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Advances in Formulation of Orally Disintegrating Dosage Forms: A Review Article

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ABSTRACT: Oral disintegrating tablets are solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue The products are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need for chewing the tablet, swallowing an intact tablet, or taking the tablet with water. ODT is general form of nomenclature for tablets that disintegrate rapidly or instantly in the oral cavity. Other alias are Quick Dissolve, Rapid Dissolve, Rapid Disintegrating, Fast Disintegrating, Fast Melt, Flash Melt and Mouth Dispersing.

KEYWORDS: Orally Disintegrating Tablets; ODT Technology; Taste Masking.

INTRODUCTION

All fast disintegrating tablets approved by USFDA are classified as Orally disintegrating tablets. European Pharmacopoeia[1] adopted the term Orodispersible Tablets for tablets that dispersed or disintegrate in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or gel like structure, allowing easily swallowing by patients. As per recent USFDA guideline[2] on Orally Disintegrating Tablets (Dec'2008), disintegration time of ODT should have an invitro disintegration time of approximate 30 seconds or less, when based on United State Pharmacopeia (USP) disintegration test method or alternative. Secondly tablet weight should not exceed 500 mg. as larger tablets may have an effect on patient safety and compliance.

WHO REQUIRES OR PREFER ORALLY DISINTEGRATING TABLETS:

This mode of administration was initially expected to be beneficial to pediatric and geriatric patients, to people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult (e.g., for psychiatric disorders).

1. Around 35% of general population as well as additional 30-40% of elderly institutionalized patients and 18-22% of all persons in long term facilities have difficulty in swallowing in conditions such as Parkinson, Migraine, Epilepsy and

Schizophrenia. Common complaints about the difficulty in swallowing tablets in order of frequency of complaints are size, surface, form and taste of tablets.

2. Convenience "on-the-move", requires no water intake: Geriatric and pediatric patients and traveling patients who may not have ready access to water are most in need of this dosage form.

3. Patient Compliance and Quicker onset of action in some of the indications like migraine and insomnia may be another advantage associated with ODTs.

Examples:Zolmatriptan ODT were an effective and convenient alternative to a conventional tablet, allowing migraine attacks to be treated anytime a migraine strikes, which can facilitate earlier treatment [3-4]. Olanzapine ODT, Zyprexa Zydis®, facilitated antipsychotic medication compliance in acutely ill, noncompliant patients[5].

It has been observed that ODTs can promote pregastric absorption of the active ingredients through buccal, sublingual, oropharyngeal and esophageal membranes. As a result ODTs can provide a quick onset of action. Piroxicam is known to be absorbed from rat mucosa[6]. Its ODT is considered as an alternative in spine postoperative control during the early postoperative period[7], the treatment of patients with acute low back pain[8], the acute treatment of acute migraine[9], and in emergency renal colic treatment[10] because of its quick onset, long duration, low side effects and high toleration. Pfizer has marketed Piroxicam ODT (Feldene melt®) using zydis technology.

Acetylsalicylic acid from an ODT was absorbed faster than from plain tablets, and yet two formulations were bioequivalent with regard to absorption extent.[11] No statistical difference in Cmax and $AUC_{0\text{-}inf}$ between the acetaminophen ODT and the conventional tablet was observed. However t_{max}(15 min) of the ODT was significantly (p,0.05) shorter than that of the conventional tablet (130 min). The same value of t_{max}between the ODT and the solution was observed. Mcneil Consumer has launched acetaminophen ODT with the brand name of Tylenol® meltaways.

Pre gastric absorption avoids the first pass metabolism, the drug dose can be reduced if a significant amount of drug is lost through the hepatic metabolism.

4. "Preference for the wafer drug delivery system over tablets was noted by 75% of the sample population in case of Famotidine Wafers[12]. The findings were consistent for younger (<60 years) and older (>60 years) subjects"

5. Recent study shows that around 70% of patients prefer OlanzapineODTs over swallow tablets[13].

In addition to providing ease of delivery of different kinds of patients, fast disintegrating dosage forms may also benefit Pharmaceutical companies as a means of Life Cycle Management. These dosage form offers huge benefits to the patients (ease and convenience of delivery) but the Phamraceutical company benefit from extended Patent Protection and/or market exclusivity for its Products. Recently Pfizer has launched 5 mg of Atorvastatin Chewable Tablets for Pediatric patients in Europe under pediatric investigation plan. This is also a part of strategy for life cycle management of drug.

CHALLENGES IN FORMULATION OF ODTS:

As ODTs are different from conventional tablets, they need to overcome several challenges to maintain its unique properties.

A. Fast Disintegration:

As mentioned earlier, ODTs need to disintegrate in mouth as soon as possible in small amount of saliva of the patient.

B. Taste of Active ingredients

A pleasant taste inside the mouth becomes critical for patient acceptance. If a product taste bad, the consumer could care less about convenience of carrying ODT and will prefer swallow tablet. If a product taste great then patient may prefer ODT over conventional Tablet. Unless the drug is tasteless or does not have an undesirable taste, taste masking techniques should be used. An ideal taste masking technology should provide drugs without grittiness and with good mouth feel.

C. Drug Properties:

ODT technology should be versatile enough to accommodate unique properties of drugs such as solubility, crystal morphology, particle size, hygroscopicity, compressibility and bulk density of drug. These drug properties can significantly affect the final tablet's characteristics such as tablet strength and disintegration.

D. Tablet Strength and Porosity:

Strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure. There should be proper balance of these two properties in tablets to get the quality ODT. Low compression pressure causes ODTs to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring special packaging to handle fragile tablets should be provided.

E. Moisture Sensitivity:

Theoretically ODTs should have low sensitivity to moisture. But practically, it is very challenging as many high water soluble excipients are used in formulation to enhance fast dissolving properties as well to create good mouth feel. These highly water soluble excipients are susceptible to moisture, some will even deliquesce at high humidity. A good packaging should be provided to ODTs to protect from various environmental conditions.

TECHNOLOGIES USED FOR MAKING ORALLY DISINTEGRATING TABLETS:

The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent & using highly water-soluble excipients in the formulation. Following technologies have been used by various researchers to prepare ODT: -

- Freeze-Drying or Lyophilization
- Tablet Molding
- Spray Drying
- Sublimation
- Direct Compression
- Cotton Candy Process
- Mass-Extrusion
- Nanonization
- Fast Dissolving Film

Freeze-Drying or Lyophilization

Freeze drying is the process in which solvent is sublimed from a frozen drug solution or suspension containing structure forming excipients. This technique creates an amorphous highly porous structure that allows rapid dissolution or disintegration. List of commonly used excipients[14] for Lyophilization of small molecules are presented in figure 1:

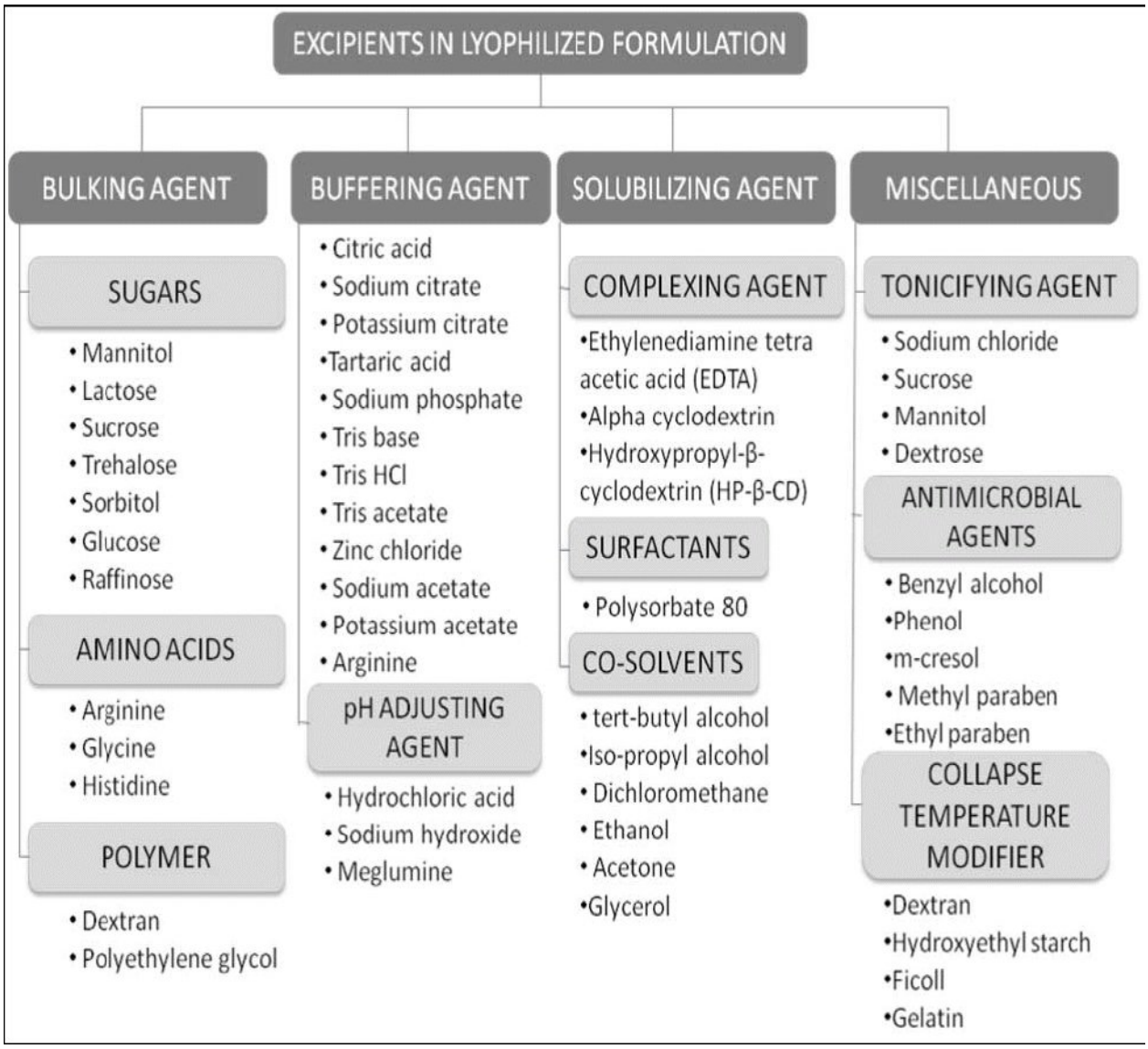


Figure 1 Classification of commonly used excipients used in Lyophilization of small molecules

A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is dosed by weight and poured in the pockets of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped.

The Zydis®technology is the most well known example of the freeze drying. In the Zydis® formulation, the drug is physically trapped in a matrix compound of two components, a saccharide (e.g; mannitol) and a polymer. Other standard excipients can be

incorporated to adjust pH or add flavor, color and modify texture. When working with coated drug particles, excipients such as xanthan gum can be added to the liquid admixture because it improves the ability of the liquid composition to suspend relatively large particles during the manufacturing process. Products manufactured using Zydis® technology and marketed in USA are presented in Table 1.

Brand	**Active Ingredient**	**Indication**	**Innovator/Partner**
Claritin® /Reditabs®	Loratadine	Allegies	Cardinal/Schering
Maxalt MLT®	Rizatriptan	Migraine	Cardinal/Merck
Zyprexa®	Olanzapine	Schizophrenia	Cardinal/Eli Lilly
Zofran ODT®	Ondansetron	Emesis	Cardinal/GSK
Feldene® Melt	Piroxicam	Pain, Inflamation	Cardinal/Pfizer
Ativan®	Lorazepam	Anxiety disorder	Cardinal/Wyeth
Imodium®	Loperamide	Diarrhea	Cardinal/J&J
Motilium®	Domperidone	Emesis	Cardinal/J&J
Zelapar®	Selegiline	Parkinson's	Cardinal/Elan
Pepcidine Rapitab	Famotidine	Heartburn/Indigestion	Cardinal/Merck
Risperdal® M- Tab™	Risperidone	Schizophrenia	Janssen
Klonopin Wafer	Clonazepam	Sedation	Roche
Childrens's Dimettap® ND	Loratadine	Allergy	Wyeth Consumer Healthcare
Seresta Expidet®	Oxazepam	Anxiety disorder	Wyeth

Table 1

Quicksolv® (Janssen Pharmaceutica) and Lyoc®(Farmalyoc Laboratories L) are also produced by freeze drying method.

In the Quicksolv® formulation, the matrix compositions are dissolved in the first solvent (usually water), and then the solution is frozen. Components of the matrix generally include a water soluble hydratable gel or foam-forming material(such as gelatin), a rigidifying agent (such as mannitol or other saccharide), and one or more amino acids. At the temperature at which the first solvent will remain in the solid form, the frozen solution contact the second solvent, which is substantially miscible with the first solvent. For example, ethanol, methanol or acetone is used as the second solvent with water as the first solvent. The matrix composition should be immiscible to the second solvent. Thus, the first solvent is substantially removed after a few hours of contacting the second solvent to result in a usable matrix. The final product disintegrate almost instantly. This method is claimed to

prevent or reduce incidence of cracking during the final preparation, having uniform porosity and adequate strength for handling. Products manufactured using Quicksolv™ technology and marketed in USA are presented in Table 2.

Brand	**Active Ingredient**	**Indication**	**Innovator/ Partner**
Risperdal Quicklet™ M Tab™	Risperidone	Schizophrenia	Janssen
Propulsid® Quicksolv (discontinued)	Cisapride	heartburn, GERD	Janssen

Table 2

In the Lyoc® formulation, the porous solid is obtained by freeze drying an aqueous solution, suspension, or oil in water emulsion of the active principle and ingredients, filling into preformed blister, and freeze drying the product. In order to prevent inhomogeneity by sedimentation during freeze drying this formulation requires a large proportion of undissolved inert filler to increase the viscosity of the suspension. The high portion of filler reduces the porosity of the tablet, and as a result, the disintegration is slower. Products manufactured using Lyoc® technology and marketed in USA are presented in Table 3

Brand	**Active Ingredient**	**Indication**	**Innovator/ Partner**
Spasfon®	Phloroglucinol	Spasmodic Pain	Cephalon
Sermion®	Nicergoline	Cerebral metabolic Vascular disorder	Cephalon
Vogalene®	metopimazine	Emesis	Cephalon
Proxalyoc®	Piroxicam	Pain Inflammation	Cephalon
Paralyoc®	Acetaminophen	Pain Fever	Cephalon
Seglor®	dihydroergotamine	Headache, migraine	Cephalon
Loperamide Lyoc®	Loperamide	Diarrheaa	Cephalon

Table 3

NanoCystal™ technology (Elan Drug Delivery Inc) uses nanoparticles into a highly porous, microfine tablet matrix. The nanoparticles are less than two microns and are produced by a proprietary milling technique. Direct compression and standard tabletting are then used to produce the finished orally disintegrating tablets. In addition, an alternative approach to manufacturing Nanocrystal ODT dosage forms has been developed to facilitate the preparation of small scale clinical supplies. Nanocrystal colloidal dispersions of drug substance are combined with water soluble GRAS ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in small quantities of water in seconds. This approach is ideal when working with highly potent or hazardous materials because it avoids manufacturing operations (for example: granulation, blending and tableting) that generate large quantities of aerosolized powder. The freeze drying approach also enables small quantities of drug to be converted into ODT dosage forms because manufacturing losses are negligible.

The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

Tablet Molding

The preparation of ODT using molding technology employs water-soluble ingredients so that the tablet dissolves completely and rapidly. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Molding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution.

The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30˚ under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture[15]. Masaki uses an agar solution as a binding agent and a blister packaging as well as a mold to prepare an intrabuccally fast disintegrating tablet[16].

Spray Drying

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing ODT.

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or cross carmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium[17].

Allen and Wang[18-21]have reported this technique for preparing fast dissolving tablets. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate& crosscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

Sublimation

The key to rapid disintegration of ODT is preparation of a porous structure in the tablet matrix[22-27]. To generate such a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane, hexamethylene tetramine and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec.

Vacuum drying technique has been very often used by researchers to sublime the volatile ingredients and thus maximize the porous structure in the tablet matrix[22-27]. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and disintegrate rapidly.

Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants & sugar based excipients.

(a) Superdisintegrants:

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

Ethylpharm (France) has introduced a Flash- dose technology, which contains coated crystals and micro granules along with the disintegrants. In this technology, two types of granules are used; a disintegrating agent (e.g. modified cellulose- cross carmellose) which has a high swelling force, and a swelling agent (e.g. starch) which has a low swelling force.

Orasolv®, Durasolve® and Oravescent® technology:

Orasolv® technology developed by Cima Lab produces tablets by low compression force. It uses an effervescent disintegration agents that releases gas upon contact with water or saliva. The carbon dioxide evolved provide some fizzing which provide good sensation in the mouth. As low compression force produced soft and friable tablets, so special packaging system PakSolv ®was developed by Cima to handle the tablets during shipment and consumer usage

Durasolv ®technology:

Second-generation technology developed by Cima Labs produces robust and durable oral dosage form with an orally disintegrating technology. DuraSolv product may be packaged in conventional packaging, such as foil pouches or bottles , mouth dissolving tablets.

OraVescent®, an enhanced absorption drug delivery system that improves the transport of active drug ingredient across the sublingual or buccal mucosal membranes. It may provide improvement in bioavailability and accelerate the onset of action of some drug ingredients. OraVescent tablets are manufactured using direct compression maufacturing technique using GRAS (generally regarded as safe) excipients

Cephalon has launched FENTORA® (fentanyl buccal tablet) using OraVescent technology for the management of breakthrough pain in patients with cancer.

(b) Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel.

WOWTAB® Technology:

Yamanouchi's WOWTAB® (WithOut Water) technology employs a combination of saccharides to produce fast dissolving tablets using conventional granulation, blending, drying and direct compression of tablets.

Taste masking is provided by the combination of one or more sugar-like excipients or microencapsulation of the active ingredients. These tablets exhibit significant hardness allowing packaging in conventional bottles or blisters.

Products manufactured using WOWTAB® technology and marketed in USA are presented in Table 4

Product	**Marketer**
Benadryl® Allergy & Sinus Fastmelt® (OTC)	Pfizer Consumer
Children's Benadryl® Allergy & Cold Fastmelt® (OTC)	Pfizer Consumer
Gaster-OD® (famotidine)	Yamanouchi
Nasea® (ramosetron)	Yamanouchi
Cytock D (allopurinol)	Yamanouchi
Noctan D (ambroxol HCl)	Yamanouchi
Terbomin D (atenolol)	Yamanouchi
Psychoplen (bromperidol)	Yamanouchi
Balantin (etizolam)	Yamanouchi
Helparol (haloperidol)	Yamanouchi
Yamaolol (procaterol)	Yamanouchi
Transact (ethyl loflazepate)	Yamanouchi
Aramol (alacepril)	Yamanouchi

Table 4

Cotton Candy Process

The cotton candy process is also known as the “candy floss” process and forms the basis of the technologies such as Flash Dose (Fuisz Technology).[28-30]

Flash dose rapidly dissolving tablets are based on Shearform technology developed by Biovail. Flash Dose dosage forms are produced using a special process whereby a unique blend ofsugars or similar ingredients are placed in a fast-spinning centrifuge and subjected to flash heat. A specially designed machine head produces long, cotton candy-like fibers (referred to as "floss"). Shearform matrices are are of two types. Single floss or Unifloss, consisting of a carrier, and two or more sugar alcohols, of which one is xylitol.

Dual floss consists of a first shearform carrier material (termed “base floss”, contains a carrier and at least one sugar alcohol generally sorbitol), and a second shearform binder matrix (“binder floss”, contains a carrier and xylitol).

The candyfloss can then be milled and blended with active ingredients and other excipients and subsequently compressed into ODT. However the high processing temperature limits the use of this technology to thermostable compounds FlashDose tablets canaccommodate up to 600 mg of active ingredient, and typicallydissolve in the oral cavity within 5-15 seconds. Products developed by Biovail (now Valeant) using Flash dose technology are presented in Table 5.

Product	Indication	Technology	Innovator/ Partner
Nurofen® Meltlets ibuprofen	pain, inflammation	FlashDose®	Biovail (Now Valeant)
Fluoxetine	Depression	FlashDose®	Biovail (Now Valeant)
Paroxetin	Depression	FlashDose®	Biovail (Now Valeant)
Ralivia FlashDose (tramadol)	Pain management	FlashDose®	Biovail (Now Valeant)
Zolpidem	Insomnia	FlashDose®	Biovail (Now Valeant)

Table 5

Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets[31]. Other Technologies that can be used for manufacturing of new Oral disintegrating dosage forms (tablets/Films) are as follows:

Supercritical Fluid technology:

Ferro Corporation has developed a portfolio of novel supercritical fluid (SCF)[32] processes. The preferred process medium is carbon dioxide. It is supplied to the reactor in a supercritical state or is heated and pressurized in the reactor to attain a supercritical state. Supercritical fluid processes can be used to obtain stable aqueous suspensions of water-insoluble drugs, low bulk density porous particles for inhalation and composite particles comprised of porous particles of polymer that are infused with the biologically active ingredient. The particles have sizes ranging from 10 nm to several microns. The finely divided particles produced using Ferro's supercritical fluid processes can be incorporated into ingestable formulations, such as tablets or capsules. Ferro's uses the following:

SCF extraction of emulsions (SFEE):

Pure drug or pure drug plus a polymer is dissolved in an organic solvent and dispersed in water using surfactants to form an emulsion. The organic solvent is then extracted using super critical fluid (SCF). This process can be used with small actives, lipids, polymers, and some biologics. The advantages of the SFEE process include a processing time of only a few minutes, low residual solvent in the final product, low cost, and narrow particle size distribution.

Spray-freeze drying with CO2:

Active ingredient is dissolved inwater to form a solution that is then saturated with CO2. Thesolution is then sprayed using a nozzle to form fine frozen droplets.Porous or hollow particles are then formed by removing the waterby freeze drying. This process can be used to formulate proteins. Advantages of the spray-freeze drying method are that it is suitable for sugar stabilization and is more efficient than other lyophilization techniques.

Expansion of SCF saturated solutions:

Polymer plus drug mixtureis saturated with SCF creating a liquified solution, which is thensprayed to form particles via cooling and SCF diffusion from themelt. This process allows for coating at mild temperatures.

SCF antisolvent with enhanced mixing: Material is dissolved in anorganic solvent to form a solution that is injected into supercriticalCO2. This results in precipitation of the material as particles. Thisprocess is can be used with poorly water soluble drugs and smallactives.

Oral films and wafers

Oral films and wafers are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle,

opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. They have the advantage of a large specific surface area for disintegration. One or a combination of the following processes like hot-melt extrusion, solid dispersion extrusion, rolling and solvent casting are used to manufacture these films. A major limitation of these dosage forms is low drug loading capacity and limited taste masking option[36].

DISSOLVABLE FILM TECHNOLOGY:

Corium is developing fast and slow dissolving oral films based onits proprietary Corplex™ hydrogel-based technology platform[37-40].Corplex hydrogels share the properties of both hydrophobicpressure-sensitive adhesives (PSAs) and hydrophilicbioadhesives. The hydrophilic PSAs are prepared by non-covalentcross-linking of film-forming hydrophilic polymers (e.g., polyvinylpyrrolidone), with a short-chain plasticizer (typically PEG) bearingcomplementary reactive hydroxyl groups at the chain ends.Specific balance between enhanced cohesive strength and largefree volume in PVP-PEG miscible blends provides their pressure sensitive adhesive (PSA)behavior. The hydrogels prepared by the "carcass-like" crosslinkingof the film-forming polymer make up the Corplex-100™series. The pressure-sensitive bioadhesive hydrogels of theCorplex-200™ series are obtained by additional cross-linking ofthe film-forming polymer in the Corplex-100 hydrogels by ahydrophilic polymer that contains complementary reactive groupsin the repeating units of the backbone and forms H-bondedinterpolymeric complex of a ladder-like structure.

Two general types of oral films can be developed: fast-dissolving or slow-dissolving. Depending on the application and product requirements, these films can be designed for immediate release, sustained release, delayed release or a combination thereof. The films can be designed to dissolve completely (from seconds up to eight hours) or they can be designed as mucosal patches which can be removed afer a period of time (from minutes up to 8-10 hours). Products can be developed for OTC and Rx drug applications, as well as for personal and/or oral care (such as breath fresheners). Specific variables related to Corium's
dissolvable films include:

- Range of loading capacity: less than 10 mg up to 75 mg
- Range of surface area: 2 cm^2-6 cm^2
- Range of thickness: 0.0025-0.250 mm (up to several mm formucosal patches)
- Range of dissolve time: five seconds to 180 seconds (up toseveral hours for mucosal patches)
- Range of geometric shape: various shapes such as round,elliptical, square, etc.

ORALLY RAPID DISSOLUTION FILM

Orally rapid dissolution film[41] based comprising an edible polymeric composition (preferablyhydroxypropyl methylcellulose and polyvinyl pyrrolidone), a saccharide (preferably a reduced maltose syrup), and a therapeutic agent. The oral thin film disintegrates in the oral cavitywithout water within 30 seconds.

This technology is designed for delivery of medications without water. A variety of therapeutic agents can be delivered provided they are water and/or ethanol soluble and preferably do not have a very strong bitter or sour taste. The formulation can contain active ingredient up to 30% of its total weight (20-100 mg). The company is also working with the technology for topical local effect (sustained release delivery of drugs in the oral cavity) and for systemic effect (transmucosal delivery).

RAPIDFILM TECHNOLOGY DEVELOPED BY LABTEC GMBH

Rapidfilm[42] is a thin, drug containing film with an area of 1- 10 cm2. The rapid dissolution in water or saliva is ensured by a special matrix of water soluble polymers; complete disintegration occurs within 20 seconds. Drug loading can be up to 25 mg per single dose and the typical Rapidfilm composition consists of an a drug (1-25 percent), water soluble polymers (40-50 percent), softener (0-20 percent) and fillers (0-40 percent). Examples of polymers that can be employed include cellulose ethers, PVP, PVA or gelatin. An unpleasant taste can be masked by the addition of flavors and/or sweeteners. The primary packaging is made of a sealing pouch, which affords enough space for logos, codes, instructions or other information. The films are manufactured by a laminating process and packaging costs are comparable to tablets.

Labtec has developed the following products for out licensing:

Medicinal Products:

• Loratadine (10 mg/6 cm^2strip)

• Sildenafil citrate (25 mg/6 cm^2strip)

• Meclizine hydrochloride (25 mg/6 cm^2strip)

• Pergolide mesylate (1 mg/6 cm^2strip)

• Ondansetron (4 mg/6 cm^2strip)

• Doxazosin (8 mg/6 cm^2strip)

• Paroxetine (20 mg/6 cm^2strip)

• Fluoxetine (20 mg/6 cm^2strip)

Famotidine (20 mg/6 cm^2strip)

• Zolpidem/Zopiclone (10 mg/6 cm^2strip)

• Glimepiride (3mg/6 cm^2strip)

Rapidfilm® formulation with the active ingredient (Ondansetron) was approved by the EU Authorities for marketing. It is the first Rx oral dispersible film approved worldwide.

Donepezil Rapidfilm® - Fast dissolving oral film

5 and 10 mg Donepezil are under final development using the oral dispersible RapidFilm® technology - easy to swallow as water is not needed.

Olanzapine Rapidfilm® Fast dissovling oral film

5, 10 and 15 mg drug substance Olanzapine uses oral film dosage form dissolving within seconds without need of water. Olanzapine RapidFilm® is widely used in treating bipolar disorders and other psychotic diseases, like Schizophrenia. The film strip technology is a novel, non-mucoadhesive, fast dissolving oral dosage form, based on a water soluble polymer. Placed on the top of the tongue, the film dissolves within seconds, promoting a gastro-intestinal absorption comparable to immediate release oral solid dosage forms.

Quick-Dis™ Drug Delivery System by Lavipharm Laboratories, Inc.

The Quick-Dis drug delivery system[43] comprises a thin, printable, low-moisture, non-tacky film suitable for dosing and labeling. The thickness of a typical film ranges from 1- 10 mm and its surface area can be 1 to 20 cm^2 for any geometry. Upon contact with saliva, a typical Quick-Dis film (thickness=2 mm) will begin to disintegrate within 5 to 10 seconds and will dissolve completely within 30 seconds. The disintegration and dissolving times will vary depending on film thickness and formulation composition. One or a combination of processes can be used to manufacture Quick-Dis films including hot-melt extrusion, solid dispersion extrusion, rolling, semi-solid casting and solvent coating. The current preferred manufacturing process is solvent casting. Quick- Dis films can be packaged using various options such as single pouch, blistercard with multiple units, multiple unit dispenser, and continuous roll dispenser.

The following OTC prototypes (successfully tastemasked) have been developed:

- Dextromethorphan
- Chlorpheniramine
- Pseudoephedrine
- Ketoprofen
- Famotidine
- Loratadine
- Caffeine
- Menthol
- Nicotine

Oral disintegrating film containing prochlorperazine[44], a dopamine D2 receptor antagonist with anti-emeticproperty, was newly developed by *Tsukioka Co., Ltd., Kagamihara, Gifu, Japan*using microcrystalline cellulose, polyethlene glycol and hydroxypropylmethyl cellulose as the base materials. The uniformity of dosage units of the preparation was acceptableaccording to the criteria of JP15 or USP27. The film showed an excellent stability at least for 8 weekswhen stored at 40 ◦C and 75% in humidity. The dissolution test revealed a rapid disintegration property,in which most of prochlorperazine dissolved within 2 min after insertion into the medium. Subsequently,rats were used to compare pharmacokinetic properties of the film preparation applied topically intothe oral cavity with those of oral administration of prochlorperazine solution. None of the parameters,including *T*max, *C*max, area under curves, clearance and steady-state distribution volume was significantlydifferent between oral disintegrating film and oral solution. These findings suggest that the presentprochlorperazine-containing oral film is potentially useful to control emesis induced by anti-cancer agentsor opioid analgesics in patients who limit the oral intake.

Buccal Wafers[45-48]

This kind of wafers have been developed by LTS Lohmann Therapie-Systeme, which can be designed toprovide quick release or sustained release in the oral cavity. Theappearance and consistency of these foil-like buccal wafers canvary from rigid and brittle to flexible and paper- or film-like. Thequick release wafers have typical disintegration times ranging fromfive seconds to about two minutes. Sustained release wafersexhibit mucoadhesive properties and may be used to deliver drugfor up to eight hours. They can be designed to slowly disintegrate or to be removable after a specific application period. Dependingon the desired effect, the active ingredient can be releasedimmediately or in a sustained manner. Further, depending on itsdose and physicochemical properties, the

active ingredient can beabsorbed buccally or from the stomach. Each wafer can be loadedwith up to 20 mg of drug. Different types of shape and size can be preparedwithin broad limits for each individual drug or application purpose.Basic formulations consist ofhydrophilic film-forming polymers, fillers with or without texturizingproperties, and modifying agents. Like transdermal systems, quickreleasebuccal wafers are produced by the coating of process foilsand subsequent drying. With the coating and drying conditions, themechanical properties and release profiles may be controlled.

List of some Oral Thin film developed by different companies[49] is presented in the Table 6:

Product	**Indications**	**Company**
Betamethasone	Asthma	APR Applied PharmaResearch S.A.
Caffeine	Alertness aid	FlatMints
Caffeine	Alertness aid	Lavipharm Laboratories, Inc.
Caffeine	Alertness aid	Lavipharm Laboratories, Inc.
Dextromethorphan	Cough suppression	APR Applied Pharma Research S.A.
Dextromethorphan	Cough suppression	Lavipharm Laboratories, Inc.
Doxazosin	BPH, hypertension	Labtec GmbH
Famotidine	Heartburn	Labtec GmbH
Famotidine	Heartburn	Lavipharm Laboratories, Inc.
Fluoride	Dental caries	APR Applied Pharma Research S.A.
Fluoxetine Folic acid/B-12	Depression Supplement	Labtec GmbH FlatMints
Folic acid/B-12	Supplement	Watson
Glimepiride	Diabetes	Labtec GmbH
Ketoprofen	Pain, inflammation	Lavipharm Laboratories, Inc.
Loratadine	Allergies	Labtec GmbH
Loratadine	Allergies	Lavipharm Laboratories, Inc.
Loratadine	Allergies	MonoSolRx, LLC
Meclizine	Motion sickness	Labtec GmbH
Melatonin	Jet lag	Labtec GmbH
Menthol	Breath freshening	Lavipharm Laboratories, Inc.
Multivitamins	Supplements	BioTec Films LLC
Nicotine	Smoking cessation	Lavipharm Laboratories, Inc.
Nicotine	Smoking cessation	LTS Lohmann Therapie-Systeme AG
Ondansetron	Emesis	Labtec GmbH
OTC analgesics	Pain, fever	BioTec Films LLC
Paroxetine	Depression	Labtec GmbH
Pergolide	Parkinson’s	Labtec GmbH

Pseudoephedrine	Allergies, colds	Lavipharm Laboratories, Inc.
Sildenafil	Erectile dysfunction	Labtec GmbH
Sildenafil	Erectile dysfunction	MonoSolRx, LLC
Tizanidine	Muscle relaxation	APR Applied Pharma Research S.A.
Vitamin C	Supplement	FlatMints
Vitamin C	Supplement	Labtec GmbH
Zinc histidinate	Supplement	Labtec GmbH
Zolpidem or zopiclone	Insomnia	Labtec GmbH

Table 6

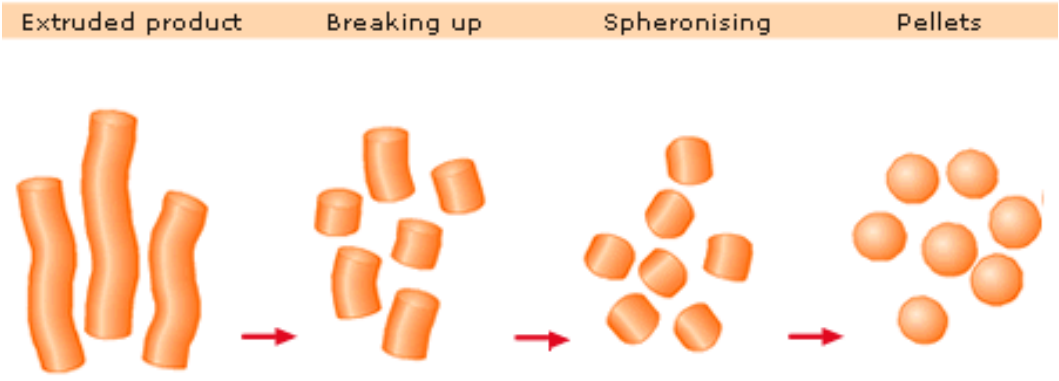
TASTE MASKING STRATEGIES FOR ORAL DISINTEGRATING TABLETS:

Taste Masking

One of the major limiting factors to the success of orally disintegrating dosage forms isunpleasant taste. It is imperative that the product taste pleasant and have good mouthfeel. Flavor masking and processing approaches are the two primary methods forachieving taste masking. Flavor masking includes the addition of flavors, sweeteners,acidic amino acids, lipids, and surfactants to attempt to overwhelm the bitter taste.Processing approaches include microencapsulation with various resins and proteins,gelatinized starch, gums, cyclodextrins, chitosan, liposomes, and removal of bittercontaminants by ion exchange resins. Chemical modification and specific saltpreparation of an active ingredient have also been used to reduce bitterness. A numberof different microencapsulation processes can be used to taste mask actives and includeboth physical and chemical processes. Examples of some of these processes include coacervation, spray-drying, spray-chilling, spray-congealing, fluidization, phase separation, and extrusion.

1. **Pelletization:**

i) Extrusion / Spheronization



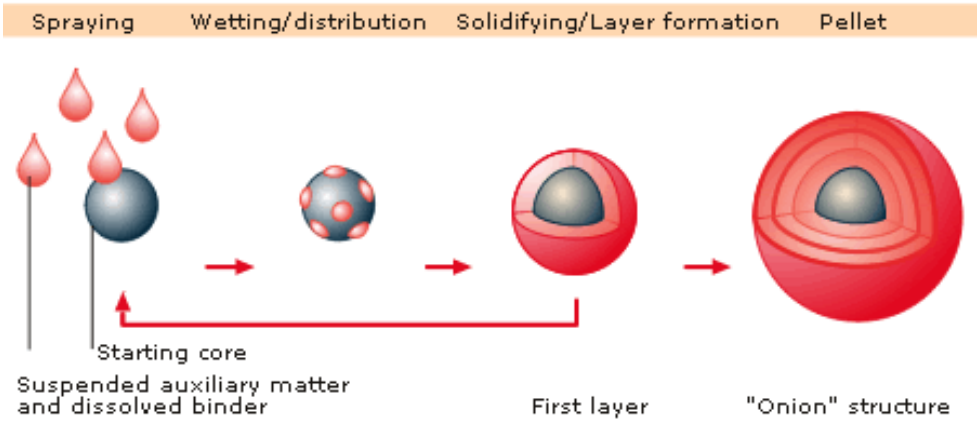
This processing option is the eldest known industrial pelletizing technique. First all ingredients are blended, then by adding liquid a wet dough is formed, which is passed through an extruder with defined dye sizes. If a thick-wall extruder (approx. 4 mm) is used and the ratio liquid/solids is well adjusted the extrudates break up into 1mm particles during the beginning of spheronization, warranting a high yield of homogenously sized pellets. However, minimum particle size is limited to about 500 µ. Despite a high reproducibility

this is a somewhat tedious process as it involves many process steps, i.e. dry blending, wet massing, extrusion, spheronization, drying and involves different equipment with a large total product contacting surface. The uniform particle size allow for an equally uniform subsequent functional coating

Advantages:

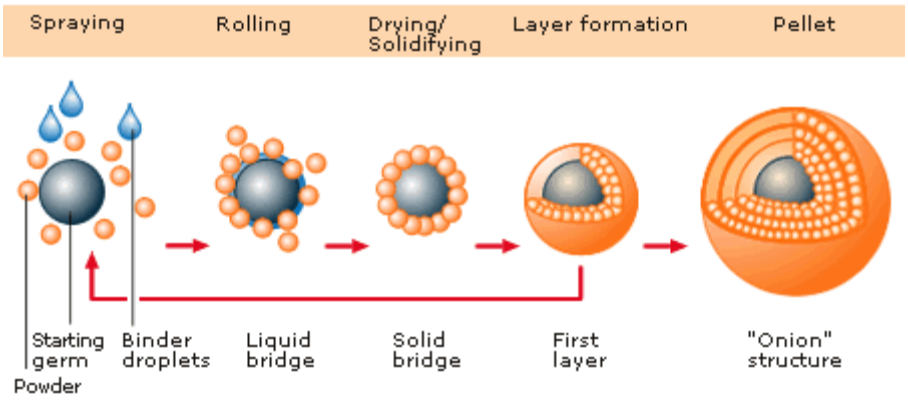
• Dust free
• High spherocity
• Free flowing
• Compact structure
• Low hygroscopicity
• High bulk density
• Low abrasion
• Narrow particle size distribution
• Smooth surface

Suspension / Solution Layering



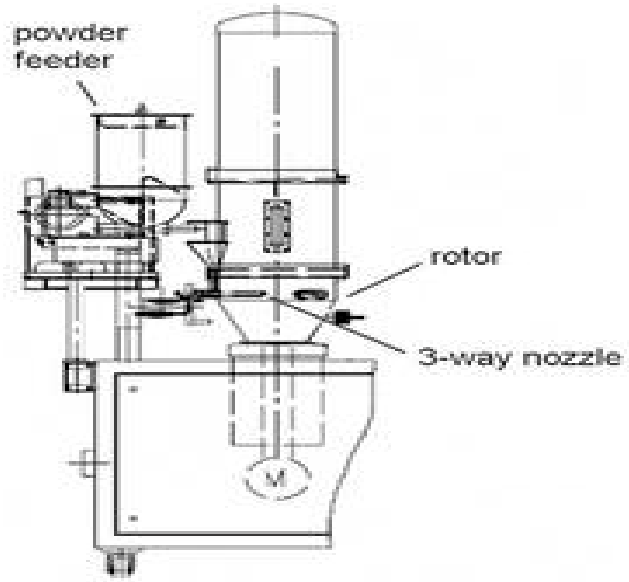
The most common processing option is to apply the layer from a solution or suspension. Physically the layering process differs not from the coating process, but layers are usually much thicker (60-200 % weight gain) and consist from an active ingredient, whereas the film is formed from some inert material. Very often layering and subsequent filmcoating are two steps of the same process. To achieve very uniform layers the bottom spray method (batch or continuous) should be the processing option of choice. Meanwhile, neutral starter spheres from 100 to 1000µ are available. Average weight gain per processing hour is about 15-20 %, because 80 – 85 % liquid vehicle have to be evaporated. All features of spray coating also apply to suspension and solution layering

Dry Powder Layering:



A rotor insert (or free-standing rotary pelletizer) is usually used for this processing option, as the rolling motion of the neutral spheres strongly assists the process, similar to that of a snowball effect, i.e. rolling about a larger particle in a slightly wetted mass. Very often, only a little water has to be sprayed onto the nuclei in order to bind the dry powder to its surface, which is dosed via the venturi effect of the air atomized nozzle on the rotating bed. As usually micronized powders are fed from an external charge hopper, care has to be taken that the powder does not form lumps on the way from the hopper towards the product bed because of coagulation, compacting or static electricity. If the process is set-up properly, hourly weight gains of up to 300 % are possible, which renders this processing option very fast and efficient. Fully contained dosing of the powder is however so far not known, which may render this processing option not suitable for the pharmaceutical industries.

The structure of a powder layer can neither be as compact as a layer produced from a solution or suspension, nor can the surface be as smooth. It is recommended to apply a thin neutral film layer prior to administering a subsequent functional film.

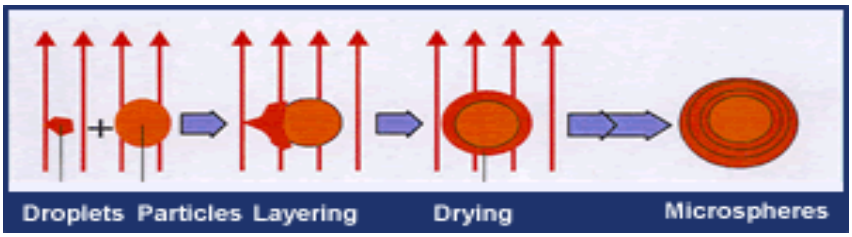


Product features

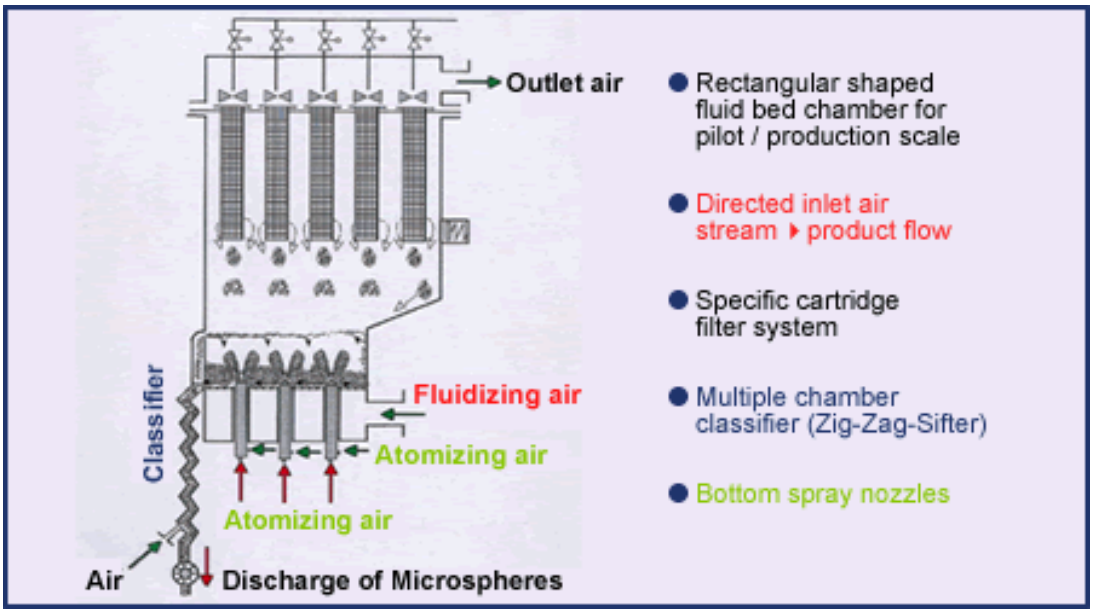
• Dust free
• High sphericity
• Free flowing
• Compact structure
• Low hygroscopicity
• Low abrasion
• Narrow particle size distribution

2. MicroPx™ Pelletization Technology:

It consists of a continuous fluid bed process. After liquid spraying and coating of APIs, generated micropellets are classified by applying a vertical online air sifting system. The entire process constitutes of a well balanced system of spray drying and consecutive drug layering. This process results in manufacturing of high drug loaded matrix-type micropellets. Drug loadings of produced pellets can be up to 95%.



This process can be also applied for taste masking, which usually have an ideal particle size distribution between 200 to 400 µm. Any functional excipient can be integrated into the coated micropellet matrix.



Micro Px™ Technology process takes place in a rectangular shaped fluid bed processing chamber. A directed fluid bed air stream provides for the specific circulation of coated products. Micropellets matured to the desired particle size distribution are being discharged through a hooked-up multiple chamber classifier. In this device bigger and smaller particles are separated and unmature pellets are led back to the ongoing pelletization process by air pressure.

Advantages of the Micro Px™ Pelletization Technology

- Small particle size
- Spherical pellet shape
- Manufactured Micro Px™ pellets reach very homogeneous and narrow particle size distribution
- Drug loads achievable of up to 95%

CPS™ Pelletization Technology

This innovative CPS™ Pelletization Technology is a direct fluid bed pelletization technology, originally invented by Glatt GmbH in Binzen, Germany, in 2000.

Its special features are characterized by a modified fluid bed rotor system with a conical shaped rotating disc plus additional devices for directed movement of coated particles. To start processing, no inert starting beads are required. Spraying of various liquids (organic and inorganic) as well as dry powder is also possible. By means of rolling particles movement, CPS™ Pelletization Technology clearly defines the densification of particles.

Description of the pelletization process: After intensive mixing of various excipients (preferably MCC, dicalcium-phosphate, methacrylic polymers, disintegrants, solubilizers, e.g. Tween 80, and others) and active pharmaceutical ingredient (API) in a modified fluid bed, the mixture is wetted with pharmaceutical grade water. In this process, drug concentrations can vary from low dose (<1%) to high dose (up to about 90%), depending on the core pellet for coating. Using selected excipients for the coating process, a modified release pellet matrix can be generated that get by without a further functional coating step, thus saving precious manufacturing time. In addition, depending on process time and quantity of sprayed liquid, a wide range of mean particle size between about 100 µm to 1400 µm can be obtained. Moreover, a narrow particle size distribution with a deviation of ±100 µm can be reached, accounting for the great homogeneity of the processed API matrix.

With this Pelletization Technology, coated products results in great uniformity and homogeneity of the matrix of coated pellets.

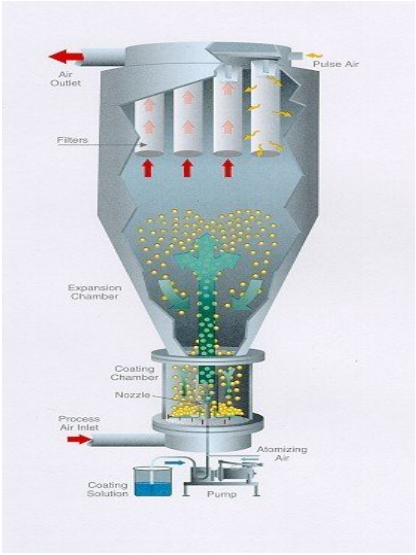
Outstanding product characteristics are feasible resulting in:

- spherical and smooth pellet surfaces
- high density and loading of drug substance
- low porosity of pellets
- low attrition and friability
- dust free surfaces

Wurster Coating Process:

The Wurster process is a coating technique that is well suited to uniformly coat or encapsulate individual particulate materials. This technology is characterized by the location of a spray nozzle at the bottom of a fluidized bed of solid particles. The particles are suspended in the fluidizing air stream that is designed to induce a cyclic flow of the particles past the spray nozzle. The nozzle sprays an atomized flow of coating solution, suspension, or other coating vehicle. The atomized coating material collides with the particles as they are carried away from the nozzle. The temperature of the fluidizing air is set to appropriately evaporate solution or suspension solvent or solidify the coating material shortly after colliding with the particles.

All coating solids are left on the particles as a part of the developing film or coating. This process is continued until each particle is coated uniformly to the desired film thickness. The Wurster process is an industry recognized coating technique for precision application of film coat to particulate materials such as powders, crystals, or granules. The technology can be used to encapsulate solid materials with diameters ranging from near 50µm to several centimeters. The process has a greater drying capacity than other coating systems due to a relatively high fluidizing air velocity. Since the particles actually separate as they are carried away from the nozzle, it is possible to coat small particles without agglomeration. Coating possibilities are relatively unlimited including the ability to place a hydrophilic coat on a hydrophobic core, or a water-based coat on a water-soluble core. Coating properties can be optimized with coat formulation parameters, processing conditions, and layering.



Coacervation or Phase Separation:

Interaction of two oppositely charged polyelectrolytes in liquid medium to form a polymer rich coating solution is called coacervate. A coacervate is a tiny spherical droplet of assorted organic molecules (specifically, lipid molecules) which is held together by hydrophobic forces from a surrounding liquid. Coacervates measure 1 to 100 micrometers across, possess osmotic properties and form spontaneously from certain dilute organic solutions. Here, the drug particles are coated or encapsulated with taste masking materials like cellulose, PEGs, polymethacrylated, waxes etc. The resulting pellets may be compressed into tablets. Microcaps® technology has been developed by Eurand to provide superior taste masking by microencapsulating drug particles by coacervation technique.

Microcaps enhances overall patient adherence and acceptability by improving the products' features. This includes taste- and odor-masking, customized release profiles, conversion of liquids to solids, and the separation of incompatible drug materials.

Advantages of Microcaps

- Complete and uniform taste masking via a proprietary microencapsulation technique
- Smooth, pleasant mouth-feel
- Used in more than 12 marketed products

Eurand's patented Microcaps technology employs versatile, precise coating techniques to uniformly encapsulate drug particles using solvent- and aqueous-based coacervation. This process completely encapsulate each drug particle in a polymeric membrane of adjustable thickness and porosity. The polymeric membrane eliminates unpleasant taste and/or odor by forming an inert barrier in the mouth, minimizing the need to add sugar or flavors to the tablet.

This patented taste-masking technique can be used to achieve:

- Uniform, precise taste masking
- Customized drug release profiles
- Conversion of liquids to solids
- Separation of incompatible materials.

Rapid Release

To balance the necessary polymer membrane with the desired release profile, Eurand has used their Pore Former Technology to control the porosity of the membrane which accelerate the release of drug through the polymeric membrane.

Bitter Blocker:

Using proprietary biochemical assays that mimic the human taste system, Linguagen has discovered "bitter blockers" that act by blocking the perception of the bitter agent. This is much more effective at controlling bitterness than conventional approaches that rely on masking or confounding bitterness with overwhelming amounts of sweeteners or artificial flavor additives. The first bitter blocker to be discovered and tested extensively is Adenosine 5'-monophosphate or AMP. The compound blocks a protein called gastducin, a receptor that seems to be intrinsically involved in registering bitter tastes in the mouth. Linguagen was granted a US patent on the technology in April 2003. AMP has been cleared by US FDA for use in food and pharmaceuticals and is Generally Recognised as Safe (GRAS).

Taste masking using Sweeteners and Flavors:

Taste masking often involves the use of flavors and/or sweetening agents to literally cover up unpleasant tastes that might be present. Many pharmaceutical actives have characteristic medicinal flavor notes, which can be quite unpleasant to children. Good flavor work can help quite a bit to reduce these medicinal notes by finding complementary flavors that mask or hide any medicinal tastes thereby making the product more tolerable. Hence, the red berry flavors that are characterized by aldehydes, esters, and ionones are excellent complementary flavors to mask chemical tastes. Citrus flavors are also commonly used as their characteristic aldehydes, esters, ketones, and other character impact flavor components also provide excellent complimentary masking of many chemical notes. When usingflavors to mask unpleasant tastes it is important not to over-flavor the formulation as these complex flavor systems can accentuate chemical notes if they are not balanced in the formulation.

Delivery System Based on Inorganic Carriers by Nanohybrid Co[50]

Functional, negatively-charged organic molecules can been encapsulated in zinc basic salt and hydrotalcite-type metal hydroxide layers via a direct co-precipitation route. Intercalation oforganic molecules into metal hydroxide layers results in well ordered, layered nanohybrids with different interlayer distances and packing structures, depending upon the molecular geometriesof guest species and inorganic matrix. The layered nanohybrids are mainly composed of nanometer-sized particles. The heterostructural nature of the nanohybrids, their particle morphology, and textural characterizations have been determined via Powder X-ray Diffraction and Field Emission Scanning Electron Microscopy.

The technology can be used for encapsulation and controlled release of negatively-charged organic molecules with pharmaceutical, and nutraceutical activity. The nanohybrids work well with vitamin compounds such as retinoic acid (Vitamin A),

ascorbic acid (Vitamin C), and tocopherol (Vitamin E). In oral tablets and capsules, the technology provides improved solubilization, stabilization, and tastemasking.

Coating Technology for taste masking of bitter drugs[51]:

United States Patent 5,728,403describes the use of triglycerides for taste masking of bitter drugs. Triglycerides which, when mixed together, melt at body temperature and a polymer, that is insoluble at pH 7.4 and soluble in the stomach (i.e. which dissolves at a pH of 5.5 or lower) are used in this . Emulsifying and suspending agents are also used. In practice, the patient places the medication in his/her mouth and for that brief moment, the triglyceride portion of the coating begins to melt since it is now at body temperature. The coating remains intact, however, since the polymer portion will only dissolve once it reaches a pH of 5.5, which is much more acidic than the pH of the mouth. The medication then travels down the esophagus and enters the stomach. Once in the acidic environment of the stomach, dissolution occurs and the medication is then available for absorption by the body.

Eudragit E™ is the tradename for an FDA approved cationic copolymer based on dimethylaminoethyl methacrylates and neutral methacrylic acid esters. It dissolves in gastric juice. Any non-toxic polymer that is insoluble at pH 7.4 and soluble in the stomach would be an acceptable alternative. Such polymers are those that are subject to acid catalyzed decomposition, e.g., hydrolysis, yet are stable at neutral pH. Fattibase™ is the tradename for an FDA approved composition of triglycerides derived from palm, palm kernel, and coconut oils. It also contains glyceryl monostearate and polyoxyl stearate as emulsifying and suspending agents, respectfully, but neither is necessary for the coating to function properly. It is the triglycerides which cause the composition to melt at body temperature.

Alternative triglycerides which may be used are any non-toxic acids derived from vegetable oils such as coconut and palm kernel oil that have been modified by esterfication or hydrogenation. These may be mixtures of monoglycerides, diglycerides, and triglycerides of saturated acids derived from these oils. Typically, these can be derivatives of fatty acids of carbon chain length C6 to C18; in particular derivatives of lauric, myristic, and palmitic acids. These are solid to semi-solid materials at room temperature. The characteristic melting points of these triglycerides is in the range of 37°-40°C. Some examples include Cotomar.RTM. by Proctor & Gamble which consists of partially hydrogenated cottonseed oil; Wecobee FS.RTM. consisting of coconut and palm kernel oils; Witepsol E7S.RTM.; and Massa Estariorm A.RTM. by Edellett-Werke Werner Schluter of Hamburg, Germany which consists of a mixture of triglycerides, diglycerides, and monoglycerides of saturated fatty acids. Eudragit E™ and Fattibase™ are the preferred compounds since they are both already FDA approved for oral use in the production of pharmaceutical preparations. In addition, they both possess the required chemical properties, i.e. melting and dissolution points, for successful use of the invention. However, other polymers or triglyceride combinations may also be used so long as they possess the same requisite chemical properties.

The amount of triglyceride/polymer used to coat a particular drug is related to the amount and surface area of the drug being coated. The formulator will determine the amount of coating material needed to give a coat of specified thickness. The formulation from the example used 33% by weight of coating material. This ratio could be varied considerably depending on the particular size and porosity of the core material and amount to be coated. It would also depend upon the relative bitterness of the drug.

In general, triglycerides are preferred over mono or diglycerides for being more generally compatible with drugs. Triglycerides contain no free carboxyl groups and, thus, these groups are not free to chemically react with functional groups present on drugs. Acetone is an organic solvent used for dissolving the Eudragit E™ and Fattibase™ in the example. The choice of organic solvent is related to its volatility, safety, and ability to dissolve both the triglycerides and polymer. Alcohols, such as methanol, ethanol and isopropyl, are therefore suitable as well as acetone. In addition, a co-solvent mixture, such as 50% by volume isopropyl alcohol, ethanol and acetone, would be another workable possibility.

While metronidazole is used in the example, this process, in principle, could be applied to any solid drug which has a disagreeable or bitter taste when it dissolves in the mouth. Examples of classes of drugs which are problematic include but are not limited to antibiotics, analgesics, antihistamines, decongestants, antitussives, and steroids.

The coating materials may be easily applied using a variety of different methods, including spray coating and pan coating. As stated, the coating may be applied to any orally administered drug. For suspensions, the coating material will maintain its integrity to mask disagreeable taste in a liquid medium with a pH greater than 5.5 and stored at refrigerated temperatures.

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