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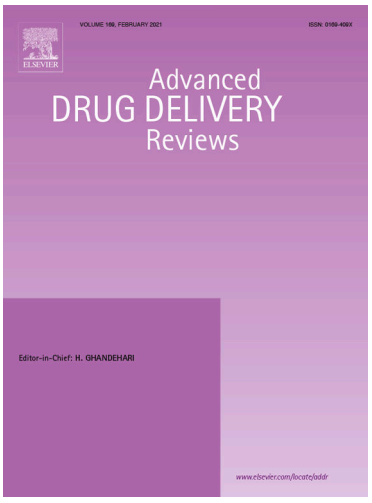


# A Review of Emerging Technologies Enabling Improved Solid Oral Dosage Form Manufacturing and Processing

Muhammad Sohail Arshad, Saman Zafar, Bushra Yousef, Yasmine Alyassin, Radeyah Ali, Ali AlAsiri, Ming-Wei Chang, Zeeshan Ahmad, Amal Ali Elkordy, Ahmed Faheem, Kendal Pitt

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# A Review of Emerging Technologies Enabling Improved Solid Oral Dosage Form Manufacturing and Processing

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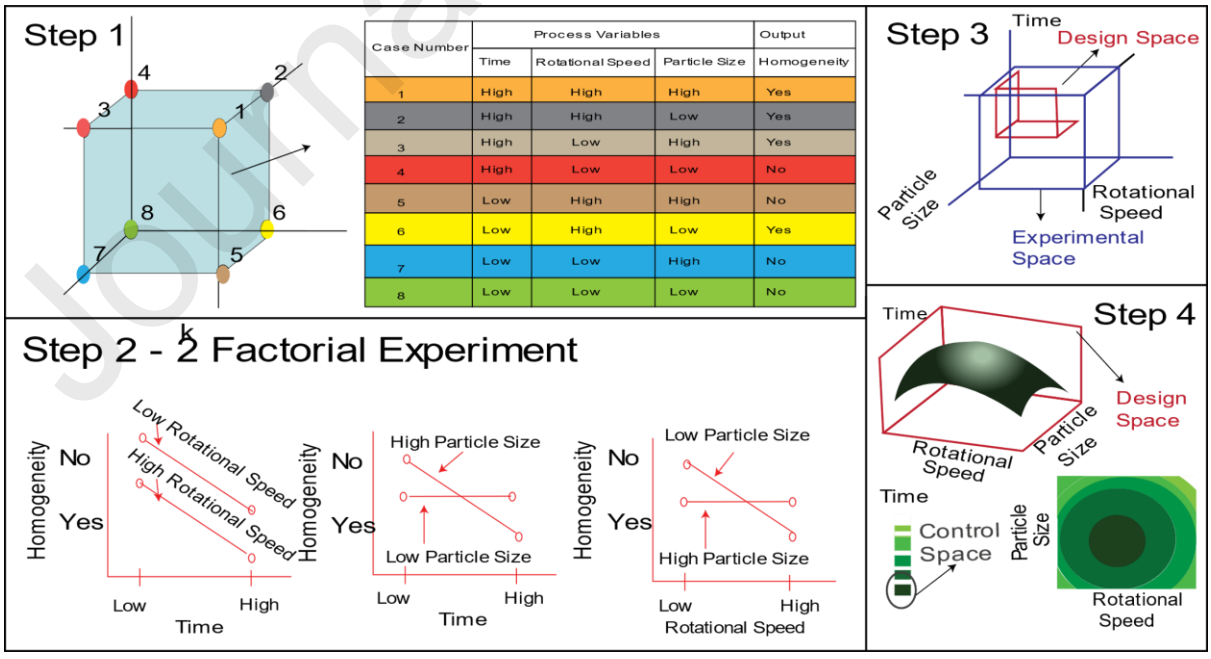


Emerging Technologies Enabling Improved Solid Oral Dosage Form Manufacturing and Processing


## Abstract

Tablets are the most widely utilized solid oral dosage forms because of the advantages of self-administration, stability, ease of handling, transportation, and good patient compliance. Over time, extensive advances have been made in tableting technology. This review aims to provide an insight about the advances in tablet excipients, manufacturing, analytical techniques and deployment of Quality by Design (QbD). Various excipients offering novel functionalities such as solubility enhancement, super-disintegration, taste masking and drug release modifications have been developed. Furthermore, co-processed multifunctional ready-to-use excipients, particularly for tablet dosage forms, have benefitted manufacturing with shorter processing times. Advances in granulation methods, including moist, thermal adhesion, steam, melt, freeze, foam, reverse wet and pneumatic dry granulation, have been proposed to improve product and process performance. Furthermore, methods for particle engineering including hot melt extrusion, extrusion-spheronization, injection molding, spray drying / congealing, co-precipitation and nanotechnology-based approaches have been employed to produce robust tablet formulations. A wide range of tableting technologies including rapidly disintegrating, matrix, tablet-in-tablet, tablet-in-capsule, multilayer tablets and multiparticulate systems have been developed to achieve customized formulation performance. In addition to conventional invasive characterization methods, novel techniques based on laser, tomography, fluorescence, spectroscopy and acoustic approaches have been developed to assess the physical-mechanical attributes of tablet formulations in a non- or minimally invasive manner. Conventional UV-Visible spectroscopy method has been improved (e.g., fiber-optic probes and UV imaging-based approaches) to efficiently record the dissolution profile of tablet formulations. Numerous modifications in tableting presses have also been made to aid machine product changeover, cleaning, and enhance efficiency and productivity. Various process analytical technologies have been employed to track the formulation properties and critical process parameters. These advances will contribute to a strategy for robust tablet dosage forms with excellent performance attributes.

## 1. Introduction

Oral solid dosage forms are administered for attaining a local therapeutic effect in the mouth, throat, digestive tract or for a systemic effect in the body after oral or gastrointestinal absorption. For preparing oral solid dosage forms, active ingredients and suitable excipients can be milled, dried, encapsulated, blended, granulated or tableted. Various oral solid dosage forms such as tablets, capsules, lozenges, powders and granules etc. have been widely used for delivering active pharmaceutical ingredients (API) due to their convenience and consequent patient compliance. Tablet formulations which provide a unit dose which is either immediate drug release or modified release or is taste masked are some of the most popular and extensively explored aspects of oral solid dosage form development. Tablet manufacturing (apart from the direct compression method) is a multistep process and hence is a complex process with many potential variables. The processes and parameters associated with tablet manufacture are still not fully understood. Extensive research is ongoing to develop understanding in all areas of the tablet manufacturing process.

Numerous advances have been introduced to improve material attributes, engineering of manufacturing equipment and development of efficient analytical techniques. Quality by design-based formulation development approaches have been applied to reduce the variability in the processes to develop robust tablet dosage forms. In addition, new raw materials have been deployed to improve manufacturability and functionality of tablet formulations. These include the modification of existing excipients with enhanced purity or physical properties (e.g., particle size) and co-processing with other materials to improve their performance in manufacturing processes. Moreover, development and use of multi-functional materials provide lean manufacturing opportunities with significant economic impact.

The last few years have seen the development of novel tabletting technologies which improve machine performance. These advances in machine design aim to overcome limitations associated with conventional manufacturing approaches such as the denaturation of thermolabile active ingredients, material wastage, multiple processing steps and elevated costs due to protracted processing time, labour and maintenance of equipment. In addition, lean and

continuous manufacturing concepts have been employed to ensure rapid, safe and efficient manufacturing operations.

Developments relating to engineering and to machine design have also been implemented in the pharmaceutical industry. The concept of quality by design has been applied to enhance productivity by the application of novel process analytical technologies that track quality attributes of formulations. These also can document data as a function of input variables (materials and process) in a real time manner.

This manuscript aims to provide a comprehensive summary of numerous recent advances regarding material design, manufacturing technologies and process analytics of tablet dosage forms in order to provide a clear and overarching insight on this extensively researched area of pharmaceuticals.

## 2. Excipients

Conventionally, excipients have been used as formulation aids e.g., binders, disintegrants, lubricants, fillers and glidants. However, in the recent years, the applications of functional excipients have been extensively explored for drug release modulation, prolonging tablet residence time by mucoadhesion, taste masking and solubility enhancement. The selection of excipients for oral solid dosage forms is affected by key technical considerations such as desired pharmacokinetic performance of the formulation, physical or chemical attributes of the API and dose levels. The functionality of the excipients being selected for enhanced bioavailability, modified release or drug stability etc [1]. Moreover, ready to use, co-processed excipients have also been introduced to improve manufacturability of tablets.

### 2.1. Formulation Aids

Classes of excipients commonly employed as formulation aids include super-disintegrants, pH adjustors, fillers, binders and lubricants (Table 1).

#### 2.1.1. Super-disintegrants

Disintegration of a tablet is crucial as it prompts dissolution of drug substance. Presence of a natural polymer (e.g., starch) as a disintegrant in a formulation may lead to enhanced viscosity of the surrounding medium (due to the partially soluble nature of the polymer) and thus hamper disintegration and dissolution. This issue can be circumvented by cross-linking the polymer chains (to reduce the impact of disintegrant on medium viscosity) and by incorporating carboxyl functions into the polymer backbone (to enhance the hydrophilicity). Synthetic polymers i.e. crospovidone (CP, physically cross-linked polyvinylpyrollidone), croscarmellose sodium (CCS, cross-linked carboxymethyl cellulose) polacrilin potassium (PP, chemically

cross-linked methacrylic acid / divinyl benzene copolymer), sodium starch glycolate (SSG, chemically cross-linked carboxymethyl starch) were introduced to achieve these desired effects [2].

The mechanisms of tablet disintegration comprise swelling, strain recovery and wicking effect of the disintegrant. In swelling, tablet disintegration is due to the omni-directional enlargement of particles leading to the build-up of pressure and exertion of stress on the overall system. Strain or shape recovery involves destruction of bonds and release of energy stored in the system upon contact with physiological fluid and heat. Wicking involves penetration of water into the system (leading to destruction of hydrogen bonds and Vander Waals and electrostatic forces) via capillary action [3]. Other disintegration mechanisms are adsorption (heat of wetting) and repulsive forces [2, 4].

Van Kamp investigated the disintegration performance of potato starch (20 %), SSG (4 %) and CP (4 %). Results demonstrated the superior performance of cross-linked superdisintegrants as disintegration times of CP (26 sec) and SSG (49 sec) were significantly shorter than the one recorded with potato starch (149 sec) [5]. Tablet formulations of irbesartan [6], amoxicillin [7], spironolactone [8], flurbiprofen and metoclopramide [9] containing novel cross-linked superdisintegrants disintegrated rapidly.

### 2.1.2. pH Adjustors

The microenvironment pH influences the solubility, dissolution, degradation rate and stability of solid dosage forms. Following disintegration, the pH-adjusting excipients (solid buffers e.g., adipic, glutaric, succinic, itaconic, fumaric, tartaric acids (acidifiers) and meglumine, bentonite, arginine, disodium hydrogen orthophosphate, magnesium oxide, sodium carbonate (alkalizers) dissolve in the medium of the digestive tract and adjust the pH of the stagnant boundary layer surrounding each drug particle. The modulation of microenvironment pH has been explored to improve dissolution of formulation and achieve pH-independent drug release [10, 11]. Enhanced drug dissolution of various formulations was observed by the addition of fumaric acid (e.g. dipyridamole, verapamil) and citric acid (e.g. furosemide, pelanserin HCl) [11, 12]. The dissolution profiles of aceclofenac and telmisartan formulations have been successfully improved by adjusting the microenvironment pH using the alkalizers sodium carbonate and magnesium oxide, respectively [13, 14].

### 2.1.3. Fillers and binders

Fillers provide bulk to the formulation mass which enables its processing into dosage forms and allows convenient administration as unit doses. Two groups of fillers are used in the

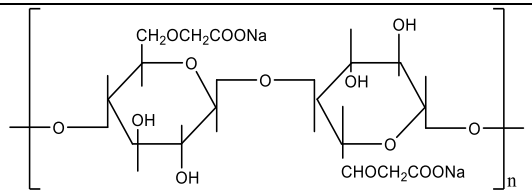
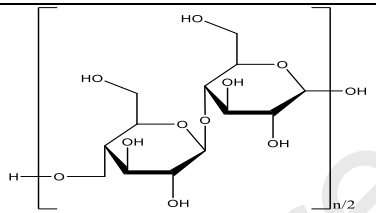
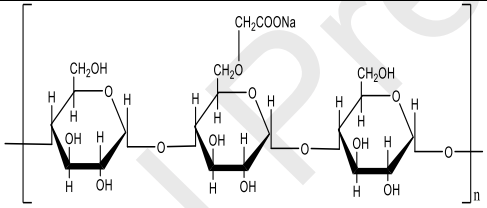
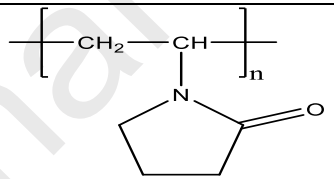
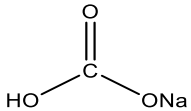
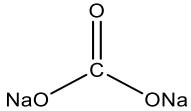
pharmaceutical industry, namely, water soluble (e.g., α-lactose monohydrate, sucrose, PEG (polyethylene glycol) 6000) and water insoluble (e.g., calcium hydrogen phosphate anhydrous or dihydrate) fillers [10, 15, 16].

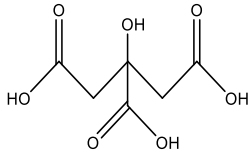
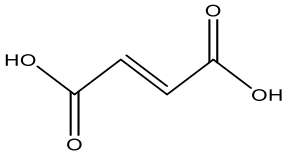
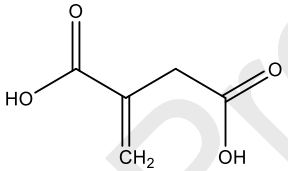
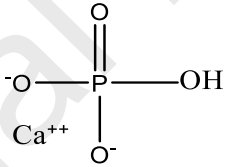
Binders impart plasticity as well as enhance the binding strength of formulation constituents at the interparticulate level by cohesive and adhesive forces (Vander Waals and electrostatic forces, hydrogen bonding, solid bridges, mechanical interlocking) [17]. Several types of binders such as aqueous (e.g. gelatin, pregelatinized starch, starch, PEG, gum acacia, okra, xanthan) and dry binders (e.g. cellulose, MCC (microcrystalline cellulose), methyl cellulose, PVP (polyvinyl pyrollidone), PEG) are being used for tablet manufacturing [18]. Various co-processed materials e.g., silicified MCC, α-lactose monohydrate-MCC, hydroxypropyl methylcellulose (HPMC)-α-lactose monohydrate, vinyl pyrollidone-vinyl acetate and corn starch-MCC-α-lactose monohydrate have been employed as binders in tablet formulations containing tramadol HCl, hydrochlorothiazide, acetyl salicylic acid [19-22].

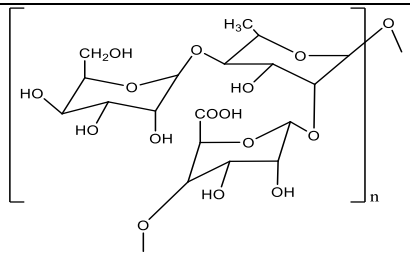
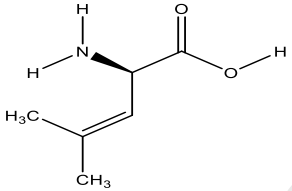
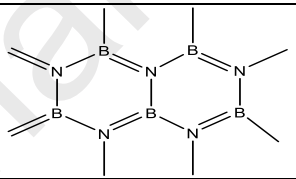
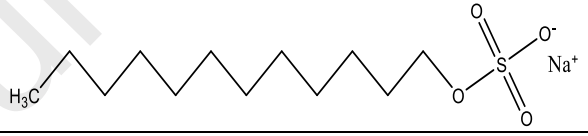
#### 2.1.4. Lubricants / Anti-adherents

Lubricants are added in small quantities (0.25-0.5 % w / w) in the tablet formulation to avoid sticking, picking and capping issues. They act by forming a stable layer around particles / surfaces. Several factors such as type and concentration of lubricant, manner of incorporation of the lubricating agent and method of lubrication i.e., internal (within the formulation) or external (spraying on to punches and dies) impact the tablet compression process. Various lubricants include metallic salts of fatty acids (magnesium stearate, zinc strearate, aluminium stearate), fatty acids / fatty alcohols / hydrocarbons (stearic acid), fatty acid esters (glyceryl behenate, sodium stearyl fumarate, sucrose monopalmitate), alkyl sulphates (magnesium lauryl sulphate, sodium lauryl sulphate) inorganic materials (magnesium silicate) and polymers (polyoxyethylene-polyoxypropylene copolymer, polytetrafluoroethylene, PEG 4000) [23, 24]. Studies showed the potential of L-leucine [25] and hexagonal boron nitride [26] as novel lubricating agents.

**Table 1 Classes of excipients as formulation aids for tablets**

| Name | Type | Chemical structure | Mechanism of action | Practical applications | References |
|---|---|---|---|---|---|
| Superdisintegrants | Croscarmellose sodium |  | Swelling | Irbesartan | [6, 27] |
| | Nano / micro crystalline cellulose |  | Wicking | Calcium carbonate, Spironolactone, Ascorbic acid, Ibuprofen and Aspirin | [8, 28, 29] |
| | Sodium starch glycolate |  | Swelling | Flurbiprofen, Metoclopramide | [9] |
| | Crospovidone |  | Wicking followed by secondary swelling | Amoxicillin | [7] |
| pH adjustors | Sodium bicarbonate |  | pH adjustment of microenvironment / stagnant diffusion layer | Paracetamol | [30] |
| | Sodium carbonate |  | | Aceclofenac | [13] |

| | | | | | |
|---|---|---|---|---|---|
| | Citric, fumaric and itaconic acid |  <br>Citric acid<br>  <br>Fumaric acid<br>  <br>Itaconic acid | | Verapamil HCl | [31] |
| Fillers | Dibasic calcium phosphate, microcrystalline cellulose |  <br>Dibasic potassium phosphate<br>Microcrystalline cellulose mentioned earlier | Provide desired bulk to the formulation | Phenylpropanolamine hydrochloride | [32] |
| Binders | Plasdone S-630 copovidone (polyvinyl acetate and polyvinyl pyrollidone) | Mentioned earlier | Enhancement of interparticulate binding strength | Acetylsalicylic acid, Hydrochlorothiazide | [20] |

| | | | | | |
|---|---|---|---|---|---|
| | Okra gum |  | by adhesive or cohesive forces | Naproxen sodium | [33] |
| Lubricants / antiadherents | L-leucine and polyethylene glycol |  L-leucine  PEG | Formation of film / layer / coating on drug and excipient particles | ---- | [34] |
| | Hexagonal boron nitride |  | | ---- | [26] |
| | Sodium Lauryl sulfate |  | | Celecoxib | [35] |

## 2.2. Functional Excipients

Different classes of functional excipients along with their practical applications are represented in the Table 2.

### 2.2.1. Taste Maskers

A variety of active ingredients exhibit undesirable organoleptic sensations (i.e., nauseating, unpalatable, bitter taste) which hamper patient compliance as well as treatment efficiency. Due to these reasons, the application of taste masking approaches remains a key area for the development of oral dosage forms. Various taste masking approaches including functional, physical and biochemical masking are applied in pharmaceutical development [36]. Functional masking involves the incorporation of flavours (e.g. raspberry, wild cherry), sweeteners (e.g. sucralose, aspartame, neotame, saccharin, stevioside, inositol) and amino acid / peptide derivatives which block bitter taste receptors, e.g. γ-aminobutyric acid, L-ornithyl-β-alanine, L-ornithinyltaurine, benzoyl-ε-amino caproic acid) [36, 37]. Physical masking employs the application of barrier hydrophobic coatings (e.g., glyceryl monostearate, waxes) and polymer film coatings (e.g., Eudragit, ethyl cellulose, hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), carbopol, cellulose acetate butyrate) which impede interaction between the active ingredient and the taste buds. In chemical masking, a drug is enclosed in the cavity of complexing agent e.g., ion-exchange resins (amberlite IRP 69, indion 234, indion CRP 244 and CRP 254) and cyclodextrins (hydroxypropyl β-cyclodextrin, β-cyclodextrin). Other approaches include the addition of effervescent agents, development of prodrug formulations, solid dispersion systems and salt preparation. The bitter taste of tramadol HCl, terfenadine, morphine, quinine, gabapentin and cimetidine has been successfully masked by employing various aforementioned taste masking approaches [36, 38].

### 2.2.2. Solubility / Dissolution Enhancers

The majority of new drug entities belong to BCS (Biopharmaceutical Classification System) class II, that have low solubility and high permeability; the former being a rate limiting step in defining overall bioavailability. Various strategies (i.e., physical, chemical modifications of active ingredient and other miscellaneous techniques) have been employed to enhance the dissolution of these drugs. Physical modifications in a drug substance include particle size reduction (micronization, nanosuspension), alteration of crystal habit (co-crystallization, polymorphism, amorphization) and drug dispersion in carriers (solid solutions / dispersions, eutectic mixtures, cryogenic approaches). Chemical changes in the drug molecule include salt or prodrug formation, addition of buffer, derivatization and complexation. Other approaches

applied to improve the dissolution of a drug include supercritical fluid methods and the incorporation of adjuvants e.g. solubilizers, hydrotropic agents, surfactants and cosolvents to prepare solid dispersions [39, 40]. Solubility enhancement of various drugs (e.g., paclitaxel, adriamycin, doxorubicin, lonidamine, famotidine, ondansetron, furosemide, itraconzole, ibuprofen) by novel excipients like sulfobutylether-β-cyclodextrin, HP-β- cyclodextrin, HPMC acetate succinate, polyethylene glycol / polyvinyl acetate / polyvinylcaprolactame graft copolymer, xyloglucan, dextran, chondroitin sulphate / pluronic copolymer and silica is reported in the literature [41-43].

### 2.2.3. Drug Release Rate Modifiers

Controlled drug release is desirable in many cases as it ensures optimal plasma concentrations, prolonged duration of therapeutic effect, reduced frequency of dose administration and hence, enhanced patient compliance. Different formulation approaches include monolithic, reservoir, osmotic, ion-exchange and membrane diffusion systems, which are designed to achieve modified drug release [44].

Several factors control the release of drug from the candidate formulations, including the properties of the excipients and active ingredient (particularly drug loading and solubility), tablet dimensions (shape, size, surface area) and coating membrane (material, thickness) [44-46].

Various polymers e.g. polyvinyl alcohol, polymethacrylate, ethyl cellulose, chitosan, polyethylene oxide, polyacrylic acid, polydextrose, gelatin, pectin, sodium alginate, xanthan gum, tragacanth gum and poloxamers have been studied for their role as matrix or barrier membrane formers for oral controlled release systems (multiparticulates, matrix, osmotic and enteric coated tablets) [44, 45, 47-49]. Porogens, hydrophilic molecules with a high swelling capacity inside a matrix and which subsequently escape by dissolving out, are incorporated in a hydrophobic polymer-based formulation to improve the porosity. The pore forming agents include sugars and sugar alcohols, hydrophilic polymers, polyethylene glycols (PEGs) and sodium chloride and L-menthol [50, 51].

Various lipids materials are also used for the preparation of controlled release matrices; these include caprylocaproyl polyoxyl-8 glycerides, linoleyl polyoxyl-6 glycerides, lauroyl polyoxyl-32 glycerides and stearoyl polyoxyl-32 glycerides. Some examples of commercially available drugs prepared using these polymers and lipids include felodipine, gliclazide, ritonavir, verapamil, fenofibrate and enzalutamide [45]. More recently, inorganic materials

with adsorbent properties (e.g. montmorillonite [52], mesoporous silica [53]) have been reported as carriers offering controlled drug release.

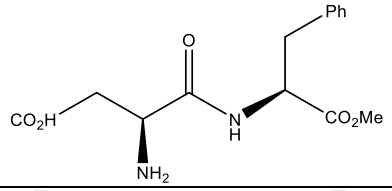
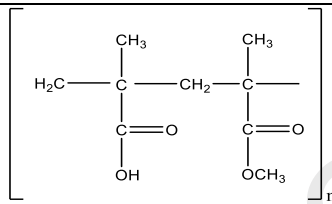
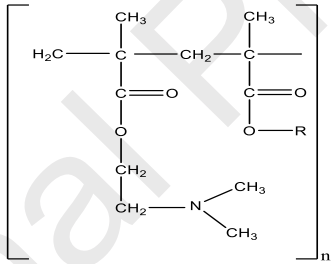
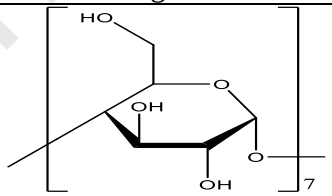
### 2.2.4. Mucoadhesives

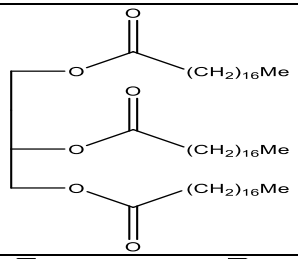
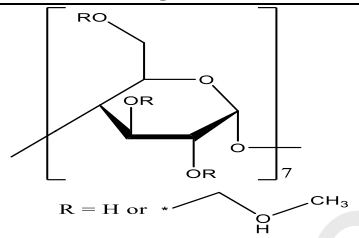
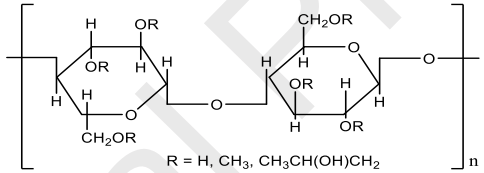
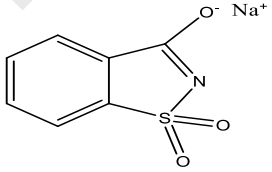
A mucoadhesive agent / polymer adheres to the mucosal surface and extends the residence time of formulation within the spatial regions of the GI (gastrointestinal) tract. Mucoadhesion of a carrier is accomplished in two stages; adhesion to the mucosal surface (wetting or swelling) and penetration of the mucoadhesive agent into the mucous secretion (interpenetration). Various theories have been presented to elaborate the mechanism of interaction between mucoadhesive polymers and mucous membrane including fracture, wetting, electronic, mechanical, diffusion and adsorption theory. Fracture theory suggests that adhesion is based on the forces required to detach the two surfaces from each other after adhesion. According to wetting theory, mucoadhesion takes place due to the variations in surface and interfacial energy. Electronic theory suggests that electron transfer between polymer and mucosal surface epithelium results in mucoadhesion. According to mechanical theory, interlocking of mucoadhesive liquid into the irregularities on a rough surface leads to mucoadhesion. Diffusion theory states that mucoadhesion takes place due to the diffusion of polymer chains into the mucosal layer glycoprotein chain network. Mucoadhesion is based on hydrogen bonding and Vander Waals forces as per adsorption theory [54, 55].

Several factors such as mucin turnover rate, pH at the mucoadhesive polymer-substrate (mucus) interface and polymer characteristics (swelling, stereochemistry, molecular weight, concentration and flexibility of polymer chains) affect mucoadhesion phenomena [55].

Commonly employed mucoadhesive agents include hydroxypropyl cellulose, polyacrylic acid, carboxymethyl cellulose, HPMC, poloxamer 407, polyacrylic acid-cysteine, alginate-cysteine, carboxymethyl cellulose-cysteine, chitosan and its derivatives (e.g., half-acetylated chitosan, carboxymethyl chitosan, chitosan-thioglycolic acid, acrylated chitosan etc.). These mucoadhesive candidates have been utilized to formulate risperidone, buspirone, piroxicam, miconazole, ketoconazole, nimesulide, carvedilol and nitroglycerin mucoadhesive tablets [54-56]. The thiolation of mucoadhesive polymers increases mucoadhesion by ~140 fold by formation of disulphide bonds with the cysteine-rich sub-domains of mucin [57].

**Table 2 Functional excipients for tablets**

| Name | Type | Chemical structure | Mechanism of action | Practical applications | References |
|---|---|---|---|---|---|
| Taste maskers / modifiers | Aspartame |  | Sweetener | Acetaminophen | [58] |
| | Eudragit L100 and Eudragit E100 |  Eudragit L100  Eudragit E100 | Polymer coating | Diclofenac sodium | [59] |
| | β- Cyclodextrin |  | Complexation | Famotidine | [60] |

| | | | | | |
|---|---|---|---|---|---|
| | Glyceryl tristearate |  | Lipid coating | Praziquantel | [61, 62] |
| Solubility / dissolution enhancers | Hydroxypropyl-β-Cyclodextrin and Hydroxypropyl methylcellulose |  HP- β- Cyclodextrin  HPMC | Complexation | Carbamazepine | [63] |
| | β- Cyclodextrin | Mentioned earlier | Complexation | Eslicarbazepine | [64] |
| | Sodium saccharinate and Sodium cyclamate |  Sodium saccharinate | Salt formation | Benexate hydrochloride | [65] |

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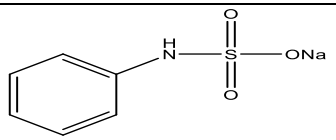
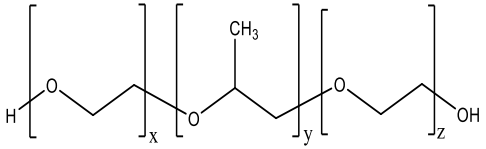
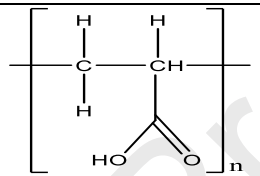
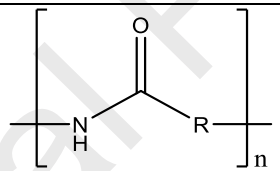
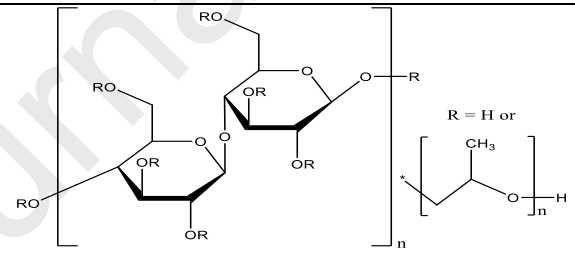
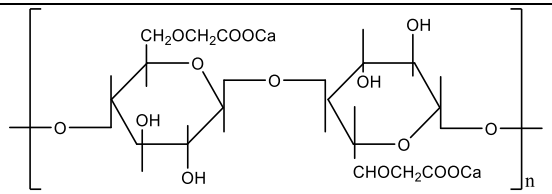
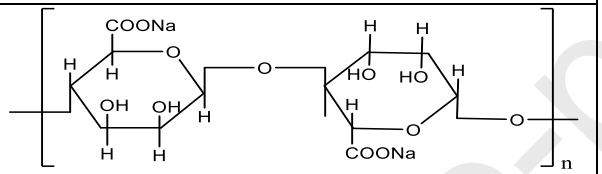
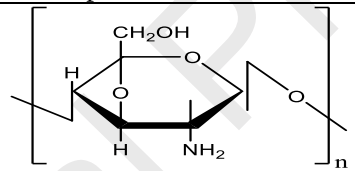
| | |  Sodium cyclamate | | | |
| | Kolliphor P 188, P 237 (polyoxyethylene and polyoxypropylene glycol) |  | Solid dispersion formation | Disulfiram | [66] |
| Release controllers | Carbopol 974P-NF |  | Matrix formation | Ibuprofen | [67] |
| | HPMC | Mentioned earlier | | Indapamide | [68] |
| | Zein |  | | Captopril | [51] |
| Mucoadhesives | Hydroxypropyl cellulose and carboxymethyl cellulose calcium, carbomer |  HPC | -Contact between mucus membrane and mucoadhesive agent (wetting stage) -Establishment of the adhesive interactions (consolidation stage) | Sodium nimesulide | [69] |

| | | | | | |
|---|---|---|---|---|---|
| | |  CMC calcium<br>Carbomer mentioned earlier | | | |
| | Sodium alginate and carbopol |  Sodium alginate<br>Carbopol mentioned earlier | | Risperidone | [70] |
| | Chitosan |  | | Ibuprofen | [71] |

## 2.3. Co-processed, Ready to Use Excipients

Several co-processed, ready to use excipients are mentioned in the Table 3.

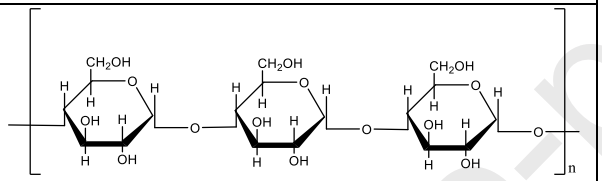
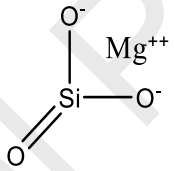
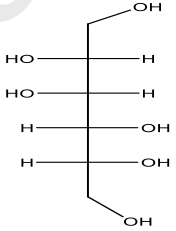
### 2.3.1. Co-processed Excipients

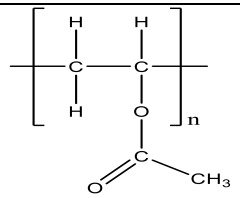
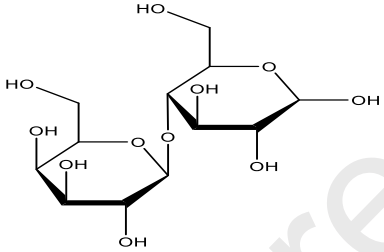
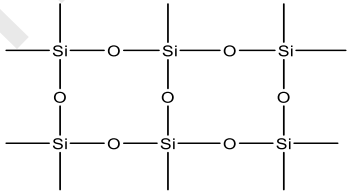
Co-processed excipients are used to improve flow properties, sensitivity to moisture, lubricant sensitivity, disintegration performance, strain-rate sensitivity, providing high drug loading capacity, tensile strength and working efficiency. A co-processed product usually comprises a combination of plastic and brittle materials interacting at subparticle level. Several co-processing approaches can be employed such as melt extrusion, granulation, spheronization, co-crystallization, co-drying, co-milling, spray drying and co-precipitation [72]. Novel co-processed excipients include calcium carbonate-MCC, cellulose-lactose (cellactose), silicified MCC, magnesium silicate-maize starch, MCC-dicalcium phosphate dehydrate and α-lactose monohydrate-crosslinked PVP-HPMC E3 [72-75]. These multifunctional co-processed excipients can serve as potential candidates for continuous manufacturing. Excipients are fed in at a suitable rate and in an appropriate ratio during continuous manufacturing; it can be costly to dedicate a separate feeder to each ingredient. Hence, the use of multifunction composite excipients can play a significant role in reducing the number of input materials as well as variability in a continuous process [76].

### 2.3.2. Ready to Use Excipients

A recent advancement includes the development of ready to use multifunctional fillers as co-processed excipients which only require the blending of active ingredient (and / or 1-2 excipients e.g., lubricant etc.) and compression. Examples of such ready-made fillers include Ludipress (lactose, povidone, crospovidone), ludiflash (D-mannitol, crospovidone, polyvinyl acetate) and HiCel SMCC (silicified MCC) [77-79].

**Table 3 Co-processed, Ready to Use excipients for tablets**

| Name | Type | Chemical structure | Mechanism of action | Practical applications | References |
|---|---|---|---|---|---|
| Co-processed excipients | Microcrystalline cellulose and dicalcium phosphate dehydrate | Mentioned earlier | Perform multiple functions and improve manufacturability | Hydrochlorothiazide | [73] |
| | Starch and magnesium silicate |  Starch  Magnesium silicate | | Paracetamol | [75] |
| Ready to use excipients | Ludiflash (containing mannitol, crospovidone and polyvinyl acetate) |  Mannitol | Mannitol as filler, crospovidone as disintegrant and polyvinyl acetate as binder | Risperidone, Paracetamol, Ibuprofen | [80] |

| | | | | | |
|---|---|---|---|---|---|
| | |  <br>PVAc<br>Others mentioned earlier | | | |
| | Ludipress (composed of lactose, polyvinyl pyrollidone and crospovidone) |  <br>Lactose<br>Others mentioned earlier | Lactose as carrier-filler, polyvinyl pyrollidone as binder and crospovidone as disintegrant | Vitamin E, β-Carotene, Famotidine, Glibenclamide, Propranolol hydrochloride | [81] |
| | Prosolv Easytab SP (containing microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, sodium stearyl fumarate) |  <br>Sodium stearyl fumarate<br>  <br>Silicon dioxide<br>Others mentioned earlier | Microcrystalline cellulose as binder- filler, colloidal silicon dioxide as glidant, sodium starch glycolate as superdisintegrant and sodium stearyl fumarate as lubricant | Carbamazepine | [82] |

| | | | | | |
|---|---|---|---|---|---|
| | PanExcea MHC300G (contains microcrystalline cellulose, hydroxypropyl methylcellulose and crospovidone) | Mentioned earlier | Microcrystalline cellulose as filler, Hydroxypropyl methylcellulose as binder, Crospovidone as disintegrant | Ibuprofen, Famotidine, Naproxen sodium, Hydrochlorothiazide | [83] |

# 3. Advances in Tablet Manufacturing processes

Tablet manufacturing routines involving advanced granulation approaches, hot melt extrusion, extrusion / spheronization, injection molding, spray drying, spray congealing, coprecipitation and nanotechnology-based approaches have been developed over a number of years to produce robust tablet formulations with improved performance characteristics.

## 3.1. Advanced Granulation Approaches

Preparation of tablets via granulation involves multiple steps. During recent years, several advances in both wet and dry granulation have been made in order to reduce process variability and improve efficiency.

### 3.1.1. Wet granulation

Wet granulation involves use of a granulating liquid (i.e., binder or solvent) to promote the agglomeration of powder particles by forming a wet mass on the basis of adhesion phenomena. Different variables e.g., binder type, rate of addition and incorporation method, solubility of particles in the binder, impeller speed, kneading elements, wet massing time and barrel temperature etc. influence the quality of final product. Despite the fact that granulation is time consuming and comprises multiple unit processes, it is a widely used to produce free-flowing, dust-free granules which are easy to compress. Different physicochemical attributes such as moisture, porosity, density, size, compressibility, hardness and content uniformity of the granules must be within permissible limits in order to produce an acceptable quality [84]. Over the years, various advances in wet granulation technology in terms of equipment and processes have been made.

Mechanical, fluid bed and twin-screw granulators have been employed to prepare granules. Mechanical granulators include low shear (< 150 rpm) and high shear (> 200 rpm) wet granulators. Low shear granulators have been widely used for shear sensitive materials. Moreover, these granulators permit mixing and granulation within the same equipment. Ribbon and paddle blenders, planetary and rotating-shape mixer / granulators, twin shell or V-blender, orbiting screw and sigma-blade granulators are examples of widely employed low shear granulators. In high shear wet granulation, the powder mixture is processed in a closed vessel by using an impeller rotating at high speed, and granulating liquid is sprayed onto it. Variables affecting physical or mechanical properties of granules prepared in a high shear granulator include fill ratio, impeller properties (shape, size, speed), geometry of granulator bowl and bowl material. The shear granulation approach is advantageous as it requires a lower volume

of binding liquid, short processing times and produces granules with a uniform drug distribution. Nevertheless, suboptimal processing may result in lump formation due to over-wetting, and chemical or mechanical degradation of fragile or thermolabile materials [85, 86].

In fluid bed granulation, binder is sprayed as liquid droplets using atomisers onto the fluidized powdered ingredients resulting in their coating and agglomeration as granules which are subsequently dried in the drying chamber. Two configurations (top spray, bottom spray / Wurster) of fluid bed granulator are applied to prepare granules. The Wurster configuration has also been explored for tablet coating applications. Process variables impacting the quality of granules formulated using fluid bed granulators comprise fluidizing air temperatures, spray rates and properties of the binding liquid. Granules produced by fluid bed granulators are less dense, more porous and compressible as compared to high shear wet granulators. However, the primary limitation of this approach is size reduction due to attrition, which can be partly overcome by using granulators with a tapered geometry. Also, fluid bed granulation cannot usually densify granules which may be an issue if densification is needed to assist with flowability.

The twin screw granulator is equipped with two co-rotating screws for transporting feed material and binder at specific location to mix and push the mass through rotating dies or a screen to produce granules. Various parameters impacting granule properties include rotational speed, screw design, binder introduction and positioning of auxiliary units such as feeders and pumps. Compared to high shear wet granulation, the granules formulated using twin screw granulation exhibit improved tensile strength, disintegration and friability [85].

Process related advancements in wet granulation include moist, thermal adhesion, steam, melt, freeze, foam and reverse wet granulation. Moist or moisture-activated dry granulation employs very small amounts of water (1-4 %) as a granulating agent. The process is time and energy efficient as it requires short processing and drying times. However, this technique is not suitable for hygroscopic or moisture-sensitive active ingredients and may not form a strong granule.

Thermal adhesion granulation utilizes minimal amounts of granulating liquid (water / solvent). In thermal adhesion, the powdered ingredients are subjected to heat (30-130°C) in a closed assembly under continuous mixing by tumble rotation till granules are formed. A drying process is not employed in thermal adhesion granulation because the granulating liquid (due to its small amount) is easily consumed by the powder during agglomeration. A major advantage

of this method includes reduced moisture-associated variabilities due to low amount of binder. However, high energy input and specialized equipment is required for generation and maintenance of heat. Other drawbacks include sensitivity to thermolabile agents and so it is not suitable for all binders [84, 87].

Steam granulation involves the use of water-based steam as a binding medium. This approach is efficient as steam provides fast and uniform diffusion into the powder particles and better thermal balance during drying. Limitations of this process include requirement of high energy inputs for the production of steam, and so it is inappropriate for thermolabile active ingredients [84].

Melt or thermoplastic granulation involves agglomeration of powder particles by using meltable binders (melting at 50-90°C) e.g., stearic acid, PEG 6000, PEG 3350, lauroyl polyoxyl-32 glycerides (Gelucire 44 / 14), poloxamer P407 and vinylpyrollidone-vinyl acetate copolymer. The melting binder can be incorporated in the powder blend either as a molten liquid (spray on technique) or as a solid that softens / melts during the process (melt-in / in-situ melt granulation). The absence of water eliminates the wetting and drying steps, making this process less energy or time consuming. Nevertheless, the use of high temperatures may result in thermal degradation or oxidative instability of formulation components [84, 88, 89].

Freeze granulation technique, introduced by the Swedish Ceramic Institute in the late 1980s, involves spray freezing (spraying of droplets of a suspension into liquid nitrogen) followed by freeze-drying of granules. The density of granules can be controlled via the solids content of the suspension. Other advantages include formulation of granules without cavities and the use of thermolabile molecules due to mild drying [84].

Foam granulation involves the addition of a binder (e.g., methyl cellulose, HPC, HPMC) as a foaming agent. Surfactants (e.g., sodium lauryl sulphate, poloxamer) can also be incorporated as foam generating aids. Foamed binders exhibit better spread-to-soak ratio permitting binders to coat the powder particles resulting in uniform binder distribution and agglomeration. Several other advantages of this process include less processing time and ability to process potent / low dose and water sensitive drugs [84, 90, 91].

In reverse phase wet granulation, the powder materials are immersed into the agitated granulating liquid, in a controlled manner, followed by controlled breakage to obtain granules [92]. This technique can efficiently process poorly aqueous-soluble drugs into granules

exhibiting improved flowability, uniform wetting and erosion. However, this approach requires large amounts of binder and increased processing times [85].

### 3.1.2. Dry granulation

A major advance in dry granulation technology includes pneumatic dry granulation (PDG) which employs the classical roller compaction technique in combination with a proprietary pneumatic system to develop granules with better flowability and compressibility. In PDG, a mild compression force is applied by a roller compactor on the powder particles in order to produce a compact mass containing fine particles and granules. The granules of desired size range are separated in a fractioning chamber by using a pneumatic system. PDG allows the use of high drug loads (70 – 100 %). Several other advantages include fast processing speed, little or no material wastage, suitable for moisture, solvent or heat sensitive drugs, improved flowability and compressibility. Major constraints of this manufacturing technique include impact of recycling on the quality of developed granules and friability [84, 93].

## 3.2. Hot Melt Extrusion

Hot melt extrusion (HME) involves blending of formulation components along a rotary screw(s) inside a barrel at high temperature. The molten blend is passed through an extruder and extrudates can be pelletized or compressed into tablets [94].

Several factors such as feed rate, local temperature, resident time, configuration or speed of extruder screw and cooling rate influence the quality of prepared formulation. The HME technique has been widely explored in the pharmaceutical industry for the preparation of solid dispersions. The hot melt extruded mass exists as an amorphous solid solution with a high inherent free energy, offering higher drug solubility and bioavailability. However, the process is energy demanding and inappropriate for thermolabile drugs [95].

HME technology was employed to prepare taste masked sildenafil citrate-loaded orally disintegrating tablets by using ethyl cellulose as a matrix material. The screw configuration was reported to impact the taste masking efficiency of formulation as it alters the physical state (solid solutions) of the active ingredient [96]. Floating gastreoretentive hot melt extruded sustained release tablet formulations of acetohydroxamic acid and chlorpheniramine maleate with floating time > 24h were fabricated using Eudragit RS PO, Eudragit E PO and sodium bicarbonate [97]. Solid dispersion (prepared by HME approach) based tablets of itraconazole [98] and nimodipine [99] have been formulated using HPMC acetate succinate, HPMC and PVP. Two solid dispersion based tablet dosage forms, Viekirax / Technivie (ombitasvir,

paritaprevir and ritonavir) and Maviret / Mavyret (glecaprevir and pibrentasvir), have been approved by FDA (Food and Drug Administration) in 2015 and 2017, respectively [95].

## 3.3. Extrusion-spheronization

Extrusion-spheronization, accomplishes granulation in four steps; preparation of wet mass, shaping the granules and forming extrudates (extrusion), breaking up the extrudates and forming spheres (spheronization) and finally drying of formed pellets. Various formulation parameters (granulating liquid, moisture content, physicochemical properties of the formulation components), equipment parameters (extruder design, type of mixer, friction plate of spheronizer, extrusion screen) and process parameters (extrusion speed and temperature, spheronization time and speed, spheronizer load, drying method) impact the quality of pellets. The extrusion process densifies the material to a saturation point while the spheronization introduce plastic deformation to the extrudates, which results in the formation of spheres / pellets. Drying induces shrinkage and confers additional densification of the granules [100].

Various materials such as HPMC, Carbopol, PVP, coprocessed MCC-Eudragit, starch-dextrin mixtures have been tested as suitable base materials for pellet fabrication [101-103]. In a study, a ram extruder and a modified double arm counter-rotating roller (for spheronization) were employed to develop phenylpropanolamine hydrochloride-loaded sustained release beads [104]. More recently, bi-layered self-emulsifying pellets containing the poorly aqueous soluble drug, vinpocetine, were reported to exhibit improved *in-vivo* bioavailability [105].

## 3.4. Injection Moulding

This approach involves fusion of the formulation components, injection of liquifies mass into a closed mould, solidification and detachment of this mixture. The moulded mass is occasionally subjected to curing in order to achieve desired mechanical characteristics.

The process parameters such as injection pressure, softening and cooling temperature play a significant role in physicochemical properties of the formulation. Injection moulding is advantageous as it is suitable for different scales manufacturing, including continuous manufacturing, and does not require water or other solvents. As the process involves heat and pressure, there is a possibility of auto-sterilization of the formulation [106]. However, upon drying, non-uniform shrinkage may lead to variations in the dimensions of the formulated mass. Eggenreich *et al*. prepared injection moulding based fenofibrate solid dispersion-based matrix (comprising polyvinyl caprolactone, polyvinyl acetate and polyethylene glycol graft copolymer) tablets which showed zero-order kinetics [107]. The injection moulding process

has been reported to fabricate a sustained release metoprolol tartrate-loaded matrix (comprising ethyl cellulose and HPMC) tablets [108]. The Egalet Corporation developed a prolonged release erodible matrix tablet dosage form, using the injection moulding process, for the oral delivery of opioids (such as morphine, hydrocodone) to decrease the daily dosing frequency (which may reduce the risk of opioid abuse) [106, 109]. Desai *et al*. used an integrated hot melt extrusion – injection moulding process to manufacture maltodextrin-based griseofulvin loaded immediate release tablets. A powder blend was extruded using a twin-screw extruder and the extrudate was directly injected into the integrated moulding unit. The method was reported to continuously manufacture a robust tablet formulation with acceptable properties, performance and stability profile [110].

## 3.5. Spray Drying / Congealing

Spray drying is a single step granulation process involving conversion of a liquid into fine, dustless and agglomerated powders (with pre-determined properties i.e., size and appearance) by the evaporation of solvent. The spray drying process comprises four steps including atomization of feed into a spray, spray-air contact, drying of spray and finally separation of dried formulation from the drying gas. Different features of the dried mass including particle size, density, distribution, moisture content, porosity and flowability can be controlled by modulating the spray drying process. The variables affecting the product quality include feed rate, type of polymer, concentration, viscosity, drying gas velocity, inlet and outlet temperature [111, 112]. Equations have been developed which relate the correlation between the droplet diameter, atomizer type and properties of feed solution including density, surface tension, viscosity, equipment and solution properties [113].

Spray drying is advantageous to granulation as it offers improved stability, flowability, colour uniformity, tablet hardness and lower lubricant requirements. Moreover, it is valuable in improving bioavailability of poorly water-soluble drugs, processing macromolecules and heat-labile pharmaceuticals. The limitations of the spray drying process are the high maintenance cost and the use of solvents [111].

Cerpnjak *et al*. prepared spray dried SMEDDS (self-microemulsifying drug delivery system, comprising maltodextrin as a solid carrier) of naproxen showing significantly improved in-vitro dissolution profile [114]. Soulairol *et al*. demonstrated spray dried amorphous solid dispersion-based tablets containing co-processed nifedipine and vinyl caprolactam- vinyl acetate- PEG 6000 to achieve improve the dissolution kinetics [115]. Recently, a spray dried dispersion comprising ziprasidone and poloxamer 188, loaded into osmotic pump tablets,

showed significantly enhanced solubility and in-vivo studies in beagle dogs depicted sustained release with prolonged action. [116]. Additionally, spray drying is a known technique to produce co-processed pharmaceutical excipients as mentioned above, for example; recently, this technique was used to prepare a high quality multifunctional co-processed excipient composed of rice starch with carboxymethyl rice starch and silicon dioxide. The aim of the prepared spray dried co-processed rice starch was to be used as a filler-binder with disintegrant effect for tablet production by direct compression [117].

Spray congealing, like spray drying, is based on the production of droplets via the atomisation of a fluid, followed by hardening of molten material by rapidly reducing the temperature below the fusion point. Spray congealing involves the atomisation of a solution / suspension of active ingredient prepared in a melted vehicle (the temperature is raised above its fusion point) within a chamber maintained at a temperature below the vehicle's fusion point. The small molten droplets obtained after atomisation solidify upon cooling within the chamber. This method is less time and energy consuming as compared to other approaches used to formulate solid dispersions [118].

Sulfamethizole-lipid-lipase matrix spray congealed granules were fabricated into timed-release tablets which provide drug release over 10 h [119]. Advances in spray drying / congealing technology include nozzle modifications (i.e. vibrational or pressure nozzle to produce larger particles with improved flow properties) and rotary atomisers, which do not require high maintenance costs [111, 112].

## 3.6. Coprecipitation

The coprecipitation method involves solubilization of the formulation contents in a solvent, followed by addition of an anti-solvent at a specific rate under constant stirring to obtain a precipitate. A well-controlled process would yield coprecipitates with predictable and reproducible characteristics i.e., size of the coprecipitated granules, percent recovery of active ingredient and flowability index. Dissolution of poorly water-soluble drugs have been improved by coprecipitation [120].

Coprecipitation serves as an attractive alternative to hot melt extrusion or spray drying for formulating solid dispersions, as the former does not involve a thermal challenge to the materials. Nevertheless, a prompt phase transition of drug and polymer is desirable; the time duration for phase transition must be short enough to overcome molecular arrangement for crystallization [121].

Khan *et al*. prepared extended release co-precipitates of ibuprofen and Eudragit S100 by using alcohol (as solvent) and water (as antisolvent) [120]. In another study, co-precipitation was employed to prepare amorphous solid dispersions of a weekly acidic compound (a potential candidate drug belonging to BCS class II) and copovidone using tetrahydrofuran as solvent and methyl-t-butyl ether as antisolvent. Co-precipitated solid dispersion approach improved the dissolution rate of this compound under study [121].

Nanoprecipitation (patented by Fessi *et al*. in 1989) or flash nanoprecipitation and sonoprecipitation are some of the advances reported in coprecipitation. Both these techniques are being widely used for formulating nanoparticles which can be compressed into tablets [122, 123]. Biodegradable polymers such as polylactide, polylactide-co-glycolide and poly-ε-caprolactone have been employed for encapsulating drugs using nanoprecipitation approach. Silymarin nanosuspensions were prepared by sonoprecipitation using ethanol as solvent and water (containing PVA (polyvinyl alcohol) and mannitol) as antisolvent phase. These nanosuspensions were formulated as lyophilized tablets and significant improvements in saturation solubility and dissolution rate of silymarin were observed [122].

## 3.7. Nanotechnology-based approaches

Nanotechnology-based fabrication approaches include development of nanoparticle or nanofiber incorporated tablets. Most widely used methods for fabricating nanoparticles / nanofibers include precipitation, nanomilling and electrospinning. The precipitation method has already been described in the section 2.6.

Nanomilling includes reduction of drug particle size (<100 nm) by wet media milling (an organic solvent-free process) and the intermediate product obtained is a drug nanoparticle suspension (nanosuspension). Process variables comprise stirring / agitation rate, drug concentration, bead loading and size. Advantages of nanomilling process include the ability to run continuously, tunable and relatively higher drug concentrations and less excipient. A prepared nanosuspension also offers numerous advantages, such as enhanced dissolution rate and higher mass packing, thus, a higher dose per injection volume. Challenges associated with nanomilling include the difficulty in achieving truly nanosized drugs, and the risk of solid-state changes which may affect solubility and contamination due to media (i.e., bead) wear. Furthermore, wet stirred media mills vary in mode of operation, power density and geometry as compared to other milling equipment hence, moving from one type of mill to another is also challenging [124].

Electrospinning involves electrification of a liquid droplet (which leads to the generation of a jet), followed by stretching as well as elongation to produce a fiber. Various environmental (humidity, temperature), operational (applied electric field, flow rate, distance between needle and collector) and solution-related (solution conductivity, viscosity, solvent and concentration of polymer) factors influence the nanofiber fabrication by electrospinning process [125]. Advantages of this process include the ease of use and production of quality fibers (exhibiting high surface area-to-volume ratio as well as large number of intra / inter fibrous pores). Challenges associated with this technique include clogging and cleaning of needles, undesirable interactions (e.g. fiber-fiber bonding, non-homogenous fibers, poor distribution of nanofibers in the mat), controlling the diameter as well as morphology of nanofibers and deposition of nanofibers on the collector [126]. Tablets containing aripiprazole [127], acetaminophen [128], melatonin [129] and amphotericin B [130] loaded nanomilled or electrospun nanoparticles / nanofibers, prepared using HPC, pluronic F127, PVP, cellulose acetate, Eudragit, PVA and gelatin have been described in the literature.

## 3.8. Tablet compression

Granules, extrudates, spheres, beads, spray dried / congealed droplets, co-precipitates, nanofibers can be compressed into tablets in order to deliver a uniform dose and to achieve a reproducible compact geometry. Direct compression offers several advantages, including cost effectiveness and convenience. Complete understanding of powdered materials and their suitability for compaction under a specific compression force / pressure, is important to develop a tablet dosage form and manufacturing process control. Multiple factors e.g., plastic / elastic deformation, fragmentation and rearrangement of particles are accomplished during densification of powders after die filling. Various models / equations (e.g. Heckel, Cooper-Eaton, Kawakita, etc.) have elaborated powder compressibility (defined as a correlation between porosity and compression pressure) [131, 132].

Despite a plethora of studies and comprehensive understanding regarding powder compression behaviour, a major problem encountered during compression is sticking of the material to the surface of tablet punch. Various formulation parameters including particle size distribution of granules, tablet design, tablet-press conditions, properties of tablet tools and their maintenance influence tablet sticking.

This problem can be addressed by applying external lubrication, in which a suitable lubricant is sprayed as a fine layer onto punch faces and dies. External lubrication prevents sticking, and

minimizes the ejection or scrape-off forces. This approach is an effective alternative to the use of lubricating agents within a formulation, as the latter may affect tablet dissolution or hardness [133].

Proper tooling and maintenance is advised to avoid this problem to some extent. A seven step maintenance approach comprising cleaning, analyzing for any damage / wear, repairing, measuring to assure the maintenance of critical tooling dimensions, polishing, lubricating and storing, is advised [133]. Neglecting of any one step usually guarantees failure of compression due to that cause. Distinct coatings (e.g. diamond-like carbon, nickel, chromium, chromium nitride, titanium nitride, titanium aluminium nitride) have been applied by electroplating, physical vapour deposition (PVD) or ion beam enhanced deposition (IBED) to provide protection against corrosion, improve wear resistance, resolve sticking problems and increase product release [134]. The Tableting Science Anti-stick Research (TSAR) project, which involves the use of an insert, comprising carbide, vulcalon, adiprene or polytetrafluoroethylene to counter tablet sticking, [133, 135] is an example of logical coating selection based on API chemical parameters..

Operational parameters such as increased tableting speed, short dwell time, and low compression pressure, all aggravate tablet sticking. Corrective measures including slowing down the tablet press and increasing compression pressure may resolve sticking problems, however, subsequent heat / high temperature in the tablet press could negatively affect the tableting process. An alternative approach to avoid sticking involves machine tooling approaches (i.e. modification in the configuration of punch head i.e. flattened) that prolong dwell time [136].

## 4. Continuous Manufacturing

In continuous manufacturing; starting materials are continuously fed and finished products are continuously taken out from the system at the same rate in order to maintain a constant hold-up mass during steady-state processing. All unit operations are integrated in a single production line without any start or stop in between the unit operations. The quality of continuous manufacturing processes can be assured by continuous, regular and real-time monitoring of quality attributes of raw materials, intermediates, the finished dosage form and critical process parameters through measurements during the process, using process analytical technology (PAT) [137-139]. The concept of end-to-end continuous manufacturing was presented, based on the aliskiren tablet production. The conversion from a batch to continuous process decreased

the number of unit operations as well as residence time utilized by the manufacturing plant. The idea "from powder to tablet" involved creation of an integrated production line with model-based control systems to achieve final product at the end, based on a quality by design approach [138]. GEA pharma systems introduced a continuous tableting line (i.e. ConsiGma) for the first time [139]. GlaxoSmithKline (GSK) and Pfizer collaborated for designing the next generation of Pfizer's already existing PCMM (portable, continuous, miniature and modular) prototype to produce oral solid dosage forms [140]. Recently, GSK, AstraZeneca and CPI Pharma collaborated to establish a continuous wet granulation manufacturing facility (equipped with PAT) for preparing oral solid dosage forms (tablets) [141]. A licensed, continuously produced tablet formulation, Severin (nimesulide), by Chinion is available in the Mexican market [138]. Currently, the pharmaceutical industry is undergoing a paradigm shift from conventional batch production to continuous manufacturing due to easier scale-up, robust and flexible operation, reduced chances of variability (which may occur due to discontinuity in the process), smaller factory footprint, improved product quality and reliable and safe manufacturing [137-139]. However, the continuous manufacturing approach presents several quality and regulatory challenges, such as sampling strategy, product collection or rejection, batch release and recalls, control strategy and traceability of raw materials, all of which have to be overcome [138].

## 5. Novel Tableting Technologies

During the recent years, various novel tableting technologies including fast disintegrating, matrix, tablet-in-tablet, tablet-in-capsule, multi-layered, multi-particulate systems have been developed to benefit product performance.

### 5.1. Fast Disintegrating Tablets

A fast disintegrating tablet (FDT) disintegrates within 30 seconds – 3 minutes in mouth without requiring an additional volume of water. The porous light-weight matrices of FDTs exhibit high affinity for water which disintegrate rapidly in the oral cavity following contact with saliva, which can then be conveniently swallowed [142].

Commonly employed FDT fabrication strategies include freeze drying, direct compression and three-dimensional (3D) printing. The formulation components of FDTs formulated by freeze drying technologies include fillers (mannitol, lactose), taste modifiers (sugars, aminoacids), cryoprotectants (e.g. mannitol, sorbitol), binders (e.g. gelatin, PVP, gelucire) and viscosity modifying polymers (carbopol 974P-NF, pluronic F127) [143]. Freeze drying technologies

employed for the preparation of FDTs include Zydis, Lyoc, Quicksolv, Nanomelt. In Zydis technology, the liquid solution / suspension of formulation is filled into the pre-formed blisters, freeze dried and packed. In Lyoc technology, the formulation, in the form of a suspension, is homogenously distributed in the alveolar packs and freeze-dried on dryer shelves. In Quicksolv technology, aqueous dispersion / solution of formulation is frozen and water is eliminated by using an excess of alcohol. Nanomelt technology is based on the nanocrystallization of drug [144]. Lyophilization technology has been recently investigated for formulating vaccines (e.g. live-attenuated trivalent enterotoxigenic *E. coli* vaccine) incorporating FDTs due to minimal chances of drug degradation [145].

The FDTs prepared by direct compression frequently include excipients named super-disintegrants (e.g. CP, SSG, CCS), effervescent agents (e.g. sodium carbonate, maleic acid, fumaric acid, ascorbic acid), sublimation agents (e.g. thymol, camphor, menthol) or melting binders (e.g. glyceryl behenate, hydrogenated castor oil, glyceryl palmitostearate) to induce prompt disintegration [142, 146]. Disintequick MCC-25, which is a co-processed lactose/MCC, was applied to enhance the characteristics of FDTs (regarding tablet hardness and disintegration time) produced by direct compression [147]. Recent advancements in direct compression or compaction techniques include Flashtab (compression of taste masked granular microcrystals), Advatab (compression using external lubrication system), Pharmaburst (compression of powder mixtures), Orasolv and Durasolv (compression with / without effervescent mixture), Frosta (compression after granulation) and Wowtab (compaction and humidity treatment) [144].

3D printing provides an opportunity to formulate patient-specific fixed dose combinations with complex shapes and internal structures. Various 3D printing techniques have been used in customized dosage forms including stereolithography, inkjet printing, fused deposition modelling, powder bed fusion, binder deposition, semi-solid extrusion and selective laser sintering [148, 149]. Other key production methods include moulding, spray drying and solvent casting (QuickDis) [144].

Despite the advantages of FDT i.e. unit dosing, improved stability and ease of administration, their manufacturing poses numerous challenges. Their hygroscopic nature requires controlled humidity during manufacturing and specialized packaging of FDTs [150]. In vitro taste masking efficiency assessment of the excipients, another challenge, has been partly addressed by the artificial electronic tongue project [151].

Ternary solid dispersion-based FDTs containing glyburide, prepared using a hydrophilic carrier (PEG 6000) and a surfactant (sodium lauryl sulphate) demonstrated a ~5.5 fold higher dissolution rate as compared to conventional counterparts [152]. Gugulothu *et al*. employed freeze drying technology to fabricate sumatriptan succinate-loaded FDTs with PVP and gelatin as matrix formers, and camphor as a pore former. A disintegration time of <10 seconds and ~90 % drug release within 10 minutes suggested an improved biopharmaceutical performance of the formulation [153]. Various orally disintegrating tablets are already commercially available e.g. zomig-ZMT (zolmitriptan) [154], maxalt-MLT (rizatriptan benzoate) [155], zofran ODT (ondansetron) [156], pepcid RPD (famotidine) [157] and feldene melt (piroxicam) [158].

## 5.2. Matrix Tablets

Matrix tablet, comprising inert or water-soluble matrices, are designed to provide chronomodulated drug release. The rate of drug release from a matrix tablet is governed by the wettability of the polymeric framework, porosity and drug loading [50]. It is postulated that drug contents in a matrix must be present above the percolation threshold in order to promote its release through the pores (Leuenberger *et al*.) [159].

A comprehensive detail of polymeric materials used to formulate matrix systems have been described in Section 1.4. Fabrication of various inert (e.g. niflumic acid [160], diphenhydramine HCl [161], tripelennamine HCl [162]) and hydrophilic matrix tablets (e.g. metoprolol tartarate [163], cefpodoxime proxetil [164], isoniazid [165]) are reported in the literature.

Matrix tablets have also been prepared for mucoadhesive drug delivery (section 1.6). Indomethacin [166], captopril [167] and albendazole [168] loaded mucoadhesive type matrix tablets have been developed.

## 5.3. Tablet-in-Tablet

Tablet-in-tablet or compressed coated tablet comprises an inner drug core and outer coating shell. The outer shell controls the drug release, strength and stability of formulation [169].

The conventional dry coating approach for the preparation of tablet-in-tablet was associated with problems such as non-core, double-core, off-centre (core on the side, not in centre), inlay (incomplete coating, top surface is exposed) and cocking (tilted core). The novel single-step dry coating (OSDrC) equipment (capable of accurately positioning the core and producing precision quality tablet with accurate weight of layers and modified release characteristics in a single-step solvent-free process) has revolutionized this tableting approach [169].

The release of drug from a tablet-in-tablet dosage form is greatly influenced by the compression forces and amount of coating layer. The increased thickness and compression force of the coating layer results in protracted lag time [170].

The tablet-in-tablet technique is advantageous as it protects hygroscopic drugs from moisture, can accommodate two different or incompatible drugs (in the inner core or outer coating layer) and permits drug release from these layers in different anatomical areas of the digestive tract. Some challenges include the lack of bonding between core and coat, the chances of cross-contamination between the layers and swallowing difficulties (dysphagia) due to a large tablet size [169].

Compressed coated di-matrix depot tablet dosage forms of nifedipine prepared using low viscosity HPC (in the inner layer) and middle viscosity HPC and Eudragit RSPO (in the coating layer) exhibited zero order drug release profile [171]. Maity *et al*. prepared prednisolone-loaded compression coated tablets for colon targeting. The inner layer contained drug, MCC, magnesium stearate, CP, trisodium orthophosphate dodecahydrate; outer coating layer comprised sodium alginate and calcium ion cross-linked carboxymethyl xanthan gum [172]. Compression coated tablets containing diclofenac sodium as the inner core and micronized ethyl cellulose in the coating layer produced a delayed drug release with a lag time of ~16.3 hours [170]. Recently, a tablet-in-tablet formulation of capecitabine and phosphamide within a fixed dose combination has been patented (US 20190142755) [173].

## 5.4. Tablet-in-Capsule

The tablet-in-capsule system includes filling and sealing of single or multiple tablets in a capsule. Site-specific drug delivery or controlled release rate is achieved by enclosing multiple tablets with different coatings within a capsule.

A tablet-in-capsule system comprising an impermeable capsule body with a hydrophilic cap and layered tablets can provide pulsatile drug release, which assimilates a periodic dose administration [174]. In another study, pseudoephedrine hydrochloride-loaded coated mini-tablets (two immediate release and 3 sustained release) were filled in HPMC capsules to provide drug released within 1 and 8 – 10 hours, respectively [175]. Zahaby *et al*. reported a tablet-in-capsule dosage form, containing gastroretentive levofloxacin floating mini-tablets for the eradication of *Helicobacter pylori* [176].

## 5.5. Multilayer Tablets

Multilayer tablets comprise two (bi) to five (multi) layers; different drugs with incompatibilities or varying release profiles can be incorporated in each layer. Multilayer tablets with an active ingredient layer and one or more modulating / inactive layers have also been prepared. The active ingredient layer is usually sandwiched between inactive layers which serve as swellable / erodible barriers and control the drug release rate. Various factors influence the mechanism of drug release and formulation performance such as drug solubility, tablet structure, polymer ratios and characteristics (e.g., swellable, erodible etc.). Moreover, the multilayer tablets can deliver fixed dose combinations of different active ingredients and control their administration rate, separate incompatible therapeutic moieties form each other by loading them in different layers and prolong the life cycle of drug product. However, a comprehensive understanding of process and formulation is required in order to overcome several challenges such as accuracy in weight control of each layer, the possibility of layer separation during fabrication and storage, cross-contamination between the layers (particularly in case of incompatible active ingredients) and inadequate tablet breaking forces [177, 178]. Hwang *et al*. reported novel double-layered gastroretentive tablets comprising a drug (ranitidine HCl MCC, lactose and HPMC) layer and a swellable, highly porous gastroretentive layer (polyethylene oxide and milled camphor) [179]. Andrews *et al*. reported biphasic release of simvastatin and aspirin (loaded in a fixed dose combination) from bilayered tablets. Aspirin was loaded in the immediate release layer which was composed of vinylpyrollidone-vinylacetate copolymer while simvastatin was incorporated in the delayed release layer comprising Eudragit L100-55, Eudragit L100 and HPMC acetate succinate HF grade [180]. Park *et al*. developed once-a-day three-layered tablet formulation of hydrophilic drug terazosin HCl. Upper and bottom swellable layers comprised polyox WSR coagulant and magnesium stearate, while the middle hydrophilic layer contained terazosin HCl, copovidone and a filler (lactose, dextrate or MCC). As compared to conventional matrix tablets (comprising polyethylene oxide (PEO), drug and magnesium stearate), prepared novel tablets exhibited relatively consistent release kinetics [181].

## 5.6. Multi-particulate Systems

Multiparticulate systems comprise multiple small discrete drug delivery units (e.g., minitablets, pellets, granules, beads, microcapsules etc.) which can be administered in the form of sachets, tablets or capsules. Each unit in the multiparticulate system exhibits inherent functional properties that provide an opportunity to control the drug release pattern. Multiparticulate

systems provide several advantages such as site-specific drug delivery in the digestive tract, easier dose-weight proportionality than single-unit systems, flexibility in dose titration and swallowing (by mixing with the food). Challenges associated with multiparticulate systems including robustness of subunit functionality coating, particle size, tableting (by compression) of coated granules / minitablets / beads / pellets / microcapsules without damaging their coat and risk of variability due to multiple, complex manufacturing steps [182, 183].

Domperidone pellets were prepared using Celphere 102 (MCC) and Suglet (containing sucrose and starch) as core seed, and polyvinyl acetate as a rate controlling polymer. Prepared pellets were compressed into tablets using Ceolus (MCC) granules and Ludipress (comprising lactose, povidone and CP). The prepared multiple unit pellet system provided sustained release of domperidone [184]. Liu *et al*. described vinpocetine-incorporated self-emulsifying pellets to acheive pH-dependent release of drug with improved bioavailability [185].

Mucoadhesive biphasic capsules of cefuroxime axetil containing immediate release and sustained release minitablets were formulated by Liu *et al*. The immediate release minitablets were fabricated using poloxamer 188 and sylysia 350, while sustained release minitablets comprised chitosan, HPMC K100M and sodium CMC (carboxymethyl cellulose). An in-vitro dissolution study of capsule revealed a biphasic release profile (i.e., immediate burst release of drug was followed by sustained release up to ~12 hours. In-vivo studies in rabbits showed ~4 fold improvement in oral bioavailability [186]. Song *et al*. reported spray dried mesoporous granules of pravastatin by using D-mannitol (as the dispersion medium) and ammonium bicarbonate (as the sublimating agent). Sublimation of ammonium bicarbonate during spray drying resulted in mesoporous granules with a high surface area. The prepared FDTs manifest quick disintegration due to rapid water uptake by a mesoporous framework showing complete dissolution within ~30 minutes [187].

## 6. Quality by Design

The International Conference on Harmonization (ICH) presented several regulatory guidelines and set forth the concept of quality by design (QbD) as a holistic approach for producing quality drug products. Pharmaceutical QbD is defined as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". Typically for solid dose projects, the QbD process is composed of Ishikawa analysis (Figure 1) to identify potential key factors risk analysis and Design of experiments to elucidate the design and control spaces.

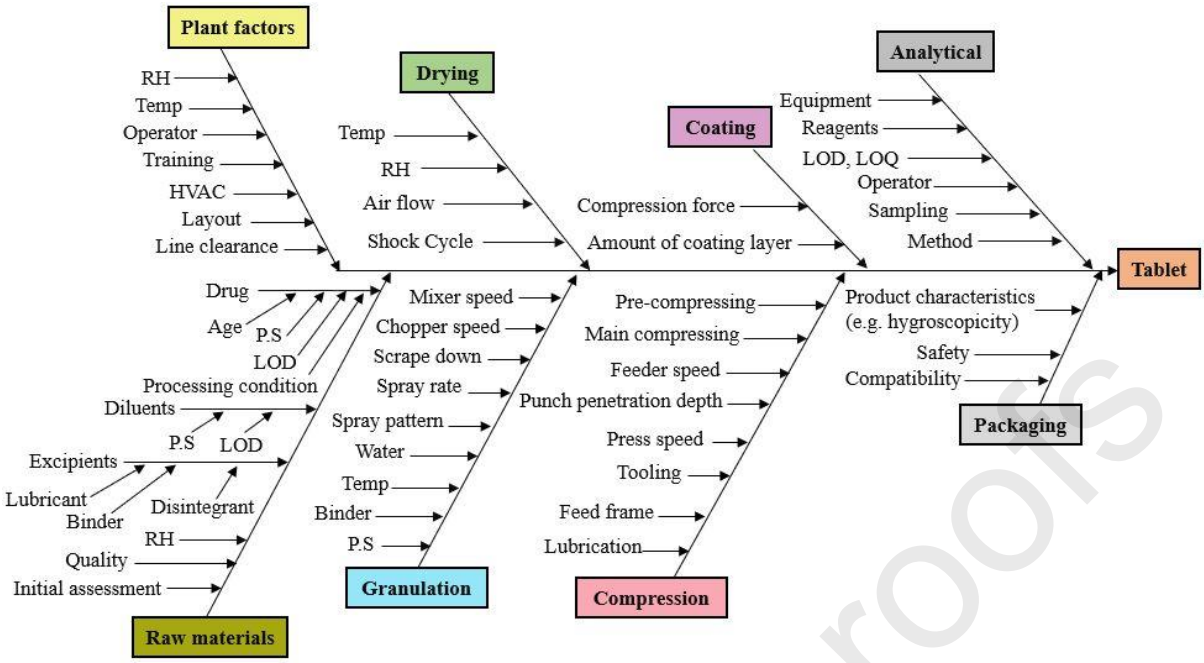
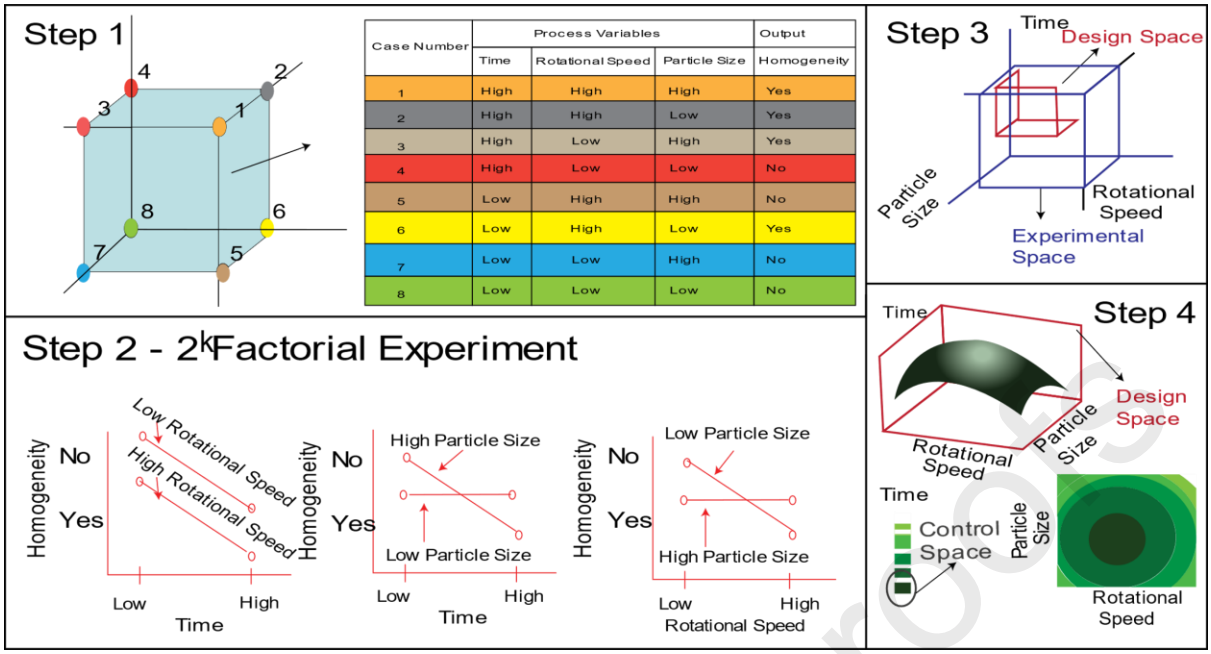



**Figure 1 Ishikawa diagram for tablet dosage form [188]**

QbD provides various benefits such as regulatory flexibility, reduced consumer generic skepticism and rapid product launch. The framework of QbD includes ascertaining drug product objectives, identifying critical quality, material and process attributes, risk assessment, selecting optimization designs, identifying design space and optimum formulation and finally defining a control strategy for continuous improvement [189]. In 2013, FDA approved the Biological License Application for Genentech's (Roche) Gazyva (obinutuzumab); the first product with a proposed design space along with QbD elements [190]. A QbD approach is widely applied for the fabrication of quality products (Figure 2). Zhang *et al*. employed the Box-Behnken design to perform formulation optimisation studies for fabrication of 3D printed tablets containing ibuprofen [191].




| Case Number | Process Variables | | | Output |
|---|---|---|---|---|
| | Time | Rotational Speed | Particle Size | Homogeneity |
| 1 | High | High | High | Yes |
| 2 | High | High | Low | Yes |
| 3 | High | Low | High | Yes |
| 4 | High | Low | Low | No |
| 5 | Low | High | High | No |
| 6 | Low | High | Low | Yes |
| 7 | Low | Low | High | No |
| 8 | Low | Low | Low | No |

**Figure 2 Quality by Design methodology [189]**

## 7. Advanced Analytical Approaches

The disintegration, porosity, density, presence or absence of structural irregularities and viscoelastic properties are physical-mechanical quality attributes of tablets that help control the performance of the formulation. The majority of the conventional characterization approaches are invasive to the samples and barely manifest spatial mapping. Moreover, these approaches provide off-line / at end of batch monitoring which are least helpful in making judgemental real-time operational corrections. Recent advancements related to software, technology, instrumentation and design have led to an emergence of novel non-invasive analytical approaches which are currently being employed for evaluation of tablets [192].

### 7.1. Process Analytical Technology

Process analytical technology (PAT) refers to “design, analysis and control of manufacturing process via timely evaluation of critical quality attributes of materials, intermediates and processes”. The PAT concept was launched by FDA in 2004 to encourage the pharmaceutical industry to transform from off-line to real-time quality measurements. PAT can be employed during all stages of formulation development (from pre-clinical to commercial manufacturing). This technology can improve the Research & Development (R&D) efficiency and evaluate parameters which are difficult to measure via conventional off-line approaches (e.g., heterogenous systems, high / low temperature systems, highly hazardous materials, transient intermediates and low / high-pressure systems). Other advantages associated with PAT include better process understanding and control, faster process optimization, improved product. As

well as process safety and the ability to rectify any error in a timely manner without removal of final product from the manufacturing lines. PAT data may be raw, mathematically pre-processed, univariate or multivariate [193, 194]. Widely investigated PAT tools include spectroscopy (acoustic emission, x-ray fluorescence, near-infrared, light induced fluorescence, broadband acoustic resonance dissolution, terahertz, Raman), FBRM (focussed beam reflectance measurement), spatial filtering velocimetry, microwave resonance technology, tomography, magnetic resonance imaging, near-infrared chemical imaging, RGBI (red, green and blue colour imaging), photometric stereo imaging, 3D imaging. Various studies have reported the implementation of these PAT tools for in-line, on-line and at-line monitoring of continuous processes (e.g., blending, granulation, compression, coating) (Figure 3) and measurement / analysis of tablet weight, texture, colour, coating, hardness, density, tensile strength and porosity etc. [192, 195, 196] (Table 4).

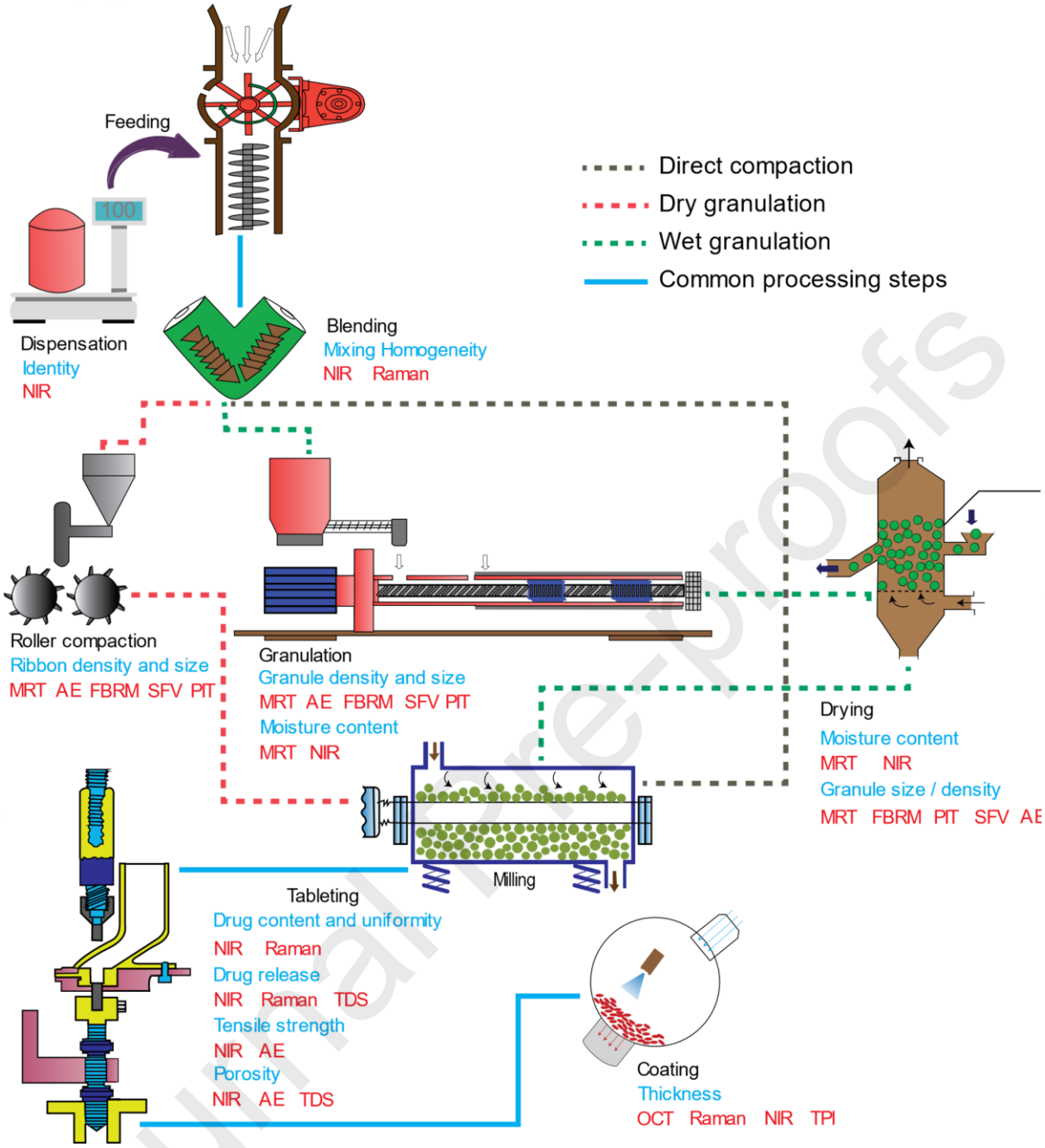



**Figure 3 Application of various PAT tools for monitoring tablet formulation development [139, 195]**

**Table 4 Non-invasive techniques for tablet evaluation**

| PAT tool | Parameters | Monitoring | Practical applications | References |
|---|---|---|---|---|
| Flash sizer | Surface roughness | | | [197] |
| ILSC technique | Structural analysis | | Mefenamic acid | [198] |
| Laser induced fluorescence | Drug content | | Caffeine, Triamterene | [199, 200] |
| | Blend uniformity | On-line | | [201] |

| | | | | |
|---|---|---|---|---|
| Optical coherence tomography | Coating thickness, homogeneity | In-line | Acetylsalicylic acid | [202] |
| X-ray computed tomography | Internal tablet defects, density variations | | | [203, 204] |
| | Matrix erosion and swelling, | | Felodipine | [205] |
| Near infrared (NIR) spectroscopy | Coating | In-line | | [206] |
| | Drug concentrations | In-line | Ibuprofen | [207] |
| | Residence time | In-line | | [208] |
| | Determination of degradation products | | Aspirin | [209] |
| | Blend uniformity | On-line | | [210] |
| | Prediction of tablet hardness and porosity | | Theophylline | [211] |
| Raman spectroscopy | Multi-layered film coating | In-line | Caffeine anhydrous | [212] |
| | Quantification of tablet components with individual nominal concentration | | Paracetamol, caffeine, phenylephrine | [213] |
| | Dehydration process | | Caffeine | [214] |
| | Crushing strength | | Theophylline | [215] |
| Laser induced breakdown spectroscopy | Contents and minor elemental species in a tablet | | Vitamin C, paracetamol, ibuprofen, | [216] |
| Terahertz pulsed imaging | Porosity and drug mass fraction | | Indomethacin | [217] |
| | Crystallinity | | L-tartaric acid | [218] |
| | Analysis of inner structure of tablets incorporated with pellets | | Theophylline | [219] |
| Nuclear magnetic resonance imaging | Screening of enteric coatings properties | | Paracetamol | [220] |
| | Structural changes in tablets during disintegration | | Ibuprofen | [221] |
| | Water transport mechanism | | Cardura XL (doxazocin) | [222] |
| Acoustic emission | Estimation of particle size, flowability and compressibility of high shear granulation process | On-line | | [223] |
| | Monitoring of lubricant addition / blending | In-line | | [224] |
| Contact ultrasonic testing | Young's moduli | | Ibuprofen | [225] |
| | Tablet core and coat thickness, young's moduli, mass densities | | | [226] |

| | | | | |
|---|---|---|---|---|
| Photo-acoustic testing | Coating layer irregularities, internal cracks, delamination | | | [227] |
| Acoustic resonance spectroscopy | Identify and differentiate tablets of similar size and shape | | Aspirin, acetaminophen, ibuprofen, vitamin C, vitamin B12 | [228] |

## 7.2. Flash Sizer

Surface roughness can serve as a valuable parameter to predict the tensile strength of tablets. Halenius *et al*. used a novel 3D imaging method, flash sizer, for estimating tablet surface roughness and compared the results with the conventionally employed laser profilometer. Tablets were placed on a measuring table under a microscope, then illuminated from four different directions (one after another) by using LED (light emitting diode) light sources and photographed. 3D surface of samples was recorded from the images and the roughness value for the tablet surface was calculated. Results showed that the flash sizer method was roughly thousand times quicker in estimating surface roughness as compared with the laser profilometer, hence, this can serve as a promising in-line PAT tool to predict mechanical attributes of tablets in development [197].

## 7.3. Intelligent Laser Speckle Classification Technique

Orun and Smith proposed a low-cost system "intelligent laser speckle classification technique", based on optical and artificial intelligence methods for the structural analysis of mefenamic acid tablet surface layers. The functionality of the developed technique was based on texture analysis of laser (visible, infrared laser sources) speckle images followed by the optimization of texture attributes by using Bayesian networks. The developed system was used to detect micro-sized surface defects produced following the tablet sticking. This system was also adopted for studying subsurface granule micro-structures [198].

## 7.4. Tomography

Two tomography approaches, including optical coherence tomography (OCT) and x-ray microtomography / x-ray microcomputed tomography, are being used for the evaluation of tablets. OCT permits analysis of coating attributes i.e. thickness or homogeneity of the outer layer irrespective of the changes in the tablet core [202]. Three types of OCT techniques, including swept source, spectral domain and time domain full field OCT, have been employed for imaging tablet coatings [229]. Koller *et al*. employed OCT during an industrial spray coating process and performed in-line measurement thickness and homogeneity of the tablet

coatings [202]. However, window fouling during in-process control, proper positioning of sensor and decreased penetration depth due to strong scattering of some coating formulations, are some of the challenges associated with this approach [229].

In x-ray microtomography, 2D (two-dimensional) images are obtained which can be coupled with suitable algorithms to generate a 3D map of the sample. X-ray microtomography has been employed to examine the microstructure of orally disintegrating tablets, detect internal / external defects, or the presence of foreign matter in tablets [192, 203]. This technique was used to analyze the changes in tablet density by producing a density map. The standard technique was modified by using collimators and applying mathematical algorithms to the standard curve to lessen scatter and beam hardening issues [204]. In a study, the feasibility of x-ray microfocus computed tomography was investigated, to estimate the compact homogeneity of binary mixtures of formulation constituents (i.e. excipients) in order to predict the tablet mechanical attributes (i.e. Young's modulus, hardness and tensile strength) [230]. This computed tomography approach can also be employed to characterize the surface and core of a tablet formulation (Figure 4A) [231]. X-ray microtomography exhibits high penetration power and satisfactory image resolution (i.e., 5-20 mm). Advancements in detectors permit faster data acquisition with higher intensity and strong alignment. However, a calibration curve is required to correlate the experimental data. Other limitations of this approach include ring artefact and / or beam hardening. Furthermore, accurate evaluation of multi-component systems is challenging due to the dependency of sample attenuation on material density as well as the atomic number of constituents [192].

## 7.5. Laser Induced breakdown Spectroscopy

Laser induced breakdown (LIB) spectroscopy is used for the monitoring of tablet coating and the distribution of active ingredient within the tablets. The technique is also valuable in recording the transfer of nicardipine in the formulation (toward the surface) over the course of storage (Yokoyama *et al.*) [232]. Madamba *et al*. studied photodegradation within coated tablets [233]. Zou *et al*. used LIB for locating as well as identifying the elemental impurities in the tablet coatings (Figure 4B) [234]. Advantages of LIB spectroscopy as an analytical tool include non-invasive measurement of the core content, feasibility for standoff detection and on-site plus remote analysis. Drawbacks of this approach include complexity, high installation costs and the need for skilled expertise. Moreover, elevated sample temperatures and the enhanced mass of ablated elements results in background noise. However, the use of laser shots prior to characterization can overcome this problem [192].

## 7.6. Nuclear Magnetic Resonance Spectroscopy

Application of nuclear magnetic resonance (NMR) imaging as a PAT is scarce. However, studies report the utility of NMR imaging for determination the drug content, relative density distribution in a tablet (Figure 4C) [235] and evaluation of enteric coatings. Moreover, it has been employed to study the distribution of elements on or around the tablet matrix, and the microstructure of tablets during release of active ingredient in order to gain better understanding of release mechanisms [192]. Broadbent *et al*. studied water transport mechanisms (hydration) in Cardura XL, a commercial gastrointestinal therapeutic system tablet by employing NMR imaging [222]. Zhang *et al*. used $^{1}H$ and $^{19}F$ NMR imaging to study the dissolution process of commercially available Lescol XL tablets. This study provided an insight about dissolution media uptake, drug dissolution, matrix swelling and media activity within the swelling matrix [236]. Advantages of NMR imaging include analytical efficiency, sensitivity to structural, physical or chemical characteristics of the sample. Moreover, NMR analysis does not require chemical additives, provides significant details about the internal features of the sample and multiple measurements from a single sample. However, this technique is costly and requires trained personnel for operation and data analysis [192].

## 7.7. Terahertz Pulsed Imaging

The wavelength region between infrared and millimetres, (from 300 gigahertz to 10 terahertz) on the electromagnetic spectrum depicts terahertz region [237]. Terahertz pulsed imaging utilizes non-ionizing radiations to record the refractive index and physicochemical features of the tablet mass without inducing thermal stress within the sample. Terahertz pulsed imaging has been employed to evaluate crystallinity, polymorphism, density distribution, hardness, porosity, drug content and microstructure of tablets [192, 218, 238, 239]. Moreover, terahertz pulsed imaging has been used to measure tablet coating thickness (Figure 4D) [240]. In a study, terahertz time-domain spectroscopy was used to study optical attributes as a function of varying porosity and drug content of indomethacin tablets [217]. This analytical technique can detect cracks between layers that result in layer separation. Niwa *et al*. studied the internal structure of a tablet and identified the zones of potential layer separation in bilayer tablets [241].

Although the technique is non-invasive, its efficiency in the presence of moisture is compromised. Moreover, analysis of large-sized samples requires manual imaging set-up and data analysis which is time consuming and requires optimal technical skill [192].

## 7.8. Raman Spectroscopy

Raman spectroscopy has been used for monitoring pharmaceutical unit operations including blending, granulation, drying, compression and coating. Furthermore, different features of compressed tablets including drug content, density, moisture content, crushing strength and spatial distribution of constituents are also studied by this technique (Figure 4E) in a non-invasive manner [192, 242]. Wabuyele *et al*. used dispersive Raman spectroscopy for quantifying the amorphous fractions of MK-A (compound under development) in the tablets [243]. Radtke *et al*. used Raman spectroscopy as an in-line PAT tool for predicting and monitoring the coating mass of three distinct coating layers on a caffeine core [212]. Advantages of Raman spectroscopy include small sample size, easy operation (minimal training needed), good reproducibility of results and ability to analyze samples within their packaging material. However, this approach presents some challenges such as underestimated measurements due to shallow laser penetration (in the case of backscattered Raman spectroscopy), an interference in the spectrum due to intrinsic or impurity-associated florescence (can be circumvented by shifting the wavelength to the NIR region) and thermal decomposition of the sample at higher excitation intensities. In addition, this analytical technique can be cost prohibitive for routine analysis [192, 214].

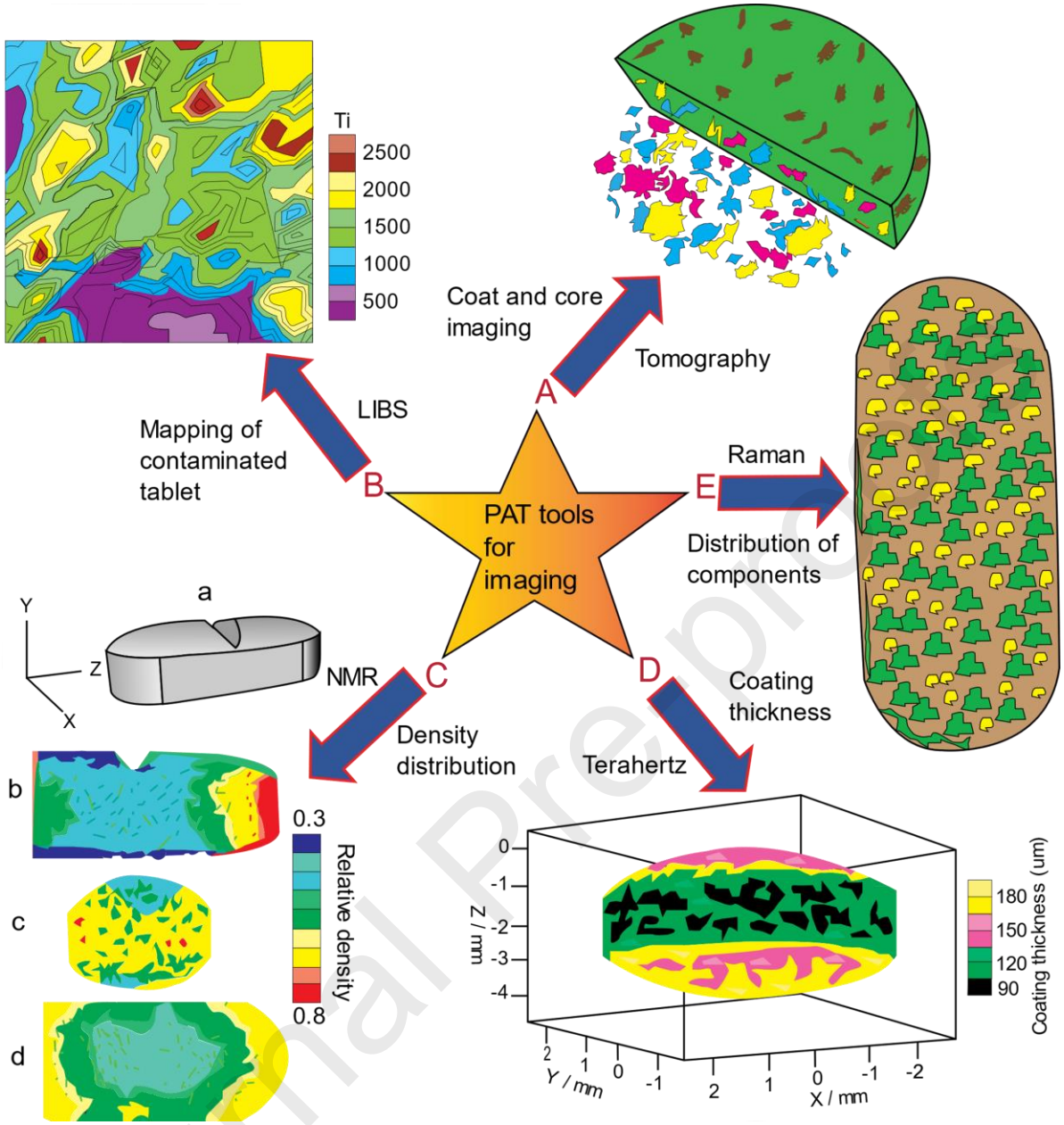



**Figure 4 (A) visualization of tablet core and coat with the help of computed tomography [231] (B) 2D chemical mapping of contaminated tablet coatings displaying spatial distribution of Ti (titanium) using light induced breakdown spectroscopy (LIBS) [234] (C) 3D mapping of relative density distribution (in Y-Z (b), X-Y (c) and X-Z (d) cross sections) within a tablet using NMR imaging [235] (D) analysis of tablet coating thickness by using terahertz pulsed imaging [240] (E) colour-coded Raman images of a tablet showing the spatial distribution of formulation components at different scales [192, 242]**

## 7.9. Near Infrared spectroscopy

The wavelength region from 780 to 2526 nm of the electromagnetic spectrum represents the near infrared region. The intensity of spectral peaks depicting the interactions between functional groups of the chemicals and NIR radiation, are used to track various pharmaceutical processes. Being a non-invasive measurement tool, NIR spectroscopy is used to measure the moisture content and 3D mapping of the formulation ingredients. Furthermore, numerous

studies have investigated the potential use of NIR spectroscopy for the analysis of dissolution rate, coating, density, tensile strength, hardness, porosity, particle size, compaction force and detection of counterfeit tablets and degradation products in intact tablets [192, 244]. Dalvi *et al*. reported the suitability of NIR spectroscopy to monitor the concentration of ibuprofen both inside the feed frame of tablet press and in compressed tablets [207]. Avila *et al*. used MEMS-based NIR sensor to monitor the moisture content during drying of granules in a fluidized bed dryer (Figure 5A) [245]. The advantages of NIR spectroscopy over traditional characterization approaches include flexibility between in-line, at-line and off-line uses, faster speed of data analysis, portability and use and opportunity to analyze packaged samples through the packing material. Moreover, most of the NIR instruments are robust and can be operated with minimal training / supervision. However, several challenges are also associated with this technique including a high signal-to-noise ratio, complicated post-scanning data processing or interpretation (which requires chemometric techniques to extract necessary information from the NIR spectra exhibiting broad, overlapping and fused peaks) and low sensitivity [192].

## 7.10. Light Induced Florescence

As per reports, ~60 % of therapeutic moieties undergo fluorescence in light. This feature enables the analysis of the active ingredient in a tablet. This approach can be employed reliably for detecting and mapping active ingredient(s) in a tablet formulation [192]. In a study, total drug concentration was successfully estimated in two sets of tablets (containing different active ingredients) by using this approach [199]. More recently, Lai *et al*. demonstrated the development of 3D-printed tablets containing a layer of triamterene and highlighted the utility of the light induced florescence technique for qualitative online analysis of drug content that could be applied during the tablet fabrication process (Figure 5B) [200]. The light induced florescence approach permits analysis of florescent drugs with high sensitivity, faster rate, high accuracy and comparatively low cost. Contrary to UV and NIR spectroscopy, increasing the intensity of incident radiations in the light induced florescence approach enhances the florescence intensity, which leads to better detection. Limitations associated with this approach include self-quenching, non-linear detector response due to saturation of the detector (in the case of high fluorophore concentration) and sensitivity to temperature and pH fluctuations which are capable of influencing the florescence intensity [192].

## 7.11. Acoustic techniques

Materials permit the propagation of sound waves as a function of their compressibility. This variation in velocity of sound propagation is used to characterize and monitor unit operations

of tablet manufacturing. Various acoustic techniques such as acoustic emission (AE), contact ultrasonic (CU) testing, photo-acoustic (PA) testing and acoustic resonance (AR) spectroscopy have been used for evaluation of tablets.

This analytical technique has been used to measure / analyze density, coating thickness, particle size, mechanical defects (variations in the breaking force due to core and coat irregularities) and structural defects (e.g., capping, cracking and lamination etc.) of tablets.

Another type of acoustic technique i.e., broadband acoustic resonance dissolution spectroscopy (BARDS) has been reported for tracking the dissolution process of a coated pantoprazole tablet formulation. Briefly, the BARD spectrometer comprised a chamber housing a dissolution vessel, a stir bar, a magnetic stirrer and a microphone (Figure 5C). The acoustic resonances were recorded by microphone and transformed into a spectrum using a computer system equipped with a sound card, and a generic software. A typical BARDS dissolution profile, shows an initial decrease in the fundamental acoustic frequency curve due to the release of entrained gas in the outer polymeric coating. A subsequent depressed frequency plateau (lag time) indicates erosion of the coating polymer. During this lag time, drug release was not observed by concurrent UV-Vis profile. Subsequently, a downward slope of the BARDS spectrum develops that describes the disintegration of the tablet core; the frequency minimum of BARD spectrum corresponds with the completion of disintegration of the tablet core. The frequency minimum of BARD spectrum was ascribed with ~50 % drug release as correlated with the UV-Vis data. The de-aggregation of the formulation constituents for releasing the remaining drug was indicated by the return of the frequency profile to steady-state in the BARDS spectrum [246].

Acoustic techniques are advantageous owing to their cost-effectiveness, simplicity, utility (of acoustic emission technique) in harsh processing conditions i.e., high temperatures, pressures or presence of corrosive materials / media. Challenges of employing acoustic techniques include low efficiency i.e. <0.1 % in generating ultrasound waves, slow speed (in case of acoustic resonance spectroscopy), noise-related errors, the need for multivariate modelling to accurately analyze the outcomes and the chances of false negative observations (in the case of the acoustic emission approach) [192].

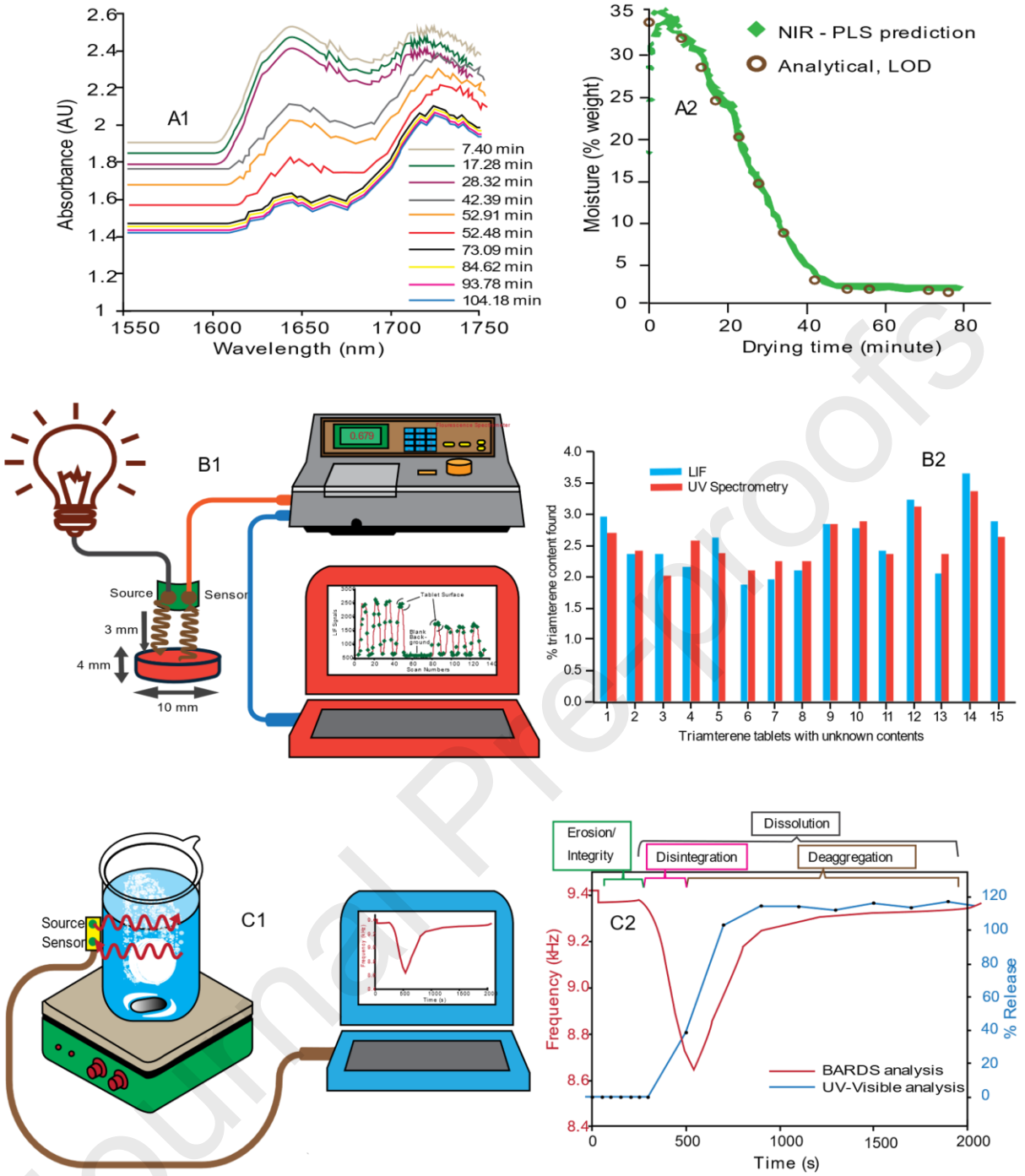



**Figure 5 (A) represents the utility of a near infrared (NIR) sensor for monitoring the moisture content during drying of granules in a fluidized bed dryer. Spectral measurements (A1) were transformed into moisture content values using PLS regression model (A2). The results were comparable with loss on drying data measured using thermogravimetric moisture analyzer [245]. (B) demonstrates the application of light induced fluorescence (LIF) spectroscopy for on-line determination of total drug content in layered triamterene tablets of different depths (B1). Triamterene layer level of each tablet differed from the other by an increment of ~400 um (depth-wise). Unknown triamterene concentration measurements were within the range (1.65 % - 4.75 %) when estimated by LIF approach and the results showed a good correlation with UV spectrometry data ($R^2$ = 0.995) (B2) [200]. (C) represents the utility of broadband acoustic resonance dissolution spectroscopy (BARDS) for tracking dissolution process of pantoprazole tablet formulation (C1). The results of BARDS analysis were supported by percentage drug release profile obtained by UV-Vis analysis (C2) [246]**

## 7.12. UV-Visible spectroscopy coupled dissolution testing

During recent years, a fiber-optic probes-based UV-visible spectrophotometry has been reported for in-situ dissolution of tablet formulations (Cho *et al*.) [247]. In this system, a deuterium lamp coupled fiber-bundle was split into seven fibers which served as independent sources for each dissolution vessel, and permitted simultaneous evaluation of seven dissolution vessels. The detection section comprised fibers connecting the sample and detector / imaging spectrograph. The dispersed light from each fiber-optic probe is imaged on the liquid nitrogen cooled charge-coupled device (CCD) and the signals are processed using Matlab programs to produce absorption spectra (Figure 6A). Development of wavelength calibration algorithms ensured reproducibility of spectra recorded on all probes. The study ensured reproducibility (day-to-day, probe-to-probe), no interference from excipients and linearity of developed method. This technique is efficient as it saves time and operate at a rapid rate with low noise [247].

Another advancement, UV imaging assisted micro-dissolution technique, comprising a low volume capacity flow cell and a UV-visible camera. The cell comprises a polyetheretherketone (PEEK) sample holder (containing the sample, usually, as a compressed formulation) located inside a quartz tube (containing the dissolution medium). The dissolution medium is pumped into the cell via a temperature-controlled chamber using a syringe pump.

A broad-spectrum flash lamp provides the light with the wavelength of interest which, via a fiber-optic cable, passes through the cell onto the complementary metal oxide semiconductor (CMOS) camera chip (Figure 6B). The recorded images can then be processed to obtain absorbance values. This approach is advantageous as it permits dissolution testing with relatively low amounts of formulation and volume of dissolution medium. However, interpretation of absorbance maps involving the dissolution of complex formulations is potentially erratic, as light absorbance is recorded at one wavelength during an experiment. It is difficult to differentiate physical light blockage, absorbance and light scattering by using one wavelength. Moreover, the low pixel size of UV camera results in reduced spatial resolution. A UV imaging system is now commercially available as Actipix SDI (surface dissolution imager) 300 [248, 249].

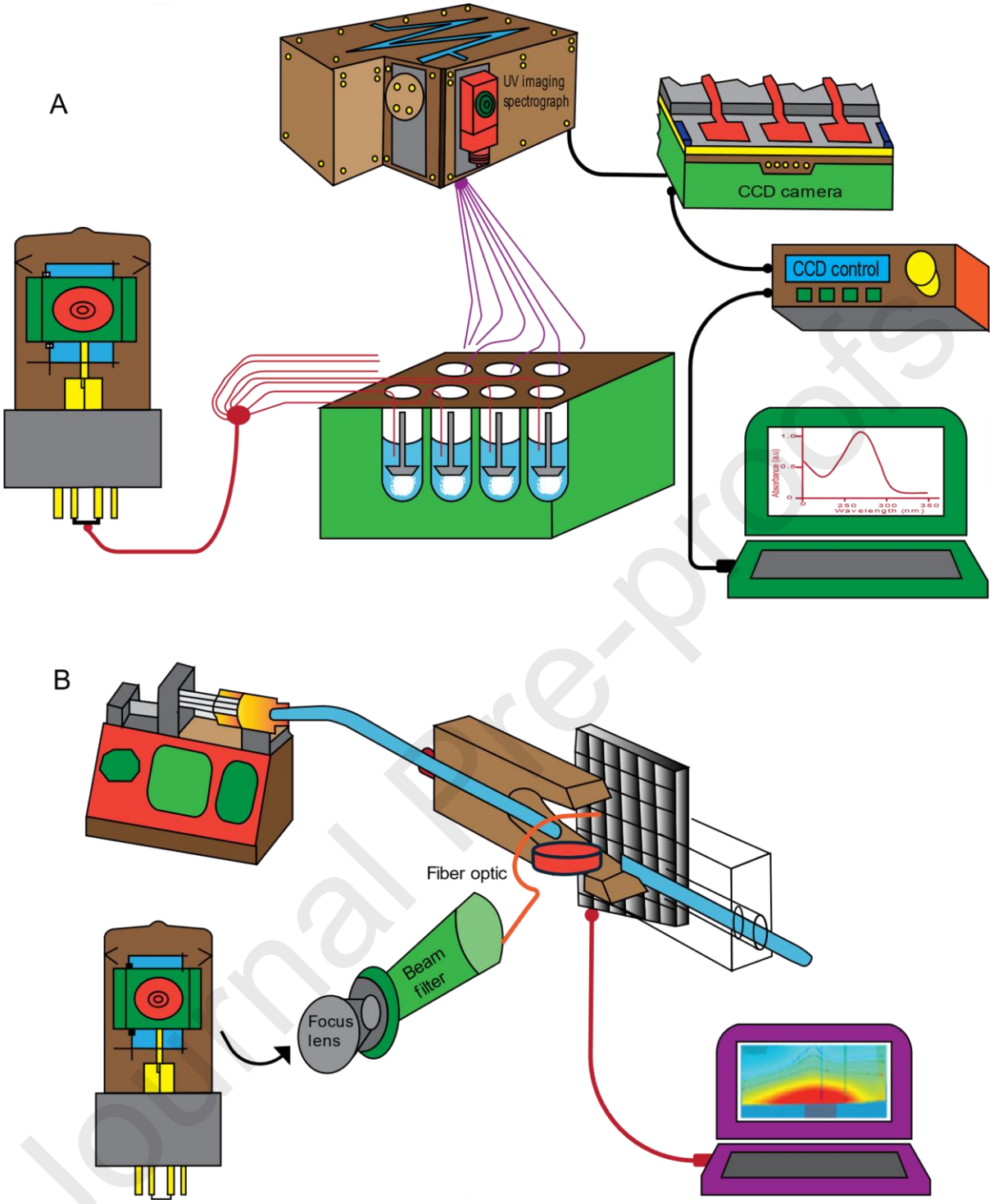



**Figure 6 (A) fiber-optic probes-based UV-visible spectrophotometry method [247] and (B) UV imaging spectrograph for dissolution testing of tablet formulations [248, 249]**

## 7.13. *In-vivo* tracking approaches

During the recent years, various non-invasive imaging techniques (e.g., x-ray, scintigraphy, magnetic moment imaging, magnetic resonance imaging, ultrasonography) have been studied for tracking or visualization of tablets *in-vivo*.

### 7.13.1. X-ray imaging

X-ray imaging has been extensively used for *in-vivo* performance of tablets. This approach was used to analyze barium sulphate incorporated tablets in a rabbit stomach [250]. In another study, the floating behaviour of losartan potassium floating matrix tablets was visualized in a rabbit stomach using x-ray imaging [251]. Intragastric location of the tablets can be confirmed with x-rays. For analysing whole GI transit, various x-rays images have to be recorded over an extended period of time. The use of this imaging technique has decreased due to significantly high radiation dose and lack of anatomical reference as to where the dosage form is in the GI tract [252].

### 7.13.2. Scintigraphy

Scintigraphy offers an efficient *in-vivo* tracking of tablet dosage forms due to its sufficient temporal and spatial resolution. In scintigraphy, a radionuclide is added to a formulation and used as a probe for in-vivo tracking of drug [253]. Theodorakis *et al*. employed Technetium 99m to acquire high resolution images of disintegrating tablets [254]. Razavi and colleagues recorded transit of samarium (III) oxide labelled floating gastroretentive metformin hydrochloride tablets in the GI tract of rabbits using gamma scintigraphy [255]. However, this approach is less commonly employed due to regulatory issues regarding risk of radiation exposure to healthy subjects [252].

### 7.13.3. Magnetic marker monitoring

Magnetic marker monitoring is considered as a promising alternative of scintigraphy and x-ray imaging for tracking gastrointestinal transit and disintegration of a tablet, *in-vivo*, without applying radiation. In this technique, a tablet is co-formulated with a permanent magnetic dipole (by adding small amounts of suitable ferromagnetic material e.g., iron oxide and manganese ferrite) and magnetized. The spatial changes in magnetic strength as a function of time are used to identify 3D localization and orientation of the dosage from [256]. Goodman *et al*. investigated the feasibility of this technique for tracking disintegration and gastrointestinal transit of technetium-99m-diethylenetriaminepentaacetic acid labelled three different tablet formulations (i.e. immediate release, enteric-coated and non-disintegrating) [257]. This approach can be limited as it requires an adequate magnetic dipole moment and detects only one signal at a time [252].

### 7.13.4. Magnetic resonance imaging

Magnetic resonance imaging (MRI) involves labelling of a formulation for an accurate monitoring of a dosage form within the GI tract. A sampling rate of ~0.5 $min^{-1}$ is considered

sufficient for analyzing dosage form transit [252]. Steingoetter *et al*. labelled a tablet formulation using iron oxide particles as a negative MRI contrast marker for monitoring gastro-retentive tablet position in human stomach in the fed state. The impact of body posture on floating / emptying behaviour was recorded in an efficient manner [258]. Curley and co-workers employed the MRI technique to visualize *in-vivo* disintegration of three different paracetamol tablet dosage forms [259]. Advantages of this approach include high temporal and spatial resolution, lack of ionizing radiations, decreased risk of radiation exposure to subjects and high soft tissue contrast. Furthermore, any harmless paramagnetic / superparamagnetic MRI contrast agents can be included to increase or decrease the signals of fluids / tissues of interest. Thus, allowing improved delineation and study of organs [260]. However, higher installation costs and specialised scientific expertise are major restrictions to this technology.

### 7.13.5. Ultrasonography

Ultrasonography exhibits high temporal resolution; however, its spatial resolution is relatively low. Novel ultrasonographic devices are portable and convenient to use. However, a major limitation of this technique includes hampered signal acquisition due to the presence of gases in the digestive tract [252]. In a study reported by Maublant *et al*., a tablet was detected in the stomach (for ~1.5 hours) by using an echograph equipped with a 3.5 MHz transducer but the signal disappeared when the tablet passed into the intestine [261]. Hence, this technique is only suitable for non-disintegrating or slow release dosage forms [252].

### 7.13.6. Capsule endoscopy

Capsule endoscopy involves oral administration of a non-invasive capsule supplied with two cameras at both ends which can provide video recording. Blaabjerg *et al*. employed this technique for visualizing the disintegration / dissolution behaviour of acetaminophen tablets in beagle dogs [262]. Despite of its ease of administration and integrity of sensor in the body, this technique encounters limited wireless communication and lacks an efficient control of the sensor [263].

### 7.13.7. Digital pill

The digital pill comprises a capsule containing medicament with an edible sensor, an adhesive wearable detector patch, a patient mobile phone application and a provider web portal. Following ingestion, the sensor activates in the acidic environment of the stomach and emits a radiofrequency signal detectable by the wearable patch. Ingestion and other physiological parameters (e.g. heart-beat, daily steps) data is recorded and transmitted by the patch to the patient's mobile phone application and provider's web portal [264]. This technology promises

better disease management, continuous monitoring, self-tracking and improved treatment adherence [265]. Moreover, there is minimal chance of missing a dose because medication dose reminders are sent to the patient's phone as push notifications [266]. Some limitations of this technology include ethical challenges for patients and providers, affordability, and risk of adverse events in the case of system malfunction [265]. A digital pill system for the management of schizophrenia (FDA approved) [267, 268], tuberculosis [269], acute fracture pain [270], hypertension and type 2 diabetes mellitus [271] is already reported in literature.

## 8. Discussion

According to a report regarding novel drug approvals, published by FDA's Centre for Drug Evaluation and Research, in 2018, tablet dosage forms were the first choice, in ~39 % cases, when developing medicines from drugs, due to the convenience and ease of use [272]. Despite various advancements (in terms of novel excipients, equipment manufacturing methods, tableting technologies and analysis approaches), pharmaceutical manufacturers are facing a variety of challenges associated with manufacturing efficiency and cost containment. Continuous manufacturing, QbD and PAT are some major advancements to counter these challenges.

The QbD concept is advantageous at it improves productivity and minimizes the manufacturing costs. PAT is considered an enabling technology for QbD. The implementation of PAT tools promises higher yields, less material wastage, more efficient use of equipment and a shorter time-to-market. Moreover, these PAT tools are capable of transforming a batch process into a continuous one by providing real time quality data [273]. The implementation of PAT tools is still a challenge to the pharmaceutical industry. These challenges include installation of reliable PAT, construction of calibration curves, data acquisition rates, data analysis routines and deriving inferences and comparison with the conventional analytical technologies. Furthermore, robustness of the PATs, compliance with good manufacturing regulatory guidelines and adaptation of process analysis methodologies in the manufacturing cycles are additional operational blockers to implementation [274].

Using multiple PATs for monitoring / analyzing a process or product is an attractive approach to achieve reliable data. The utility of fusion of PAT tools e.g. NIR-Raman spectroscopy and red, green and blue colour imaging-NIR-light induced fluorescence spectroscopy for measuring the content / composition of specified constituents in polymeric / powder blends [201, 275] is an example.

In addition to the application of monitoring techniques, improvements in the design of tableting machines have been proposed in order to enhance the efficiency as well as the productivity. Insertion of a screw / vibratory rod into the feeder agitates the materials. The use of hoppers with an optimal wall angle (rear wall angle 60° ± 2°, front wall angle 55° ± 2° [276]) prevents material bridging resulting in starvation (i.e., no material) or overfilling (resulting into lack of freely flowing powder and weight variation) of powders. Optimal configuration of the feeder paddle can improve the filling of die bore and tablet weight uniformity. Implementation of a feeder paddle at a 45-degree angle on the leading edge of paddle blade reduced standard tablet weight deviations by ~75 % [277]. The design of fill cams can affect cleaning of compression machines and tablet weight variability.

Exchangeable turrets offer flexibility in terms of tooling types that may be used on the same press and reduces the time required for cleaning of a tableting press and product changeover. However, after removing the turret, the complex interior of the machine still requires cleaning. For this purpose, press manufacturers have introduced tablet presses with improved structures in terms of openness and accessibility. Complete exchangeable compression modules have been introduced which permits rapid product changeover and a significantly higher level of dust containment, as compared to the conventional machines [278].

Recent improvements in tablet press designs focussed on enhancing the output of machines. A design of a tablet press comprising five segments and ten segment blocks claims a ~70 % reduction in turret setup time. This relatively simple and efficient technique offers several benefits, such as up to 40% higher output, minimal product loss, easy refitting / resetting / cleaning, less chances of human error and easier compliance with hygienic requirements [279]. An exchangeable die disc approach also promises higher output [278].

External lubrication reduces wear on tooling and ejection cams. Tablet machine feeders for accurate dispensing of powdered lubricants on the punches and die wall surfaces have been engineered [280].

In addition to improvements in the tableting press design, operational adjustments including rotation speed of feeder and turret, settings of upper punch penetration and compression force are applied to solve common problems encountered during tableting e.g., tool damage, inadequate tablet strength / hardness, irregular powder flow through the feeding system and improper die bore filling [277].

Human-machine-interface-controlled operating systems have been installed in modern tableting machines. These systems are capable of adjusting tablet weight by statistical process control based on compression pressure / forces. However, the reliability of such systems may be compromised due to worn parts, software issues or inaccurate calibration.

The implementation of novel control strategies and modern sensors into the tableting machines can help achieve advanced process control.

## 9. Conclusion

The formulations and processes relating to tablets, the most commonly prescribed dosage form, have been consistently improved to broaden the application of this dosage form in order to benefit the population with controlled release, taste masking and site-specific drug release. Advancements in different unit operations such as powder flow, drying, granulation, compression as well as machine features have been reported to improve the manufacturing efficiency. The application of quality by design and process analytical routines has revolutionized the manufacture of this conventional yet, challenging dosage form.

## References

[1] A. Siew, Key considerations in excipients selection for solid dosage forms, PharmTech, (2015) https://www.pharmtech.com/view/key-considerations-excipients-selection-solid-dosage-forms (accessed 22 November 2020).
[2] J. Quodbach, P. Kleinebudde, A critical review on tablet disintegration, Pharm. Dev. Technol. 21 (2016) 763-774.
[3] D. Markl, J.A. Zeitler, A review of disintegration mechanisms and measurement techniques, Pharm. Res. 34 (2017) 890-917.
[4] W. Lowenthal, Disintegration of tablets, J. Pharm. Sci. 61 (1972) 1695-1711.
[5] H. Van Kamp, G. Bolhuis, C. Lerk, Improvement by super disintegrants of the properties of tablets containing lactose, prepared by wet granulation, Pharm. Weekbl. 5 (1983) 165-171.
[6] V. Suryadevara, S.R. Lankapalli, L.H. Danda, V. Pendyala, V. Katta, Studies on jackfruit seed starch as a novel natural superdisintegrant for the design and evaluation of irbesartan fast dissolving tablets, Integr. Med. Res. 6 (2017) 280-291.
[7] A.C. Lardée, Tablet comprising crospovidone, Google Patents, (2018) https://patents.google.com/patent/US20160193153A1/en (accessed 24 January 2021).
[8] J. Rojas, S. Guisao, V. Ruge, Functional assessment of four types of disintegrants and their effect on the spironolactone release properties, AAPS PharmSciTech 13 (2012) 1054-1062.
[9] M. Mushtaq, N. Fazal, A. Niaz, Formulation and evaluation of fast-disintegrating tablets of flurbiprofen and metoclopramide, J. Pharm. Innov. (2020) 1-20.
[10] J. Van der Merwe, J. Steenekamp, D. Steyn, J. Hamman, The role of functional excipients in solid oral dosage forms to overcome poor drug dissolution and bioavailability, Pharmaceutics 12 (2020) 1-17.
[11] P.H.-L. Tran, T.T.-D. Tran, K.-H. Lee, D.-J. Kim, B.-J. Lee, Dissolution-modulating mechanism of pH modifiers in solid dispersion containing weakly acidic or basic drugs with poor water solubility, Expert Opin. Drug Deliv. 7 (2010) 647-661.

[12] S.I.F. Badawy, M.A. Hussain, Microenvironmental pH modulation in solid dosage forms, J. Pharm. Sci. 96 (2007) 948-959.
[13] W.-H. Kang, H. Van Nguyen, C. Park, Y.-W. Choi, B.-J. Lee, Modulation of microenvironmental pH for dual release and reduced in vivo gastrointestinal bleeding of aceclofenac using hydroxypropyl methylcellulose-based bilayered matrix tablet, Eur. J. Pharm. Sci. 102 (2017) 85-93.
[14] P.H.L. Tran, H.T.T. Tran, B.-J. Lee, Modulation of microenvironmental pH and crystallinity of ionizable telmisartan using alkalizers in solid dispersions for controlled release, J. Control. Release 129 (2008) 59-65.
[15] K. Sako, T. Sawada, H. Nakashima, S. Yokohama, T. Sonobe, Influence of water soluble fillers in hydroxypropylmethylcellulose matrices on in vitro and in vivo drug release, J. Control. Release 81 (2002) 165-172.
[16] Encompress JRS Pharma, https://www.jrspharma.com/pharma_en/products-services/excipients/fillers/emcompress.php (accessed 22 November 2020).
[17] Å. Adolfsson, C. Caramella, C. Nyström, The effect of milling and addition of dry binder on the interparticulate bonding mechanisms in sodium chloride tablets, Int. J. Pharm. 160 (1998) 187-195.
[18] Tablet binders, LFA Tablet Presses, https://www.lfatabletpresses.com/articles/tablet-binders (accessed 22 November 2020).
[19] A. Komersová, V. Lochař, K. Myslíková, J. Mužíková, M. Bartoš, Formulation and dissolution kinetics study of hydrophilic matrix tablets with tramadol hydrochloride and different co-processed dry binders, Eur. J. Pharm. Sci. 95 (2016) 36-45.
[20] A. Moroni, A novel copovidone binder for dry granulation and direct-compression tableting, Pharm. Technol. 25 (2001) 8-13.
[21] J. Mužíková, Š. Hávová, P. Ondrejček, A. Komersová, V. Lochař, A study of tablets with a co-processed dry binder containing hypromellose and α-lactose monohydrate, J. Drug Deliv. Sci. Technol. 24 (2014) 100-104.
[22] J. Mužíková, A. Srbová, P. Svačinová, A study of a novel coprocessed dry binder composed of α-lactose monohydrate, microcrystalline cellulose and corn starch, Pharm. Dev. Technol. 22 (2017) 964-971.
[23] J. Wang, H. Wen, D. Desai, Lubrication in tablet formulations, Eur. J. Pharm. Biopharm. 75 (2010) 1-15.
[24] J. Li, Y. Wu, Lubricants in pharmaceutical solid dosage forms, Lubricants 2 (2014) 21-43.
[25] G. Zayed, M.A. Ibrahim, D.H. Alshora, O.H. El-Garhy, I. Kamal, M.A. Amin, A.G. Bakr, F.E. Ali, Novel water-soluble lubricant for the preparation of tiemonium methylsulfate fast-dissolving tablets, J. Drug Deliv. Sci. Technol. 60 (2020) 102031.
[26] T. Uğurlu, M. Turkoğlu, Hexagonal boron nitride as a tablet lubricant and a comparison with conventional lubricants, Int. J. Pharm. 353 (2008) 45-51.
[27] Tablets containing irbesartan, Google Patents, https://patents.google.com/patent/JP5686452B2/en (accessed 24 January 2021).
[28] C. Wang, H. Huang, M. Jia, S. Jin, W. Zhao, R. Cha, Formulation and evaluation of nanocrystalline cellulose as a potential disintegrant, Carbohydr. Polym. 130 (2015) 275-279.
[29] P.M. Desai, P.X.H. Er, C.V. Liew, P.W.S. Heng, Functionality of disintegrants and their mixtures in enabling fast disintegration of tablets by a quality by design approach, AAPS PharmSciTech 15 (2014) 1093-1104.
[30] T. Grattan, R. Hickman, A. Darby-Dowman, M. Hayward, M. Boyce, S. Warrington, A five way crossover human volunteer study to compare the pharmacokinetics of paracetamol following oral administration of two commercially available paracetamol tablets and three development tablets containing paracetamol in combination with sodium bicarbonate or calcium carbonate, Eur. J. Pharm. Biopharm. 49 (2000) 225-229.
[31] K. Dvořáčková, P. Doležel, E. Mašková, J. Muselík, M. Kejdušová, D. Vetchý, The effect of acid pH modifiers on the release characteristics of weakly basic drug from hydrophlilic–lipophilic matrices, AAPS PharmSciTech 14 (2013) 1341-1348.

[32] Y.-E. Zhang, J.B. Schwartz, Effect of diluents on tablet integrity and controlled drug release, Drug Dev. Ind. Pharm. 26 (2000) 761-765.
[33] A. Hussain, F. Qureshi, N. Abbas, M.S. Arshad, E. Ali, An evaluation of the binding strength of okra gum and the drug release characteristics of tablets prepared from it, Pharmaceutics 9 (2017) 1-8.
[34] B. Rotthäuser, G. Kraus, P.C. Schmidt, Optimization of an effervescent tablet formulation containing spray dried L-leucine and polyethylene glycol 6000 as lubricants using a central composite design, Eur. J. Pharm. Biopharm. 46 (1998) 85-94.
[35] J. Dun, F. Osei-Yeboah, P. Boulas, Y. Lin, C.C. Sun, A systematic evaluation of dual functionality of sodium lauryl sulfate as a tablet lubricant and wetting enhancer, Int. J. Pharm. 552 (2018) 139-147.
[36] X. Zheng, F. Wu, Y. Hong, L. Shen, X. Lin, Y. Feng, Developments in taste-masking techniques for traditional chinese medicines, Pharmaceutics 10 (2018) 1-22.
[37] J.P. Ley, Masking bitter taste by molecules, Chemosens. Percept. 1 (2008) 58-77.
[38] H. Sohi, Y. Sultana, R.K. Khar, Taste masking technologies in oral pharmaceuticals: Recent developments and approaches, Drug Dev. Ind. Pharm. 30 (2004) 429-448.
[39] P. Khadka, J. Ro, H. Kim, I. Kim, J.T. Kim, H. Kim, J.M. Cho, G. Yun, J. Lee, Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability, Asian J. Pharm. Sci. 9 (2014) 304-316.
[40] K.T. Savjani, A.K. Gajjar, J.K. Savjani, Drug solubility: Importance and enhancement techniques, ISRN Pharm. 2012 (2012) 1-10.
[41] E. Cho, S. Jung, Supramolecular complexation of carbohydrates for the bioavailability enhancement of poorly soluble drugs, Molecules 20 (2015) 19620-19646.
[42] M. Basha, A. Salama, S.H. Noshi, Soluplus® based solid dispersion as fast disintegrating tablets: A combined experimental approach for enhancing the dissolution and antiulcer efficacy of famotidine, Drug Dev. Ind. Pharm. 46 (2020) 253-263.
[43] H. Havel, Aqueous solubility-enhancing excipient technologies: A review of recent developments, European Pharmaceutical Review, (2018) https://www.europeanpharmaceuticalreview.com/article/70540/aqueous-solubility-enhancing-excipient-technologies-review-recent-developments/ (accessed 23 November 2020).
[44] H. Wen, K. Park, Introduction and overview of oral controlled release formulation design, in: H. Wen, K. Park (Eds.) Oral controlled release formulation design and drug delivery: Theory to practice, John Wiley & Sons, New Jersey, 2011, pp. 1-19.
[45] J. Siepmann, A. Faham, S.-D. Clas, B.J. Boyd, V. Jannin, A. Bernkop-Schnürch, H. Zhao, S. Lecommandoux, J.C. Evans, C. Allen, Lipids and polymers in pharmaceutical technology: Lifelong companions, Int. J. Pharm. 558 (2019) 128-142.
[46] G. Kaur, J. Grewal, K. Jyoti, U.K. Jain, R. Chandra, J. Madan, Oral controlled and sustained drug delivery systems: Concepts, advances, preclinical, and clinical status, in: A.M. Grumezescu (Ed.) Drug Targeting and Stimuli Sensitive Drug Delivery Systems, Elsevier, Netherlands, 2018, pp. 567-626.
[47] Z. C Loh, A. A Elkordy, Formulation and evaluation of different floating tablets containing metronidazole to target stomach, Curr. Drug Deliv. 12 (2015) 425-443.
[48] S.A. Rahim, P.A. Carter, A.A. Elkordy, Design and evaluation of effervescent floating tablets based on hydroxyethyl cellulose and sodium alginate using pentoxifylline as a model drug, Drug Des. Devel. Ther. 9 (2015) 1843-1857.
[49] S.A. Rahim, P. Carter, A.A. Elkordy, Influence of calcium carbonate and sodium carbonate gassing agents on pentoxifylline floating tablets properties, Powder Technol. 322 (2017) 65-74.
[50] G. Vasvári, J. Kalmár, P. Veres, M. Vecsernyés, I. Bácskay, P. Fehér, Z. Ujhelyi, Á. Haimhoffer, Á. Rusznyák, F. Fenyvesi, Matrix systems for oral drug delivery: Formulations and drug release, Drug Discov. Today Technol. 27 (2018) 71-80.
[51] A. Raza, U. Hayat, H.-J. Wang, J.-Y. Wang, Preparation and evaluation of captopril loaded gastro-retentive zein based porous floating tablets, Int. J. Pharm. (2020) 119185.

[52] J.-H. Park, H.-J. Shin, M.H. Kim, J.-S. Kim, N. Kang, J.-Y. Lee, K.-T. Kim, J.I. Lee, D.-D. Kim, Application of montmorillonite in bentonite as a pharmaceutical excipient in drug delivery systems, J. Pharm. Investig. 46 (2016) 363-375.
[53] A. Szewczyk, A. Skwira, A. Konopacka, R. Sądej, G. Walker, M. Prokopowicz, Mesoporous silica pellets as bifunctional bone drug delivery system for cefazolin, Int. J. Pharm. 588 (2020) 119718.
[54] J.D. Smart, Theories of Mucoadhesion, in: V.V. Khutoryanskiy (Ed.) Mucoadhesive materials and drug delivery systems, John Wiley & Sons, United Kingdom, 2014, pp. 159-174.
[55] S. Mansuri, P. Kesharwani, K. Jain, R.K. Tekade, N. Jain, Mucoadhesion: A promising approach in drug delivery system, React. Funct. Polym. 100 (2016) 151-172.
[56] E. Russo, F. Selmin, S. Baldassari, C. Gennari, G. Caviglioli, F. Cilurzo, P. Minghetti, B. Parodi, A focus on mucoadhesive polymers and their application in buccal dosage forms, J. Drug Deliv. Sci. Technol. 32 (2016) 113-125.
[57] V. Puri, A. Sharma, P. Kumar, I. Singh, Thiolation of biopolymers for developing drug delivery systems with enhanced mechanical and mucoadhesive properties: A review, Polymers 12 (2020) 1-27.
[58] H. Suzuki, H. Onishi, S. Hisamatsu, K. Masuda, Y. Takahashi, M. Iwata, Y. Machida, Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feeling, Int. J. Pharm. 278 (2004) 51-61.
[59] H.F. Alotaibi, S. Elsamaligy, G.M. Mahrous, M.A. Bayomi, H.A. Mahmoud, Design of taste masked enteric orodispersible tablets of diclofenac sodium by applying fluid bed coating technology, Saudi Pharm. J. 27 (2019) 354-362.
[60] A.R. Patel, P.R. Vavia, Preparation and evaluation of taste masked famotidine formulation using drug/β-cyclodextrin/polymer ternary complexation approach, AAPS PharmSciTech 9 (2008) 544-550.
[61] J. Walsh, A. Cram, K. Woertz, J. Breitkreutz, G. Winzenburg, R. Turner, C. Tuleu, E.F. Initiative, Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients, Adv. Drug Deliv. Rev. 73 (2014) 14-33.
[62] R. Witzleb, V.-R. Kanikanti, H.-J. Hamann, P. Kleinebudde, Solid lipid extrusion with small die diameters–electrostatic charging, taste masking and continuous production, Eur. J. Pharm. Biopharm. 77 (2011) 170-177.
[63] W. Kou, C. Cai, S. Xu, H. Wang, J. Liu, D. Yang, T. Zhang, In vitro and in vivo evaluation of novel immediate release carbamazepine tablets: Complexation with hydroxypropyl-β-cyclodextrin in the presence of HPMC, Int. J. Pharm. 409 (2011) 75-80.
[64] S. Desai, A. Poddar, K. Sawant, Formulation of cyclodextrin inclusion complex-based orally disintegrating tablet of eslicarbazepine acetate for improved oral bioavailability, Mater. Sci. Eng. C 58 (2016) 826-834.
[65] O. Dwichandra Putra, D. Umeda, E. Fujita, T. Haraguchi, T. Uchida, E. Yonemochi, H. Uekusa, Solubility improvement of benexate through salt formation using artificial sweetener, Pharmaceutics 10 (2018) 1-12.
[66] M. Shergill, M. Patel, S. Khan, A. Bashir, C. McConville, Development and characterisation of sustained release solid dispersion oral tablets containing the poorly water soluble drug disulfiram, Int. J. Pharm. 497 (2016) 3-11.
[67] G.M. Khan, Z. Jiabi, Formulation and in vitro evaluation of ibuprofen-carbopol® 974P-NF controlled release matrix tablets III: Influence of co-excipients on release rate of the drug, J. Control. Release 54 (1998) 185-190.
[68] J. Tazri, M.M.R. Moghal, S.M.R. Dewan, W. Noor, N. Mohammad, Formulation and quality determination of indapamide matrix tablet: A thiazide type antihypertensive drug, Adv. Pharm. Bull. 4 (2014) 191-195.
[69] P. Maffei, S.L. Borgia, A. Sforzini, V. Bergamante, G. Ceschel, A. Fini, C. Ronchi, Mucoadhesive tablets for buccal administration containing sodium nimesulide, Drug Deliv. 11 (2004) 225-230.
[70] B. Çelik, Risperidone mucoadhesive buccal tablets: Formulation design, optimization and evaluation, Drug Des. Devel. Ther. 11 (2017) 3355-3365.

[71] I.A. Sogias, A.C. Williams, V.V. Khutoryanskiy, Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen, Int. J. Pharm. 436 (2012) 602-610.
[72] S. Saha, A.F. Shahiwala, Multifunctional coprocessed excipients for improved tabletting performance, Expert Opin. Drug Deliv. 6 (2009) 197-208.
[73] A. Viscasillas Clerch, F. Fernandez Campos, A. del Pozo, A.C. Calpena Campmany, Pharmaceutical design of a new lactose-free coprocessed excipient: Application of hydrochlorothiazide as a low solubility drug model, Drug Dev. Ind. Pharm. 39 (2013) 961-969.
[74] S. Wang, J. Li, X. Lin, Y. Feng, X. Kou, S. Babu, R. Panicucci, Novel coprocessed excipients composed of lactose, HPMC, and PVPP for tableting and its application, Int. J. Pharm. 486 (2015) 370-379.
[75] I. Rashid, M. Al-Remawi, S.A. Leharne, B.Z. Chowdhry, A. Badwan, A novel multifunctional pharmaceutical excipient: Modification of the permeability of starch by processing with magnesium silicate, Int. J. Pharm. 411 (2011) 18-26.
[76] C.A. Challener, Key ingredients needed to drive the success of continuous manufacturing, PharmTech, (2020) https://www.pharmtech.com/view/key-ingredients-needed-to-drive-the-success-of-continuous-manufacturing (accessed 23 November 2020).
[77] Ludiflash® – The taste of success, BASF, https://pharmaceutical.basf.com/global/en/drug-formulation/products/ludiflash.html (accessed 22 November 2020).
[78] Ludipress® – Enabling efficient direct tabletting, BASF, https://pharmaceutical.basf.com/global/en/drug-formulation/products/ludipress.html (accessed 22 November 2020).
[79] HiCel SMCC, Pharmaceutical Technology https://www.pharmaceutical-technology.com/products/hicel-smcc/ (accessed 22 November 2020).
[80] S. Brown, Ludiflash® – The taste of success, BASF, https://www.btc-europe.com/fileadmin/user_upload/Downloads/Pdf_s/Industries/Ludiflash_Brochure_EN.pdf (accessed 27 November 2020).
[81] Ludipress, BASF, http://www2.pharm.u-szeged.hu/phtech/tananyagok/tablettazo/Ludipress.PDF (accessed 27 November 2020).
[82] A. Aljaberi, A. Ardakani, A. Khdair, S. Abdel-Rahim, E. Meqdadi, M. Ayyash, G. Alobaidi, N. Al-Zoubi, Tableting functionality evaluation of Prosolv Easytab in comparison to physical mixtures of its individual components, J. Drug Deliv. Sci. Technol. 23 (2013) 499-504.
[83] Excipient tailored for tablet performance, Manufacturing Chemist, (2011) https://www.manufacturingchemist.com/technical/article_page/Excipient_tailored_for_tablet_performance/63444 (accessed 27 November 2020).
[84] S. Shanmugam, Granulation techniques and technologies: Recent progresses, BioImpacts: BI 5 (2015) 55-63.
[85] P. Suresh, I. Sreedhar, R. Vaidhiswaran, A. Venugopal, A comprehensive review on process and engineering aspects of pharmaceutical wet granulation, Chem. Eng. J. 328 (2017) 785-815.
[86] C. Appelgren, Recent advances in granulation technology and equipment, Drug Dev. Ind. Pharm. 11 (1985) 725-741.
[87] H.-L. Lin, H.-O. Ho, C.-C. Chen, T.-S. Yeh, M.-T. Sheu, Process and formulation characterizations of the thermal adhesion granulation (TAG) process for improving granular properties, Int. J. Pharm. 357 (2008) 206-212.
[88] W. Grymonpré, G. Verstraete, V. Vanhoorne, J.P. Remon, T. De Beer, C. Vervaet, Downstream processing from melt granulation towards tablets: In-depth analysis of a continuous twin-screw melt granulation process using polymeric binders, Eur. J. Pharm. Biopharm. 124 (2018) 43-54.
[89] H.J. Prado, P.R. Bonelli, A.L. Cukierman, In situ fluidized hot melt granulation using a novel meltable binder: Effect of formulation variables on granule characteristics and controlled release tablets, Powder Technol. 264 (2014) 498-506.
[90] S.L. Cantor, S. Kothari, O.M. Koo, Evaluation of the physical and mechanical properties of high drug load formulations: Wet granulation vs. novel foam granulation, Powder Technol. 195 (2009) 15-24.

[91] M.R. Thompson , P.J. Sheskey , M. Thompson , P. Sheskey Foam granulation PharmTech, (2013) https://www.pharmtech.com/view/foam-granulation (accessed 25 November 2020).
[92] J. Wade, G. Martin, D. Long, Feasibility assessment for a novel reverse-phase wet granulation process: The effect of liquid saturation and binder liquid viscosity, Int. J. Pharm. 475 (2014) 450-461.
[93] N. Sandler, R.F. Lammens, Pneumatic dry granulation: Potential to improve roller compaction technology in drug manufacture, Expert Opin. Drug Deliv. 8 (2011) 225-236.
[94] L.D. Bruce, N.H. Shah, A.W. Malick, M.H. Infeld, J.W. McGinity, Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid, Eur. J. Pharm. Biopharm. 59 (2005) 85-97.
[95] M.F. Simões, R.M. Pinto, S. Simões, Hot-melt extrusion in the pharmaceutical industry: Toward filing a new drug application, Drug Discov. Today 24 (2019) 1749-1768.
[96] J.T. Morott, M. Pimparade, J.-B. Park, C.P. Worley, S. Majumdar, Z. Lian, E. Pinto, Y. Bi, T. Durig, M.A. Repka, The effects of screw configuration and polymeric carriers on hot-melt extruded taste-masked formulations incorporated into orally disintegrating tablets, J. Pharm. Sci. 104 (2015) 124-134.
[97] M. Fukuda, N.A. Peppas, J.W. McGinity, Floating hot-melt extruded tablets for gastroretentive controlled drug release system, J. Control. Release 115 (2006) 121-129.
[98] N.G. Solanki, K. Lam, M. Tahsin, S.G. Gumaste, A.V. Shah, A.T. Serajuddin, Effects of surfactants on itraconazole-HPMCAS solid dispersion prepared by hot-melt extrusion I: Miscibility and drug release, J. Pharm. Sci. 108 (2019) 1453-1465.
[99] Z. Sun, H. Zhang, H. He, L. Sun, X. Zhang, Q. Wang, K. Li, Z. He, Cooperative effect of polyvinylpyrrolidone and HPMC E5 on dissolution and bioavailability of nimodipine solid dispersions and tablets, Asian J. Pharm. Sci. 14 (2019) 668-676.
[100] S. Muley, T. Nandgude, S. Poddar, Extrusion–spheronization a promising pelletization technique: In-depth review, Asian J. Pharm. Sci. 11 (2016) 684-699.
[101] A. Goyanes, C. Souto, R. Martínez-Pacheco, Co-processed MCC-Eudragit® E excipients for extrusion–spheronization, Eur. J. Pharm. Biopharm. 79 (2011) 658-663.
[102] D.H. Alshora, M.A. Ibrahim, E. Ezzeldin, M. Iqbal, Optimized flurbiprofen sustained-release matrix pellets prepared by extrusion/spheronization, J. Drug Deliv. Sci. Technol. 59 (2020) 101902.
[103] S.A. Prieto, J.B. Méndez, F.O. Espinar, Starch–dextrin mixtures as base excipients for extrusion–spheronization pellets, Eur. J. Pharm. Biopharm. 59 (2005) 511-521.
[104] S. Lee, M.-S. Kim, S.W. Jun, J.-S. Park, S.-J. Hwang, Preparation of controlled release spheronized beads by a simple extrusion and modified spheronization process, Arch. Pharm. Res. 28 (2005) 619-625.
[105] T. Iosio, D. Voinovich, M. Grassi, J.F. Pinto, B. Perissutti, M. Zacchigna, U. Quintavalle, F. Serdoz, Bi-layered self-emulsifying pellets prepared by co-extrusion and spheronization: Influence of formulation variables and preliminary study on the in vivo absorption, Eur. J. Pharm. Biopharm. 69 (2008) 686-697.
[106] L. Zema, G. Loreti, A. Melocchi, A. Maroni, A. Gazzaniga, Injection molding and its application to drug delivery, J. Control. Release 159 (2012) 324-331.
[107] K. Eggenreich, S. Windhab, S. Schrank, D. Treffer, H. Juster, G. Steinbichler, S. Laske, G. Koscher, E. Roblegg, J. Khinast, Injection molding as a one-step process for the direct production of pharmaceutical dosage forms from primary powders, Int. J. Pharm. 505 (2016) 341-351.
[108] A. Melocchi, G. Loreti, M.D. Del Curto, A. Maroni, A. Gazzaniga, L. Zema, Evaluation of hot-melt extrusion and injection molding for continuous manufacturing of immediate-release tablets, J. Pharm. Sci. 104 (2015) 1971-1980.
[109] P.H. Hemmingsen, A.-M. Haahr, C. Gunnergaard, J.-M. Cardot, Development of a new type of prolonged release hydrocodone formulation based on Egalet® ADPREM technology using in vivo–in vitro correlation, Pharmaceutics 3 (2011) 73-87.
[110] P.M. Desai, R.C. Hogan, D. Brancazio, V. Puri, K.D. Jensen, J.-H. Chun, A.S. Myerson, B.L. Trout, Integrated hot-melt extrusion–injection molding continuous tablet manufacturing platform: Effects of

critical process parameters and formulation attributes on product robustness and dimensional stability, Int. J. Pharm. 531 (2017) 332-342.
[111] J. Broadhead, S. Edmond Rouan, C. Rhodes, The spray drying of pharmaceuticals, Drug Dev. Ind. Pharm. 18 (1992) 1169-1206.
[112] M. Davis, G. Walker, Recent strategies in spray drying for the enhanced bioavailability of poorly water-soluble drugs, J. Control. Release 269 (2018) 110-127.
[113] D. Santos, A.C. Maurício, V. Sencadas, J.D. Santos, M.H. Fernandes, P.S. Gomes, Spray Drying: An Overview, in: R. Pignatello, T. Musumeci (Eds.) Biomaterials-Physics and Chemistry-New Edition, IntechOpen, United Kingdom, 2017.
[114] K. Čerpnjak, A.Z. Pobirk, F. Vrečer, M. Gašperlin, Tablets and minitablets prepared from spray-dried SMEDDS containing naproxen, Int. J. Pharm. 495 (2015) 336-346.
[115] I. Soulairol, N. Tarlier, B. Bataille, T. Cacciaguerra, T. Sharkawi, Spray-dried solid dispersions of nifedipine and vinylcaprolactam/vinylacetate/PEG6000 for compacted oral formulations, Int. J. Pharm. 481 (2015) 140-147.
[116] M. Yanfei, C. Guoguang, R. Lili, O. Pingkai, Controlled release of ziprasidone solid dispersion systems from osmotic pump tablets with enhanced bioavailability in the fasted state, Drug Dev. Ind. Pharm. 41 (2015) 1353-1362.
[117] K. Trisopon, N. Kittipongpatana, O.S. Kittipongpatana, A spray-dried, co-processed rice starch as a multifunctional excipient for direct compression, Pharmaceutics 12 (2020) 1-18.
[118] S. Bertoni, B. Albertini, N. Passerini, Spray congealing: An emerging technology to prepare solid dispersions with enhanced oral bioavailability of poorly water soluble drugs, Molecules 24 (2019) 1-21.
[119] K.A. Javaid, J.H. Fincher, C.W. Hartman, Timed-release tablets employing lipase-lipid-sulfamethizole systems prepared by spray congealing, J. Pharm. Sci. 60 (1971) 1702-1704.
[120] M.A. Khan, S. Bolton, M. Kislalioglu, Optimization of process variables for the preparation of ibuprofen coprecipitates with Eudragit S100, Int. J. Pharm. 102 (1994) 185-192.
[121] A.K. Mann, L. Schenck, A. Koynov, A.C. Rumondor, X. Jin, M. Marota, C. Dalton, Producing amorphous solid dispersions via co-precipitation and spray drying: Impact to physicochemical and biopharmaceutical properties, J. Pharm. Sci. 107 (2018) 183-191.
[122] A.H. Ibrahim, E. Rosqvist, J.-H. Smått, H.M. Ibrahim, H.R. Ismael, M.I. Afouna, A.M. Samy, J.M. Rosenholm, Formulation and optimization of lyophilized nanosuspension tablets to improve the physicochemical properties and provide immediate release of silymarin, Int. J. Pharm. 563 (2019) 217-227.
[123] C.J.M. Rivas, M. Tarhini, W. Badri, K. Miladi, H. Greige-Gerges, Q.A. Nazari, S.A.G. Rodríguez, R.Á. Román, H. Fessi, A. Elaissari, Nanoprecipitation process: From encapsulation to drug delivery, Int. J. Pharm. 532 (2017) 66-81.
[124] M. Li, M. Azad, R. Davé, E. Bilgili, Nanomilling of drugs for bioavailability enhancement: a holistic formulation-process perspective, Pharmaceutics 8 (2016) 1-35.
[125] A. Haider, S. Haider, I.-K. Kang, A comprehensive review summarizing the effect of electrospinning parameters and potential applications of nanofibers in biomedical and biotechnology, Arab. J. Chem. 11 (2018) 1165-1188.
[126] J. Xue, T. Wu, Y. Dai, Y. Xia, Electrospinning and electrospun nanofibers: Methods, materials, and applications, Chem. Rev. 119 (2019) 5298-5415.
[127] A.A. Abdelbary, X. Li, M. El-Nabarawi, A. Elassasy, B. Jasti, Comparison of nanomilling and coprecipitation on the enhancement of in vitro dissolution rate of poorly water-soluble model drug aripiprazole, Pharm. Dev. Technol. 19 (2014) 491-500.
[128] M. Hamori, K. Nagano, S. Kakimoto, K. Naruhashi, A. Kiriyama, A. Nishimura, N. Shibata, Preparation and pharmaceutical evaluation of acetaminophen nano-fiber tablets: Application of a solvent-based electrospinning method for tableting, Biomed. Pharmacother. 78 (2016) 14-22.

[129] M. Vlachou, S. Kikionis, A. Siamidi, K. Tragou, E. Ioannou, V. Roussis, A. Tsotinis, Modified in vitro release of melatonin loaded in nanofibrous electrospun mats incorporated into monolayered and three-layered tablets, J. Pharm. Sci. 108 (2019) 970-976.
[130] A. Laha, M.K. Gaydhane, C.S. Sharma, S. Majumdar, Compressed nanofibrous oral tablets: An ingenious way for controlled release kinetics of Amphotericin-B loaded gelatin nanofibers, Nano-Structures and Nano-Objects 19 (2019) 100367.
[131] I. Wünsch, J.H. Finke, E. John, M. Juhnke, A. Kwade, A mathematical approach to consider solid compressibility in the compression of pharmaceutical powders, Pharmaceutics 11 (2019) 1-19.
[132] K. Kawakita, K.-H. Lüdde, Some considerations on powder compression equations, Powder Technol. 4 (1971) 61-68.
[133] J. Markarian, Tablet-sticking solutions, PharmTech, (2013) https://www.pharmtech.com/view/tablet-sticking-solutions-0 (accessed 24 January 2021).
[134] A. Deutchman, D. Natoli, Tablet punch performance can be improved with precision coatings, Beamalloy Technologies L.L.C., (2002) https://docplayer.net/8058565-Tableting-punch-performance-can-be-improved-with-precision-coatings.html (accessed 24 January 2021).
[135] R. Blanchard, TSAR Predict service solves age-old 'sticking' conundrum in hours, European Pharmaceutical Manufacturers (2014) https://www.epmmagazine.com/blogs/elizabeth-valeros-blog/tsar-predict-service-solves/ (accessed 24 November 2020).
[136] S. Chattoraj, P. Daugherity, T. McDermott, A. Olsofsky, W.J. Roth, M. Tobyn, Sticking and picking in pharmaceutical tablet compression: An IQ consortium review, J. Pharm. Sci. 107 (2018) 2267-2282.
[137] A. Domokos, B. Nagy, M. Gyürkés, A. Farkas, K. Tacsi, H. Pataki, Y.C. Liu, A. Balogh, P. Firth, B. Szilágyi, End-to-end continuous manufacturing of conventional compressed tablets: From flow synthesis to tableting through integrated crystallization and filtration, Int. J. Pharm. (2020) 119297.
[138] M. Teżyk, B. Milanowski, A. Ernst, J. Lulek, Recent progress in continuous and semi-continuous processing of solid oral dosage forms: A review, Drug Dev. Ind. Pharm. 42 (2016) 1195-1214.
[139] V. Vanhoorne, C. Vervaet, Recent progress in continuous manufacturing of oral solid dosage forms, Int. J. Pharm. (2020) 119194.
[140] E. Palmer, Pfizer and GSK to work together on continuous manufacturing, Fierce Pharma, (2015) https://www.fiercepharma.com/manufacturing/pfizer-and-gsk-to-work-together-on-continuous-manufacturing (accessed 23 November 2020).
[141] CPI Works with GSK and AstraZeneca on Pharma Manufacturing, CPI, (2019) https://www.uk-cpi.com/news/delivering-effective-continuous-wet-granulation-processes (accessed 23 November 2020).
[142] F. Cilurzo, U.M. Musazzi, S. Franzé, F. Selmin, P. Minghetti, Orodispersible dosage forms: Biopharmaceutical improvements and regulatory requirements, Drug Discov. Today 23 (2018) 251-259.
[143] R. Chandrasekhar, Z. Hassan, F. AlHusban, A.M. Smith, A.R. Mohammed, The role of formulation excipients in the development of lyophilised fast-disintegrating tablets, Eur. J. Pharm. Biopharm. 72 (2009) 119-129.
[144] N. Saigal, S. Baboota, A. Ahuja, J. Ali, Fast-dissolving intra-oral drug delivery systems, Expert Opin. Ther. Pat. 18 (2008) 769-781.
[145] M. Lal, S. Priddy, L. Bourgeois, R. Walker, W. Pebley, J. Brown, J. Desai, M.J. Darsley, D. Kristensen, D. Chen, Development of a fast-dissolving tablet formulation of a live attenuated enterotoxigenic E. coli vaccine candidate, Vaccine 31 (2013) 4759-4764.
[146] B. Evrard, K. Amighi, D. Beten, L. Delattre, A. Moës, Influence of melting and rheological properties of fatty binders on the melt granulation process in a high-shear mixer, Drug Dev. Ind. Pharm. 25 (1999) 1177-1184.
[147] A. Solaiman, A.S. Suliman, S. Shinde, S. Naz, A.A. Elkordy, Application of general multilevel factorial design with formulation of fast disintegrating tablets containing croscaremellose sodium and Disintequick MCC-25, Int. J. Pharm. 501 (2016) 87-95.

[148] E. Mathew, G. Pitzanti, E. Larrañeta, D.A. Lamprou, 3D printing of pharmaceuticals and drug delivery devices, Pharmaceutics 12 (2020) 1-9.
[149] M. Pandey, H. Choudhury, J.L.C. Fern, A.T.K. Kee, J. Kou, J.L.J. Jing, H.C. Her, H.S. Yong, H.C. Ming, S.K. Bhattamisra, 3D printing for oral drug delivery: A new tool to customize drug delivery, Drug Deliv. Transl. Res. (2020) 1-16.
[150] T. Comoglu, E. Dilek Ozyilmaz, Orally disintegrating tablets and orally disintegrating mini tablets–novel dosage forms for pediatric use, Pharm. Dev. Technol. 24 (2019) 902-914.
[151] M. Podrażka, E. Bączyńska, M. Kundys, P.S. Jeleń, E. Witkowska Nery, Electronic tongue—A tool for all tastes?, Biosensors 8 (2018) 1-24.
[152] M. Cirri, F. Maestrelli, G. Corti, P. Mura, M. Valleri, Fast-dissolving tablets of glyburide based on ternary solid dispersions with PEG 6000 and surfactants, Drug Deliv. 14 (2007) 247-255.
[153] D. Gugulothu, P. Desai, P. Pandharipande, V. Patravale, Freeze drying: Exploring potential in development of orodispersible tablets of sumatriptan succinate, Drug Dev. Ind. Pharm. 41 (2015) 398-405.
[154] Zomig ZMT, Food and Drug Administration, https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20768s012lbl.pdf (accessed 25th September 2020).
[155] MAXALT® (max-awlt) and MAXALT-MLT®, Merck & Co., Inc., https://www.merck.com/product/usa/pi_circulars/m/maxalt/maxalt_ppi.pdf (accessed 25th September 2020).
[156] Zofran ODT, Food and Drug Administration, https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020103s031,020605s015,020781s015lbl.pdf (accessed 25th September 2020).
[157] Pepcid RPD, Food and Drug Administration, https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20752lbl.pdf (accessed 25th September 2020).
[158] Feldene Melt 20mg tablets, EMC, https://www.medicines.org.uk/emc/product/112/smpc#gref (accessed 25th September 2020).
[159] H. Leuenberger, B. Rohera, C. Haas, Percolation theory—A novel approach to solid dosage form design, Int. J. Pharm. 38 (1987) 109-115.
[160] J. Barra, F. Falson-Rieg, E. Doelker, Modified drug release from inert matrix tablets prepared from formulations of identical composition but different organisations, J. Control. Release 65 (2000) 419-428.
[161] H.P. Huang, S.C. Mehta, G.W. Radebaugh, M.B. Fawzi, Mechanism of drug release from an acrylic polymer-wax matrix tablet, J. Pharm. Sci. 83 (1994) 795-797.
[162] A. Dakkur, L.D. Butler, P.P. Deluca, Sustained release from inert wax matrixes III: Effect of povidone on tripelennamine hydrochloride release, J. Pharm. Sci. 67 (1978) 357-360.
[163] S. Klein, N. Seeger, R. Mehta, S. Missaghi, R. Grybos, A. Rajabi-Siahboomi, Robustness of barrier membrane coated metoprolol tartrate matrix tablets: Drug release evaluation under physiologically relevant in vitro conditions, Int. J. Pharm. 543 (2018) 368-375.
[164] A. Mujtaba, K. Kohli, In vitro/in vivo evaluation of HPMC/alginate based extended-release matrix tablets of cefpodoxime proxetil, Int. J. Biol. Macromol. 89 (2016) 434-441.
[165] P.S. Hiremath, R.N. Saha, Controlled release hydrophilic matrix tablet formulations of isoniazid: Design and in vitro studies, AAPS PharmSciTech 9 (2008) 1171-1178.
[166] Y. Ikeuchi-Takahashi, M. Sasatsu, H. Onishi, Evaluation of matrix type mucoadhesive tablets containing indomethacin for buccal application, Int. J. Pharm. 453 (2013) 454-461.
[167] J. Saurí, M. Zachariah, R. Macovez, J.L. Tamarit, D. Millán, M. Suñé-Pou, E. García-Montoya, P. Pérez-Lozano, M. Miñarro, J. Ticó, Formulation and characterization of mucoadhesive controlled release matrix tablets of captopril, J. Drug Deliv. Sci. Technol. 42 (2017) 215-226.
[168] S. Mansuri, P. Kesharwani, R.K. Tekade, N.K. Jain, Lyophilized mucoadhesive-dendrimer enclosed matrix tablet for extended oral delivery of albendazole, Eur. J. Pharm. Biopharm. 102 (2016) 202-213.

[169] S.S. Gaikwad, S.J. Kshirsagar, Review on Tablet in Tablet techniques, Beni-Suef Univ. J. Basic Appl. Sci. 9 (2020) 1-7.
[170] K.H. Lin, S.Y. Lin, M.J. Li, Compression forces and amount of outer coating layer affecting the time-controlled disintegration of the compression-coated tablets prepared by direct compression with micronized ethylcellulose, J. Pharm. Sci. 90 (2001) 2005-2009.
[171] T. Liu, Y. Shi, J. Li, W. Jiang, T. Yin, Y. Zhang, H. He, Y. Wang, X. Tang, Nifedipine di-matrix depot tablets prepared by compression coating for obtaining zero-order release, Drug Dev. Ind. Pharm. 44 (2018) 1426-1433.
[172] S. Maity, B. Sa, Compression-coated tablet for colon targeting: Impact of coating and core materials on drug release, AAPS PharmSciTech 17 (2016) 504-515.
[173] Tablet-in-tablet pharmaceutical composition comprising cyclophosphamide and capecitabine Justia Patents, https://patents.justia.com/patent/20190142755 (accessed 25th September 2020).
[174] B. Li, J. Zhu, C. Zheng, W. Gong, A novel system for three-pulse drug release based on "tablets in capsule" device, Int. J. Pharm. 352 (2008) 159-164.
[175] M. Ishida, K. Abe, M. Hashizume, M. Kawamura, A novel approach to sustained pseudoephedrine release: Differentially coated mini-tablets in HPMC capsules, Int. J. Pharm. 359 (2008) 46-52.
[176] S.A. El-Zahaby, A.A. Kassem, A.H. El-Kamel, Design and evaluation of gastroretentive levofloxacin floating mini-tablets-in-capsule system for eradication of Helicobacter pylori, Saudi Pharm. J. 22 (2014) 570-579.
[177] S. Abdul, S. Poddar, A flexible technology for modified release of drugs: multi layered tablets, J. Control. Release 97 (2004) 393-405.
[178] S.R. Vaithiyalingam, V.A. Sayeed, Critical factors in manufacturing multi-layer tablets—Assessing material attributes, in-process controls, manufacturing process and product performance, Int. J. Pharm. 398 (2010) 9-13.
[179] K.-M. Hwang, T.-T. Nguyen, S.H. Seok, H.-I. Jo, C.-H. Cho, K.-M. Hwang, J.-Y. Kim, C.-W. Park, Y.-S. Rhee, E.-S. Park, Swellable and porous bilayer tablet for gastroretentive drug delivery: Preparation and in vitro-in vivo evaluation, Int. J. Pharm. 572 (2019) 118783.
[180] G. Andrews, S. Li, A. Almajaan, T. Yu, L. Martini, A. Healy, D. Jones, Fixed dose combination formulations: Multilayered platforms designed for the management of cardiovascular disease, Mol. Pharm. 16 (2019) 1827-1838.
[181] J.S. Park, J.Y. Shim, J.S. Park, Y.W. Choi, S.H. Jeong, A novel three-layered tablet for extended release with various layer formulations and in vitro release profiles, Drug Dev. Ind. Pharm. 37 (2011) 664-672.
[182] A.R. Rajabi-Siahboomi, Overview of Multiparticulate Systems for Oral Drug Delivery, in: A.R. Rajabi-Siahboomi (Ed.) Multiparticulate drug delivery: Formulation, processing and manufacturing, Springer, New York, 2017, pp. 1-4.
[183] A. Lyire, A.R. Mohammed, Multiparticulate Systems for Paediatric Drug Delivery, in: A.R. Rajabi-Siahboomi (Ed.) Multiparticulate drug delivery: Formulation, processing and manufacturing, Springer, New York, 2017, pp. 213-236.
[184] S. Patel, N. Patel, M. Misra, A. Joshi, Controlled-release domperidone pellets compressed into fast disintegrating tablets forming a multiple-unit pellet system (MUPS), J. Drug Deliv. Sci. Technol. 45 (2018) 220-229.
[185] M. Liu, S. Zhang, S. Cui, F. Chen, L. Jia, S. Wang, X. Gai, P. Li, F. Yang, W. Pan, Preparation and evaluation of Vinpocetine self-emulsifying pH gradient release pellets, Drug Deliv. 24 (2017) 1598-1604.
[186] K.V. Rao, V. Venkatchalam, Mucoadhesive biphasic minitablets of cefuroxime axetil: Formulation development, characterization and in vivo bioavailability study, J. Drug Deliv. Sci. Technol. 35 (2016) 260-271.
[187] H. Song, C. Moon, B.-J. Lee, E. Oh, Mesoporous pravastatin solid dispersion granules incorporable into orally disintegrating tablets, J. Pharm. Sci. 107 (2018) 1886-1895.

[188] L. Zhang, S. Mao, Application of quality by design in the current drug development, Asian J. Pharm. Sci. 12 (2017) 1-8.
[189] S. Beg, M.S. Hasnain, M. Rahman, S. Swain, Introduction to quality by design (QbD): Fundamentals, principles, and applications, in: S. Beg, M.S. Hasnain (Eds.) Pharmaceutical Quality by Design, Elsevier, Netherlands, 2019, pp. 1-17.
[190] H.B. Grangeia, C. Silva, S.P. Simões, M.S. Reis, Quality by design in pharmaceutical manufacturing: A systematic review of current status, challenges and future perspectives, Eur. J. Pharm. Biopharm. 147 (2020) 19-37.
[191] J. Zhang, R. Thakkar, Y. Zhang, M. Maniruzzaman, Structure-function correlation and personalized 3D printed tablets using a quality by design (QbD) approach, Int. J. Pharm. 590 (2020) 119945.
[192] V.S. Dave, H.I. Shahin, S.R. Youngren-Ortiz, M.B. Chougule, R.V. Haware, Emerging technologies for the non-invasive characterization of physical-mechanical properties of tablets, Int. J. Pharm. 532 (2017) 299-312.
[193] A. Chanda, A.M. Daly, D.A. Foley, M.A. LaPack, S. Mukherjee, J.D. Orr, G.L. Reid III, D.R. Thompson, H.W. Ward, Industry perspectives on process analytical technology: Tools and applications in API development, Organic Process Research and Development 19 (2015) 63-83.
[194] L.L. Simon, H. Pataki, G.r. Marosi, F. Meemken, K. Hungerbühler, A. Baiker, S. Tummala, B. Glennon, M. Kuentz, G. Steele, Assessment of recent process analytical technology (PAT) trends: A multiauthor review, Organic Process Research and Development 19 (2015) 3-62.
[195] L. Zhong, L. Gao, L. Li, H. Zang, Trends-process analytical technology in solid oral dosage manufacturing, Eur. J. Pharm. Biopharm. 153 (2020) 187-199.
[196] M. Fonteyne, J. Vercruysse, F. De Leersnyder, B. Van Snick, C. Vervaet, J.P. Remon, T. De Beer, Process analytical technology for continuous manufacturing of solid-dosage forms, Trends Analyt. Chem. 67 (2015) 159-166.
[197] A. Halenius, S. Lakio, O. Antikainen, J. Hatara, J. Yliruusi, Fast tablet tensile strength prediction based on non-invasive analytics, AAPS PharmSciTech 15 (2014) 781-791.
[198] A. Orun, G. Smith, Micro-structural analysis of tablet surface layers by intelligent laser speckle classification (ILSC) technique: An application in the study of both surface defects and subsurface granule structures, J. Pharm. Innov. 12 (2017) 296-308.
[199] R. Domike, S. Ngai, C.L. Cooney, Light induced fluorescence for predicting API content in tablets: Sampling and error, Int. J. Pharm. 391 (2010) 13-20.
[200] C.K. Lai, A. Zahari, B. Miller, W.E. Katstra, M.J. Cima, C.L. Cooney, Nondestructive and on-line monitoring of tablets using light-induced fluorescence technology, AAPS PharmSciTech 5 (2004) 1-10.
[201] P. Durão, C. Fauteux-Lefebvre, J.-M. Guay, N. Abatzoglou, R. Gosselin, Using multiple process analytical technology probes to monitor multivitamin blends in a tableting feed frame, Talanta 164 (2017) 7-15.
[202] D.M. Koller, G. Hannesschläger, M. Leitner, J. Khinast, Non-destructive analysis of tablet coatings with optical coherence tomography, Eur. J. Pharm. Sci. 44 (2011) 142-148.
[203] E. Yost, P. Chalus, S. Zhang, S. Peter, A.S. Narang, Quantitative X-ray microcomputed tomography assessment of internal tablet defects, J. Pharm. Sci. 108 (2019) 1818-1830.
[204] I. Sinka, S. Burch, J. Tweed, J. Cunningham, Measurement of density variations in tablets using X-ray computed tomography, Int. J. Pharm. 271 (2004) 215-224.
[205] X. Yin, H. Li, Z. Guo, L. Wu, F. Chen, M. de Matas, Q. Shao, T. Xiao, P. York, Y. He, Quantification of swelling and erosion in the controlled release of a poorly water-soluble drug using synchrotron X-ray computed microtomography, AAPS J. 15 (2013) 1025-1034.
[206] C.-V. Möltgen, T. Puchert, J. Menezes, D. Lochmann, G. Reich, A novel in-line NIR spectroscopy application for the monitoring of tablet film coating in an industrial scale process, Talanta 92 (2012) 26-37.

[207] H. Dalvi, A. Langlet, M.-J. Colbert, A. Cournoyer, J.-M. Guay, N. Abatzoglou, R. Gosselin, In-line monitoring of Ibuprofen during and after tablet compression using near-infrared spectroscopy, Talanta 195 (2019) 87-96.
[208] F. De Leersnyder, V. Vanhoorne, A. Kumar, C. Vervaet, T. De Beer, Evaluation of an in-line NIR spectroscopic method for the determination of the residence time in a tablet press, Int. J. Pharm. 565 (2019) 358-366.
[209] J.K. Drennen, R.A. Lodder, Nondestructive near-infrared analysis of intact tablets for determination of degradation products, J. Pharm. Sci. 79 (1990) 622-627.
[210] S.S. Sekulic, H.W. Ward, D.R. Brannegan, E.D. Stanley, C.L. Evans, S.T. Sciavolino, P.A. Hailey, P.K. Aldridge, On-line monitoring of powder blend homogeneity by near-infrared spectroscopy, Anal. Chem. 68 (1996) 509-513.
[211] M. Donoso, D. Kildsig, E.S. Ghaly, Prediction of tablet hardness and porosity using near-infrared diffuse reflectance spectroscopy as a nondestructive method, Pharm. Dev. Technol. 8 (2003) 357-366.
[212] J. Radtke, P. Kleinebudde, Real-time monitoring of multi-layered film coating processes using Raman spectroscopy, Eur. J. Pharm. Biopharm. 153 (2020) 43-51.
[213] J. Griffen, A. Owen, P. Matousek, Comprehensive quantification of tablets with multiple active pharmaceutical ingredients using transmission Raman spectroscopy—A proof of concept study, J. Pharm. Biomed. Anal. 115 (2015) 277-282.
[214] R. Takeshima, Y. Hattori, S. Managaki, M. Otsuka, Analysis of the dehydration process of caffeine using backscattering and transmission Raman spectroscopy, Int. J. Pharm. 530 (2017) 256-262.
[215] S. Virtanen, O. Antikainen, J. Yliruusi, Determination of the crushing strength of intact tablets using Raman spectroscopy, Int. J. Pharm. 360 (2008) 40-46.
[216] A.K. Myakalwar, S. Sreedhar, I. Barman, N.C. Dingari, S.V. Rao, P.P. Kiran, S.P. Tewari, G.M. Kumar, Laser-induced breakdown spectroscopy-based investigation and classification of pharmaceutical tablets using multivariate chemometric analysis, Talanta 87 (2011) 53-59.
[217] P. Bawuah, N. Tan, S.N.A. Tweneboah, T. Ervasti, J.A. Zeitler, J. Ketolainen, K.-E. Peiponen, Terahertz study on porosity and mass fraction of active pharmaceutical ingredient of pharmaceutical tablets, Eur. J. Pharm. Biopharm. 105 (2016) 122-133.
[218] J. Ornik, D. Knoth, M. Koch, C.M. Keck, Terahertz-spectroscopy for non-destructive determination of crystallinity of L-tartaric acid in smartFilms® and tablets made from paper, Int. J. Pharm. (2020) 119253.
[219] A. Novikova, D. Markl, J.A. Zeitler, T. Rades, C.S. Leopold, A non-destructive method for quality control of the pellet distribution within a MUPS tablet by terahertz pulsed imaging, Eur. J. Pharm. Sci. 111 (2018) 549-555.
[220] P. Dorożyński, W. Jamróz, K. Niwiński, M. Kurek, W.P. Węglarz, R. Jachowicz, P. Kulinowski, Novel method for screening of enteric film coatings properties with magnetic resonance imaging, Int. J. Pharm. 456 (2013) 569-571.
[221] J. Dvořák, J. Tomas, D. Lizoňová, M. Schöngut, O. Dammer, T. Pekárek, J. Beránek, F. Štěpánek, Investigation of tablet disintegration pathways by the combined use of magnetic resonance imaging, texture analysis and static light scattering, Int. J. Pharm. 587 (2020) 119719.
[222] A.L. Broadbent, R.J. Fell, S.L. Codd, K.A. Lightley, S. Konagurthu, D.G. Koehler-King, J.D. Seymour, Magnetic resonance imaging and relaxometry to study water transport mechanisms in a commercially available gastrointestinal therapeutic system (GITS) tablet, Int. J. Pharm. 397 (2010) 27-35.
[223] M. Whitaker, G.R. Baker, J. Westrup, P.A. Goulding, D.R. Rudd, R.M. Belchamber, M.P. Collins, Application of acoustic emission to the monitoring and end point determination of a high shear granulation process, Int. J. Pharm. 205 (2000) 79-91.
[224] A. Crouter, L. Briens, Monitoring lubricant addition using passive acoustic emissions in a V-blender, Powder Technol. 301 (2016) 1119-1129.
[225] I. Akseli, D.C. Becker, C. Cetinkaya, Ultrasonic determination of Young's moduli of the coat and core materials of a drug tablet, Int. J. Pharm. 370 (2009) 17-25.

[226] J. Liu, C. Cetinkaya, Mechanical and geometric property characterization of dry-coated tablets with contact ultrasonic techniques, Int. J. Pharm. 392 (2010) 148-155.
[227] I. Varghese, C. Cetinkaya, Noncontact photo-acoustic defect detection in drug tablets, J. Pharm. Sci. 96 (2007) 2125-2133.
[228] J. Medendorp, R.A. Lodder, Acoustic-resonance spectrometry as a process analytical technology for rapid and accurate tablet identification, AAPS PharmSciTech 7 (2006) E175-E183.
[229] H. Lin, Z. Zhang, D. Markl, J.A. Zeitler, Y. Shen, A review of the applications of OCT for analysing pharmaceutical film coatings, Appl. Sci. 8 (2018) 1-12.
[230] V. Busignies, B. Leclerc, P. Porion, P. Evesque, G. Couarraze, P. Tchoreloff, Investigation and modelling approach of the mechanical properties of compacts made with binary mixtures of pharmaceutical excipients, Eur. J. Pharm. Biopharm. 64 (2006) 51-65.
[231] B. Muehlhauser, N. DeRoo, Computed tomography: Applications for evaluating tablets and capsules, Tablets and Capsules, (2016) https://tabletscapsules.com/wp-content/uploads/pdf/tc_20160101_0014.pdf (accessed 24 January 2021).
[232] M. Yokoyama, M. Tourigny, K. Moroshima, J. Suzuki, M. Sakai, K. Iwamoto, H. Takeuchi, A novel rapid quantitative analysis of drug migration on tablets using laser induced breakdown spectroscopy, Chem. Pharm. Bull. (Tokyo) 58 (2010) 1521-1524.
[233] M.C. Madamba, W.M. Mullett, S. Debnath, E. Kwong, Characterization of tablet film coatings using a laser-induced breakdown spectroscopic technique, AAPS PharmSciTech 8 (2007) 184-190.
[234] L. Zou, B. Kassim, J.P. Smith, J.D. Ormes, Y. Liu, Q. Tu, X. Bu, In situ analytical characterization and chemical imaging of tablet coatings using laser induced breakdown spectroscopy (LIBS), Analyst 143 (2018) 5000-5007.
[235] A. Djemai, I. Sinka, NMR imaging of density distributions in tablets, Int. J. Pharm. 319 (2006) 55-62.
[236] Q. Zhang, L. Gladden, P. Avalle, M. Mantle, In vitro quantitative 1H and 19F nuclear magnetic resonance spectroscopy and imaging studies of fluvastatin™ in Lescol® XL tablets in a USP-IV dissolution cell, J. Control. Release 156 (2011) 345-354.
[237] C.A. Challener, Rising interest in terahertz spectroscopy in pharmaceutical analysis, PharmTech, (2013) https://www.pharmtech.com/view/rising-interest-terahertz-spectroscopy-pharmaceutical-analysis (accessed 10 December 2020).
[238] R.K. May, K. Su, L. Han, S. Zhong, J.A. Elliott, L.F. Gladden, M. Evans, Y. Shen, J.A. Zeitler, Hardness and density distributions of pharmaceutical tablets measured by terahertz pulsed imaging, J. Pharm. Sci. 102 (2013) 2179-2186.
[239] L. Ho, R. Müller, M. Römer, K. Gordon, J. Heinämäki, P. Kleinebudde, M. Pepper, T. Rades, Y. Shen, C. Strachan, Analysis of sustained-release tablet film coats using terahertz pulsed imaging, J. Control. Release 119 (2007) 253-261.
[240] I.-S. Russe, D. Brock, K. Knop, P. Kleinebudde, J.A. Zeitler, Validation of terahertz coating thickness measurements using X-ray microtomography, Mol. Pharm. 9 (2012) 3551-3559.
[241] M. Niwa, Y. Hiraishi, N. Iwasaki, K. Terada, Quantitative analysis of the layer separation risk in bilayer tablets using terahertz pulsed imaging, Int. J. Pharm. 452 (2013) 249-256.
[242] Pharmaceutical applications of Raman spectroscopy, Azo Materials, (2013) https://www.azom.com/article.aspx?ArticleID=10141 (accessed 10 December 2020).
[243] B.W. Wabuyele, S. Sotthivirat, G.X. Zhou, J. Ash, S.S. Dhareshwar, Dispersive Raman spectroscopy for quantifying amorphous drug content in intact tablets, J. Pharm. Sci. 106 (2017) 579-588.
[244] J. Luypaert, D. Massart, Y. Vander Heyden, Near-infrared spectroscopy applications in pharmaceutical analysis, Talanta 72 (2007) 865-883.
[245] C.R. Avila, J. Ferré, R.R. de Oliveira, A. de Juan, W.E. Sinclair, F.M. Mahdi, A. Hassanpour, T.N. Hunter, R.A. Bourne, F.L. Muller, Process monitoring of moisture content and mass transfer rate in a fluidised bed with a low cost Inline MEMS NIR sensor, Pharm. Res. 37 (2020) 1-19.

[246] N. O'Mahoney, J.J. Keating, S. McSweeney, S. Hill, S. Lawrence, D. Fitzpatrick, The sound of tablets during coating erosion, disintegration, deaggregation and dissolution, Int. J. Pharm. (2020) 119216.
[247] J. Cho, P. Gemperline, A. Salt, D. Walker, UV/visible spectral dissolution monitoring by in situ fiber-optic probes, Anal. Chem. 67 (1995) 2858-2863.
[248] P. Zarmpi, T. Flanagan, E. Meehan, J. Mann, N. Fotaki, Surface dissolution UV imaging for characterization of superdisintegrants and their impact on drug dissolution, Int. J. Pharm. 577 (2020) 119080.
[249] J. Østergaard, J. Lenke, S.S. Jensen, Y. Sun, F. Ye, UV imaging for in vitro dissolution and release studies: Initial experiences, Dissolution Technol. 21 (2014) 27-38.
[250] O.P. Sharma, M.V. Shah, D.C. Parikh, T.A. Mehta, Formulation optimization of gastroretentive drug delivery system for allopurinol using experimental design, Expert Opin. Drug Deliv. 12 (2015) 513-524.
[251] S. Saisivam, M. RahamathUlla, F. Shakeel, Development of floating matrix tablets of losartan potassium: In vitro and in vivo evaluation, J. Drug Deliv. Sci. Technol. 23 (2013) 611-617.
[252] F. Schneider, M. Koziolek, W. Weitschies, In Vitro and in vivo test methods for the evaluation of gastroretentive dosage forms, Pharmaceutics 11 (2019) 1-29.
[253] C.G. WILSON, In-vivo monitoring of dosage forms, J. Pharm. Pharmacol. 50 (1998) 383-386.
[254] M.C. Theodorakis, D.R. Simpson, D.M. Leung, M. Devous Sr, External scintigraphy in monitoring the behavior of pharmaceutical formulations in vivo I: Technique for acquiring high-resolution images of tablets, J. Pharm. Sci. 72 (1983) 130-135.
[255] M. Razavi, H. Karimian, C.H. Yeong, L.Y. Chung, S. Nyamathulla, M.I. Noordin, Gamma scintigraphic evaluation of floating gastroretentive tablets of metformin HCl using a combination of three natural polymers in rabbits, Drug Des. Devel. Ther. 9 (2015) 4373-4386.
[256] W. Weitschies, O. Kosch, H. Mönnikes, L. Trahms, Magnetic marker monitoring: An application of biomagnetic measurement instrumentation and principles for the determination of the gastrointestinal behavior of magnetically marked solid dosage forms, Adv. Drug Deliv. Rev. 57 (2005) 1210-1222.
[257] K. Goodman, L.A. Hodges, J. Band, H.N. Stevens, W. Weitschies, C.G. Wilson, Assessing gastrointestinal motility and disintegration profiles of magnetic tablets by a novel magnetic imaging device and gamma scintigraphy, Eur. J. Pharm. Biopharm. 74 (2010) 84-92.
[258] A. Steingoetter, P. Kunz, D. Weishaupt, K. Mäder, H. Lengsfeld, M. Thumshirn, P. Boesiger, M. Fried, W. Schwizer, Analysis of the meal-dependent intragastric performance of a gastric-retentive tablet assessed by magnetic resonance imaging, Aliment. Pharmacol. Ther. 18 (2003) 713-720.
[259] L. Curley, J. Hinton, C. Marjoribanks, A. Mirjalili, J. Kennedy, D. Svirskis, Magnetic resonance imaging to visualize disintegration of oral formulations, J. Pharm. Sci. 106 (2017) 745-750.
[260] A. Steingoetter, D. Weishaupt, P. Kunz, K. Mäder, H. Lengsfeld, M. Thumshirn, P. Boesiger, M. Fried, W. Schwizer, Magnetic resonance imaging for the in vivo evaluation of gastric-retentive tablets, Pharm. Res. 20 (2003) 2001-2007.
[261] J.C. Maublant, H. Hassine, M. Sournac, M. Dapogny, A. Veyre, J.M. Aiache, E. Goutay, Ultrasonic visualization of tablets in the gastrointestinal tract, J. Nucl. Med. 29 (1988) 129-129.
[262] L.I. Blaabjerg, L. Fan, X. Chen, P.J. Sassene, The use of capsule endoscopy to determine tablet disintegration in vivo, Pharmaceutics 12 (2020) 1-11.
[263] R. Koprowski, Overview of technical solutions and assessment of clinical usefulness of capsule endoscopy, Biomed. Eng. Online 14 (2015) 1-23.
[264] A. Martani, L.D. Geneviève, C. Poppe, C. Casonato, T. Wangmo, Digital pills: A scoping review of the empirical literature and analysis of the ethical aspects, BMC Med. Ethics 21 (2020) 1-13.
[265] C.M. Klugman, L.B. Dunn, J. Schwartz, I.G. Cohen, The ethics of smart pills and self-acting devices: Autonomy, truth-telling, and trust at the dawn of digital medicine, American Journal of Bioethics 18 (2018) 38-47.

[266] P. Moorhead, A. Zavala, Y. Kim, N.S. Virdi, Efficacy and safety of a medication dose reminder feature in a digital health offering with the use of sensor-enabled medicines, J. Am. Pharm. Assoc. (2003) 57 (2017) 155-161. e151.
[267] A. Kopelowicz, R.A. Baker, C. Zhao, C. Brewer, E. Lawson, T. Peters-Strickland, A multicenter, open-label, pilot study evaluating the functionality of an integrated call center for a digital medicine system to optimize monitoring of adherence to oral aripiprazole in adult patients with serious mental illness, Neuropsychiatr. Dis. Treat. 13 (2017) 2641-2651.
[268] FDA approves pill with sensor that digitally tracks if patients have ingested their medication, Food and Drug Administration, https://www.fda.gov/news-events/press-announcements/fda-approves-pill-sensor-digitally-tracks-if-patients-have-ingested-their-medication#:~:text=Abilify%20was%20first%20approved%20by,made%20by%20Proteus%20Digital%20Health. (accessed 27th September 2020).
[269] S. Browne, C. Peloquin, F. Santillo, R. Haubrich, L. Muttera, K. Moser, G. Savage, C. Benson, T. Blaschke, Digitizing medicines for remote capture of oral medication adherence using co-encapsulation, Clin. Pharmacol. Ther. 103 (2018) 502-510.
[270] P.R. Chai, S. Carreiro, B.J. Innes, B. Chapman, K.L. Schreiber, R.R. Edwards, A.W. Carrico, E.W. Boyer, Oxycodone ingestion patterns in acute fracture pain with digital pills, Anesth. Analg. 125 (2017) 2105-2112.
[271] J. Frias, N. Virdi, P. Raja, Y. Kim, G. Savage, L. Osterberg, Effectiveness of digital medicines to improve clinical outcomes in patients with uncontrolled hypertension and type 2 diabetes: Prospective, open-label, cluster-randomized pilot clinical trial, J. Med. Internet Res. 19 (2017) e246.
[272] S. Dai, B. Xu, Z. Zhang, J. Yu, F. Wang, X. Shi, Y. Qiao, A compression behavior classification system of pharmaceutical powders for accelerating direct compression tablet formulation design, Int. J. Pharm. 572 (2019) 118742.
[273] Quality and efficiency in pharma manu-facturing, CHEManager, (2015) https://www.chemanager-online.com/news/quality-and-efficiency-pharma-manu-facturing (accessed 10 December 2020).
[274] J. Markarian, Overcoming obstacles in process analytical technology, PharmTech, (2017) https://www.pharmtech.com/view/overcoming-obstacles-process-analytical-technology (accessed 9 December 2020).
[275] S. Zhu, Z. Song, S. Shi, M. Wang, G. Jin, Fusion of near-infrared and Raman spectroscopy for in-line measurement of component content of molten polymer blends, Sensors 19 (2019) 1-11.
[276] Designing a hopper - material properties and size, Syntron Material Handling (2019) https://www.syntronmh.com/news-events/designing-a-hopper-material-properties-and-size#:~:text=Hopper%20Recommendations&text=Syntron%20Material%20Handling%20Engineering%20Manager,rate%20on%20the%20back%20wall. (accessed 13 December 2020).
[277] D. Kirsch, Fixing tableting problems, PharmTech, (2015) https://www.pharmtech.com/view/fixing-tableting-problems (accessed 5 39).
[278] J. Vogeleer, Tablet compression: Changing trends, more demands, PharmTech, (2010) https://www.pharmtech.com/view/tablet-compression-changing-trends-more-demands (accessed 9 December 2020).
[279] Tooling Fette Compacting https://www.fette-compacting-parts.com/tooling/ (accessed 9 December 2020).
[280] Tablet press feeder for die wall lubrication, Pharmaceutical Online, https://www.pharmaceuticalonline.com/doc/tablet-press-feeder-for-die-wall-lubrication-0001 (accessed 9 December 2020).