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Formulation Additives Used in Pharmaceutical Products: Emphasis on Regulatory Perspectives and GRAS

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22.1 INTRODUCTION: BACKGROUND OF ADDITIVES

Drugs are always administered in the form of a dosage form that consists of two basic parts: the active pharmaceutical ingredient (API) and different fraction and changeable figure of the additive. Additives are pharmacologically inactive supplies from a different genesis (biological, minerals, chemical, or synthesis-based, etc.). Most pharmaceutical dosage forms could not be finished without the use of additives. The quantity of additives in the formulation can be superior to API and depending on whether they are organic or inorganic molecules may be of different character, up to highly complex materials.

Initially, the safety of additives was ignored and no distinct safety evaluation was usually performed because they were deemed as inactive. But they are not dormant; they have considerable impact on the drug substance safety and effectiveness (bioavailability and stability) and also on a dosage form. Several exemplars have demonstrated that partial understanding of additives functionality can directly affect process control and final product eminence. Some additives are inert in nature but some can form toxic reactions in the concentrations used in dosage form.

The Federal Food, Drug, and Cosmetic Act of 1938 (the Act) was sanctioned after the disaster of sulfanilamide in 1937 in which an additive which was not tested for effectiveness was accountable for the casualty of several children who taken the formulation (U.S. Department of Health and Human Services, Administration, 2005). Earlier it was

considered that additives, or their impurities, can be linked with unfavorable events, either by direct action or by creation of undesirable adducts. However this fact has been distorted over times and at present it is accepted that the added substances' lethality is not immaterial and should not be disregarded, because it could directly interact with the pharmaceutical ingredient, with the body or with other additives, which may lead to a potential change in the connection between toxicity and effectiveness (Tekade et al., 2018).

The hazard and advantage of using additives should always be assessed on the basis of not merely their manufacturing and quality but also of their safety and toxicity. Good Manufacturing Practices (GMPs), Toxicology Assessment, Good Laboratory Practices, and Good Distribution Practices requirements are needed for additives also like API or dosage form those pretense exceptional challenges in terms of attaining pharmaceutical grade material and in regulatory control.

As added substances are an indispensable piece of every single pharmaceutical plan it is significant for the pharmaceutical researcher to perceive the distinctive sorts/evaluations of added substances that are accessible. It is further fundamental to perceive whether new added substances will be necessary (understanding the cost, accessibility, and biopharmaceuticals) inside the definition and how these new added substances can get administrative approval. There are about 8000 nondynamic fixings being utilized as a part of food, makeup, and pharmaceuticals (de Jong, 1999).

Added substances makers, for the most part, supply their material to various end clients, i.e., pharmaceuticals, nourishment, corrective, and so forth. Henceforth, providers of added substances don't really know the last utilization of their items, i.e., it is regularly troublesome helping end clients select fitting evaluations and grades are frequently not between variable. However, added substances for pharmaceutical use may require additional quality, usefulness, and safety requirements.

There are no controls in most developed countries that address the enrollment of added substances as a different element. Presently, the Food and Drug Administration (FDA) investigates and facilitates the utilization of additives under same process as that of New Drug Application (NDA) process. Drug master file (DMF) for an additive is checked on just as a component of the NDA procedure. The FDA obviously supports the utilization of financially settled additives, nourishment added substances, and substances that have been assigned "Generally Recognized As Safe (GRAS)." The current regulatory methodology does not give a prepared procedure for picking up endorsement of new additives that are not as of now allowed in approved drugs (Steinberg et al., 1996).

Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (the Act) state that any substance that is deliberately added to food as a food additive, is obligated to premarket evaluation and guaranteeing by FDA unless the substance is recognized, as having been acceptably appeared to be safe under the circumstance of its planned use, or unless the use of the substance is generally excepted from the meaning of a food additive (Generally Recognized as Safe (GRAS) FDA, 2016).

22.2 ROLE OF ADDITIVES IN PHARMACEUTICAL FORMULATION

Pharmaceutical additives are secondary constituents present in both pharmaceutical formulation and over-the-counter (OTC) drug formulations. Additives are classified on the

bases of their function and interactions influencing drug administration due to their chemical and physicochemical properties. The major classes are the coating additives, emulgents, taste and smell-improvers, ointment bases, antioxidants, consistency or viscosity enhancers, and disintegrating materials. Few additives have more than one function, e.g., methylcellulose works as both coating material, viscosity enhancer, disintegrating agent, or binder in tablets (Kalász and Antal, 2006).

Additives carry out a key function in drug development operation in the formulation of stable dosage forms and in their administration. Their work is to take delivery of the dosage form with ease, to escalate the stability of active ingredients, to be used as filler so that it can properly fill a dosage form, or to serve as preservatives for enhancing the shelf life of the product or API

A direct selection of additive can even lead to harsh intoxications, as experienced by epileptic patients in Australia in the late 1960s who were using phenytoin capsules. The calcium sulfate that served as a diluent in the capsule had been substituted with lactose and this substitution was believed to be harmless. However, lactose aggravated an abrupt and massive release of phenytoin higher than the toxic threshold (Furrer, 2013).

Additive's functional roles in dosage form and on drug substance consist of:

- Influence on solubility and bioavailability of the active ingredient(s).
- Improving stability of the API in finished products and also inside the subject after administration.
- Preserve physiochemical property of drug substance.
- Work as preservatives, lubricant, adhesives, propellants, glidants, flavors, colors, disintegrant, diluents and bulking agents, fragrances, coating agents, sweetening agents, polishing agents etc.
- Protecting physical and chemical entity of dosage form.
- Amending predetermined physiological or immunogenic response toward API.
- Maintenance of the formulation for long period: Additives are incorporated in formulations which aid in the stability or enhance the time of the product in its original form for its shelf life period.
- To form bulk of content if API does not have required concentration for making a dosage.
- Get better patient acceptance.
- Helps in improving bioavailability of active constituents: In most of the cases, an API for, e.g., aspirin is poorly absorbed or soluble in body fluid easily. In these instances, additives are incorporated which support the absorption of the drug from the external environment to inside the body.
- Increase the safety and stability throughout the product shelf life.

22.3 CLASSIFICATION AND SOURCES OF FORMULATION ADDITIVES

The natural world has offered us an extensive assortment of substances to aid, improve, and maintain the health of patients. It can be direct or indirect. Mucilage and gums are naturally obtained for both new and old dosage forms. Natural substance have advantages over synthetic because of their chemically stability, nontoxicity, low price,

TABLE 22.1 Additives Classification on the Basis of Their Origin

Animal Origin	Vegetable Origin	Mineral Origin	Synthetic
<ul style="list-style-type: none"> • Stearic acid • Honey • Lactose • Gelatin • Musk • Lanolin, etc. 	<ul style="list-style-type: none"> • Turmeric • Guar gum • Acacia • Starch • Peppermint, etc. 	<ul style="list-style-type: none"> • Talc • Asbestos • Kaolin • Calcium phosphate • Silica • Paraffin, etc. 	<ul style="list-style-type: none"> • Polyethylene glycols • Boric acid • Saccharin • Polyethylene glycols • Polysorbates • Boric acid • Saccharin, etc.

TABLE 22.2 Additives Classification on the Basis of Their Therapeutic Value

Anesthetics	Laxatives	pH Modifiers	Astringent	Carminative	Nutrient Sources
<ul style="list-style-type: none"> • Chloroform, etc. 	<ul style="list-style-type: none"> • Bentonite • Psyllium • Xanthan gum • Guar-gum, etc. 	<ul style="list-style-type: none"> • Citric acid 	<ul style="list-style-type: none"> • Cinnamon • Alum • Zinc sulfate 	<ul style="list-style-type: none"> • Cinnamon water • Dill water • Anise water 	<ul style="list-style-type: none"> • Agar • Lactose, etc.

biodegradability, and they are commonly obtainable (Ramesh Kumar and Mohan, 2014). Categorization of additives can be done based on their source or the function they perform as:

22.3.1 Additives Based on Their Origin

Table 22.1 show different additives classified on the basis of their origin.

22.3.2 Classification of Additives Based on Their Functions

1. Additives for solid dosage forms: disintegrating agent, binders, plasticizers, etc., e.g., 5% starch paste acts as a binder in solid formulations, in dry form it works as disintegrant.
2. Additives for liquid dosage forms: solvents, antimicrobial agents, emulsifying agents, cosolvents, flavor, buffers, sweetening agents etc.
3. Additives for semisolid dosage form: gelling agent, preservative, emollients, suppository bases, solubilizing agents, etc.

22.3.3 Classification of Additives Based on Their Therapeutic Values

Table 22.2 shows different additives classified on the basis of their therapeutic value (Chaudhari and Patil, 2012).

22.4 PROCESSING OF ADDITIVES AS PER GOOD MANUFACTURING PRACTICE

GMP is that piece of value certification which guarantees that things are always conveyed and controlled to the quality standards apropos to their normal use. GMP is aimed chiefly to protect pharmaceutical production and human health from hazards, e.g., cross contamination and mix-ups of material due to false labeling. Under recent GMP rules and regulations, it is the pharmaceutical manufacturer who is accountable for the whole operations including the quality of material: API, the active, the additives, and the packaging materials ([Ptael and Chotal, 2010](#)).

Various regulatory agencies provide GMP guidelines for APIs. Unlike APIs, additives receive the slightest oversight from regulatory authorities. WHO published GMP Guidelines exclusively for additive manufacturers in 1999 and as a consequence of which the industry has to follow the guidelines which were not there in the past ([Silverstein, 2002](#)). UK based Pharmaceutical Quality Group (PQG) built “PS 9100:2002 Pharmaceutical Excipients” which includes both a GMP guide and an audit standard based on ISO 9001:2000 for additive regulatory and safety. In 2006, the International Pharmaceutical Excipient Council (IPEC) of Europe and America mutually published “Good Manufacturing Practices Guide for Pharmaceutical Excipients” ([IPEC, 2006](#)).

U.S. Pharmacopeia 31-NF 26 also cited a distinct chapter for GMP for Bulk Pharmaceutical Excipients ([Ptael and Chotal, 2010](#)). The regulatory process for additives was subject to enhancement in Europe by the introduction of new pharmaceutical laws in 2005. According to which the manufacturer has to go through GMP requirements for approval of new or novel material. Directive 2004/27/EC implements the follow-up of GMP for “certain additives” including:

- Additives from a Transmissible Spongiform Encephalopathy relevant animal species, with the exception of lactose.
- Additives resourced from animal or human which have contamination risk.
- Sterile additives.
- Additives without pyrogen and endotoxin.
- Specific additives like propylene glycol and glycerol.

Implementation of Additive GMPs to the manufacturing process initiated with an assurance concerning when full added substance GMP requirement must be connected. This starts with the review of the process involved. Working back from the packaging of finished additive, the manufacturer must decide at which step the final molecule is formed or where the last purification occurs. For polymeric additives, full GMPs are connected at the polymerization step on the grounds that after the polymer is formed there is no decontamination or reformulation technique to make it useful for work ([Katdare, 2006](#)).

22.4.1 Processing

An operation methodology normally can be categorized as one of two general categories: first is batch process, second one is continuous processing. There ought to be clear

and complete manufacturing guidance for the laborers to follow. There ought to be record generation which gives assurance that the work is done under guidelines. Added substance creation premises ought to be kept in a decent condition of repair and with incredible housekeeping in order to display a respectable appearance to administrative inspector, e.g., no peeling paint, loose insulation, rust, and so on. Premises should be inaccessible for insects and flies. Apparatus and equipment should be appropriately stored and cleaned on a regular basis. Pharmaceutical additives must be operated under appropriate instructions, equipment, base materials, quality test procedures, and records. Records and documents should be well maintained for the inspecting team whether all the instructions of GMP were followed or not.

22.4.2 Production Records

All records related to production are official reports. Each batch or product is mentioned with its barcode for ease of access with records of the date and time the testing was done. Individual pages of the records ought to contain numbering alongside the aggregate page number in the document. Blank production records should be issued to the production unit only as needed to control the number of copies, which will ease migration to a newer version when the production record is updated. Records ought to be archived with the finish of each progression. Records ought to never be closed until the errand has been executed nor should assignments be finished with the sections still to be completed. All notations expected on the production record must be either finished or the record should indicate why no entry was necessary. Finished generation records ought to be checked by a senior person to affirm that the record is done with no unfilled spaces and those reasonable entries have been added with a signature and date of checking.

22.4.3 Training of Employees

Workers ought to be capable of the employment they execute with training for their work and function. For work preparation, the coach should finish an agenda affirming that important training has been given to employees. At regular intervals, the trainer should convey the rules of GMP that are applicable to their process. Finally, they ought to be educated that it is important to inform their manager of any sickness, particularly open sores, that they have, which may contaminate the added substance and effect directly or indirectly the execution of its function.

22.4.4 Control of Raw Materials

Raw materials quality and processing should be done in a GMP consistent way. Crude materials ought to be acquired just from providers acknowledged by the Quality Unit. For raw commodities whose feature is vital to conformance of the added substance to compendia or particular necessities, or to execution desires, the provider endorsement methodology ought to be an amalgamation of a visit to the site and an appraisal of quality of the crude material. For other crude materials, it should be of prediscussed specification and

quality. GMP implementation and quality testing prevent the product from adulteration and significant substances causing impurities that might be there in the crude material. Labeling of raw material should be adequate to prevent the mix up of materials in processing. Each part of a crude material ought to be inspected and the research facility should do no less than a personal investigation notwithstanding confirmation from the providing Certificate of Analysis (COA) to verify the added additives from any supplier. Consumable water is imperative wherever water makes contact with the materials amid handling, specifically the completed added substance atom. It is desirable to acquire consumable water from a municipal corporation, which can give a certificate for the water regarding the Environmental Protection Agency (EPA) requirement for consumable drinking water.

22.4.5 Preventing Contamination

During the production of pharmaceutical additives contamination must be prevented, starting with the packaging of crude materials of the additive through to the final container. In general, problems emerge for two reasons: introduction of the additives to the outside environment during production and defects in the machine. For the most part amid the synthesis of additives, the danger of environmental contamination just arises during the charging of crude materials, additives, or preparing aids, or whilst filling the final container. So special care and measures should be adopted to prevent contamination of the additive at all phases of production caused by environmental factors. Sources of contamination arise from dust or other chemical processing, nearby fields, flying insects, and processing fumes. Mainly environmental contamination occurs in the packaging room so the packaging process should be done under a enclosed air-filtered room. The enclosed packaging room must be built of washable walls, floor, and ceiling. It is recommended that rooms have an air filtering system in which air is passing through a 2 mm filter operating at 95% efficiency with about 20 air changes per hour and there must be an uncontaminated indefinite interval of time before every packaging operation.

The second risk or source of contamination is "operating equipment." Equipment leads to additive contamination by two means: cross-contamination due to use of the other processing machine, or due to the equipment itself, e.g., corrosion or damage. It can be possible for the same equipment to be used for different chemical moieties, so the manufacturer should take care of cross-contamination by cleaning the equipment at every change of product processing of a new chemical moiety. Maintenance like greasing, oil changing, adding lubricant should also be done regularly to prevent both equipment working problems and processing contamination problems.

22.4.6 Qualification of Manufacturing Equipment

At the first stage from where the procedure of overall GMP conformity commences, the additive has to be processed in validated apparatus by means of a validated production method. Testing and cleaning must be completed using a validated method. The qualification activity for equipment will be described by a protocol used in the process. Qualification of

apparatus starts with an installation qualification (IQ), which is followed by an operation qualification (OQ) and wrapped up with performance qualification (PQ). In IQ, equipment has been introduced legitimately, as specific either to the equipment producer or by the buyer. OQ shows that the apparatus works as anticipated. The capacity of the apparatus is contrasted with the apparatus maker's specification or as indicated by the additives producer's outline design. At last, the PQ demonstrates that the equipment performs and works as proposed. In processing, PQ includes running a test substance, e.g., water or a production batch. So additives production should use a qualified and an approved procedure. For IQ and OQ, an approved technique is readied that shows how maintenance and generation records will be utilized to give confirmation that the equipment was introduced appropriately and is in action as planned. At that point, the technique/convention is implemented by investigating the maintenance and production paperwork for the supporting information. At last, information is framed stating that establishment and operation of the equipment conforms to protocol necessities.

22.4.7 Process Validation

After working on IQ, OQ, and PQ of equipment, process validation can proceed. There should be creation of a master validation plan (MVP) that will describe the validation method like retrospective, concurrent, or perspective which will show the preparing stages that need validation, and establishes an arrangement for implementation of every validation. For the most part, the MVP covers the preparing steps that affect additives quality for the purpose of the start of full GMP consistency. The most settled validation strategy is perspective. This validation approach takes a shot at the finishing of the validation before production starts and the item marketed so the maker requires no less than three back to back batches amid protocol execution. The groups are assessed and affirmed by the protocol needs; a report is arranged and endorsed. At that point, the finished batch is freely available to be purchased and generation is initiated utilizing the approved procedure. Concurrent validation is another typical way to deal with beginning the protocol. However, the testing prerequisites for concurrent validation are ordinarily harsher than for prospective validation so it will limit the danger of discharging a batch whose execution may be unsatisfactory. Testing in concurrent validation is undertaken parallel to the finished product analysis.

22.4.8 Cleaning Validation

Final quality validation program in production is cleaning. The reason for cleaning validation is to verify the theory that the cleaning strategy is successful in expelling contamination deposits from the chosen apparatus. In cleaning, validation specialists need to clean the apparatus in a standard and regular protocol and in this manner, there ought to be detailed command and guidelines with reference to how to clean the equipment, in addition to looking after the paperwork to authenticate that the protocol were followed.

Cleaning validation description involves:

- Cleaned equipment,
- Procedure to be followed for cleaning,

- Material use for cleaning,
- Evaluation of cleaning,
- Limit of acceptance for cleaning,
- Recognizable proof of the complicated area of the apparatus to clean,
- Number of duplicates to demonstrate the cleaning system has been validated.

Cleanliness validation of the equipment includes determining the deposits remaining on a recognized range of the apparatus. This is done by swabbing the checked range with a decent solvent for the deposit. Laboratory testing evaluates various remains in the swabbed range after cleaning operation to determine if any deposit left in the equipment can be assessed. If the test consequence of the deposit is beneath the limit points from the risk analysis above, at that point the apparatus has been acceptably cleaned.

22.4.9 Process Monitoring and Control

In-process monitoring is typically an amalgamation of online estimations and sampling. Individual measuring devices either show the quality of the manufacturing level or are utilized to direct processing factors for the purpose of affecting product quality must be made using a calibrated instrument. The calibration process necessitates that for all apparatus there is:

- Separate assessment;
- Establishment of due date for calibration;
- Validated calibration process;
- Calibration against NIST traceable calibration standards;
- Calibration operators should be qualified; and
- Evidence of every calibration that incorporates, in addition to the information indicated, the discoveries of the calibration.

Tagging of instrument has to be done so that it can be labeled with the next due calibration. It causes the administrator to make sure that the apparatus is inside its calibration period.

22.4.10 Sampling and Testing

An in-process sampling includes a composed procedure which ought to be taken after. The Standard Operating Procedure (SOP) or generation direction ought to represent when and how and from where in the production, an example is to be taken, from where the specimen is to be taken, e.g., taking an amount of a sampling point or distribution through an sampling loop for a fixed interval before taking the specimen, which sampling apparatus is to be utilized for taking the specimen and how it is to be cleaned, amount of test to be taken, a depiction of the storing container into which the specimen is gathered, and labeling of item. The consequences of in-process testing are key to verifying the best possible working of the hardware. In this manner, it is important to give affirmation of cleaning the equipment according to protocol.

In the event that the testing is performed via a prepared workforce, the accompanying prerequisites ought to be met: There ought to be the preparation of faculty with direction. Preparing of assembling staff ought to be finished by qualified mentors. Testing instructions ought to be promptly accessible. Test records should be appropriately reported. Periodic evaluation by the trained personnel has to be done using techniques, such as inspection, performing the test or measurement, and comparing the sample with reference standard. Sample planning should be done on finished additives. The arrangement ought to be as per the in-process sampling rules.

COA: When a single sample indicating an additive lot is utilized for quality checking, the records of those investigations are accounted for by the COA. When a number of specimens from the completed item are taken and exclusively tried for quality, the matter of reporting results on the COA must be addressed.

22.4.11 Packaging and Labeling

Packaging and labeling operations will add up the risk of quality and regulatory compliance. The risk is due to the experience of finished additives to airborne contamination and humidity. To guard the additive, a positive pressure area using filtered/purified air should be used for filling of additives containers. This area should be cleaned on a regular basis to avoid contamination. Therefore, a manufacturing unit should be built according to the GMP so that the walls, floor, and roof ought to be launderable to permit cleaning. Packaging which could get in contact with additives must not be unfastened until the time they are passed to the packaging area. Received containers ought not to be unfastened until the time they are in the enclosed wrapping area; or else they will be presented to contamination. Filling, closing, and sealing should be done while in the packaging controlled environment.

Faculty engaged in packaging operations should wear proper clothing and ought to be prepared for the operation. Packaging and labeling operation guarantees administrative consistency to GMP necessities. It is imperative to pack in a similar are for each one in turn and the room ought to be utilized for a single batch/group of the additive. This is to prevent mix-ups of multiple batches.

Additive marks might be either printed or obtained preprinted. Where labels are purchased, the Quality Unit should approve their receipt by matching the incoming label content against an approved reference label. Weight adjustment must be done in the same controlled environment. Weight adjustments should be done with the same additive lot in order to prevent contamination and adulteration. A tamper evident device should be affixed which gives evidence of final sealing.

22.4.12 Quality Release

Last Quality Release includes the validation that every single required record is appropriately finished and incorporated for the batch being referred to. After finishing the quality release task, a lot of finished additives are appropriate for sale.

The Quality Unit should check the records of the following operations:

- Record and documentation of batch operation.
- Packaging document.
- Labeling record.
- The quality control (QC) record.

The above task should be properly signed with date and time which is then reviewed by supervision as required.

22.4.13 Storage

At last the finished product is stored in the facility. The storage area should be properly maintained so to prevent the additives' packaging and label from deterioration by water or sunlight. The lot should be kept in predefined manner and precise location written in records so that searching is easy and the storeroom should be well lighted. Like all facilities, the warehouse also should be cleaned on a regular basis. The manufacturer should provide the storing conditions to warehouse controller. Insect and rodent control program should also be done with occasional inspection by a quality team or supervisor.

If somehow quality department wants sample from finished product then sampling should be done in the same controlled environment as the packaging area and then the packaging of product resealed well.

22.5 ADDITIVES INTERACTION IN PHARMACEUTICAL PRODUCTS

Additives interaction involves kinetics principals and occurs frequently. These may be additive–drug, additive–additive interactions. These interactions are either due to physical interaction (i.e., modification of the dissolution speed or uniformity of the dosage) or chemical interaction (i.e., drug degradation and/or the formation of degraded products) (Katdare, 2006).

Additives even though considered inert substance, have the tendency to react with drug components, other additives, and also the packaging system. Impurities present in additives can also lead to deterioration of API. Fig. 22.1 shows different types of interactions.

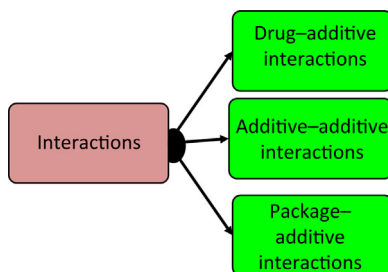


FIGURE 22.1 Different types of interactions.

Drug–Additive interaction: In pharmaceutical formulations, the API are in close contact with the additives which are present in larger quantities than the drug. Incompatibilities between both may lead to drug–additive interaction. Additive interactions are classified as physical, chemical, and physiological/biopharmaceutical (Katdare, 2006).

Physical interactions are different from chemical interactions because the components retain their molecular entity. Chemical interactions involve chemical reactions leading to the formation of a different molecule(s). The crucial variation between physical and chemical interactions is that in physical interactions the molecules are not chemically modified or changed by any means.

Example of chemical interaction: esters are susceptible to pH change and also the presence of alkaline earth metal and salts. The Milliard reaction occurs in primary amines due to reducing sugar.

Physiological interactions involve interactions between the additive(s) and the body fluids after administration. For example, change of dissolution time, Ph, disintegration time, etc. This interaction is beneficial in control release formulation (Katdare, 2006).

Additive–Additive interactions: Additive–Additive interactions occurs very rarely, but, it is very important to establish the stability of additives used in a formulation before the operation begin. Additive–Additive interactions can be undesirable or sometimes they are desired to contribute to the formulations to get the required product attributes. An example is coprocessed additives.

22.6 FORMULATION ADDITIVES FOR DESIGNING OF SOLID DOSAGE FORMS

Solid dosage forms contribute a lot for the treatment of patients and a large population depends upon the solid dosage forms for their wellness. Broadly, solid dosage forms include but are not limited to tablets, capsules, freeze-dried (lyophilized) powders, powder aerosol formulations, spray-dried powders, etc. Solid dosage forms, such as tablets, granules, and powders, have lots of advantages for both patients and medical practitioners. All the solid dosage forms utilize a number of additives which may include diluents, binders, lubricants, etc. Depending upon their use in solid dosage forms additives are classified as follows:

Diluents/fillers: These additives increase the bulk content of the dosage form whenever the active constituent in the formulation is of less quantity. Example: lactose, lactose anhydrous, lactose spray dried, directly compressible starch, hydrolyzed starch, MCC, other cellulose derivatives, dibasic calcium phosphate dihydrate, mannitol, sorbitol, sucrose, etc.

Binders: These may be dry powders or liquid, they are added at a specific stage in wet granulation to promote formation of granules or to provide cohesive force between particles during direct compression for mechanical strength. Example: cellulose, methyl cellulose, polyvinyl pyrrolidone, polyethylene glycol (PEG), gelatin, polyvinylpyrrolidone, hydroxypropyl methylcellulose, sucrose, starch, etc.

Disintegrants: Disintegrants are added to the formulation to facilitate the fragmentation of the tablet and capsule into smaller particles that will provide increased surface area and

thus aid a quick release of the API from formulation. Example: starch, starch derivatives, clay, cellulose, alginates, Polyvinylpyrrolidone, cross-linked sodium carboxymethylcellulose (NaCMC), etc.

Wetting Agents: In solid dosage form wetting agents aid water uptake by reducing surface tension and thereby enhancing disintegration and dissolution. Example: Sodium lauryl sulfate.

Chelating Agents: Chelating agents tend to respond with overwhelming metal particles inactivating their synergist action in the oxidation of medicaments by forming soluble complexes. Example: ethylenediaminetetraacetic acid, glycine, citric acid, or tartaric acid, etc.

Lubricants: Lubricants are intended to decrease the friction between surfaces in mutual contact like tablets and die cavity. It works to make efficient ejection of tablet from die cavity. Example: stearic acid salt, surfactants, waxes, etc.

Glidants: Glidants are used to improve the flowability of granular mixture by reducing interparticle friction and that is used in the pharmaceutical production of tablets and capsules. Actually, glidants, lubricant, and antiadherent have a close relationship because in different concentration glidants work as lubricants and antiadherents. Example: talc, corn starch, etc.

Film Former: Coating is a process in which coating material is spread over a surface of a dosage form like tablet and capsule in order to remove disadvantages of uncoated tablet like taste and odor. Example: ethylcellulose, PG, cellulose acetate phthalate, HPMCP, etc.

Plasticizer: Glycerine and Sorbitol are the two most common plasticizers. Glycerine is in general used with oil-based fills. Sorbitol is not soluble in PEG and therefore will not leach out of the shell into the PEG based fill like Glycerin would (Raj, 2015).

Opacifier: Titanium dioxide is used as opacifier to produce an opaque shell to avoid photodegradation of light sensitive components and also to hide the content color or appearance.

Stabilizer: It is a chemical that is used to prevent degradation by environmental stresses, and physical and chemical stress during manufacturing. These may contribute to changes that affect quality of product. These additives play a vital role in turning an unstable drug or formulation into an acceptable one. Example: saccharides work to stabilize lyophilized protein formulation (Chan and Chew, 2007).

Miscellaneous

- *Adsorbent:* In solid dosage form if there is a requirement to add a liquid or semisolid material in the formulation; adsorbents absorb or adsorb the liquid part on to the dry powder. Example: magnesium oxide, bentonite, etc.
- *Flavors:* Used to improve the flavor, mask the taste and give a pleasant and acceptable taste to the formulation.
- *Colorants:* Colorants used in the formulation to increase the patient compliance like formulation for pediatric patient. Example: food-drug and cosmetics and drug and cosmetics approved dyes and lakes.
- *Sweeteners:* lactose, saccharine, etc.

- *Preservatives*: Preservatives are an important part of formulation, they prevent the development of microorganisms. E.g., benzoate derivatives like methyl and propyl are used as preservatives

Some of the commonly utilized additives are examined below along with their numerous utilizations in the strong dose frames:

- *Lactose hydrous or anhydrous or monohydrate or spray dried*: work as binding agent, function as diluent for dry-powder inhalers, tablet, and capsule, lyophilization aid. Also, lactose was reported to help to deliver carrier-based protein dry powder aerosols. Lactose carrier produced a higher fine particle fraction.
- *Starch*: diluent for tablet and capsule. Retain water quickly for proper disintegration.
- *MCC (Microcrystalline cellulose)*: suspending agent, tablet and capsule diluents, adsorbent.
- *Calcium phosphate di or tri*: anticaking agent, diluent, buffer, dietary supplement; glidant; nutrient.
- *Mannitol*: sweetening agent, tablet and capsule diluent, tonicity agent, vehicle.
- *Sucrose*: suspending agent, sugar coating adjunct, binder, diluent, viscosity-increasing agent, sweetening agent.
- *Polyvinylpyrrolidone*: disintegrant, adhesive, emulsifier.
- *PEG*: plasticizer, solvent, surfactant, base, and tablet, and lubricant, etc.
- *Alginate*: tablet binder, tablet disintegrant.
- *NaCMC*: tablet and capsule disintegrant, adhesive.
- *Talc*: anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.
- *Stearic acid and derivatives*: tablet and capsule lubricant, softening and thickening agent.
- *Silicone dioxide*: anticaking agent; adsorbent; glidant; suspending agent, emulsion stabilizer.
- *MgO*: tablet and capsule diluent, absorbent.
- *Kaoline*: absorbs some active drugs when used in tablet formulations at very low concentrations
- *Gelatin*: coating agent, film-former, gelling agent, suspending agent, tablet binder. It is a translucent, colorless, brittle (when dry), flavorless food derived from collagen obtained from various animal body parts. Hard-shelled capsules are generally made up of gelatine base and contain dry powdered material mix. TYPE A Derived from acid treated precursor. It is extract out from pork skin. Type B Derived from alkali treated precursor. It is extract out mainly from animal bones (Raj, 2015).

22.6.1 Additives in Spray-Dried Powders

Spray drying is a process where a drug solution is sprayed through a nozzle into a chamber that simultaneously has hot air blown into it for evaporating the moisture content of formulation to convert a mixture from its liquid form to a powder. Trehalose is used to prevent denaturation of protein in dry powder formulation; polysorbate 20 to stabilize aggregation of proteins; silica to increase the flow of powder; polyvinylpyrrolidone prevented the sublimation of salicylic acid during spray-drying; dibutyl phthalate were used

as plasticizers for controlled-release microspheres of theophylline and sulfamethazine prepared by spray drying.

22.6.2 Additives in Controlled Release Solid Dosage Forms

Controlled release dosage is formed by using polymeric additives which coat around a drug core by microencapsulation or as a matrix in which the drug is embedded. It includes water-soluble resins (e.g., gelatin, starch, polyvinylpyrrolidone, and water-soluble celluloses), water-insoluble resins (e.g., polymethacrylate, silicones, and water-insoluble celluloses), waxes and lipids (e.g., paraffin, beeswax, stearic acid), enteric resins (e.g., shellac cellulose acetate phthalate). Surfactant like tween 20 and PEG additives have been used in microencapsulation of macromolecules for various effects (Chan and Chew, 2007).

22.7 FORMULATION ADDITIVES FOR DESIGNING OF SEMISOLID DOSAGE FORMS

It contains a major portion of pharmaceutical formulations. It is used to deliver a drug by way of skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining. But topically applied drugs have some problems in their permeation, but to minimize this issue additives play a vital role in delivering the drug in an efficient manner (Barry, 1983). Additives work on the physical properties of the vehicle, which make them capable to change the stratum corneum property, e.g., alcohol, or the mucosa to deliver the drug effectively. Semisolid dosage forms usually are intended for localized drug delivery. Semisolids have rheological properties in which they impart solid-like properties until they are disturbed; disturbance easily breaks down particle forces. Semisolids includes creams, ointments, pastes, and gels (Katdare, 2006).

Bases: The base is the central ingredient used in semisolid dosage formulation. Base of ointment does not merely act as the transporter of the drug but influences the absorption of drug. Bases are categorized as follows:

Water-soluble base: They are mixtures of high and low MW PEG which have the general formula $\text{CHCH}_2 \text{CH}_2\text{OCH}_2 \text{CH}_2\text{OH}$. The CH_2OH . The characteristics of these bases are:

- Low molecular weight as liquids; those with moderately higher molecular weight are unctuous and the high molecular weight are solids.
- No water is required for their preparation.
- Suitable combination of high and low molecular weight PEG yield material having ointment-like consistency. It melts when applied to the skin.
- Presence of many polar groups make it water soluble.
- Also called greaseless ointment bases.

The macrogols or carbowax are polycondensate mix materials of ethylene oxide and water and they are denoted by their average molecular weights, e.g., microgel 1500 (semisolid), 200, 300 (viscous), 3000, 4000 (waxy), etc.

PEG: Like paraffine, their consistency differs from viscous liquids to waxy solids, e.g., PEG 200, PEG 400, PEG 1000, PEG 1540, and PEG 6000. Different grade of PEGs are mixed together to get desired consistency of formulation.

Water-miscible bases: Excess of water is used to make them soluble, that is why formulation using these bases can be removed after use or application, e.g., cetrimide, cetomacrogol. For o/w type, e.g., antifungal benzoic acid ointment.

Importance of water-miscible bases:

- Promptly miscible with the exudates.
- Reduced impedance with ordinary skin functioning.
- Effective in touch with the skin, in view of their surfactant content.
- Elevated corrective agreeableness, and it makes less probability of the patients discontinuing treatment.
- Easy expulsion from the hair.

Absorption base: The absorption bases have absorbing or emulsifying property. The name does not express their action on the skin. These bases absorb considerable amounts of water but their consistency will not change (sometimes called emulsifiable ointment bases) Preparations of these bases not contain any water but if water may be used then it converts to w/o type emulsion.

Some commonly used bases are discussed below:

- *Wool Fat (Anhydrous Lanolin):* Fat obtained from the wool of sheep. Water solubility is very poor but can absorb water of about 50%. Hence, preparation using wool fat can hold the water in a large amount. It is used with other bases for better consistency.
- *Hydrous Wool Fat (Lanolin):* It is a mix of wool fat and water (70:30%). It is a w/o emulsion. It can be incorporated as an emollient.
- *Wool Alcohol:* It is emulsified part wool fat. Wool fat is alkaline treated from which cholesterol and alcohol is separated. It has around 30% cholesterol. It absorbs water to maximum extent in w/o formulation (emulsifying agent).
- *Beeswax:* It is purified wax obtained from honeycomb of honey bees, contains very low quantity of cholesterol and acts as a stiffening agent in preparation. It is available in two types yellow and white.
- *Cholesterol:* Widely available from animal sources. Source of cholesterol is wool fat. It helps in absorbing water in preparation.
- *Oleaginous Base:* These are mixture of oils and fats. Important one is hydrocarbons, i.e., petrolatum, paraffin, and mineral oils.
- *Petrolatum (Yellow Soft paraffin) MP 38–56°C:* It is a mixture of hydrocarbons obtained from heavy lubricating oil. Antioxidants, e.g., butylated hydroxytoluene (BHT), etc. may also be used with this base to make the formulation stable.
- *White Soft Paraffin (White Petroleum Jelly, White Petrolatum):* It is a mix of semisolid hydrocarbons, also known as white petroleum jelly. It is decolorized by percolating yellow paraffin. When you apply it to the skin it leaves a layer of oil on the surface of the skin that prevents water evaporating from the skin surface.
- *Hard Paraffin (Paraffin):* It colorless, odorless wax type mix of solid hydrocarbons obtained from petroleum. Above 50°C it solidifies. It is used as a stiffening agent.

- *Liquid Paraffin (Liquid Petrolatum/White Mineral Oil)*: It is transparent, colorless refined mineral oil which is a mix of liquid hydrocarbons obtained from petroleum used in cosmetics. On long storage, it may oxidize, therefore antioxidant like tocopherol or BHT incorporated in preparation. It may combine with other bases for desired consistency.

Other additives used in semisolid dosage forms include the following:

- *Antioxidant*: free radical which is very highly reactive, if formed in formulation may cause damaging effect to product stability and shelf life. So, antioxidant is a molecule that inhibits the oxidation of other molecules or prevents formation of free radical. E.g., butylated hydroxyanisole (BHA), BHT.
- *Antioxidant Synergist*: tartaric acid, etc.
- *Antioxidants*: BHA, BHT, etc.
- *Reducing Agents*: potassium and sodium metabisulfite, thiosulfite, etc.
- *Humectants*: glycerine, etc.
- *Gelling Agent*: tragacanth, pectin, gelatin, etc.
- *Emulsifiers*:
 - *Anionic*: soaps, sulfonates, sulfosuccinates, etc.
 - *Cationic*: quaternary ammonium compounds, etc.
 - *Nonionic*: alkyl-aryl ethers, sorbitan esters, glyceryl fatty acid esters, etc.
- *Buffers*: sodium citrate, potassium meta phosphate, etc.

22.8 FORMULATION ADDITIVES FOR DESIGNING OF LIQUID DOSAGE FORMS

Compared to solid dosage form, liquids are processed and formulated as solutions, suspensions, and emulsions according to the dosage form required or API solubility and stability. Powder may also be delivered as syrups, solutions, suspensions, and emulsions by reconstitution in which powder and vehicle are combined prior to delivery.

Liquid formulation (LDF) requires various additives (Fig. 22.2) which are elaborated as follow:

Vehicles: That carry drug APIs and other additives in dissolved or dispersed state.

- *Aqueous Vehicles*: water (SWFI, WFI, USP purified water), propylene glycol, ethyl alcohol, glycerine.
- *Oily Vehicle*: Vegetable oils, mineral oils, organic oily bases or emulsified bases.

Solubilizers: Breaking the hydrogen bond between the particles so they get soluble in water. Solubility can be modified by use of cosolvent, pH change, complex formation, or the use of surfactants. Example of solubilizers in LDF are ethanol, PEGs such as PEG-400, etc. (Katdare, 2006).

Sweeteners: Generally, sweeteners are used in between 30% and 50% of the total formulation concentration except for cold syrups that contain 80% of sweetener.

- *Natural Sweeteners*: Sucrose, lactose, mannitol, etc.
- *Artificial Sweetener*: Aspartame, saccharin, etc.

pH Modifiers and Buffering Agents: Buffers used to control or prevent changes in the formulation pH which could prevent and increase the stability.

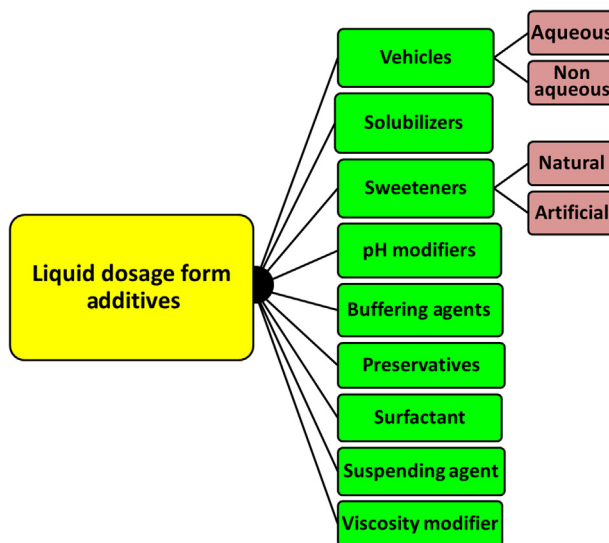


FIGURE 22.2 Different additives used in liquid dosage forms.

Antimicrobial Preservatives: Preservative used in preparation to prevent the growth of microbes so it should be of wide spectrum. It should be nontoxic, nonsensitizing, compatible with other additives, and have no taste and odor, e.g., parabens (0.015%–0.2% w/v.), Phenol, benzyl alcohol (2%), chlorocresol, etc. (AULTON pharmaceuticals).

Surfactant: Anionic Sodium lauryl sulfate (SLS), 2-naphthalene sulfonate sodium, docusate sodium.

- Cationic: cetylpyridinium chloride.
- Nonionic: poloxamer, polysorbate.

Suspending Agent and Viscosity Modifying Agent: Cellulose derivatives: MCC (and derivatives such as carboxymethylcellulose (CMC)); Clays: magnesium aluminum silicate; sodium alginate, xanthan gum, carbomer povidone, tragacanth, guar gum; colloidal silicon dioxide; BHA, BHT, EDTA; fumaric acid tartaric acid, ascorbic acid, alpha tocopherol, citric acid (Katdare, 2006).

Color: Different colorants are frequently used in the liquid dosage forms and most of the time the purpose is to enhance the elegance of the formulation and thereby the acceptability of the dosage forms, e.g., food, drug, and cosmetic colors

22.9 CURRENT GUIDELINES FOR PHARMACEUTICAL ADDITIVES (FDA, EU, JAPAN)

Sources of additives vary according to their origin like animal, plants, minerals and synthetic but they have to go through the quality check and control for assurance of safety

and stability. The new technology in pharmaceutical formulation additives has to be also modified for better functioning like coprocessed additives which can be a new entity or combination of old additives. Currently, thousands of additives are in use in manufacturing.

In the past, additives were recognized as an inactive part of the formulation but with new trends, these assumptions are changed because additives also have function, like API which interact with the other ingredient and also effect the ADME of dosage form, plus they also have toxicity effects.

The safety assessment of pharmaceutical additives is the major issues in different countries. To popularize additives there is no regulatory prerequisite to demonstrate that there ought to be a monograph of this substance. If there is an additive monograph in a pharmacopeia, the additive should be complemented with the monograph because the regulatory authorities require conformity.

For the supplier, it is always preferable to present an additive with a monograph or a complementary document about it that is relevant, because it means that this additive has quality for pharmaceutical use. National pharmacopeias depict quality prerequisites for pharmaceutical additives and these get priority over the three main pharmacopeia (USP-NF, Ph. Eur., and JP). The US FDA describes a new additive as any inactive fixings that are purposefully added to the therapeutic and diagnostic items, however that are not anticipated that would apply remedial impacts at the planned dosage, regardless of the way that they may act to improve item delivery that present well-being data concerning the correct now proposed level of introduction, exposure time, or route of administration.

As per Japan, a substance which has no prior record as additives in overseas or in Japan qualifies to be new additives if, additives are administrated orally, have cosmetic use in pharmaceutical formulation. If the route of administration is newer than the marketed formulation then it is treated as a new additive (Uchiyama, 1999). Responsibilities for regulating additives approval and safety are divided among MHW (Ministry of Health and Welfare) and National Institutes for Hygienic Sciences (NHS) and Central Pharmaceutical Affairs Council (CPAC). Monograph for additives approval is given in Pharmacopeia of Japan (JP) and Japanese Standards of Pharma Ingredients (JSPI) (Uchiyama, 1999).

The European Union regulatory authority, EMEA, defines novel additives as new additives which are in first-time use in a drug product or have new route of administration in EU and outside EU for human administration. New additives are treated as a new entity or drug in the EU. European commission released recently guidelines on additive labels and packaging information for all market authorization applications for additives used in pharmaceutical formulation. And for other products, if any additives show some effect then it should be mentioned on the label (Guideline on Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product, June 2007).

United States of America: The US FDA has issued guidelines for new additives to establish the safety of dosage forms entitled "Non-Clinical Studies for the Safety Evaluation of Pharmaceutical Excipients." It will help in QC and safety assessment of formulation intended for use in human. New additives manufacturers should clearly mention and document the safety profile to support the use of novel additives.

OTC Products: 21 CFR 330.1(e) section for OTC requires the following condition to be fulfilled: "The additives used in formulation have to be used in safe concentration and do

not interfere with effectiveness and quality tests which can decide whether the item meets its maintained models of character, quality, quality, and purity. Guidance for Color additives are given in section 721/subchapter A of this chapter.”

Generic Products: The USFDA requires that the generic formulation planned for parenteral, ophthalmic, or optic use ought to contain an indistinguishable added substances in similar concentration from the reference standard, except for buffer, preservative, and antioxidant. However, for this, the condition is that the applicant distinguishes and characterizes the difference and gives data showing that the changes doesn't influence the safety of product. For different courses of administration, there is no necessity that the added substances in the final formulation are the same as those in the reference, but they do not influence the safety, efficacy, and quality of the planned product.

The European Union: The IPEC Europe has in print a parallel guideline for the evaluation of safety of the potential novel additives. In Europe, the information about the novel additive to be used in the dosage form is to be provided in the application for marketing authorization application by the applicant. The information to be included by the applicant is according to the guidance entitled “Guideline on additives in the dossier for application for marketing authorization of a medicinal product” (Bajaj and Budhwar, 2012). The following data are to be submitted:

- Full particulars of manufacturer, characterization, and controls with safety data according to the guideline.
- Detail about the functioning and condition for use of additives. For mixture of additives quality and quantity, data should be provided.
- For mixture of additives chemistry and toxicology and the field in which the product is already used should be mentioned.
- Document related to the international specifications of additives according to (FAO/WHO/JECFA), and other publications, like Food Chemical Codex.
- Safety data for cosmetic additives used for topical formulation.
- Data concerning the toxicology of the new additive according to the dosage form and the route of administration of the medicinal product in Module 4, which is the safety section of the dossier.

Documentation on science of additives is required for every single novel additives, on the principle of the CPMP Guideline (Chemistry of New Active Substances) including:

- Origin, name and manufacturer details.
- Process of manufacturing and purification.
- Chemistry.
- Identification and purity test procedure.
- Validation method for operation and equipment.
- Miscellaneous information (microbiological tests, etc).
- Test result for contamination and impurity presence.
- Novel additives having mixture of numerous components, properties of all the content should be described.
- Stability data and document.

Japan: There are a few reference materials that have to be attached to an application for endorsement of another pharmaceutical substance containing an added substance. All applications require data concerning the explanations behind the added substance's consideration in the planning, points of reference of utilization, and a suitable quality model. For things with recently added substances, it is vital to give information on the beginning and change of the additional substance, including a depiction of its uses abroad and its qualities, and in addition a correlation with different additives. Stability and safety information are likewise required and submitted for new additives (Uchiyama, 1999).

The regulation for additives in Japan is the same as for other countries. Guidelines are issued by Pharmacopoeia of Japan (JP) and the Japanese Standard of Pharmaceutical Ingredient (JSPI). Japanese Pharmacopoeia states that: "Additives are incorporated for giving indicated properties and quality amid capacity or upgrade the efficacy of medication product yet it ought not to meddle with the therapeutic efficacy or the testing of the product."

On regulatory provision on additives, JP resides in the pharmaceutical affair bureau of the Ministry of Health, Labor and Welfare organization (MHLW). Monographs of JP contained mandatory standards for the most broadly used excipients. Quality and safety is evaluated by a subcommittee designated by Central Pharmaceutical Affair Council (CPAC) and approval process by pharmaceuticals and Medical Devices Evaluation Center (PMDE).

NEW RULE: In July of 1997 new evaluation system was put in effect by the Ministry of Health and Welfare (MHW), application for affirming pharmaceutical substance is made through a prefectural office of the Pharmaceuticals and Medical Devices Evaluation Center (PMDE Center). In the event that application for new item contains an added substance with no past use as added substance in Japan then the quality and safety of the additives must be tested by the Subcommittee on Pharmaceutical Additives of the Central Pharmaceutical Affairs Council (CPAC) and PMDE. The duty of the drug regulatory agency is to verify all documents attached with NDAs.

All applications require to submit the data for additives including why it is incorporated in the preparation, past use, and quality standards. For new additives, the origin, manufacturing operation of the additive, overseas use, and its property are to be submitted, as well as a comparison with other additives (Uchiyama, 1999).

It is imperative to perform chance benefit testing on new additives to set up passable and permitted limit for these substances. This requires proper planning with possible toxicology test of an additive in a relatively efficient manner. The centers perceive that current human information for a few additives can substitute with documented earlier human presentation and not require assessment in the full set of toxicology studies given in the rules. Under some situations (e.g., similar route, height, and length of exposure, patient population) prior use may effectively qualify an additive. Note that the consideration of an additive in a USP/NF monograph or other non-FDA archive isn't an indication that the substance has been investigated by the FDA and discovered safe for utilize (Verma et al., 2016).

22.10 REGULATORY ASPECTS OF ADDITIVES APPROVAL

22.10.1 Current Regulatory Status of New Additives

In the United States, specific requirements for “new” additives are given in the US FDA *Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, May 2005. Overall, the International Conference on Harmonization (ICH) has not given additives rules, but rather the FDA takes ICH safety testing direction papers for leading safety tests.

However, these guidelines address only one aspect of the approval process leaving a major gap i.e., the precise definition of “newness”. As per the ICH, “new” or novel additives are defined by the use for the first time for a pharmaceutical drug product or have a new route of administration. US FDA document the Inactive Ingredient Database (IID) has lists of approved products, administration routes, and dosage concentration. The definition does not separate between totally new chemical elements and previously approved additives that have been changed, different routes of administration, or coprocessed material. Supporting data for other new additives can be given in an application which is comparative and have similar detail like new drug substance e.g. chemical properties, all the data of quality and safety, etc.

22.10.2 The IPEC Procedure

According to the IPEC, the manufacturer has to submit all relevant data and records in the DMF to propose a new additive for safety and quality assurance. An expert panel, having highly experienced persons from academia, industry, and regulatory, evaluates the information of the additive in the DMF considering guidelines proposed by FDA and ICH. This panel will conclude the conformance to the sponsor if they find all the data relevant. Applications for global acceptance is a work under process

If the panel concludes that the data submitted to the FDA do not meet the specifications, then it recommends particular steps to pass the dossier application information into conformity. That allows the resubmission of the dossier document with the asked for changes. The expert report is possessed by the sponsor and discharged at their discretion. The additive manufacturer can consult the summary and table of content of studies with cost-based consultants before submission. The consultant provides the candidate with a report with the DMF needed pattern for drug product application.

IPEC only reviews the application but does not play any role in this process or evaluation. The evaluation of the application procedure is kept private between the panel and sponsor which is not known by IPEC.

22.10.3 Additive Master Files and Other Filings

DMF is an accumulation of specialized understated elements identified with the manufacture of the added inactive substance and is arranged according to or similar to Common Technical Document (CTD) format for effortless upcoming submission. DMF ordinarily incorporates particulars and test techniques for crude substances, testing in

between processing, and the completed added substance item, an entire depiction of the assembling procedure, safety information, packaging information, and information printed on the label.

In the United States, an added substance provider will frequently present a DMF to the FDA to give classified data in respect to the added substance, safety data, and certificate for processing as per GMP necessities. Both Canada and Japan follow the identical or similar rules. In Europe, compilation of drug product information by a pharmaceutical producer should be provided specifically to the client for consideration for their approval, utilizing secrecy understandings where important.

22.10.4 Recommended Strategies to Support Marketing of New Additives in Drug Products

22.10.4.1 Safety Pharmacology

All novel or effective new excipients are fittingly assessed for pharmacological effect utilizing a run of standard tests as indicated by ICH direction for industry S7A Safety Pharmacology Studies for Human Pharmaceuticals. Pharmacology studies are valuable for this information to be gotten at an early level amid the safety assessment of additives, since, if additives are pharmacologically dynamic, this data can impact results and the development process.

22.10.4.2 Potential Additives Intended for Short-Term Use

Newer additives that are intended for use in products that are limited by labeling to clinical use of 14 or fewer consecutive days per treatment episode and are infrequently used include at least the following:

- Toxicity studies.
- Pharmacokinetics studies of an additive with toxicokinetics.
- 1-month toxicity studies are performed in first rodent animal types and second mammalian nonrodent animal groups by the course of treatment planned for clinical use with an assessment of clinical pathology, toxicokinetics, and histopathology analysis.
- Toxicity in reproductive stage.

22.10.4.3 Potential Additives Intended for Intermediate Use

New added substances that are expected for use in a drug product that is labeled for clinical utilization of over 2 weeks yet not exactly or equivalent to 3 months for each treatment episode require:

- All trial of safe pharmacology and in-between use aside from 1-month repeated dose toxicity trial.
- 3-month repeat-dose toxicity studies are processed in which studies include assessment of clinical pathology, toxicokinetic, and histopathology analysis in both rodent and non-rodent animal.
- Other study (e.g., studies for Parenteral administration).

22.10.4.4 Potential Additives Intended for Long-Term Use

New ingredient that is expected for use in a drug product named for clinical utilization of above 3 months in a specified patient (either a single treatment scene or because of different courses of treatment to treat an incessant or chronic condition) requires:

- All tests have to be done like safety, pharmacology, short-term and intermediate use test. One or three-month test is not essential or may be done for better safety assessment.
- 6-month repeat-dose toxicology study on rodent including full assessment of clinical pathology, toxicokinetic, and histopathology analysis. FDA recommends that less toxic additives are tested in their higher concentration.
- If no toxicity and pharmacologic effect were found then 6-month study is sufficient. But when toxic effect is shown in small duration of test than chronic study should be conducted in nonrodent of 9 to 12 months.
- Carcinogenicity study according to ICH(S1A).

22.10.4.5 Potential Additives for Use in Pulmonary, Injectable, or Topical Products

- Have to perform all required studies like Safety assessment, Pharmacology test, for concluding its duration (short, long, intermediate) of safe exposer and administration route.
- Sensitization study (e.g., guinea pig maximization study or murine local lymph node assay) with respect to CDER guidance. Immunotoxicology evaluation of IND for more information can be done.
- Things to be considered for additives used in injectable:
 - Hemolytic study (IV bolus and/or infusion).
 - The plasma creatinine kinase determination for I.M. or S.C. injectable can provide study data on potential muscle injury.
 - Protein binding test.
- Additives expected for topical administration may involve support from toxicology determination by both the planned clinical course and the oral or parenteral course.
- For topical and ophthalmic formulation, ocular irritation study should be conducted.

Photostability Testing: FDA suggests that additives be assessed with respect to the requirement for photo testing given in the CDER guidelines. Either the added substance or the entire medication item could be tried.

22.11 REGULATORY PERSPECTIVES OF FORMULATION ADDITIVES

Regulatory perspectives of the United States, Europe, and Japan have already been discussed in this chapter earlier. Now here we will discuss IPEC, GRAS, and Inactive Ingredient Guide (IIG) regulatory perspectives.

22.11.1 IPEC Perspectives

The IPEC Federation, a worldwide association comprising of local affiliations sorted out to advance quality in pharmaceutical added substances, was formally made in January 2010 at a meeting in Cannes, France. IPEC Europe right now holds the Presidency of the IPEC Federation, and IPEC-Americas and IPEC Japan fill in as Vice-President and Treasurer separately.

The purpose of IPEC is to encourage the harmonization of different standards for manufacturing and use of pharmaceutical additive, develop improved consumer safety in the manufacture and use of pharmaceutical additive, and introduce new pharmaceutical additives. There are various national additive regulation registration systems that have yet to be internationally harmonized. The lack of regulatory provision is to be identified by IPEC. The IPEC Federation is a worldwide association that advances quality in pharmaceutical added substances. The IPEC Federation speaks to the five-existing provincial International Pharmaceutical Excipient Councils (IPECs)—IPEC-Americas, IPEC Europe, IPEC Japan, IPEC China and IPEC India—and gives a bound together voice to advance the best utilization of added substances in drugs as a method for enhancing persistent treatment and well-being.

IPEC has objectives with respect to the International Harmonization of Excipient Standards. The IPEC's principal work is introduction of novel added substance with commercial center and advancement of well-being assessment guidelines. The Safety Committee of IPEC (SCIPEC) incorporates qualified researchers and creates security testing of the added substances. The guidelines depend on chemical and physical properties of the added substance, survey of the logical writing, presentation, condition (Including measurement, dosage length, recurrence, course and client populace), and nonattendance or nearness of pharmacological activity.

The IPEC recommended the guidelines for the safety assessment of new added substances and good manufacturing guides for mass pharmaceutical additives. The guidelines give adequate information to characterize the safe state of utilization of new additives. The additive poisonous quality guidelines are compressed, which were created with reference to the FDA proposed usage archive (Steinberg et al., 1996). ICH has affirmed direction archives on specialized prerequisites for medicate products containing new fixings. Additives are controlled intently by characterized detail, or monographs, accumulated in three noteworthy Pharmacopoeias in the United States, Japan, and Europe. Pharmacopoeial Harmonization likewise maintains a strategic distance from superfluous deferrals in the administrative procedure, while guaranteeing their quality, safety, and viability. Pharmacopoeial Discussion Group (PDG) was set up in 1989, and harmonization might be done reflectively to existing monographs or sections or tentatively for new monographs. So far 25 of the 35 general sections and 39 of the 62 additive monographs have been harmonized (IPEC Federation, 2017).

22.11.2 Regulatory Perspectives: GRAS, IIG

22.11.2.1 *Generally Recognized As Safe Food Status*

GRAS is an American Food and Drug Administration (FDA) assignment that a concoction or substance added to food is viewed as protected by specialists, and is exempted

from the typical Federal Food, Drug, and Cosmetic Act (FFDCA) food additive resistance prerequisites. Food Additives Amendment of 1958 firstly explained the concept of GRAS for food additives and entire additives introduced after this concept were required to be analyzed by new standards. Under this provision, different data like testing, exposure, manufacture, etc. were supposed to be evaluated by a GRAS specialist panel. After approval by GRAS experts, the approved additive can be used only with those food products and within that concentration for which approval was taken. Though it is not a mandatory procedure but some manufacturers opt for GRAS notification steps just to cross-check whether FDA is also in consent with the GRAS findings or not. More than 3000 additives have been endorsed by this strategy to date and this speaks to a model of industry and regulator participation (Burdock et al., 2006).

Substances which go under GRAS status and which are formally seen by the FDA are recorded in the regulations at 21C.F.R. 182, 184, and 186. FDA notes in its direction, "it is unfeasible to list every single such substance that are GRAS." It is improbable that an ingredient that does not have some formal position with the FDA will be acknowledged by the office as safe for use in a different medication without the full investigations that are essential for novel additives, in particular for pharmaceutical additives. The GRAS procedure is an open rulemaking technique where the information supporting the GRAS status is set in an open docket for input. At the point when all comments are evaluated, the FDA will make a confirmation on whether the additive should be seen as GRAS. The GRAS confirmation process requires a impressive effort regarding an organization to procure toxicological information (frequently long-haul information) that is adequate to the FDA. The FDA at that point frequently takes a long time to survey the information and issue the direction. Subsequently, this procedure is occasionally utilized.

GRAS Notification: Rather than the formal GRAS confirmation request, the FDA started another methodology for GRAS ingredients, the GRAS notice. Under the notice procedure, a producer makes an assurance that an ingredient is GRAS and notice to the FDA to take additive data it in consideration for GRAS assurance. Inside 90 days, the FDA reacts to the producer that either the office does not scrutinize the reason for the maker's GRAS assurance, or that FDA presumes that the notice does not give an adequate premise to a GRAS assurance. In any occasion, the FDA does not formally perceive the GRAS status of the ingredient as it did under the certification procedure. The notification procedure has been profitable to food and food ingredient makers, as it is significantly quicker and less oppressive than the GRAS affirmation process; in any case, its utility for pharmaceutical added substance producers is less certain. Under the affirmation process, the component had an official acknowledgment as GRAS in FDA regulations. Under the notice procedure, no finding is made by FDA regarding ingredient's GRAS status and therefore, ingredients under notification process consideration are possibly less worthy to the FDA as pharmaceutical additives.

For a long time, chemical makers and pharmaceutical firms (clients) and additionally FDA commentators casually utilized these FDA food freedom components to give new drug analysts (e.g., toxicologists and pharmacologists) a level of solace about the safety of an additive contained in a finished pharmaceutical formulation. At the point when a utilization of a substance does not meet all requirements for the GRAS exception, that utilization of the substance is liable to the premarket endorsement ordered by the Federal Food,

Drug, and Cosmetic Act. Under these conditions, the FDA can make authorization move to stop dissemination of the food substance and foods containing it in light of the fact that such foods are unlawful or these food items contain a few unlawful food additives ([Generally Recognized as Safe \(GRAS\) FDA, 2016](#)).

IIG: IIG is a piece of FOI Special Topics, which goes under Drug Information division of CDER. IIG comprise of all the dormant ingredient introduce in endorsed drug item or restrictively affirmed drug items right now marketed for human utilize. IIG is prepared by DDIR (Division of Drug Information Resources). IIG does not show contaminant found in affirmed drug items. DDIR does not generally incorporate Proprietary names of Ingredient in IIG. In such circumstances, one needs to scan information for such ingredient under individual segment passages. The IID contains idle ingredients particularly proposed in their original form by the producer. Inert ingredients can likewise be viewed as dynamic ingredients in specific situations, as per the meaning of an active ingredient given in 21 CFR 210.3(b) e.g., Alcohol.

IID gives data on inert additives available in FDA-affirmed drug items. Industry can be utilized the data as a guide in creating drug items. For new drug advancement purposes, if additive is get listed in approved drug product for a specific course of organization, the idle ingredient is not viewed as new and may require a less broad examination whenever it is incorporated into another drug product.

It has turned out to be normal practice in creating drug products to counsel the FDA's IIG to acquire data on "satisfactory levels" of additives utilized as a part of already affirmed items. The FDA likewise considers whether the states of use of the latent additive in the already affirmed item are similar to (or more prominent than) those of the proposed new item.

Other factors that the FDA considers in this investigation are

- Administration route,
- Level and duration of exposure,
- Population of patient

Administration Route—This foundation is the one for which the FDA permits the best adaptability. Information on levels of inactive additive can, by and large, be utilized conversely when the course of organization of the drug item is the same (e.g., information from oral tablet details can be utilized for oral containers, information from topical gel definitions can be utilized for topical creams). Besides this, an additive utilized as a part of a topical formulation like cream might not have a similar safety profile if utilized as a part of an occlusive topical PATCH. In this way, extra safety data might be expected to qualify the utilization of the additive in an alternate detailing regardless of the possibility that the course of organization and every other factor influencing use are the same.

Level and Duration of Exposure—In considering related knowledge with a inactive additive, the FDA assesses whether the earlier use in the affirmed item is in any event of a comparable length as the utilization of the proposed formulation. Despite the fact that the IIG gives data on the level of an additive present for each measurement unit, it doesn't give data on the level of presentation of the patient who utilizes the item. Day by day measurements considered by the FDA while assessing the sufficiency of the IIG data. The rate of administration is especially imperative in considering parenteral formulations.

A inactive additives considered safe when implanted gradually may not be considered similarly safe when infused quickly.

IIG description includes Name, Route/Dosage Form, CAS No., NDA Count, Last NDA Approval Date and Potency Range. Numerous inactive ingredients have CAS Registry Numbers, which are helpful in looking different databases for chemical. FDA refreshes the database quarterly, in April, July, October, and January tenth working day. The IID Download is given as delimited content and Excel documents ([US Food and Drug Administration, 2017](#)).

Patient Population—The patient populace is additionally a critical factor that is considered while surveying whether earlier presentation at a level referred to in the IIG is sufficient to qualify that idle ingredient in a planned formulation. Additives essential for the conveyance of lifesaving treatments might be satisfactory to the FDA at larger amounts or with to a lesser extent a safety database than if the additives are utilized as a part of items planned for patients with more considerate conditions. Additionally, quiet populaces contrasting in age or malady status may likewise vary in their capacity to endure certain additives (e.g., benzyl liquor, an antimicrobial additive, is not endured in neonates on the grounds that their capacity to utilize the additive is not completely created).

22.12 WHO PERSPECTIVES

These guidelines supplement the specific GMP guidelines for pharmaceutical formulation in print by WHO which are similar like GMP guidelines for additives. Additives essentially influence the completed product value, in few cases making up nearly the whole formulation. Numerous additives are utilized as a part of substantially more prominent amounts in different industries like the food, cosmetic or industrial chemical industry.

In pharmaceuticals formulation there are so many additives are in use. That's why a program must be set up which will screen these added substances and give the essential confirmation that they conform to the quality parameters for pharmaceutical production operations.

Equivalence ("biobatch") production and commercial scale-up batches to give satisfactory confirmation of product performance *in-vivo*, the additives used to produce business batches ought not to contrast differ from that utilized as a part of biobatches. Where critical difference might be normal, extra testing by the completed measurements maker might be required to build up the bioequivalence of the final product. It remains similarly imperative to guarantee that the bioequivalence of ensuing, post-approval batch of product is not unfavorably affected after some time.

Generally, added substances are utilized as acquired, with no additional alteration or purification. Thusly, impurity influences exhibit in the added substance will be extended to the completed measurements shape. While dosage form makers may have a constrained control over added substance quality acquiring testaments of investigation and testing reference sample. The added substance producer has more prominent control over physical attributes, quality, and the existence of trace contamination in the additives. The manufacturer must execute evaluation and testing in regular basis.

Some additives manufacturing operation may require recognition of GMP appropriate to completed product or bulk active ingredient in light of the added substance's use. It may not be necessary but the necessities increase as the process progresses. GMP should be maintained before finishing step or operation. Application of GMP in which step is done by the qualified personnel which have thorough knowledge of production.

ISO "certification" for additive manufacturing is more and more being required by manufacturer of USA, Europe, and Japan. International Standards of ISO 9000 series, in particular to ISO 9002, help in supporting suitability of additive in world market. This system will enhance the quality standard of additive use with GMP guidance.

Self-inspection and quality audits An assessment group comprising of correct personnel (e.g., reviewers, engineers, research center examiners, acquiring operators, PC specialists) who should take an interest in examinations. The operational confinements and endorsement of the essential preparing steps of an era procedure should be inspected, to ensure that the maker is finding a way to watch that the procedure works reliably.

Use of equipment: Multipurpose equipment is used to manufacture additives. Fermentation tanks, reactors, dryers, grinders, centrifuges and some others type are gladly used or modified for a variety of products. Equipment use for multiple processing of substance should be adequately cleaned according to written procedures. Falter or sticky residues present in equipment that can't be removed easily ought to be dedicated for use with these items as it were.

Cleaning program where multipurpose equipment is being used, it is vital to be able to determine previous usage when investigating cross-contamination or the likelihood of such impurity or contamination, equipment cleaning and use log, while desirable and perhaps preferable, is by all account, not the only method of determining earlier use. Any documentation system which clearly identifies the previous bunch and demonstrates that the equipment was cleaned is acceptable.

Materials: On account of labile items that might be touchy to natural factors, e.g., air, light, water, hot or cool, suitable assembling and capacity conditions must be utilized to guarantee substance quality all through the procedure. The added substance producer ought to check that the provider of beginning materials and parts can meet the settled upon necessities. Any beginning material or completed additives not consenting to particulars must be obviously recognized and isolated to avoid coincidental use or discharge available to be purchased. In the event that returned additives containers are reused, all past label ought to be evacuated or ruined. In the event that the container is utilized over and again exclusively for a similar additive, all past label should totally be destroyed. Pharmaceutical added substances ought to be put away under conditions set up by the manufacturer on the grounds of stability data.

22.12.1 Documentation

General: The added substance maker ought to have a framework to cover all records and information that identify with the necessities of the quality framework. Records and consequent changes to the reports have to be looked into and endorsed by assigned supervisor before being issued to the fitting zones distinguished in the archives. Beginning

material particulars ought to be sorted out to isolate those tests that are standard from those that are performed rarely or just for new providers. All this can be done easily by using computer system monitoring and documentation.

Preventing contamination: The manufacturer of additives must be shield the additives contamination from starting point like raw material container opening to final marketed container filling. In general contamination sources: introduction of the added substance to environment or open air amid the production procedure and defects in the equipment. For the most part amid the blend of additives, the danger of natural contamination just emerges during the changing of crude materials, added substances, or preparing helps, or during the packaging of the finished product in container. Prevented steps ought to be taken to shield the additive from environmental contamination in all phases of production. The operation of packaging and manufacturing should be performed in an enclosed room with good or efficient air flow system. It should be cleaned on regular basis and record should also be maintained.

The other critical risk of additives contamination originates from the working equipment. Whatever equipment is utilized to deliver or manufacture numerous substance moieties with same equipment, the producer must have satisfactory techniques for cleaning the equipment in regular change in moiety. The cleaning of equipment is additionally examined under cleaning validation. The devices must be traps, seals, and preventive maintenance procedure should be employed.

Process validation: After working on IQ, OQ, and PQ of equipment, process validation can proceed. There should be creation of MVP that will describe the validation method like retrospective, concurrent, or perspective which will show the preparing steps that need validation, and Establishes an arrangement for implementation of every validation. For the most part, the MVP covers the preparing steps that effect additives quality from the purpose of a start of full GMP consistency.

Cleaning validation: The reason for cleaning validation is to affirm the theory that the cleaning method is powerful in expelling production deposit from the assigned apparatus. It needs that laborers sanitized the apparatus in a tedious way. There should be detailed instruction with reference to how they should clean the equipment and in addition records to affirm the guidelines were taken after.

Water system and quality: While drinking water is utilized for some additives forms refined water is utilized broadly. Due to impurities, deionizers and ultra-filtration or RO framework were utilized to deliver cleansed water. Appropriate QC technique ought to be built up which legitimately validate and check the security and nature of water utilized.

Packaging and labeling: Packaging and labeling operations will add up the risk of quality and regulatory compliance. The risk is due to the experience of finished additives to air-borne contamination and humidity. To guard the additive, positive pressure area using filtered/purified air should be used for filling of additives containers. This area should be clean on a regular basis so to avoid from becoming contaminated. Therefore, manufacturing unit should be built according to the GMP like the walls, floor, and roof ought to be launderable to permit cleaning. Packaging which could get in contact with additives should not be unlocked till the time they are transferred to the packaging area. Received containers ought not to be unfastened till the time they are in the enclosed wrapping space; or else they will be presented to contamination. Filling, closing and sealing should

be done while in packaging control environment. Faculty engaged in packaging operations should wear proper clothing and it ought to be prepared for the operation.

Good practices in QC: The QC unit having the duties and expert to affirm and dismiss all parts, in-process material, packaging material, and completed product.

Starting material: Starting material must be verified and tested prior to use.

In process testing: examination and testing should be performed by testing which should give the result in limit.

Quality records: the manufacturer ought to build up and kept up methodology for ID, collecting, ordering, documenting and maintaining and accessibility of record.

Calibration testing of equipment: All equipment uses for measurement and testing distinguished as being a piece of quality framework ought to be appropriately calibrated and kept clean. Reagent, instruments, apparatus, gauges and measuring gadgets not meeting determination ought not be utilized ([Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipient, 1999](#)).

22.13 STUDY OF DIFFERENT TYPES OF ADDITIVES

22.13.1 Antioxidant

The efficacy and safety of drugs administered are in close proximity with different problems like permeability, solubility, and stability. The stability of the drugs may be compromised due to different physical factors like temperature, light, etc. which ultimately results in the aggravation of different chemical reactions, e.g., oxidation, reduction, hydrolysis, etc. Antioxidants are added in the formulations with an objective to enhance the stability as well as shelf life of the formulations ([Celestino et al., 2012](#)).

Antioxidants are the chemicals which are when added in the formulations, even in the minute concentrations, having chemicals which are prone to oxidation, significantly interrupt or stop the oxidation. A variety of substances are included in this category, e.g., peroxide inactivators, metal chelators, free radical scavengers, etc. The chemical category of antioxidants includes two types of chemical, firstly those which are added in products to increase the stability and secondly those which are present in food articles and body and are supposed to have good effects on health ([Shahidi, 2000](#)).

The intention of inclusion of antioxidants in pharmaceutical several formulations is to exclude the oxidation reaction. Oxidation responses don't really require atomic oxygen. For instance, the oxidation of cytidine analogs to the proportional uridine analogs can happen within the sight of water even without oxygen ([Remington et al., 2006](#)).

These materials are balanced out, amid fabrication, by assembling under a nitrogen cover to reject oxygen or by inclusion of antioxidants. It is imperative to know which material is balanced out, in light of the fact that an adjustment in the source may prompt sudden stability issues due to the nearness or nonattendance of the antioxidant agent, and along these lines changes in the potential for interaction. Most antioxidant agent work by giving electron or labile H^+ which will be acknowledged by any free radical to end the chain response. A large number of the lipid-solvent antioxidant goes about as scavengers.

Antioxidants can likewise go about as chain eliminators, responding with free radicals in answer for stopping the free-radical propagation cycle (Decker et al., 1998).

22.13.1.1 Synthetic Antioxidants

As free radicals were observed to be in charge of lipid oxidation, several natural and manufactured mixes have been assessed for their adequacy as radical scavengers or for their other inhibitory impacts. Among synthetics, just four antioxidants are generally utilized; to be specific, BHA, BHT, propyl gallate (PG), and *tert*-butyl hydro-quinone (TBHQ). All antioxidants have purposes of qualities and shortcomings. In this manner, certain focuses, e.g., thermal stability, concentration required, and synergism, ought to be thought about while choosing antioxidants for use specifically in food products. Administrative (regulatory) status is another factor that can't be overlooked, particularly for a few antioxidants that have been accounted to indicate potential unfriendly well-being impacts. Synthetic antioxidants have been tested for safety and approval for use in food at low concentrations on the basis of complex toxicity studies. Reasonable breaking points for utilization of antioxidants shift extraordinarily from nation to nation and rely upon the nourishment item underthought.

22.13.1.2 Butylated Hydroxyanisole and Butylated Hydroxytoluene

BHA is an antioxidant comprising of a blend of two isomeric natural mixes, 2-*tert*-butyl-4-hydroxyanisole and 3-*tert*-butyl-4-hydroxyanisole. It is formed from 4-methoxyphenol and isobutylene. Since 1947, BHA has been added to palatable fats and fat-containing nourishments for its antioxidant properties as it avoids rancidification of food which makes offensive smells. BHA is a white, waxy solid that is sold as flake or tablet. It is a very fat-dissolvable monophenolic antioxidant that is widely utilized as a part of mass oils and additionally oil-in-water emulsions. BHT (3,5-di-*tert*-butyl-4-hydroxytoluene) is a white crystalline structure with traits like BHA. It is proper for thermal treatment, however not as steady as BHA. BHT does not have an ideal fixation; more often than not, BHA/BHT blends are added at levels of up to 0.02%. Albeit engineered antioxidants have broadly been utilized as a part of the food business, there are a few contentions about their well-being. Notwithstanding the cancer-causing nature of BHA in the forestomach of rodents, BHA and BHT have been accounted for to be cytotoxic. In spite of positive and negative reports of these manufactured antioxidants on human well-being, their utilization is liable to the direction of different regulatory bodies. As per the current food added substance controls distributed by the FDA, BHA and BHT are legitimate for use separately or in a mix at a most extreme level of 0.02%, or 200 ppm.

TBHQ: It is an aromatic compound which is a sort of phenol. It is a subordinate of hydroquinone, substituted with a *tert*-butyl gathering. Both the EFSA and the USFDA have evaluated TBHQ and determined that it is safe to consume at the concentration allowed in foods. The FDA sets a highest level of 0.02% of the oil or fat substance in nourishment. At high measurements, it has some negative well-being consequences for lab creatures, e.g., leading to precursors of stomach tumors and harm to DNA. Various investigations have demonstrated that drawn-out presentation to high measurements of TBHQ might be cancer-causing, particularly for stomach tumors. TBHQ displayed a nontypical method of cell demise and demonstrated cytotoxicity toward human monocytic leukemia

cells. As per directions concerning the utilization of antioxidants in nourishments, TBHQ is allowed for food use by the FDA and the USDA at under 0.02% and 0.01%, separately. At levels higher than 0.02%, TBHQ may apply an expert oxidant impact. In Japan and Europe, the expansion of TBHQ in nourishment is not permitted.

22.13.1.3 Gallates

Three esters of gallic acid are affirmed for use in nourishment, in particular, PG, octyl gallate, and dodecyl gallate. PG is a white crystalline powder that is somewhat soluble in both water and fat. Although the higher octyl and dodecyl gallate are for all intents and purposes insoluble in water, they get solubilized effortlessly in fats and oils. PG is generally utilized as a part of foods where lipid-solvent antioxidants, e.g., BHA, BHT, and TBHQ are not appropriate. They prevent autooxidation of oils and peroxide development in ether and display synergistic impacts with different antioxidants, e.g., BHA.

22.13.1.4 Natural Antioxidants

Worries about the security of engineered antioxidants have led to the increased research on characteristic wellsprings of antioxidants. They bring less thorough weight of security confirmation than that required for engineered ones. Be that as it may, natural antioxidants may have a few disadvantages, including high use levels, low antioxidant productivity, undesirable flavor or smell, and conceivable misfortune amid preparation. Ascorbic acid and tocopherols are the most critical business normal antioxidants.

22.13.1.5 Tocopherols and Tocotrienols

Tocopherols and tocotrienols, on the whole, known as tocols, are monophenolic and lipophilic compounds that are broadly dispersed in plant tissues. When all is said in done, tocotrienols have a more grounded antioxidant impact on lipid oxidation than tocopherols. Tocols are solvent in vegetable oils but insoluble in water. They work as a free radical eliminator in autooxidation responses. As common antioxidants, tocopherols have GRAS status, and they are viewed as safe food added substances. In the United States, common tocopherols are constrained to 0.03%, i.e., 300 ppm in animal fats, and 0.02% in blend with BHA, BHT, and PG.

22.13.1.6 Ascorbic Acid

L-Ascorbic acid (Vitamin C) and its salts (sodium ascorbate and calcium ascorbate) are extensive in plant tissues or are created artificially in huge amounts. Ascorbic acid is a white or somewhat yellow crystalline powder. It is an antioxidant with numerous capacities, including extinguishing different types of oxygen, diminishment of free radicals, and regeneration of essential antioxidants. Ascorbic acid and ascorbate salts have GRAS status with no usage limits. As indicated by the literature, vitamin C is protected at supplementation levels of up to 600 mg/day, and larger amounts of up to 2000 mg/day are without the chance. As common or characteristic indistinguishable items, they are much perceived as antioxidant supplements by customers.

22.13.2 Preservatives

In the pharmaceutical business, a significant number of the components utilized as a part of the formulation can advance microbial development. Such formulations are subsequently powerless to undesirable tainting. To keep this from happening, antimicrobial agents or preservatives should be added to the formulation. Theoretically, such preservatives protect the product against microbial proliferation but should not compromise product performance. Preservatives are substances added to different pharmaceutical dose structures and cosmetics to anticipate or hinder microbial development. A perfect preservative would be compelling at low concentration against all conceivable microorganism, be nonlethal and good with different constituents of the formulation, and be steady for the life span of the formulation. In practice, this means that any preservative or antimicrobial agent should:

- Apply a wide range of antimicrobial action against all microorganisms at low consideration levels.
- Maintain effectiveness all through item fabrication, the time span of usability and utilization.
- Be nontoxic and compatible with other constituents of the preparation.
- Not bargain the quality or execution of formulation, package or delivery system.
- Not unfavorably influence patient well-being or resistance of the formulation.

Criteria for choosing antimicrobial preservatives include:

- Preservative dose.
- Effects on the active ingredient.
- Antimicrobial functionality.

Classification of Preservatives

Based on their source of origin preservatives are classified as:

Natural Preservatives: These drugs are obtained by natural sources that are plant, mineral sources, animal, etc., e.g., neem oil, salt (sodium chloride), lemon, honey, etc.

Artificial Preservatives: These preservatives are man-made by chemical synthesis and active against various microorganisms in small concentration, e.g., benzoates, sodium benzoate, sorbates, propionates, nitrites, etc. (Shaikh et al., 2016).

Preservatives may be categorized based on their chemical nature as:

1. *Acids:* e.g., benzoic acid, sorbic acids, boric acids.
2. *Esters:* e.g., parabens, sodium propionate, potassium sorbate.
3. *Alcohols:* e.g., chlorobutanol, benzyl alcohol, phenyl ethyl alcohol.
4. *Phenols:* e.g., phenol, chlorocresol, *O*-phenyl phenol.
5. *Mercurial compounds:* e.g., thiomersal, nitromersol, phenylmercuric nitrate, phenylmercuric acetate.
6. *Quaternary ammonium compounds:* e.g., cetyl pyridinium chloride, benzalkonium chloride.

22.13.3 Colors

Colorants or shading specialists are for the most part used to bestow a particular appearance to the pharmaceutical dosage forms. We can likewise say that the colorants are the beautifying agents for the pharmaceutical formulations in light of the fact that the stylish appearance of dose structures can be improved by utilizing appropriate colorants. The fundamental classes of formulations that are shaded are tablets (either the center itself or the covering.), capsules, oral fluids, topical creams, toothpaste, balms, etc. The elegance and eye interest of a hued item are important. Pharmaceutical products are hued essentially to:

- Augment suitability.
- For detection.
- Amplify stability.

22.13.3.1 Classification

1. Organic Dyes and Lakes

Dyes: these are manufactured, chemical compounds that show their shading power or tinctorial quality when solubilized in a solvent. They are normally 80%–93% (infrequently 94%–99%) unadulterated colorant material. Dyes are likewise soluble in propylene glycol and glycerin. They are accessible at less expensive cost. E.g., tartrazine, sunset yellow patent blue V, erythrosine (Kanekar et al., 2014).

Lakes: They have been characterized by the FDA as the “Aluminum salts of FD&C water-dissolvable dyes stretched out on a substratum of alumina.” Lakes arranged by expanding the calcium salts of the FD&C colors are likewise allowed, however to date, none has been made. Lakes likewise should be confirmed by the FDA. Lakes, dissimilar to dyes, are insoluble, e.g., Sunset yellow lake, Indigo carmine lake (Allam and Kumar, 2011).

2. *Inorganic or mineral colors:* Light stability is a vital trademark showed by these materials, some of which have a valuable opacifying capability, e.g., TiO₂ (Allam and Kumar, 2011).
3. *Natural colors or vegetable and animal color:* This is an artificially and physically assorted gathering of materials. Some of these hues are the results of substance amalgamation as opposed to extraction processes, like beta-carotene. Examples of natural colorants include anthocyanins, curcumin, beetroot red, etc. (Kanekar et al., 2014).

22.13.4 Flavoring Agents

Flavor alludes to a blended vibe of taste, touch, notice, sight, and sound, all of which include a mix of physiochemical and physiological activities that impact the view of substances. With the extension of innovation in the flavor business, numerous artificial or impersonation flavors have been made. Pediatric and geriatric products now are accessible in an assortment of flavors which effectively cover unpalatable tastes without influencing the physical and chemical stabilization (Sharma and Sharma, 1988). Flavor acknowledgment is likewise influenced by age. As a rule, youngsters like organic product seasoned

syrup; grown-ups incline toward a more acidic taste, while numerous old individuals discover mint or wine enhancers more pleasing. Reaction to the flavor may not be the same as well-being and infection while a flavor satisfactory for a brief timeframe may end up noticeably questionable if the treatment is drawn out.

Flavors are likewise chosen on the premise of the essence of the medication to be joined. For example, to mask the salty taste butterscotch flavor is added, whereas for acidic taste citrus flavors are added. A portion of the flavors are favored for specific sorts of pharmaceuticals relying on their peculiar taste. For example, for antibiotics orange, vanilla, butterscotch, etc. are used, while on the other hand for decongestants and expectorants apricot, cherry vanilla, raspberry, etc. are preferred (Sharma and Sharma, 1988).

22.13.5 Emulsifying Agent

Emulsions are balanced out by including an emulsifier or emulsifying agents. These agents have both a hydrophilic and a lipophilic part in their substance structure. All emulsifying agents aggregate at and are adsorbed onto the oil: water interface to give a defensive obstruction around the scattered droplets. Notwithstanding this defensive boundary, emulsifiers settle the emulsion by lessening the interfacial strain of the framework. A few agents improve stability by giving a charge on the droplet surface consequently lessening the physical contact between the drops and diminishing the potential for coalescence. Some ordinarily utilized emulsifying agents incorporate SLS, Spans and Tween, sodium dioctyl sulfosuccinate, etc.

Emulsifying agents can be grouped by (1) structure; or (2) mode of action. Classes, as indicated by structure are synthetic, natural, finely dispersed solids and auxiliary agents. Classes, as indicated by mode of action, are monomolecular, multimolecular, and particle films. Notwithstanding their grouping, all emulsifying specialists must be steady in the framework, dormant and chemically nonresponsive with other emulsion parts, and non-toxic and nonirritant. They ought to likewise be sensibly scentless.

Natural Emulsifying Agents: They are gotten from plant and animal tissues and for the most part as hydrated lipophilic colloids. These emulsifiers influence the defensive sheath around the droplets, to render droplets a charge with the goal that they repulse each other and swell to boost up the consistency of the fluid. Albeit natural emulsifiers are modest, safe, and nonlethal, yet they are moderate in action in real life. So, the vast amount of emulsifier is required for legitimate activity. Additionally, the natural emulsifiers require preservatives as these are subjected to microbial development. The animal subordinates are more grounded than the plant ones. The best case of this is lecithin and cholesterol. A few people are hypersensitive to these so should be used in the wake of knowing the derivatives. Both semisynthetic and synthetic emulsifying agents require no preservative as these are not inclined to microbial development. They support the emulsion preparation by different mechanisms like interfacial tension reduction, interfacial film formation, and electrical double layer formation.

Categorization of emulsifiers can also be done as:

- Surfactants of synthetic origin.
- Hydrophilic colloids (natural and semisynthetic).
- Solid particles (finely divided).

Examples of Emulsifiers: soap, diacetyl tartaric acid esters, gum, lecithin, cetyl alcohol, methylcellulose, stearic acid, sodium carboxymethylcellulose, etc.

Soaps: Soaps or detergents may be anionic, cationic, and nonionic. They are amphipathic. One end sticks to oil (hydrophobic) and one end sticks to water (hydrophilic). Soap or synthetic detergent contains a long nonpolar tail and a polar or ionic head. The nonpolar end of the molecule dissolves well in nonpolar grease and oil while the polar or ionic head dissolves in water. The tail of soap molecule penetrates into oil or grease and breaks it up into tiny micelles.

Gum: Gum may be cationic, nonionic, or anionic, e.g., xanthan gum is anionic (natural), cationic guar gum (seminatural) is cationic, and guar gum is nonionic (natural). Gums are hydrocolloids that bind, thicken, and emulsify gluten-free ingredients. Guar gum is an emulsifier, thickener, and stabilizer endorsed for use in an extensive variety of food, beauty care products, and pharmaceuticals. It thickens without application of heat. It can act as a light emulsifier as it prevents oil droplets from coalescing. It can be easily solubilized in hot as well as cold water, has resistance to oil, greases, and solvents, with high viscosity, is functional at low temperature, and a better thickening agent. In baking it increases dough yield, in dairy products it thickens milk, yogurt, and liquid cheese products, for meat, it functions as a binder.

Lecithin: It is a sort of phosphoglyceride present in a variety of plant and animal substances, e.g., egg yolk. Naturally occurring phospholipids are derived from soybean. Both oil and water loving, lecithin is a vitamin supplement and a dietary supplement. An important component of cells, it can help nourish damaged cells and tissues and also helps in keeping skin soft and supple. Used in making surfactant, to improve flow property of chocolate, to reduce cholesterol level, and helps keep our blood's cholesterol circulating freely.

Methylcellulose: Series of methyl ethers of cellulose. Hydrophilic thickening agent and stabilizer for o/w emulsion; weak o/w emulsifier.

Stearic acid: An assortment of solid acid from fat, primarily stearic and palmitic. It is a lipophilic thickening agent and stabilizer for o/w lotion.

Sodium carboxymethylcellulose: Sodium salt of carboxymethyl ester of cellulose, hydrophilic thickening agent, and stabilizer for o/w emulsion

22.13.6 Suspending Agent

The particles in suspensions are encounter each other in a form of Brownian motion and the particles may overcome the repulsive power between them and shape bigger particles which will then settle quickly. Suspending agents decrease this development of the particles by expanding the consistency of the medium.

As per Stoke's law, the rate of sedimentation is inversely related to the thickness of the medium. So, the settling of the particles, either in flocculated or deflocculated framework, can be reduced by expanding the drag drive on the moving particles by increasing the consistency of the medium.

A number of suspending agents perform two capacities. Other than going about as a suspending specialist they likewise confer thickness to the arrangement. Suspending

agents shape film around particle and lessening interparticle fascination. Suspending agents likewise go about as thickening agents. They increment thickness of the arrangement, which is important to counteract sedimentation of the suspended particles according to Stoke's law. A decent suspension ought to have very much created thixotropy. The arrangement is adequately gooey when it avoids sedimentation and consequent accumulation or building up of the particles. At the point when fomentation is connected the thickness is diminished and gives great stream flow from the mouth of the container. Example: methylcellulose, carboxymethylcellulose, bentonite, gelatin, etc.

Examples of Suspending Agents: methylcellulose, hydroxyethylcellulose (HEC), acacia, carboxymethylcellulose, tragacanth, etc.

Methylcellulose: Methylcellulose is accessible in a few thickness grades, differences in methylation, and polymer chain length. Methylcellulose is more solubilized in chilly water than high-temperature water. Including methylcellulose in boiling water and cooling it with consistent blending gives a clear or opalescent gooey arrangement. Methylcellulose is steady at pH range of 3–11. As methylcellulose is nonionic, it is good with numerous ionic adjuvants. On warming to 50°C, the arrangement of methylcellulose is changed over to gel form and on cooling, it is again changed over to the arrangement of a solution.

Hydroxyethylcellulose: HEC has to some degree comparative attributes to methylcellulose. In HEC hydroxyethyl groups are connected to a cellulose chain. Not at all like methylcellulose, HEC is soluble in both hot and icy water and does not form gel on warming.

CMC: Carboxymethylcellulose is available at various consistency grades i.e., low, medium, and high. The choice of proper grade of CMC is dependent on the viscosity and stability of the suspension. If there should be an occurrence of HV-CMC, the thickness essentially diminishes when temperature increases to 40°C from 25°C. This may turn into a formulation stability concern. In this manner to enhance consistency and stability of suspension, MV-CMC is generally recommended.

Acacia: Acacia is not a decent thickening agent but rather generally utilized as a part of the unpremeditated suspension product. For thick powder, acacia alone is not fit for giving suspending activity; for this manner, it is blended with tragacanth, starch, and sucrose which are together known as Compound Tragacanth Powder BP.

Tragacanth: Tragacanth solution is gooey in nature, it gives thixotropy to the solution. It is a superior thickening agent than acacia. The greatest thickness of the arrangement of Tragacanth is accomplished after a few days, in light of the fact that it takes a few days to hydrate totally.

22.14 FUNCTIONAL AND COPROCESSED ADDITIVES

Inventions occur in the pharmaceutical industry on a regular basis to cope with the latest problems arising all around the globe. Besides all the advancement in novel drug delivery systems, unit dosage forms like tablets are still a priority for researchers due to the several advantages provided by the tablets, e.g., easy manufacturing, patient compliance, etc. (Patel and Pingale, 2014). Along with the advancement in the formulations

formulation, scientists have also focused on the manufacturing and development of multi-purpose additives with improved attributes in order to have better product quality. Emergence of new APIs having a variety of physical and chemical properties has also forced researchers to focus on the development of new additives to match the properties of new drug molecules. There are other factors too which have led to the development of new additives:

- Demand of direct compression methods.
- Need of multifunctional additives to substitute two or more additives during process.
- Enhanced production capacity of manufacturing machines which require additives also to maintain the quality of the product.
- Demand of patient specific products, e.g., hypertensive patients, diabetic patients, etc.
- Requirement to amend the attributes of the drug molecules, e.g., solubility, etc. (Babu et al., 2013).

Due to the excess utilization of additives for a variety of intentions, they have been treated as “functional ingredients” rather than “inactive ingredients.” A desirable property of an additive is the one which can upgrade the level of manufacturing or which can perk up the quality and thereby the performance of the formulation when utilized. The additives may be utilized to aid in the manufacturing process e.g., with compression, flow, ejection, etc. or to aid the product quality e.g., better dissolution, etc. (Katdare, 2006).

Coprocessing is a fresh notion of varying additive attributes by the addition of new attributes with the aid of a second additive by keeping the needed properties of the parent additive untouched (Bansal and Nachaegari, 2002; Nachaegari and Bansal, 2004).

A coprocessed additive is any combination of two or more additives obtained by physical coprocessing that does not lead to the formation of covalent bonds. Coprocessed additives have functionalities that are not achievable through sample blending.

22.14.1 Approaches for Development of Coprocessed Additives

Characteristics of the additives can be altered easily and on a large scale with the aid of either coprocessing or particle engineering. Earlier coprocessing was adopted in the food industry only to overcome some issues like solubility, stability, etc. For example, glucomannan and galactomannan were used to enhance the gelling traits of food products. In the pharmaceutical world, coprocessing was introduced in the late 1980s in the coprocessing of MCC with calcium carbonate followed by the coprocessing of cellulose and lactose (Cellactose) in the year 1990.

Coprocessing: In this process additives interact at subparticle level with an objective to provide the enhanced and improved synergistic traits of both the additives and at the same time mask the undesired characteristics of each additive. Generally, it is done with the aid of codrying and coprecipitation. Both the additives are dispersed in a solvent followed by drying, resulting into a physical mixture which is brought to a desired size range. While making a coprocessed additive the selection of components should be done wisely in such a manner that the properties of each component should complement each other.

A typical process of coprocessing may involve the following steps:

- Selection and identification of group of additives to be co-processed.
- Selection of different ratio of the additives.
- Determination of particle size of coprocessed additives.
- Finalization of proper drying process.
- Process optimization.

Particle engineering as a source of new additives: This is a technique where the alteration of different properties of particles such as size, shape, etc. is involved. These alterations result in the transformation of the bulk properties, e.g., flow, compression, etc. Characterization of solids can be done at three different levels, i.e., molecular level, particle level, and bulk level. These three levels are interrelated in such a way that minute changes in a single level will result in alterations in other levels. As stated earlier modulation in particle level will alter the traits at bulk level too. This interrelation provides the scientific basis for development of new additives. The formulation of the new additive must start at the particle design. The crystal lattice modulation can be easily done by altering the conditions of crystallization, drying, etc. It is also possible to engineer particles without affecting the preceding molecular level. The modulation of single additive provides limited improvement in the functional traits, therefore, to have the improved traits at a larger scale coprocessing of multiple additives is needed.

22.14.2 Properties and Advantages of the Coprocessed Additives

No chemical modification: A number of studies on coprocessed additives have shown that no chemical modulation happens after coprocessing. This helps in reducing regulatory compliance.

22.14.2.1 Alteration in Physicomechanical Traits

Better flow properties: Alteration in the size and size distribution results in excellent flowability which excludes the addition of glidants.

Improved compressibility: Quasi-hornification is a phenomenon where an additive loses the compressibility on water addition which can be regained after coprocessing, e.g., MCC regains its compressibility when coprocessed to SMCC.

Improved dilution capacity: It is an attribute where additives compressibility remains unaltered even after dilution with others, e.g., Cellactose.

Fill weight variation: Bad flowability results in the higher fill weight variations but this doesn't occur with coprocessed additives which may be due to the particle to particle matrix impregnation.

Reduced lubricant sensitivity: Coprocessed additives are made of two opposite behavior materials which complement each other, e.g., brittle material (lactose monohydrate) and plastic substance (cellulose). In the mentioned combination cellulose offers better bonding, whereas lactose monohydrate gives low lubricant sensitivity (Tatavarti et al., 2005).

22.15 CLASSIFICATION OF PHARMACEUTICAL DILUENTS

Pharmaceutical diluents which are also termed as filler or thinner are diluting substances. These are static materials which serve as fillers in different formulations during their manufacturing processes, e.g., tablet and capsule, etc. These make up the major portion of a tablet or capsule. Lactose is used often because it is inexpensive, stable, and does not react with other medicinal substances. Furthermore, lactose has rapid solubility in water which is an advantage for the quick release of a drug substance. Other diluents used are starch (from wheat, corn, rice, and potato) sucrose, mannitol, avicel, and celutab, etc. Some fluids are unable to flow properly due to their higher viscosity which can cause a serious financial problem as it is costlier to transport such liquids. But this problem can be easily solved by the use of diluents which can decrease the viscosity and thereby the carrying costs of the viscous liquids.

Tablets are designed in a manner so that the possible punchable sized tablet can be manufactured. Where the dose is very small, a large quantity of diluents are added to prepare the tablets of desired size, whereas for higher dose drugs fewer diluents are needed. The addition of diluents may induce physical or chemical changes which can result in unstable product hence the choice of diluents should be made wisely. The intention of addition of diluents to different formulations is to have some advantages like:

- Better cohesion.
- Enabling direct compression.
- Improved flow properties.
- Weight adjustment as per die/machine capacity.

Categorization of tablet diluents can be done as follows:

- Organic diluents—e.g., Carbohydrate and tailored carbohydrates.
- Inorganic diluents—e.g., Calcium phosphates and others.
- Coprocessed Diluents.

During wet granulation process, carbohydrate, e.g., sugars, starches, and celluloses, can also serve as binders but they can also serve as diluents if utilized during direct compression process, unlike inorganic diluents.

Also, solubility can be used as criteria to classify the diluents. Sugars, e.g., sucrose, mannitol, etc., are in the insoluble diluent category, whereas MCC, starch, etc. are in the insoluble category.

22.15.1 Organic Diluents

Lactose Monohydrate (Hydrous): This is utilized in wet granulation as it is not directly compressible. Also, it is water soluble, economic, doesn't affect drug release, has poor flow attributes and results in hard tablets which continue hardening during storage. Lactose monohydrate containing formulations are more prone to instability as it includes 5% of hydrous composition.

Spray-Dried Lactose: This diluent is also utilized in the pharmaceutical industry due to its inherited attributes like direct compressibility, free-flowing, etc. But it is costlier when compared to hydrous and anhydrous lactose. Also, it gets darker in color with amines and similar compounds and due to excess moisture which may be attributed to furaldehyde.

Lactose Anhydrous: Unlike hydrous lactose, it is directly compressible. It has poor flow characteristics, undergoes Maillard reaction to very little extent, is cheap, and can absorb moisture under high humidity conditions.

Mannitol: It is water soluble, costly, has bad flowability, less hygroscopic, noncarcinogenic, and inherited with low caloric value and popularly used in chewable tablets.

MCC: It has good compressibility and is popularly used as tablet diluent and results in good hardness of tablets even at low pressure. Also, it has satisfactory flowability and is comparatively pricey. It also exhibits binding and disintegrant properties. During compression of tablets, it may face plastic deformation and thereby is more susceptible to lubricants. Variants of MCC, i.e., silicified MCC, provide some advantages over MCC, e.g., augmented compactibility, improved flowability, etc.

22.15.2 Inorganic Diluents

Calcium Phosphates: Calcium phosphates are low priced have good flow attributes, non-hygroscopic, compressible, and result in hard tablets, while at the same time their abrasive behavior causes machine wear and tear and the alkaline pH results in instability.

They include hydrated and anhydrous variants of dibasic and tribasic calcium phosphate. They have found their wide application in both direct compression as well as in wet granulation. A variant of dicalcium phosphate, i.e., spherically granulated dicalcium phosphate anhydrous has found good flowability, good compressibility, and increased moisture uptake under high humid conditions as a contrast to dicalcium phosphate dihydrate (DCPD).

22.15.3 Coprocessed Diluents

Cal-Tab: It is a combination of Calcium sulfate and vegetable gum (93:7).

Sugartab: It is a blend of Sucrose (90%–93%) and invert sugar (7%–10%).

Emdex: It is an intermingle of Dextrose (93%–99%) and maltose (1%–7%).

22.16 PHARMACEUTICAL SOLVENTS

Solvents are chemical substances that can dissolve, suspend, or separate different substances more often than not without chemically changing either the solvents or alternate materials. Solvents can be organic, which means the solvent contains carbon as a major aspect of its constitution, or inorganic, which means the solvent does not contain carbon. For example, hydrocarbon and oxygenated solvents are organic solvents that can adequately dissolve numerous materials.

Viable synthesis of an API is, as a rule, a multilevel and confounded process. Generally, chemical synthesis comprises of four stages: reaction, separation, purification, and drying. Regularly employments of solvents in the union are solubilization (reaction medium), extraction, and crystallization. They may likewise participate in reactions, as reactants or catalysts and furthermore partake in azeotropic or extractive refining processes as entrainers. The principle capacity of solvents in a reaction step is solubilization. Solvents make solutes more responsive by breaking strong bonds that hold crystalline and fluid solutes together. An assortment of solvents are utilized as a part of the extraction process, e.g., chlorinated solvents, e.g., chloroform as well as ketones, ethers, esters, and alcohols. In numerous crystallizations the control of properties, e.g., size and shape, is an imperative factor (Grodowska and Parczewski, 2010).

Organic solvents can also be utilized as a segment of the last product and don't need to be evacuated. Generally, they satisfy the capacity of diluents or solubilizers, primarily in fluid and semisolid dosage forms when water can't be utilized. Fluid production comprises of dissolving the dynamic pharmaceutical ingredient in a proper solvent, regularly with different preservatives and different additives, and blending the ingredients totally.

The most famous and the most alluring solvent for these medications is water. The most up to date innovations effectively maintain a strategic distance from organic solvents for water. Nonetheless, here and there the utilization of nonaqueous solvents is fundamental. In such cases, they can be utilized independently or in blends of at least two solvents (cosolvents).

In the wet granulation procedure of tablet generation, solvent (granulation liquid) causes massing of a dry blend powder. Solvents for granulation might be utilized alone or with the expansion of different substances that enhance the adhesive properties of particles. Much of the time, water is utilized for the granulation procedure.

Previously, the pharmaceutical business expected to bring together regulations and breaking points for residual solvents (RSs). For a long time, the United States Pharmacopeia was the main pharmacopeia setting limits for RSs in pharmaceutical items. In 1990, limits for RS were recommended in Pharmeuropa and, all the more as of late, in the second International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) rule draft. The ICH distributed its Guidance for Industry Q3C, in December 1997. ICH guideline traded off regulatory specialists from Europe, Japan, and the United States, and also agents of the research-based pharmaceutical companies. As per Q3C guideline, solvents are isolated into four groups.

The primary gathering (*Class 1*) contains known human cancer-causing agents, compounds emphatically associated with being human cancer-causing agents, and natural risks, e.g., 1, 2-dichloroethane, carbon tetrachloride, benzene, etc.

Class 2 comprises of solvents which should be constrained in light of the fact that they are nongenotoxic animal cancer-causing agents or conceivable causative specialists of irreversible toxicity, e.g., neurotoxicity or teratogenicity. They are additionally associated with other huge, reversible toxicities, e.g., chlorobenzene, cyclohexane, 1,2-dichloroethene, etc.

Class 3 solvents have authorizations of day by day exposures of 50 mg (0.5%) or less on per day basis.

Class 4 solvents. For this group, there is no sufficient toxicological information empowering a plan of satisfactory limits. On the off chance that makers need to utilize Class 4 solvents, they should make available advocacy for residual levels of this class of solvents in a formulation (ICH-Q3C(R6), 2016). The solvents are classified as inorganic solvents and organic solvents

22.16.1 Inorganic Solvents

Water: It is polar in nature and considered as a universal solvent. Like other pharmaceutical substances, water must affirm to GMP standards. It must be versatile and consent to WHO rules for drinking water quality.

Types of pharmaceutical water:

Bulk form:

- Purified water.
- Water for injection (WFI).

Packaged form:

- Bacteriostatic water for injection.
- Sterile water for inhalation.
- Sterile water for injection.
- Sterile water for irrigation.
- Sterile purified water.

Purified Water: It is a sort of water that has been mechanically separated or handled to expel debasements and make it appropriate for utilization. It may come from either a spring or surface or groundwater source or straightforwardly from the tap. Since the cleaning procedure is intended to expel practically a wide range of polluting influences, the nature of the source water has small bearing on the nature of the last item. Purified water is typically created by the cleansing of potable water. The contaminations that may be required to be separated out are organic compounds, inorganic ions, bacteria, endotoxins, and nucleases.

WFI: This is pyrogen-free water, purified by distillation for the manufacturing of parenteral formulations. It is intended for use as solvent only in solution, i.e., to be sterilized after preparation and endotoxin content must be controlled. Water for injection can be prepared under aseptic conditions. It does not contain any additive. It must meet the standards of pyrogen test and sterility test for purified water.

Types of WFI

- Potable Water: Utilized in early stages of chemical synthesis.
- Purified Water: Utilized as additives in production of pharmaceuticals.
- Bacteriostatic Water for injections (USP): Contains added antimicrobial preservatives which prevent the growth of microorganisms.

Sterile Water for Injection (USP): It is a nonpyrogenic and sterile form of water for infusion which contains no bacteriostat, antimicrobial, or included buffer and is provided just

in the single-measurement container to dilute or solubilize drugs for the parenteral purpose. For I.V. products, an adequate solute is added to make an isotonic arrangement. This parenteral formulation is demonstrated just to dilute or dissolve drugs for intravenous, intramuscular, or subcutaneous products, as indicated by guidelines of the producer of the medication to be administered.

Bacteriostatic Water for Injection (USP): It is a nonpyrogenic, sterile form of water for injection containing 0.9% (9 mg/mL) of benzyl alcohol included as a bacteriostatic additive. Bacteriostatic water for injection is made up from WFI that is disinfected and reasonably bundled, containing at least one appropriate antimicrobial specialist.

Sterile Water for Irrigation (USP): It is a hypotonic, nonpyrogenic, sterile irrigating liquid or pharmaceutical aid completely made out of Sterile Water for Injection USP. It is made up by distillation and contains no antimicrobial or bacteriostatic additives or included buffer and have pH 5.7 (5.0–7.0).

Sterile Water for Inhalation Injection: It is packed and made sterile and is planned for application and preparation of inhalational formulations. It conveys less stringent particulars for bacterial endotoxins than sterile water for injection, and in this way, is not appropriate for parenteral products.

22.16.2 Organic Solvent

Organic solvents are always present in the pharmaceutical manufacturing procedures. The pharmaceutical business is one of the biggest clients of organic solvents per measure of the final formulation. For toxicological causes, makers try to limit the number and measure of solvents connected in a drug manufacturing process. Due to some physical and chemical hindrances, organic solvents can't be totally disposed of from the item by manufacturing processes, e.g., by drying in a raised temperature under diminished pressure or by lyophilization. Normally some little measures of solvents may stay in the final product. They are called RSs, additionally regularly known as organic volatile impurities. Extraordinary headings distributed in pharmacopeias and ICH guidelines decide the greatest reasonable measures of RS in pharmaceutical products. If the measures of RS are beneath the limits the examined product is cleared as available to be purchased.

Organic solvent use in pharmaceutical drug manufacturing processes ([Bauer and Barthélémy, 2001](#)):

- *Alcoholic solvents*: ethanol, butanol, 2-ethylhexanol, isobutanol, isopropanol propanol, etc.
- *Ketones*: methyl ethyl ketone, acetone, methyl isopropyl ketone, etc.
- *Halogenated solvents*: Chloroform, etc.
- *Amides*: dimethylformamide, etc.
- *Ethers*: ethyl ether, etc.
- *Sulfur containing*: DMSO, etc.
- *Nitriles*: acetonitrile, etc.

22.17 EVALUATION AND QUALITY TESTING OF PHARMACEUTICAL ADDITIVES

The FDA's key role is to verify safety issues for drug items and additives because the pharmacologically inactive additives make up the majority of a drug product. Shockingly, there are some outstanding cases of patient mischief that came about because of additive impurity influences. This section concentrates on the issues expected to guarantee that the additives utilized as a part of drug product fabrication are truly what they are proposed to be. They should meet manufacturing determinations and regulatory prerequisites (Petersen et al., 2004).

In the blend with the extension of reasonable manufacturing procedures, the additive maker ought to create suitable Quality test techniques, where the additive is marked as meeting the requirements of a monograph. Test techniques that don't take the majority of the points of interest portrayed in the monograph ought to be invalidated. This involves recorded logical proof demonstrating additive meets the assigned monograph determination parameter.

In the event that different strategies are created and considered more agreeable, they should be validated against the detailed techniques or strategy and observed to be proportionate to or superior to the compendial technique. Their utilization ought to be legitimized. If there is an irregularity between the outcomes accomplished utilizing the compendia strategy and the manufacturer's technique, the compendia technique is considered the official outcome. Frequently an additive manufacturer will build up its own test technique for different processes, e.g., to give affirmation the additive meets the planned execution necessities or to screen or manage the existence of different ingredients. These noncompendial systems must match the necessities for a reasonable test procedure as ordered in the compendia. Test procedures fall into two characterizations; those which can and those which can't be approved. Instances of systems which can't be approved include estimations, ordinarily including physical procedures, e.g., bulk density and refractive index which rely upon organizing estimation using adjusted instruments. Such techniques can't be validated in the classical manner.

Another characterization is for procedures which can be approved. There should be a validation rule and report for the entirety of procedures that are noncompendial. The validation protocol ought to depict the examination with a specific end goal to demonstrate the strategy is proper, including such points of interest as a portrayal of the test technique, reagents, standards, and so on. The protocol ought to likewise depict the test outcomes that must be accomplished keeping in mind the end goal to consider the technique validated. After commencement of validation has been coordinated, there should be a report filing the test results and conclusion. Test strategy approval may consolidate appraisal of things, e.g., exactness, specificity, linearity, etc. ICH Q2 validation direction gives extra points of interest on validation (ICH-Q2(R1), 2005).

22.17.1 Additive Specifications

A specification should be in accordance with the established material monograph. Draft or conditional specifications ought to be produced that are as per acknowledged standards

and are reliable with the manufacturing procedure and its procedure ability. The additives end use (oral, sterile, dermal) should moreover be considered in building up these specifications. The specifications ought to incorporate control of the composition (e.g., RSs) identified with both the crude materials and the manufacturing procedure. It is essential that proper cutoff points for the addition of microbial tallies and compendial marker organisms ought to be built up in light of the probability for microbial contamination and the capacity of the additive to help microbial development. If the additive is planned for use in parenteral drug items, proper points of confinement ought to likewise be built up for endotoxins.

The draft specification for compendial additives ought to contain determined extents for all results that guarantee the additive meets the compendial prerequisites. If the additive is not compendial, at that point the predetermined extents ought to guarantee the additive matches the specialized and regulatory prerequisites fitting the utilization and route of administration.

22.17.2 Additive Stability

The additive stability should be sufficient that the additive stays within sales specification until past its expiration period. The additive provider ought to give information to demonstrate soundness in the commercial packs and characterized stockpiling conditions that are expected to shield the additive from spoilage all through the inventory network. If stability information is not accessible; the additive client may need to create it themselves. Preliminary data can be created utilizing accelerated stability studies and conditions portrayed in the ICH guideline Q1A. This guideline was created for drug substances (APIs) and drug formulations, so assessment of additive stability is done under the guidance of these guidelines. Preferably, tests of three commercial batches of the additive ought to be utilized to set up the stability of the additive in the commercial pack. Tests of the additive from these batches ought to be put away in commercial conditions or in the most pessimistic scenario of packing material under the prescribed stockpiling conditions. Occasionally, additives ought to be examined from the three batches and tested to ensure they exhibit conformance of stability through the expressed expiry time frame ([Kadtare, 2006](#)).

22.17.3 Receipt, Sampling, Testing, and Approval of Raw Materials

The COA is the additive manufacturer's duty: to check the item and guarantee that it is legitimately tested, handled, and stocked after production. Upon supply of a shipment, each batch of additive should be withheld from use until the point that the parcel is inspected, tried, or analyzed by the specified methodology. The QC workforce will inspect every package for the manufacturer's name, the lot number, any kind of leakage, contamination, infringed containers, packaging and labeling, and Material safety data sheet.

Samples of every shipment must be gathered for testing. The quantity of containers to be examined relies upon the component inconstancy, confidence level, level of precision, past quality history of the provider, and the amount required for investigation and reserve

stock. For dangerous or profoundly toxic crude materials, in which on-site testing might be unreasonable, providers' COA ought to be gotten, demonstrating that the raw materials conform to specifications by examining its labeling and packaging. The absence of on-site testing for perilous raw materials ought to be reported. Each sack or container of raw materials ought to be related to a special code, lot, or receipt number which is utilized as a part of recording the disposition of each parcel. Crude materials should be put in custody under isolated conditions until the point when they are inspected, tested, and discharged. Raw materials ought to be deliberately handled and put away to maintain a strategic distance from any contamination or cross-contamination. When sacked and boxed crude materials are secured, it must be done as such in enough cleaned structures that are free of invasion by rodents, fowls, creepy crawlies, and other vermin, and the building ought to be maintained. A controlled environment might be important to maintain a strategic distance from microbial contamination or degradation caused by the introduction of temperature, air, or light. When the crude materials are secured outside, the container should be acceptable for the outdoors stockpiling. A sample of each package will be assembled for testing according to the developed technique. A number of compartments to test and the illustration measure should be established on indicated criteria as required (Tatavarti et al., 2005). Test containers ought to be appropriately labeled. The label ought to incorporate information about the example name, manufacturer name, test size, and date and hour of examining. Raw material containers chosen for examining ought to be opened, sampled, and resealed in a control condition to protect from contamination of the crude materials themselves or other material. After QC controller stamp is endorsed, the material is discharged and the item is exchanged from quarantine to the accessible stock range to be used. If QC lab rejects the material, it will be moved into a different region. Raw materials ought to be reevaluated, as fundamental, to decide their reasonableness for utilization (e.g., after prolonged stockpiling or after introduction to temperature or high mugginess).

22.17.4 Packaging and Labeling Control

Stockpiling conditions ought to be mentioned on the label of containers. Point by point composed strategies clarifying the accepting, handling, recognizing, putting away, and testing of the crude materials ought to be set up. Crude material container names ought to contain the material name, provider's name, lot number, stockpiling conditions, retesting date, and some other notices or risks. Named stockpiling conditions should be according to standard definitions for "Controlled Room Temperature," "Cold," or "Freezer," as characterized in the USP or guidelines of the ICH. The label on every container ought to likewise involve any notices to watch the contents from unjustifiable warmth, light, dampness, or freezing. Any labeling or packing substances that don't meet the specifications ought to be disposed of properly.

22.17.5 Analytical Procedures

Analytical techniques and references ought to be open if the systematic strategy utilized is in the present revision of another FDA-perceived standard reference (e.g., AOAC

International Book of Methods), and the referenced expository methodology is not adjusted. In any case, the validated systematic methodology for novel additives ought to be given. The ICH guidelines (Q2A, Q6B) can be used to facilitate.

22.18 CURRENT DEVELOPMENTS IN ADDITIVE SCIENCE

With the progress from basic formulations to drug delivery frameworks, the interest in synthetic or semi-engineered utilitarian polymers, e.g., acrylates, has increased colossally. In the current scenario, as the pharmaceutical business needs to manage the patent cliff, reduced healthcare spending, and more thorough regulations, drug advancement has turned out to be muddled. In any case, new additives offer open doors. A novel additive could reformulate endorsed drugs to show signs of improving quality and safety of the pharmaceutical or to trim down its assembling costs. Regardless of the quantity of modulated and coprocessed additives to have gone to the market as of late, all producers avoid their advancement in light of the fact that the procedure is time-consuming, requires assets, and is related with high disappointment risks.

There's a formulation change in many aspects. First of all, the API is coming up in many novel formats. For biologics, we've seen changes in the regime from monoclonal antibodies to multivariations of antibody formats. In formulation research, people are looking for further stable formulations with extended life cycles and longer shelf life. Aside from dependable qualities, the progression and assessment of new additives involve a multidisciplinary comprehension of technical, safety, quality, and regulatory perspectives. The technical complexities linked with drug development have amplified over the years. This is mainly due to the challenges associated with the drug solubility problems, complex drug actives, and stability of the drugs. More often than not, the present arrangement of additives in endorsed products is not sufficient to plan challenging molecules, compelling pharmaceutical researchers to explore new additives. International pharmacopias had defined the list of purposes for which certain additives are used. Many additives have more than one use, which can be a plus since it shrinks the number of additives needed and minimizes the risk of interactions between them (Steinberg et al., 1996).

Right now, it is expected that an additive is "accepted" when a novel formulation, of which it is an ingredient, gets regulatory acknowledgment. Existing regulations and guidelines demonstrate that the latest additives ought to be tested for full toxicological assessment like a new chemical entity. No authority is accessible for possibly valuable materials (basically new additives) available from different businesses, e.g., established additives with another application, e.g., route of administration change. Be that as it may, regardless of this state, drug organizations are effectively assessing new materials or applying new uses to existing additives (Baldrick, 2000).

In spite of the absence of regulatory direction, the advancement of new or change of existing additives has been growing as of late. What's more, the use of new additives in old drug formulations for a variety of pharmaceutical classes is being researched, e.g.,

- Different applications are being examined for the polysaccharide chitosan which is an acknowledged nourishment additive. These look at the use in controlled-discharge

matrix tablets, in novel formulation (e.g., for hormone discharge) in transmucosal drug delivery and in wound recovering. Preclinical assessment to date has demonstrated no unfavorable toxicity (Illum, 1998).

- Aquateric watery enteric coating in solid dose forms has as of late experienced subchronic and formative toxicity examinations in light of IPEC proposals with no antagonistic impacts or genotoxicity found (Batt and Kotkoskie, 1999).
- PEGs are recognized as a settled part of protected pharmaceutical additives. The protection of these substances as enhancers has been evaluated in different toxicity quality investigations with just mellow local toxicity observed (Hjortkjaer et al., 1999). PEG 400 exhibited no unfavorable impacts on the morphology and respectability of the nasal mucosa when tried as an enhancer (Rahman and Lau-Cam, 1999).
- A variety of distributed information exists for the utilization of liposomes (phospholipid-based vesicles) or smaller particles (micro/nano) having additives to advance the delivery of applicant drugs. It has improved stability and toxicity with a sustained life span of activity and has a part in particular site delivery. No unfriendly impacts have been accounted for liposomes (Maheshwari et al., 2012, 2015).
- Microspheres/nanospheres prepared from polymer-like PLGA are right now being assessed for an assortment of controlled-discharge drug delivery applications. A humanized monoclonal antibody administered intravitreally of PLGA microspheres demonstrated no unfavorable impacts with the additive from its toxicology and pharmacokinetics data (Tekade et al., 2017).
- The polyol erythritol has been assessed for metabolic and toxicological evaluation in animal and tests with human has been appeared to be very much endured with no toxicological reporting (Munro et al., 1998).

22.19 INTERNATIONAL PATENTED ADDITIVES

22.19.1 Sustained Release Excipient and Tablet Formulation (US5128143 A)

The present invention relates to a sustained release pharmaceutical excipients product that may be intermingled with a variety of therapeutically active agents and tableted. A controlled-released additive embraced of hydrophilic gum matrix having combination of two gums, i.e., xanthan and galactomannan gum proficient of cross-linking under the environment of gastric fluid with xanthan gum. The proportion of said xanthan to said galactomannan gum being from in regards to 3:1 to question 1:3, and a dormant diluent, the proportion of said idle diluent to said hydrophilic gum grid being from around 4:1 to around 0.67:1, and a productive amount of a medicament to render a therapeutic impact, the proportion of said medicament to said hydrophilic gum framework being from around 1:3 to around 1:10 (Baichwal and Staniforth, 1990).

22.19.2 Cross-Linked Cellulose as Some Tablet Excipients (US5989589 A)

Cross-linked cellulose is a magnificent binder disintegrant that can be utilized as a part of the formulation of pharmaceutical tablets. The tablets that are so arranged are made of

a compacted blend of a powder of a pharmaceutically dynamic ingredient with a powder of a pharmaceutical additive including a pharmaceutically worthy type of cross-linked cellulose in an amount up to 35% by weight of the aggregate weight of the tablet. The cross-linked cellulose is detailed by cross-linking microcrystalline or fibrous cellulose with a cross-linking mediator. Tests have exhibited that cross-linked cellulose is anything but difficult to integrate and has low binding/disintegrating which is determined by the degree of cross-linking degree. At low cross-linking degree, cross-linked cellulose is more a binder than a disintegrant although at a degree of high cross-linking, it is more a disintegrant than a binder (Cartilier and Chebli, 1997).

22.19.3 Low-Melting Moldable Pharmaceutical Excipient and Dosage Forms Prepared Therewith (US5004601 A)

An additive for a pharmaceutical compound dissolving at body temperature but that won't immediately distort at higher temperatures experienced in shipment was readied. A low-melting pharmaceutical additive consisting essentially of low MW PEG 75%–90% (M.P. about 37°C), medium to high MW PEG 0%–4%, long-chain saturated carboxylic acid 0%–4%, polyethylene oxide 0%–4%, and (MW 100,000–5,000,000) colloidal silica 10%–20% (Snipes, 1988).

22.19.4 Pharmaceutical Excipient Having Improved Compressibility (US5585115 A)

An additive based on MCC having improved compressibility, regardless of whether used in direct compression, dry granulation, or wet granulation formulations, was readied. The additive is the blend of MCC particles and silicon dioxide particles (0.1%–20% by weight of the MCC), wherein the MCC and silicon dioxide were in suggested association with each other. The silicon dioxide used in the novel additive has a molecule estimate from around 1 nm to around 100 μ m (Sherwood et al., 1995).

22.19.5 Trehalose as Stabilizer and Tableting Excipients (US4762857 A)

An improved method for preparing tablets useful in diagnostic and therapeutic applications, utilizing trehalose as an additive and stabilizer, was provided. In the method of tableting powders for therapeutic applications, wherein the powders were the product of an spray freezing process, for obtaining frozen droplets by spraying an aqueous solution of ingredients useful in therapeutic applications onto the surface of a moving bath of boiling perfluorocarbon liquid, followed by lyophilization of the droplets to dried powders suitable for tableting, the improvement comprising tableting the dried powders with the use of trehalose as tableting additive and stabilizer (Ernest Bollin and Fletcher, 1987).

22.19.6 Coprocessed Tablet Excipient Composition Its Preparation and Use (US20130177649 A1)

The development relates to a coprocessed additive piece reasonable for tableting, said creation involving no less than one filler-binder, no less than one disintegrant and no less than one lubricant which has been subjected to granulation mutually, and said arrangement to some degree or entirely covered with lactose, ideally in crystalline form. The creators defeated the bias contrary to the utilization of lubricants in tableting additive structures right on time in the tableting procedure. It was discovered that the claimed negative impacts of the lubricant as far as binding and disintegration could promptly be controlled in an additive arrangement wherein the lubricant is coprocessed in the matrix, and the composition is furnished with a lactose coat. The coprocessed additive comprising 40%–70% lactose, 20%–50%, MCC, 10%–10% cross-linked sodium starch glycolate and 0.2%–1% lubricant, based on total dry weight of the composition (Gessel, 2010).

22.19.7 Chemical Additives to Make Polymeric Materials Biodegradable (US8513329 B2)

In the present development another additive material that was physically mixed with polymeric material to make no less than a mostly biodegradable product, was prepared. An admixture which was used for enhancing biodegradation of polymeric material when added thereto comprising a furanone; a glutaric acid; a carboxylic acid compound comprising a chain length from about 2 to about 36 carbons; a polymer chosen from the cluster of poly-caprolactone, polycaprolactone, poly(lactic acid), poly (glycolic acid), and poly(lactic-co-glycolic acid); and a carrier resin selected from the collection consisting of polydivinyl benzene, ethylene vinyl acetate, polyethylene, polypropylene, polystyrene, polyethylene terephthalate, polyvinyl chloride, methyl methacrylate, polycarbonate, polyamide, poly olefins and any copolymers of said polymers (Lake and Adams, 2008).

22.19.8 Coprocessed Microcrystalline Cellulose and Sugar Alcohol as an Excipient for Tablet Formulations (US 8932629 B2)

A particulate coprocessed synthesis containing MCC and no less than one sugar alcohol was formulated. The flavored sugar alcohol was mannitol. The structure had a better compressibility profile, lubricant affectability, and ejection profile than MCC and the no less than one sugar alcohol, either alone or in a blend as a simple dry mix, in the development of solid dose formulations, e.g., tablets. The composition of said additive was MCC and at least one sugar alcohol in ration 70:30 to 95:5 (Li et al., 2007).

22.20 FDA GRAS ADDITIVES

Under the 1958 Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act, any substance purposely added to food is a food additive and is liable to premarket

endorsement by FDA unless the utilization of the material is GRAS (the GRAS arrangement) (or generally excepted from the meaning of food additive, e.g., color additive). By 1961, FDA had revised its regulations to incorporate a rundown of food substances that are GRAS under specific states of utilization (“the GRAS list”). In the 1960s, numerous producers asked for FDA’s judgment on whether their decisions of GRAS status were advocated and received “opinion letters.” In 1969, FDA expelled cyclamate salts from its GRAS list because of safety inquiries, and afterward, President Nixon guided FDA to reexamine the safety of GRAS substances.

In the 1970s, FDA announced that it was leading a “comprehensive review” of assumed GRAS substances and built up rulemaking methods to affirm the GRAS status of substances that were either on the GRAS list or the subject of an appeal (“GRAS affirmation”). To remove the rulemaking methodology, in 1997, FDA proposed to supplant the GRAS affirmation to process with a notice strategy (“GRAS notification”) (Burdock et al., 2006).

22.20.1 Substances That Are Generally Recognized as Safe

1. It is not reasonable to list all material that is GRAS for their proposed utilization. Be that as it may, basic food ingredients, such as pepper, vinegar, monosodium glutamate, etc., are viewed as safe for their proposed utilization. Extra substances are incorporated here that, when utilized for the reasons showed, as per GMP, are viewed as GRAS for such employment.
2. For the motivations behind this segment, GMP should be characterized to incorporate the accompanying limitations:
 - a. The measure of a substance added to food does not outperform the whole sensibly critical to finish its proposed physical, supporting, or other specific effect in nourishment; and
 - b. The measure of a substance that turns into a constituent of food because of its utilization in the manufacturing, preparing, or packaging, and this is not planned to achieve any physical or other specialized impact in the food itself, might be diminished to the degree reasonably conceivable.
 - c. The substance is of proper food grade and is arranged and dealt with as a food ingredient. Based on specification and expected use, it is viewed as safe for the reason proposed, by specialists qualified to assess its safety.
3. The consideration of substances in the rundown of nutrients does not constitute a finding with respect to the Department that the substance is valuable as a supplement to the eating regimen for people.
4. Substances that are GRAS for their proposed use inside the importance of segment 409 of the act, but when status of additive or ingredient is revised, it will be erased from this part, and will be issued as another control under the suitable part.

22.20.2 Examples of GRAS Additives

Spices and Other Natural Seasonings and Flavorings: e.g., angostura (cusparia bark), anise, capsicum, caraway, cardamom, spearmint, turmeric, vanilla, etc.

Multiple Purpose GRAS Food Substances: aluminum sodium sulfate, caffeine, calcium phosphate, caramel, glycerin, methylcellulose, monoammonium glutamate, monopotassium glutamate, sodium carboxymethylcellulose, etc.

Anticaking Agents: calcium silicate, etc.

Chemical Preservatives: sorbic acid, calcium ascorbate, potassium bisulfite, sodium bisulfite, sodium sorbate, tocopherols, etc.

Stabilizers: *Chondrus* extract.

Nutrients: ascorbic acid, calcium pyrophosphate, choline bitartrate, etc.

22.21 CONCLUSION

The pharmaceutical additives are being used in each and every formulation, but due to the lack of awareness as well as regulations regarding the additives, patients, being the end consumers, may have to suffer the serious side effects. A few countries like the United States, China, Japan, and India have put the efforts into developing the regulations for the additives along with FDA but still their implementation during the manufacturing process of additives as well as formulations is still in doubt. All the additives should be manufactured, tested, stored, and utilized according to the specific guidelines. The GRAS status to different additives has sorted a variety of problems related to additives but still the GRAS additives should be utilized within the specified limits as per the guidelines. The mere GRAS status to different additives doesn't justify the irrational utilization of the additives. As discussed, different countries and regulatory bodies have focused on framing the regulations but the implementations of those regulations should also be considered for the well-being of human society.

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ABBREVIATIONS

API	Active pharmaceutical ingredient
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxy tocopherols
CAS	Chemical Abstracts Service
CFCs	Chlorofluorocarbons
CMC	Carboxy methyl cellulose
COA	Certificate of Analysis
CPAC	Central Pharmaceutical Affairs Council
CTD	Common Technical Document
DMF	Drug master file
EEC	European Economic Community
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GMP	Good manufacturing practice
GRAS	Generally Recognized As Safe
HFA	Hydrofluoroalkanes

I.M.	Intramuscular
ICH	International Conference on Harmonization
IPEC	International Pharmaceutical Excipient Council
M.P.	Melting point
MCC	Microcrystalline cellulose
mg	Milligram
MHW	Ministry of Health and Welfare
mL	Milliliter
MW	Molecular weight
NaCMC	Sodium carboxymethylcellulose
NDA	New Drug Application
PEG	Polyethylene glycols
PMDE	Pharmaceuticals and Medical Devices Evaluation
ppm	Parts per million
PQG	Pharmaceutical Quality Group
QC	Quality control
RS	Residual solvents
S.C.	Subcutaneous
SLS	Sodium lauryl sulfate
SOP	Standard Operating Procedure
WFI	Water For Injection
WHO	World Health Organization
W/O	Water in oil

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