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Pharmaceutical excipients

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Abstract
Excipients are crucial for creating a dosage form. These are the components that make up the dosage forms, together with the active pharmaceutical components. The following overview addresses the many types and sources of excipients along with their purposes, and they can be employed for diverse activities. Excipients operate as protective agents, bulking agents, and can also be used to increase bioavailability of medications in particular situations. The selection criteria for excipients and numerous interactions that an excipient can experience throughout the length of its stay in formulation have been covered in this review. Particular excipients are better suited for a specific dosage form. There are several excipient interactions that can be harmful and should be avoided. The interaction section contains further information about this. Excipients, like other active pharmaceutical substances, must be stabilized and standardized; the following study provides a brief overview of these processes as well as the excipients' safety evaluation criteria. Excipients are crucial for creating dosage forms. Excipients serve a variety of purposes in pharmaceutical dosage forms, including aiding with disintegration, lubrication, binding, and suppliers as well as increasing active substances in dosage forms. Each excipient has unique properties. An extensive list of studies on the purpose and makeup of solid excipients in solid dosage forms is provided in this study. Different compositions might employ a variety of options, therefore the difference will also change. Describe the many types of excipients that may be used for different solid preparation components in this example. Choose the appropriate type of excipient based on the required solid preparation's characteristics. A method for mixing and characterising solid excipients to determine their quality was also described in this review. Low properties, compressibility index, Hausner index ratios, and angle of repose are the most used techniques for analysing solid excipients. Even though Fourier transform infrared spectroscopy (FTIR), H and CNucleo magnetic resonance (H-CNMR), scanning electron microscopy (SEM), Particle size analysis (PSA), X-ray diffraction (XRDP), and differential scanning calorimeter are among the instruments often employed (DSC).

Keywords: Excipient, Ideal Properties, various classifications of pharmaceutics, role of excipient, drug-excipient interactions

1. Introduction

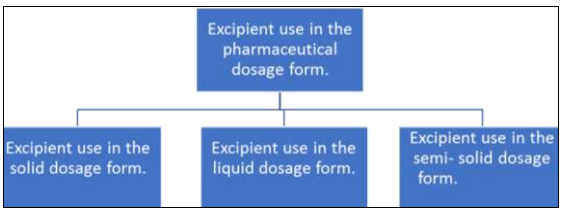
Many dosage forms created today are complex systems with several parts in addition to the active pharmacological ingredient. These substances are typically included in combination with active pharmaceutical components to safeguard, sustain, or improve the formulation's stability. In order to stabilise the active pharmaceutical ingredient (API), excipients are added. These ingredients help to maintain the stability of the product and ensure that API retains its stability for a significant amount of time, improving the shelf life of dosage formulation. It is frequently observed that the active pharmaceutical ingredient (API) in its pure form does not retain its stability for long, resulting in its denaturation, or sticking to the container wall, rendering it unfit. If the medicine is strong, add more substance to the formulation to help create an exact dosage form. This boost the acceptability of the patient. Increase the active drug's bioavailability with:- Excipients, for instance, frequently assist in enhancing the bioavailability of the active medicinal component. Many times, an active component—like aspirin—is not readily absorbed by the human body. In these situations, the active ingredient is dissolved in or combined with an excipient, which may either serve as a solvent or aid in the drug's absorption in the body. Enhance the formulation's overall safety and efficacy during storage and usage. These substances are typically referred to as excipients, and excipient is defined as "Any material other than active drug or pro-drug that is included in the manufacturing process." finished pharmacological dosage forms comprise.
Excipients are categorised in the US Pharmacopoeia-National Formulary (USPNF) based on the tasks they carry out in the formulations, such as disintegrants and binders. Excipients can be categorised as follows based on their place of origin, dose type, and functions they carry out.

Based on the origin of the excipient: Lactose, gelatin, stearic acid, beeswax, honey, musk, lanolin, etc. are all animal-derived products.
Sources of vegetables include starch, peppermint, turmeric, guar gum, arginates, acacia, and peppermint oil.
Calcium phosphate, Silica, Talc, Calamine, Asbestos, Kaolin, Paraffin, etc. are examples of mineral sources.
Boric acid, saccharin, lactic acid, polyethylene glycols, polysorbates, povidone, and other synthetic substances [1].

2. The excipient should have the following ideal properties: It should be chemically and physically inert.

- ✓ It shouldn't cause any issues with bioavailability.
- ✓ It shouldn't be poisonous.
- ✓ It ought to work well with the medication and other substances.
- ✓ It ought to work with the basic packing material.
- ✓ It must be acceptable organoleptically.
- ✓ It should be economically viable and lack independent therapeutic activity.
- ✓ It ought to provide the needed functionality [2].

3. There are the various classification of excipients used in pharmaceutical dosage forms.



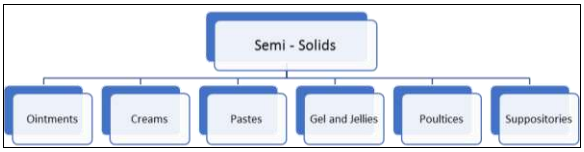
3.1 Excipient use in the solid dosage form

Excipients in pharmaceuticals are components used in the production process or found in the dosage form of a finished pharmaceutical product that are not pharmacologically active drugs or active ingredients. Excipients play a variety of roles in pharmaceutical preparations, including modifying solubility and API bioavailability, improving the stability of the active ingredient in dosage forms, assisting the active ingredient in maintaining preferred polymorphic forms or conformations, and acting as a disintegrant, lubricant, binder, and filler. When choosing drug excipients, the excipient needs to meet a standard to ensure its constant quality and functionality in dosage forms, drug products, and dosage forms. In the solid dosage form, the drug and one or more excipients are in close contact , these excipients may have an impact on the medication's stability. The proper excipients may be selected by formulators with the help of knowledge about drug excipient interactions. For well-known medications, this knowledge may already be available. Excipients lack purity. It is essentially made of minerals, and its production uses beginning materials, reagents, and solvents whether it is synthetic, semi-synthetic, or natural. Excipient similarity tests enable us to identify excipient interactions that may be avoided or modified for successful usage. This aids in reducing the risk associated with excipients. The selection of an excipient must be based on the attributes it offers. An excipient needs to be chemically stable, non-responsive, process and hardware insensitive, inert to human body, non-toxic, acceptable in terms of organoleptic qualities, affordable, and effective in terms of the intended use [3].

3.2 Pharmaceutical liquid dosage forms

Liquid dosage form are those that contain a combination of active drugs and excipients (emulsifying, dispersing, solubilizing, stabilising, suspending, wetting, thickening agent, preservative, sweetening agent, flavouring agent, and colouring agent) that are dissolved or suspended in appropriate solvents and used as a drug or medication. It is the most basic kind of pharmaceutical preparation for quick onset and high absorption of therapeutic medications, in which two components are improved to produce a liquid dosage form, including solvents and solutes (a component that dissolves) (the medium in which the solute willdissolve). Parenteral ways for administering pharmaceutical liquid preparations are available in sterile forms, however oral liquids are non-sterile and can be taken orally or parenterally (Injectable, inhalation, otic, tropical, nasal and ophthalmic) [4].

3.3 Excipient use in the semi- solid dosage form [5]



4. There are various Classification of excipients based on their functions [6].

- **Different type of classification of excipients**.

1. Fillers.
2. Binders.
3. Disintegrants.
4. Glidants
5. Colouring Agent.
6. Antiadherent.
7. Lubricants.
8. Coatings.
9. Preservatives.
10. Anfioxidants.
11. Flavoring Agents.
12. Sweeting Agents.
13. Sorbents.
14. Solvent & Co – Solvent.
15. Buffering Agents.
16. Chelating Agents.
17. Viacosity Imparting Agents.
18. Surface Active Agents.
19. 19.Humectants.

(1) **Fillers:** Fillers usually also enlarge the size of a tablet or capsule, making it easier to manufacture and more user-friendly.

- ✓ **Purpose:** Fillers increase the volume and bulk of a pharmacological component, making it easier to metre and handle precisely when creating a dosage form. Use in capsules and tablets.
- ✓ **A characteristic of Fillers is:** A good filler should generally be non-hygroscopic, compatible with the other ingredients in the formulation, affordable, compactible, or have a nice flavour.
- ✓ As an example, dibasic calcium phosphate and plant cellulose are frequently used as fillers. Soft gelatine

capsules can be made with a variety of vegetable fats and oils.

- ✓ Additional illustrations include lactose, sucrose, mannose, calcium carbonate, and magnesium stearate.

(2) **Binder:** Binders keep a tablet's constituents together. Binder offer low dosage tablets volume and guarantee that tablets and granules may be made with the necessary mechanical strength.

- ✓ A binder should have adequate cohesiveness of the powders and should be compatible with other formulation items.
- ✓ Examples include the dissolution of solution binders in a solvent Examples include gelatine, cellulose, derivatives of cellulose, starch, and sucrose.
- ✓ One example is the addition of dry binder to a powder mixture either before or after a wet granulation stage in a (DC) recipe. Examples include polyethylene glycol, cellulose, and methylcellulose.

(3) **Disintigrants:** Disintigrants are a chemical or combination of compounds added to the medicine formulation that help break down tablets and capsule contents into tiny pieces so they can dissolve more quickly when they come into contact with water in the gastrointestinal tract (GIT).

- ✓ Examples include polyvinylpyrrolidone, carboxymethyl cellulose, sodium starch glycolate, etc.
- ✓ **Properties:** Good hydration capacity, weak solubility, poor gel forming capacity.

(4) **Glident:** A chemical used in the manufacturing of tablets and capsules in the pharmaceutical industry that improves the flow of a granular mixture by minimising inter-particular friction.

- ✓ **Purpose:** Glident are used to encourage powder floe by lessening cohesion and friction between parts. These cannot reduce die wall friction, hence they are used in conjunction with other lubricants.
- ✓ Talc, fumed silica, and magnesium carbonate are a few examples.

(5) **Coloring Agent:** Colorants or colouring agents are primarily employed to provide pharmaceutical dosage forms a unique look. Because the visual appeal of dosage forms can be improved by the application of suitable colourants, we can also argue that colourants are cosmetics for pharmaceutical preparations.

- ✓ Example: (2) Brilliant blue; (1) white: titanium dioxide. (3) Amaranth carmine in red; (4) Saffron in yellow; (5) Green; and (6) Caramel in brown.

(6) **Antiadherent:** Antiaderents or anti-sticking agent prevent adhesion of the tablet surface to the die walls and the punches and as a consequence couneter the picking or sticking of tablets.

- ✓ Example: water insoluble lubricant such as the magnesium strarates can be use d as antiadhrents, ascantalc, and starch.

(7) **Lubricant:** Lubricants keep ingredients from adhering to the tablet punch or capsule filling machine and clumping together. Additionally, lubricant makes sure that there is little friction between the solid and die wall during tablet generation and ejection.

- ✓ Examples include stearic acid, magnesium stearate, and polyethylene glycone.

(8) **Coating:** Coating is the process of applying a coating material—usually a dry layer—on the surface of dosage forms. The coating agent used in this coating process is referred to as coating.

- ✓ **Purpose:** identification, masking, elegance, protection, and ease of swallowing.
- ✓ Consider HPMC, MC, and HPC.

(9) **Preservatives:** To extend the shelf life of different foods and pharmaceutical products, preservatives are substances that are frequently added.

- ✓ Examples include sorbic acid and its salts, methyl and ethyl parabens, and propyl paraben.

(10) **Preservatives:** Preservatives are compounds that are regularly added in order to prolong the shelf life of various foods and pharmaceutical items.

- ✓ Examples include propyl paraben, methyl and ethyl parabens, and sorbic acid and its salts..

(11) **Flavoring agent:** These are added to products to improve patient acceptability. The four primary tastes are sour, salty, sweet, and bitter. It has been suggested that certain flavours be used to cover up these distinct tastes.

- ✓ **Example:** Menthol, rose oil, glycerin, citric acid, and syrup.Sweetening Agent: In liquid formulations intended for oral administration, sweeteners are used specifically to improve the palatability of the medicinal ingredient

.

(12) **Sweeting agent:** Sucrose, saccharine, aspartame, and sorbitol are a few examples.

(13) **Sorbents:** Materials that absorb oil from water are known as sorbents.

- ✓ Peat moss, sawdust, feathers, and any other naturally occurring carbon-containing material are examples of natural sirbents.
- ✓ Nylon and polyethylene-based synthetic sorbent.

(14) **Solvent and Co-Solvent:** A solvent is a substance that has the ability to dissolve a solute and produce a solution. Although it can also be solid or gaseous, a solvent is often a liquid. A solvent will never transform into a solution.

- ✓ Examples include using water as a solvent when a medicine is easily soluble in it and using oils for emulsions, intramuscular injections, and liquid-filled oral preparations.
- ✓ A solvent is a substance that has the capacity to dissolve a solute and create a solution. A solvent is often a liquid although it can also be solid or gaseous. Never can a solvent become a solution.
- ✓ Examples include employing oils for emulsions, intramuscular injections, and liquid-filled oral preparations as well as using water as a solvent when a medication is readily soluble in it.

(15) **Buffering Agent:** These are substances that, when dissolved in a solvent, allow a solution to withstand pH

changes caused by the addition of an acid or alkali. The needed buffering capacity and p H determine the type of buffer to use.

- One illustration is that the majority of buffering systems rely on carbonate, citrates, gluconates, lactates, and tartrates.

(16) Chelating Agent: A complex compound has one or more rings in its structure and chelating agents are molecules capable of building complexes with drugs involving multiple bonds.

- ✓ Ethylene diamine tetraacetate (EDTA) is used to estimate the presence of metal ions.
- ✓ Disodium edentate is a medication for hypercalcaemia. Additionally, it helps in the management of cardiac arrhythmias.

(17) Viscosity importing agent: These agents are utilised when it is necessary to either raise or reduce a liquid's viscosity in order to enhance flavour or pourability. They go by the name thickening agents as well.

- ✓ Hydroxyethylcellulose is the viscosity imparting substance most frequently employed. Hydroxypropylmethylcello. Methylcelulose. vinyl alcohol polymer.

(18) Surface Active Agent: The term surfactant is a blend of surface active agent. Surfactant are usually organic compound that are amphiphilic, meaning they contain both hydrophobic group and hydrophilic group.

(19) Humectant: A humectant draws water vapore and below the organism surface by absorption, attracting and holding moisture in the neighbouring air. Humectants absorb atmospheric water vapour up until a particular point of dilution.

- ✓ **Example:** Inorganic humectants are mostly employed in cosmetic products. One illustration is calcium chloride. It is caustic and has compatibility issues. As a result, it is rarely utilised in cosmetics.
- ✓ Metal organic humectants: Due to compatibility issues, caustic nature, and strong flavour, they are only sometimes utilised in cosmetics.
- ✓ Orgainc humectants are frequently found in cosmetics. They include the ethers and esters of polyhydric alcohols.

5. Dosage form and the role of excipients

There are many different medications available in different dose forms, including liquid and semisolid creams, gels, ointments, pills, capsules, powders, granules, and suppositories as well as solutions, suspensions, emulsions, and elixirs (Haywood and Glass, 2011). The effects of the excipients used in various dosage forms.

Pharmaceutical excipients can represent up to 90% of the total mass/volume of pharmaceutical products and are typically present in dosage forms in higher concentrations than the API. In the pharmaceutical dosage form, the excipient offers the required physicochemical and biological properties.

The APIs are transported using the excipient as either the vehicle (or foundation) or a component of the carrier. One or more excipients make up the carrier. For liquid preparations, a vehicle word is used, but for solid and semisolid preparations, a basic term is used.

The excipient plays its part and could or might not be included in the finished product. For the manufacture of granules, anhydrous ethanolic solution of polyvinylpyrroli done is employed as a binder. The ethanol is vaporised while the granules are drying, and it is then eliminated from the dried granules [7].

Excipient category	Role in dosage form
Tablets	
Diluents/ fillers	- produce the bulk of the tablets
Binders	- bind the tablet powder ingredient together
Disintegrants	- decrease disintegration time for faster release
Glidants	- promote powder flow by reducing interparticle friction
Antiadherents	- reduce adhesion between powder(granules)
Colouring agents	- improve the appearance
Flavouring agents	- mask the unpleasant taste
Sweeteners	- reduces the bitterness and improve the patient compliance
Coating polymer	- produces film around the tablet to modify the release
Capsules	
Shell material	- to form the capsule body to fill the required material
Diluents/ fillers	- ensure regular flow of powder
Absorbents	- prevent degradation of hygroscopic material
Disintegrants	- increase disintegration rate of filled content to up the action
Plasticizers	- imparts softness, elasticity, hardness to capsule shell
Antidusting agents	- prevent dusting that results from automatic capsuling
Polymers	- control the rate of dissolution of drug
Liquid dosage forms	
Vehicles	- means of solubilizing different components
Buffers	- control the pH and important in storage
Tonicity modifiers	- maintain tonicity with the body's natural fluids
Complexing agents	- binds reversibly with drugs to form stable complex
Surfactants	- increase solubility of the drugs and stabilise the system
Suspending agents	- keep the insoluble particles in suspended form
Emulsifying agents	- keep oil and water phases together
Colouring agents	- impart colour to the formulation

Flavouring agents	- impart flavour to the formulation
Sweetening agents	- impart sweetness to the formulation
Preservatives	- preserve the formulation
Semisolid dosage forms	
Antioxidants	- protect from oxidation
Humectants	- prevent the loss of moisture
Colouring agents	- impart colour to the formulation
Flavouring agents	- impart flavour to the formulation
Preservative	- prevent the growth of microorganisms

6. Drug-excipient interactions

✓ There are two different kinds of excipients available.

6.1 Direct Physical Contact.

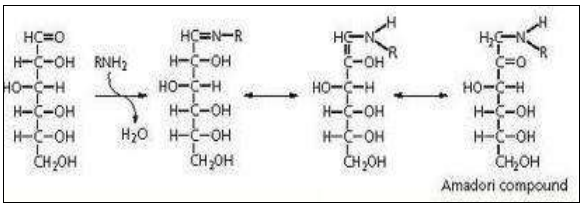
6.2 Chemical interaction, part two.

6.1 Physical Interaction: It happens frequently but is extremely hard to notice. There are no chemical alterations during a physical encounter. Physical interactions are widely employed in dosage form production, for instance, to alter medication solubility. The unplanned nature of many physical contacts, however, is typically what leads to issues. Physical contact may either improve or worsen a product's performance. The physical interaction between primary amine medicines and microcrystalline cellulose is an illustration of an API and excipient. A tiny portion of the medication may be retained on the microcrystalline cellulose after water-based dissolution. This might not be a significant problem for high-dose medications, butbut for low dose drugs it can lead to dissolution failures. This has previously been an issue, but it may be fixed by performing dissolution with a mild electrolyte solution as the dissolving medium (e.g., 0.05 M HCl). Adsorption onto the microcrystalline cellulose is much decreased under these updated dissolution test conditions, and 100% dissolution is possible even for low-dose APIs. Interactive mixing is a broad illustration of a physical interaction. In this scenario, physical forces are used to interact between the surface of the smaller particles (usually the APIs) and the larger carrier particles (generally the excipients). We achieve a more uniform powder mix in this method. The aqueous environment of the gastrointestinal tract (GIT) either causes the smaller API particle or other carrier particles to dissolve after the medication, such as a tablet, has been given to the patient, or it changes the surface interactions so that the smaller particles can be released from the larger carrier particles. But as we've already said, physical interactions can also be harmful, and the pharmaceutical industry is aware that magnesium stearate can lead to issues like decreased tablet "hardness" and dissolving from tablets and capsules.

Reduced bioavailability may come from drug molecules adhering to excipient surfaces, making the medication incapable of dissolving and diffusing. For instance, when magnesium stearate was employed as lubricants in tablets containing cetylpyridinium chloride, the antibacterial activity of the compound diminished; this was caused by the adsorption of the cetylpyridinium cation by the stearate anion on the magnesium stearate particle . In one study, it was shown that the drug's adsorption on the surface of microcrystalline cellulose caused a reduction in the drug's ability to dissolve. Similar to this, microcrystalline cellulose's adsorption of a new k-opioid agonist caused only partial drug release from the capsules. Adsorption might start a chemical reaction. It has been demonstrated that colloidal silica can catalyse the breakdown of nitrozepam in tablet form. This action may be caused by adsorptive interactions that change the electron density around the labile azo group, making it easier for hydrolyzing agents to attack. Complexing agents, like cyclodextrin, are frequently used to improve the bioavailability of medications that are poorly water soluble because they bind reversibly with pharmaceuticals to create complexes that prevent them from dissolving. However, it was shown that while the solubility was improved when cyclodextrin was complexed with the NSAIDs naproxen and tolbutamide, there was no comparable improvement in bioavailability. With PEG-400, phenobarbital produced an insoluble compound that slowed dissolution and reduced absorption. Prednisolone's in-vivo bioavailability may be decreased due to the complexes' high molecular weight and potential inability to permeate past the GI membrane. This was discovered during an in-vitro examination of the complexation of steroids with water-soluble excipients.

6.2 Chemical Interaction: Drugs and excipients or drugs and impurities/residues contained in the excipients undergo chemical reactions to generate distinct molecules. Chemical interactions nearly always harm the product since they result in degradation products, which are categorised according to ICH guideline ICHQ3B. In the literature, a variety of chemical drug-excipient interactions have been identified.

Drug and excipient interactions in terms of chemistry: The glycosidic hydroxyl group of dextrose, a reducing sugar, and the primary amine group of chlorpromazine conduct a Maillard reaction to generate imine, which eventually breaks down to form Amidori compounds.



- In a different investigation, it was shown that the polymer chitosan hindered the release of diclofenac sodium from matrix tablets at low pH, most likely by forming an ionic complex between the two substances (Block etal., 1997)
- Reducing sugars and secondary amines may also interact. However, the chemical cascade does not continue once the imine is formed, and no colour results (Baertschi *et al*., 1998).
- In a process resembling a Michael addition reaction, primary amines can interact with double bonds (for instance, in fluvoxamine maleate, where the fluvoxamine primary amine group can interact with the double bond in the maleic acid counterion). Sorbitan

monooleate and sodium stearyl fumarate are two excipients that contain double bonds.

- Sorbitan monooleate and fumarate. Some APIs, such as atorvastatin and cytidine nucleoside analogues, are prone to oxidation. Such oxidation processes can be aided by fumed metal oxides, such as fumed zirconia, titania, and silica.
- These reactions are less predictable and more complicated in certain respects. Due to the near proximity of heteroatoms and an active hydrogen atom in the molecule, such as benazepril, lactone production occurs.
- When medications like neomycin and polymixin—whose active ingredients are positively charged—are combined in aqueous systems, suspension agents like sodium alginate, which dissolve in water to generate massive negatively charged anions, precipitate.
- Diethylstilbestrol is oxidised by silicon dioxide to produce conjugated quinone and peroxide as breakdown products. Colloidal silicon dioxide has been found to speed up the air-auto-oxidation of methyl linoleate to peroxides with subsequent breakdown to aldehydes . Chloramphenicol stearate undergoes polymorphic transition when it interacts with colloidal silica while being ground, illustrating that excipient side effects are not limited to chemical changes [8].

7. Co-processed excipients

In recent years, scientists have discovered that single-component excipients do not always provide the necessary performance to enable the formulation or production of certain active medicinal components. To date, the excipients business has been a growth area for the food industry. Excipients are also products of the food industry, which has contributed to their high level of safety. An worldwide organisation called the International Pharmaceutical Excipients Council was created as a result of increasing regulatory pressure on the purity, safety, and standardisation of excipients (IPEC).Pharmaceutical excipients are any substance, other than the active drug product, that has undergone a proper safety evaluation and is added to a drug delivery system in order to protect, support, or improve stability, bioavailability, or patient acceptability, or to help identify the product or to improve any other aspect of the overall safety and efficacy of the drug product during storage and use. Co-processed excipients are "a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing and without significant chemical change," according to the International Pharmaceutical Excipient Council (IPEC).

The creation of fresh and cutting-edge excipients is a hot topic right now. Excipient innovations include those for controlled-release formulations and orally disintegrating tablets. In order to boost the amount or rate of medication absorption with novel excipients, different methods are being examined. Future research on the use of nanotechnology might focus on creating fresh excipients for innovative treatment approaches.

Since Metoprolol succinate and poorly water soluble anhydrous Theophylline serve as model drugs, this work concentrated on developing directly compressible co-processed excipients made of polyethylene oxide and hydroxypropyl methyl cellulose by roller compaction method and evaluating them as sustained release matrix forming polymers. The three main processes of roller compaction are ribbon creation, predensification, and powder feeding. The powder material was fed into two counter-rotating rolls during the feeding process using either gravity or force-feed screws. The pre-densification process begins when the powder material brushes against the roll surface after being brought into the nip angle area. The predensified powder material was then sent through revolving rolls, where under hydraulic pressure, the particles were bent or broken up to produce ribbons. The granules created by sizing these ribbons via the appropriate screens were then crushed into tablets.

Accurately weighed polymers were combined for 10 minutes to create a homogenous blend in the ratios stated (1:9 to 9:1). These mixtures were compacted using a roller compactor (Clit roller compactor, India). The obtained ribbons were put through a 40# and a 60# sieve for screening. The produced fine powder was then recycled to create uniform-sized granules. To get the granules of the specified size, around 9 cycles of roller compaction were completed. For additional research, material retained on a 60 # filter was employed. In a lab-scale double cone blender, physical mixes of Polyox® WSR 301 and Methocel® K4M were also made in the same ratio.

- ✓ Advantages And Disadvantages of Co – Process Excipient:

7.1 Advantage of Co- Process Excipient

- Provide a single excipient with multiple functionalities.
- Overcome the limitation of existing excipients.
- Improvement of organoleptic properties.
- Production of synergism in functionality of individual components.
- Improvement in physico-chemical properties has expanded their use in the pharmaceutical industry.
- Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations.
- The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations
- This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms.
- The chances of wear and tear of punches and dies are less.
- Better mouth feel and improved palatiblity
- Removal of undesirable properties.
- Improvement of organoleptic properties
- Delivery of low doses of very potent compounds that require contaminent.
- Improved Flow properties.
- Improved compressibility.
- Better dilution potential.
- Fill weight variation.
- Reduced lubricant sensitivity.

7.2 Disadvantage of Co-Process Excipient

- Specalised filling equipment and high temperature processing are required.
- Some lipidic excipients are not well tolerated by pre-clinical species.

- The high materials losses.
- Process is expensive because of labour, space, time special equipment and energy requirement.
- Loss of material during various stages of processing.
- Moisture sensitive and thermolabile drugs are poor cancidates.
- The frequency of direct interaction of the formulator with the production personal in the manufacturing area will be reduced.
- Long duration.
- Large number of equipment are needed.
- High material loss.

7.3 Properties of Co-Process Excipient

a) No chemical alterations

Numerous thorough investigations into the chemical characteristics of excipients following co-processing have demonstrated that these excipients do not exhibit any chemical change. In-depth analyses of SMCC using X-ray diffraction analysis, solid state NMR, IR spectroscopy, Raman spectroscopy, and C13 NMR spectroscopy have not revealed any chemical alterations and point to similarities with MCC's physicochemical characteristics. This lack of chemical modification lessens a company's development-phase regulatory issues.

b) Physico mechanical properties

1. Improved Flow Properties

Co-processed excipients with controlled ideal particle size and particle size distribution provide enhanced flow characteristics without the use of glidants. In contrast to MCC, the volumetric flow characteristics of SMCC were investigated. These excipients' range of particle sizes was discovered to be comparable to that of their parent excipients, but the flow of co-processed excipients was superior than that of straightforward physical mixes. Cellactose's flow characteristics were compared as well. Cellulose was shown to have better flow properties than lactose or a combination of cellulose and lactose based on measurements of the angle of repose and the Hausner ratio. The spherical form and even surfaces of the spray-dried product enhanced the flow characteristics.

2. Improved compressibility

Since direct compression tabletting results in a net improvement in the flow characteristics and compressibility profiles and produces an excipient that is a filler-binder, co-processed excipients have been employed primarily in this procedure. When plotted and compared with basic physical mixes, the pressure-hardness relation of co-processed excipients revealed a noticeable improvement in the compressibility profile. Excipients like Cellactose SMCC and Ludipress perform better in terms of compressibility than basic physical mixes of the excipients that make up those excipients. Wet granulation is still favoured even though direct compression appears to be the ideal approach for pharmaceutical manufacture because it has the ability to increase flow characteristics and compressibility when an additional granular binder is supplied For low dosage medications, it also produces a higher content homogeneity. Excipients like MCC experience quasihornification—the loss of compressibility—when water is added. But when it is co-processed into SMCC, this feature is enhanced.

3. Better dilution potential.

The excipient's capacity to maintain compressibility even when diluted with another substance is known as dilution potential. In order to maintain adequate compaction even when diluted with a poorly compressible agent, excipients must have superior compressibility qualities than the majority of active medicinal compounds. It has been demonstrated that cell actose has a higher diluting potential than a physical amalgamation of its component excipients.

4. Fill weight variation

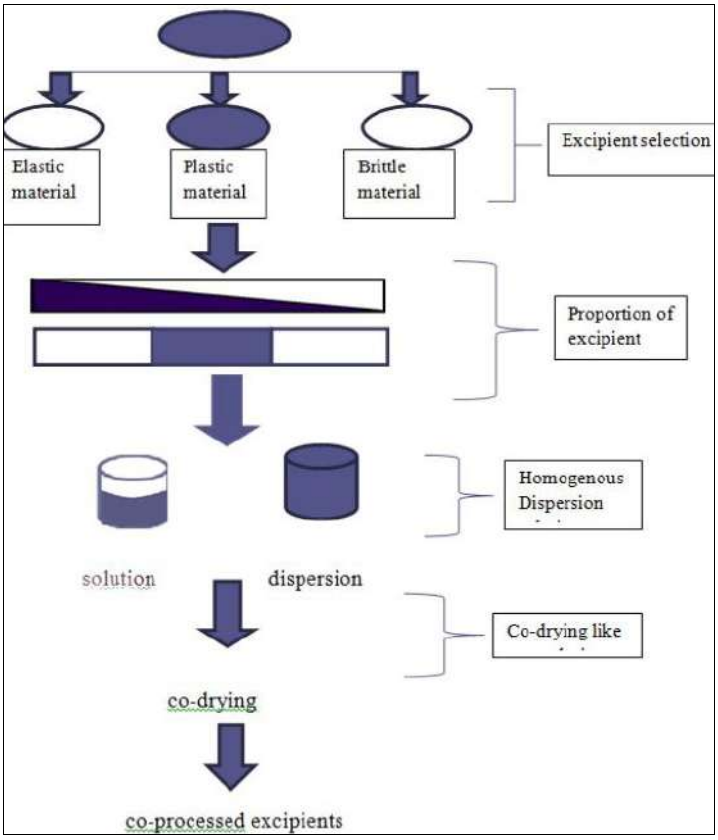
Due to their poor flow qualities, materials for direct compression often exhibit substantial fill weight variations, although co-processed excipients have been proven to have less fill weight variation issues when compared to simple mixes or parent materials. This effect is primarily caused by the impregnation of one particle into the matrix of another particle, which decreases the rough particle surfaces and produces a size distribution that is close to ideal, leading to superior flow characteristics. With high speed compression machines, fill weight fluctuation is often more obvious. The fill weight fluctuation of SMCC and MCC was examined at various machine speeds, and SMCC demonstrated less fill weight variation than MC.

5. Reduced lubricant sensitivity

A relatively significant amount of brittle material, such lactose monohydrate, and a lesser amount of plastic material, like cellulose, which is fixed between or on the brittle material's particles, make up the majority of co-processed goods. Because it produces a continuous matrix with a sizable area for bonding, plastic material has high bonding characteristics. Due to the considerable amount of brittle material, which precludes the creation of a coherent lubricant network by exposing new surfaces during compression and dispersing the lubricant network, the material has poor lubrication sensitivity [9].

7.4 The co-processed excipient involve the following steps

1. Recognition the excipient group to be co- processed by carefully study. The material characteristics and functionality required.
2. Select the proportions of various excipients.
3. Evaluate the particle size required for co-processing. this is mostly important when one of the components is processed in a dispersed phase post processing, the particle size of the latter depends on its initial particle size.
4. Selecting appropriate drying process such as spray or flash drying Schematic representation of the co-processing method shown in figure.



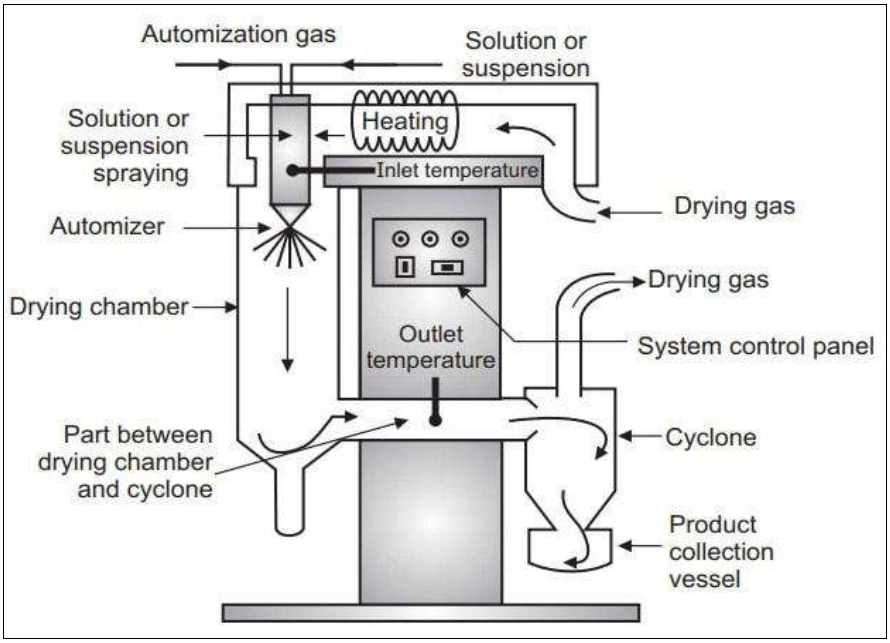
7.5 Methods of cop processing

1. Spray drying .
2. Solvent evaporation .
3. Crystallization .
4. Melt extrusion.
5. Granulation/Agglomeration.

- **Spray drying**

This spray drying technique allow the conversion of feed from a fluid state into dried particle.The feed can be a solution ,suspension, dispersion or emulsion .the dried product can be form in the powders, granules or agglomerates and these are depending upon the physical and chemical properties of feed and the dryer design final powder properties required. it is a continuous particle processing drying operation. the spray drying process parameter like inlet air temperature ,atomization air pressure, feed rate, liquid viscosity, solid content in feed, disc speed can be help in design particle with desire characteristics. hence spray drying process can be desire as consisting of four steps.

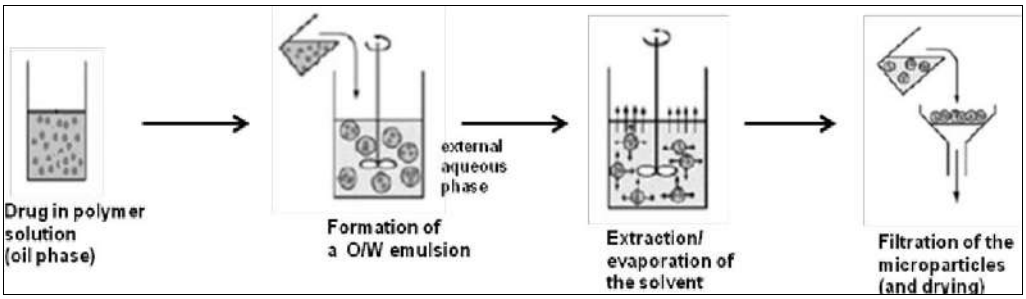
- ✓ Atomization of the liquid into droplets.
- ✓ Contact of the droplet with the warm drying gas.
- ✓ Fast evaporation of the droplets to form dry particles.
- ✓ Recovery of the dry particles from the drying gas, using a cyclone.



- **Advantages of spray drying**
- ✓ Possibility to associated non-missible products in continuous operation.
- ✓ It allows blending and drying simultaneously soluble and insoluble compound.
- ✓ Provides opportunity to fix and protect sensitive active compound on natural carrier.
- ✓ Improves hardness and compressibility.
- ✓ Enhances machine tableting speed, decreases disintegration time.

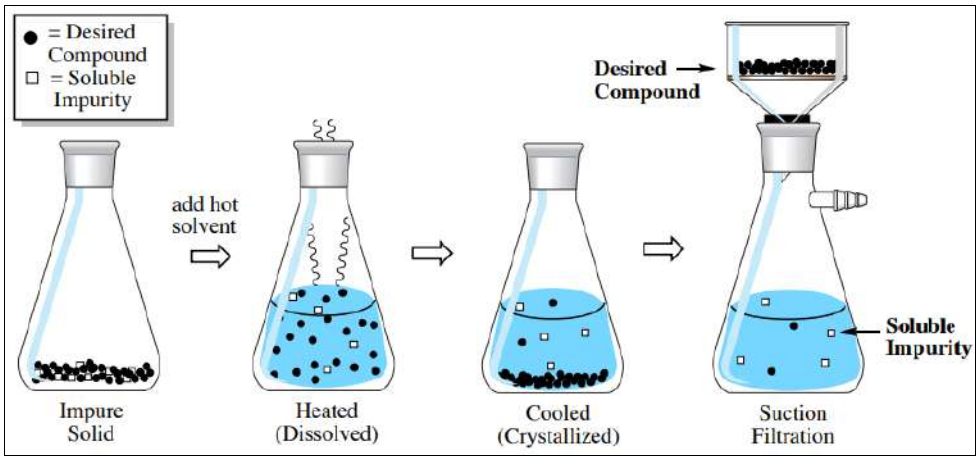
- **Solvent evaporation**

The procedure is completed in a liquid production machine. The liquid production vehicle phase and the volatile solvent in which the coating excipient is dissolved are incompatible. An agitated coating polymer solution is used to dissolve or scatter a core excipient substance that will be microencapsulated. To create the correct size microcapsule, the core coating material combination is disseminated in a liquid production vehicle phase. After the combination is heated to evaporate, the temperature of the liquid is lowered to room temperature while it is still being stirred. At this point, microcapsules can be employed as powders, coatings, or suspensions on surfaces. Either water-soluble or water-insoluble materials can make up the fundamental components.



- **Crystallization**

Crystallization, which can occur naturally or artificially, is the process by which solid crystals form from melts, solutions, or, less frequently, gases when they are precipitated from these sources. Crystallization from a solution requires supersaturation. This indicates that the solution must have more dissolved solute entities (molecules or ions) than it would have at equilibrium (saturated solution). The most often employed techniques in industrial practise are (1) solution cooling, (2) addition of a second solvent to decrease the solubility of the solute (technique known as antisolvent or drown-out), (3) chemical reaction, and (4) change in pH. Sugar Tab is an illustration [Sucrose, Invert sugar].



- **Melt extrusion**

Melt extrusion is a method that turns molten substance that is extruded through an extruder into tiny beads and pellets. Extruders have four distinctive sections.

- An opening though which material enters the barrel that may have a hopper that is filled with the materials to be extruded.
- A conveying section (process section), which comprises the barrel and the screws that transport, and where applicable, mix the material.
- An orifice (die) for shaping the material as it leaves the extruder.
- Downstream auxiliary equipment for cooling, cutting and/or collecting the finished product. Example: Compressol S [Mannitol, Sorbitol].

- **Advantages**
- ✓ Excellent repeatibility.
- ✓ Complicate and intricate shapes are possible.
- ✓ Time required is less.

- **Disadvantages**
- ✓ Equipment and die cost high.
- ✓ Minimum economic length high.

- **Granulation/agglomeration**

The process of forming or crystallising into grains is called granulation. Depending on their intended purpose, granules might be anywhere from 0.2 and 4.0 mm in size. Agglomeration is a word used to describe granulation. Particle size enlargement methods, often known as

agglomeration techniques, are excellent instruments for changing a product's qualities. Powder aggregation is frequently used to enhance product appearance and physical qualities including wettability and flowability.

- Advantages:
- ✓ It eliminates the use of water or any other solvent.
- ✓ Short processing time.
- ✓ It can be suitable for conventional equipment [10].

8. Natural Excipients in Novel Drug Delivery Systems

Excipients are largely employed in conventional dosage forms like tablets and capsules as diluents, binders, disintegrants, adhesives, glidants, and sweeteners. Recently, researchers have been increasingly interested in herbal excipients since synthetic excipients have difficulties with toxicity assessment and regulatory licencing. Compared to their synthetic equivalents, herbal excipients' lack of toxicity, ease of availability, and cost benefits in the pharmaceutical business outweigh the disadvantage of heavy metal contamination that is frequently associated with them. Consumers today seek for natural substances in their food, medications, and cosmetics because they think that anything natural will be safer and free of adverse effects.

Excipients are now understood to have the capacity to affect a drug's rate and/or amount of absorption, contrary to the long-held belief that they are inert and have no therapeutic or biological effects or alter the biological activity of the pharmacological ingredient. Herbal excipients play a significant part in pharmaceutical formulation since they are non-toxic and compatible. Therefore, the goal of this research is to evaluate the herbal excipients utilised in NDDS.

8.1 Polysaccharides in pharmaceuticals

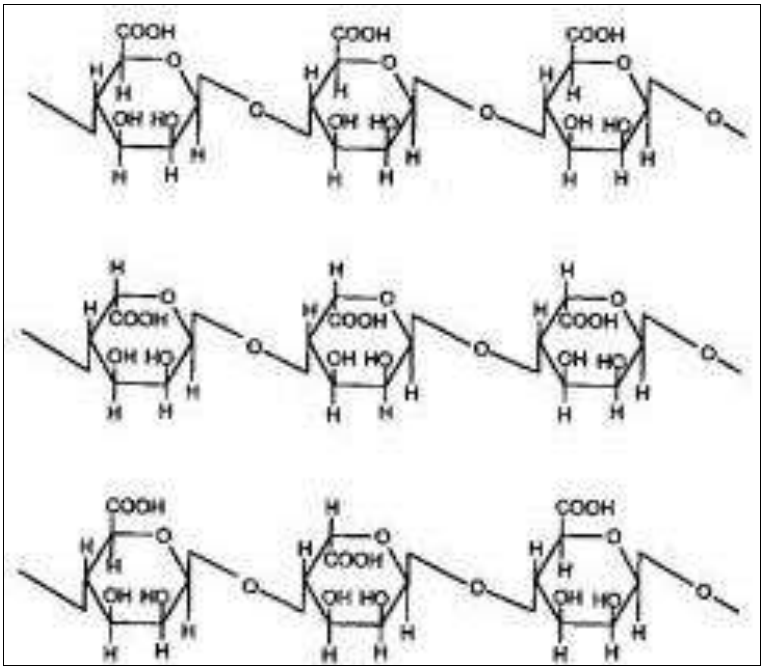
Solid dose formulations are frequently created using natural polysaccharides. These monosaccharide polymers (also known as sugars) are pricey and come in a wide range of forms and characteristics. They naturally form gels and are hydrophilic, safe, and very stable substances. Several polysaccharides that are often employed in dosage forms include pectins, starches, guar gum, amylase, and karaya gum. Non-starch, linear polysaccharides are destroyed by the bacteria that dwell in the human colon, making them potentially helpful in targeted delivery systems to the colon. They stay intact in the physiological environment of the stomach and small intestine, however.

8.2 Pectins

Pectins are linear polysaccharides that aren't starches that are taken from plant cell walls. Containing a few hundred to approximately a thousand building units per molecule, they are mostly linear polymers with (1-4)-linked D-galacturonic acid residues that are interrupted by 1,2-linked L-rhamnose residues. This corresponds to an average molecular weight of about 50 000 and 1 80 0002. Pectin cannot successfully protect its pharmacological load throughout its passage through the stomach and small intestine because it is soluble in water. It was discovered that under simulated *in vivo* situations, a covering of appreciable thickness was needed to protect the drug core. As a result, attention was turned toward the creation of less soluble pectin derivatives that the colonic microbiota could break down. Pectin's solubility was decreased by calcium salts of pectin, which took on an egg-box shape. Mixed flms of pectin and ethyl cellulose were studied as a coating material for colon-specific medication administration in order to get over the problem of pectin's high solubility. These films coupled the protective qualities of the water-insoluble polymer with the colon-specific breakdown capabilities of pectin. As controlled release matrix tablets, polymeric hydrogels are frequently employed. For its possible use in controlled-release matrix compositions, high-methoxy pectin was explored. Investigations were also conducted on how matrix tablets' ability to release drugs was affected by compression force, drug to pectin ratios, and pectin types. According to the findings of the *in vitro* release investigations, the amount and type of pectin used to make the compressed matrix tablets may be changed without altering the drug release from them. Excipients for pelletization by extrusion/spheronization were found to be well suited for a very low solubility pectin-derivative (pectinic acid, degree of methoxylation 4%). It was discovered to have a high capacity as an extrusion aid; even formulations containing only 20% pectinic acid produced pellets that were almost spherical. In simulated stomach ß uid (0.1M HCl) and intestinal ß uid, all pectinic acid pellets were mechanically stable, had an aspect ratio of about, and released 30-60% of a poor solubility model medication after 15 minutes (phosphate buffer pH 6.8).

8.3 Alginates

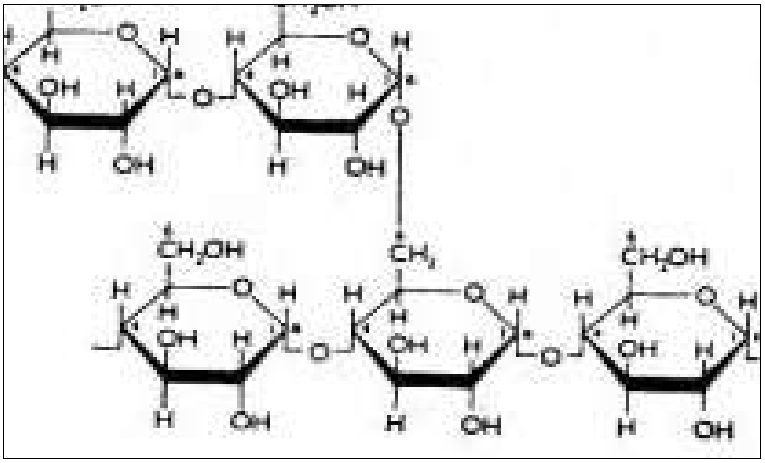
Natural polysaccharide polymers called alginates were found in brown seaweed (Phaeophyceae). Alginate may be transformed into its salts, of which sodium alginate is the most widely utilised kind right now. A homogeneous linear polymer formed of D-mannuronic acid and L-guluronic acid residues is placed in blocks along the polymer chain, and these blocks are separated by blocks made of randomly alternated mannuronic and guluronic acid units. Alginates have a wide range of uses in drug administration, including the delivery of biomolecules in tissue engineering applications, matrix type alginate gel beads, liposomes, and modifying gastrointestinal transit time. To circumvent the first-pass effect, bioadhesive sodium alginate microspheres of metoprolol tartrate were produced for intranasal systemic distribution for better therapeutic effectiveness in the treatment of hypertension and angina pectoris as an alternative to injectable therapy. The procedure of emulsification-cross linking was used to create the microspheres. As opposed to oral and nasal delivery of drug solution, *in vivo* trials showed considerably better therapeutic effectiveness of metoprolol from microspheres, with prolonged and regulated suppression of isoprene lineinduced tachycardia.

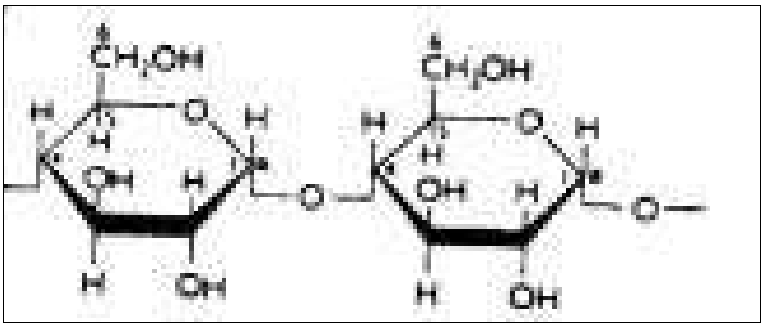


8.4 Starches

Green plants mostly store this kind of carbohydrate in the form of seeds and subterranean organs. Granules (starch grains) are the physical form in which starch is found. They are unique to each species in terms of their size, shape, and ratio of the two main components, amylose and amylopectin. Several starches are approved for use in medications (g. 2). These include potato, wheat (Triticum aestivum), rice (Oryza sativa), and maize (Zea mays).

A novel pregelatinized starch product's wide application in directly compressible controlled-release matrix systems was evaluated using modified starch. It was made by enzymatically degrading potato starch, which was then retrograded, precipitated, filtered, and washed with ethanol. The material's benefits include ease of tablet manufacture, the possibility for a steady release rate (zero-order) for a long time, and its capacity to include high concentrations of medications with various physicochemical features. Retrograded pregelatinized starch tablets can have their release rates increased or lowered to meet a certain profile depending on a number of factors, including the tablet's geometry, compaction force, and the presence of extra excipients.



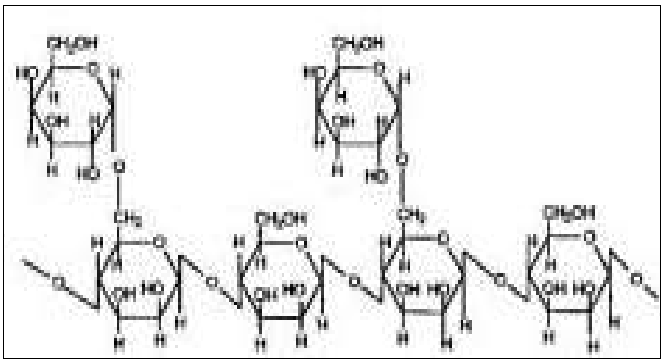


8.5 Gums

Gums are transparent, amorphous compounds that plants make. Gums are often pathological products that are formed when a plant is harmed or developing in poor conditions. Gums are plant hydrocolloid polysaccharides that can be anionic or nonionic. Gum hydrolysis produces sugar and uronic acid salts.

8.6 Guar gum

Guar gum is a naturally occurring galactomannan polysaccharide that is obtained from the seeds of Cyamopsis tetragonolobus (Family Leguminosae). It consists of a linear chain of D-mannopyranose units connected to D-galactopyranosyl units through 1, 6 links in a 1:2 ratio. Due to its ability to delay medication release and vulnerability to microbial breakdown in the large intestine, guar gum is employed in colon-delivery systems. Wet granulation with starch paste was used to create the 5-aminosalisylic acid (5-ASA) core tablets, which were then compression coated with coating formulations including varying amounts of guar gum. The study confirmed that utilising guar gum as a carrier in the form of a compressive coating over the medication can enable selective delivery of 5-ASA to the colon. Additionally, rofecoxib guar gum-based matrix tablets were created with the goal of using them in the chemoprevention of colorectal cancer. Rofecoxib was transported to the colon, causing a sluggish absorption of the medication and making it available for local action in the human colon, according to *in vivo* tests that demonstrated delayed Tmax, extended absorption time, and lowered Cmax.



8.7 Gum acacia

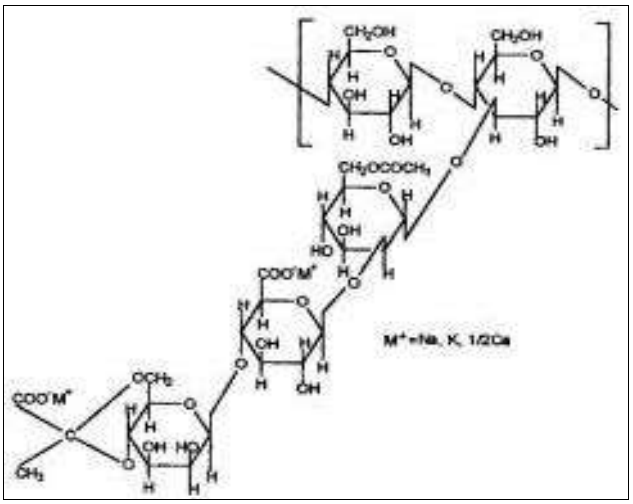
The dried sticky exudate collected from the stem and branches of Acacia senegal (Linne) Willdenow and other similar acacia species is known as gum acacia or gum arabic (Family Leguminosae). D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid are all present in the gum, which is known to be an acidic polysaccharide. Acacia is frequently used with tragacanth in pharmaceutical formulations for topical and oral use as a suspending and emulsifying agent. Additionally, it is employed as a tablet inder and in the production of pastilles and lozenges. Sustained release of ferrous sulphate was obtained for 7h by making gum arabic pellets. By covering the pellets with polyvinyl acetate and ethylene vinyl acetate, respectively, the release was further prolonged for more than 12 hours. Due to gum arabic's ability to gel, an increase in its content in the pellets resulted in a decrease in the rate of release. As a barrier, the gel layer slows the rate at which FeSO4 diffuses through the pellet.

8.8 Karaya gum

Karaya gum is a partly acetylated polymer containing galactose, rhamnose, and glucuronic acid that is derived from Sterculia urens (Family: Sterculiaceae)26. In order to produce directly compressed matrices, swellable hydrophilic natural gums like xanthan gum and karaya gum were utilised as release-controlling agents. As model pharmaceuticals, caffeine and diclofenac sodium were chosen because of their differing solubilities in aqueous media. A dissolving device (basket technique) was used to conduct research on drug release, hydration, and gum erosion at two different agitation rates. In the case of xanthan gum, neither the speed of agitation nor the solubility of the medicine significantly affected the amount of water that was absorbed, while matrices with a smaller proportion of gum generated a lower level of hydration. In contrast, karaya gum showed a significantly greater rate of degradation and a substantially lower capacity for hydration. Influenced by the rate of agitation Thus, it was determined that agitation speed, solubility, and drug percentage were factors in how quickly drugs released from xanthan and karaya gummatrices. Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices 29. In order to achieve zero-order drug release, Park *et al*. 30 demonstrated that mucoadhesive tablets made with karaya gum for buccal distribution exhibited superior adhesive qualities than guar gum. However, concentrations higher than 50% w/w may be necessary to provide adequate sustained release.

8.9 Xanthan gum

High molecular weight extracellular polysaccharide Xanthomonas campestris, a gram-negative bacteria, produces xanthan gum. The fundamental structure of this naturally occurring cellulose derivative consists of an alternative glucose residue main chain, a cellulosic backbone (-D-glucose residues), and a trisaccharide side chain of -D-mannose—D-glucuronicacid—D-mannose. Depending on the bacterial strain and the fermentation circumstances, the terminal D-mannose residue may have a pyruvate function. The side chain's non-terminal D-mannose unit has an acetyl function. Due to the side chain's inclusion of glucuronicacid and pyruvic acid groups, this polymer has an anionic structure.

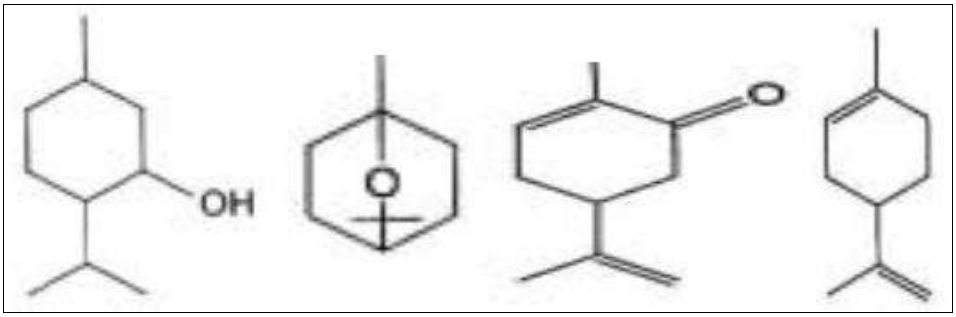


8.10 Tragacanth

This gum is made from the branches of the Leguminosae family plant Astragalus gummifer. Tragacanth, either alone or in combination with other polymers, achieved excellent release prolongation when utilised as the carrier in the construction of 1- and 3-layer matrices.

8.11 Volatile oils

Hydrocarbons and oxygenated chemicals produced from these hydrocarbons are typically mixed to form volatile oils. Many oils have terpenoid origins; some of them contain terpenes combined with aromatic compounds (e.g. cinnamon and clove). A few substances, including thymol and carvacrol, are terpenoid-derived while having an aromatic structure [11].



9. Conclusion

Excipients must be assessed for their stability and safety because they are an essential part of pharmaceutical formulations. Excipients can become dangerous when used in formulations due to a variety of excipient interactions, including as those between drugs and excipients, excipients and excipients, and packages and excipients. Various stability testing processes are carried out where the excipients are exposed to harsh circumstances of temperature, humidity, etc. in order to avoid the use of incompatible excipients and to ensure that they are safe and stable for use in the designing of the formulation. Excipients are further examined for safety, which is the most crucial component of any formulation designed for use in people or animals, if the stability testing results support their usage in formulation. It's critical to recognise novel excipients' possible applications in a variety of intricate delivery systems, and the IPEC approach thoroughly evaluates the safety of new excipients with an eye toward prospective human usage. By using excipients that are both effective and safe, the formulator is able to create a dosage form that is both safe and efficacious. Therefore, in order for an excipient to be used in a formulation, it must be extremely stable, safe, and effective. But most importantly, it must operate as predicted.

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