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Review

Research on Technology of Medicinal Functional Food

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Abstract: Particle coating is one of the oldest pharmaceutical processes that is still in existence. It is the process of applying a thin polymer-based film to a particle or granule containing the active pharmaceutical ingredient. The widely used methods for particle coating are sugar coating, film coating, and enteric coating and the techniques are pan coating, fluidized bed coating, and compression coating. Sugar coating was the earlier coating method, and it was gradually replaced by film coating because it required skilled manipulation. With the technology developing, enteric coating draws more attention. Pan coating is the most classic coating technique, which is applied to sugar coating, film coating and enteric coating. Fluid bed coating is used for a mixture of multiple materials and medicines and keeps the bioavailability high. Compression coating can avoid the harmful effects of moisture and high temperature, while it requires highly accurate machinery.

Keywords: coating; compression coating; enteric coating; fluidized bed coating; film coating; pan coating; sugar coating

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1. Introduction

Coating is the most direct method for taste masking. Coating may be applied to a range of oral solid dosage forms, including particles, capsules, and functional food crystals [1]. Coating provides a physical barrier for functional food particles so that it can reduce the contact between the functional food and the taste buds [2]. Coating can not only mask the bad taste or odor of functional foods, it can also play a role in avoiding damp, darkness, and isolating from the air, improving functional food stability and controlling the functional food release rate and the site of release.

Coating is a process in which a basically dry outer coating material is applied to the surface of a preparation to achieve a wide range of specific benefits ranging from facilitating product identification to altering the functional food release of the preparation [3]. Starch is widely sourced, non-toxic, and completely biodegradable. It can form a transparent film after gelatinization and drying, has good biocompatibility, and is easy to master, so it can be used as drug carrier material [4]. A particle is a pharmaceutical dosage form consisting of a mixture of active substances and excipients, usually in powder form or compacted into a solid dose [5].

2. Coating Method

As a rule, there are three methods used for particle coating: film coating, sugar coating, and enteric coating [6–8].

2.1. Sugar Coating

Earlier, sugar coating was adopted for pharmaceutical from confectionary industry. Sugar coating forms the bulk of the coated particle, and it includes five separate procedures:

2.1.1. Sealing the Particle Core

The application of a water-impermeable polymer, such as polyvinyl acetate phthalate and shellac, can protect the core particle from humidity, harden the surface, and extend the particle's shelf life.

2.1.2. Subcoating

This causes a rapid building up to grind the particle edges by adding the building agents.

2.1.3. Smoothing

First, the coating surface is smoothed with sucrose syrup, and the particle size is enlarged to a predetermined size.

2.1.4. Coloring

This procedure includes finishing the particle's color and molding the final size.

2.1.5. Polishing

This procedure is mainly to give the particle a characteristic shine, commonly using beeswax or carnauba wax. Waxes are one of the materials that can be used to coat for the release of functional food.

In the early years, sugar coating was adopted for pharmaceuticals. However, as it had a tedious process and required skilled manipulation, film coating started to be preferred over sugar coating [9].

2.2. Film Coating

This method is widely used in present processing production. It can coat particles, capsules, and pellets with a thin layer of polymeric material. Particle film coating is divided into two kinds: water-based film coating (general water as a solvent) and non-water-based film coating (general organic solvent) [10]. Film coating contains four parts: the polymer, plasticizer, colorant, and solvent [9].

A combined low substituted hydroxypropyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, TiO_2, and sucrose with fatty acid ester mixture masked the bitter taste of Sparfloxacin [11,12]. Microcrystalline cellulose and low substituted hydroxypropyl cellulose as polymers masked the unpleasant taste of Amoxycillin trihydrate [13]. The polymers combining polyethylene glycol with Eudragit L 100-55 coated Roxithromycin [14]. Matteo Cerea and Weijia Zheng et al. used Eudragit® E PO as the delayed release polymer for theophylline tablets. A theophylline-containing particle was coated with micronized acrylic polymer using a powder coating technique [15]. P.C. Kayumba and N. Huyghebaert et al. used Eudragit® E PO as the taste-masked formulation for quinine sulphate. The results of an in vitro dissolution test and electronic tongue suggested the coating process was successful [16]. Randale et al. prepared granules to mask the bitter taste of chlorpheniramine maleate. The taste-masking particles were prepared from aminoalkyl methacrylate copolymers (Eudragit E-100) by extrusion. By panel testing, the particles disintegrated in the oral cavity within 30 s, and the bitterness decreased. Complexing metoclopramide HCl with aminoalkyl methacrylate copolymer (Eudragit® EPO) by the extrusion–precipitation method obtained the desired result according to a taste evaluation in the oral cavity and molecular properties [17]. Yasser Shahzad et al. prepared granules of docosahexaenoic acid (DHA) using wet granulation with Carbopol 934 P, sodium metabisulphite, and methyl paraben sodium in 120 mL of distilled water. In the coating process, Opadry® enteric, methylene chloride, and isopropyl alcohol (IPA) were used as coating materials. The tests showed that they can efficiently reduce the bitterness by coating the surface of granules [18]. N. Pearnchob, J. Siepmann, and R. Bodmeier found that shellac can effectively protect moisture and mask undesired taste. At the same time, it was suitable for extended-release particles [19]. Using cellulose or shellac as a polymer

masked the taste of pinaverium bromide [20]. Eudragit E-100, microcrystalline cellulose, and hydroxypropyl cellulose can mask the bitter taste of Pirenzepine and Oxybutynin [21]. The composition of the taste-masking coating includes acrylate with a quaternary ammonium group, a copolymer of methacrylate with sodium carboxymethyl cellulose, and a polyvinyl alcohol-polyethylene glycol copolymer [22].

American scientists invented a multi-layered coating technology for taste masking. In one embodiment of the present invention, there is an aqueous suspension that includes water, a functional food substance, a first coating on the functional food substance, and a second coating on the first coating on the functional food substance. At least one of the coatings is insoluble in aqueous solution with a pH greater than about 6 [23].

2.3. Enteric Coating

Enteric coating means it can prevent the release of medication before it reaches the small intestine. An enteric coating is a barrier that controls the location of oral medication [24]. An enteric coating material can be made alone or blended with other materials for coating preparation.

With 5% polyvinylpyrrolidone (PVP) as the binder, microcrystalline cellulose (MCC) for the assigned agent, and starch as the diluent, the berberine: MCC: starch ratio is 1:0.75:3.25. Through the machine for coating, berberine hydrochloride particles were obtained [25]. The bitter taste of Linezolid was masked by a combination of microencapsulation by coacervation and subsequent functional membrane coating on the microcapsules with Eudragit L30D [26]. The unpleasant taste of Levofloxacin was eliminated by polymers combing Eudragit E100 with cellulose acetate phthalate [27]. Shellac is a natural polymer that is used as an enteric coating material in pharmaceutical applications and provides a moisture-protective and taste-masking coating [19,28]. The patent US 4415547A describes coating particles with an organic spray solution consisting of hydrophilic polymers (PVP), hydrophobic polymers (ethyl cellulose), and other conventional coating components, which are then added with other excipients and compressed into particles [29]. The patent US 5523095A describes a taste-masking coating based on cellulose acetate or cellulose acetate butyrate and polyvinyl alcohol pyrrolidone. The polymer is dissolved in an organic solvent, and the spray solution has a solid content of between 8 and 10%. The amount necessary for flavor masking is 12–15% by weight [30]. Flash tab involves coating a functional food with a Eudragit polymer to provide the rapid release of the functional food in the stomach and formulating this microencapsulated functional food with an effervescent capsule to produce flash a of particle dispersal [31]. Eudragit was used to develop taste-masked microspheres of ofloxacin and to prepare oral dispersible particles of the formulated microspheres using a natural superdisintegrant [32]. Comparison of coating methods is shown in Table 1 [33,34].

Table 1. Comparison of coating methods.

Film Coating	Sugar Coating	Enteric Coating	References
single-stage process can be automated, small weight increase	low cost of materials, aesthetically pleasing, simple device	strong gastric acid resistance, high safety	[33,34]
the core material properties are consistent with the formula	operation cannot be automated, multistage process	low dissolution, a certain amount of pollution	[33,34]

3. Coating Techniques

In laboratory and industrial production, there are several kinds of coating methods, such as pan coating, fluidized bed coating, and compression coating.

3.1. Pan Coating Method

Also called the roll coating method, it is a classic and widely used method of coating. It can be used for the sugar coating, film coating, and enteric coating, including the ordinary roll coating method and the buried pipe coating method. The pan coating method involves adding coating materials to a spinning coating pot and fully wetting particles

with continuous rolling under the action of hot air. Through constant rotation and drying, particles are enshrouded gradually. The method is low cost and has a simple equipment structure and convenient operation. The ordinary pot-type coating is mainly used for poor coating conditions. When slow release and controlled release affect good pills and particles and functional food requirements are not high, the scope is limited. Different FC techniques and processes (A) Conventional FC pan, (B) Fluid bed FC, (C) Phases of FC, (D) Phases of microencapsulation is shown in Figure 1 [35].

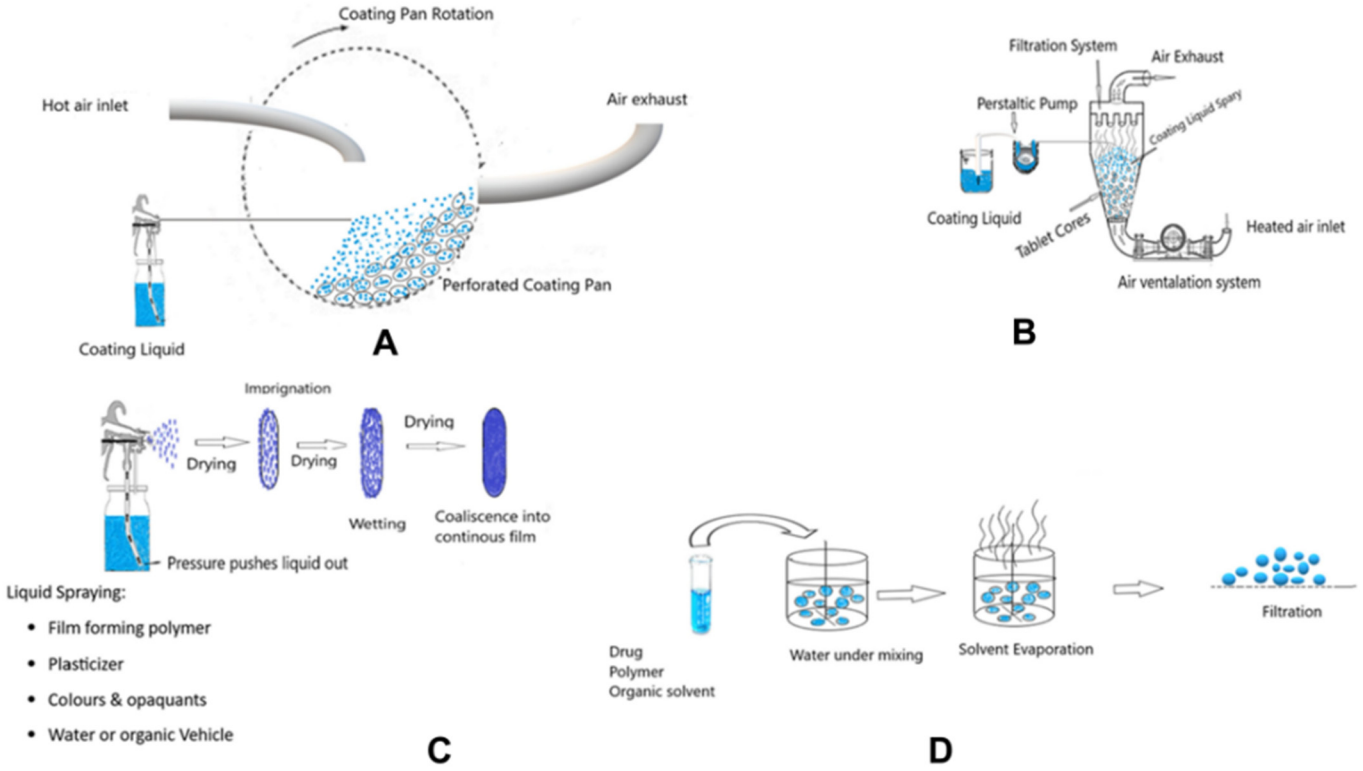

Figure 1. Different FC techniques and processes (**A**) Conventional FC pan, (**B**) Fluid bed FC, (**C**) Phases of FC, (**D**) Phases of microencapsulation.

The process of encapsulation involves many methods: phase separation, coacervation, air suspension, spray drying and solvent evaporation, congealing, pan coating, and the multiorifice centrifugation method [36]. A.A. Zaghloul and S.R. Vaithiyalingam et al. obtained Naproxen controlled-release particles by compressing its microspheres with Eudragit L100-55. During the procedure, the pan coating technique was applied [37]. Swati C. Jagdale and Amit J. Agavekar et al. obtained propranolol hydrochloride particles with hydroxypropyl methylcellulose (HPMC) K4 M and hydroxypropyl cellulose (HPC) by pan coating, and they found that when the pan speed is low the functional food release rate was significantly lower after coating [38]. The US20100247646A1 disclosure is a method for preparing extended-release particles of nisoldipine, which were coated with the pan coating technique [39].

3.2. Fluidized Bed Coating Method

The fluidized bed method, also called the air suspension method, was first put forward by Wurster. Fluidized bed coating is based on the physical and mechanical principles to make powder. Crystalline functional food forms the main method of the micro capsule [40]. Depending on the position of the spray, fluidized bed coating can be divided into three kinds: the bottom spray type, top spray type, and side spray type. Batch fluidized bed granulator is shown in Figure 2 [41].

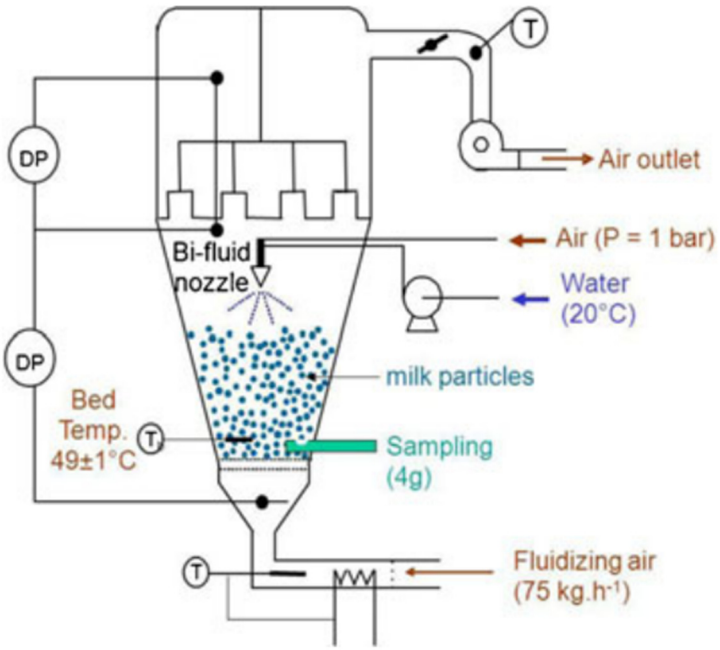

Figure 2. Batch fluidized bed granulator (UniGlatt).

There are studies that have found that the bottom-spray-type coating fluidized state is a stable, continuous, smooth, and uniform coating film, and it is a commonly used method at present.

Ibuprofen taste masking is formed by using air-suspended coating technology to form microcapsules, which include a crystalline ibuprofen and a methacrylate copolymer coating pharmaceutical core that helps formulate chewing taste-masking particles [42]. Astragalus extract was in the fluidized bed and coated with coating liquid. After coating and curing, the membrane completely healed [12]. Using 3% hydroxypropyl methyl cellulose solution as an adhesive, the particle size of the berberine hydrochloride with 75~150 μm was prepared by the fluidized bed lateral jet method again with Eudragit E100 coating material by using the bottom-spray-type method of the fluidized bed spray for coating functional food particles [43]. Satoru Watano and Hideya Nakamura et al. prepared the core particle of cornstarch and Geldart Group C powder, which was sprayed by a hydroxypropylcellulose aqueous solution, and the particle coating was conducted by rotating a fluidized bed [44]. The polymers consisted of Eudragit S100 and Eudragit L100, which were coated onto the indomethacin pellets using the fluidized bed technique [45]. Lee F. Siew, Abdul W. Basit, and J. Michael Newton obtained a series of 5-aminosalicylic acid pellets by using a fluidized bed coater according to the proportions of amylose-butan-1-ol and ethylcellulose [46]. Jorg Breitkreutz and Firas EI-Saleh et al. developed a microcapsule formulation that consists of a lipophilic core with a high sodium benzoate load and a saliva-resistant coating. The extrudates were rounded off and coated by a fluidized bed coater. In this way, children did not recognize the undesirable taste and accepted the medication [47]. Taste masking of cetirizin HCl is used by a fluidized bed coating using Eudragit RL30-D at levels between 15% and 40% w/w. The berberine hydrochloride powder particles were coated by a bottom-spraying technology in a fluidized bed, and the coating rate was 80% [48]. Stange U et al. used a new fluid-bed coating approach to mask the taste of naproxen sodium, and the optimum ratio between naproxen sodium granules and Eudragit® E was found to be 1:1.576 [49]. Dinkar Sharma et al. used flash tab technology to make granules of paracetamol that were prepared by coating the granules of the functional food using the pH-sensitive polymer Eudragit EPO in a fluidized bed coater [50]. The experiment conducted by Julia Z.H Gao and A Jain et al. suggested that wet granulation particles of a high dose that are poorly soluble in water and low-density and micronized functional food

can be produced by fluidized bed granulation [51]. Erythromycin A or a derivative thereof and alginic acid were in a ratio of 2.5:1, and the dispersion was coated on microcrystalline cellulose beads in a fluidized bed processor. The particle size of erythromycin A or a derivative thereof can be less than 50 microns [52]. The lamotrigine-containing granules were prepared by the granulation of lamotrigine crystals with sugar alcohol as a disintegrant and microcrystalline cellulose as a filler in a high shear granulator or a fluid-bed granulator using a solution of polymeric binders and dried in fluid bed equipment to produce the lamotrigine-containing granules [53].

Although the fluidized bed coating is an ancient pharmaceutical technology, it is still often used in the manufacture of pharmaceutical dosage forms [54]. The fluidized bed coating effect is good, with strong adaptability, and can be used for a variety of materials and functional food packages. Fluidized bed coatings are mainly used to develop modified release or pulsation release, or to improve the bioavailability of functional foods [55–57].

3.3. Compression Coating Method

The compression method of coating, which is also called dry coating, is a relatively new coating process that applies a granular coating material to the particle after direct pressure molding on the particle. This is a technique in which large particles completely or partially surround small particles. This technology can be safely applied to coatings with solvent-sensitive or moisture-sensitive functional foods or any particles that provide delayed- or enteric-release products. It is an accurate, uniform, repeatable enteric-soluble coating applied to core particles [58].

Law D. and Zhang Z. et al. developed a new formulation to stabilize the nutraceutical enzyme Nattokinase in powders and to control its release rate by direct compression coating using Eudragit L100-55 and hydroxypropylcellulose [59]. V.R. Sinha and Asmita Singh et al. developed a colon-specific 5-fluorouracil compression coating system using xanthan gum and hydroxypropyl methyl cellulose (HPMC) as coating materials for the treatment of colorectal cancer. Core particles containing 50 mg of 5-FU were prepared by direct compression [60]. Schematic representation of the film-coating process flow diagram for side-vented coating pans is shown in Figure 3 [61]. Comparison of coating techniques is shown in Table 2 [62–64].

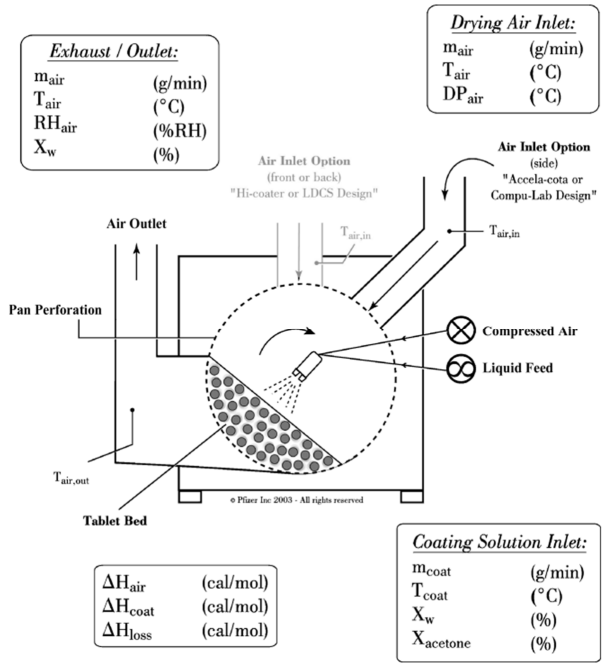

Figure 3. Schematic representation of the film-coating process flow diagram for side-vented coating pans.

Table 2. Comparison of coating techniques.

Fluid Bed Coating	Pan Coating	Enteric Coating	References
good controllability	applicable to many types	strong gastric acid resistance, Security is strong	[62–64]
affected by operation and equipment, etc., poor functional food loading capacity	the range of functional foods is limited, slow-release effect is not good	low dissolution, a certain amount of pollution	[62–64]

4. Conclusions

In recent years, with the improvement in people's living standard, the requirements of functional food are not confined to efficacy; the color of the functional food, packing, flavor, and edible convenience are also taken into consideration. Especially for functional foods containing Chinese herbal medicine ingredients, the effective ingredients were mostly bitter substances with poor taste and patient compliance.

In this review, there are a plenty of studies on the bitter taste-masking method for functional foods. The recent research focuses on the particle coating, which effectively eliminated the bitterness of functional foods and disintegration speed and is suitable for special people. However, the process of coating is time-consuming, and it still requires professional skills.

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