2. Theoretical overview

2.1 Basics of bioadhesion

2.1.1 Advantages and applications of bioadhesive dosage forms

Bioadhesive drug delivery has been applied as a desirable system to various administration routes. In particular, the study has been intensively carried out for the development of better oral bioadhesive dosage forms [5, 21-25]. The advantages of the bioadhesives in oral drug delivery can be summarized [1-5]:

a) can prolong GI transit time and improving oral drug absorption should ideally be nontoxic, non-absorbable from the GI tract,
b) preferably form a strong non-covalent bond with mucin-epithelial cell surfaces
c) adhere quickly to moist tissue
d) allow easy incorporation of drug and offer no hindrance to its release
e) possess specific sites of attachment
f) and be economical

Several dosage forms for oral use have been reported as follows [4]:

a) Tablets
Multilayered tablet allows a variety of geometrical arrangement.
Such systems that consist of acrylic polymers or cellulose provide immediate and high adhesion strength at a certain site for a prolonged period of time.

b) Micro- and/or Nanoparticles
Despite the limited loading capacity of drug, bioadhesive micro- and/or nanoparticles have been widely investigated for three major features:

- immobilization of particles on the mucosal surface by adhesion after modification of surface properties via bioadhesive polymers,
- very large specific surface between the dosage form and the oral mucosa, and
- sustained release of entrapped drug, leading to higher absorption.

c) Capsules
Capsules, usually gelatin capsules containing a suspension or liquid, include bioadhesive polymers such as polycarbophil or carbopol. Gelatin interacts with the bioadhesive polymer during or

following dissolution, and thus bioadhesiveness of the polymer is lost before the bioadhesive polymer has a chance to interact with the mucus layer.

2.1.2 Bioadhesive polymers

Polymers which can adhere to either hard or soft tissue have been used for many years in surgery and dentistry. For the purpose of bioadhesion they have been also in pharmaceutical industries extensively used and investigated. Bioadhesive polymers can be grouped into synthetic and natural polymers. Most of the current synthetic bioadhesive polymers are [5, 26]:

a) Polyacrylic acid-based polymers :
carbopol, polycarbophil, polyacrylic acid, (PAAc), polyacrylate, poly(methylvinylether-co-methacrylate), poly(methacrylate), poly(acrylcyanoacrylate), poly(isohexylcyanoacrylate), and poly(isobutylcyanocrylate), etc.

b) Cellulose derivatives :
Carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, and methylhydroxyethyl cellulse, etc.

c) Semi-natural polymers :
chitosan,, various gums such as guar, xanthan, gellan, carrageenan, pectin, and alginate

Choice of a particular polymer type will depend on a number of formulation issues as well as patent status. Some properties and characteristics of bioadhesive polymers used commonly are described in table 2.1.

Tab. 2.1: Some Bioadhesive Polymers and their Properties [4]

Bioadhesives	**Properties**[a]	**Characteristics**
Carbopol/carbomer	• Mw 1 x 10^6 ~ 4 x 10^6 • pH 2.5~3.0 • ϕ water, alcohol, glycerin • η 29,400~39,400 Pa s at 25°C (0.5% aq.soln.)	• synthesized by cross-linker of allyl sucrose or allyl pentaerythritol • excellent thickening, emulsifying, suspending, gelling agent • common component in bioadhesive dosage forms
Sodium carboxymethyl cellulose	• Mw 9 x 10^4~ 7 x 10^5 • η 1200 Pa s (1.0%aq.soln.) • pH 6.5~8.5 • ϕ water	• sodium salt of a polycarboxymethyl ether of cellulose • emulsifying, gelling, binding agent good bioadhesive strength

Hydroxymethylcellulose	• pH 6~8.5 • ρ 0.6 g/ml	• suspending or viscosity increasing agent • binder, film former, thickener
Alginate	• pH 7.2 • η 20-400 Pa s (1% aq.soln.)	• stabilizer in emulsion, suspending agent, tablet disintegrant, tablet binder

([a] η: dynamic viscosity; ρ: density; Mw: molecular weight; pH measured at 1.0%-aqueous solution(aq.soln.); ϕ: soluble solvent)

2.2 Theory of granule formation

2.2.1 Methods of granulation

The principal methods of granulating pharmaceuticals may be classified into three main categories: wet processes, dry processes, and other processes [Tab.2.2].

Tab. 2.2: Processes used for pharmaceutical granulation [6]

General process	Specific methodology
Wet processes	• Wet massing • Fluid bed granulation • Spray drying • Pan granulation • Extrusion and spheronization
Dry processes	• Roller compaction • Slugging
Other processes	• Humidification • Prilling • Melt pelletization

Although some or all these methods are used in the pharmaceutical industry, wet granulation has been, and continues to be the most widely used agglomeration process. Typically, the wet massing of pharmaceutical powders is carried out in high-shear mixers before wet screening, and often, the moist granules are dried in fluidized-bed granulators in which the liquid phase is sprayed onto fluidized powders as the hot airflow simultaneously dries the granules.

2.2.2 Fluid-bed granulation

2.2.2.1 System description

Fig.2.1 and 2.2 show the fluid bed granulator and its components used in this study (GPCG 1, Glatt GmbH, Germany).

Fig. 2.1: Fluid-bed granulator (GPCG 1, Glatt, Germany)

A fluid bed processor is a system of unit operations involving the heating of process air, directing it through the material to be processed, and then have the same air (usually laden with moisture) exit the unit void of the product.

Fig. 2.2a: Product container

Fig. 2.2b: Control panel of parameters

Two types of disc are used in container [Fig. 2.2a]- hatched and smooth type. The hatched one is employed for granulation process from the powdery starting material, and the smooth type is used

in the coating procedure of core granules. At the downstream end of the fluid bed processor, an exhaust blower or fan is situated to draw the air through the entire unit. This arrangement provides negative pressure in the fluid bed, which is necessary to facilitate material loading, maintain safe operation, prevent material escape, and carry out the process under good manufacturing practices (GMP). Mixing of dry powders, granulating and drying can be successively carried out within a single piece of equipment. Reduction in the manufacturing process steps results in overall shortening of manufacturing time. Fluid bed granulation and drying also reduces handling of raw materials, and hence, reduces operator exposure to irritating and/or toxic compounds. The theory and techniques of fluidization have been known for many years and have been described extensively in the literatures. Fluidized bed technique has been used in pharmaceutical industry for drying, coating, and recently granulating. Wurster (1959) first described granulation in the fluid bed [6, 7].

2.2.2.2 Variables in the fluid-bed granulation process

Granulation is a dynamic process affected by many variables. To produce a desirable product, these variables are understood and properly controlled. Factors affecting the fluid bed granulation process can be divided into three categories [6, 7, 130, 131].

1. Formulation-related variables
2. Equipment-related variables
3. Process-related variables

- **Formulation-related variables**

a) Properties of primary Materials

Ideally, the particle properties desired in the starting material include, a low particle density, a narrow particle size range, a particle shape that approaches spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing. Properties such as cohesiveness, static charge, particle size distribution, crystalline or amorphous nature, and wettability are some of the properties that impact on the properties of the granules formed. The cohesiveness and static charges on particles present fluidization difficult.

b) Binder

Different binders have different binding properties and the concentration of individual binder may have to be changed to obtain similar binding of primary particles. Thus, the type of binder, the binder content in the formulation, and the concentration of the binder have major influence on the granule properties. These properties include friability, flow, bulk, density, porosity, and size distribution.

c) Binder Solvent

The selection of solvent, such as aqueous or organic, depends on the solubility of the binder and the compatibility of product being granulated. Generally, organic solvents, because of their rapid evaporation from process, produce smaller granules than the aqueous solution. Different solvents have different heats of vaporization. The requirement of solvent for the binder can be eliminated by incorporating binder, or a mixture of binders, of low melting point and incorporating it with the drug substance in the dry form. The temperature of the incoming air is sufficient to melt the binder and form the granules [6, 7, 130, 131].

- **Equipment-related variables**

a) Design

The availability of the fluid bed processors from different suppliers of the equipment is essentially similar. But the differences in design of different suppliers sometime provide difficulty in scaling-up from the laboratory units in a linear scale.

b) Air Distributor Plate

Air distributor plates provide an appropriate means of supplying air to the product. These plates are identified by their percentage of open area. Air distributor plates that have 3-40% open area are normally available. A plate that having a small open area to give large enough pressure drop may provide uniform fluidization of such a product without reaching entraining velocity. To overcome this deficiency, an overlap gill plate has recently been introduced.

c) Pressure Drop

The airflow through the fluid bed processor is created by the blower or a fan located downstream from the process chamber. Blower size is determined by calculating the pressure drop (ΔP) created by all the components of the fluid bed-processing system. Proper selection of a blower is essential in fluid bed design. A blower with an appropriate ΔP will fluidize the process material adequately. However, a blower without enough ΔP will not allow proper fluidization of the product, resulting in longer process time and important granulation. A properly sized blower or fan should develop a ΔP sufficient for the exhaust damper to be used in the 30-60% position.

d) Shaker and Blow-Back Cycle Mechanism

To retain entrained particles of a process material, process filters are used. To keep these filters from building up layers of fine process material, causing a high-pressure drop and, thus, improper fluidization, these filters are cleaned during the granulation process. When bag filters are used, mechanical means are used to clean them. This mechanical cleaning of the bag filters requires a cessation of airflow and thus the fluidization during the filter-cleaning process. To avoid process interruptions, a multi-shaking filter bag arrangement is desired, so that the granulation process is

continuous. The continuous process is also achieved by use of bag filters with a blow-back or use of stainless steel filter bags in which air under pressure is pulsed through the filters. Generally, filters should be frequently during the granulation step, to incorporate the fines in the granulation.

e) Other equipment factors

Granulator bowl geometry is considered to be a factor that may impact on the agglomeration process. Generally, a conical shape of the container and expansion chamber is preferred in which the ratio of cross-sectional diameter of the distributor plate to the top of the vessel is 1:2. Most of the suppliers of this equipment offer units with a multiprocessor concept, for which a single unit can be used for drying, agglomerating, air suspension coating, or rotor processing, by changing the processing container, whereas the rest of the unit is common [6, 7, 136-139].

- **Process-related variables**

Among all variables, the process variables are considered especially interesting because they could be relative easily controlled by a worker during the process.
Those most important to consider are listed as follows:

- Process inlet air temperature
- Nozzle atomization air pressure and volume
- Fluidization air velocity and volume
- Liquid spray rate
- Nozzle: position and number of spray heads
- Product and exhaust air temperature
- Filter porosity and cleaning frequency
- Bowl capacity

Each process variable should be properly selected and well controlled during granulation process. The significant process parameters and their effect on the granule properties are summarized in Tab.2.3.

Tab. 2.3: Effect of Process Parameters on Granule Properties [7]

Process parameter	**Effect**
Inlet air temperature	Higher: finer granules Lower: larger, stronger granules
Humidity	Increase in humidity: larger granule size, longer drying times

Fluidizing airflow	Proper airflow should fluidize the bed without clogging the filters. Higher airflow will cause attrition and rapid evaporation, generating smaller granules and fines.
Nozzle and nozzle height	A binary nozzle produces finest droplets and is preferred. Optimum nozzle height should cover the bed surface. Too close to the bed: will wet the bed faster, producing larger granules. Too high position: creates finer granules, and increase granulation time.
Atomization air volume & pressure	Liquid is atomized by the compressed air. This mass/liquid ratio must be kept constant to control the droplet size, and granule size. Higher liquid flow rate will produce larger granules and the reverse will produce smaller granules. At a given pressure, an increase in orifice size will increase droplet size and liquid throughput.
Binder spray rate	Droplet size is affected by liquid flow rate, binder viscosity, and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.

2.3 Dry-coating technique

2.3.1 Concept and advantages

Pharmaceutical coating technologies are commonly ‘wet process’ by spraying of a liquid phase solution of coating materials. But recently, in addition to this liquid-based coating, a new dry powder coating has been introduced. This technique directly attaches polymer particles onto the surface of a solid substrate without organic solvents and large volumes of water [Fig.2.3]. Softening, melting and curing are the principal stages in the film formation during dry powder coating [41, 42].

The advantages of powder dry coating include:

a) a reduction in processing time, due to the absence of large amount of solvents or water;
b) environmental friendliness (no organic solvents, lower energy costs), and
c) applicable also when the material used is unstable in water or in other solvents [41-43].

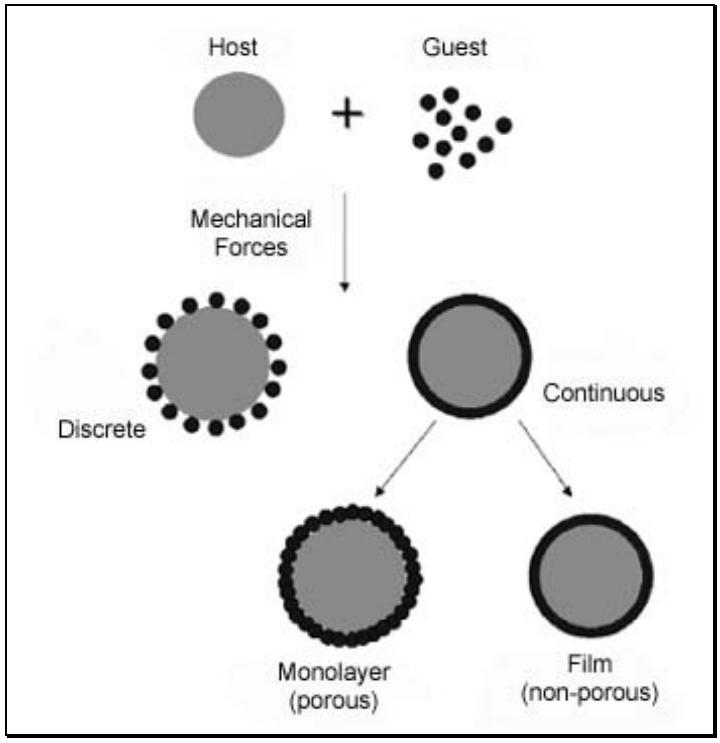

Fig. 2.3: Schematic of dry particle coating [43]

2.3.2 Applications of dry particle coating

In most of the early work reported, the hybridizer was used to produce controlled-release properties. As an example, fines of isoproterenol HCl, 5% by mass, were coated onto potato starch followed by a coating of carnauba wax, 5% by mass, to achieve time-released control of isoproterenol HCl. Furthermore, it has been reported that the hybridizer was useful in preparing composite and encapsulated-coated particles. For instance, if inorganic fine particles were used as coating materials, they were fixed and embedded in the surface of core particles, and if polymer or metallic fine particles were used as coating materials, they partially melted and produced a continuous film coating on the core particle. In pharmaceutical industries dry-coating was introduced as an alternative of conventional liquid-based coating process [41, 42].

2.3.3 Dry-coating by fluid-bed coater

Fluidized bed coater is currently the most widely used equipment for bead coating. Therefore, in this study, the dry coating was examined using a fluidized bed coater. Firstly, the core pellets were prepared and secondly, dry coating technique was employed as a method to layer carbomer powder onto these core pellets. Because this process is carried in dry condition, it was investigated as a way to apply carbomer without the sticking problem commonly occurred in wet processes.

2.3.3.1 System description

The schematic of fluidized bed coater is shown in Fig.2.4.

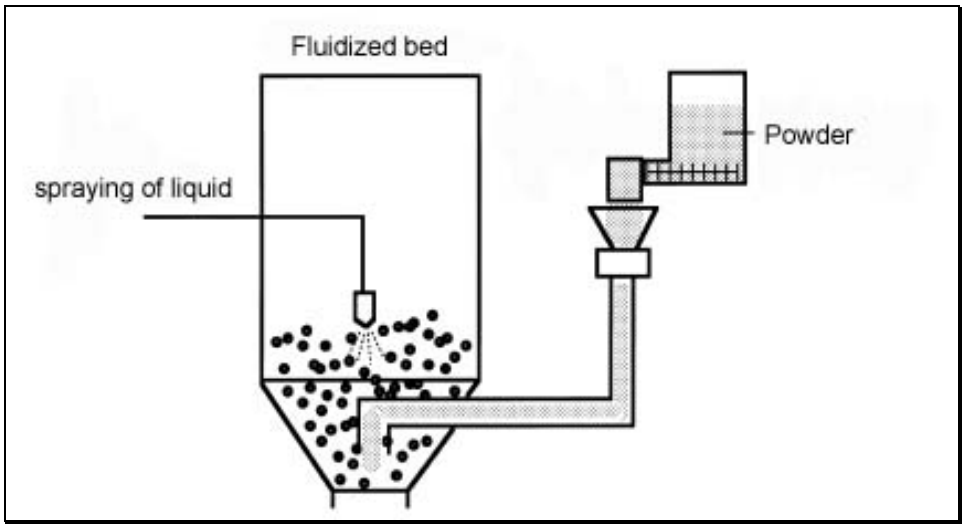

Fig. 2.4: Schematic of dry coating with fluid-bed equipment [42]

The host and guest powder mixture are placed into the rotating bed and is fluidized by the radial flow of gas through the porous wall of the cylindrical distributor, as seen in Fig.2.4, due to the high rotating speeds, very high centrifugal and shear forces are developed within the fluidized gas–powder system leading to the break-up of the agglomerates of the guest particles. Moreover, the very large flow of air needed to fluidize the particles at high rotating speeds and the motion of bubbles when operating the bed above minimum fluidization. That creates strong mixing and hence good coating is achieved [42].

2.3.3.2 Procedures

The powder coating process for solid substrate consisted of three phases: pre-heating, powdering, and curing. In the first phase, the uncoated granules are heated to a selected temperature. During the powdering phase, the polymer powder is transferred into the coating equipment, distributed onto the cores, adhered to the surface of the substrate and a polymeric film coating layer is formed around the granules. Powder adhesion onto the granules is promoted by the partially melted polymer that generated binding forces between particles, and between particles and the granule surfaces. Curing is required as the last step to enhance coalescence of the coating powder particles and the formation of the final film [44, 223].

2.3.3.3 Important process parameters

a) Airflow

A minimum air volume is needed at each gap setting in order to avoid loss of pellets into the plenum below the disk. Excessive air volume may cause loss of active ingredient during powder layering, which occurs when the powder is exhausted from the bed before it adheres to the pellets.

b) Spray rate and powder application rate

Spray rate and powder application rate are considered to be the most critical variables in the process. Adding the powder too slowly leads a wet bed and pellet agglomeration. Adding the powder too quickly results in a dry bed with excessive loss of powder through the exhaust system, powder caking on the walls of the pan, and formation of seedless drug agglomerate of various sizes.

c) Spray atomization

The airless spray system is the most commonly used spray system during drug powder layering in the pan. The main advantage of the airless spray system of the airless spray system over the air-spray system is that it avoids the high air velocity that tends to fluidize the pellets excessively during application.

d) Rotor Speed

Disk rotation speed studies demonstrated that the granules did not tumble and mix at low rotation speed, whereas higher rotation rates resulted in excessive friability of the cores and loss of the coating powder.

e) Inlet and Bed temperature

In powder layering, it is necessary to achieve a state of wetness throughout run. Therefore, for better adhesion and smoother surfaces of pellets, it is ideal to keep the bed temperature at the low range. However, the higher temperatures may also be used when the binder is water [6, 7, 45, 46].