World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

A review on tablet binders as a pharmaceutical excipient

Rajeshwari Gokul Khairnar *, Ashwini Ramdas Darade and Rupali Rajesh Tasgaonkar

Department of Pharmaceutics, Yadavrao Tasgaonkar Institute of Pharmacy, University of Mumbai, Mumbai, India.

World Journal of Biology Pharmacy and Health Sciences, 2024, 17(03), 295–302

Publication history: Received on 11 February 2024; revised on 24 March 2024; accepted on 27 March 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.17.3.0142

Abstract

The tablet formulation contains binders that increase the inter-particulate bond power inside the tablet. Research and progress of novel accessories remains a priority for potential use as a binder in formulations tablet. Tablet binder or binding agent are the substances that are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets. E.g., starch, pregelatinized starch, PEG, sorbitol, and HPMC, etc. Tablet Binder and disintegrants have the opposite used in an oral solid formulation. Binder delay tablet disintegration while disintegrant increase tablet disintegration. They play a vital role in making sure pellets or granules and tablets remain in shape until they reach their target by holding all ingredients (API and Excipients) together in any solid dosage form. Selecting the correct binder is critical to maintaining the integrity of the tablet. Natural binders such as various starches, Gums, mucus and dried fruits, among other things, have the ability to bind. Features such as Natural polymers, fillers, and disintegrants are also safe more economical than synthetic polymers.

Keywords: Tablet; Binders; Excipients; Pharmaceutical

1. Introduction

Many dosage forms formulated today are complex system containing many other components along with the active pharmaceutical ingredient (API), these compounds are generally added along with the active pharmaceutical ingredients in order to protect, support or enhance stability of the formulation. Drug products contain both drug substance (commonly referred to as active pharmaceutical ingredient or API) and excipients. The resultant biological, chemical and physical properties of the drug product are directly affected by the excipients chosen, their concentration and interactions. The objective of a medicinal formulation development project is to deliver drug to the patient in the required amount, at the required rate, consistently within a batch, from batch to batch, and over the product's shelf life.

Binder excipients hold the ingredients of a formulation together, for example in a tablet. Binders ensure that tablets, powders, granules and others can be formed with the required mechanical strength. Moreover, they give volume to low active dose tablets. The role of the binder excipient is to act as a binder to bind powder, granules and other dry ingredients together to give the product the necessary mechanical strength. They can also give low-dose pills. Usually used for wet granulation, adding a binder to create more effective and predictable particle formation. These excipients can agglomerate powders into granules in a process called granulation, and also affect their properties, such as compaction, drug release, flow, solubility, and strength. Binder excipients are used in the process of drug or drug preparation to improve the disintegration, volume, bioavailability and dissolution of the drug[1].

Examples of Binders are:

Microcrystalline Cellulose, Starches, Lactose, Sugar alcohols like mannitol, Polymers like PVP and PEG, etc.[3].

* Corresponding author: Rajeshwari G. Khairnar

2. Classification of Binders [3]

2.1. Classification based on their source

- **Natural:** These are less toxicity, biodegradable, availability at low cost. Examples include starch, pregelatinized starch, Sodium alginate, and gelatin, etc.
- **Synthetic/ Semisynthetic**: These are the most widely used and required a low amount in a formulation. Examples include Polyvinyl Pyrrolidone (PVP), Methylcellulose, Hydroxy Propyl Methyl Cellulose (HPMC), Polymethacrylates, Sodium Carboxy Methyl Cellulose, Polyethylene Glycol (PEG) and Methylcellulose, etc.
- **Saccharides and their derivatives**: Disaccharides such as lactose and sucrose; Polysaccharides and their derivatives such as starches, cellulose or modified cellulose such as MCC and cellulose ethers such as hydroxypropyl cellulose (HPC); Sugar derivatives such as sorbitol, xylitol, and mannitol, etc.

2.2. Classification Based on their application in the manufacturing process

- **Dry tablet binders**: These are added to the powder blend, either after a wet granulation step or as part of a direct compression (DC) formula. Examples of Dry tablet binders include cellulose, Polyvinyl Pyrrolidone (PVP), Hydroxy Propyl Methyl Cellulose (HPMC), Sodium CarboxyMethyl Cellulose, Polyethylene Glycol (PEG), and Methyl Cellulose.
- **Solution tablet binders**: These are used in wet granulation processes. These are dissolved in a different solvent such as water or isopropyl alcohol. Examples of Solution tablet binders include cellulose, gelatin, cellulose derivatives, polyvinyl pyrrolidone, starch, sucrose, mannitol, polyethylene glycol, and liquid glucose, etc.

2.3. Natural Binders

- Starch
- Natural gums
- Dried fruits

2.3.1. Starch as binder:[3-4]

There are various types of natural polymers like starch, gums, pre-gelatinised starches are used as binding agent. Starches like rice starch, maize starch, potato starch, wheat starch, corn starch are well known for their binding and disintegrating properties but some other starches like enset starch and banana starch can also be used as binding agent. Starch is also used as fillers. Starch is widely used as thickening, stabilizing, gelling and/or filling agent in many food applications and it considered as the most used excipients in pharmaceutical formulations. It is used mainly in tablets as filler, binder or disintegrant. Starch is the major carbohydrate reserve in plant tubers and seed endosperm where it is found as granules.

It contains mainly two types of polymer molecules several million of highly branched amylopectin molecules (normally 70-80%) accompanied by a higher number of largely linear amylase molecules (normally 20-30%)

Starch is one of the most widely used excipients in the manufacture of solid dosage forms. Starches from different sources have been evaluated and used as excellent binders in either mucilage or the dry powdered form. Although maize starch is the most frequently used excipient in tableting, researchers have tried to develop botanical starches for use tablet excipients. The effects of pigeon pea and plantain starches on the compressional, mechanical and disintegration properties of Paracetamol tablets have been investigated.

Starch 1500 as a binding agent

Starch 1500 performed as an excellent binder producing a granulation that was compressible and produced Lamivudine tablets of improved hardness and friability compared with those prepared with povidone. The formulation of Lamivudine tablets with Starch 1500 exceeded the disintegration and dissolution performance of the povidone formulation that utilized a super disintegrant. The nature and amount of the binders were found to alter the disintegration and dissolution rates of the tablets by reducing their wet ability as measured by the adhesion tension of water. During pharmaceutical granulation, the objective is to produce granules that have a uniform (and repeatable) distribution of drug particles within the bulk carrier (excipient) solid. This can be difficult to achieve and both drug depletion and enrichment in granules can occur. The use of a natural product tapioca starch as binding agent in the formulation of Diclofenac tablets was identified.

To establish two other commonly used disintegrating agents potato starch and maize starch were selected and formulated for comparison. Different formulations were prepared by using above three disintegrants in the concentration of 20mg per tablet. The were prepared by wet granulation technique[4].

2.3.2. Natural gum and mucilage as binder

Most of the natural polymer (gum and mucilage) are formed by high molecular weight carbohydrates. They are biodegradable, biocompatible and non-hazardous polymers showing irregular physical-chemical properties and environmentally sustainable features. Carbohydrates represent the most abundant biological molecules, covering a large array of fundamental roles in living things: from the reserve and transport of energy, (starch and glycogen), to the development of structural components (cellulose in plants, chitin in animals), to the linking between intercellular walls (hemicellulose). The high molecular weight carbohydrates derived, are known as polysaccharides. They may be viewed as condensation polymers in which carbohydrates have been joined together by glycosidic linkage with the elimination of molecules of water[2].

$$n\ C_6H_{12}O_6 \rightarrow (C_6H_{10}O_5)n + (n-1)H_2O$$

The different macromolecular structures and chemical compositions of polysaccharides are responsible for the large array of their physical and biochemical applications. A wide range of polysaccharides, such as agar, alginate, chitin and pectin are able to hydrate in cold and hot water, thus giving rise to both viscous solutions or dispersions and gels. The great interest with these polysaccharides in aquatic animal feed is strictly related to their gelling properties (Figure 1)

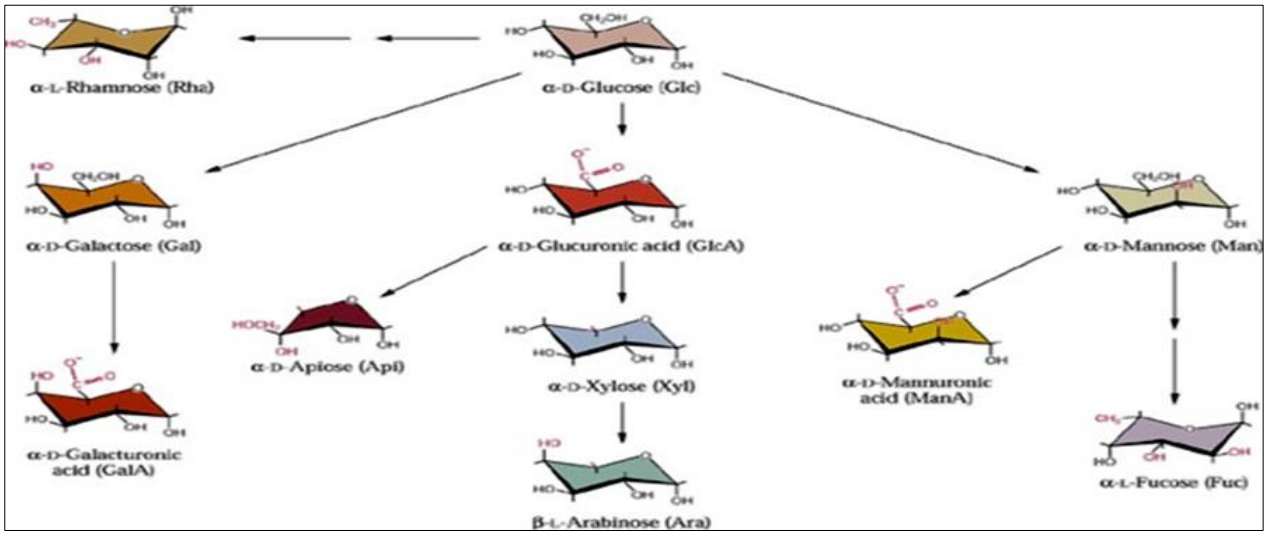

Figure 1 Natural gum and mucilage as binder

3. Ideal Properties Of Binders

- Physiologically inert.
- Acceptable to regulatory agencies.
- Physiologically and chemically stable.
- Should not interfere with the bioavailability of the drug.
- Commercially available in a stable form.
- Meet the standards of regulatory requirements.
- Able to cohesive compacts for directly compressed tablets [4].

Table 1 List of Tablet Binder used in Pharmaceutical Preparations : [4]

Name of Tablet Binder	**Concentration (%)**
Acacia	1.0 – 5.0
Copovidone	2.0 – 5.0 (In direct compression) 2.0 – 5.0 (In wet granulation)
Carbomer	0.75 – 3.0
Corn Starch and Pregelatinized Starch	Commercially known as STARCH 1500
Calcium carboxymethylcellulose; calcium cellulose glycolate; carmellosum calcium;	5.0–15.0
Carboxymethylcellulose Sodium, Carmellose Sodium	1.0–6.0
Ceratonia	0.15 – 0.75 [3]
Chitosan Hydrochloride	Chitosan is a well-known polysaccharide
Dextrates	Purified mixture of saccharides
Dextrin	Low-molecular-weight carbohydrates
Ethylcellulose	Ethylcellulose being blended dry or wet granulated with a solvent such as ethanol (95%).
Liquid Glucose	5.0 – 10.0
Guar Galactomannan,/ Guar Gum	Up to 10.0
Hydroxyethyl Cellulose	Derived from cellulose
Hydroxyethylmethyl Cellulose	Derived from cellulose
Hydroxypropyl Cellulose	2.0 – 6.0
Low-Substituted Hydroxypropyl Cellulose	Most widely used

4. Advantages

- Natural polysaccharides are widely used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, availability and low cost.
- They can also be used to modify the release of drug, thereby, influencing the absorption and subsequent bioavailability of the incorporated drug.
- They can be used to variation of the drug release and thereby influences the absorption and bioavailability of the integrated drugs.
- Natural binders are broadly used in the pharmaceutical and food industry as excipients and additives due to their low toxicity, biodegradable, accessibility and inexpensive.
- They act as vehicles which convey the integrated drug to the absorption site and are expected to swear the stability of the incorporated drug, the precision and accuracy of the dosage, and also improve the organoleptic properties of the drugs where required in order to enhance patient loyalty.
- They should optimize the performances of dosage forms during manufacturing as well as when patients consume them[6].

5. Disadvantages

- Polymers binder can lead to processing problems such as rapid over granulation, tablet hardness increases & dissolution concert diminish.
- In case of polymer binders, addition of strong disintegrates usually required but these are huge expensive and have a negative effect on product stability.
- Includes several processing steps
- Usage of various solvents may lead to drug degradation

- Enhances the hardness of the granule
- Application of heat might degrade the thermolabile therapeutic agent[8].

6. Binders Evaluation Test

There are numerous factors that affect the quality of granules These can be caused by variable process as well as the formulation, which should be constantly evaluated and monitored to determine the suitability for the tableting. Characteristics that affect the quality of granules include:

- Physical and chemical stability
- Efficacy
- Compactness
- Fast production capability
- Particle Size and Distribution

The granule size affects the disintegration time, average tablet weight, variation, granule friability, drying rate kinetics of wet granulation, and granulation flowability. The formulator determines the quality of the tablet, which in turn affects the granule size and distribution. The measurements commonly used for the size and distributions include the Conductivity Test, Microscopy, and Sieving [7].

- Tablet Surface Area

In certain instances where the drugs have limited water solubility, the surface area of the drugs is measured, usually during dissolution. Common methods used include Air Permeability and Gas Adsorption [5].

- Density

Where granules are dense and hard, higher compression load is needed to help increase the drug dissolution time and tablet disintegration. Pycnometer is usually used to determine density. The bulk density, granule, and true density can influence the porosity, flow property, dissolution, and compressibility of the tablet.

- Friability

Te Friability is important as it affects the size distribution of the granules which in turn affects the compressibility, weight variation and granule Flowability. It is measured via the Tumbler Test or the Friability Test/Roche Friabilator and the % loss is determined.

- Moisture Content

The moisture content affects the compressibility, flowability and the stability of moisture sensitive drugs and as such should be determined in order to check the granulator's quality.

7. Factors to be considered

- Compatibility

Compatibility of the binder with other components is very important. The Differential Scanning Calorimetry can be used to determine compatibility.

- Drug characteristics

Characteristics such as size, porosity, compressibility, solubility and hydrophobicity can affect the process. Drugs that have poor compressibility would require strong binders whereas porous ones would need a high level of liquid binder. Drugs that have high absorption rate would require higher volume of binder.

- Spreading of the Binder

Spreading the binder together with the powder blend is another important factor; an excellent binder is one that can be easily spread (e.g. HPMC).

- Binder Quality and Type

The uniformity of the tablet's features depends on the quality of the binder added to the formulation. A high concentration of binder can cause hard granulation, whilst insufficient quantity of the binder would result to fragile granulation. Large quantities of granulating liquid can cause coarse and hard granules. In order to ensure that variations are limited and uniformity is reached, the quantity of the liquid added should be prepared and measured beforehand.

- Temperature and Viscosity

Less viscous binders should result in better spreading.

- Method of Adding Binders

The way binders are added is also important. PVP, can be used as a dry or liquid solution when being added to the formulation. It is better to disperse the binders than to pour directly into the mix.

- Mixing Time

The quality of the granules may also be affected by the mixing time. If the wet mass time is higher, this would result in hard granules, and in turn, the tablet failing the dissolution test because the drug release time is altered.

- Granulator Construction Materials

The type of construction material affects the volume of the binder and the granule size being distributed. Vessel walls that are wetted easily by binders would require a high volume of binders; for example, stainless steel vessels would require higher binder volume than vessels that are made of plastics such as PMMA or Teflon. The use of PMMA or PTFE would narrow the particle size distribution due to the high contact angle whereby all liquids are forced directly to the powder bed. With stainless steel, this is different: less contact angle liquid layer is formed in the wall surface, causing inhomogeneous distribution of the liquid over the powder bed, resulting in broader granules.[13]

- Granulator Type

Fluidized bed granulators produce porous granules unlike those produced by the High Shear granulator.

- Variable Process

Higher impeller speed and longer wet massing time can affect the size of the granules. Agglomeration can also occur due to an increase in liquid saturation time. Variables Apparatus[9]

The apparatus used can affect the growth of the granules. Using the High Shear Mixer will result in larger granules than using Fluidized Bed Granulators; this is due to the construction of the mixer. The shape, size chopper, and impeller of the mixing chamber are different in each apparatus.

- Impeller Movement

Wet mass sticks to the vessel less if the impeller movement is helical, resulting in fewer lumps and narrow granule size. This is usually a problem when using the High Shear Mixers because wet mass sticks to the vessel; coating the vessel with polytetrafluoroethylene can reduce this problem. The correct construction of the impeller must also be observed.

8. Conclusion

A wide range of natural polymers have been employed in medicinal formulations. As a binding agent, it is possible to use natural ingredients such as starch, mucilage, gum and dried fruits. They have demonstrated strong promise as binding agents, as well as additional qualities such as disintegration agents, fillers, and maintain release agents. Polymers derived from nature demonstrated strong binding properties in wet granulation, with granules that are more stable and less friable than alternative binders.

There are large numbers of natural polymers have been used in pharmaceutical preparations. Natural substances like gums, mucilages, and also dried fruits can be used as binding agent. They have been shown good potential as binding agent as well as they possess some other properties like fillers, disintegrating agent, sustain releasing agent. Natural polymers shown good binding property in wet granulation, granules are stable and less friable in comparison with other binders. Natural binders are non-polluting renewable resources for sustainable supply of cheaper pharmaceutical excipient or product.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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