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Production of multilayer tablets via the novel Gluing Pills Technology and their characterization

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Happiness lies in the joy of achievement
and the thrill of creative effort.
- Franklin D. Roosevelt -

Abstract

During the last two decades, there is a growing interest in the manufacturing of multilayer tablets. The conventional manufacturing method is via rotary tablet presses by filling the raw materials as powder or granular blends into the die separately and compacting either simultaneously or consecutively. Drawbacks of this method are inaccurate layer weight control, insufficient interfacial bonding of layers, and cross-contamination.

In the present study, the processability of the novel "Gluing Pills Technology" was investigated for the manufacturing of multilayer tablets. In this technology, the tablet bodies are compressed separately and glued together in an additional process by applying a polymeric gluing agent to produce multilayer tablets. Plastically deforming Avicel Ph 102 and the brittle dibasic calcium phosphate dihydrate (DCPD) were used as excipients for preparing high load blends with ibuprofen free acid (30% w/w) or caffeine anhydrous (40% w/w) as active pharmaceutical ingredients (API). The compaction simulator Stylcam 200R® was used for assessing the deformation behavior of pure excipients and their binary blends with API using the Heckel's equation. Tensile strength and elastic recovery of tablets after production was measured. Tablets composing possible combinations of excipient and API were manufactured using 10 and 20 kN compaction force. Mean roughness parameter Ra of the tablet bodies was determined via Optical Coherence Tomography (OCT) and the taken images were analyzed using image analysis software. Aqueous solutions of fish gelatin and PVP K90 were used as gluing agents for manufacturing of multilayer tablets of caffeine and ibuprofen. The tendency of bilayer tablets to delamination was investigated via friability test. The impact of tablet's physical properties such as bonding behavior, elastic recovery, tensile strength, compression force and the type of gluing agent on the interfacial adherence of layers and the tendency to delamination was studied. The release profile of the API from the tablets was investigated within 2 hours and 24 hours via dissolution test.

Elastic recovery of tablets together with deformation behavior was the most important factor, its mismatching between layers significantly affected the delamination tendency. The lower viscous fish gelatin solution showed better

adhesive properties than the PVP K90, which may be due to its better penetration into the pores and microstructures on the tablet surface. The results of this study point out that by careful selection of the materials and the production process parameters, the production of quality multilayer tablets via the Gluing Pills Technology is feasible. This technology can be used for manufacturing of personalized medicine and offers the flexible and individual combinations of APIs with different release profile.

Zusammenfassung

In den letzten zwei Jahrzehnten ist das Interesse an der Herstellung von mehrschichtigen Tabletten stetig gewachsen. Das herkömmliche Herstellungsverfahren erfolgt über Rotationstablettenpressen, in denen Rohmaterialien als Pulver oder Granulat in die Matrize einzeln gefüllt und gleichzeitig oder nacheinander verdichtet werden. Nachteile dieses Verfahrens sind nicht präzise Regelung des Schichtgewichts, unzureichende Grenzflächenbindung von Schichten und Kreuzkontamination.

In dieser Studie wurde die Verarbeitbarkeit der neuartigen "Gluing Pills" Technologie für die Herstellung von mehrschichtigen Tabletten untersucht. Bei dieser Technologie werden die Tablettenkörper separat gepresst und in einem weiteren Verfahren zusammengeklebt, indem ein polymeres Klebemittel aufgebracht wird, um mehrschichtige Tabletten herzustellen. Plastisch verformendes Avicel Ph 102 und das spröde dibasische Kalziumphosphatdihydrat (DCPD) wurden als Hilfsstoffe zur Herstellung von Hochleistungsmischungen mit Ibuprofen-freier Säure (30% w/w) oder wasserfreiem Koffein (40% w/w) als pharmazeutischer Wirkstoff (API). Der Verdichtungssimulator Stylcam 200R® wurde zur Beurteilung des Verformungsverhaltens von reinen Hilfsstoffen und deren binären Mischungen mit API unter Verwendung der Gleichung nach Heckel verwendet. Zugfestigkeit und elastische Rückgewinnung von Tabletten nach der Produktion wurden gemessen. Tabletten, zusammengesetzt aus möglichen Kombinationen von Hilfsstoff und API, wurden unter Verwendung von 10 und 20 kN Verdichtungskraft hergestellt. Der mittlere Rauheitsparameter Ra der Tablettenkörper wurde mittels optischer Kohärenztomographie (OCT) bestimmt und die aufgenommenen Bilder wurden mittels Bildanalyse-Software analysiert. Wässrige Lösungen von Fischgelatine und PVP K90 wurden als Klebstoffe für die Herstellung von mehrschichtigen Tabletten aus Koffein und Ibuprofen verwendet. Die Tendenz von Zweischichttabletten zur Delaminierung wurde mittels Zerreibbarkeitstest untersucht. Die Auswirkung der physikalischen Eigenschaften der Tabletten wie Bindungsverhalten, elastische Rückgewinnung, Zugfestigkeit, Druckkraft und die Art des Klebemittels auf die Grenzflächenhaftung der Schichten und die Tendenz zur Delaminierung wurde

untersucht. Das Freisetzungsprofil des API aus den Tabletten wurde innerhalb von 2 Stunden und 24 Stunden mittels Auflösungstest untersucht.

Die elastische Rückgewinnung von Tabletten in Kombination mit dem Deformationsverhalten war der wichtigste Faktor, dessen Mismatching zwischen den Schichten die Delaminierungstendenz signifikant beeinflusste. Die niedrigviskose Fischgelatinelösung zeigte bessere Klebeeigenschaften als PVP K90, die auf eine bessere Penetration in die Poren und Mikrostrukturen auf der Tablettenoberfläche zurückzuführen ist. Die Ergebnisse dieser Studie weisen darauf hin, dass durch die sorgfältige Auswahl der Materialien und der Produktionsprozessparameter die Herstellung von hochwertigen mehrschichtigen Tabletten mittels der „Gluing Pills“ Technologie möglich ist. Diese Technologie kann für die Herstellung von personalisierter Medizin verwendet werden und bietet die flexible und individuelle Kombination von APIs mit verschiedenen Freisetzungsprofilen.

Contents

1 Introduction

Latterly, multilayer tablets have become an interesting approach in drug delivery, especially employed in Fixed Dose Combination (FDC) products and in treating diseases that request polypharmacy [1]–[3].

Conventional manufacturing of multilayer tablets is the compression of layers in sequence [4]. The challenges involved with this approach are inaccurate weight control, cross contamination in the interfacial layer, mismatch of elastic/plastic properties and impact of the storage conditions on the adhesion layer can lead to delamination, and insufficient hardness, affecting the quality of the end product [5], [6].

In the present work a novel technique of producing multilayer tablets is presented, the Gluing Pills Technology (GPT), it differs from the abovementioned manufacturing of multilayer tablets in many aspects, the layers or tablet bodies are pressed separately via conventional tableting and glued together by using a polymeric solution as a gluing agent. This technology overcomes some of the challenges encountered in common manufacturing of multilayer tablets, however, enough attention should be paid to elastic/plastic match of the layers, sufficient adherence in the interface between the gluing layer and the two individual layers, and producing a robust product to withstand the manufacturing process, storage conditions and transportation.

In this work, the processability of the GPT was evaluated. The characterization of the compaction properties of powders (excipients and mixtures with relatively high content of API) that differ in their properties, the surface characterization of the produced tablets and the selection of the appropriate gluing agent, were conducted.

The impact of storage conditions was investigated by storing the samples at room temperature (RT) and accelerated conditions (AC) *i.e.* 40°C and 75% relative humidity (RH).

Finally, the characterization of the individual tablet bodies and the produced multilayer tablets was conducted.

2 Theoretical part

2.1 Oral Drug Delivery

The oral route of drug administration is the most common route for drug delivery, amongst the oral dosage forms, tablets and capsules are the most used ones. Even though other routes of administration have many advantages (e.g. parenteral route is characterized by fast onset of action, lower dose, and bypass of the first pass effect), oral drug delivery is very often the first choice. Main advantages are the ease of administration, pain avoidance, accurate dose, flexibility in the design of the dosage forms, ease of providing desirable physical and chemical stability of the formulation, least aseptic constraints, *etc*. Drawbacks that should be mentioned are, i) difficulty in swallowing of tablets and capsules as most conventional dosage forms, especially by elderly and pediatric population, ii) not suitable for emergency cases, iii) possible bioavailability problems due to slow disintegration and dissolution, and iv) irritant effects on the gastrointestinal tract (GIT) [1].

In order to have a better understanding of the oral administration of drugs, one should consider the pathway which the dosage form passes through the GIT, a brief overview on the anatomical and physiological characteristics of different sections of the GIT is represented in *Table 1* [2].

Table 1. Overview of the anatomical and physiological characteristics of the GIT

Section	Length [m]	Absorption surface [m²]	pH		Transition time [h]	Details*
			Fasted	Fed		
Stomach	0.2	0.1	1.5-3	2-5	1-3	HCl, P, L
Duodenum	0.3	0.1	5	5.5	3-5	Bile acids, T, A, PR, L, N, M
Jejunum	3.0	60	6.1	6.1		M, A, S, LC
Ileum	4.0	60	7-8	7-8		E, L, N
Colon	1.35	0.25	8	/	4-16	R, ES, SU, AD
Rectum	0.12	Very small	7	/		

*Enzymes: P=Peptidase; L=Lipase; T=Trypsin; A=Amylase; PR=Protease; N=Nuclease; M=Maltase; S=Sucrase; LC=Lactase; R=Reductase; ES=Esterase; SU=Sulfatase; AD=Amidase; E=Enteropeptidase.

The natural function of the GIT is to break down food into nutrients that can be absorbed into the circulatory system in a selective, safe and effective manner. Passing through the GIT, basic nutrients i.e. proteins, carbohydrates, lipids, and nucleic acids are broken down into smaller fragments or building blocks by specific enzymes and then selectively absorbed. Large protein fragments are cleaved into small peptides which furthermore are cut from peptidases into amino acids and/or di- and tri-peptides; complex carbohydrates are cut into mono- and di-saccharides; lipids first solubilized from the bile acids and then cut into free fatty acids, mono- and tri-glycerides; polynucleic acids into nucleosides; similarly, vitamins and co-factors are extracted from the diet and absorbed [3].

The anatomy and physiology of the GIT and mechanisms involved in digestion are far more complex, more detailed information can be found in many medical textbooks [4].

From the above mentioned, it is clear that the GIT represents a very harsh environment for any drug substance. Hence, the development of oral dosage forms that successfully deliver the drug to its site of action becomes quite challenging, especially for the drug substances which belong to classes III and IV of the Biopharmaceutics Classification System (BCS) which are not readily absorbed. Many studies and advancements in the last decade try in various creative ways to overcome biological, chemical, and physical barriers of the GIT [3], [5].

2.2 Tablets as the most conventional oral dosage form and tableting

United States Pharmacopeia (USP) defines tablets as "solid dosage forms in which the API is blended with excipients and compressed into the final dosage" [6].

Their advantages such as ease of accurate dosing, good chemical and physical stability during the shelf life, competitive unit production costs, high level of patient acceptability and high convenience, easy to package and ship, simple to identify, self-administration, makes them the most used dosage form. Whereas their oral administration is liable for their disadvantages, as mentioned above [1], [7].

There are various types of tablets, a summary of classes of tablets depending on their application is shown in *Table 2* [1],[8].

Table 2. Types of tablets classed by their application

Tablets administered orally	Tablets used in the oral cavity
Standard compressed tablets	Buccal and Sublingual tablets
Multiple compressed tablets (*multilayer, compression coated, inlay tablets*)	Lozenges
	Dental cones
	Administered by other routes
Modified release tablets	Implant tablets
Controlled release tablets	Vaginal tablets
Delayed release tablets	**Tablets for solution preparation**
Targeted tablets (*gastro retentive or floating tablets, colon targeted tablets*)	Effervescent; Dispersible;
Chewable tablets	Hypodermic; Tablet triturates.

Manufacturing process of tablets involves several unit operations. Usually, the tablet production process starts with mixing/blending of the powder materials *i.e.* the API and excipients, and in the case of poor flowability of the powder mixture a granulation step is employed, which can be wet or dry granulation, and the last step is the compaction of the powder using tablet presses. The main purpose of granulation is the increase in size of the particles thus the flowability is enhanced, and the filling of the die is more uniform, therefore, the weight and content variation of the tablets is lowered.

In some cases when the powder mixture possesses good flowability the granulation step can be skipped and the production of tablets via direct compaction becomes feasible.

The required unit operations for producing tablets as end-product are listed in *Table 3* [9].

Table 3. Overview of the (optional) required unit operations for producing tablets

Wet granulation and compaction	**Dry granulation and compaction**	**Direct compaction**
- Blending the granulation composition	- Blending	- Sieving - Blending
- Wet massing	- Slugging	
- Sizing	- Sieving	
- Drying		
- Blending (extragranular & lubricant)	- Blending (extragranular & lubricant)	- Blending (Lubricant)
- Compaction	- Compaction	- Compaction

To avoid confusion and the ambiguity of the terms used to describe tableting, a definition of the most used terms would be out of benefit [10].

Compression

Volume reduction of the powder bed under applied pressure.

Compressibility

The ability of the powder bed to reduce its volume under applied pressure.

Compaction

Transformation of the powder bed into a compact with defined shape by powder compression.

Compactibility

The ability of the powder to increase its strength and to form a compact under applied pressure, usually described in terms of tablet strength.

Tabletability

The ability of a powder bed to form tablets, which fulfill the defined quality attributes and can be used as a pharmaceutical dosage form.

2.2.1 Tablet presses

In general, the process of tableting or the *compaction cycle* can be summarized in three steps [8]:

1) *Die filling*; is done from the feeding shoe (hopper) which goes over the die while the lower punch closes the die from the bottom, die is filled via the gravitational flow of the powder. Centrifugal and vibrational feeding shoes also can be used, so called forced-feeding.
2) *Tablet formation;* after the feeding shoe moves back, the upper punch moves down enters the die and compresses the powder into a tablet. The lower punch can be static or can move upwards. Immediately after the maximum force is achieved the upper punch rises and leaves the die, while the compacted powder goes under the so-called decompression phase.
3) *Tablet ejection;* after the upper punch exits the die, the lower punch moves upwards till its tip levels with the die and simultaneously the formed tablet exits the die and it is removed from a pushing device.

In industrial scale tablet production, two types of tablet presses are used: *the single punch press* and *the rotary (multi-station) press*.

Single-punch Press

Consists of only one set of punches and a die, filling is done from the feeding shoe which moves forward over the die and returns backward. Following the aforementioned compaction cycle the tablet is produced, in this case the pushing device is the feeding shoe itself. The position of the lower punch in the die can be adjusted regarding of that how much mass of powder is needed to be compressed. Usually, the lower punch is static (single-ended compaction), thus the compaction force is applied by the upper punch and controlled from the upper punch displacement. The production rate of tablets is about 200 tablets per minute, and mainly are used for a small production scale, for example, small batch production size, during formulation development or for clinical trials [8].

Rotary (multi-station) Press

It operates with more than one set of punches and dies, can be more than 60, thus the production rate can reach more than 10 000 tablets per minute. Punches are mounted in a circle track which passes over rolls and cams and moves on the vertical axis. Lower punches position into the die regulates the amount of powder, while the upper punches are responsible for the compression, in here the lower punch is not stationary but penetrates into the die in the moment of compression (double-ended compaction). Dies are mounted in the circular die table, which rotates along with the punches, so for every die corresponds the same set of punches. Feeding of the powder is performed from the hopper which stands above the die table and it is static, filling of the die is accomplished by the feed frame. After ejection, the tablet is pushed away by a pushing device [8].

Usually, tablet presses are instrumented at least with transducers to measure the force of the punches during the production process, as it is an important information related to the weight uniformity, the goal being the control over the tableting process [8].

Compaction Simulators

Latterly, in contrary to industry, in research and development compaction simulators are used, they are presses with a single punch or a rotary press type coupled with *data acquisition system*, and are useful for the evaluation of the compaction process and scale-up of tableting process for powders with different properties [8], [11].

In general, data acquisition system represents a pathway of the registered signal from the physical system (*e.g.* force in the punch) recorded by the sensor (transducer), following the signal conditioning (*e.g.* amplification of the received signal), then the latter *i.e.* the analog signal is converted to a digital one, which can be "read" from the computer and analyzed via analysis software. A brief schematic overview of the data acquisition system is represented in *Figure 1*, [11].

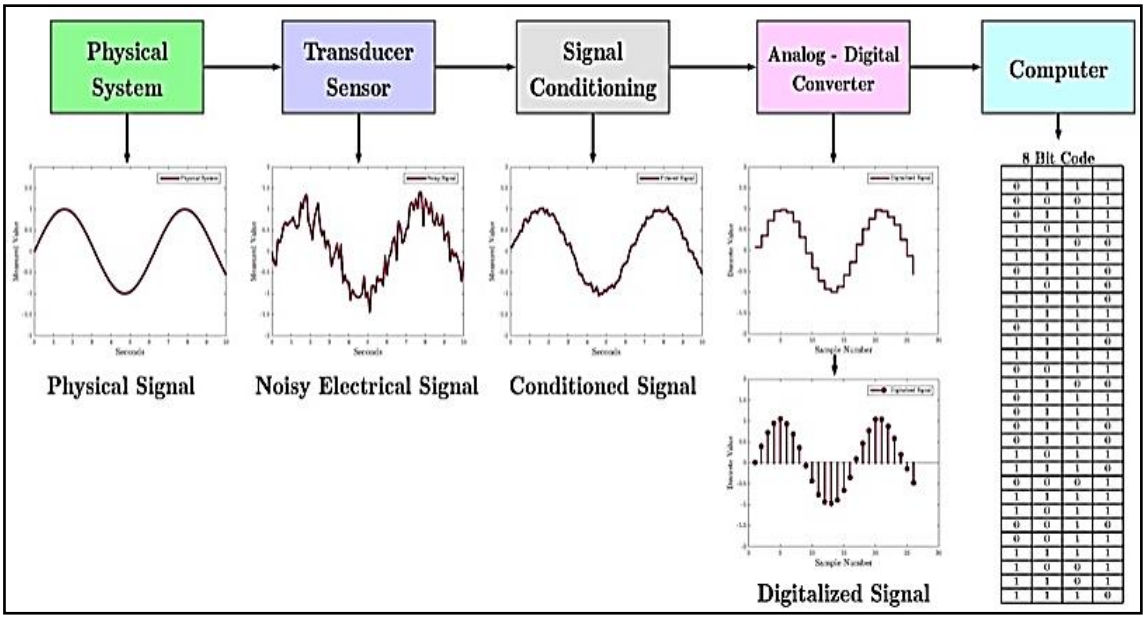

Figure 1. Digital Data Acquisition System; adapted from Ref. [12]

Compaction simulators represent a very complex tablet press instrumentation system, or data acquisition system. They offer the possibility of accurate measurement of the force in the both punches and the die, punch displacement, distance between punches, ejection force, punch speed, *etc.,* during the entire cycle of compaction, thus compaction simulators make it possible to simulate many presses which operate on a bigger scale, and are helpful in the design space for tableting in the context of Quality by Design. It should be mentioned that the calibration, resolution of the measuring system and the reproducibility of the results are very important for attaining reliable results [10], [11], [13].

There are three types: *hydraulic, mechanical linear* and *mechanical rotary cam* compaction simulators. In the present work, the compaction analysis was performed using a mechanical compaction simulator, some of the advantages and disadvantages of this type of simulator are listed in *Table 4* [11].

Table 4. Advantages and disadvantages of the mechanical rotary cam compaction simulator

Advantages	Disadvantages
- Easy to operate and small in size - Easy change of tools, calibration, and deformation - Able to simulate both single and double ended compaction - Punch displacement profile is independent of the tooling - Options to sort the tablets - Quick change of operating conditions possible	- Not possible to manufacture multilayer tablets in an automated way - Manufacturing of multilayer tablets is possible just manually, but with difficulties

2.2.2 Compression and Compaction analysis

Since in the present work the granulation of powders and consequently granule compaction are not included, compression and compaction analysis in this section will focus just on powder materials.

The compressibility of a powder material is defined as its ability to reduce the volume when undergoes the compression force. The events which happen in the powder bed, during the compression, can be described as follows [8]:

- *Rearrangement;* in the beginning, the loose particles fill the die and are randomly rearranged. When the compression starts individual particles fill the pores in between resulting in the reduction of the volume until the movement of individual particles is arrested.
- *Deformation;* afterwards, with the increase of the force the friction between particles is further increased, and eventually deformation of the particles starts to occur, depending on the nature of the material the deformation can be elastic, plastic, or viscoelastic.
- *Fragmentation;* when the applied force is further increased, particles that experienced the deformation will start to fail to hold their integrity and break, newborn smaller particles can continue to deform and break, thus a

particle can experience these events several times. Fragmentation of brittle materials is governed from brittle fracture of the particles rather than elastic or plastic deformation.

Particles during the compression undergo relatively high stress, which brings their surfaces in juxtaposition and eventually interparticle bonds can emerge.

Particle size and shape, surface roughness, and surface area of particles are factors which affect the compression and compaction mechanism, these factors/properties are prone to change during the compression process, for instance by fragmenting their shape and surface area changes, revealing more contact points which can lead to successful bonding in between particles. Crystallinity and crystal habit (geometry of the crystal) of the materials affects the compaction process, while amorphous materials have the propensity to deform plastically, the crystalline ones deform by brittle fracture [11].

Elastic, plastic and viscoelastic deformation

It is worth to note that the deformation mechanism of the majority of the pharmaceutical powder materials is not strictly distinguishable between brittle, elastic or plastic, but their behavior is mostly a combination of different deformation mechanisms, known as viscoelastic deformation [8].

Elastic deformation

An ideal elastic material recovers to its previous state after the stress is removed, thus no deformation remains, *i.e.* the deformation mechanism obeys the Hooke's law [14]. For the pharmaceutical production of tablets, this property can cause problems such as capping and lamination, also cracks can develop on the surface which is critical for coated tablets for instance. These problems arise due to the total elastic recovery after the tablet is ejected from the die and lasts for a certain time after. This phenomenon shows to have a correlation with the compression speed, at high speed the elastic recovery is higher [11].

Elasticity is a time-independent process, *i.e.* it doesn't depend on the time in which the stress is applied, but just the magnitude. Mathematical expression which describes the elasticity of the materials (Hooke's law), is given in *Equation 1*.

$$\sigma = E\varepsilon \tag{1}$$

Where σ $[Pa]$ is the applied stress, E $[Pa]$ represents the Young's modulus (specific constant for each material), and ε $[-]$ is the deformation (in case of a spring is the ratio of the elongation of the spring and its original length) [15].

Plastic deformation

In contrary to elastic materials, the ideal plastic material preserves the deformation induced by the applied force, *i.e.* the deformation remains after the stress is removed. In the context of tablet formation, the plasticity of the material gives the likelihood of bond formation between particles, by forming interparticle contacts which do not separate due to the nonexistence of elastic recovery phenomenon [11].

Plasticity is a time-independent process and can be represented as the balance given in *Equation 2*.

$$\sigma = \sigma_y \tag{2}$$

Where $\sigma_y[Pa]$ is the yield stress or the minimal applied stress which deforms the material plastically [10].

Viscoelastic deformation

It is a time-depended process which comprises of elastic and viscous elements, *i.e.* deformation mechanism is in between the purely elastic deformation and the viscous one [8].

Viscosity is a material property which relates the deformation rate with the applied stress for a certain time span, *Equation 3* [15], [16].

$$\sigma(t) = \eta \frac{\partial \varepsilon}{\partial t} \tag{3}$$

Where η $[Pa \cdot s]$ is the dynamic viscosity, $\sigma[Pa]$ is the applied stress for a certain time, and $\frac{\partial \varepsilon}{\partial t}[s^{-1}]$ is the deformation rate.

For the description of the deformation behavior of the viscoelastic materials several mechanical models exist, these models consist of springs (elastic component)

and dashpots (viscous component), combining these components a deformation behavior of a material can be modeled, and thus predicted under certain stress conditions. Simple models like Maxwell model (series of springs and dashpots) and Voigt model (parallel combination of springs and dashpots) exist but are oversimplified for instance, Maxwell model cannot describe the creep motion, whereas the Voigt model cannot describe the stress relaxation. More advanced models, as the complex combination of spring and dashpot elements and particle-based models (numerical simulations, DEM [17], *etc.*) are used with the attempt to describe more accurately the viscoelastic deformation behavior. It is very important in the context of the formulation design and to satisfy the quality attributes of the end product to have a model that successfully describes the material's mechanistic behavior when it undergoes stress conditions during tableting [11].

Bonding mechanisms

Bond formation between small particles according to Rumpf classification [18] can occur via five different mechanisms, which can be enlisted as follows:

1. Solid bridges
2. Moveable liquids (capillary and surface tension forces)
3. Non-moveable liquids (viscous binders and adsorption layers)
4. Inter-particle attraction forces
5. Mechanical interlocking

Solid bridges, inter-particle attraction forces, and mechanical interlocking are more relevant for the description of the bonding mechanism in the compaction of powder materials than the forces created by the presence of movable and non-movable liquids between particles which are important for bonding in granule formation [11], [19].

Solid bridges

Due to the friction and high pressure at the inter-particle contact points during the compaction of pharmaceutical materials, temperature increases locally which brings to the melting of the asperities of the particles in contact, this localized melting crystallizes after the release of pressure (melting temperature over all the sample is not reached, but just locally), and thus particles 'fuse' together via the solid bridge formation, which occurs between more than two individual particles and a net-like structure is created giving the compact high strength [20]. Formation of solid bridges during compaction is similar to the sintering process, but no temperature is applied to the system [21].

Amorphous or semi-amorphous materials have higher propensity to form solid bridges than the pure crystalline ones, this becomes important in the case when the API content is relatively high, and hence the crystalline properties of the drug can affect the bonding mechanism of the tablet. The appropriate moisture content of the material is also an influencing factor, it facilitates the movement of the amorphous phase and it acts as a plasticizer, thus improving the bridge formation and consequently the strength of the tablet [11].

Interparticle attraction forces

Within the interparticle attraction forces, major contributors to tablet formation are Van der Waals forces and hydrogen bonding.

Van der Waals forces are classified as of three types: *Dipole - dipole* interaction or Keesome forces, occur between molecules which are permanent dipoles, and thus they orient their respective local counter charges to one another and attract each other. One kind of such attraction force is the hydrogen bonding, in the formation of hydrogen bonds the hydrogen atom of a molecule loses the single electron, and thus just the proton remains which can create bond with the negatively charged region of another molecule; *Dipole - induced dipole* or Debye forces, in this case, the polarized molecule induces a polarization to the adjacent non-polar molecule creating attraction force in between molecules; *Induced dipole - induced dipole* forces or London dispersion, occurs between non-dipole molecules, via a complex quantic mechanism in the presence of each other both molecules are able to form induced dipole [10], [11].

Mechanical interlocking

It is strongly influenced by the particle shape of materials involved in a compaction process and their deformation mechanism. Irregular particles which have an atypical shape and usually relatively high roughness is likely to interlock or hook to each other, and thus raising the strength of the whole compact [8], [11].

The three abovementioned bonding mechanisms are schematically depicted in *Figure 2*.

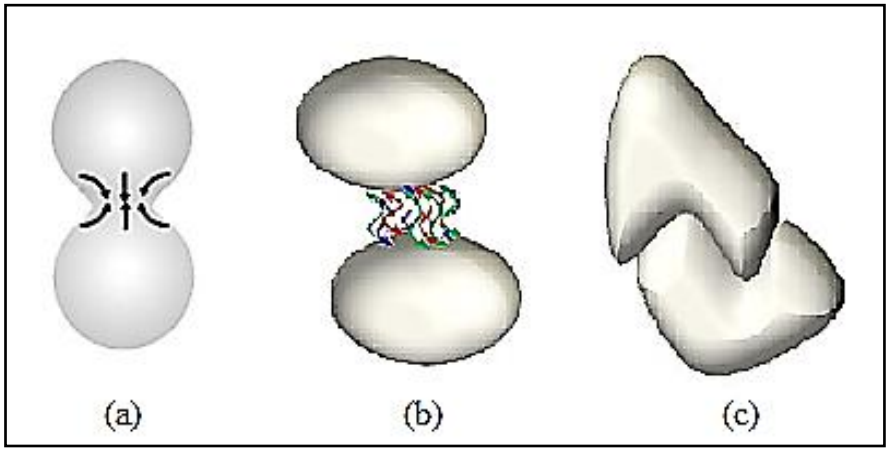

Figure 2. Bonding mechanisms (a) solid bridge formation, (b) interparticle attraction forces, (c) mechanical interlocking; adapted from Ref. [22], [23].

Compression analysis – Heckel's equation

There are several approaches to characterize the compaction/compression behavior of powder materials, beginning with the *porosity – pressure* relations, *force – displacement* profiles or *work of compaction*, and latterly *computational modeling* (DEM, FEM, *etc.*) and *the percolation theory and fractal geometry*. The simplicity and the possibility of gaining considerable knowledge on the powder compaction behavior from the porosity – pressure functions made them widely used in the area of analysis of compression behavior of pharmaceutical powder materials, from which Heckel's equation is extensively used [8], [11], [24].

Heckel equation was derived under the assumption that the reduction of the volume (porosity) of a powder bed due to the applied pressure obeys the first order reaction kinetics, *Equation 4*.

$$ln\left(\frac{1}{1-D}\right) = KP + A \qquad (4)$$

Where D [-] is the relative density while $(1-D)$ is the porosity usually denoted with the symbol ε [-], K is the slope of the function, P [Pa] represents the compression pressure and A[-] is the intersect of the linear function with the abscissa [25].

Relevant information that should be known beforehand is the true density, usually determined via helium pycnometry.

It is distinguished between "*in die"* or "at pressure" and "*ejected tablet"* or "at zero pressure" methods on how to obtain data which are relevant for the use of Heckel's equation.

"In die method" relies on the use of compaction simulator or instrumented press which is able to measure the height of the filled powder into the die and the distance between punches and to record the force in the both punches during the entire compaction cycle. Knowing the distance between punches at any time and the dimensions of the die/punches one can easily calculate the volume of the powder bed, after the ejection the weight of the compact has to be measured accurately, thus the apparent density of the powder in the column can be determined, from which the ratio of the apparent density and the true density gives the relative density D. The registered force is simply converted to pressure by knowing the diameter or the area of the punch tip [8], [25].

"At zero pressure" or "ejected tablet method" requires the measurement of dimensions of the compact after it is ejected, and the registration of the maximum compression pressure. Again, by knowing the true density and the volume of the compact/tablet apparent density is determined and relative density can be calculated. Several compacts are needed to obtain the data required for the use of Heckel equation, which makes the at zero pressure method tedious [8], [25].

Information on the compaction behavior that can be extracted from the Heckel's analysis are [10], [25]:

- The *yield pressure* P_y, which is the inverse of the slope of the linear region obtained from the Heckel's plots. It is a constant specific for each material and relates the ability of the material to deform plastically when it undergoes certain pressure. High values would mean that the material deforms dominantly via a brittle/fracture mechanism, and low values are related to plastic deformation.

- The parameter *A,* indicates the low pressure densification of the powder. At zero pressure relative density of the powder filled in the die is denoted as D_A and represents the total degree of densification and is calculated by the *Equation 5*; the ratio of the bulk density and the true density is denoted as D_0 and it describes the rearrangement of the powder when it fills the die; and the relative density D_b is calculated as the difference between D_A and D_0 representing the initial phase of compression (particle fragmentation)

$$D_A = 1 - e^{-A} \quad (5)$$

Depending on the material properties and their compaction behavior the Heckel's plots are classified mainly into three types: Type A, materials which undergo plastic deformation; Type B, an intermediate behavior between plastic and brittle/fracture deformation; Type C, are harder brittle materials and the dominant deformation mechanism is by fragmentation [25], [26].

Even though the Heckel equation itself is linear the Heckel plots obtained from experimental data are not, but they consist of three different regions: Region I, at the beginning there is a distinguishable curvature of the plot, which is regarded to the particle rearrangement and particle fragmentation; Region II, the so-called linear region from which the slope K and A parameter are obtained, describe either elastic or plastic deformation; Region III, is regarded to the elastic deformation, and sometimes it is referred to as the work hardening of the compact [24].

In *Figure 3*, three main types of Heckel's plots and the three distinct regions are depicted.

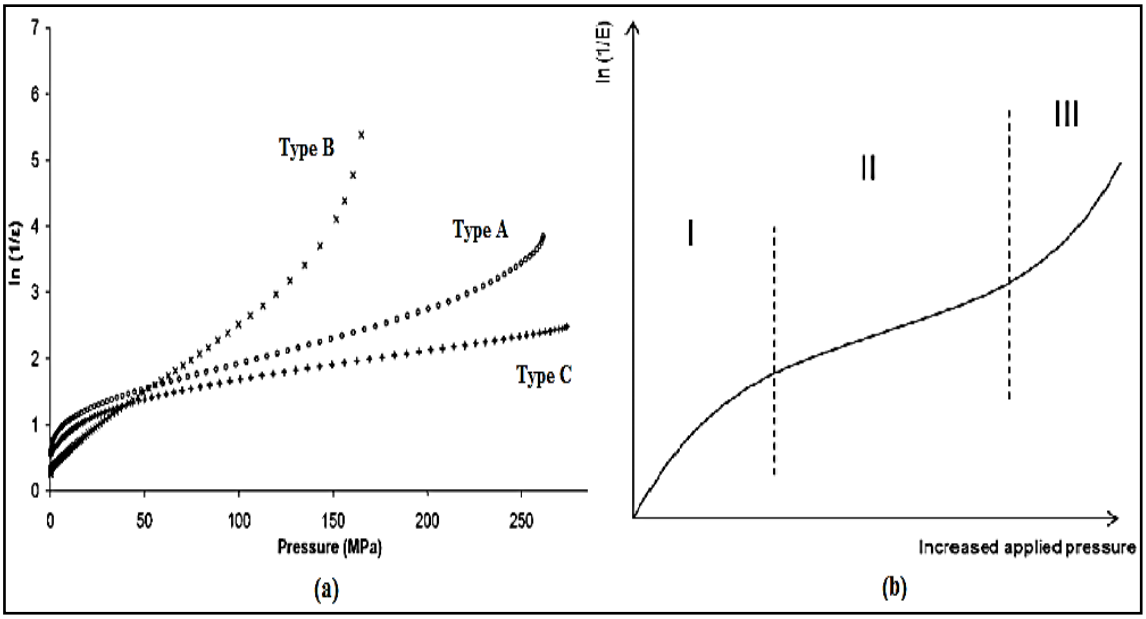

Figure 3. Three main types of Heckel plots (a), three regions of a Heckel profile (b); adapted from Ref. [24], [26]

General remarks on Heckel analysis

The use of Heckel equation as a tool to describe the compaction behavior of powders is accepted as fairly accurate, but it has its own limitations. Variable pressure yield parameter for the same material, which is attributed to the different methods to determine the linear region. Some deviations can originate from the true density measurements and the accuracy and reliability of the obtained data from the instrumented press. The tableting parameters such as maximal compression force, punch velocity, the diameter of the punch, and the machine deformation strongly affect the results obtained from the Heckel analysis. Furthermore, the effect of particle size distribution of the materials and the degree of lubrication on the variability of the results is known [24], [25], [27].

2.3 Multilayer tablets

Multilayer tablets have been gaining more interest over the last two decades, because of the increased demand on the development of effective and cost-saving therapeutic strategies for improving the patient adherence to therapy [28], [29]. A considerable number of therapies indicated in type 2 diabetes, HIV/AIDS, cardiovascular diseases, pain, asthma, parkinsonism, Alzheimer's, *etc.*, require polypharmacy, which negatively affects the patients' adherence to treatment strategies. Development of FDC is highly supported by U.S. Food and Drug Administration (FDA), World Health Organization (WHO) and European Medical Agency (EMA) as the effective measure against polypharmacy by reducing the number of taken dosage forms per day. Multilayer tablets are the most common form of such FDCs [30], [31].

Multilayer tableting offers several advantages. There are many reported cases of incompatibilities between APIs and excipients in the case of dosage forms containing more than one API [32]–[34]. Multilayer tablets offer the benefit of physical separation of incompatible substances, also the best possible composition of the materials can be selected for each layer. In addition to the conventional purpose of multilayer tablets, i.e., having different APIs with same or different release profiles in different layers, this dosage form can also be designed with the same API in the layers but with each layer having a different API release profile. In these manners the dosing unit burden is reduced and patient compliance improved, also the patent life of the product can be prolonged (Life Cycle Management) [35].

Some different design of formulations for achieving modified release profile are listed below, which use the multilayer tableting approach [29]:

Zero order sustained release

The system consists of the core (matrix) which can either be hydrophobic or hydrophilic and barrier layers which are pressed to the both faces of the core layer leaving the side face of the core uncovered and revealed to the dissolution media. Hydrophilic or hydrophobic barrier layers usually are of polymeric nature [36].

Quick/slow delivery system

This system contains an immediate release layer, a modulating barrier in the middle and a third slow release layer. The objective is to develop a new system bioequivalent to the sustained release formulations, which is characterized by a rapid rise in the plasma concentration, followed by an extended release at a constant rate [37].

Time-programmed delivery system (press coated tablets)

The system is able to release the drug at predetermined time point, which is preferable for drugs used in diseases which depend on the circadian rhythm, and subsequently the chance of developing tolerance is reduced. The core tablet (conventional or modified release formulation) is press coated within the barrier layer, the latter can be either erodible (hydrophobic) barrier or swellable barrier (hydrophilic), depending on the time the barrier layer is eroded or swelled the release of the API can be regulatedfrom the core tablet. [38].

Bimodal release profile

As the pH across the different sections of the GIT and the absorption rate are different to achieve a zero order release profile or to maintain the absorption level constant, the bimodal release is desirable. A bimodal release is characterized by possessing an initial immediate (rapid) release, followed by a constant release and a second step of a rapid release of API from the system. This can be achieved by employing multilayer tablet which consists of the core tablet which on two sides has barrier layers, and on top an initial dose layer. It is intended to compensate the slow absorption in the stomach by the initial rapid release of API from the initial dose layer. The following slow release from the core tablet is helped by the barrier layers, as a result, the high absorption rate of the small intestine is retarded, and at the end after the disintegration of the barrier layers an immediate release from the exposed core tablet should compensate the slow absorption rate of the large intestine [39].

Several techniques use the aforementioned design approaches, *i.e.* applying multilayer tableting, e.g. OROS® push-pull technology, L-OROS®, EN SO TROL®, DUROS®, DUREDAS®, Geomatrix® technology, *etc.* [28].

2.3.1 Manufacturing process

Compaction of multi-layered powders shares many similarities with the compaction of conventional tablets. The tableting of multilayer tablets is performed in special rotary tablet presses in the following sequence: The first powder layer is filled in the die and tampered with a low pressure; on top of the first layer is placed the second powder layer and pressed with the main compression force; consequently the bilayer tablet is ejected from the die; in the case when more than two layers are wanted the steps can be repeated [40].

Recently several presses are developed for the production of multilayer tablets. Korsch XL 400 FT® is one example of a very sophisticated press, which gives the opportunity of production of a single layer, bilayer, trilayer and compression coated tablets, by customizing its working mode via exchangeable components [41].

2.3.2 Problems/challenges in manufacturing of multilayer tablets

The most common problems are i) inaccurate layer weight control, ii) the risk of delamination as the consequence of the difference in the compaction behavior of the layers and/or the insufficient adherence between the layers, iii) cross contamination, due to the direct contact between the layers, especially in case of potential incompatibility between APIs or API and excipients in different layers, resulting in the instability of the end-product during the shelf-life.

To produce a multilayer tablet that meets the quality requirements, the formulation composition of each layer and the process parameters should be selected carefully [35].

Comments on the mentioned important problems/challenges and the possible ways to avoid them are given below.

Inaccurate layer weight control

In conventional tableting of single layer tablets two ways of controlling the weight and thus the content uniformity are employed, force controlled compression and compression with constant thickness. The same principles are employed in the

production of multilayer tablets. However, in manufacturing of multilayer/bilayer tablets, no press is able to sample separately the second layer and thus measure its weight. Therefore, the material of the second layer should have a very good flowability, in order to be able to fill the die properly and thus to reduce the variability in weight and content. [35], [42].

Delamination of layers:

- *Impact of the mechanistic properties of selected material*

Differences in the deformation mechanism of materials and their compaction behavior and elastic recovery can lead to delamination of layers. Therefore, mechanistic properties of layers should be matched to avoid this problem [35].

Another factor that influences the adhesive strength between layers is the surface characteristics of each layer, which are dependent on the mechanistic properties of the material, the rougher surface would mean better adhesion of the layers [42].

- *Impact of the compression forces*

The magnitude of the compression force applied to the first layer and then the main compression force compacting both layers have a strong influence on the adhesion and interfacial strength between two layers. Plastic materials are sensitive to the compression force for the both layers, increasing the force for tampering the first layer results in a decrease of the adhesion strength, this is attributed to the reduction of the surface roughness. On the other hand, brittle materials don't show strong sensitivity to the increase of compression force of the first layer and provide higher interfacial strength. Keeping a low compression force for the first layer gives more chance of interfacial bonding during the main compression, but low force gives rise to the lack of accuracy of weight force control system [35].

Cross-contamination

The risk of cross contamination exists due to the available dust/powder residue from the two different powder blends during the production. Many presses consider the solving of available dust/powder problem by employing clean in place (CIP) techniques like scrapers, suction nozzles, and also some technical solutions like

interchangeable turrets and centrifugal die filling. Cross contamination can originate also from the direct interfacial contact between the two layers, a clear separation is desired, which is difficult to achieve. Sometimes the problem was tried to solve by applying a buffer layer between two main layers [35].

Characterization of multilayer tablets

Using conventional characterization approaches as for single layer tablets is not completely applicable for the multilayer tablets, thus the challenge of developing new testing approaches is evident. Non-invasive methods like X-ray micro computed tomography is used to detect defects in the interfacial bonding and density distribution. The bonding strength between layers is tested with new techniques like the tensile tester and flexural bending test [35], [43], [44].

2.4 Gluing Pills Technology

In this thesis, the novel GPT was used for the production of the multilayer tablets and overcoming the mentioned challenges involved with their conventional manufacturing. The prototype machine was co-developed from the Research Center Pharmaceutical Engineering[1] (RCPE) and M&R Automation[2] and as it is in its first phase of development, it is intended for small scale laboratory production.

2.4.1 Overview

The basic production principle of this new approach differs from the abovementioned manufacturing of multilayer tablets, the layers or tablet bodies are pressed separately via conventional tableting and glued together by using a polymer as a gluing agent, the latter makes the gluing layer.

This manufacturing principle is developed to overcome the mentioned main problems/challenges encountered in the conventional manufacturing of multilayer tablets i.e. the inaccurate layer weight control, the risk of delamination and the risk of cross-contamination during the production process.

[1] Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria
[2] M&R Automation GmbH, Teslastraße 8, 8074 Grambach/Graz, Austria

The adhesion between two layers in this case mainly depends on the adhesive properties of the gluing agent. Migration of the APIs between the layers is just possible, if the API is soluble in the gluing agent and can cross-over the gluing layer. Thus, special care is required for selecting the gluing agent and medium [45].

As same as conventional production of multilayer tablets, the characterization of the produced multilayer tablets via this new technique requires tests, which are different from the classical ones dedicated to the single layer tablets.

2.4.2 Equipment design and operation

The operation is carried out in an automated process consisting of several stations, the main stations are for feeding of the first tablet layer, application of gluing agent, feeding of the second tablet layer, hardening the gluing agent between the two tablet layers, resulting in the production of bilayer tablets, and unloading of bilayer tablets.

Multilayer production can be applied, if necessary. The prototype machine consists of grips for holding the first tablet layer and transferring it from one to another station. The gluing station comprises of a syringe-like cartridge which is filled with the gluing agent either dissolved in a proper medium or in the molten sate. The nozzle system for glue application is a high-speed micro dispensing system based on piezo technology. It has a heating unit for melting the gluing medium in the nozzle. Both aqueous and organic solutions of binding agents can be applied. Molten polymers can be used as a gluing agent by using the nozzle, combined with the heating unit [46].

The system operates via a combination of electrical components and pressure driven parts, air pressure is used to operate the grips and the nozzle.

3 Aims of the thesis

The main objective of this thesis was to evaluate the novel GPT as a new technique for the production of multilayer tablet. Physical properties that might influence the quality of the end product were investigated, specifically:

- To determine the compaction behavior of the excipients and the formulations, and to investigate the effect of different compaction mechanisms by producing each layer separately, on the lamination tendency of the multilayer tablets

- To investigate the influence of elastic recovery of single layer tablets on the lamination tendency

- To investigate the influence of combination of single layer tablets compacted at different forces on the delamination tendency

- To investigate the impact of surface roughness, as a function of different tableting compositions or different compaction forces on the binding strength between two layers with the glue layer

- To investigate the impact of changes in surface roughness, due to the storage conditions, on the binding strength between two layers with the glue layer

- To evaluate the binding strength of polymeric solutions with different viscosities

- To determine if there is a significant change in the dissolution profiles due to the storage conditions and the type of the glue layer

4 Materials

Ibuprofen free acid (ibuprofen)

Ibuprofen 38®, was used as a model API and purchased from BASF, Ludwigshafen, Germany. Ibuprofen belongs to the non-steroidal anti-inflammatory drugs class, and it is a derivative of propionic acid (*isobutyl phenyl propionic acid*). The chemical structure of ibuprofen is shown in *Figure 4*.

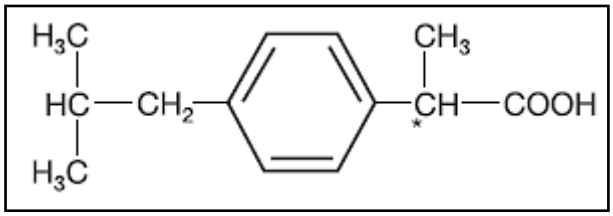

Figure 4. Chemical structure of Ibuprofen

Some of its chemical and physical properties are listed in *Table 5* (reported from the producer).

Table 5. A few physicochemical properties of Ibuprofen

Properties	Description
Appearance	Crystalline powder
Color	White
Melting temperature range	75 – 78 °C
Solubility in phosphate buffer pH=7,2	5,2 mg/ml
Partition coefficient n-octanol/water	3.3
Particle size	Range 2 – 150 μm; mean ~38 μm

Caffeine anhydrous (caffeine)

Caffeine anhydrous fine powder, supplied from BASF, Ludwigshafen, Germany was used as the second model API. Chemically it is a purine base derivative, more precisely methylxanthine derivate (*1, 3, 7 – Trimethyl xanthine),* its chemical structure is shown in *Figure 5*. It acts as a stimulant by blocking the action of adenosine in the neural receptors thus prevents the onset of drowsiness, other effects are an increase in blood pressure, diuresis, raise of the tone of cerebral vessels and inhibition of phosphodiesterases [47]. Caffeine is usually combined with analgesics like Ibuprofen, increasing the analgesic's effectiveness [48].

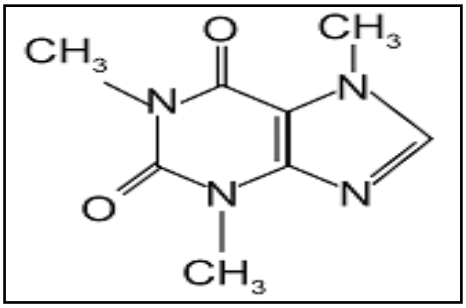

Figure 5. Chemical structure of Caffeine

Some of caffeine's physicochemical properties are shown in *Table 6* (reported from the producer) [49].

Table 6. A few physicochemical properties of Caffeine

Properties	Description
Appearance	Crystalline powder
Color	White
Melting temperature range	235 – 239 °C
Solubility in water	20 mg/ml at 20 °C
Partition coefficient n-octanol/water	Log Pow -0.0091 at 23°C
Particle size	Not less than 97% pass 150 μm sieve

Microcrystalline Cellulose – Avicel® PH 102

Avicel® PH 102, herein referred as Avicel, was used as binder for direct compression (FMC Biopolymer, Little Island, Cork, Ireland). Avicel represents a cellulose polymer of β (1 – 4) linked D-glucose units, after processing (hydrolysis) mainly consists of the crystalline part, *Figure 6*.

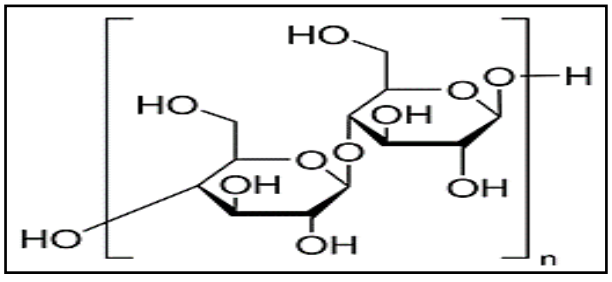

Figure 6. Chemical structure of cellulose unit

Some of Avicel's physicochemical properties are listed in *Table 7* (reported from the supplier).

Table 7. A few physicochemical properties of Avicel

Properties	Description
Appearance	Crystalline powder
Color	White
Melting temperature range	260 – 270 °C
Particle size distribution	D50 = 80 – 140 μm
Degree of polymerization	Not more than 350 units

Dibasic Calcium Phosphate Dihydrate (DCPD)

DCPD was purchased from Chemische Fabrik Budenheim KG, Budenheim, Germany. It is a dihydrate of calcium phosphate salt (*Figure 7*) and was used as a direct compression binder.

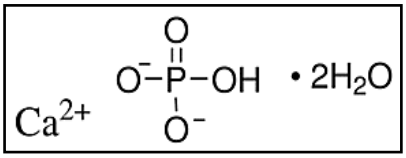

Figure 7. Chemical structure of Dibasic Calcium Phosphate Dihydrate

Some of its physicochemical properties are represented in *Table 8*, [50].

Table 8. Physicochemical properties of Dibasic Calcium Phosphate Dihydrate

Properties	Description
Appearance	Crystalline powder
Color	White
Particle size distribution	Mean ~150 μm
Calcium content	23,3 %
Phosphorous content	18,1 %

Guling agents

Fish Gelatin

It was purchased from Sigma-Aldrich, Steinheim, Germany. The slightly brown to yellow powder was dissolved in distilled water to prepare the gluing solution.

Polyvinylpyrrolidone K90 (PVP K90)

It was purchased from Alfa Aesar, Karlsruhe, Germany. The white/beige odorless powder was dissolved in distilled water to prepare the gluing solution. The molecular weight of PVP K90 is ~360 000.

Other excipients

Magnesium Stearate was used as a lubricant, and it was purchased from Sigma-Aldrich, Steinheim, Germany.

Aerosil 200 Pharma®, represents a colloidal silicon dioxide and it was used as a glidant, it was purchased from Evonik, Rheinfelden, Germany.

Salts for buffer preparation

Potassium Phosphate Monobasic KH_2PO_4 and *Sodium Phosphate Monobasic Dodecahydrate* $Na_2HPO_4 \times 12H_2O$ were purchased from Sigma-Aldrich, Steinheim, Germany.

Beeswax yellow

It was used to stick/fix the tablets in a glass slide for OCT measurements. Purchased from Carl Roth GmbH, Karlsruhe, Germany.

5 Methods

5.1 Tableting

5.1.1 Preparation of blends for each tablet layer

Ibuprofen free acid and caffeine anhydrous were selected as model substances. Avicel and DCPC were used as fillers for direct compaction. Formulations containing either ibuprofen free acid or caffeine anhydrous with either Avicel or DCPD were prepared for tableting. These formulations and the blending/mixing procedure are presented in *Table 9*.

Table 9. Formulation recipes for each tablet layer, and the blend preparation procedure

Formulation code	Recipe	Content w/w	Procedure
CA	Caffeine anhydrous Avicel Magnesium stearate Aerosil 200	40 % 59 % 0.5 % 0.5 %	Manually sieved using 630 µm sieve tray Mixing in Stephan Mixer for 15 min at 12% of the maximal rotation speed
CD	Caffeine anhydrous DCPD Magnesium stearate	40 % 59 % 1 %	Manually sieved using 630 µm sieve tray Blending for 10 min in Turbula blender at 62 rpm
IA	Ibuprofen free acid Avicel Magnesium stearate	30 % 69 % 1 %	Manually sieved using 630 µm sieve tray Blending for 10 min in Turbula blender at 62 rpm
ID	Ibuprofen free acid DCPD Magnesium stearate	30 % 69 % 1 %	Manually sieved using 630 µm sieve tray Blending for 10 min in Turbula blender at 62 rpm

Blending of the powders was performed in the Turbula blender TC2 (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland), for the CA formulation which was more cohesive the Stephan Mixer (Stephan machinery GmbH, Hameln, Germany) was used with the intent to employ higher energetic mixing, and in addition glidant (Aerosil 200 Pharma) was added to enhance the flowability.

5.1.2 Tablet compaction

Production of tablets was carried out in the Stylcam 200R (Medelpharm, Beynost, France) compaction simulator, flat faced cylindrical tablets were produced, the diameter of the punches (Euro-B standard) and the die (Natoli Engineering Company Inc., Missouri, USA) was 8 mm.

Every formulation was compressed in two different compression forces 10 and 20 kN, except for the formulation IA which consists of Ibuprofen free acid and Avicel which was compressed just in 10 kN, compression in 20 kN was not feasible due to lamination or capping of the tablets during the compaction cycle. No pre-compaction step was involved.

Tablets produced by the abovementioned parameters were used for tablet characterization tests and for the production of the multilayer tablets.

5.1.3 Tablet porosity calculation

Porosity of the single layer cylindrical tablets was calculated from the measured dimensions i.e. height and diameter out of 10 tablets, thus the volume of the tablets was computed. Knowing the true density of the powder blend and the mass of each tablet the solid fraction volume was calculated. Difference between tablet volume and solid fraction volume resulted in the porosity of the tablets, *Equation 6*.

$$\varepsilon_t[\%] = \left(\frac{V_t - V_s}{V_t}\right) \cdot 100 \implies V_t = \frac{d^2\pi}{4} H \; and \; V_s = \frac{m_t}{\rho_{true}} \qquad (6)$$

Where, $\varepsilon_t[\%]$ is the porosity of the tablet, $V_t[mm^3]$ tablet's volume, $V_s[mm^3]$ solid fraction volume, $d[mm]$ diameter and $H[mm]$ height of the cylindrical tablet, $m_t[mg]$ mass of the tablet and $\rho_{true}\left[\frac{mg}{mm^3}\right]$ is the true density of the specific powder blend.

5.2 Compression analysis

5.2.1 Preparation of blends for compression analysis

Compression analysis was conducted for the excipients suitable for direct compression *i.e.* Avicel and DCPD lubricated with 0.5% magnesium stearate. Compression analysis was done also for the formulations but it must be noted that the preparation of the recipes differs from the abovementioned formulations. The recipes are shown in *Table 10*. The Turbula blender TC2 was used and the time of blending was 5 min.

Table 10. Formulation recipes of blends prepared for compression analysis

Formulation code	Recipe	Content w/w
Avicel	Avicel	99.5 %
	Magnesium stearate	0.5 %
DCPD	DCPD	99.5 %
	Magnesium stearate	0.5 %
CA'	Caffeine anhydrous	40 %
	Avicel	59.5 %
	Magnesium stearate	0.5 %
CD'	Caffeine anhydrous	40 %
	DCPD	59.5 %
	Magnesium stearate	0.5 %
IA'	Ibuprofen free acid	30 %
	Avicel	69.5 %
	Magnesium stearate	0.5 %
ID'	Ibuprofen free acid	30 %
	DCPD	69.5 %
	Magnesium stearate	0.5 %

5.2.2 True density measurements

True density measurements were performed for each prepared blend for compression analysis. The helium pycnometer AccuPyc II 1340 (Micromeritics, Georgia, USA) was used. Mean of five runs was reported, the measured true densities were used to calculate the relative density of the powders in the compaction analysis *i.e.* using Heckel's equation.

5.2.3 Heckel's analysis

Different tableting parameters were used to conduct the compaction analysis of the powders, the same Stylcam 200R compaction simulator was used but the diameter of the punches (Euro-B standard) and die (Natoli Engineering Company Inc., Missouri, USA) in this case was 11.28 mm, and the compression pressure was 300 MPa.

Up to ten replicates were compacted, the weight of each compact was set to be the equivalent of 0.250 cm^3 powder and was calculated using the true density of powders, five replicates for which a 300 MPa compression pressure was achieved were selected for analysis. From the acquired data using the ANALIS Software (Medelpharm, Beynost, France) which is coupled with the Stylcam 200R compaction simulator the force in the upper and the lower punch, and the distance between punches recorded during the entire compaction cycle were extracted and saved in an Excel spreadsheet (Excel 2013, Microsoft Office), which was used to construct the Heckel's plots using the Heckel's equation (*Equation 4*) and by visual inspection of the graphs the linear region was selected to fit the linear function, fitting was also done using the Excel's linear regression fit from which the linear function was obtained.

Pressure yield P_y parameter was calculated from the inverse of the value of the slope of the linear function, and parameter A was obtained from the intersect of the linear function with abscissa, D_0 was calculated from the ratio of the bulk density of the powder in the column and the true density of the powder, D_A or the total degree of densification was calculated by *Equation 5,* and D_b is calculated subtracting D_A and D_0. These parameters were used for the determination of the compaction behavior of the powders, and thus the bonding mechanism.

5.2.4 Elastic recovery measurements

Elastic recovery of the compacted tablets was determined by measuring the height of the tablets 2 to 3 days after their compaction using a micrometer (Mitutoyo, Illinois, USA), the recorded minimal distance between punches corresponding to the highest compression force was taken as the minimum height of the tablet, *Equation 7* was used to calculate the elastic recovery expressed in percent [44].

$$ER = \frac{(H_{max} - H_{\min})}{H_{min}} \times 100\% \quad (7)$$

Where ER [%] is the elastic recovery, H_{max} $[mm]$ is the height of the tablet measured after compaction, and H_{min} $[mm]$ is the minimum distance between punches that the tablet has experienced at the highest force.

5.3 Multilayer tablet production

5.3.1 Preparation of the gluing solutions

Fish gelatin, and PVP K90 were selected for the production of the multilayer tablets. Aqueous solutions of 40% (w/w) and 20% (w/w) of fish gelatin and PVP K90, respectively, were provided. Distilled water was used as medium, the solutions were stirred with a magnetic bar at 100 rpm overnight and next day the freshly prepared glue was used.

5.3.2 Gluing of tablet layers

Multilayer tablets were produced via the GPT, using the available prototype.

The nozzle system used for the application of the gluing agents was a 754V-SS aseptic dispense valve system (Nordson, Oberhaching, Germany). Nozzle's components in contact with the polymeric solution are made of stainless steel and polytetrafluoroethylene in accordance with the biopharmaceutical regulations. The amount of the dispensed polymeric solution depends on the valve open time, applied pressure, fluid viscosity, and tip size. This system allows a precise and uniform application of aqueous solutions of gluing agents on the tablet.

The system is controlled from a touch screen monitor. The amount of the gluing medium applied on the surface of the tablet is controlled by setting the time of the applied air pressure to the cartridge. Depending on the type of the polymer and the desired amount of the glue time can vary, several trials are required until the amount and time are fixed for a proper operation.

A schematic representation of the stations involved during the operation of the machine is represented in *Figure 8*.

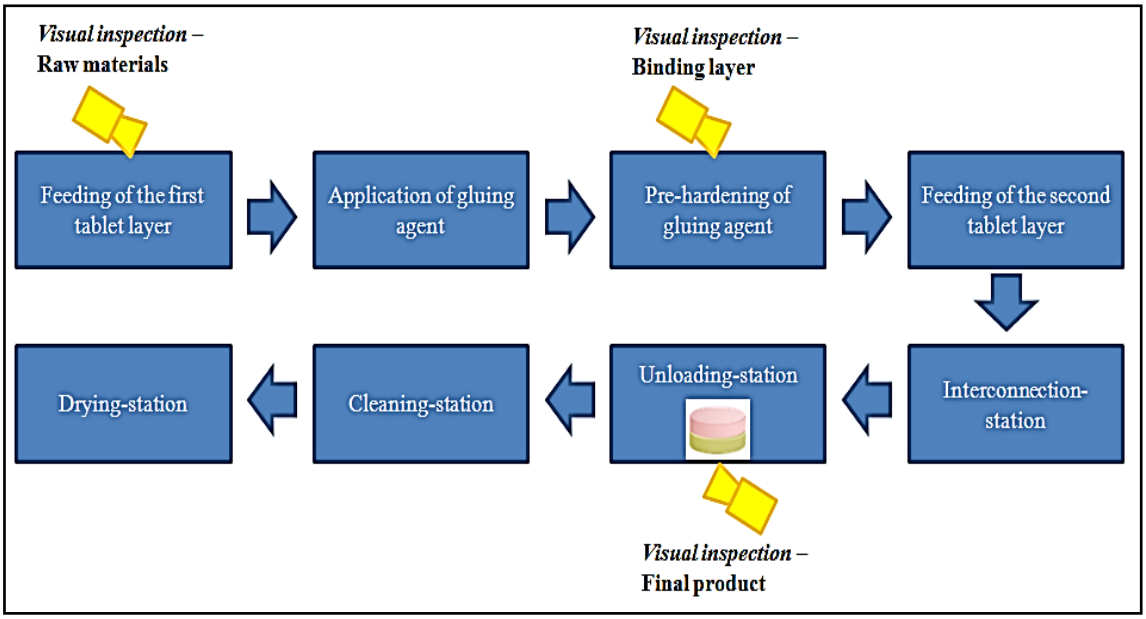

Figure 8. Schematic representation of the operation of the Gluing Pills machine

Tablets containing Ibuprofen and the ones containing caffeine were glued together, every possible combination of tablets *i.e.* compressed in 10 and/or 20 kN force and each formulation were combined.

The amount of each glue applied on the tablets was defined in preliminary trials and approximately 6.8 µg was chosen as the proper amount so the glue did not overflow from the edges of the interfacial area when the tablets were interconnected.

The produced multilayer tablets were packed and sealed in plastic bags and stored under two different conditions; at RT 25°C and 40% RH, and in AC conditions 40°C and 75% relative humidity.

5.4 Analytical methods

5.4.1 Surface roughness characterization

Optical Coherence Tomography (OCT) measurements

Basic working principle of OCT is low coherence interferometry, which is very suitable for imaging structures which are made up of layers, *e.g.* coated tablets, multilayer tablets and also surface topographical characterization [51], [52].

OCT combines the NIR spectroscopy and Tetrahertz pulse imaging, using NIR spectrum of the light contrary from the Tetrahertz pulse imaging which employs submillimeter wavelengths, making the OCT a very fast technique. It uses the difference in the refractive index of different materials present in the sample and is sensitive to the density variations (trapped air, cracks, pores *etc.*) within the sample, for example layers in the coated tablet, and has a penetration of approximately half a millimeter. Two dimensional images are produced by using the backscattered light from the sample and the interferometer combines it with the reference beam, thus the depth of originated backscattered light within the sample is encoded and then read from the spectrometer resulting in a spectrogram from which via Fourier transformation the depth information is decoded, the end result being the so-called *A-scans,* repeating A-scans in a line and over the surface of the sample the two dimensional image or *B-scans* are obtained [53].

OCT system can be utilized with a software which is able to construct three dimensional images from typically 512 B-scans. Absorption and attenuation of the light beam through the sample affects the backscattered light intensity and thus limiting the penetration into the sample [52].

System description

Spectral-domain OCT system was used for the measurements, the system can be interchangeably used with the 1D or 2D sensor head, in the present work the 2D sensor head was used. The system uses a super-luminescent diode as a light source, the light beam passes a directional coupler DC directing it to the probe head, a non-polarizing beam splitter BS splits the beam in 50:50 ratio between the probe beam and the reference. The reference arm is terminated from a gold-coated mirror M, while

in the sample arm the beam hits a galvanometer mirror GM which is used to scan a certain area of the sample, before hitting the sample the beam passes through a broadband scan lens L1. The back reflected light from both the reference and the sample arm is directed to the spectrometer via the same directional coupler DC, the spectrometer comprises of the fiber collimator FC, the transmissive diffraction grating DG, an achromatic lens L3, and a line scan camera (2048 pixel charged coupled device array). 1000 A-scans are recorded for each 512 B-scans. Sampling area is computed from the voltage range of the galvanometer which causes a displacement of the beam for 2.94 µm. A schematic description of the OCT system can be seen in *Figure 9*, [54].

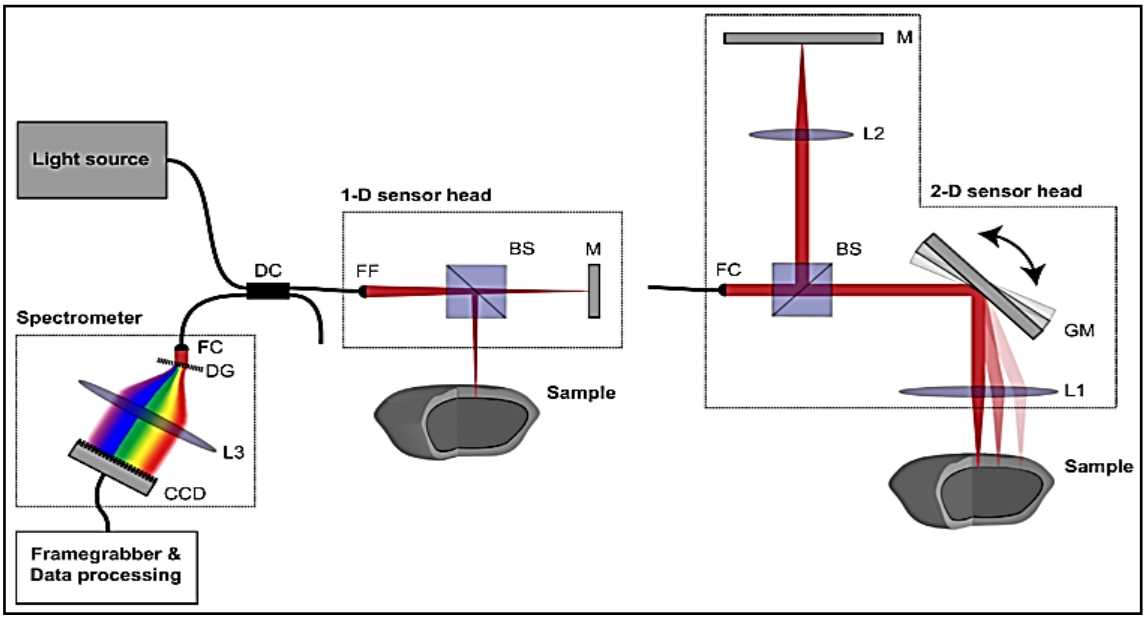

Figure 9. Schematic depiction of the OCT system; adapted from Ref. [54]

Preparation of sample tablets for OCT measurements

Single layer tablets of each formulation, with and without glue was measured with OCT. The application of the glue was performed using the GPT machine. In this case, the second layer was replaced by a polytetrafluoroethylene layer to spread evenly the gluing agent on the surface of the tablets. The polytetrafluoroethylene layer was easily removed after drying, revealing the gluing layer. Twenty samples of each formulation with each gluing agent were prepared for OCT measurements, then the time zero measurements were performed. Afterwards, the samples without glue layer were divided into ten samples each into sealed plastic bags and placed in the storing chambers keeping constant conditions as explained above.

To be able to detect any change of the tablet's surface over storing time in different conditions, it was crucial to scan the same area of the samples at time zero and after two months storage. Therefore, tablets were fixed by sticking them onto glass slides with beeswax. Also, the position of the mechanical stage of the OCT probe was fixed to ensure the same positioning of the glass slide and consequently tablets.

Measurement parameters

The OCT Application software developed by RCPE was used to set the selected measurement parameters, which were the offset filter of 0.09 and a beam quality factor of 1.7. The beam quality factor determines how much a laser beam variates from an ideal Gaussian distributed beam. The sampling area was 3.13 mm^2; upper wavelength 875 nm and lower wavelength 750 nm; frame size 1024 x 512 pixels; 512 B-scans were taken for each measurement.

Data processing

The acquired data from the OCT measurements were processed using the OCT Offline Application software developed by RCPE, the program is able to construct a 3D profile from the B-scans.

Surface roughness evaluation

From the obtained 3D model generated by OCTOfflineApplication software, a greyscale snapshot 2D picture with 0.753 contrast was taken, the same was done for all samples. The collected 2D greyscale pictures were evaluated using the image analysis software Gwyddion® [55], the software offers the possibility of statistical analysis of the greyscale pictures including the assessment of the surface roughness parameters. Schematic representation of the surface roughness evaluation procedure is shown in *Figure 10*.

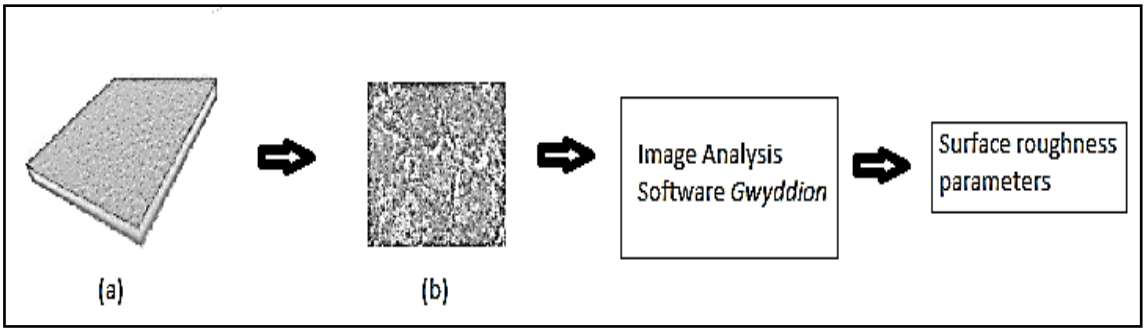

Figure 10. Evaluation of the roughness parameters: 3D model of the surface (a); 2D greyscale picture of the 3D model (b).

This procedure was repeated for all samples at time zero and after two months of storage, to obtain the *Ra* and *Rms* parameters. The average and the standard deviation of these parameters were calculated, making the comparison between the surface roughness of the sample measured at time zero and after storage under different conditions possible.

Ra [μm] and *Rms* [μm] parameters are defined as follows:

Ra – mean roughness

Ra is the most used roughness parameter, which represents the mean of the amplitudes of the deviation of the surface profile from the central line. Ra is calculated using the following *Equation 8* [56].

$$Ra = \frac{1}{L}\int_0^L |z(x)|dx \tag{8}$$

Rms – root mean square

It is considered to be more representative than R_a and its value typically is 10 to 25% higher than mean roughness. It is calculated via *Equation 9*, [56].

$$Rms = \sqrt{\frac{1}{L}\int_0^L z(x)^2 dx} \tag{9}$$

In the above *Equations 8 and 9*, z [μm] represents the magnitude of deviations from the central line, x is the direction of measurements for a certain surface and L [mm] is the sampling length.

Remarks

The calculated roughness parameters are reported in micrometers. Nevertheless, the obtained values from the image analysis software are not physically true because the grayscale height label was manually set to 1mm and the software's algorithm calculates the roughness according to the given scale. This means that the software creates its own profile of the surface which is not identical to the one obtained via OCT measurements [55]. However, these reference values are helpful in determining the change of the texture of 2D images after the storage time of the same sample, because the same area was measured and the measurement parameters were kept constant.

5.5 Single layer and multilayer tablet characterization

The following standardized tests were conducted in accordance with Ph. Eur. 8.0.

5.5.1 Weight uniformity

Measurements for weight uniformity were performed for single layer tablets, the weight of individual 20 tablets was measured using the analytical scale Sartorius BT 224S (Sartorius AG, Goettingen, Germany). The average and the relative standard deviation of the weight were reported.

5.5.2 Hardness

The crushing strength test was carried out for 10 tablets using the hardness tester Pharma Test PTB 311E (Pharma Test, Hainburg, Germany). The diametral tensile strength of the tablets was calculated using *Equation 10* [26].

$$\sigma_{ts} = \frac{2F}{\pi dH} \tag{10}$$

Where $\sigma_{ts}[MPa]$ is the tensile strength, F $[N]$ represents the crushing force, d $[mm]$ is the diameter and H $[mm]$ the height of the cylindrical tablet.

5.5.4 Friability test

The friability tester PTF 20E/ER (Pharma Test, Hainburg, Germany) was used. Friability test was performed both for single layer tablets and multilayer tablets. For the multilayer tablets, friability test was used with the intent of investigating the delamination tendency of multilayer tablets, after 100 rotations per minute the number of delaminated tablets was counted.

5.5.5 Dissolution test and HPLC analysis

Dissolution test of multilayer tablets was performed in triplicates using the automatic sampling dissolution tester DT820LH (Erweka, Heusenstamm, Germany) applying a paddle stirring speed of 100 rpm. The dissolution medium was phosphate buffer pH 6.8 ($\pm$0.1), temperature 37°C ($\pm$0.5°C) and the vessels were filled with 500 ml buffer. Sampling volume was 1 ml. At first, the sampling times were set as follows; point zero (baseline), 30 min, 60 min and 120 minutes. As it was not possible to achieve 100% of API release after 120 minutes for all formulations, for the remaining multilayer tablets dissolution test was performed for total run time of 24 hours. The sampling times were point zero (baseline), 30 min, 60 min, 120 min, 180 min, 240 min, 300 min, 360 min, 420 min, 480 min, 540 min, 600 min, 660 min, 720 min, 24h.

Samples from the dissolution test were analyzed using two HPLC instruments. On Waters Alliance 2695 (Waters, Milford, Connecticut) equipped with auto-sampler and UV-Visible photodiode array detector Waters 2996. The other instrument was Agilent 1260 series Infinity HPLC system (Agilent, Waldbronn, Germany) equipped with an autosampler and an UV-visible diode array detector Agilent 1260 (Agilent Technologies, Santa Clara, CA). Detection was performed at 225 nm.

A Hibar Purospher STAR RP-18 end capped column (125 x 4 mm, 5 µm, Merck, Darmstadt, Germany) served as a stationary phase, whereas mobile phase was a mixture of 670 ml acetonitrile, 5 ml of 8.5 % o-phosphoric acid filled up with water to 1 liter. Analyses were carried out under isocratic elution conditions with a flow rate of 0.7 ml/min. The column temperature was set to 21 °C and an aliquot of 7 µl of the

sample solution was injected into the HPLC system, each sample was analyzed two times.

For each HPLC measurement six standard solutions were prepared, solutions were a mixture of Ibuprofen free acid and Caffeine with known concentrations.

In order to compare the profiles for their similarity *i.e.* for different storage conditions and different glue layers, the similarity factor f_2 was used, a value of 50% or bigger implies that the compared dissolution profiles are similar, and values less than 50% are an indicator that the profiles are dissimilar. Similarity factor f_2 for the first three time points is calculated via *Equation 11*, [57].

$$f_2 = 50 \cdot \ log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{0.5} \cdot 100\right\} \qquad (11)$$

Where n is the number of time points, R_t is the percent API release at time point t for the first profile, and T_t is the release values for the second profile.

5.5.6 Content assay and UV-Vis analysis

Five tablets of each formulation were crushed and pulverized with a mortar and a pestle, powder amounts equivalent of one tablet was placed each in a 250 ml volumetric flask (triplicates) and dissolved in 200 ml phosphate buffer, flasks were put in a sonic bath for 15 min and shaken intensively manually every 3 min, until no powder material was visually observed. Then up to 10 ml was taken using a 10 ml syringe and using a 0.45 µm pore filters (Yeti Nylon Syringe Filters, 0.45 µm, 25 mm, Merz Brothers GmbH, Haid, Austria)the turbid solutions were filtrated. 1 ml of the filtrate was taken and diluted in 9 ml phosphate buffer. Finally, the samples for UV-Vis analysis were prepared.

High precision quartz cells (Hellma Analytics, Muellheim, Germany) and the UV-Vis Perkin Elmer Lambda 950 spectrophotometer (Perkin Elmer, Massachusetts, USA) were used for the analysis. Calibration was performed for each API, by preparing a fresh stock solution and diluting to five different concentrations, which were used as standards. The concentration range for Ibuprofen standard was 4 – 20 µg/ml and was scanned at its maximum absorption wavelength of 223 nm, whereas for caffeine five different concentrations between 5 – 25 µg/ml were scanned at the maximum

absorption wavelength of 273 nm. The maximum absorption for each API was determined by scanning the solutions in the wavelength range of 200-400 nm.

Results of the calibration are shown in the following linear equations including the correlation coefficient R-squared, for ibuprofen *Equation 12* and for caffeine *Equation 13*.

- Ibuprofen:

$$y = 0.0466x; R^2 = 0.9979 \quad (12)$$

- Caffeine:

$$y = 0.0508x; R^2 = 0.9979 \quad (13)$$

5.6 Characterization of gluing agents - Viscosity

The adhesiveness strength of the gluing agents depends on various parameters such as viscosity, the evaporation time of solvents and the thickness of applied gluing layer. In this work, the viscosity was chosen as the critical parameter which affects the binding strength.

Viscosity measurements were carried out with the Physica MCR 300 rheometer (Anton Paar, Graz, Austria). Analyses were performed using a temperature range of 20-80 °C. The selected aqueous solutions were fish gelatin 40(%w/w), PVP K90 20(%w/w).

5 Results and Discussion

5.1 Compression Analysis

Results obtained for the pressure yield (P_y parameter) of pure excipients as binder (Avicel and DCPD) and for the different formulations are presented in *Table 11*. The standard deviation (SD) from the mean of five replicates is written in brackets, and the correlation coefficient R^2 of the linear fitting is reported. The Heckel's plots of the excipients are shown in *Figure 11*.

Table 11. Pressure yield values (Py) for pure excipients and formulations prepared for compression analysis

Powder/blend	P_y (SD) [MPa]	R^2 (SD)
Avicel	121.20 (8.14)	0.9965 (0.002)
DCPD	385.51 (21.80)	0.9970 (0.001)
ID'	138.18 (8.79)	0.9841 (0.007)
IA'	111.75 (21.13)	0.9938 (0.003)
CD'	211.15 (22.30)	0.9965 (0.001)
CA'	99.93 (6.46)	0.9966 (0.003)

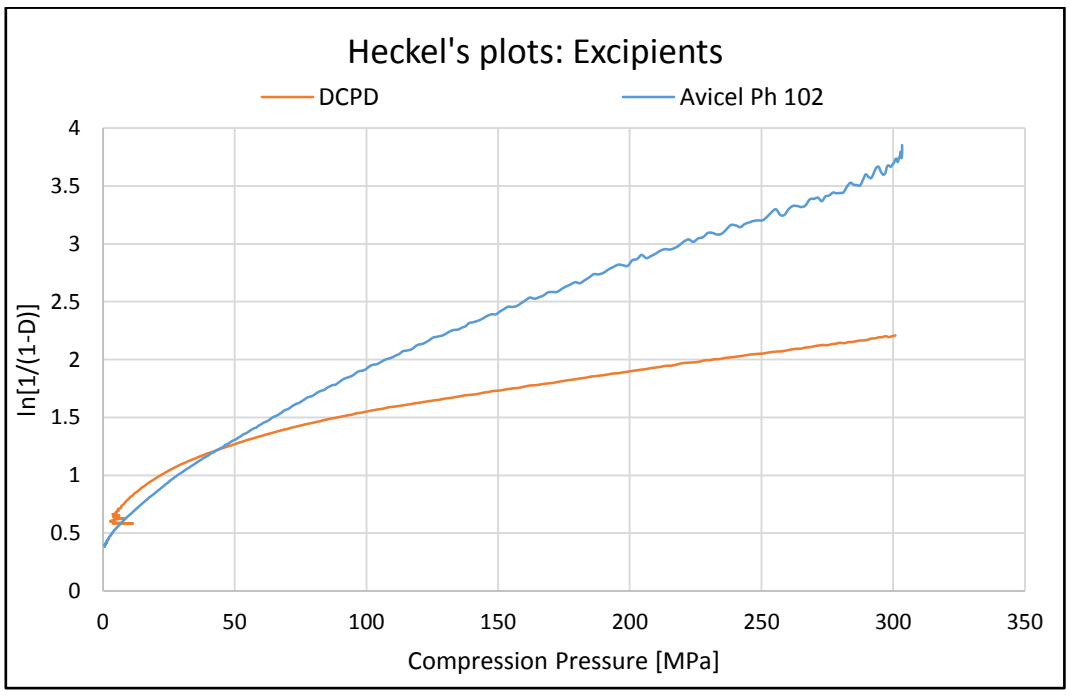

Figure 11. Heckel's plots of excipients/binders

Excipients

The pressure yield (P_y) of DCPD was e approximately three folds higher than of Avicel. This difference is in accordance with the literature and implies that the main deformation mechanism of DCPD is brittle/fracture, whereas Avicel mainly undergoes plastic/elastic deformation [58]–[61].

The above statement can be confirmed by the the Heckle profiles of pure excipients. As can be seen from *Figure 11*, Avicel gives a type A profile, typical for materials which undergo plastic deformation, while DCPD belongs to type C, characteristic for brittle/fracture deformation [25], [62].

In general, reported values for pressure yield in the literature differ from each other. This is attributed to Heckel's equation dependency on experimental parameters, such as compression force, the geometry of the compacts, compression speed, *etc.,* and also due to the method of fitting the linear function to the linear region of the Heckel's plots [27].

According to literature, the main bonding mechanism of microcrystalline cellulose (Avicel) is via a large number of weak attraction forces (intermolecular forces), which is attributed to relatively small particle size and pronounced surface roughness, and the high plasticity of this material. Same for DCPD, as fragmenting brittle material, its bonding mechanism is dominated by the intermolecular attraction forces, and its existent but limited plasticity and low elasticity contribute to sufficient binding strength of the tablet [63].

Binary mixtures

The Heckel's plots of binary mixtures of DCPD and Avicel with respective APIs are presented in *Figure 12* and *Figure 13*, respectively.

Since the API load in the formulations was relatively high, it is expected that the compaction properties of the APIs will affect the overall compaction behavior of the powder blend.

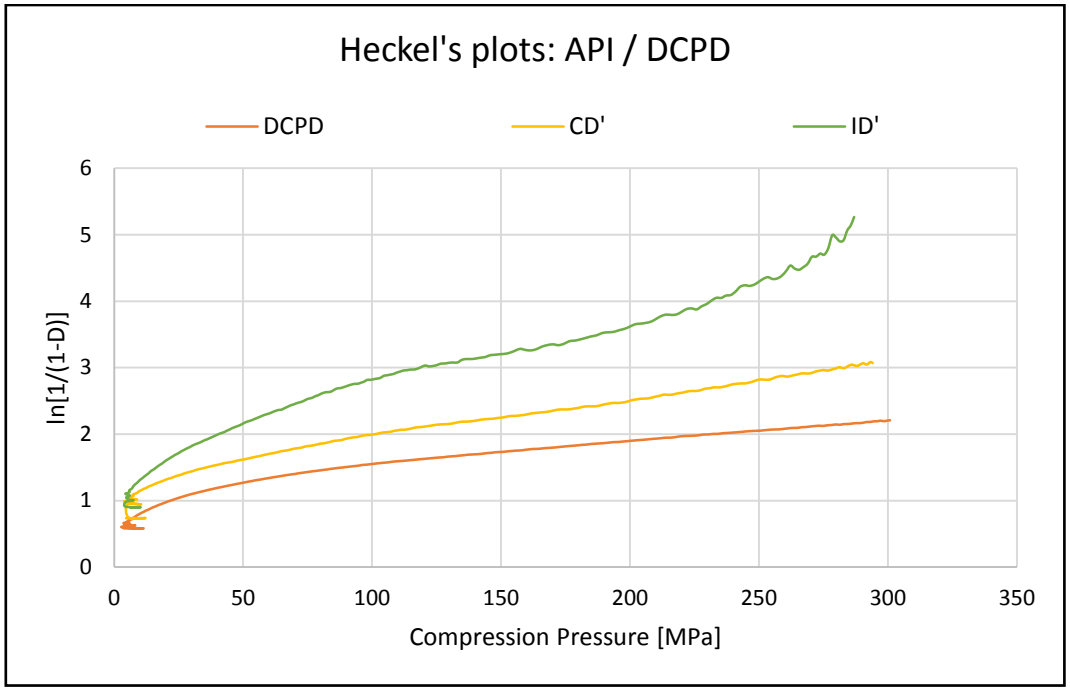

Figure 12. Heckel's plots of DCPD mixture with respective model APIs

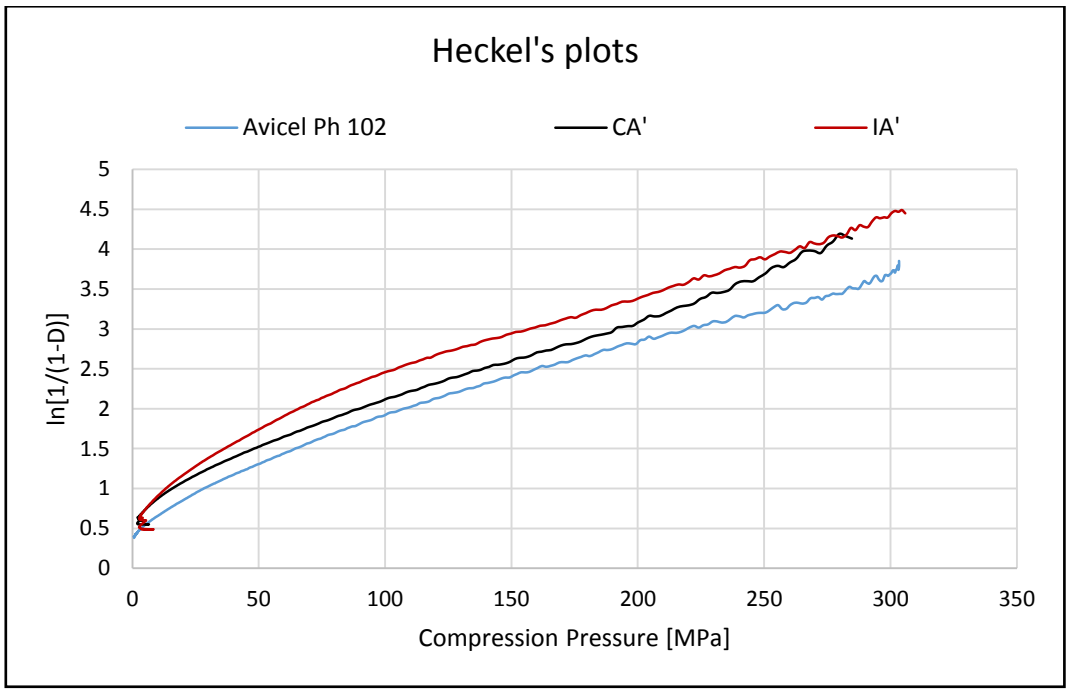

Figure 13. Heckel's plots of Avicel mixture with respective model APIs

Compaction analyses of pure APIs *i.e.*, ibuprofen free acid and caffeine anhydrous were not conducted in the present work. However, according to previous works ibuprofen shows a very poor tabletability [64], and its deformation mechanism is described as plastic – elastic, in other words viscoelastic, thus its disability to form a compact *i.e.* low interparticle bonding is attributed to its elasticity [65].

Caffeine anhydrous behaves plastically under compression, thus in combination with plastic filler/binder is expected that the deformation behavior will still remain plastic [66].

From the above stated results for the pressure yield and Heckel's plots of binary mixtures it can be concluded that the combination of DCPD with caffeine anhydrous results in an overall brittle fragmentation deformation, the Heckel's profile is typical for this kind of deformation and the relatively high pressure yield (211.15 MPa, *Table 11*) confirms the same. Even though caffeine itself behaves plastically, still its propensity of fragmentation is noticeable [67].

In contrary, the binary mixture of Ibuprofen free acid and DCPD gives a Heckel's profile typical for plastic/elastic deformation, also the pressure yield (138.18 MPa) is in the range of plastically deforming materials. This stems from the above-mentioned plastic-elastic deformation of ibuprofen, particles of the latter trickle between the DCPD particles buffering the pure brittle fragmentation of DCPD particles, resulting in an overall plastic/elastic deformation of the mixture [68].

Binary mixtures of Avicel and APIs behaved more or less similar to pure Avicel, regarding their Heckel's profiles (*Figure 13*), *i.e.* typical for plastic deforming materials. Pressure yield value of the mixture with caffeine anhydrous (*Table 11*) was slightly lower than the one for pure Avicel which implies slightly higher plasticity of the powder blend. Almost same values of pressure yield for Ibuprofen free acid and Avicel mixture were obtained as for Avicel itself, once again implying high compressibility and plasticity.

Tensile strength and elastic recovery of single layer tablets

Regarding the bonding strength which is reflected in the measured tensile strength of the tablets (represented in *Figure 14 and 15*), it has been shown that the highest strength was obtained for the mixture caffeine anhydrous and Avicel, slightly

exceeding even the tensile strength of the pure excipient. Same, higher values of tensile strength than the pure DCPD tablets for both compaction forces were observed for caffeine and DCPD mixture. This may be attributed to the plasticity of the caffeine.

Compaction of ibuprofen free acid with DCPD mixture in 10 kN showed a slightly higher tensile strength than of the pure excipient. But for the same mixture compacted in 20 kN, the tensile strength was lower than pure DCPD, this stems from the elasticity of Ibuprofen which increases the magnitude of axial relaxation.

In the case of Avicel with ibuprofen free acid blend, the compaction was just possible by applying 10 kN force, compression in 20 kN resulted in capping or lamination of tablets during the compaction cycle. The low bonding capacity of mixtures containing Ibuprofen free acid is attributed to its elasticity and very poor tabletability, shown also at the measured elastic recovery represented in *Figure 16*, where the tablets prepared from this mixture showed the highest elastic recovery, this was additionally a contribute of elasticity of Avicel.

Higher elastic recovery was determined for tablets containing Avicel than DCPD (*Figure 16*), certainly, this is attributed to the deformation behavior of Avicel as mentioned above.

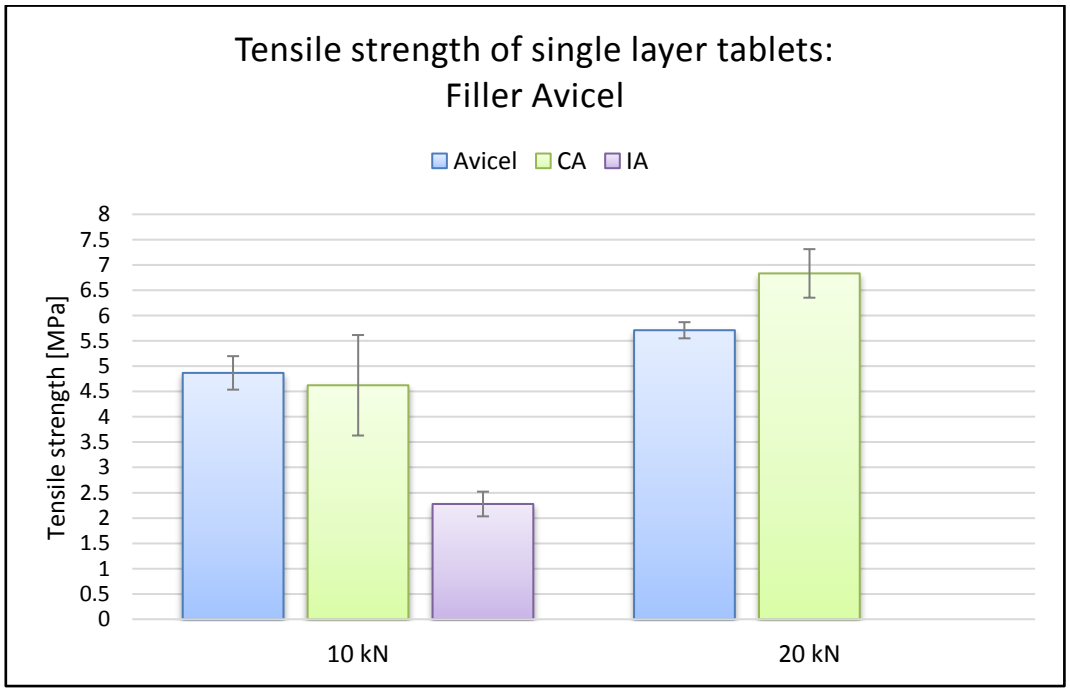

Figure 14. Tensile strength of single layer tablets containing Avicel, compacted in 10 and 20 kN

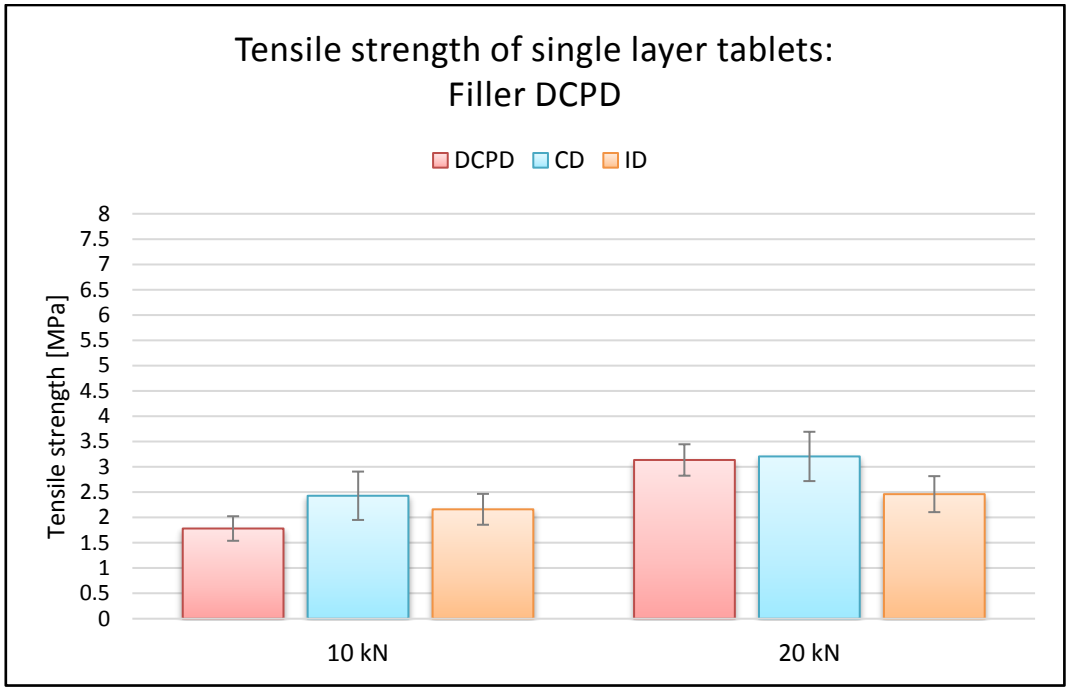

Figure 15. Tensile strenght of single layer tablets containing DCPD, compacted in 10 and 20 kN

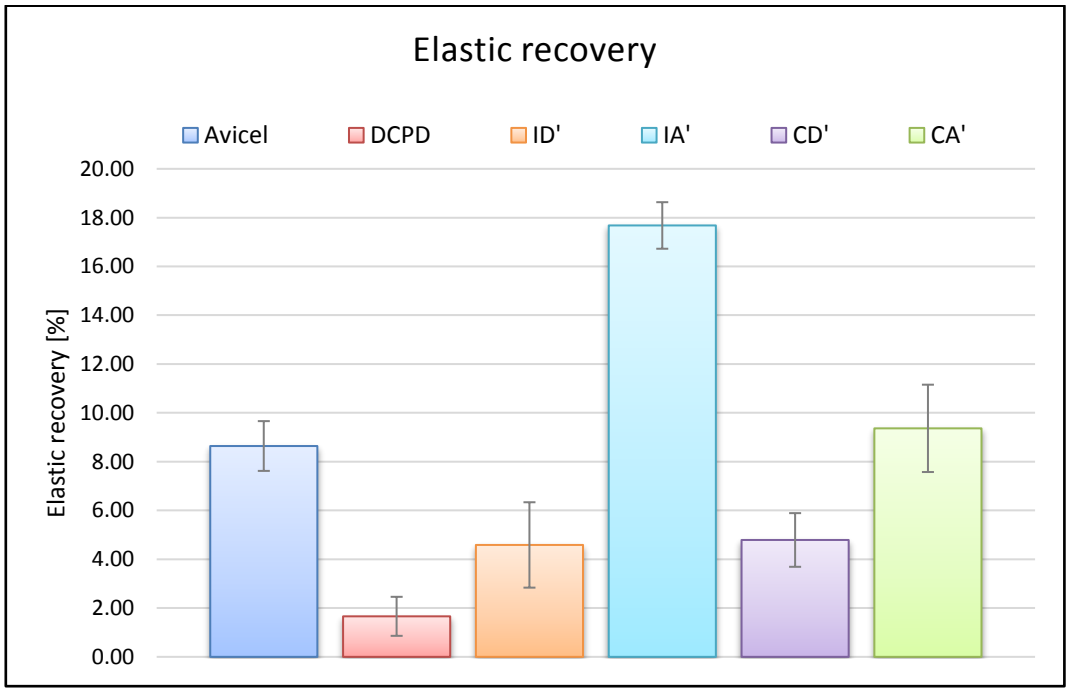

Figure 16. Elastic recovery of single layer tablets compressed at 300 MPa compression pressure, data from the tablets prepared for the compression analysis

High load of the APIs in the mixtures with fillers with well-known deformation mechanisms, namely, Avicel as plastic/elastic and DCPD as brittle/fragmenting materials, influenced the deformation mechanism and even more the resulting tensile

strength and elastic recovery of the tablets. Specifically, ibuprofen free acid which possesses a plastic/elastic behavior with expressed elasticity, in combination with both APIs, resulted in a plastic/elastic deformation mechanism, significantly higher elastic recovery than the pure excipient, and low tensile strength. On the other hand, mixtures with caffeine anhydrous and fillers, rendered in relatively high tensile strength and low elastic recovery. Caffeine's deformation behavior is reported as plastic/elastic but in some extent it shows brittleness, this was shown also in the mixtures where the blend with Avicel kept the plastic/elastic behavior and the blend with DCPD showed brittle/fragmenting behavior.

5.2 Surface roughness analysis

Surface roughness of tablets is an important factor which is related to the bonding strength between two layers when compressed together, or in the case of GPT when gluing them together, always with the intent of producing multilayer tablets.

Generally, compression of materials with different deformation behavior results in tablets with different surface roughness. Rougher surface provides more contact points between the layers, and results in increased probability of mechanical interlocking and thus stronger adhesion between layers. Decrease in the surface roughness with the increase of the compaction force has been noticed, especially for plastic materials [69].

Surface roughness is characterized by the so-called roughness parameters. In the present work *mean roughness Ra* and *root mean square Rms* were evaluated to characterize the surface roughness of the tablets [56]. The presented data are considering just the mean roughness *Ra*, because this parameter is the most used one. As mentioned above, the evaluated parameter has no physical meaning as the maximal height of the profile in the image analysis software Gwyddion® was manually set to 1 mm. A high precaution should be taken if one would attempt to compare roughness parameters in between different types of tablets and tablets with different gluing layers. However, these measurements are helpful for detecting the alterations in roughness parameters due to the storage conditions, if the same area of a tablet with gluing layer is scanned directly after applying the gluing layer and after storage by

keeping both OCT parameters and parameters of image analysis with Gwyddion® constant.

Figure 17 – 18, show the roughness parameters of tablets with different formulations, with and without gluing layer. The abbreviations IA, ID, CA, and CD correspond to the formulations presented in *Table 9*, the numbers 10 and 20 are index of the compaction force in kN.

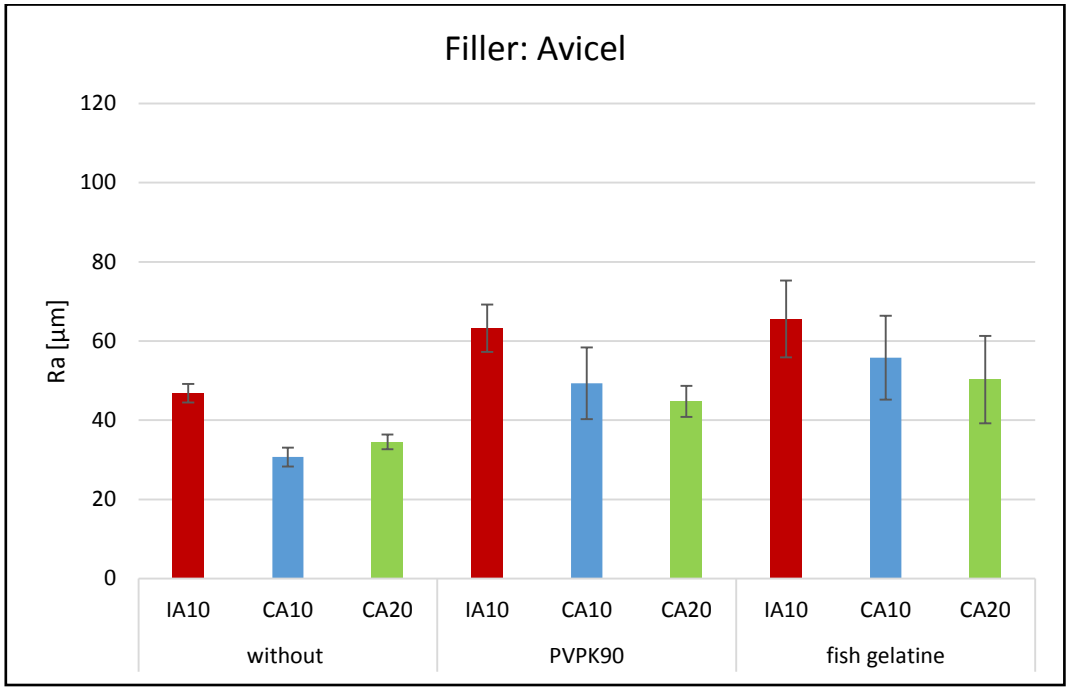

Figure 17. Roughness of single layer tablets containing Avicel and API, without and with applied respective glue layer at time zero

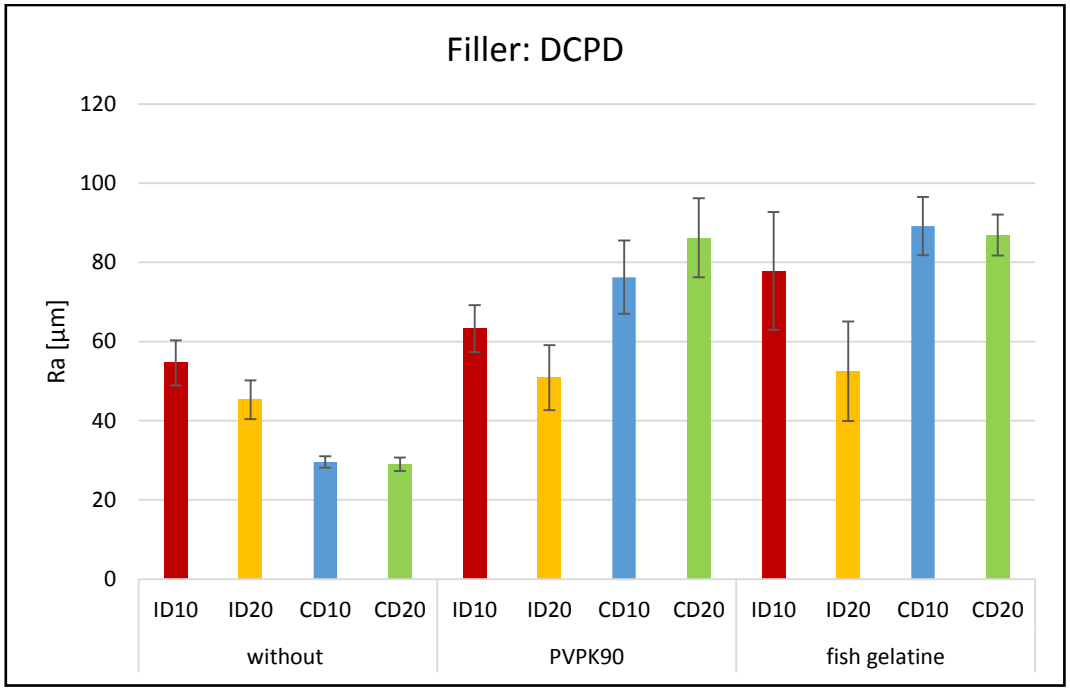

Figure 18. Roughness of single layer tablets containing DCPD and API, without and with applied respective glue layer at time zero

Comparing the surface roughness of the tablets without glue showed that tablets containing ibuprofen had higher values than the ones containing caffeine, independent on the type of the binder. According to the literature, brittle materials generally provide higher surface area and roughness than the plastic materials [70]. The surface roughness studies in this work revealed the opposite results, as tablets containing brittle DCPD showed lower surface roughness than tablets containing Avicel, which can be correlated to several facts; firstly the impact of high amounts of API on the physical properties of tablets, secondly the impact of high compression forces (10 kN, and 20 kN) applied in this study, resulting in more pronounced deformation of tablets; and finally the limitation of image analysis method to give true values of the roughness parameters.

Comparing the magnitude of the roughness parameter *Ra*, higher values were determined for tablets having a glue layer of PVP K90 or fish gelatin than the plain tablets. This is in agreement with the results of the investigation of surface roughness of tablets during film coating with polymeric solutions, where an increased surface roughness was reported during the initial phase of coating process [71].

Generally, it is reported that increasing the compaction force results in the less air entrapment in the tablet and thus forming stronger solid bridges. This results in tablets with lower porosity and increased hardness [72] . It is of note that the level of porosity depends also on the bonding behavior of tableting materials. It is expected that tablets containing materials with fragmenting behavior have a higher degree of porosity, compared to tablets containing material with plastic behavior. The porosity of tablets produced in this study and the correlation between porosity and surface roughness are shown in *Figure 19*. As can be observed, tablets of same formulation compacted with 20 kN compaction force were less porous than tablets compacted with 10 kN. It can be also observed that tablets compressed using 10 kN, containing Avicel and API (caffeine and ibuprofen) or DCPD and caffeine (IA10, CA10, CD10) had significantly higher levels of porosity than other tablets. In the case of IA and CA, this can be due to the higher elastic recovery of compressed tablets. The important effect of elastic recovery of materials after compaction on the physical properties of tablet is not enough investigated and should be the topic of further studies.

According to literature, a linear relationship between the roughness parameter Ra and the porosity of the tablet it was shown, the lower the porosity the lower the Ra [73]. This was not the case for the measured *Ra* and porosity in the present work. Merely for reference, in *Figure 19* is shown that such a trend of *Ra vs* porosity, is not given in this study.

It is important to note that pharmaceutical materials do no follow one strict deformation behavior. The complex structure of these materials provides a combination of different bonding mechanisms at different stages of the tableting process and results in tablet properties, which may show discrepancies to expected properties.

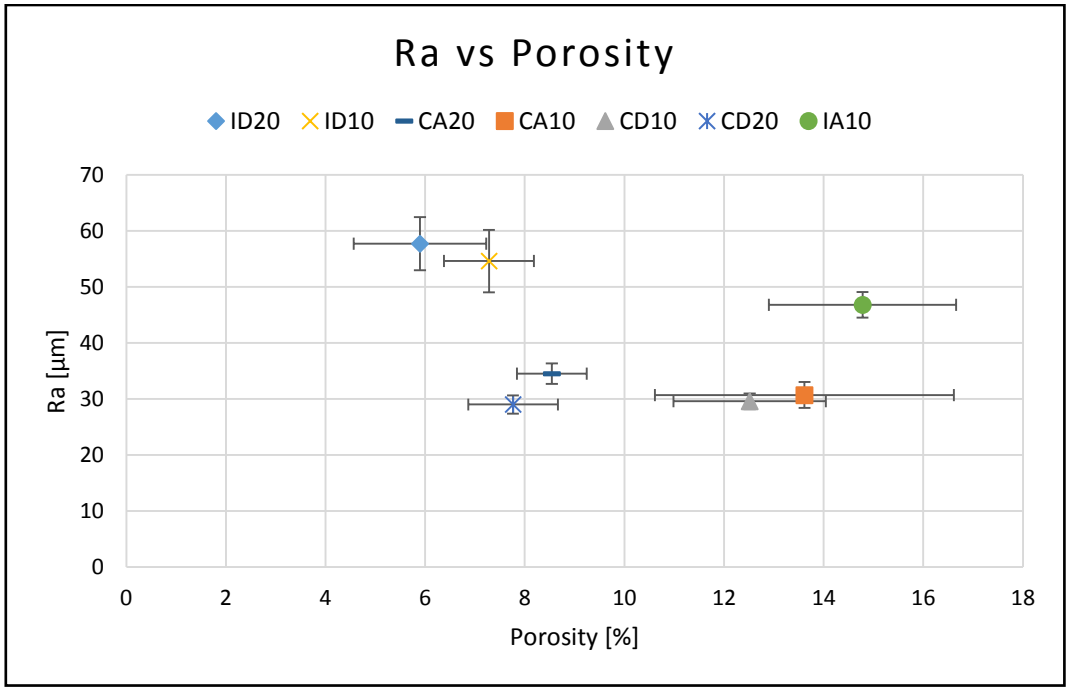

Figure 19. Roughness parameter Ra vs Porosity for different formulations

In order to ease the detection of the change of the *Ra* parameter of tablets without glue layer due to the storage conditions, the ratio between values after the storage and at time zero were calculated and presented in *Figure 20 and 21*. Abbreviation *RC* stands for room conditions (25°C and 40% RH), *AC* for accelerated conditions (40°C and 75% RH), and *T0* for time zero.

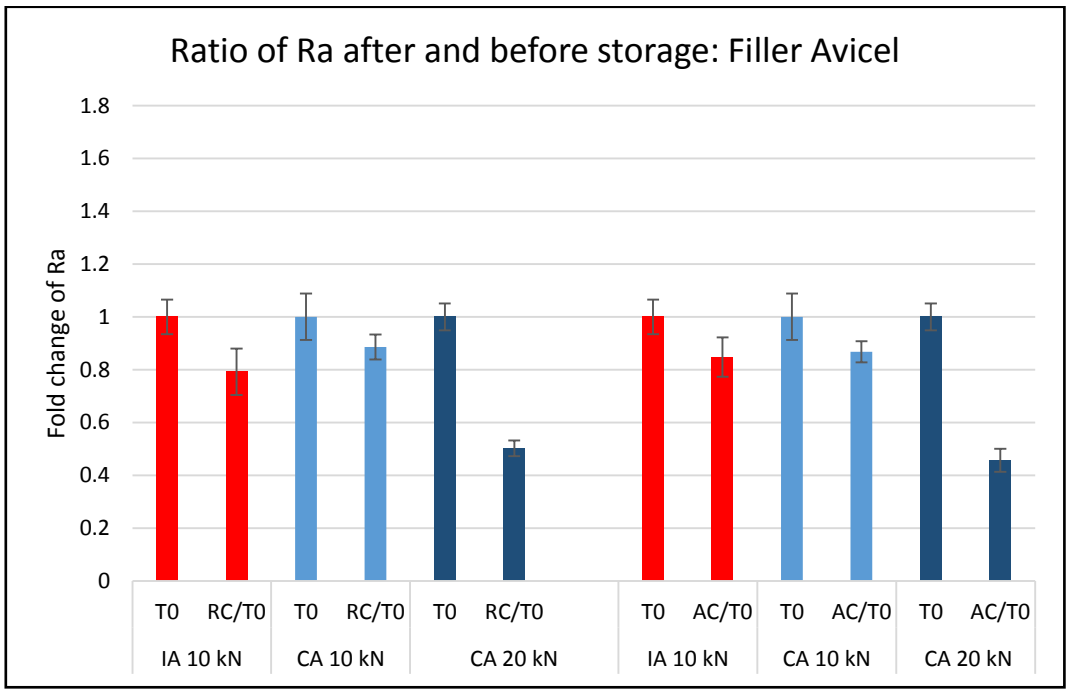

Figure 20. Ratio of Ra values after and before storage, tablets containing Avicel and no glue layer

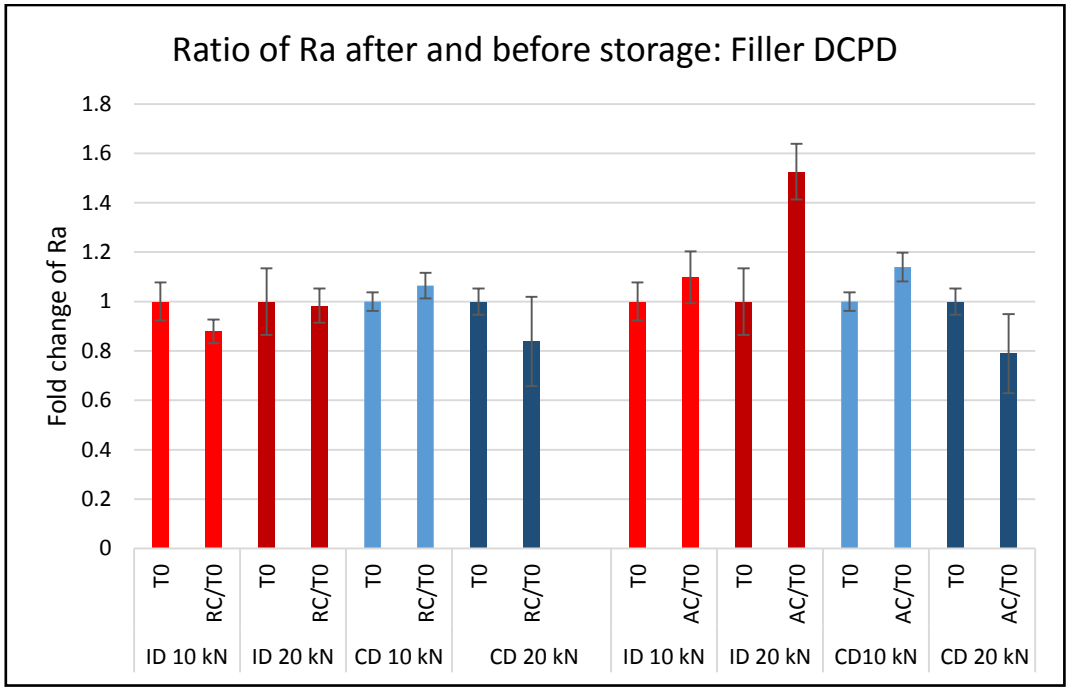

Figure 21. Ratio of Ra values after and before storage, tablets containing DCPD and no glue layer

In case of tablets containing Avicel as binder and without gluing layer, there are a slight reduction of surface roughness for IA10 and CA10 tablets, which was not significant in all cases. The CA20 tablets showed however a marked decrease in surface roughness after storage under both room and accelerated conditions. The surface roughness of tablets containing DCPD did not show significant changes after storage, except of ID20 tablets with significantly higher surface roughness after storage under accelerated conditions. This may be a measurement error, caused by changing the position of the probe head of the OCT and/or because the measured area of the tablet's surface was not the same area measured at time zero.

5.3 Viscosity of polymeric solutions (Gluing agents)

The results of the viscosity measurements are shown in *Figure 22*. PVP K90 with the concentration of 20% (w/w) has a higher viscosity than fish gelatin 40 % (w/w).

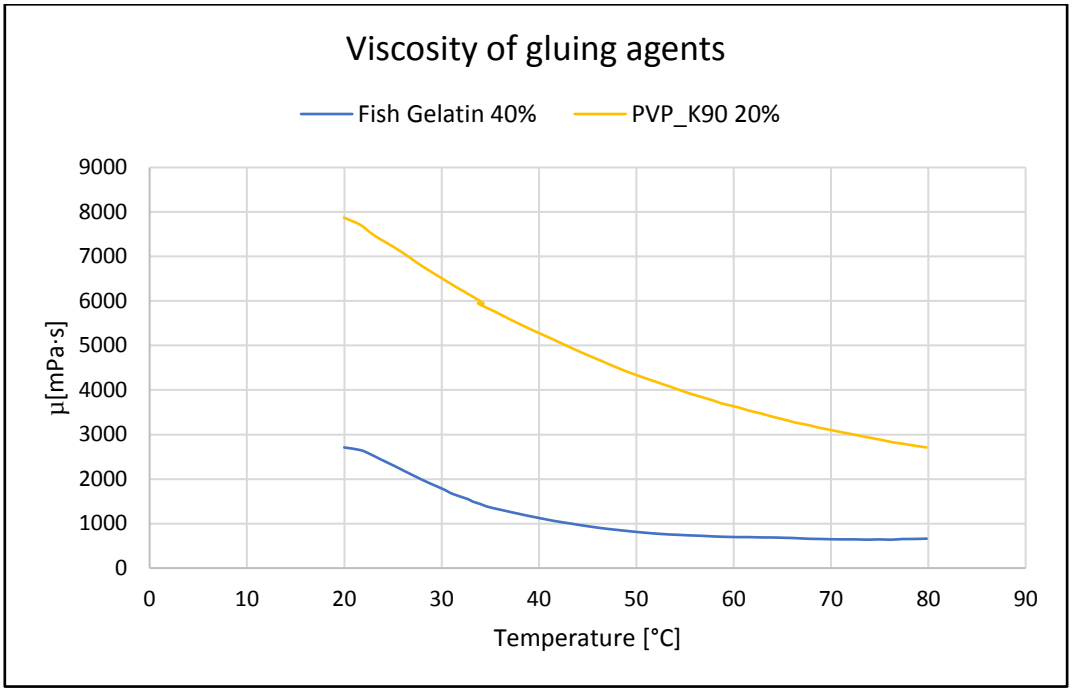

Figure 22. Dynamic viscosity (μ) of polymeric solutions in a 20 – 80 °C temperature range

Regarding the binding strength of polymeric solutions, an analogy to the granulation process can be drawn, the lower viscosity facilitates the distribution of the binder solution between particles creating more contact and resulting in a higher granule strength [74].

Similarly, for the film coating process, a better adhesion was observed when a lower viscous organic based polymeric binder was used, because of the easier penetration into the pores and microstructures on the surface of the tablets [75]. The validity of the same argument for suitability of polymeric solutions with lower viscosity (fish gelatin in this study) has been proofed for gluing the tablet.

5.4 Investigation of the delamination tendency of bilayer tablets

All of the monolayer tablets passed the friability test, showing less than 1% friability, according to Ph. Eur. 0.8 requirements. Delamination tendency of bilayer tablets was also investigated using the friability test. The results listed in *Table 12 and 13*, represent the bilayer combinations which showed no/or just one case of delamination and bilayer combinations which showed more than one case of delamination, respectively.

The matching of deformation behavior (DB), elastic recovery (ER), tensile strength (TS), and compression force (CF) of two combined layers are shown with "+", mismatching of the same properties between combined layers is shown as "-". Of note, that surface roughness is not listed in *Table 12 and 13*, as a higher surface roughness was calculated for tablets containing ibuprofen independent to the kind of excipient. Therefore calculated roughness for all combinations listed in these two tables is mismatched.

Table 12. Bilayer tablets without delamination or one delamination after friability test measured at T0, and storage under accelerated condition (AC) and room condition (RC). Abbreviations: ER = elastic recovery, CF = compression force, DB = deformation behaiviour, TS = tensile strength. The matching or mismatching of these properties between two combined layers is shown as "+" or "-", respectively.

Bilayer tablet	Physical properties matching between two layers				
	DB	ER	TS	CF	Delamination
IA10_PVPK90_CA10	+	-	-	+	no
ID20_PVPK90_CA20	+	+	-	+	no
ID10_PVPK90_CA20	+	+	+	-	no
ID20_PVPK90_CA10	+	+	+	-	no
ID10_PVPK90_CD20	-	+	+	-	no
ID20_PVPK90_CD10	-	+	+	-	no
ID20_PVPK90_CD20	-	+	+	+	AC (1)
ID10_FishGelatin_CD10	-	+	+	+	no
ID10_FishGelatin_CA10	+	+	-	+	no
ID20_FishGelatin_CD20	-	+	+	+	no

ID20_FishGelatin_CA20	+	+	-	+	no
ID20_FishGelatin_CA10	+	+	+	-	no
ID20_FishGelatin_CD10	-	+	+	-	no
ID10_FishGelatin_CA20	+	+	+	-	T0 (1)
ID10_FishGelatin_CD20	-	+	+	-	RC (1)

Table 13. Bilayer tablets with more than one delaminated bilayer tablet after friability test, tested at T0, and storage under accelerated condition (AC) and room condition (RC). Abbreviations: ER = elastic recovery, CF = compression force, DB = deformation behaiviour, TS = tensile strength. The matching or mismatching of these properties between two combined layers is shown as "+" or "-", respectively

Bilayer tablet	**Physical properties matching between two layers**						
	DB	ER	TS	CF	Delam. T0	Delam. RC	Delam. AC
IA10_PVPK90_CD10	-	-	+	+	1	0	2
ID10_PVPK90_CA10	+	+	-	+	0	0	4
ID10_PVPK90_CD10	-	+	+	+	1	1	3
IA10_PVPK90_CA20	+	-	-	-	0	1	1
IA10_PVPK90_CD20	-	-	+	-	3	8	2
IA10_FishGelatin_CA10	+	-	-	+	2	0	2
IA10_FishGelatin_CD10	-	-	+	+	1	0	3
IA10_FishGelatin_CA20	+	-	-	-	0	3	2
IA10_FishGelatin_CD20	-	-	+	-	2	0	2
Total number of delaminated tablets					**10**	**13**	**21**

To better understand the influence of the factors involved in the delamination of the bilayer tablets produced via GPT, in the following *Figure 23*, the number of separated multilayer tablets is presented in percentage.

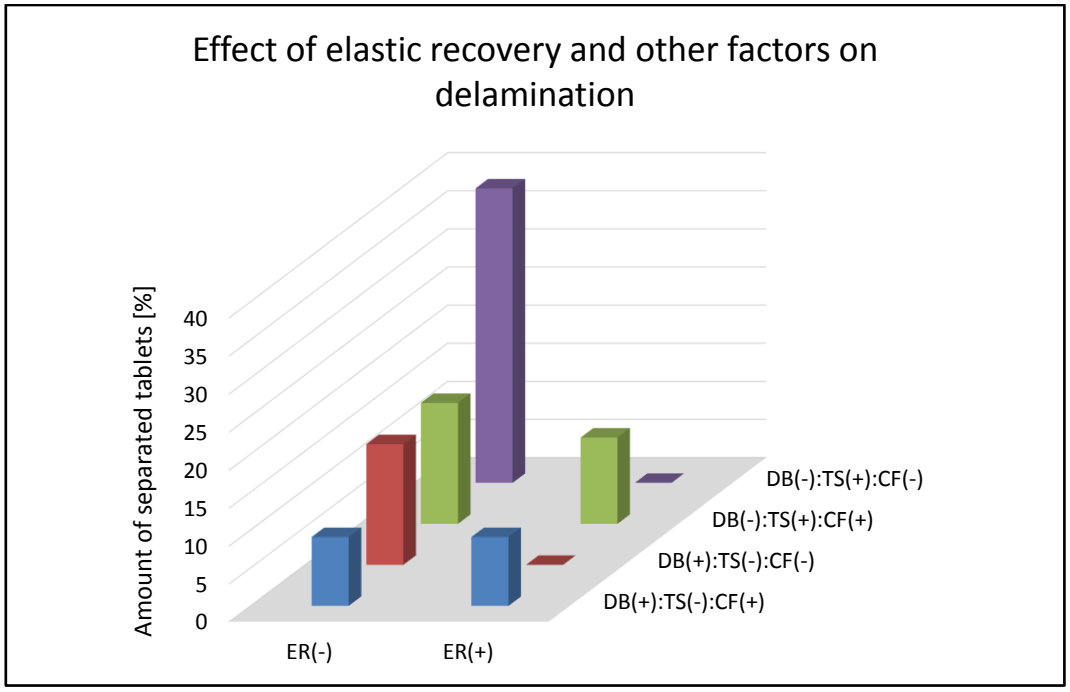

Figure 23. Effect of different factors on the amount of separated multilayer tablets. Abbreviations: ER = elastic recovery, CF = compression force, DB = deformation behaiviour, TS = tensile strength. The matching or mismatching of these properties between two combined layers is shown as "+" or "-", respectively

As can be observed from *Table 12*, the most important factor, whose matching between layers ensured the enough robustness of bilayer tablets was the elastic recovery [35]. As can be seen from this table, in all bilayer tablets; except the first combination, elastic recovery was matched between the layers and the matching of other three parameters played a role in combination with elastic recovery.

Same in *Figure 23*, presence of ER mismatch of the tablets in relation with any of other factors gave the highest amount of separations. Especially combined with a mismatch in deformation behavior and compaction force.

The highest amount of separations occurred in the combination of tablets with different deformation behavior coupled with ER mismatch. The mismatch in elastic, plastic and brittle properties of the two layers has been shown to decrease the interfacial strength, and thus increase the delamination tendency for bilayer tablets produced in a conventional way [76]. The mismatch in deformation behavior caused

also delamination of bilayer tablets produced via GPT, however at most cases as it was combined with mismatch of elastic recovery.

In all combinations showed in *Table 12*, additional to matched ER, the matching of one or two other optional parameters was enough to produce robust bilayer tablets.

Regarding to the type of the glue layer present at the separated bilayer tablets, fish gelatin shows better adhesive properties than PVP K90. From 15 combinations of robust bilayer tablets listed in *Table 12*, eight combinations were glued with fish gelatin, and in *Table 13*, it can be seen that more separations occurred in bilayer tablets containing PVP K90 as a glue layer (27 out of 44). Moreover, two combinations highlighted in yellow and orange colors underwent delamination by using PVP K90 as gluing agent. The same combinations showed no delamination as glued with fish gelatin (*Table 12 and 13*).

This might be due to the lower viscosity of fish gelatin solution, allowing better penetration of gluing agent into the pores and microstructures on the surface of the tablets. Another factor is the intermolecular attraction forces between the gluing agent and the surface of the tablet, especially the formation of hydrogen bonds [77]. Out of the two gluing agents, fish gelatin has much more hydrogen bond donor and acceptor chemical groups due to its protein structure than PVP K90 [78].

A higher number of separations occurred for tablets stored for two months under accelerated conditions (AC) *i.e.* 40°C and 75% relative humidity, which is probably attributed to the stresses developed within the glue layer during the storage. Shrinkage of the layer because of the rest solvent (water) evaporation; thermal stresses, the difference in thermal expansion of the glue layer; and the volumetric stress due to the change in volume, reflected also at the change of the roughness [77].

It can be concluded that the greater part of the bilayer tablets which underwent the friability test showed no delamination, which indicates that with a careful selection of the materials and production process parameters, the production of multilayer tablets with advanced performance is possible.

5.5 Dissolution profiles of multilayer tablets

The dissolution profiles of multilayer tablets are shown in *Figure 24 – 27*.

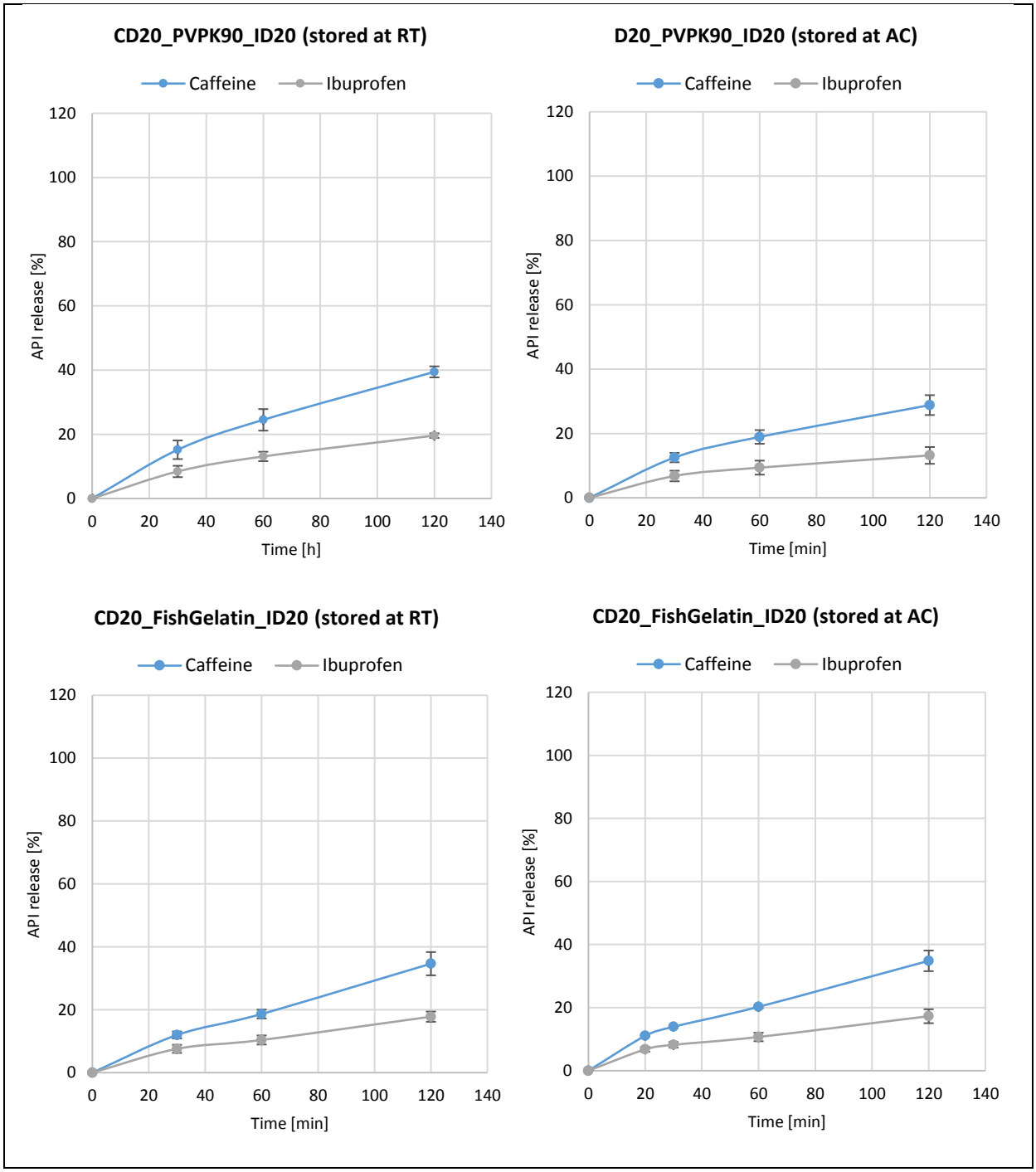

Figure 24. Dissolution profiles of the multilayer tablet CD20_ID20 with respective gluing agents and stored at two different storage conditions

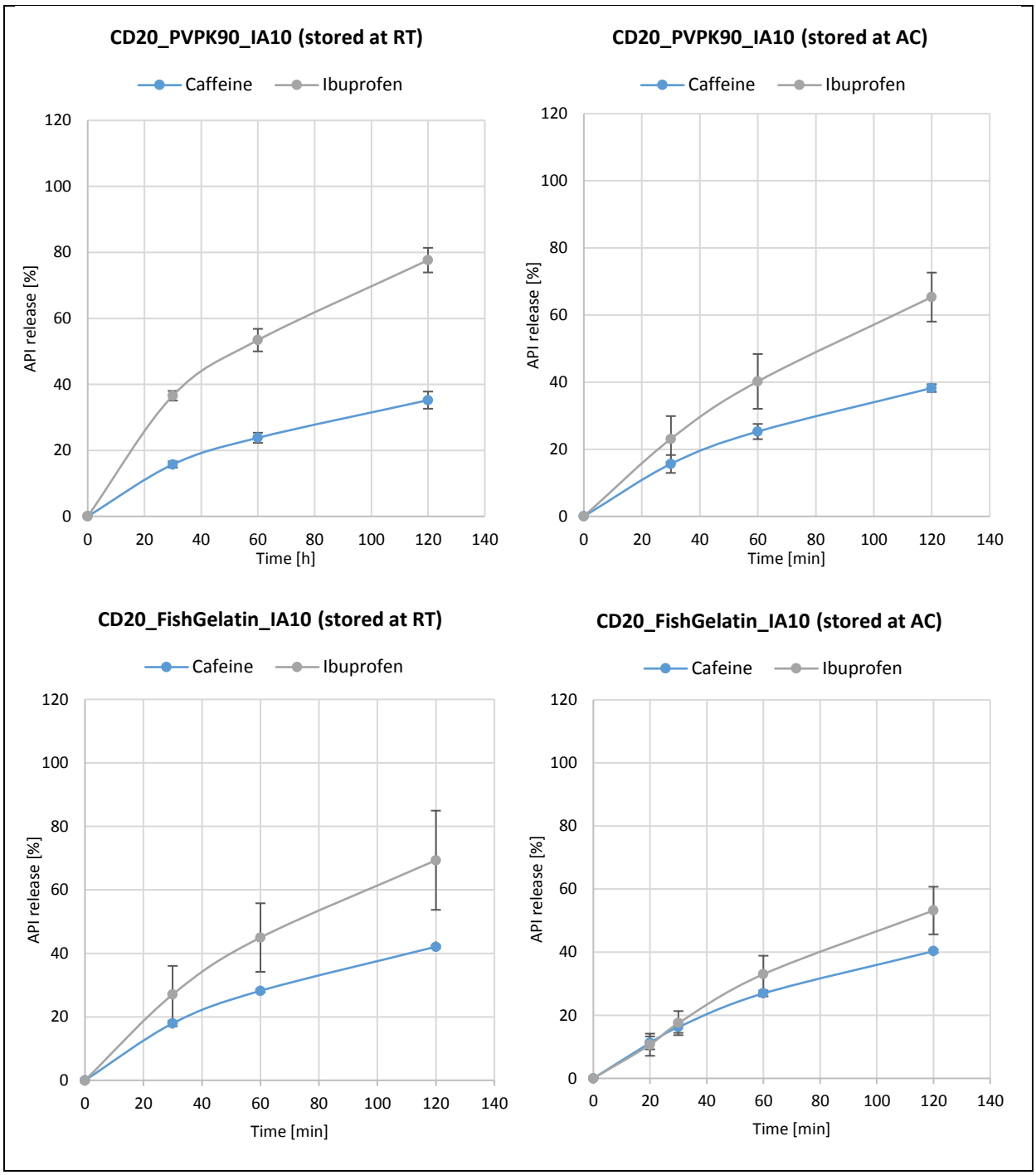

Figure 25. Dissolution profiles of the multilayer tablet CD20_IA10 with respective gluing agents, and stored at two different storage conditions

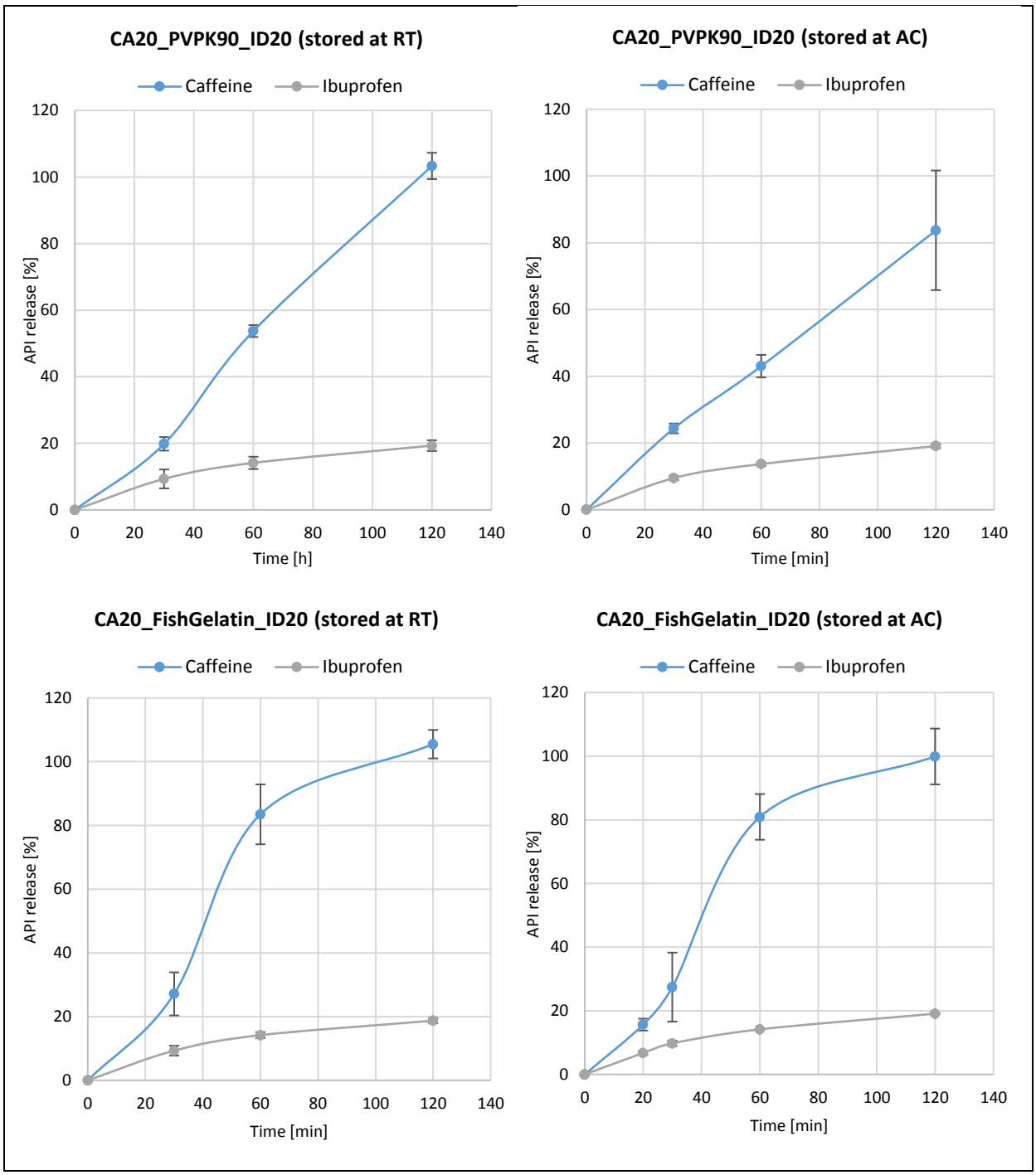

Figure 26. Dissolution profiles of the multilayer tablet CA20_ID20 with respective gluing agents, and stored at two different storage conditions

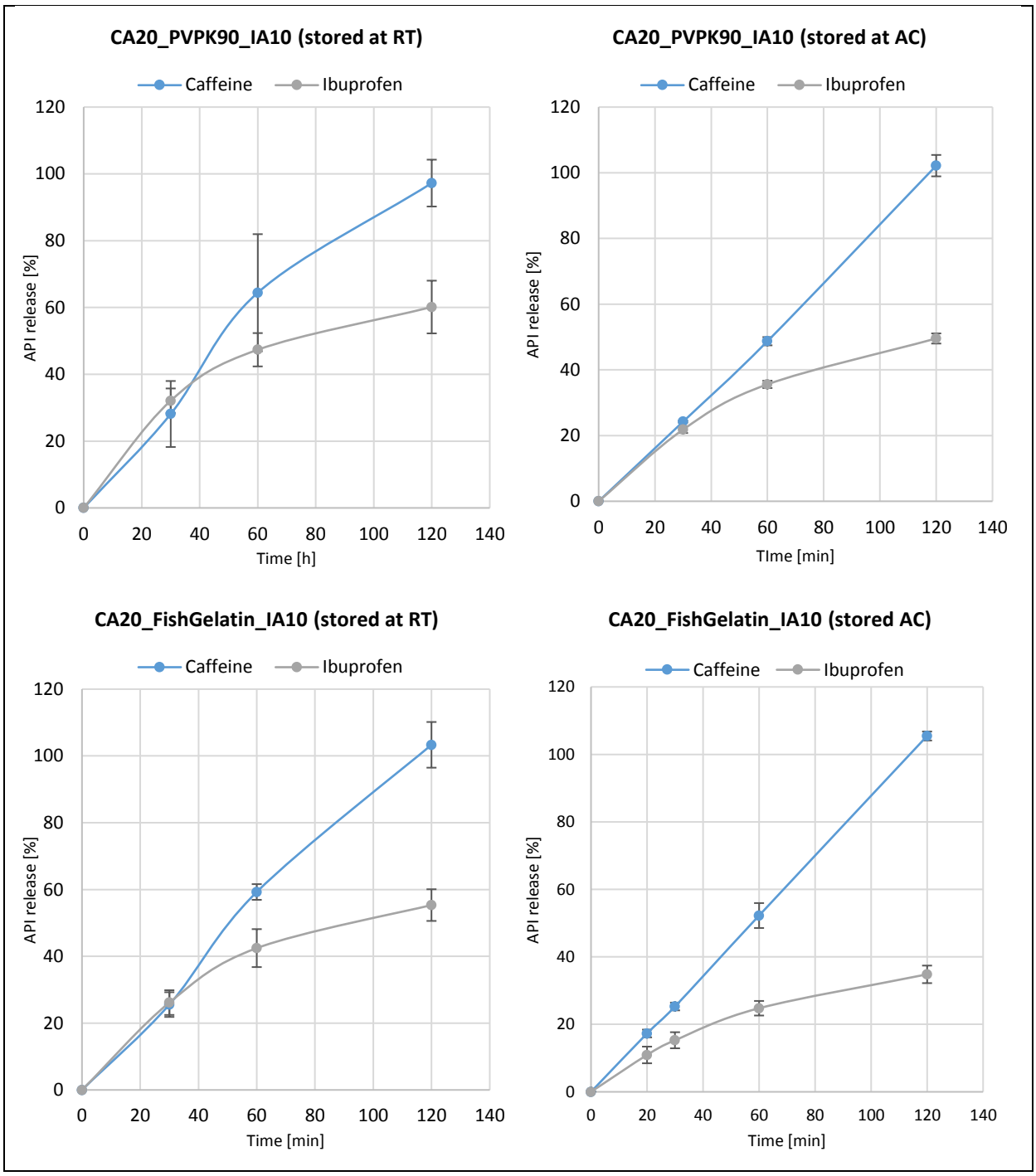

Figure 27. Dissolution profiles of the multilayer tablet CA20_IA10 with respective gluing agents, and stored at two different storage conditions

It is important to note that the dissolution tests were performed for bilayer tablets after storage under room and accelerated conditions, but not for monolayer and bilayer tablets directly after preparation. This was because of time-frame issues and resulted in the fact that the impact of storage on the release profile cannot comprehensively be determined.

However, from the above data it can be concluded that the type of gluing agent did not significantly affect the release of API from tablets. The release profiles for caffeine or ibuprofen from certain combinations did not change by using different gluing agents.

This can be clearly observed by considering the similarity factor f_2, where a value less than 50% indicates a dissimilar profiles, results are presented in *Table 14* (abbreviation *caf* stands for caffeine and *ibu* for ibuprofen). Results are grouped depending on the comparison of the dissolution profiles *i.e.* same type of multilayer tablet stored at room temperature (RT), and accelerated conditions (AC) 40°C and 75% RH, as well as same storage conditions but different glue layer.

Table 14. Values of the similarity factor (f_2) for the dissolution profiles, values of the dissimilar profiles are bolded

Multilayer tablet	RT vs AC glue: Fish Gelatin	RT vs AC glue: PVP K90	Gelatin vs PVP K90 at RT	Gelatin vs PVP K90 at AC
CA20_ID20	f_2(caf) = 71.6%	**f_2(caf) = 44%**	**f_2(caf) = 37.5%**	**f_2(caf) = 31.1%**
	f_2(ibu) =98.7%	f_2(ibu) = 99%	f_2(ibu)= 98.8%	f_2(ibu)= 98.5%
CD20_IA10	f_2(caf) = 86.4%	f_2(caf) = 83%	f_2(caf) = 65.1%	f_2(caf) = 86.4%
	f_2(ibu) =44.5%	**f_2(ibu) = 44%**	f_2(ibu) =52.6%	f_2(ibu) =52.7%
CA20_IA10	f_2(caf) = 71.6%	**f_2(caf) = 44%**	**f_2(caf) = 37.5%**	f_2(caf) = 76%
	f_2(ibu) =98.7%	f_2(ibu) = 99%	f_2(ibu) =98.8%	**f_2(ibu) =47.4%**
CD20_ID20	f_2(caf) = 87.5%	f_2(caf) = 57.2%	f_2(caf) = 65.7%	f_2(caf) = 71%
	f_2(ibu) =97.5%	f_2(ibu) =67.3%	f_2(ibu) =83%	f_2(ibu) =77.5%

From the f_2 results it can be concluded that neither the storage conditions nor the type of the glue layer had any impact on the dissolution profiles. However, the dissimilar profiles would rather be related to the off-limit values of the weight uniformity test for IA10 and CA20 tablets, respectively. The weight uniformity results for both tablets are shown in *Table 15.*

Table 15. Weight uniformity of CA20 and IA20 tablets, off-limit values are bolded

	CA20		IA10	
Tablet	**Weight [mg]**	**Deviation [%]**	**Weight [mg]**	**Deviation [%]**
1	0.1756	**8.46**	0.1524	0.18
2	0.1656	2.29	0.1539	1.17
3	0.1777	**9.76**	0.156	2.55
4	0.172	6.24	0.1541	1.30
5	0.1739	7.41	0.16	5.18
6	0.1682	3.89	0.1562	2.68
7	0.1701	5.07	0.1521	0.0098
8	0.1741	**7.54**	0.151	0.73
9	0.178	**9.95**	0.156	2.55
10	0.1689	4.33	0.1371	**9.87**
11	0.1744	**7.72**	0.1523	0.12
12	0.1646	1.67	0.1581	3.93
13	0.1694	4.63	0.1616	6.23
14	0.1675	3.46	0.119	**21.76**
15	0.175	**8.09**	0.1544	1.50
16	0.1678	3.65	0.1543	1.43
17	0.1769	**9.27**	0.1566	2.94
18	0.1765	**9.02**	0.147	3.36
19	0.1686	4.14	0.1564	2.81
20	0.172	6.24	0.1538	1.10
Mean	0.17184		0.1521	
STD	0.00415		0.00929	
RSD	2.41629		6.11293	

As expected the release rates of API from tablets containing DCPD were extremely lower than those containing Avicel. However, comparing the release of caffeine and ibuprofen from tablets with same excipient and compression force showed the higher dissolution rate of caffeine compared to ibuprofen, which is due to the higher solubility of caffeine in the medium.

As can be observed from above figures, it was not possible to reach the 100% of release of caffeine from DCPD tablets and ibuprofen from both Avicel and DCPD tablets. Therefore, multilayer tablets stored at room temperature and having PVP K90 as gluing agent were conducted to the dissolution test for 24 hours. This selection was because of time limitations. The results are presented in *Figure 28*.

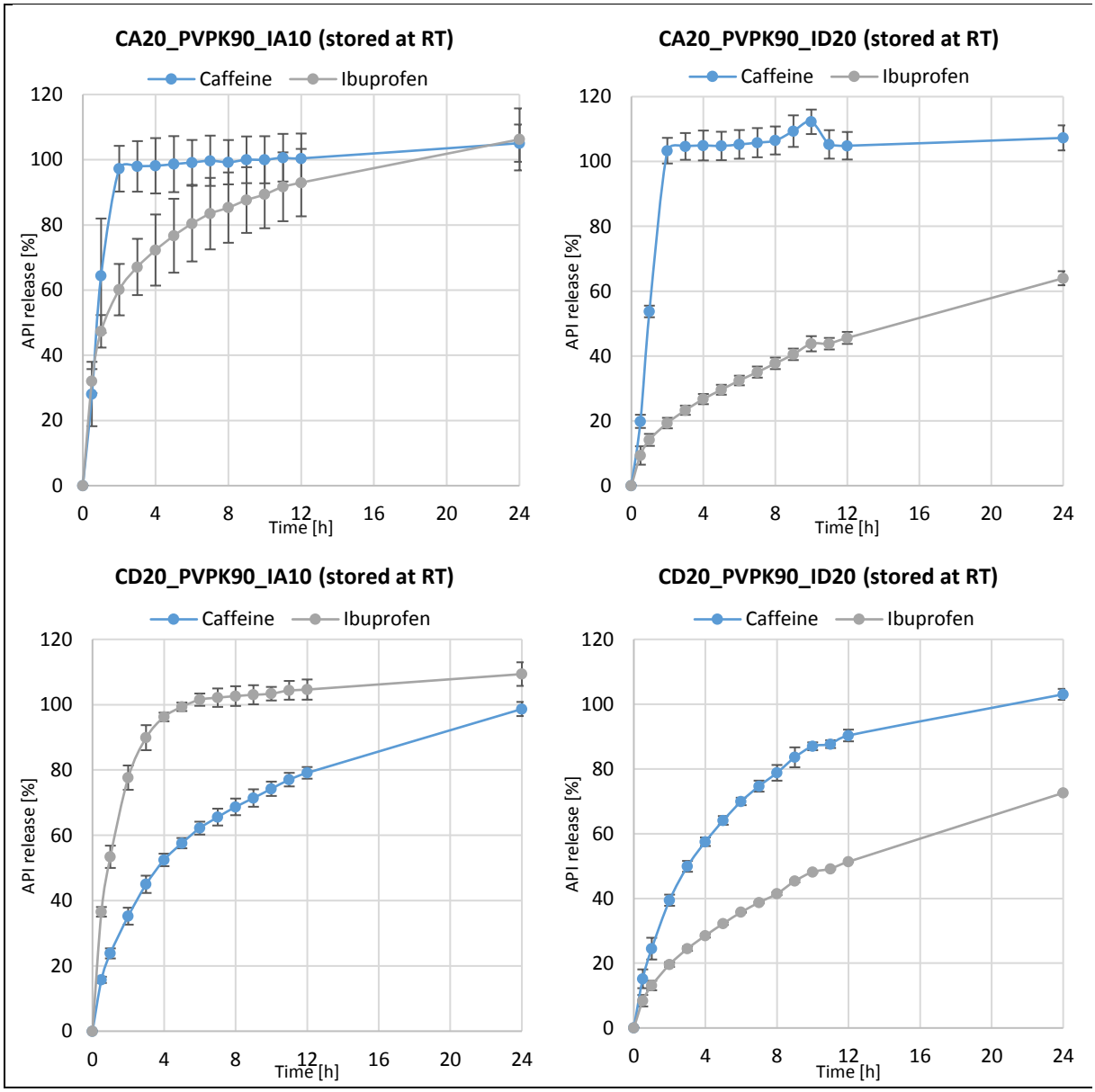

Figure 28. Dissolution profiles of the 24 hours test of multilayer tablets stored at room temperature and glued with PVP K90

Investigation of the release profile of tablets for 24 h revealed that for all tablets containing caffeine as API, the 100% release could be achieved 24 h. However, in case of ibuprofen, the 100% of release could be achieved for tablets containing Avicel as excipient but still not for tablets containing DCPD as excipients. This is on one hand due to the better solubility of caffeine than ibuprofen in the dissolution medium, and on the other hand because of differences in the physical properties of DCPD and Avicel. The faster release of API from Avicel tablets is because of the easier disintegration of tablets due to the higher swelling properties of Avicel, compared to DCPD. In contrary, DCPD as an inorganic compound, provides a slower release kinetic due to its high density. These observations are in agreement with other studies [79].

These behaviors offer the best condition for providing bilayer tablets with same or different APIs but different release profiles using GPT. Tablets containing Avicel could provide an immediate release profile of API and tablets containing DCPD could provide a sustained release profile. In case of having same API in both layers, the immediate release profiles will provide the loading dose, while the extended release profile provides the maintenance dose. Of course the available formulations would need improvements in order to reach of specifications for proper immediate and extended released profiles.

6 Conclusions and Outlook

The feasibility of GPT was investigated in this work as a novel technology for the manufacturing of multilayer tablets.

The deformation behavior of Avicel Ph 102 and DCPD and their blends with caffeine or ibuprofen was investigated. It was concluded that Avicel Ph 102 shows a plastic/elastic and DCPD brittle/fragmenting deformation behavior. Binary mixtures of Avicel Ph 102 with caffeine anhydrous and with ibuprofen free acid resulted in plastic/elastic deformation mechanism, same as the blend of DCPD and ibuprofen free acid. Whereas, the blend of DCPD with caffeine anhydrous showed a brittle/fragmenting deformation behavior.

Highest elastic recovery was observed for ibuprofen free acid and Avicel Ph 102 tablets, while for others elastic recovery was relatively low. Tablets containing Avicel Ph 102 showed more than two fold higher tensile strength than the ones with DCPD, except the ones with ibuprofen free acid which lowered the strength to the level of the tablets containing DCPD. These phenomena were attributed to the elasticity of ibuprofen free acid.

Tablets containing ibuprofen free acid showed higher surface roughness than the ones with caffeine anhydrous, independently of the binder.

Elastic recovery was the physical property that affected the most the delamination of the multilayer tablets. A mismatch of elastic recovery, coupled with the mismatch in deformation behavior of the single layer tablets, exhibited the highest amount of separations after the friability test of multilayer tablets.

Fish gelatin appeared to have better adhesiveness than the higher viscous PVP K90, multilayer tablets glued with the latter separated more. The lower viscous films show better adhesion to the tablet's surface due to their better penetration and distribution into the pores and microstructures on the surface.

GPT is a novel technology for producing personalized medicine and has a high potential for the future developments. Firstly, the problems encountered in the conventional way of producing bilayer/multilayer tables can be avoided, and secondly in the near future it can be implemented in the life cycle management of many fixed dose combination products. It offers the flexible and individual combinations of APIs

and doses, especially for the development of new therapeutic strategies for treatment of HIV/AIDS and multidrug resistance infections, where such individual and flexible combinations are necessary. Moreover, a real-time production on miniaturized equipment can be achieved in the field of translational pharmaceutics, immediately prior to clinical testing, creating the opportunity to modify dose and formulation compositions in response to emerging clinical data.

However, for manufacturing of robust multilayer tablets via GPT, a mechanistic understanding on the physical property of materials is necessary to provide proper matching of physical properties of tablet layers and gluing agents, offering optimal interfacial strength between layers.

More investigations are necessary on the impact of elastic recovery on tablet's physical properties and adherence capacity, and on the impact of surface tension and tack behavior of gluing agents on adhering properties.

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List of abbreviations

FDC	Fixed Dose Combination
API	Active Pharmaceutical Ingredient
GIT	Gastrointestinal tract
BSC	Biopharmaceutical Classification System
USP	United States Pharmacopeia
DEM	Discrete Element Method
FEM	Finite Element Method
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immune Deficiency Syndrome
WHO	World Health Organization
EMA	European Medical Agency
CIP	Clean in Place
RCPE	Research Center Pharmaceutical Engineering
DCPD	Dibasic Calcium Phosphate Dihydrate
Avicel	Microcrystaline cellulose – Avicel Ph 102
Caffeine	Caffeine anhydrous
Ibuprofen	Ibuprofen free acid
CA	Tablets containing Caffeine anhydrous and Avicel PH 102
CD	Tablets containing Caffeine anhydrous and DCPD
IA	Tablets containing Ibuprofen free acid and Avicel PH 102
ID	Tablets containing Ibuprofen free acid and DCPD
CA'	Powder mixture of caffeine with Avicel prepared for compression analysis
CD'	Powder mixture of caffeine with DCPD prepared for compression analysis
IA'	Powder mixture of ibuprofen with Avicel prepared for compression analysis
ID'	Powder mixture of ibuprofen with DCPD prepared for compression analysis
rpm	Rotations per minute

ER	Elastic recovery
NIR	Near Infrared Spectroscopy
Ph.Eur	European Pharmacopeia
HPLC	High Pressure Liquid Chromatography
UV-Vis	Ultraviolet – Visible Spectroscopy
Py	Pressure yield
SD	Standard deviation
DB	Deformation behavior
TS	Tensile strength
CF	Compaction force
ibu	Ibuprofen
caf	Caffeine