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Implementation of Quality by Design (QbD) for Development of Bilayer Tablets

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Abstract

Bilayer tablets offer various drug release profiles for individual drugs incorporated in each layer of a bilayer tablet, which is rarely achievable by conventional tablets. These tablets also help avoid physicochemical incompatibilities between drugs and excipients. Successful manufacturing of such more complex dosage forms depends upon screening of material attributes of API and excipients as well as optimization of processing parameters of individual unit operations of the manufacturing process that must be strictly monitored and controlled to obtain an acceptable drug product quality and performance in order to achieve safety and efficacy per regulatory requirements. Optimizing formulation attributes and manufacturing processes during critical stages, such as blending, granulation, pre-compression, and main compression, can help avoid problems such as weight variation, segregation, and delamination of individual layers, which are frequently faced during the production of bilayer tablets.

The main objective of this review is to establish the basis for the implementation of Quality by Design (QbD) system principles for the design and development of bilayer tablets, encompassing the preliminary and systematic risk assessment of critical material attributes (CMAs) and critical process parameters (CPPs) with respect to in-process and finished product critical quality attributes (CQAs). Moreover, the applicability of the QbD methodology based on its purpose is discussed and complemented with examples of bilayer tablet technology.

Keywords: Bilayer Tablet; Delamination; Weight Variation; Segregation; Drug release; Process Analytical Technology (PAT)

I. Introduction

Bilayer tablets have been considered one of the best options for the development of fixed-dose combination (FDC) formulations, circumventing not only the problem of physicochemical incompatibilities of drugs but also providing different drug release profiles for each drug present in the individual layer of bilayer tablets (Janczura et al., 2022; Singh et al., 2019; Won et al., 2021). Bilayer tablets can provide unique product performance regarding drug delivery and patient compliance, as they are considered one of the alternatives to overcome the oral delivery problems of drugs such as those faced with conventional or matrix tablets. A bilayer tablet is necessary when prompt drug release is required to relieve the symptoms of diseases, such as inflammation and hypertension while maintaining the appropriate drug blood level over the desired prolonged administration interval (Dey et al., 2012). Nevertheless, a new set of challenges is anticipated to bilayer tablets regarding the formulation and manufacturing parameter controls and product performance requirements compared to conventional tablets (Vaithiyalingam and Sayeed, 2010).

Formulation development by Quality by Testing (QbT) ensures the quality of the drug product only after its analytical testing in a quality control laboratory; however, this is not guaranteed during the design and development stage itself. The Quality by Design (QbD) concept in pharmaceutical development has evolved as a systematic method of development strategy offering several benefits, such as high-quality drug products with operational flexibility within optimized ranges of critical factors, regulatory flexibility in drug product application approvals, and post-approval change management (Lee et al., 2022). QbD is a systematic step-by-step approach that begins with predefined objectives in the form of a quality target product profile (QTPP), profound drug product formulation and manufacturing process understanding, and process controls based on sound science and quality risk management principles. The identification and optimization of critical material attributes (CMAs) and critical process parameters (CPPs) for the development of design space (DS) through a systematic series of design of experiments (DoE) along with the implementation of a control strategy with the adaptation of the continuous improvement throughout the drug product lifecycle (Chun et al., 2021; ICH Q8 (R2) 2009) will help in likely meeting some of the critical challenges, that is, segregation of Active Pharmaceutical

Ingredient (API) from blend, weight variation of layers, content variability of APIs in different layers, and delamination of layers, during commercial manufacturing of bilayer tablets.

A detailed understanding of bilayer tablet formulation design and its manufacturing process is most relevant to flexible operational and regulatory frameworks. The level of operational and regulatory flexibility highly depends on the scientific knowledge provided during the dossier application for marketing approval (ICH Q8 (R2)), 2009). The increasing application of the QbD concept in the pharmaceutical industry has been very successful as it helps improve pharmaceutical development efficiency with effective drug product formulation optimization and provides a robust manufacturing process. Furthermore, it improves communication between regulators and the pharmaceutical industry, provides regulatory relief and flexibility, manages post-approval changes, and allows real-time quality control with a subsequent real-time release (ICH Q8 (R2)), 2009; Pramod et al., 2016; Weitzel et al., 2021). Therefore, applying the QbD concept to bilayer tablet development would significantly benefit the pharmaceutical industry and regulatory authorities. An incomplete mechanistic understanding of the more complex manufacturing processes of bilayer tablet compression has encouraged researchers to implement the systematic QbD concept for bilayer tableting process development (Chun et al., 2021; Vaithiyalingam and Sayeed, 2010). Nevertheless, early scientific evaluations of bilayer tablets have been published previously (Stephenson and Spence, 1964; Sastry and Khan, 1998; Narendra et al., 2006).

The application of QbD in marketing authorizations for drug products is increasing (ter Horst et al., 2021). This is a valuable strategy for developing formulations containing more than one drug, particularly if different drug release profiles are required within the same pharmaceutical dosage form (Fernandez-Garcia et al., 2020). A large number of unit operations involved in its manufacture require more intense and validated control according to regulatory requirements to ensure a quality system based on efficacy, quality, and safety (Grangeia et al., 2020). Applying the QbD concept to optimize bilayer tablets might reduce the number of experiments required to produce a cost-effective drug product with extended-release properties (Chappidi et al., 2019). Several literature reviews have reported the critical steps (Abebe et al., 2014; Vaithiyalingam and Sayeed, 2010; Akhtar et al., 2020)

and relevance of the QbD concept (Kottala et al., 2012b, Kottala et al., 2012c) regarding the pharmaceutical development of bilayer tablets, but there is no published review comprising a systematic approach to the implementation of QbD for bilayer tablet development, to the best of our knowledge.

In this review, we explained the risk identification, analysis, and evaluation of CMAs and CPPs of bilayer tablets with respect to critical quality attributes (CQAs) through systematic risk assessment, along with the implementation of a control strategy for the implementation of QbD for the development of bilayer tablets. This will indeed help us meet some of the critical challenges, that is, segregation of the active ingredient from the blend, weight variation of layers, content variability of active ingredient(s) in different layers, and delamination or separation of layers during the commercial manufacturing of bilayer tablets. Along with QbD, in-process parametric online or inline releases for in-process quality checks through the Process Analytical Technology (PAT) framework are also discussed. Thus, the main objective of this review is to elucidate and provide a practical framework appropriate and suitable for the application of a systematic step-by-step QbD strategy for the pharmaceutical development of bilayer tablets.

2. Quality by Design approach – bilayer tablet development strategy

2.1. Definition of bilayer tablet QTPP and CQAs

In QbD, ‘What we want?’ should be defined from the first stage as the QTPP, which records the voice of the customers, that includes pharmacists, physicians, and patients. In the QTPP, the quality characteristics of drug products are summarized, which ideally should be achieved to ensure its desired quality. From the QTPP, Quality Attributes (QAs) of drug products are summarized, which preferably should be achieved to ensure the desired quality, considering its safety and efficacy. Of all QAs, CQAs of drug products are determined based on impact analysis by changes in formulation and/or process variables and severity of harm to patients. CQAs are defined by ICH Q8 guidance as a "physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality."

Any change in bilayer tablet formulation or processing parameters that may impact any of the CQAs, which may in turn affect efficacy and safety, must be investigated and discussed in detail to achieve the predefined product quality (Chun et al., 2021). Tables 1

and 2 summarize the definition of QTPP and determination of CQAs for bilayer tablets, respectively; the details mentioned in the last column of both tables justifies the purpose of the definition of QTPP and determination of CQAs, respectively.

Table 1. Example for definition of QTPP for a generic drug product based on bilayer tablets.

QTPP	**Target**	**Justification**
Dosage form	Bilayer Tablet	Requirements of Pharmaceutical Equivalence
Dosage design	Immediate Release and Modified Release Combination	
Route of administration	Oral	
Dosage strength	x mg for 1st API and y mg for 2nd API	
Drug Product quality attributes	Must meet the same compendia or other applicable reference standards	
	Identity, Assay (Weight Variation and Content Uniformity), Purity (Impurity, Microbial limits, Water Content, Residual Solvents), Quality (Appearance, Hardness, Friability) and Performance (Disintegration, Dissolution)	
Primary packaging	HDPE plastic Container and PP closure to protect the product from heat, moisture, oxygen, light and microbial attack to achieve the target shelf-life	
Pharmacokinetics	Fasting and Fed BE Study	Requirements of Bio-Equivalence
	90 % confidence interval of the PK parameters, AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}, should fall within bioequivalence limits of 80-125 % with the reference product	
Ease of storage and distribution	Can be stored and distributed at real-time storage conditions as a regular practice with desired stability to handle the product easily and to ensure product integrity	Requirements of Patient Acceptance and Compliance
Stability and shelf-life	It should be stable against hydrolysis, oxidation, photodegradation and microbial growth. At least a 24-month shelf-life is required at room temperature. Equivalent to or better than Reference Product shelf-life	
Patient acceptance and compliance	It should be suitably size, shape for swallowing and suitably colored for possessing acceptable shade similar to Reference Product. It can be easily administered similarly to Reference Product labeling to achieve the desired patient acceptability and suitable compliance	

Abbreviations: API- Active pharmaceutical ingredient; AUC- Area under the curve; BE- Bioequivalence; C_{max}- Maximum concentration; HDPE- High density polyethylene; PK- Pharmacokinetics; PP- Polypropylene

Table 2. Example for determination of CQAs for a generic drug product based on bilayer tablets.

In process and /or finished product quality attributes of drug product		**Change in formulation and/or process variables impacts this quality attribute?**	**Is failure to meet this attribute severely harm to the patient?**	**Is this a CQA?**
Physical Attributes		Yes	No (appearance same as innovator, so patient compliance is not an issue)	**No**
Identification		No (controlled at API release stage)	Yes	**Yes**
Assay		Yes	Yes	**Yes**
Impurities		Yes	Yes	**Yes**
Weight Variation	**Weight of 1st Layer**	Yes	Yes	**Yes**
	Weight of 2nd Layer	Yes	Yes	**Yes**
Content Uniformity	**Content of 1st Layer**	Yes	Yes	**Yes**
	Content of 2nd Layer	Yes	Yes	**Yes**
Tablet Hardness	**Thickness / Hardness of 1st Layer**	Yes	Yes (indirectly affecting capping, lamination/ separation, friability, disintegration and dissolution)	**Yes**
	Thickness / Hardness of 2nd Layer	Yes		**Yes**
Tablet Friability		Yes	Yes (patient compliance essential)	**Yes**
Disintegration		Yes	Yes	**Yes**
Dissolution		Yes	Yes	**Yes**
Water Content		Yes	Yes (indirectly affecting impurities)	**Yes**
Residual Solvent		No (controlled at API and excipient stages)	Yes	**Yes**
Microbial Limits		No (controlled at API and excipient stages)	Yes	**Yes**

Abbreviations: API- Active pharmaceutical ingredient; CQA- Critical quality attribute

Once the QTPP and CQAs were established based on prior knowledge and the literature, an initial risk assessment was performed. This procedure aims to identify potential high-risk variables and critical risk factors that will be prioritized for further optimization and control. Risk assessment is a systematic process exploited in quality risk management (ICH Q9 2005) to determine which CMAs and/or CPPs are critical for bilayer tablet quality and, eventually, which need to be experimentally assessed and controlled within appropriate ranges to ensure the desired drug product quality (ICH Q9 2005). Risk assessment should be performed early in pharmaceutical development, but it is essential to repeat it at different developmental stages as further information becomes available and improved understanding is achieved (Destro and Barolo, 2022; Tomba et al., 2013). Figure 1 schematically illustrates the QbD concept.

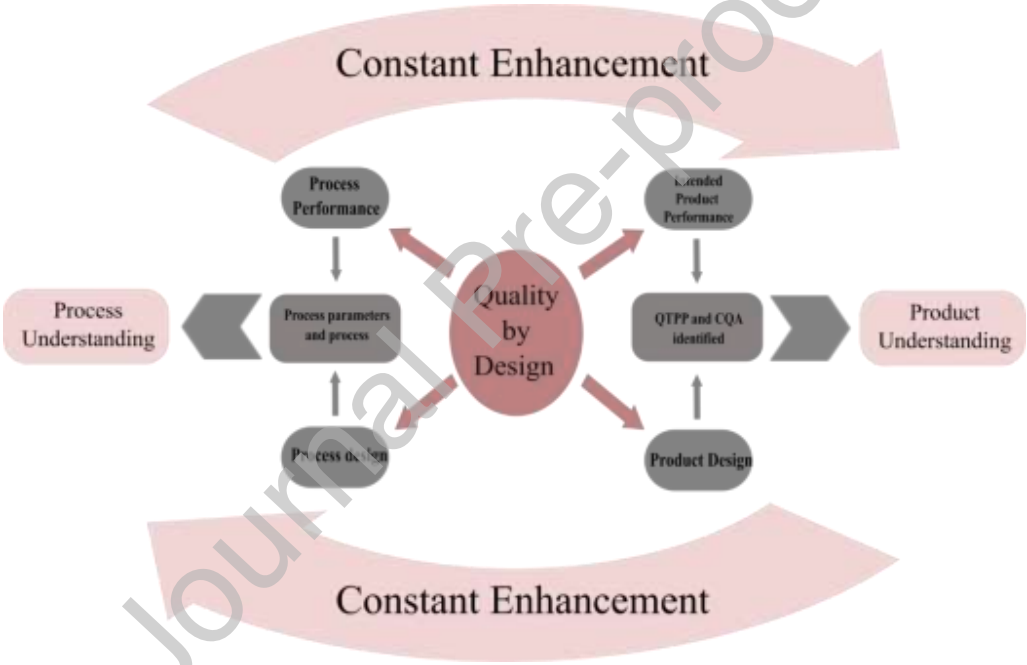

Figure 1. The QbD concept's representative scheme which consists of two main parts: process and product understanding in the form of CMAs and CPPs. The result is a complete understanding of both parts that guarantees that the final drug product complies with predefined QTPP and predetermined CQAs

The starting point of risk assessment is anticipated to systematically identify all the possible variables that may be responsible for any variability or defect in the bilayer tablet. Therefore, tracking all probable risk factor variables is recommended using an Ishikawa Fishbone diagram. An Ishikawa Fishbone diagram is usually the first step in identifying potential risk variables for CQAs. It is a multivariable overview represented as a horizontal line with the underlying CQAs of the drug product, and diagonal lines representing potential risk factors (Kovacs et al., 2021) (Saydam and Takka, 2018). An Ishikawa diagram for bilayer tablets manufactured after wet granulation is presented in Figure 2 based on experience and literature data, where formulation and process variables, among others, are hierarchically organized. The major categories of variables included in this diagram are related to raw material attributes, process parameters, and environment. This fishbone diagram represents a cause-effect correlation between potential material attributes and process parameters impacting CQAs. It has been used in the development of bilayer tablets (Lee et al., 2017) to map the different stages of a process; it helps depict where quality issues might arise and dictate which resources are essential at specific times.

However, the relative levels of impact of the described variables may differ for each CQA. The qualitative levels of the individual formulation variables can be represented through a risk estimation matrix (REM). REM is a systematic and proactive method for identifying and mitigating possible failure modes that are most likely to generate product failure. Therefore, this risk analysis tool aims to identify and prioritize the formulation and process parameters with the highest risk to CQAs and, thus, must be studied in more detail. Each factor mentioned in the Ishikawa diagram should be ranked later in REM analysis. Table 3 displays the REM of the bilayer tablet formulations and the manufacturing process parameters. If a bilayer tablet's formulation and process parameters are based on the disclosed data of a marketed drug product, the formulation parameters may be evaluated as low-risk through REM. Accordingly, only the processing parameters, such as blending, granulation, and tableting operation for bilayer tablets, are likely to be optimized by the further DoE (Won et al., 2021).

The most threatening risk factors are those that rarely occur but exhibit a high severity of impact on product QAs, and their detection often occurs at a late stage, not allowing adequate correction of the problem. Low-risk factors mean that no further investigation is required,

whereas high-risk factors warrant further investigation. Medium risk is commonly considered acceptable based on current literature data.

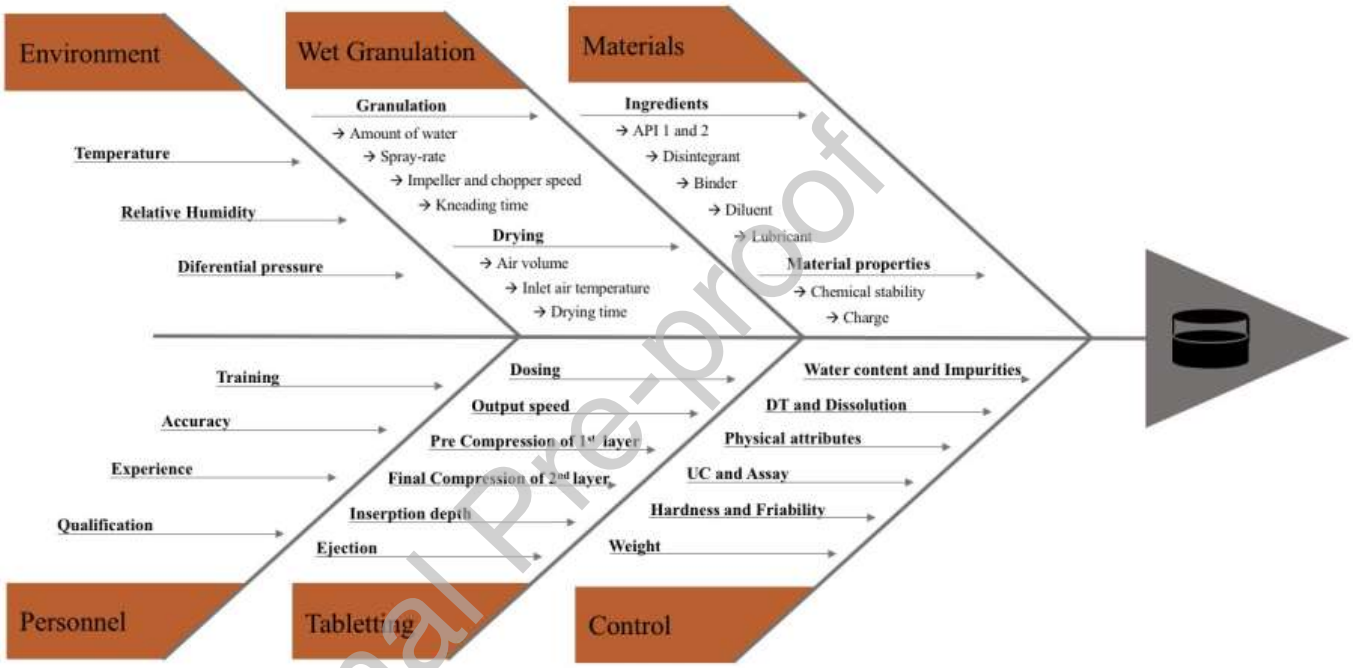

Figure 2. Typical Ishikawa Fishbone diagram for dual release bilayer tablets produced by wet granulation. **Abbreviations:** API- Active pharmaceutical ingredient; DT- Disintegration time; UC- Uniformity of content

Table 3. Risk estimation matrix (REM) presenting qualitative initial risk assessment levels of bilayer tablet formulations and manufacturing parameters.

			Physical Attributes	Assay	Impurities	Uniformity of Content	Hardness / Friability	DT / Dissolution	Water Content	Residual Solvent
RAW		API 1								

MATERIALS	1st	Diluent								
		Binder								
		Disintegrant								
		Lubricant								
	2nd layer	API 2								
		Diluent								
		Lubricant								

			Physical Attributes	Assay	Impurities	Uniformity of Content	Hardness / Friability	DT / Dissolution	Water Content	Residual Solvent
PROCESS PARAMETERS	1st layer	Co-Sifting								
		Granulation								
		Drying								
		Milling								
		Lubrication								
	2nd layer	Co-Sifting								
		Dry Mixing								
		Lubrication								
	BC	Precompression of 1st Layer								
		Final Compression of 2nd Layer								

Cell background: Gray- No correlation; Green- Low-risk factor; Yellow- Medium risk factor; Red- High-risk factor. **Abbreviations**: BC- Bilayer compression; API- Active Pharmaceutical Ingredient; CQA- Critical quality attribute; DT- Disintegration

2.2. Identification of the bilayer tablet CMAs and CPPs

Once the initial risk assessment has been established, the QbD development advantages toward identifying CMAs and CPPs of bilayer tablets. CMAs and CPPs are parameters whose variability significantly affects CQAs; therefore, their optimization, monitoring, and control are required during the development stage to ensure the commercial production of bilayer tablets with the intended quality. The values of both critical variables are believed to be within an appropriate range, limit, or distribution to ensure a predefined quality. The CMAs and CPPs underlying the different bilayer tablets for oral administration are based on data available from the relevant literature (Kottala et al., 2012a, Kottala et al., 2012b; Lee et al., 2017; Tho and Bauer-Brandl, 2011).

Formulation design and process parameters that show critical results in risk assessment should be screened and optimized through the DoE. DoE is an essential QbD element and represents a structured and organized experimental process that provides information with higher precision regarding the effect of changes in the variable(s) on the product and process response(s) and detects cause-effect relationships and interactions among these variables (ICH Q8 (R2)) 2009). The screening and optimization process requires fewer experiments than the one-factor-at-a-time (OFAT) strategy through multivariate DoE. A screening design is experimental planning that simultaneously evaluates a relatively large number of factors in a small number of experiments to screen significant critical factors out of non-significant factors. During the screening phase, all factors were tested to identify the most influential ones (CMAs and CPPs). Different experimental designs, such as fractional factorial, Placket–Burman, and 2-level full factorial designs (Maddiboyina et al., 2020), can be utilized to screen for factors impacting the critical quality and performance attributes of bilayer tablets.

After the screening experiments, the significant critical variables were further explored in the optimization phase to define their optimal operating ranges. The optimization stage enables the identification of the optimal conditions of the critical factors for the development of the DS within which all CQAs meet their predefined specifications to ensure product QTPP. Different experimental designs can be utilized to determine the optimal conditions. Response surface designs, such as the Central Composite Design (Bellini et al., 2019; Won et al., 2021) and Box-Behnken (Amit et al., 2021; Kenjale and Pokharkar, 2022; Singh et al., 2019; Tak et al., 2017), have been the most common designs for appropriate optimization. A response surface plot is a graphical representation of the effects of different

factors (or independent variables) on the identified responses (or dependent variables). This allows for the exploration of formulation and process design spaces.

2.3. Development of bilayer tablets

2.3.1. Marketed drug products

Because of its benefits over other solid dosage forms, there has been a focus on the development of this type of fixed-dose combination (FDC). Table 4 presents a list of marketed bilayer tablets consisting of two distinct layers approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA).

2.3.2. Incompatibility between ingredients

Bilayer tablets' advantages over other technologies include the possibility of incorporating incompatible ingredients in the same dosage form, which cannot be avoided, for example, in a conventional monolayer tablet. A deep understanding of the compatibility between drugs and excipients is essential. Physical separation is a good approach in the case of incompatibility between ingredients, preventing cross contamination among the layers (Vaithiyalingam and Sayeed, 2010).

A negative impact on the quality of the drug product may arise from the physical and chemical interactions between drugs and excipients. To prevent this incompatibility, in some formulations, an intermediate layer is needed to provide physical separation (Dave et al., 2015).

Eventual physical interaction among ingredients may involve a change in tablet physicochemical parameters such as dissolution and solubility (Chadha and Bhandari, 2014). Some examples of physical interactions between drugs and excipients can be found in the literature: the dissolution of drugs such as paracetamol (Hussain et al., 1992) and metformin HCl (Ariyasu et al., 2016) was affected by the use of hydrophobic magnesium stearate; the crystallinity degree of chloramphenicol in polymorphic form B was correlated with the presence of colloidal silica (Forni et al., 1988). On the other hand, beneficial interactions can also be found between drugs and excipients: in a study by Tantry et al., it was concluded that high molecular weight polyvinyl pyrrolidone (PVP) influences the phase transitions of theophylline (Tantry et al., 2007).

Chemical interaction involves a change in the molecular structure and can result in degradation of the drug substance (Chadha and Bhandari, 2014). Acid-base interactions and Maillard reactions are some of the most common drug-excipient interactions (Wirth et al., 1998).

Table 4. List of marketed tablets consisting of two distinct layers made by compression for various indications approved by the FDA or EMA. Each formulation, whenever possible, is discriminated for its indication, APIs, rationale for its production, and trademark name.

Indication	**Formulation**	**Rationale**[1]	**Example of brand name**	**Approval date**	**REF**
T2D	Glimepiride and Pioglitazone HCl	-	Duetact	2006	FDA data
T2D	Pioglitazone and Glimepiride	-	Tandemact	2007	EMA data
Diabetes mellitus / Dyslipidemia	Sitagliptin and Simvastatin	-	Juvisync	2011	FDA data
Hypertension	Telmisartan and Hydrochlorothiazide	Interaction between drugs	Kinzalkomb	2002	EMA data
Hypertension	Telmisartan and Amlodipine	-	Twynsta	2009	FDA data
Expectorant	Guaifenesin and Pseudoephedrine	IR of guaifenesin/ER of guaifenesin and pseudoephedrine	Mucinex D	2004	FDA data
Allergic rhinitis	Desloratadine and Pseudoephedrine sulphate	ER of pseudoephedrine sulphate	Clarinex-D	2005	FDA data
Allergies	Cetirizine HCl and Pseudoephedrine HCl	IR/ER of pseudoephedrine HCl	Zyrtec-D	2007	FDA data

Abbreviations: EMA- European Medicines Agency; ER- Extended Release; FDA- Food and Drug Administration; HCl- Hydrochloric Acid; IR- Immediate Release; REF- Reference; T2D- Type 2 Diabetes

[1] According to disclosed information in a common technical document (CTD).

A recent study (Rojek et al., 2021) demonstrated that atenolol is incompatible with hydroxyethyl cellulose, hypromellose, and methylcellulose. As we can see through table 4, the interaction and incompatibility between drugs can be the reason to opt for a bilayer tablet. For cases where there is incompatibility between drugs such as Kinzalkomb® (telmisartan and hydrochlorothiazide) physical separation with a layer makes it possible to overcome this obstacle.

As one of the early stages of product development, the selection of formulation components is of utmost importance (Dave et al., 2015). In light of the relevant contribution of bilayer tablets as one of the most successful applications in the field of FDCs, it is surprising that throughout the number of QbD applications in recent years, the incorporation of incompatible drugs has rarely been pointed out by authors as the main reason to develop bilayer tablets. Several formulations have used drugs presenting some incompatibilities sooner or later during formulation and manufacturing, including telmisartan and amlodipine (Lee et al., 2017). However, it seems clear that the incompatibility of drugs has not deserved academic and industrial attention regarding QbD usefulness in their design as bilayer tablets.

2.3.3. Dual release formulations

A bilayer tablet is suitable for the sequential release of one or two different drugs, in which an immediate release (IR) layer provides a drug as a loading dose, whereas a sustained release (SR) layer acts as a maintenance dose (Tak et al., 2017; Momin et al., 2015; Salatin et al., 2022). Based on these considerations, bilayer tablets have been developed based on the QbD concept to provide biphasic release of one (Dholariya et al., 2014) or two drugs (Singh et al., 2019; Lee et al., 2017) for the treatment of diabetes (Amit et al., 2021) (Chun et al., 2021), asthma (Singh et al., 2019), and hypertension (Lee et al., 2017). Although sequential release mechanistic studies of bilayer tablets containing either one or two drugs have been extensively used to improve therapeutic efficiency, studies specifically analyzing the drug release from each layer together with the effect of the mechanical properties of individual layers on bilayer tablet product quality are limited (Han et al., 2022). The development of bilayer tablets for the dual-drug release can be streamlined based on the principles of QbD. Table 5 describes the applications with an emphasis on the identification of CMAs and CPPs.

Table 5 - Application of a Quality by Design approach for bilayer tablets with dual-drug release profiles.

Parameter	Criticality	CQAs	Reference
Drug in the IR layer/total drug	CMA	DR	(Tak et al., 2017)
HPMC/drug in the SR layer	CMA		
Eudragit® RL/drug in the SR layer	CMA		
Lubricant in the IR layer	CMA	CI, CU and DR in the IR layer	(Amit et al., 2021)
Kneading time and lubrication time in the IR layer	CPP	CI, CU and DR in the IR layer	
HPMC, Compritol® and lubricant in the SR layer	CMA	CI and DR in the SR layer	
HPMC K4M, sodium bicarbonate, and ethyl cellulose	CMA	DR, 50% of drug discharge time, and floating lag time	(Maddiboyina et al., 2020)
The 1st and 2nd compression forces, turret speed, and 1st and 2nd feeder speed	CPP	Friability, hardness, drug content assay and CU, DR	(Won et al., 2021)
HPMC E4M and MCC in the SR layer	CMAs	DR	(Dey et al., 2012)
Concentration of superdisintegrants and drug/total polymer ratio in IR and SR layers, respectively	CMA	DT and DR	(Dholariya et al., 2014)
Binder concentration (sodium CMC) and SR polymer (HPMC K100M CR/ PEO/ Carbopol®)	CMA	DR	(Chinta and Pilli, 2020)
Amount of drug, sodium starch glycolate and bicarbonate in the IR layer	CMA	DT and DR	(Singh et al., 2019)
Amount of drug, HPMC and magnesium stearate in the SR layer	CMA	DR	
CMC Ca, Erythritol, HPC in the IR	CMA	Assay, CU, DR, hardness, friability	(Han et al., 2022)
Kollidon® SR, HPMC 4000 and HPMC in the SR	CMA	Assay, CU, DR, hardness, friability	
Amount of CCS and amount of Eudragit® RLPO in IR and SR layers, respectively	CMA	DT and DR	(Kenjale and Pokharkar, 2022)
Hardness	CPP	DT and DR	
Amount of guar gum and amount of xanthan gum	CMA	Swelling index and DR	(Parmar and Desai, 2022)

Abbreviations: CCS- Croscarmellose sodium; CI- Carr´s Index; CMA- Critical material attribute; CMC Ca- Carboxymethyl cellulose calcium; CPP- Critical process parameter; CQA- Critical quality attribute; CU- Content uniformity; DR- Drug release; DT- Disintegration time; HPC- Hydroxyl propyl cellulose; HPMC- Hydroxyl propyl methyl cellulose; IR- Immediate release; MCC- Microcrystalline cellulose; MS- Magnesium stearate; SR- Sustained release

2.3.4. Manufacturing Processing Parameters

Bilayer tablets are more challenging to manufacture than conventional tablets because it is difficult to predict their long term mechanical stability owing to several factors, such as the mechanical and compression properties of the materials. The first systematic approach to overcome manufacturing obstacles was based on the compressibility of wet granulation formulations incorporated with vitamin E, using a three-factor full factorial design to assess the effects of vitamin E, binder, and filler on responses such as granule flow, tensile strength, friability, tablet disintegration, and dissolution (Jin and Tatavarti, 2010). Table 6 shows the QbD-driven applications with an emphasis on identifying CMAs and CPPs while overcoming obstacles in manufacturing bilayer tablets.

Table 6- Applications of Quality by Design approaches to minimize manufacturing step obstacles in developing bilayer tablets.

Parameter	**Criticality**	**In Process and Finished Product CQAs**	**Reference**
Surface characteristics and elastic/brittle behavior of the tablet ingredients	CMA	Tensile strength of the tablets	(Papos et al., 2015)
Material properties (plastic and brittle)	CMA	DR	(Kottala et al., 2012b)
Layer ratio, dwell time, layer sequence, first- and second-layer forces	CPP	DR	
Excipients with immediate and sustained release properties	CMA	Yield Pressure, elastic recovery, and elastic work	(Bellini et al., 2019)
Pre-compaction, main compaction, and turret rotation speed	CPP	Layer adhesion	
Elastic behavior of the layer materials	CMA	Bilayer strength and cohesion	(Busignies et al., 2013)
Final tablet hardness, spray rate and exhaust air temperature	CMA, CPP	Delamination tendency/Layer adhesion	(Zacour et al., 2014)
Level of TPGS, level of the binder, Klucel ® EXF and level of extragranular filler, Prosolv® 90	CMA	Friability, Tensile strength, DT, DR	(Jin and Tatavarti, 2010)

Abbreviations: CMA- Critical material attribute; CPP- Critical process parameter; CQA- Critical Quality Attribute; DR- Drug release; DT- Disintegration time; TGPS- Vitamin E tocopheryl polyethylene glycol succinate

Bilayer tablets tend to delaminate at the interface of the layers during and after several compaction process stages, which are major bottlenecks that occur during commercial manufacturing. The main issue to be addressed is a complete and in-depth understanding of the primary sources behind the problems at the macro- and microscale levels and the establishment of effective solutions. Avoiding delamination occurring between adjacent layers either soon after the compression process or during storage requires a methodical evaluation of the raw materials and an appropriate selection of equipment and process parameters. Several studies based on the QbD concept have been conducted to improve the understanding of the formulation and process parameters that contribute to the cohesion and strength of bilayer tablets (Bellini et al., 2019) and to study the formation of cracks (Kottala et al., 2012b). The impact of the material properties and process parameters on the strength of bilayer tablets has been previously published (Kottala et al., 2012a, Kottala et al., 2012b, Chang and Sun, 2019).

The pre-compression force and main compression force are among the most critical tableting parameters required to be controlled in the production of bilayer tablets (Akhtar et al., 2020). However, an individual approach to this parameter may not succeed, as the influence of compression is material-dependent. The presence of brittle materials in both layers was the combination that least favored delamination and provided the best guarantees of a robust bilayer tablet (Kottala et al., 2012b). Owing to their characteristics, plastic and brittle materials exhibit an elastic mismatch. The elastic mismatch between brittle materials is minimal, and the interfacial strength of bilayer tablets tends to increase in the presence of brittle materials in both layers. Bilayer tablets consist of brittle materials fractured in the first layer, suggesting that the interfacial strength was greater than the strength of the individual layers (Kottala et al., 2012b). Additionally, the deformation capacity of brittle materials is low due to their rigid nature, so sufficient roughness is retained at the interface to establish connections (Kottala et al., 2012b). For plastic materials, if the pressure exerted on the first layer is too high, the surface roughness decreases, and delamination of the tablet is most likely to occur (Desai et al., 2013; Busignies et al., 2014; Akseli et al., 2013). The compaction pressure used to form the first layer should be kept to a minimum to provide sufficient surface roughness for the particles to nest and engage between the layers (Wu and Seville, 2009). With increasing compression force, the particles undergo processes such as plastic and elastic deformation (Kottala et al., 2012a). A detailed investigation of the relationships between the surface characteristics and deformation properties of tableting materials and the tendency of bilayer tablets to undergo lamination using a mixed two- and three-level half-replicated

factorial design showed the prominent role of surface characteristics in the lamination of bilayer tablets and the relevance of knowledge about materials' plastic–elastic behavior (Papos et al., 2015). Studying the behavior of powders is fundamental and helps establish a formulation that best favors tablet compression. The relationship between the bonding area (BA) and bonding strength (BS) and its evaluation allows a better understanding of different tableting behaviors (Osei-Yeboah et al., 2016).

Compression forces have a substantial impact on interfacial bonding strength (IBS). IBS depends on BA and BS. The larger the BA and BS, the greater the IBS (Chang and Sun, 2019). BA is influenced by porosity and waviness. Minimal first compression ensures that the first layer has sufficient roughness upon contact and adhesion to the second layer (Blicharski et al., 2019). The pressure exerted on the second layer has a complementary role and should also be thoroughly studied (Kottala et al., 2012b). After increasing the compression force of the first layer, the porosity was reduced, and the powder compaction increased. Consequently, the BA decreases, leading to a lower IBS. In contrast, by increasing the second layer compression force, the waviness increases and positively influences the interpenetration of particles, improving IBS (Chang and Sun, 2019). Thus, there is a need to establish a criterion for tablets' minimal interface strength (IS) (Chang and Sun, 2020). A low IS value may result in a bilayer tablet that is not sufficiently robust and may fail to meet the minimum quality parameters. An acceptance criterion can be established (Chang and Sun, 2020), demonstrating that this minimal IS can be essential for tablet formulation component selection and optimization to ensure that the proposed formulation exhibits suitable tableting ability that uses a small amount of powder early in the bilayer tablet development (Chang and Sun, 2020).

The physical properties of bilayer tablets, such as their size and shape, cannot be ignored when assessing the interface delamination risks in bilayer tablets (Tao et al., 2017). The punch shape affects the strength of the produced bilayers; convex or concave punches, compared to flat ones, have a greater capacity to enhance the interactions between the two layers because, during the pre-compression process, an increased surface area is achieved. This effect is directly proportional to the applied compression force (Zhang et al., 2018). The use of convex punches during pre-compression yielded good results. By increasing the curvature of the punch, interface resistance also increased, and deeper punches were revealed to be the ones that mainly contributed to IS (Kottala et al., 2012a).

Relative humidity can also affect tablet manufacturing, more precisely, the flowability and compressibility of the powders, tensile strength, and later storage of the drug product (Klinzing and

Zavaliangos, 2013). In addition to the effect of the plastic–elastic properties of raw materials and the force of compression, excellent reviews have focused on the impact of environmental conditions on the strength of bilayer tablets (Kottala et al., 2012c) (Zacour et al., 2014). A study of bilayer tablets consisting of different material properties (Avicel® and lactose) compressed with different process parameters, such as layer ratios and layer sequences, among others, revealed that tablets composed of Avicel®-lactose and lactose-Avicel® showed a lower strength with increasing humidity and storage time compared to tablets made of lactose-lactose due to the formation of solid bridges upon storage (Kottala et al., 2012c).

Considerable attention has been paid to the development of an experimental method that can be applied to bilayer tablets to detect bilayer lamination tendencies that are no longer visible when the tablet is ejected but only manifest after storage and handling of the compacts (Wu and Seville, 2009). A method designed to check the weight of individual layers consisted of taking samples without interrupting the manufacturing process, thus ensuring correct dosing (Gansel and Dusel, 1989; Janczura et al., 2022). The strength of adhesion in complex bilayer tablets can be assessed using statistical methods for the applied tableting forces on the first layer and for applying the second layer on the first, as well as regarding the fraction of the lubricant (Dietrich et al., 2000). Some applications (Busignies et al., 2013; Zacour et al., 2014) are related to methods for testing bilayer tablets at their interface, as the QbD concept has provided an understanding of the critical formulation and process parameters that influence layer adhesion (Busignies et al., 2013).

3. Control strategy

The control strategy is a planned set of controls taken from a current product and a thorough understanding of its production process. A control strategy ensures that the process performs as expected and maintains its quality. From the DS developed through DoE, Control Space for each and every CMAs and CPPs is proposed for future commercial manufacturing to ensure batch-to-batch consistency in bilayer tablet product quality. CQAs should comply with bilayer tablet specifications as drug product acceptance criteria. PAT, which supports innovation and increases process efficiency in the manufacturing and quality assurance of drug products, is a useful tool that foresees the implementation of analytical methods, such as Raman spectroscopy, near-infrared (NIR) spectroscopy, and terahertz pulsed spectroscopy, in conjunction with multivariate analysis (MVA), which eventually

provides real-time release testing (RTRT) for bilayer tablets. RTRT is defined as "the ability to evaluate and ensure the quality of in-process and/or final drug products based on process data, which typically includes a valid combination of measured material attributes and process controls" (ICH Q8 (R2)) 2009).

Regulatory agencies encourage scientists to use PAT tools as much as possible when developing new drug applications. The improved process knowledge gained through PAT tools is rewarding as it enhances the product and process design, ensures drug products with optimized QAs, and minimizes risks for manufacturers and consumers. Moreover, PAT tools can provide cost benefits, less time-consuming operations, fast and non-invasive testing, and low waste disposal (Peinado et al., 2011) (Sacher et al., 2022). DoE and multivariate statistical models in integrated QbD/PAT-based development have demonstrated the successful use and processing of real-time PAT data for multivariate statistical analysis. The goal is to enhance process knowledge for various unit operations and to develop a process control strategy to achieve consistent product QAs (Singh et al., 2019). PAT has been used in different operating units to manufacture bilayer tablets, such as granulation, compression, and coating processes. In this context, examples of the PAT framework applied to formulation, process parameters, and process understanding in the development of bilayer tablets are provided in Table 7.

Calibration models have been established for the non-destructive NIR analysis of API content in two layers of intact bilayer tablets. These models enable NIR transmittance spectroscopy in bilayer tableting processes to control the API content in separate layers (Ito et al., 2010). PAT was used with inline transmittance NIR spectroscopy to confirm the bulk and ribbon densities of the optimized bilayer tablet. This study suggests that integrated QbD, statistical, and PAT approaches can be used to develop a robust control strategy for FDC bilayer tablets by implementing RTRT based on the relationships among various variables (Chun et al., 2021). For example, various solutions have been proposed as substitutes for conventional dissolution tests using faster and non-destructive techniques (Galata et al., 2022).

The information obtained from the NIR and Raman spectra can be utilized to predict the dissolution profiles of the tablets. The application of transmission Raman spectroscopy to quantify the API in a bilayer tablet was reported by Zhang and McGeorge (Zhang and McGeorge, 2015). NIR spectroscopy can predict the dissolution of bilayer tablets using a non-destructive approach. The two

APIs were physically separated into layers and manufactured at three hardness levels. Spectral data of both APIs were obtained through tablet hardness, and the dissolution profile was predicted through a principal component analysis study. This non-destructive testing was performed for API-A but not for API-B. Despite these positive results, a more robust test needs to be developed in the future (Baranwal et al., 2019).

PAT, DoE, and MVA are empirical methods that monitor the relationships between the input factors (independent variables) and output factors (dependent variables). Critical process factors with a high impact on intermediate quality attributes (IQAs) and CQAs were selected, and a correlation between factors and responses was established. The process parameters were optimized using Monte Carlo simulations toward a DS, and MVA was used to determine the relationship between IQAs and CQAs. MVA established a relevant correlation between the dissolution rate, bulk density, and granule size. Thus, IQAs monitoring during the process and the integrated QbD concept using MVA can be used as a control strategy for producing bilayer tablets as high-quality drug products (Kim et al., 2021).

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Table 7- Applications of the PAT framework for formulation and process understanding in the development of bilayer tablets.

CQA	Unit Operation and/or Processing form	PAT method	Statistical tools	Measurement	Reference
● Assay	● Compression	● Raman	● -[a]	● Drug content ● Tablet thickness ● Layer thickness	(Zhang and McGeorge, 2015)
● DR	● Dry granulation ● Wet granulation	● NIR	● PCA ● PCC	● Drug content (paliperidone) ● Bulk and ribbon densities	(Chun et al., 2021)
● DR	● Granulation ● Compression	● NIR	● PLS	● Drug release ● Tablet hardness ● PSD of drugs	(Baranwal et al., 2019)
● Assay	● Compression	● NIR	● PLS	● Drug content (ascorbic acid)	(Ishikawa et al., 2014)
● DR	● Compression	● NIR	● PLS	● Drug content	(Ito et al., 2010)
● Assay	● Compression	● Raman	● PLS	● Drug content and uniformity (evogliptin tartrate)	(Won et al., 2021)
● Swelling property ● Weight gain and Mass loss ● Gel strength ● Dissolution ● Contact angle	● Wet granulation ● Dry granulation	● -[b]	● PCA	● Intrinsic dissolution rate ● Granule properties ● True density ● Bulk density ● CI ● Angle of repose	(Kim et al., 2021)
● CU ● Dissolution ● Contact angle		● -[b]		● Intrinsic dissolution rate ● Granule properties ● Ribbon density ● Bulk density ● Tapped density ● Granule uniformity	

Abbreviations: CI- Carr´s index; CU- Content uniformity; CQA- Critical quality attribute; DR- Drug release; NIR- Near-infrared; PAT- Process analytical technology; PCA- Principal component analysis; PCC- Pearson correlation coefficient; PLS- Partial least squares; PSD- Particle size distribution

[a] Not available;
[b] It does not apply.

4. Conclusions

Bilayer tablets have opened new opportunities in the pharmaceutical industry because of their ability to successfully deliver active substances to avoid incompatibilities in solubility, stability, and therapeutic efficacy in a single dosage form. The increasing relevance of bilayer tablets over the last 20 years has been particularly successful in developing dual release tablets for the oral delivery of one or two drugs, yet they face more complex formulations and manufacturing issues. According to international guidelines, optimizing formulation and process parameters are critical for achieving bilayer tablets as drug products that meet the highest quality and therapeutic efficacy standards. Moreover, the potential risks associated with manufacturing bilayer tablets remain challenging to assess and control, most of which are related to the delamination tendency.

The concept of QbD applied to bilayer tablet development in the early stages leads to a multivariate approach comprising a number of formulation attributes and processing parameters, compared to a conventional approach. The levels of binder, filler, and plastic-exhibiting materials were identified as critical formulation parameters for drug release from the bilayer tablets. Furthermore, process parameters such as the pre-compression force, main compression force, and turret rotation speed have a critical impact on layer adhesion. The QbD-based concept has led to remarkable progress in developing bilayer tablets containing different drugs at different doses and release rates. As a breakthrough, using NIR and Raman spectroscopy as process analytical technologies, QbD/PAT was revealed to be effective for the scale-up of bilayer tablets containing a low drug dose in the IR layer to control the active ingredient content in an individual layer.

Significant advances have been made in understanding the delamination tendency in bilayer tablets, among which the development of robust techniques to assess the IBS in bilayer tablets stands out. Upon validation, these techniques applied in the formulation of bilayer tablets through QbD made it easier to control critical events occurring in their manufacture, such as delamination, and to compare tensile strength through shear determination techniques. PAT provides that the design and quality used together with analytical tools are powerful tools for constructing and controlling the quality of bilayer tablets. The number of PAT applications in the manufacturing of bilayer tablets is increasing, and the number of license applications using this approach is anticipated to rise rapidly. Implementing and understanding QbD and PAT practices improves the quality of bilayer tablets as drug products and can be cost-effective in the long term.

The continuity of drug quality is indispensable for manufacturers, regulatory agencies such as the FDA and EMA, and patients, thus making these studies a priority in the pharmaceutical industry and requiring further research.

Very effective approaches such as DoE and PAT have been used in recent studies to demonstrate their effectiveness. For example, optimized concentrations of super disintegrants and polymers using the QbD concept led to the development of hydrochlorothiazide bilayer tablets, while substantially decreasing sources of variability and avoiding much of resources and time required for a traditional approach such as QbT. Therefore, the design-based planning approach dictated by QbD is a valuable strategy for optimizing the formulation and understanding of the manufacturing of bilayer tablets. Employing this planned multivariate approach to bilayer tablet development will help improve product design while also enhancing the quality, safety, and efficacy of drug products. Increasing the application of the QbD concept in the design and testing of mucoadhesive and floating bilayer tablets can surface out the way for the faster and effective development of these challenging bilayer tablets designing, development and its successful manufacturing. The identification and optimization of CMAs and CPPs for the development of DS through a systematic series of DoE along with the implementation of a control strategy with an adaptation of the continuous improvement throughout the drug product lifecycle (Chun et al., 2021; ICH Q8 (R2) 2009) will likely meet some of the critical challenges, that is, segregation of APIs from the blend, weight variation of layers, content variability of APIs in different layers, and delamination of layers, during commercial manufacturing of bilayer tablets.

CRediT authorship contribution statement

João Simão: Conceptualization, Writing – original draft, writing – review, and editing. Shivang Chaudhary: Writing, reviewing, and editing. Antonio J Ribeiro: Conceptualization, Writing – original draft, writing – review and editing, supervision.

Declaration of Competing Interest

None.

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References

Abebe, A., Akseli, I., Sprockel, O., Kottala, N., Cuitino, A.M. **Review of bilayer tablet technology**. Int. J. Pharm. 461 (2014), pp. 549-558, http://dx.doi.org/10.1016/j.ijpharm.2013.12.028

Akhtar, M., Jamshaid, M., Zaman, M., Mirza, A.Z. **Bilayer tablets: A developing novel drug delivery system**. J. Drug Deliv. Sci. Technol. 60 (2020), pp. 10, http://dx.doi.org/10.1016/j.jddst.2020.102079

Akseli, I., Abebe, A., Sprockel, O., Cuitino, A.M. **Mechanistic characterization of bilayer tablet formulations**. Powder Technol. 236 (2013), pp. 30-36, http://dx.doi.org/10.1016/j.powtec.2012.05.048

Amit, K., Sandeep, A., Neelam, S., Sukhbir, S. **Development of Bilayer Tablet Containing Saxagliptin Immediate Release and Metformin Sustained Release Using Quality by Design Approach**. Curr. Drug Ther. 16 (2021), pp. 184-203, http://dx.doi.org/10.2174/1574885516666210315100848

Ariyasu, A., Hattori, Y., Otsuka, M. **Delay effect of magnesium stearate on tablet dissolution in acidic medium**. Int. J. Pharm. 511 (2016), pp. 757-764, https://doi.org/10.1016/j.ijpharm.2016.07.034

Baranwal, Y., Roman-Ospino, A.D., Keyvan, G., Ha, J.M., Hong, E.P., Muzzio, F.J., Ramachandran, R. **Prediction of dissolution profiles by non-destructive NIR spectroscopy in bilayer tablets**. Int. J. Pharm. 565 (2019), pp. 419-436, http://dx.doi.org/10.1016/j.ijpharm.2019.05.022

Bellini, M., Walther, M., Bodmeier, R. **Evaluation of manufacturing process parameters causing multilayer tablets delamination**. Int. J. Pharm. 570 (2019), pp. 118607, http://dx.doi.org/10.1016/j.ijpharm.2019.118607

Blicharski, T., Swiader, K., Serefko, A., Kulczycka-Mamona, S., Kolodziejczyk, M., Szopa, A. **Challenges in technology of bilayer and multi-layer tablets: a mini-review**. Curr. Iss. Pharm. Med. Sci 32 (2019), pp. 229-235, http://dx.doi.org/10.2478/cipms-2019-0039

Busignies, V., Mazel, V., Diarra, H., Tchoreloff, P. **Role of the elasticity of pharmaceutical materials on the interfacial mechanical strength of bilayer tablets**. Int. J. Pharm. 457 (2013), pp. 260-267, https://doi.org/10.1016/j.ijpharm.2013.09.009

Busignies, V., Mazel, V., Diarra, H., Tchoreloff, P. **Development of a new test for the easy characterization of the adhesion at the interface of bilayer tablets: Proof-of-concept study by experimental design**. Int. J. Pharm. 477 (2014), pp. 476-484, https://doi.org/10.1016/j.ijpharm.2014.10.051

Chadha, R., Bhandari, S. **Drug–excipient compatibility screening—Role of thermoanalytical and spectroscopic techniques**. J. Pharm. Biomed. Anal. 87 (2014), pp. 82-97, https://doi.org/10.1016/j.jpba.2013.06.016

Chang, S.Y., Sun, C.C. **Insights into the effect of compaction pressure and material properties on interfacial bonding strength of bilayer tablets**. Powder Technol. 354 (2019), pp. 867-876, http://dx.doi.org/10.1016/j.powtec.2019.07.021

Chang, S.Y., Sun, C.C. **Interfacial bonding in formulated bilayer tablets**. Eur. J. Pharm. Biopharm. 147 (2020) pp. 69-75, http://dx.doi.org/10.1016/j.ejpb.2019.12.009

Chappidi, S.R., Bhargav, E., Marikunte, V., Chinthaginjala, H., Jyothi, M.V., Pisay, M., Jutur, M., Mahammad, M.S., Poura, M., Yadav, S., Syed, M. **A Cost Effective (QbD) Approach in the Development and Optimization of Rosiglitazone Maleate Mucoadhesive Extended Release Tablets - In Vitro and Ex Vivo**. Adv. Pharm. Bull. 9 (2019), pp. 281-288, http://dx.doi.org/10.15171/apb.2019.032

Chinta, R., Pilli, R. **Formulation design of empaglifozin and metformin hydrochloride extended release tablets: optimization of formulation using statistical experimental design**

Int. J. Pharm. Sci. Res. 11 (2020), pp. 6434-6447, http://dx.doi.org/10.13040/ijpsr.0975-8232.11(12).6434-47

Chun, M.-H., Kim, J.Y., Park, E.-S., Choi, D.H. **Development of a Robust Control Strategy for Fixed-Dose Combination Bilayer Tablets with Integrated Quality by Design, Statistical, and Process Analytical Technology Approach**. Pharmaceutics 13 (2021), pp. 1443, https://doi.org/10.3390/pharmaceutics13091443

Dave, V., Haware, R., Sangave, N., Sayles, M., Popielarczyk, M. **Drug-Excipient Compatibility Studies in Formulation Development: Current trends and techniques**. AAPS, FDD Section Newsletter - January 2015 (2015).

Desai, D., Wang, J., Wen, H., Li, X.H., Timmins, P. **Formulation design, challenges, and development considerations for fixed dose combination (FDC) of oral solid dosage forms**. Pharm. Dev. Technol. 18 (2013), pp. 1265-1276, https://doi.org/10.3109/10837450.2012.660699

Destro, F., Barolo, M. **A review on the modernization of pharmaceutical development and manufacturing – Trends, perspectives, and the role of mathematical modeling**. Int. J. Pharm. 620 (2022), pp. 121715, https://doi.org/10.1016/j.ijpharm.2022.121715

Dey, S., Mahanti, B., Khila, S., Mazumder, B., Gupta, S.D. **Formulation development and optimization of bilayer tablets of aceclofenac**. Exp. Opin. Drug Deliv. 9 (2012), pp. 1041-1050, https://doi.org/10.1517/17425247.2012.707187

Dholariya, Y.N., Bansod, Y.B., Vora, R.M., Mittal, S.S., Shirsat, A.E., Bhingare, C.L. **Design and optimization of bilayered tablet of Hydrochlorothiazide using the Quality-by-Design approach**. Int. J. Pharm. Investig. 4 (2014), pp. 93-101, https://doi.org/10.4103/2230-973x.133058

Dietrich, P., Bauer-Brandl, A., Schubert, R. **Influence of Tableting Forces and Lubricant Concentration on the Adhesion Strength in Complex Layer Tablets**. Drug Dev. Ind. Pharm 26 (2000), pp. 745-754, https://doi.org/10.1081/DDC-100101293

Fernandez-Garcia, R., Prada, M., Bolas-Fernandez, F., Ballesteros, M.P., Serrano, D.R. **Oral Fixed-Dose Combination Pharmaceutical Products: Industrial Manufacturing Versus Personalized 3D Printing**. Pharm. Res. 37 (2020), pp. 132, https://doi.org/10.1007/s11095-020-02847-3

Forni, F., Coppi, G., Iannuccelli, V., Vandelli, M.A., Cameroni, R. **The grinding of polymorphic forms of chloramphenicol stearic ester un the presence of colloidal silica**. Acta Pharm. Sue. 25 (1988), pp. 173-180.

Gansel, W., Dusel, R., Pharmaceutical Dosage Forms: Tablets, Volume 1, Second Edition, in: Lieberman, H., Lachman, L., Schwartz, J.B. (Eds.), Pharmaceutical Dosage Forms: Tablets, Volume 1, Second Edition. Taylor & Francis, New York, (1989) pp. 247-284.

Grangeia, H.B., Silva, C., Simões, S.P., Reis, M.S. **Quality by design in pharmaceutical manufacturing: A systematic review of current status, challenges and future perspectives**. Eur. J. Pharm. Biopharm. 147 (2020), pp. 19-37, https://doi.org/10.1016/j.ejpb.2019.12.007

Han, J.K., Kim, J.Y., Choi, D.H., Park, E.-S. **A formulation development strategy for dual-release bilayer tablets: An integrated approach of quality by design and a placebo layer**. Int. J. Pharm. 618 (2022), pp. 121659, https://doi.org/10.1016/j.ijpharm.2022.121659

Hussain, M.S.H., York, P., Timmins, P. **Effect of commercial and high purity magnesium stearates on in-vitro dissolution of paracetamol DC tablets**. Int. J. Pharm. 78 (1992), pp. 203-207, https://doi.org/10.1016/0378-5173(92)90372-9

ICH Q8 (ICH Q8 (R2)) 2009. Q8 Guideline: Pharmaceutical Development., International Conference on Harmonisation https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf, 03 May 2022.

ICH Q9 2005. Q9 Guideline: Quality Risk Management., International Conference on Harmonisation https://database.ich.org/sites/default/files/Q9%20Guideline.pdf, 03 May 2022.

Ishikawa, D., Genkawa, T., Murayama, K., Komiyama, M., Ozaki, Y. **Feasibility Study of Diffuse Reflectance and Transmittance near Infrared Spectroscopy for Rapid Analysis of Ascorbic Acid Concentration in Bilayer Tablets Using a High-Speed Polychromator-Type Spectrometer**. J. Near Infrared Spectrosc. 22 (2014), pp. 189-197, https://doi.org/10.1255/jnirs.1116

Ito, M., Suzuki, T., Yada, S., Nakagami, H., Teramoto, H., Yonemochi, E., Terada, K. **Development of a method for nondestructive NIR transmittance spectroscopic analysis of acetaminophen and caffeine anhydrate in intact bilayer tablets**. J. Pharm. Biomed. Anal. 53 (2010), pp. 396-402, https://doi.org/10.1016/j.jpba.2010.04.029

Janczura, M., Sip, S., Cielecka-Piontek, J. **The Development of Innovative Dosage Forms of the Fixed-Dose Combination of Active Pharmaceutical Ingredients**. Pharmaceutics 14 (2022), pp. 834, https://doi.org/10.3390/pharmaceutics14040834

Jin, F.Y., Tatavarti, A. **Tabletability assessment of conventional formulations containing Vitamin E tocopheryl polyethylene glycol succinate**. Int. J. Pharm. 389 (2010), pp. 58-65, https://doi.org/10.1016/j.ijpharm.2010.01.017

Kenjale, P., Pokharkar, V. **Risk Assessment and QbD-Based Optimization of Sorafenib Tosylate Colon Targeted Bilayer Tablet: In Vitro Characterization, In Vivo Pharmacokinetic, and In Vivo Roentgenography Studies**. AAPS PharmSciTech 23 (2022), pp. 184, https://doi.org/10.1208/s12249-022-02340-7

Kim, J.Y., Chun, M.H., Choi, D.H. **Control Strategy for Process Development of High-Shear Wet Granulation and Roller Compaction to Prepare a Combination Drug Using Integrated Quality by Design**. Pharmaceutics 13 (2021), pp. 80, https://doi.org/10.3390/pharmaceutics13010080

Kottala, N., Abebe, A., Sprockel, O., Akseli, I., Nikfar, F., Cuitino, A.M. **Influence of compaction properties and interfacial topography on the performance of bilayer tablets**. Int. J. Pharm. 436 (2012a), pp. 171-178, https://doi.org/10.1016/j.ijpharm.2012.05.026

Kottala, N., Abebe, A., Sprockel, O., Bergum, J., Nikfar, F., Cuitino, A.M. **Evaluation of the Performance Characteristics of Bilayer Tablets: Part I. Impact of Material Properties and Process Parameters on the Strength of Bilayer Tablets**. AAPS PharmSciTech 13 (2012b), pp. 1236-1242, https://doi.org/10.1208/s12249-012-9845-9

Kottala, N., Abebe, A., Sprockel, O., Bergum, J., Nikfar, F., Cuitino, A.M. **Evaluation of the Performance Characteristics of Bilayer Tablets: Part II. Impact of Environmental Conditions on the Strength of Bilayer Tablets**. AAPS PharmSciTech 13 (2012c), pp. 1190-1196, https://doi.org/10.1208/s12249-012-9846-8

Kovacs, B., Peterfi, O., Kovacs-Deak, B., Szekely-Szentmiklosi, I., Fulop, I., Baba, L.I., Boda, F. **Quality-by-design in pharmaceutical development: From current perspectives to practical applications**. Acta Pharm. 71 (2021), pp. 497-526, https://doi.org/10.2478/acph-2021-0039

Lee, A.R., Kwon, S.Y., Choi, D.H., Park, E.S. **Quality by Design (QbD) approach to optimize the formulation of a bilayer combination tablet (Telmiduo (R)) manufactured via high shear wet granulation**. Int. J. Pharm. 534 (2017), pp. 144-158, https://doi.org/10.1016/j.ijpharm.2017.10.004

Lee, S.H., Kim, J.K., Jee, J.P., Jang, D.J., Park, Y.J., Kim, J.E. **Quality by Design (QbD) application for the pharmaceutical development process**. J. Pharm. Investig. 52 (2022), pp. 649–682, https://doi.org/10.1007/s40005-022-00575-x

Maddiboyina, B., Hanumanaik, M., Nakkala, R.K., Jhawat, V., Rawat, P., Alam, A., Foudah, A.I., Alrobaian, M.M., Shukla, R., Singh, S., Kesharwani, P. **Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension**. Heliyon 6 (2020), pp. 05459, https://doi.org/10.1016/j.heliyon.2020.e05459

Momin, M.M., Kane, S., Abhang, P. **Formulation and evaluation of bilayer tablet for bimodal release of venlafaxine hydrochloride**. Front. Pharmacol. 6 (2015), 144 https://doi.org/10.3389/fphar.2015.00144

Narendra, C., Srinath, M.S., Babu, G. **Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention**. AAPS PharmSciTech 7 (2006), pp. E23-E29, https://doi.org/10.1208/pt070234

Osei-Yeboah, F., Chang, S.-Y., Sun, C.C. **A critical Examination of the Phenomenon of Bonding Area - Bonding Strength Interplay in Powder Tableting**. Pharm. Res. 33 (2016), pp. 1126-1132, https://doi.org/10.1007/s11095-016-1858-8

Papos, K., Kasa, P., Ilic, I., Blatnik-Urek, S., Regdon, G., Srcic, S., Pintye-Hodi, K., Sovany, T. **Effect of the surface free energy of materials on the lamination tendency of bilayer tablets**. Int. J. Pharm. 496 (2015), pp. 609-613, https://doi.org/10.1016/j.ijpharm.2015.10.061

Parmar, K., Desai, A. **Preparation and optimization of quick/slow-release bilayered tablets of prazosin HCl using DoE and PCA**. Pharmacophore 13 (2022), pp. 80-87, https://doi.org/10.51847/7Ap1qgnqwF

Peinado, A., Hammond, J., Scott, A. **Development, validation and transfer of a Near Infrared method to determine in-line the end point of a fluidised drying process for commercial production batches of an approved oral solid dose pharmaceutical product**. J. Pharm. Biomed. Anal. 54 (2011), pp. 13-20, https://doi.org/10.1016/j.jpba.2010.07.036

Pramod, K., Tahir, M.A., Charoo, N.A., Ansari, S.H., Ali, J. **Pharmaceutical product development: A quality by design approach**. Int J Pharm Investig 6 (2016), pp. 129-138, https://doi.org/10.4103/2230-973x.187350

Rojek, B., Gazda, M., Wesolowski, M. **Quantification of Compatibility Between Polymeric Excipients and Atenolol Using Principal Component Analysis and Hierarchical Cluster Analysis**. AAPS PharmSciTech 23 (2021), 3, https://10.1208/s12249-021-02143-2

Salatin, S., Alami-Milani, M., Cilvegar, H., Fereidouni, S., Maghsoodi, M., Monajemzadeh, F., Jelvehgari, M. **Development and characterization of bilayered tablets of diazepam for oral**

drug delivery: design, optimization and in vitro evaluation. Ther. Deliv. 13 (2022), pp. 221-231, https://doi.org/10.4155/tde-2021-0077

Sastry, S.V., Khan, M.A. **Aqueous-Based Polymeric Dispersion: Face-Centered Cubic Design for the Development of Atenolol Gastrointestinal Therapeutic System**. Pharm. Dev. Technol. 3 (1998), pp. 423-432, https://doi.org/10.3109/10837459809028623

Saydam, M., Takka, S. **Development and in vitro evaluation of pH-independent release matrix tablet of weakly acidic drug valsartan using quality by design tools**. Drug Dev. Ind. Pharm 44 (2018), pp. 1905-1917, https://doi.org/10.1080/03639045.2018.1496450

Singh, B., Saini, G., Vyas, M., Verma, S., Thakur, S. **Optimized chronomodulated dual release bilayer tablets of fexofenadine and montelukast: quality by design, development, and in vitro evaluation**. Future J. Pharm. Sci. 5 (2019), 5, https://doi.org/10.1186/s43094-019-0006-9

Stephenson, D., Spence, J., 1964. Sustained release tablets, US3146169-A.

Tak, J.W., Gupta, B., Thapa, R.K., Woo, K.B., Kim, S.Y., Go, T.G., Choi, Y., Choi, J.Y., Jeong, J.H., Choi, H.G., Yong, C.S., Kim, J.O. **Preparation and Optimization of Immediate Release/Sustained Release Bilayered Tablets of Loxoprofen Using Box-Behnken Design**. AAPS PharmSciTech 18 (2017), pp. 1125-1134, https://doi.org/10.1208/s12249-016-0580-5

Tantry, J.S., Tank, J., Suryanarayanan, R. **Processing-induced phase transitions of theophylline—implications on the dissolution of theophylline tablets**. J. Pharm. Sci. 96 (2007), pp. 1434-1444, https://doi.org/10.1002/jps.20746

Tao, J., Robertson-Lavalle, S., Pandey, P., Badawy, S. **Understanding the Delamination Risk of a Trilayer Tablet Using Minipiloting Tools**. J. Pharm. Sci. 106 (2017), pp. 3346-3352, https://doi.org/10.1016/j.xphs.2017.07.005

ter Horst, J.P., Turimella, S.L., Metsers, F., Zwiers, A. **Implementation of Quality by Design (QbD) Principles in Regulatory Dossiers of Medicinal Products in the European Union (EU)**

Between 2014 and 2019. Ther. Innov. Regul. Sci. 55 (2021), pp. 583-590, https://doi.org/10.1007/s43441-020-00254-9

Tomba, E., Facco, P., Bezzo, F., Barolo, M. **Latent variable modeling to assist the implementation of Quality-by-Design paradigms in pharmaceutical development and manufacturing: A review**. Int. J. Pharm. 457 (2013), pp. 283-297, https://doi.org/10.1016/j.ijpharm.2013.08.074

Tho, I., Bauer-Brandl, A. **Quality by design (QbD) approaches for the compression step of tableting**. Exp. Opin. Drug Deliv. 8 (2011), pp. 1631-1644, https://doi.org/10.1517/17425247.2011.633506

Vaithiyalingam, S.R., Sayeed, V.A. **Critical factors in manufacturing multi-layer tablets—Assessing material attributes, in-process controls, manufacturing process and product performance**. Int. J. Pharm. 398 (2010), pp. 9-13, https://doi.org/10.1016/j.ijpharm.2010.07.025

Weitzel, J., Pappa, H., Banik, G.M., Barker, A.R., Bladen, E., Chirmule, N., DeFeo, J., Devine, J., Emrick, S., Hout, T.K., Levy, M.S., Mahlangu, G.N., Rellahan, B., Venema, J., Workman, W. **Understanding Quality Paradigm Shifts in the Evolving Pharmaceutical Landscape: Perspectives from the USP Quality Advisory Group**. AAPS J. 23 (2021), 112 https://doi.org/10.1208/s12248-021-00634-5

Wirth, D.D., Baertschi, S.W., Johnson, R.A., Maple, S.R., Miller, M.S., Hallenbeck, D.K., Gregg, S.M. **Maillard Reaction of Lactose and Fluoxetine Hydrochloride, a Secondary Amine**. J. Pharm. Sci. 87 (1998), pp. 31-39, https://doi.org10.1021/js9702067

Won, D.H., Park, H., Ha, E.-S., Kim, H.-H., Jang, S.W., Kim, M.-S. **Optimization of bilayer tablet manufacturing process for fixed dose combination of sustained release high-dose drug and immediate release low-dose drug based on quality by design (QbD)**. Int. J. Pharm. 605 (2021), 120838, https://doi.org/10.1016/j.ijpharm.2021.120838

Wu, C.-Y., Seville, J.P.K. **A comparative study of compaction properties of binary and bilayer tablets**. Powder Technol. 189 (2009), pp. 285-294, https://doi.org/10.1016/j.powtec.2008.04.026

Yu, L.X., Amidon, G., Khan, M.A., Hoag, S.W., Polli, J., Raju, G.K., Woodcock, J. **Understanding Pharmaceutical Quality by Design**. AAPS J. 16 (2014), pp. 771-783, https://doi.org/10.1208/s12248-014-9598-3

Zacour, B.M., Pandey, P., Subramanian, G., Gao, J.Z., Nikfar, F. **Correlating bilayer tablet delamination tendencies to micro-environmental thermodynamic conditions during pan coating**. Drug Dev. Ind. Pharm 40 (2014), pp. 829-837, http://dx.doi.org/10.3109/03639045.2013.788014

Zhang, J.Y., Wu, C.Y., Storey, D., Byrne, G. **Interfacial strength of bilayer pharmaceutical tablets**. Powder Technol. 337 (2018), pp. 36-42, http://dx.doi.org/10.1016/j.powtec.2017.12.025

Zhang, Y., McGeorge, G. **Quantitative Analysis of Pharmaceutical Bilayer Tablets Using Transmission Raman Spectroscopy**. J. Pharm. Innov. 10 (2015), pp. 269-280, http://dx.doi.org/10.1007/s12247-015-9223-8

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