On-Demand Manufacturing of Direct Compressible Tablets: Can Formulation Be Simplified?

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On-demand manufacturing of direct compressible tablets: can formulation be simplified?

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Running Head: On-demand tablet manufacture: simplify formulation

ABSTRACT

Purpose Oral direct compressible tablets are the most frequently used drug products. Manufacturing of tablets requires design and development of formulations, which need a number of excipients. The choice of excipients depends on the concentration, manufacturability, stability, and bioavailability of the active pharmaceutical ingredients (APIs). At MIT, we developed a miniature platform for on-demand manufacturing of direct compressible tablets. This study investigated how formulations could be simplified to use a small number of excipients for a number of different API's in which long term stability is not required.

Method Direct compressible tablets of five pharmaceutical drugs, Diazepam, Diphenhydramine HCl, Doxycycline Monohydrate, Ibuprofen, and Ciprofloxacin HCl, with different drug loadings, were made using direct compression in an automated small scale system.. The critical quality attributes (CQA) of the tablets were assessed for the quality standards set by the United States Pharmacopeia (USP).

Results This miniature system can manufacture tablets - on-demand from crystalline API using the minimum number of excipients required for drug product performance. All drug tablets met USP quality standards after manufacturing and after 2 weeks of accelerated stability test, except for slightly lower drug release for Ibuprofen.

Conclusions On-demand tablets manufacturing where there is no need for long term stability using a flexible, miniature, automated (integrated) system will simplify pharmaceutical formulation design compared to traditional formulations. This advancement will offer substantial economic benefits by decreasing product time-to-market and enhancing quality.

KEYWORDS: formulation simplification, oral solid dosage, direct compressible tablets, on-demand manufacturing, integrated pharmaceutical manufacturing.

ABBREVIATIONS

API	Active pharmaceutical ingredient
AV	Acceptance value
BCS	Biopharmaceutics classification system
CIPRO	Ciprofloxacin HCl
CQA	Critical quality attributes
DARPA	Defense Advanced Research Project Agency
DC	Direct compression
DIA	Diazepam
DPH	Diphenhydramine HCl
DOX	Doxycycline monohydrate
FT	Freeman technology
ffc	Flow function coefficient
GIT	Gastrointestinal tract
GMP	Good manufacturing practice
HPLC	High performance liquid chromatography
IBU	Ibuprofen
MCC	Microcrystalline cellulose
MIT	Massachusetts Institute of Technology
NF	National formulary

PAT	Process analytical technologies
QbD	Quality-by-design
Q value	Percentage of label claim of drug dissolved
RH	Relative humidity
RSD	Relative standard deviation
SMCC	Silicified microcrystalline cellulose
t_{80}	Time it takes for 80% of the drug to dissolve
USP	United States Pharmacopeia
UV	Ultraviolet

INTRODUCTION

Oral solid dosage form is the traditional medicine administration and the most patient compliant route (1). Two-thirds of all pharmaceutical drugs are delivered orally and about half of these are in the form of tablets (2). Tablets are the most common both by the number of marketed products and volume manufactured (2). Tablets are convenient to administer and store, relatively stable, can be dosed with accuracy and reproducibility, are comparatively inexpensive and simple to manufacture on a mass scale.

A tablet is a complex multi-element mixed solid system that undergoes mechanical stresses during its production (3). Pharmaceutical tablet development usually includes formulation and process development at a small scale, scale-up and optimization of the manufacturing process, and stability studies through development (3). For example, when designing an immediate-release tablet formulation, the motivation is to have a balanced stable formulation, so it undergoes immediate disintegration in the gastrointestinal tract (GIT) while being intact to this point withstanding manufacturing, packaging, transport, and storage. Drug substances or Active Pharmaceutical Ingredient (API) alone hardly possess suitable characteristics such as lubrication, flow, compression, or bioavailability (release) for efficient manufacturing and performance. Hence, pharmaceutical dosage forms are generally incorporated with several functional and organoleptic excipients (4). An excipient is any element except the actives drug substance. Excipients are added to the tablet formulation for several reasons including stability enhancement, bulking-up and lubrication during manufacturing, and absorption/release control (5). Quality and performance attributes of tablets are depended on the drug substance and excipients properties (4).

Excipients can cause significant variation even though they can alter the stability, manufacturability, and bioavailability of drug products. The selection principles of excipients are not well-defined. Excipients are often chosen ad-hoc without methodical drug-excipient compatibility testing (6). It is essential to study formulation optimization to develop a robust formulation that can withstand manufacturing and perform as it is defined. The formulation should optimize to ensure fast tablet disintegration and dissolution by optimizing tablet hardness without applying excessive compaction force. A formulation is more likely to be high-risk without optimization studies because the impact on the quality and the drug product performance are unknown if there is any change in the formulation or raw materials properties could happen (6).

The stability of the pharmaceutical dosage form implies the physical and chemical integrity of the drug, the excipients, and integrity of the packaging. Solid dosage forms, such as tablets, can have physical instability problems, including changes in disintegration, dissolution, hardness, friability, and appearance. Solubilization of moisture sensitive drugs could occur if too much moisture is present. Toxic degradation products and reduced efficacy may occur due to the chemical instability of drugs.

The stabilizers preserve the drug, reducing the effect of micro and macro environmental factors. The antibacterial activity of preservatives could degrade due to binding to polymers and surfactants in the formulation, or to the packaging materials, which eventually causes microbial burden in the product. Additionally, the growth of pathological microorganisms becomes a greater concern. The product quality and performance attributes could be affected due to potential instabilities in the formulation that arises due to unintentional change in the inherent nature and physicochemical characteristics of excipients (7). In solid dosage forms, drug-

excipient interactions can affect drug product physical stability such as organoleptic changes and dissolution slowdown, or chemical instability causing drug degradation (7). Hence excipient compatibility studies are significant in the drug development process, despite being cumbersome (3). Drug interaction with excipients impurities may also cause drug degradation in solid dosage forms (7). Therefore, appropriate selection of excipients with good mutual compatibility to sustain desired properties throughout the shelf life is important in developing quality product formulations.

Another critical element in developing a solid dosage form is to confirm a connection between the manufacturing process and formulation design (3). An oral solid dosage form is usually accompanied by combining multicomponent heterogeneous solids in a pharmaceutical process by changing coexisting solid phases volumes and density (3). Large stresses and strains are generated during processing that may alter the thermodynamic properties of materials that eventually affect material structure due to change of mechanical and chemical equilibrium within and between solid phases (3). Materials properties (i.e. chemical, physical or mechanical) and compatibility typically affect the processability. There are no engineering and scientific models available to accurately determine or predict structure and processing behavior as complex interaction involved in solids powder that is under multiple stresses (i.e. thermal, mechanical, and gravitational) (3). Moreover, pharmaceutical manufacturing is commonly a multi-stage batch process, though efforts continue for adapting to continuous manufacturing, that creates difficulty to define the process controls and outputs due to the existence of a multitude of variations among material, formulation and process variables (3). Excipients and a process selection require an integrated consideration of materials properties, its functionality, unit operations, the interaction between them, and overall processing characteristics. Despite advances in product development

because of the quality-by-design (QbD) initiatives over the past decade, quality is a big concern in the pharmaceutical industry. Many disastrous incidences have prompted due to manufacturing complexity and quality issues, such as recalls, withdrawals, unprecedented drug scarcities, or even risk to patients (3).

Compatibility studies such as screening drug-excipient incompatibilities are routinely required to identify (7). In continuous manufacturing, from a regulatory perspective, each batch of excipients and APIs needs to be tracked to know its contribution to each produced unit (8). The traceability of the materials has to be recorded which becomes more complicated with the increasing number of materials. A decrease in the number of excipients brings a corresponding reduction in material traceability problems, as well as a reduction in facility footprint by minimizing the number of required feeders. A reduced formulation complexity also significantly reduces time spent on comprehensive stability assessments, providing long-term cost savings. Hence, simplicity is considered an important strategy for formulation design. Simplified formulations comprise a minimum number of different excipients as possible. A simplified formulation could contribute the generation of less complex powder blends as the number of excipients is reduced (9). This reduction will allow for an enhanced understanding of manufacturing as it applies to its impact on product quality, influencing product and process design for commercial production.

At MIT we developed a compact, portable, re-configurable, automated, and end-to-end manufacturing system including API synthesis, purification and formulation, for on-demand production of pharmaceutical drug product, including direct compressible tablets (10). The miniaturized system was developed considering direct compression (DC) process consists of multiple unit operations: feeding raw materials, blending, and compression. DC processes are

considerably simplified and reduce risk as well as processing cost in high-value good manufacturing practice (GMP) containment facilities (2). On-demand manufacturing requires only short- term stability data because the formulation is dosed soon after preparation. Hence, the capability of on-demand manufacturing can simplify the formulation development.

In this work, we demonstrate how on-demand manufacturing can support the formulation simplification. Five different drugs were studied. Direct compressible tablets were manufactured from API crystals by using the developed compact and portable unit. The formulations were designed to simplify such that only filler, glidant, lubricant, and other functional excipients (if necessary) were used. The critical quality attributes (CQAs) of the tablets were assessed to meet quality criterions defined by the United States Pharmacopeia (USP).

MINIATURIZED SYSTEM FOR ON-DEMAND TABLET MANUFACTURING

The system which was developed is approximately the size of a North American household oven [foot print: 0.52 m^3], to manufacture pharmaceutical tablets on-demand on a scale of hundreds to thousands per day (Figure 1a). Its design combines off-the-shelf devices with custom-designed automated mechanisms. A direct compression method is considered to make tablets as it is considered the simplest manufacturing process. Hence, approximately half of worldwide tablet manufacturing is now accomplished through direct compression (2). The whole process is split into two process streams: the upper process stream and lower process stream (Figure 1b). The upper process stream consists of feeding individual powder (API and excipients) and subsequently blending. The lower process stream consists of powder blend dispensing and ends with tablet's compression. To allow a smooth integration between two process streams, both

process streams function individually under high-level software control. A comprehensive explanation of the unit design and build can be found in (10).

MATERIALS AND METHODS

Materials

API and excipients physical properties, blend properties, tablet properties, and tablet shelf stability are typically considered for formulation design of oral solid dosage tablet manufacturing via direct compression are shown in Figure 2. Typical materials used in tablet formulation, their functionalities and few examples are given in Table1. The materials used in this study and their specific tasks, are presented in Table 2. Diazepam (DIA), Diphenhydramine HCl (DPH), Doxycycline Monohydrate (DOX), Ibuprofen (IBU) and Ciprofloxacin HCl (CIPRO) were used as model drugs. Drug solubility in water is presented in Table 2. The drugs used belong to various biopharmaceutics classification system (BCS) such as DIA class I, DPH and IBU class II, and DOX and CIPRO class IV. The number of excipients used for manufacturing tablet was minimized to simplify formulation development. Typically, excipient selection in the drug product design is based on bulk density, compression, biopharmaceutical properties, quality target product profile, drug-excipients compatibility, and stability/target shelf life. Based on their function in the oral solid dosage form excipients are classified as diluents, binders, glidants, lubricants, stabilizers (such as antioxidants, chelators, and pH-modifiers), disintegrants, film-coating polymers, plasticizers, surfactants, colorants, sweeteners, and flavors (3). In this study stability enhancement excipients were not considered as this is on-demand manufacturing.

Hence, the formulation design of model drug was done by considering one filler/diluent, flow aid/glidant, lubricant, and additional functional excipients (if necessary).

Fillers/diluents are used to rise solid dosage bulk volume, improve cohesion, enhance flow, adjust the tablet weight as per the die capacity, and allow direct compression manufacturing (1). DC filler must possess both good flow properties and compactability (the ability to form compact by using interparticular bonds) (2). The widely used fillers/diluents for manufacturing of solid dosage are lactose, starch, and microcrystalline cellulose (MCC). Lactose is water soluble, whereas starch and MCC are water insoluble. Coarse (>150 μm) lactose has good flow properties. Anhydrous lactose, SuperTab® 21AN, has better compactability, less loss of compactability than other available lactose forms (2), and is well suited to direct compression applications (11). Low level of crystalline water also makes SuperTab® 21AN efficient for process analytical technologies (PAT) (12). Microcrystalline cellulose is well known as a highly compactible binder, and can be used for high loading of the poorly compactible drug. It is typically considered as a DC binder/filler. It also promotes disintegration.

Lubricants prevent the tablet from sticking to the punch faces and reduce interface friction of a tablet and die wall. Glidants improve the flow. The cohesive force may prevent the uniform flow of the formulated blend. Glidants reduce interparticle friction and cohesion, decrease surface charge, correct surface irregularity, and subsequently improve powder flow (1). To improve powder wettability surfactants are sometimes added to the formulation. Hence, surfactant improves drug dissolution and subsequent bioavailability of poorly soluble drugs.

Anhydrous lactose (SuperTab® 21AN) or Silicified microcrystalline cellulose (Prosolv SMCC® HD 90), fumed silica (CAB-O-SIL® M-5P), and magnesium stearate (Kosher Passover HyQual™) was used as filler/diluent, glidant, and lubricant, respectively. CAB-O-SIL® M-5P is

a synthetic, amorphous, colloidal silicon dioxide (2). Polysorbate 80 (Sepitrap™ 80) was used as solubilizer. Sepitrap™ is a micro-encapsulated powder solubilizing agent for oral solid dosage forms acting as a solid solubilizer and a compression agent. Sepitrap™ 80 consists of 45−65% polysorbate 80 and 35−55% magnesium aluminometasilicate.

Methods

Physical Characterization of APIs, Excipients, and Blends

Particle and bulk properties of APIs, excipients, and blends are essential to understand its impact on the pharmaceutical formulation and finished products manufacturing (13). The formulated blend and the finished product must be obtained consistently and reproducibly. For the formulation development physical characteristics such as size, shape, bulk density, and flow properties of APIs, excipients (specifically fillers), and blends were measured. Dry powder dispersion unit (Scirocco 2000) of Mastersizer 2000 particle size analyzer (Malvern Instruments Ltd.) was used to measure particle size of as-received APIs and excipients. The Scirocco 2000 comprises an enclosed vibratory tray to place API or excipient particles and uses compressed air to transport and suspend the sample while they pass through the air cell. 50% feed rate setting was used to feed the powder in Scirocco 2000. 2 bar air pressure was used to disperse powder through the air cell. Volume-weighted particle sizes information is obtained from the Mastersizer 2000. Fumed silica CAB-O-SIL® M-5P median size is about 14 nm obtained from the literature (14). Figure 3 shows API's images that were taken using Nikon optical microscope (model: Eclipse ME600).

FT4 Powder Rheometer (Freeman Technology, Tewkesbury, UK) was used to measure bulk density and powder flow behavior of APIs, excipients, and blends. Bulk density determines how

much powder can fit in a space such as a hopper, blender, and tablet die (13). The shear cell test was done to measure powder flow properties. The shear test generates multiple data on powder flow behavior includes a flow function coefficient (ffc). It is described by the ratio of the major principal stress to the unconfined yield strength and used to determine powder flowability. In this work normal stress of 3 kPa was used for ffc test. Based on Schulze (15), ffc values can be classified into several regimes: ffc < 1, not flowing; 1< ffc < 2, very cohesive; 2 < ffc < 4, cohesive; 4 < ffc <10, easy flowing, and ffc >10, free-flowing. Powder compressibility (the ability of a powder to decrease in volume under pressure represented as the percentage change in volume after compression), an indirect flowability measurement, was also measured. A low compressibility value indicates powder is free-flowing whereas, a value greater than 30% represents poor powder flow (3). FT4 Powder Rheometer test procedure can be obtained in the literature (16).

Manufacturing of Tablets

Tablets were manufactured using the formulated blends. Table 3 presents formulated blend's composition. Based on the available marketed product, each drug's dose strength was chosen (17). The total weight was determined based on the weight of the marketed product, die volume, bulk density of the blend and maximum compression force that can be applied by the press. Magnesium stearate and silica concentrations were first chosen and finally, to complete the composition lactose or SMCC concentration was chosen (18). Lactose or SMCC, API, and silica were added into the blender consecutively to blend all materials. For DPH an additional functional excipient, polysorbate 80, was added to improve solubility. The blender impeller was rotated at 80 rpm and blended all materials for 26 min. After that, the lubricant, magnesium stearate, was added to the blender and blended at 80 rpm for an additional 4 min. To avoid over

lubrication of the formulation, minimize adverse softening or hydrophobic effects, which would interfere with bonding and reduce the tablet hardness, the magnesium stearate was not added at the beginning (19). The blend volume was 40% of the blender total volume. A total of 44.0−59.0 g of the blend (see Table S1 in supplementary for blend batch size and its composition) was produced in each blended batch depending on the drug formulation and blend density.

After completion of blending the blended powder was then dispensed into the tapping feeder hopper. Except for CIPRO, tablets of total weight 250−340 mg of all drugs was made by dispensing powder blend into a 10 mm die. For CIPRO 12 mm die was used to accommodate 500 mg powder. 35 (±5) ─56 (±5) taps were required to obtain necessary fill weight for the tablet. The weight variation of ± 10% of target tablet weight was considered as acceptable. To make tablets the dispensed powder was then compressed at a force of 450 kg (equivalent pressure of 56.22 MPa for 10 mm and 39.04 MPa for 12 mm sized tablet). The punch diameter was 10 or 12 mm and round shaped. 1.0 mm/s punch speed was used. Gamlen PCA-500D can apply 500 kg maximum compression force. Hence, 450 kg of force was chosen in this operation for safe operation. It is noted that 1000 kg version of the Gamlen PCA has recently become available which can be used in future to apply higher compression force. Tablet weight and dimensions (diameter and thickness) were measured. For dimension measurement a digital slide caliper (Fowler 54-100-000-2, Fowler Company Inc., Newton, MA, USA) was used. To test the storage stability of the manufactured tablets over time, they were stored for 2 weeks at accelerated storage conditions (30°C, 65% RH) in the humidity chamber (LHU 113, ESPEC North America, Inc., MI, USA). As the purpose of on-demand manufacturing is to produce drug product to be used immediately and not to be stored –that is why 2 weeks period was chosen. The manufactured and stored tablets were analyzed subsequently.

Tablets Characterization

Assay, content uniformity, weight, tensile strength, and dissolution performance of tablets were characterized. USP 39–NF 34 official monographs were used to follow the test procedures for characterization (20). Mobile phase and sample solution were prepared for the assay. The assay was determined using an Agilent Technologies 1200 series HPLC equipped with a UV detector. The column that meets USP specs for each drug was used in HPLC. The injection volume and mobile phase flow rate were maintained as mentioned in the USP monograph. A detailed procedure for the tablets assay of each drug is given in the supplementary.

Drug substance content within 85%─115% of the labeled content was considered as 100%. Content uniformity or weight variation (USP-39 <905> Uniformity of Dosage Units) methods were considered determining the uniformity of the tablets (21). DIA, DPH, and DOX were tested by content uniformity method while IBU and CIPRO were tested by weight variation method. For IBU and CIPRO weight variation method was selected as tablets containing ≥ 25 mg of drug substance and drug substance comprising ≥ 25 % by weight of the dosage unit. To determine uniformity 10 tablets of each drug was assayed. Using USP <905> Uniformity of Dosage Units acceptance value (AV) was calculated. AV of 15 or less was considered to meet the acceptance criteria.

Tablets weight was measured in a custom designed weighing station built on a Sartorius load cell (Sartorius WZA 224-L). Tablet hardness or breaking force was determined using the Dr. Schleuniger Pharmatron Model 6D tablet hardness tester. According to equation 1, tablet hardness was converted to tensile strength (22), where F, D, and t represent the breaking force, tablet diameter, and tablet thickness, respectively. For each drug (DIA, DPH, DOX, IBU or CIPRO) six tablets tensile strength were measured.

$$\sigma = \frac{2F}{\pi Dt} \ldots\ldots\ldots\ldots\ldots (1)$$

Tablets were stored in a humidity chamber (LHU 113, ESPEC North America, Inc., MI, USA) at 30°C and 65% RH for 2 weeks to assess stability. Tablets (after manufacturing & stability) dissolution testing was performed in a Varian VK 7025 dissolution apparatus (Varian, Inc., USA). Testing was done following USP 39–NF 34 official monographs and USP II paddle method. The dissolution media temperature was maintained at 37°C± 0.2°C and tablets were added manually. The UV values were obtained using an automatic Varian UV–Vis Cary 50 apparatus having in situ probes. Average of three tablets dissolution was reported for each drug. A detailed procedure for the tablets dissolution of each drug is given in the supplementary.

RESULTS AND DISCUSSION

Formulation Design and Simplification for On-demand Manufacturing of Direct Compressible Tablets

Typically a tablet contains 25─30% API and 75─70% excipients. Hence, in the formulation design and development of tablets excipients play a key role and its selection is critically important in designing the formulation of direct compressible tablets. Table 1 presented several types of excipients that are required for designing the formulation of solid dosage development. The excipients used in the formulation design of the current work are presented in Table 2.

For each formulation, only one filler/diluent was used to minimize the blend components number. In this work, lactose was used as filler for DIA, DPH, and IBU whereas SMCC was chosen for DOX and CIPRO. Knieke et al., (14) showed water-insoluble particles settle and form sediment cake in the dissolution vessel. Hence, during dissolution drug was captured in the sediment "cake" and prevented from being completely released due to limiting the mass transfer of the drug and the surrounding medium. A similar observation was found in the preliminary

experiments with DIA and SMCC. Hence lactose was given priority as filler in formulation design. The API properties dominate tablet compactability/hardness at high API loadings. Hence SMCC was chosen for CIPRO and DOX to obtain high tablet tensile strength especially with CIPRO which had the highest drug load.

The most commonly used powder lubricant in pharmaceutical tablet manufacturing is magnesium stearate and its effective concentration can be as low as 0.25─0.5% (2). In this study 0.5% magnesium stearate was used for all APIs except CIPRO. Tablet chipping due to powder sticking on the punch face was observed for CIPRO at 0.5% magnesium stearate. Hence, magnesium stearate concentration was increased to 1.0% for CIPRO.

Untreated fumed silica CAB-O-SIL® M-5P is widely used as the glidant in the formulation of tablet. . Colloidal silica fills the surface pores of the solids and helps particles move more freely by each other by preventing interlocking (2). Polysorbate 80 was used for DPH to improve wettability and subsequent dissolution. For other drugs solubilizer was not used as no variation in dissolution profile was observed.

During the formulation design, an ordered mixture of API and excipients was considered to minimize segregation. Segregation of blended powder components is a major concern during tablet manufacturing as it significantly impacts the content uniformity of the drug in the tablet. Segregation of particles can be minimized by making an ordered mixture in which small cohesive particles adhere to larger particles and provide a substantial degree of resistance to segregation. Hence, minimum segregation is found when micronized fine drug particles and large particle excipient is combined in the formulation design (2). The particle size of APIs and excipients was presented in Table 4. It is observed that d_{50} of API is 13−76 μm whereas, the filler is 128−189 μm. The combination works well as there was no segregation observed.

On-demand Tablet Manufacturing Using Automated Miniaturized System

Tablets were manufactured in the automated, miniaturized and portable system using the formulated blends. Before tablets manufacturing blends were characterized. During tablet production, to produce acceptable quality of tablets from a particulate solid, blends need to have three essential properties: (i) good flow properties to fill dies in a reproducible manner, (ii) particles must form a coherent structure during compaction and ejection, and (iii) smooth tablet ejection. Very few solids possess all three properties necessitating modification through the addition of excipients.

Powder flow and compaction, the bulk handling properties, may be affected by API powder properties such as particle shape, size, density, porosity, surface area, cohesiveness, and hygroscopicity (3). These could also impact tablet manufacturability especially if a blend contains a high fraction of API. Table 4 presents API and excipients particle size except for fumed silica. Figure 3 shows the morphology of all API particles captured via microscopy.

Table 4 summarizes APIs bulk and particle properties. DIA, IBU and CIPRO are small particles (with a d_{50} less than 25 μm) compared to DPH and DOX (with a d_{50} 75 μm). The microscopy image shows various particle shapes of API particles such as DIA, have irregular shapes and agglomerated particles (Figure 3a), whereas DPH and IBU have plate-like rectangular shapes (Figures 3b, d). Comparison of API and excipients properties in Table 4 shows API and magnesium stearate have high compressibility and low bulk density due to their fine size. API and excipients are cohesive and easy flowing, respectively, indicated by the flow function coefficient (ffc).Overall, all excipients (Lactose, SMCC, and Polysorbate 80) except magnesium stearate have low compressibility, high bulk densities, and are easy flowing. Lactose and SMCC showed improved ffc value due to its larger particle size. In general, with the increase

of particle size powder flowability increases, the cohesivity of the powder decreases due to weaker interparticle forces between particles (23). This helps the powder to pack in a denser state which eventually increase powder density (23).

Good tablet manufacturing can be challenging if powder blends do not meet the criteria: well flowability, readily compressible, and well lubricated. Poor powder flow causes large tablet weight variability, poor content uniformity, and inconsistent tablet properties such as hardness, disintegration, and dissolution, etc (24). Table 5 presents powder blend flow properties measured using FT4 powder rheometer. All API blends, except for CIPRO, are free-flowing powders and have ffc value > 10 (15). CIPRO has ffc <10 and is categorized as easy flowing. A low ffc value might be due to fine particle size and high drug loading. The API blends are suitable for direct compression due to their bulk density of 0.59 g/cm^3 and above. In industrial practice for continuous direct compression blend bulk density of at least 0.45 g/cm^3 is required (24, 25).

For all API blends, compressibility value is lower compared to the API compressibility. CIPRO blend has higher compressibility value compared to other API blends due to finer particles size and higher drug loading. Compressibility test indicates powder packing efficiency and is considered important to the powder tabletability (25), (15). In general, compressibility indicates a qualitative measurement of compactability (15, 16) and lower compressibility is preferred for better direct compression performance, storage in the hoppers, and transportation (26). Due to formulation composition and material physical properties differences a small difference in bulk density and compressibility among API blends was observed (Tables 3, 4). DIA and DPH have the highest bulk density as the blend properties are dominated by SuperTab® 21AN properties which is >85% w/w. Bulk density, ffc, and compressibility values indicate all

blends were suitable for direct compression. Tablets of all APIs were manufactured using the custom-built miniature tableting unit.

Tablets Characterization after Manufacturing and Stability

During development of tablet products, a considerable amount of effort is spent to ensure that resulting tablets have the appropriate characteristics. Table 6 presents tablet properties (tensile strength, weight, diameter, thickness, assay, and content uniformity) of all APIs after manufacturing and after 2 weeks of stability test. For all API blends, 10 manufactured tablets average weights with % RSD value are reported. The acceptable weight variation was considered within the ± 10% of target tablet weight 250 mg for DIA, DPH, and DOX, 340 mg for IBU, and 500 mg for CIPRO. For all drug tablets, RSD value was below 6% that indicates less tablet weight variation and uniform blend dispense into the die.

Tensile strength, the minimum force required to break a tablet, expresses the mechanical strength of a tablet. Particle size, shape, surface area, density, and interparticle interactions affect the tablet's tensile strength (3). Powder undergoes several steps such as particle rearrangement, particle fracture, and particle deformation during tableting by compression. The interparticle interaction, material properties, and compression process impacted successful tablet formation. The average tensile strength of tablets was between 0.52─1.14 MPa. The tensile strength was determined using equation 1. Six tablets diameters and thickness were measured. For all tablets, except CIPRO, the average diameter and thickness was 10.06 (±0.03) ─10.11 (±0.02) mm and 2.59 (±0.06) ─3.80 (±0.12) mm, respectively. For CIPRO tablets, the average values for diameter and thickness were 12.04 (±0.01) mm and 4.10 (±0.01) mm, respectively. After ejection, due to gradual radial recovery, a slight increase in tablet diameter is observed. A

gradual radial recovery of tablets was observed and reported by Seton et.al. (27). Tablet strength is presented by tensile strength (28). The post-compaction operations such as coating, dissolution, handling, and storage are affected by the strength of tablets (19). Powder compositions and compression process parameters affect the tablet strength (29). For a given formulation, the material strength is mainly dependent on the powder compression state that depends on the compression pressure. The tablet tensile strength increase with the increase of compression pressure (29). In general, higher compression force causes strong inter-particulate bonding and makes the tablet stronger. In this study, Gamlen PCA-500D single punch tablet press could apply maximum 450 kg compression force. The tablet tensile strength variation observed is due to the formulation composition differences. Hence, higher tensile strength is observed for IBU and CIPRO formulation due to the improved compactability caused by an increased amount of API. For DOX tablets, SMCC is a key contributor to the high tensile strength of the tablet as it is 78% of the formulated blend. On the other hand, the lactose used in other blends resulted in lower tablet strength for DIA and DPH. MCC limits the dissolution (preliminary study with DIA confirmed), a critical quality attribute (CQA). Hence, the use of MCC as a filler is limited though it has better compactability properties than lactose. Tablets manufactured with lactose showed lower tensile strength. However, tablets were strong enough to withstand manual distribution within the same facility. Here tensile strength was not categorized as a CQA since it does not have any impact to ensure the safety & efficacy of the tablets and there is no need for further development..

Based on the USP-39 official monograph, tablets contain 90%-110% of the labeled amount meet the standard of the assay. Similarly, the tablet meets USP quality standards if the calculated acceptance value of the active ingredient is less than or equal to 15.0, based on 10

dosage units (21). Table 6 shows the assay values of tablets are within the range and the acceptance value is below 15. All tablets meet the content uniformity/weight variation criteria. Compared to other API tablets, DIA showed a slightly higher AV which is due to low drug concentration in DIA tablets. Low dose tablets often encounter more challenges to meet the blend or tablet content uniformity compared to large dose tablets (30).

Figure 4 illustrates the dissolution results for the tablets after manufacturing and after 2 weeks of accelerated stability test. Drug release and stability are the most important CQAs of oral solid dosage forms. Drug release interprets availability of drug molecules for absorption that correlates product efficacy and safety. On the other hand, stability determines the feasibility of maintaining drug product quality throughout a specified period which is called shelf-life. Thus, the key to design and develop an effective, safe, and stable dosage form is to understand the impact of formulation, process, and their interplay on drug release and stability (3).

It is noted that USP dissolution test is satisfied when the Q value (which is expressed as a percentage of label claim of drug dissolved) reaches at that time or earlier. Typical Q values are in the range of 75%–80% dissolved. According to USP monograph, 75%-85% of the drug (DIA, DPH, DOX, IBU, and CIPRO) should dissolve within 30-60 min. It is observed that four out of five tablets (DIA, DPH, DOX, and CIPRO) showed fast dissolution, whereas IBU tablets showed slower dissolution. For IBU tablets t_{80} (time for 80% of the drug to dissolve) is 23 min. However, the dissolution result of IBU tablets meets the USP monograph. IBU tablets slower dissolution is attributed to slower disintegration caused by higher tensile strength to some extent and substantively higher drug loading compared to other API tablets except CIPRO. A lower tensile strength consequences in a higher tablet porosity shown by Tye et al.(28). Tablet

porosity is an essential parameter that expedites liquid infiltration, affecting disintegration and following dissolution (28).

Tablet properties such as assay, tensile strength, and dissolution after two weeks of stability are presented in Table6 and Figure-4. The bulk drug or drug product quality variation with time under accelerated storage conditions (30°C, 65% RH) can be obtained from the stability test. The assay values of tablets are within the range of 90−110% as observed in Table 6. There is no variation in tensile strength observed for DOX and IBU tablets. DIA and DPH tablets show an increase of tensile strength whereas, CIPRO tablets shows a reduction of tensile strength. The rise in tablets hardness might be due to recrystallization of the water-soluble excipient, SuperTab® 21AN, in the void spaces (31). Solid bridges between particles can develop due to the recrystallization of dissolved materials (32). The specific drug and excipient combination and their physical properties (such as hygroscopicity, aqueous solubility, and crystallinity) impacted the extent of hardness increase (31). Tablets made with microcrystalline cellulose become softer on contact to high humidity due to moisture uptake and loosening of interparticle hydrogen-bonds (2). No change in dissolution profiles of all four drugs (DIA, DPH, DOX, CIPRO) tablets were observed. However, the dissolution of IBU slows down as compared to that of freshly manufactured tablets.

The slower release of a drug could be due to the effect of chemical instability during storage or drug excipients incompatibility. The chemical instability of the API is a function of both formulation and storage environment(33). An incompatibility of API and excipients in tablets can consequence in any of the following during stability testing: color/appearance change, mechanical properties (e.g., tablet hardness) loss, dissolution performance changes, conversion of physical form , loss through sublimation, potency reduction, and an increase in

degradation products (34). There was no color change or loss in mechanical properties observed for IBU. The only change observed was in the dissolution profiles. Cory et al., (33) showed 0.1% degradation of IBU occurred during stability of 3 weeks at 70°C/75% RH, when lactose was used as an excipient. In addition, pharmaceutical solids typically contain several defects and various degrees of disordered, amorphous regions(35). Water molecules are preferentially absorbed into the interior of these regions and be incorporated into the crystal lattice through hydrogen bonding, van der Waal's interactions, or both. Water is an excellent plasticizer, increasing molecular motion in those amorphous regions, which enhances degradation of drug. The overall findings indicated that for IBU, a drug-excipients compatibility study needs to be done. The potential impact of these results on the in vivo bioavailability would require further investigation beyond the scope of this study.

CONCLUSION AND OUTLOOK

The present study of five well-known drugs manufacturing capability demonstrates that the concept of on-demand tablet production in a compact, portable, reconfigurable, and automated system can be used as a promising platform to simplify the formulation. The pharmaceutical manufacturing paradigm is slowly shifting from batch to continuous, integrated systems. In continuous manufacturing, having multiple excipients makes it more difficult from a process control perspective as formulation, a multitude of material interaction, and process variables are involved. Moreover, the conventional batch pharmaceutical manufacturing required to consider a number of excipients during formulation design as excipients are required for API processability, stability, and bioavailability enhancement makes formulation design tedious and time-consuming. We envision that on-demand manufacturing has the potential to diminish formulation complexity relative to products demanding yearlong stability. This advancement will

provide significant economic benefits by increasing product quality and decreasing time-to-market.

ACKNOWLEDGEMENTS

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Table captions

Table 1. Typical excipients used in tablets formulation.

Table 2. Materials used for making tablets, their functionality, and physical properties.

Table 3. Formulations used for making tablets of drugs.

Table 4. Properties of Active Pharmaceutical Ingredients (APIs) and excipients used for tableting.

Table 5. Properties of powder blends prepared for tableting.

Table 6. Properties of tablets (weight, diameter, thickness, tensile strength, assay, and acceptance value) prepared using blends and after 2 weeks of stability.

Table 1. Typical excipients used in tablets formulation.

Type	Functionality	Examples	Can be eliminated for on-demand DC tablet manufacturing*
Anticaking agent	Reduces caking or clumping	Talc	Yes/No
Antimicrobial preservative	*Bacteria, yeast, and mold growth inhibitor*	*Glycerin, benzyl alcohol*	Yes
Antioxidant	*Reduces oxidative reactions that could alter ingredients*	*Ascorbic acid, butylated hydroxyanisole*	Yes
Binder	Facilitates granules preparation via powder agglomeration	Povidones, starches	Yes
Chelating or complexing agent	*Stabilizes ions*	*Ethylenediaminetetraacetic acid salts, cyclodextrins*	Yes
Coating agent	May mask unpleasant tastes or odors, improve ingestion or appearance, protect ingredients from the environment, or modify release of the active ingredient	Shellac, hypromellose	Yes/No
Colorant	Produces a distinctive appearance and may protect light-sensitive ingredients	FD&C colors, titanium dioxide	Yes/No
Disintegrant	Promotes rapid disintegration to allow a drug to dissolve faster	Sodium starch glycolate, crospovidones	Yes/No

Enteric coatings	Protects from dissolution in stomach	HPMC, methylacrylate copolymers	Yes/No
Filler or diluent	Increases volume or weight	Calcium phosphate, lactose	No
Glidant	Promotes powder flow	Colloidal silicon dioxide	No
Lubricant	Lubrication during manufacturing process	Magnesium stearate, glycerides	No
pH modifier	*Controls pH to improve drug stability or avoid irritation when consumed*	*Citric acid and its salts, salts of phosphoric acid*	Yes/No
Release modifier	Provides extended-release capability	Ethylcellulose, guar gum	Yes/No
Solubilizing agent	Promotes dissolution of insoluble ingredients	Sodium lauryl sulfate, polysorbates	Yes/No
Solvent/vehicle	*Improves stability and bioavailability*	*Water*	Yes
Sweetening agent	Improves palatability	Sucrose, saccharin	Yes/No

*The excipients that cannot be eliminated to manufacture DC tablets are written as *No*; those can be eliminated are written as *Yes*; those can be used or eliminated depending on the application are written as: *Yes/No*.

Table 2. Materials used for making tablets, their functionality, and physical properties.

Drug/ Excipient	Materials	Brand/Trade name	Functionality	Solubility in water (mg/ml)
Drug	Diazepam (DIA)	Valium®	Anxiolytic and sedative	0.050
	Diphenhydramine HCl (DPH)	Benadryl®	Antihistamine	≤ 100
	Doxycycline Monohydrate (DOX)	Monodox®	Tetracycline antibiotic	Very slightly soluble
	Ibuprofen (IBU)	Advil®/Motrin®	Anti-inflammatory	0.021
	Ciprofloxacin HCl (CIPRO)	Cipro®	Antibiotic	30
Excipient	Anhydrous lactose	SuperTab® 21AN	Filler/Diluent	-
	Silicified microcrystalline cellulose (SMCC)	Prosolv SMCC® HD 90	Filler/Diluent	-
	Fumed silica	CAB-O-SIL® M-5P	Glidant/Flow aid	-
	Magnesium stearate NF/EP/JP	Kosher Passover HyQual™	Lubricant	-
	Polysorbate 80	Sepitrap™ 80	Solubilizer	-

Table 3. Formulations used for making tablets of drugs.

Drug	API strength	Tablet weight	Tablet formulation compositions						
			API	Anhydrous lactose	SMCC	Fumed silica	Magnesium stearate	Polysorbate 80	Total
	(mg)	(mg)	(%)						
Diazepam (DIA)	10	250	4.00	95.00	-	0.50	0.50	-	100
Diphenhydramine HCl (DPH)	25	250	11.44	85.56	-	0.50	0.50	2.00	100
Doxycycline Monohydrate (DOX)	50	250	20.80	-	78.20	0.50	0.50	-	100
Ibuprofen (IBU)	200	340	58.82	40.18	-	0.50	0.50	-	100
Ciprofloxacin HCl (CIPRO)	250	500	58.20	-	39.80	1.00	1.00	-	100

Table 4. Properties of Active Pharmaceutical Ingredients (APIs) and excipients used for tableting.

API, Excipients	Particle size (μm)			Bulk density	Compressibility	Flow function coefficient (ffc)
	d_{10}	d_{50}	d_{90}	g/cm^3	(%)	
Diazepam (DIA)	5.74	23.12	110.75	0.52	32.73	2.78
Diphenhydramine HCl (DPH)	15.74	71.85	245.14	0.42	35.60	2.52
Doxycycline Monohydrate (DOX)	10.43	75.56	485.40	0.72	14.63	3.60
Ibuprofen (IBU)	4.86	21.87	75.31	0.53	25.07	3.87
Ciprofloxacin HCl (CIPRO)	3.75	12.49	439.56	0.39	38.90	2.95
Anhydrous lactose	26.03	188.75	425.90	0.74	13.10	5.69
Silicified microcrystalline cellulose	38.83	127.61	324.56	0.52	6.17	>10
Magnesium stearate	2.76	6.86	15.10	0.31	38.97	5.18
Polysorbate 80	2.37	13.68	209.06	0.40	4.35	>10

Table 5. Properties of powder blends prepared for tableting.

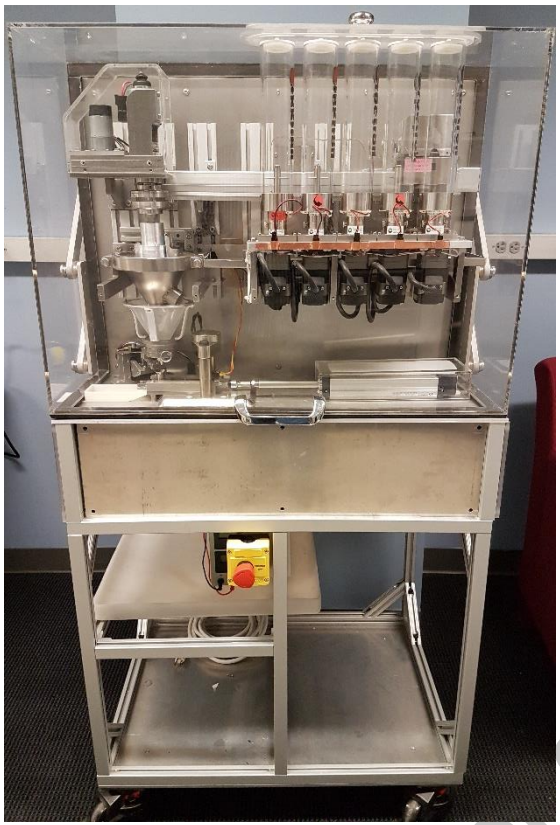
Blends	Bulk density	Compressibility	Flow function coefficient (ffc)
	g/cm^3	(%)	
Diazepam (DIA)	0.72	12.27	>10
Diphenhydramine HCl (DPH)	0.74	6.68	>10
Doxycycline Monohydrate (DOX)	0.59	5.70	>10
Ibuprofen (IBU)	0.65	5.18	>10
Ciprofloxacin HCl (CIPRO)	0.69	21.1	8.25

Table 6. Properties of tablets (weight, diameter, thickness, tensile strength, assay, and acceptance value) prepared using blends and after 2 weeks of stability.

	After manufacturing					After two weeks of stability	
Blends	**Tablet weight (Average, % RSD)**	**Tablet dimension: diameter, thickness (Average ±STDEV)**	**Tensile strength (Average ±STDEV)**	**Assay (% of the labeled content)**	**Acceptance value (AV)**	**Tensile strength (Average ±STDEV)**	**Assay (% of the labeled content)**
	(mg)	mm	MPa	(%)		MPa	(%)
Diazepam (DIA)	265.74, 1.69	10.11±0.02, 2.59±0.06	0.52±0.07	103.69	9.36	0.76±0.05	95.64
Diphenhydramine HCl (DPH)	246.72, 5.77	10.10±0.01, 2.63±0.02	0.53±0.05	97.39	7.86	0.64±0.04	101.18
Doxycycline Monohydrate (DOX)	249.26, 2.00	10.10±0.00, 2.84±0.02	1.01±0.08	95.96	7.26	1.04±0.06	95.85
Ibuprofen (IBU)	332.88, 3.36	10.06±0.03, 3.80±0.12	1.14±0.09	98.77	7.96	1.14±0.06	101.82
Ciprofloxacin HCl (CIPRO)	509.70, 3.55	12.04±0.01, 4.10±0.01	0.81±0.01	98.88	7.74	0.67±0.04	97.85

List of Figures

(a)



(b)

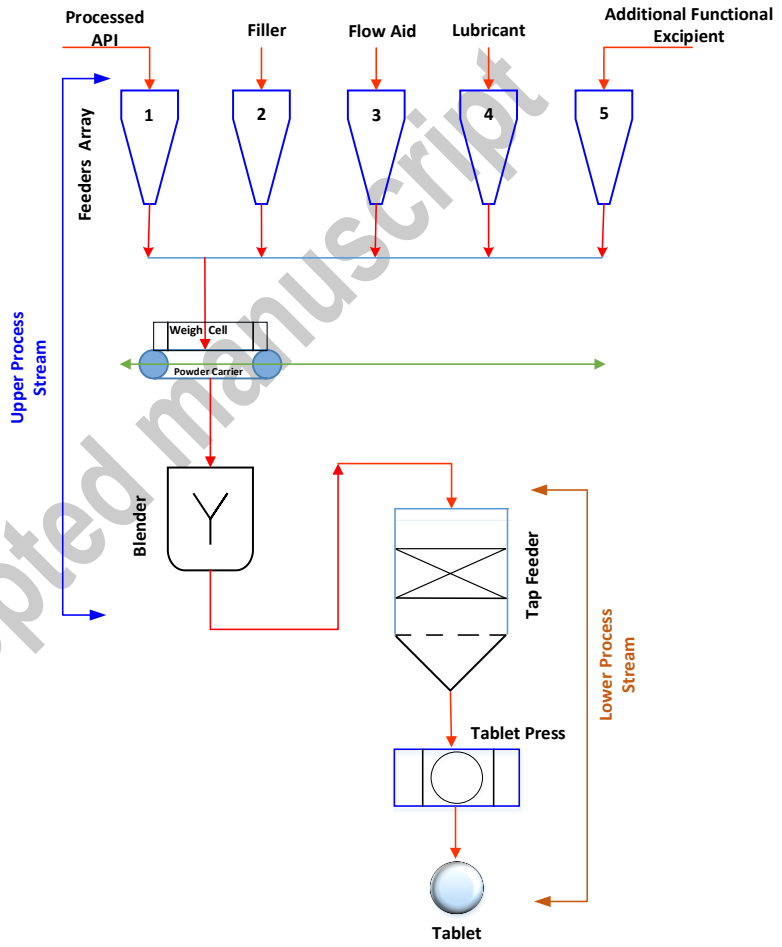


Figure 1. Azad et al. (2019), intended for *Pharm. Res.*

(a) Compact, portable, re-configurable, and automated tablet manufacturing unit [72.4 cm (length) ×53.3 cm (width) ×134.6 cm (height)], volume: 0.52 m^3; (b) Schematic of the process for direct compression tablet manufacturing.

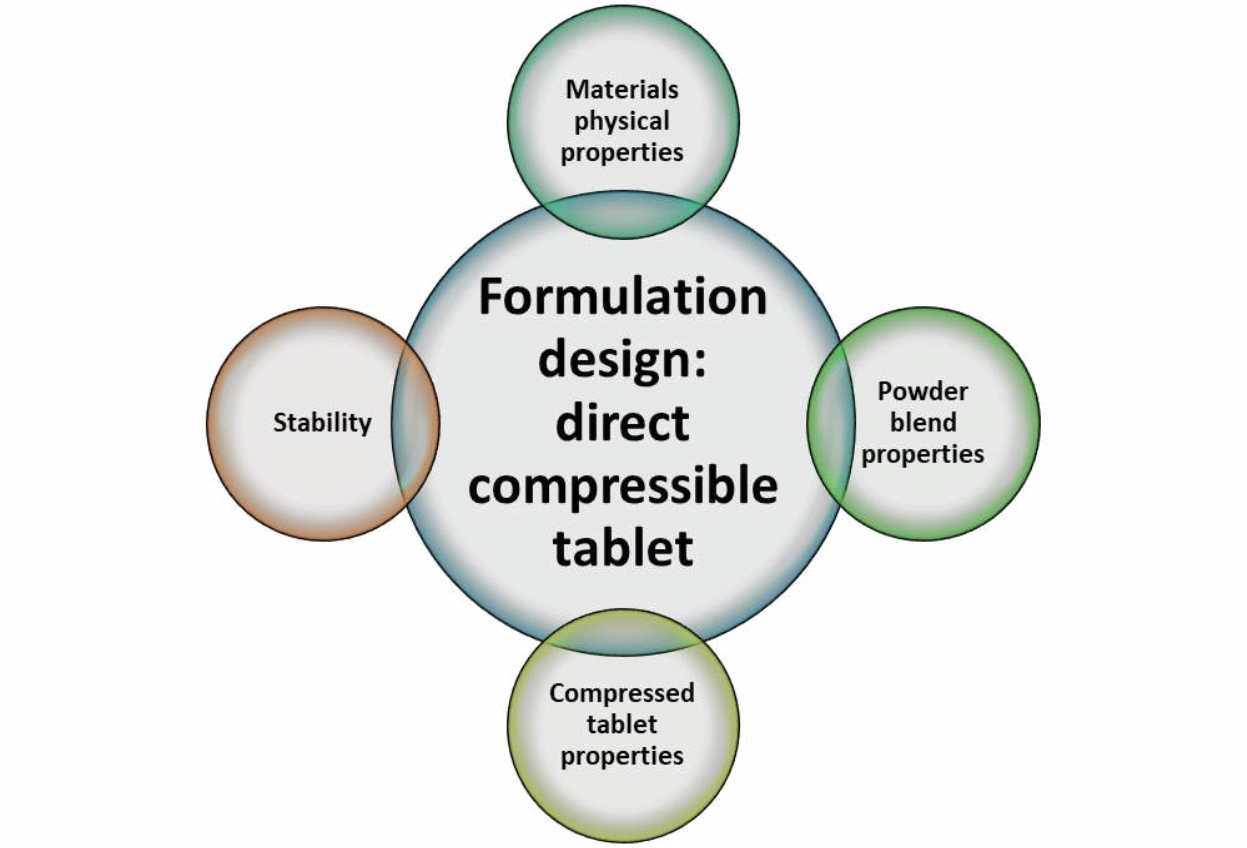


Figure 2. Azad et al. (2019), intended for *Pharm. Res.*

Factors considered for formulation design of oral solid dosage tablet manufacturing via direct compression.

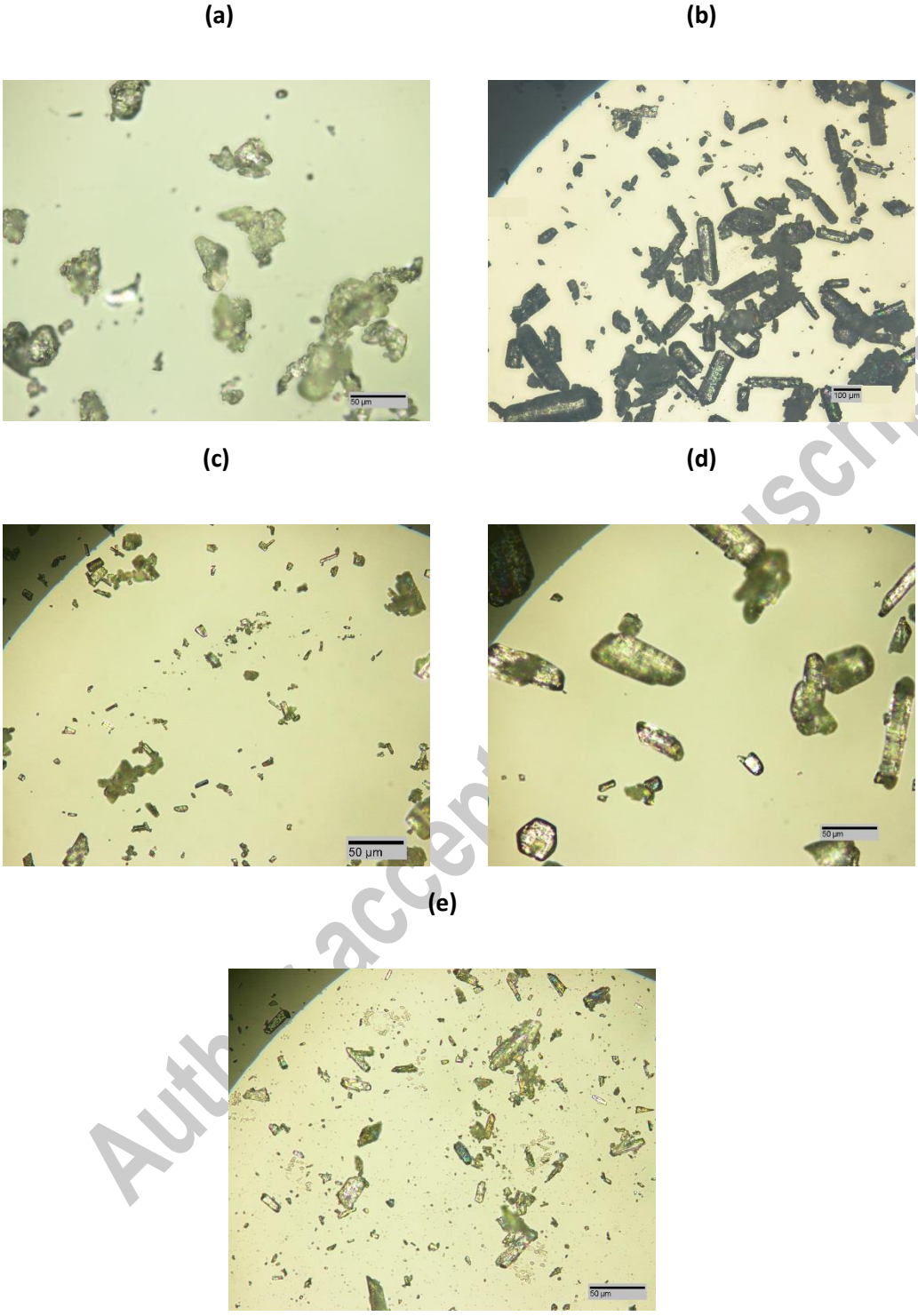


Figure 3. Azad et al. (2019), intended for *Pharm. Res.*

Optical microscope images for a) Diazepam, b) Diphenhydramine HCl, c) Doxycycline Monohydrate, d) Ibuprofen, and e) Ciprofloxacin HCl particles.

(a) **(b)**

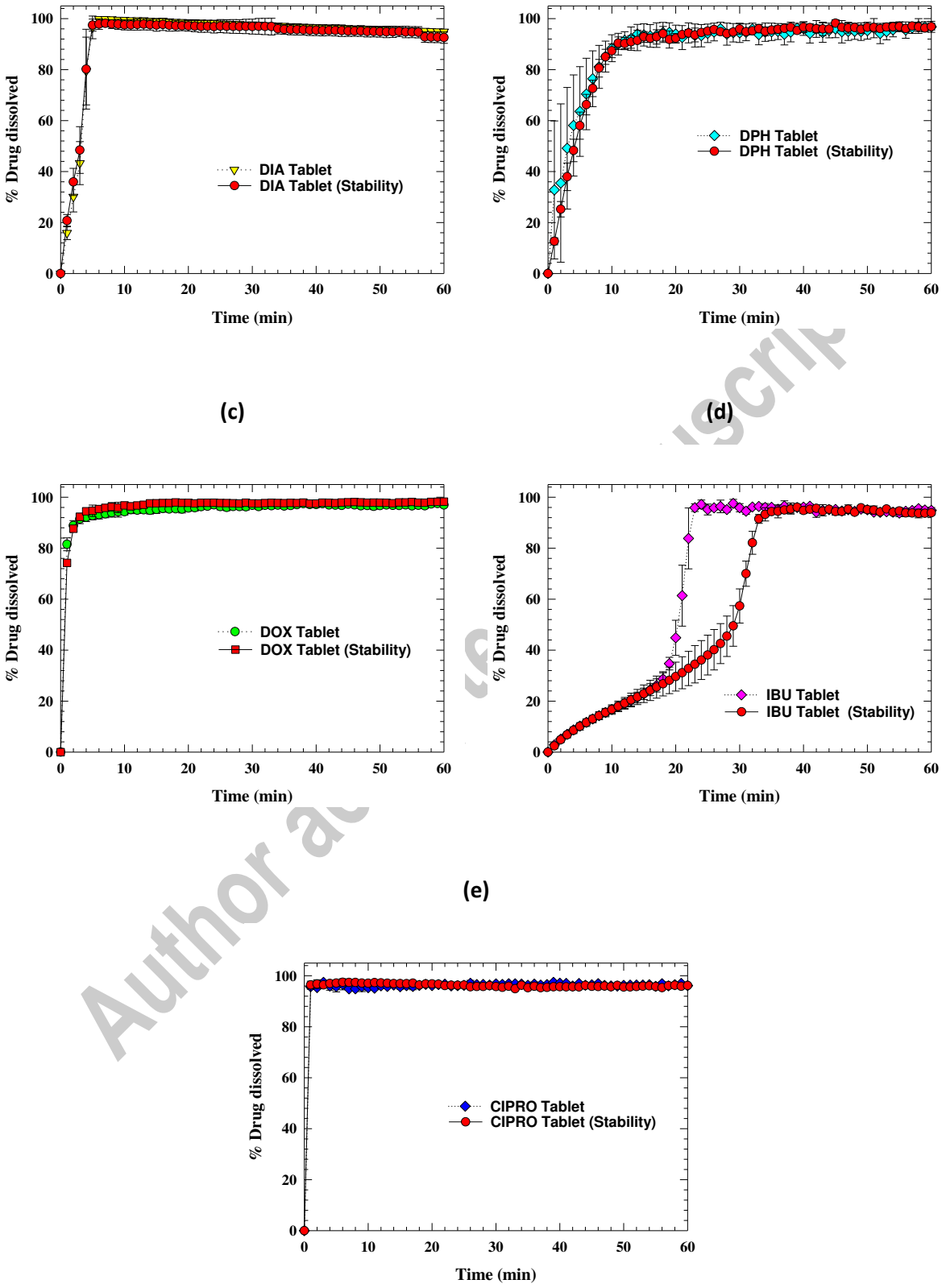


Figure 4. Azad et al. (2019), intended for *Pharm. Res.*

Evolution of dissolution of tablets after manufacturing and after stability: (a) DIA tablets, (b) DPH tablets, (c) DOX tablets, (d) IBU tablets, (e) CIPRO tablets in a USP II apparatus. Average and standard deviation are de