Product is transparent e.g. jelly gums, hard boiled candies, soft drinks, desserts, gelatin capsules, cake glazing etc.	CANDURIN® can be added directly to the product mass.
Product is not transparent but stable enough to be coated e.g. tablets, sugar coated products, chewing gums, chocolate, ice cream, marzipan, liquorice, cereals, bakery products etc.	CANDURIN® is applied within a thin, transparent film on the surface of the product.
Product cannot be coated but is semi-transparent e.g. icings, icing sugar, fat coatings/fillings etc.	To compensate for reduced product transparency, a higher amount of CANDURIN® has to be added to the product.
Product cannot be coated and is not transparent e.g. nut paste, yoghurt, milk etc.	Use of CANDURIN® not possible or economical.

Table 4: Applications of Xylitol

Chewable tablets	Diluent to impart sweetness. Binder to impart hardness to tablets.
Sugar –free Lozenges	Excellent compressibility, sweet, cooling taste, low calorie, and noncalorigenic
Sweetener	Has a sweet, cooling taste, along with low calorie, and non- calorigenic properties