In-vitro Tomography and Non-Destructive Imaging at Depth of Pharmaceutical Solid Dosage Forms

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Abstract

Tomographic imaging techniques offer new prospects for a better understanding of the quality, performance and release mechanisms of pharmaceutical solid dosage forms. It is only over the last fifteen years that tomography has been applied for the in vitro characterisation of dosage forms. This review aims to introduce the concept of pharmaceutical tomography, and describes the current state-of-the-art of the four most promising techniques: X-ray computed microtomography, magnetic resonance imaging, terahertz imaging and optical coherence tomography. The basic working principles of the techniques are introduced and the current pharmaceutical applications of the technologies are discussed, together with a comparison of their specific strengths and weaknesses. Possible future developments in these fields are also discussed.

Key words: Solid dosage form, tomography, non-destructive testing, process analytical technology (PAT), controlled release, X-ray microtomography, magnetic resonance imaging (MRI), NMR imaging, NMR microscopy, terahertz pulsed imaging (TPI), optical coherence tomography (OCT)

1. Introduction

Along with recent breakthroughs in photonics – focal plane array detectors, optical fibres and compact lasers operating over a range of frequencies, to name a few – spectroscopic imaging techniques, in particular at infrared frequencies, have featured prominently in pharmaceutical formulation research over the last decade. The ability to perform spatially-resolved investigations of molecular interactions in the formulation, during processing and in the final dosage form, has lead to a better understanding of pharmaceutical processing steps and the resulting dosage form [1–4]. This development highlights one of the advantages that can be achieved simply by transforming a spatially unresolved spectroscopic experiment to a spectroscopic image.

The recent interest in process analytical technology (PAT) was catalysed by a number of initiatives on the regulatory level: the FDA’s initiative to transform the pharmaceutical cGMP regulations towards a more risk-based framework; the ICH guidelines Q8, Q9 and Q10 focusing on quality by design (QbD) as the new paradigm in pharmaceutical development and production, and the initiative by the EMEA to implement PAT submission procedures and real time release. All these developments have lead to a strong demand for fast acquisition spectroscopic techniques. The focus on vibrational spectroscopy for PAT can be explained by the combination of rich information content provided by the spectra and simultaneous developments in technology, i.e. well developed waveguides such as optical fibres that allow the construction of spectroscopic probes for real-time processing applications in-line, on-line and at-line in a manufacturing facility along with both robust and affordable instrumentation [5, 6]. The motivation for all initiatives that have evolved around PAT is to use the data acquired from in-line sensors to subsequently control the process and thus achieve a better quality product based on the – ideally full scientific – understanding that has been built up during the product development phase. It is therefore quintessential to understand, on a fundamental level, which properties during the process have what impact on the final product in order to predict changes of the quality of the dosage form as a result of changes in processing conditions. Once this understanding is established a successful process control loop can be designed and implemented.

Most commonly, the quality of the finished solid dosage form is assessed using basic parameters such as the spatial dimensions of the dosage form, its hardness, mass, content uniformity, porosity, friability, tensile strength, moisture content, disintegration time, dissolution profile and the weight gain during coating. All of these traditional parameters are well established in the modern pharmacopoeias and have served for a long time as benchmarks during the dosage form development process. However, while they are an integral part of modern PAT development and process control, they lack specificity and/or spatial resolution and lead to an insufficient basis for the full understanding of the dosage form. Even though tight specifications are in place to monitor the quality of the final products, each year a number of dosage forms fail after approval and have to be recalled from the market. In 2007 alone, approximately sixty
recalls were documented for pharmaceutical tablets in the FDA enforcement report for the United States. About 30% of these recalls were due to wrong labels or packaging, while recalls due to problems with dissolution/disintegration, impurities or content each attributed for about 20% of the recalls [7]. These numbers only cover dosage forms that have initially passed the quality control specifications and were released on the market. The number of failed batches that are produced and have to be discarded immediately after production due to their poor quality is estimated to be orders of magnitude higher.

While a number of techniques have been successfully introduced to pharmaceutical research and development in order to investigate fundamental properties of a formulation on the molecular, particular and particle ensemble level, the present research activities and instrumentation on the level of the entire dosage form itself are somewhat less developed. With the advent of more complex dosage forms there is a need to fully characterise and understand the performance limiting properties of such dosage forms. Even though processing technology has advanced considerably over the last decade, the fundamental understanding of the processing steps is not fully yet developed and it is this lack of understanding which is the reason for the failure of some such products in recent years.

This review focuses on four techniques that have the potential to provide the required tools: X-ray computed microtomography (XµCT), magnetic resonance imaging (MRI), imaging at terahertz frequencies and optical coherence tomography (OCT). Rather than being confined to information from the surface of the dosage forms all four techniques can be considered tomographic techniques, which means they are able to non-destructively resolve the three-dimensional structure of the dosage form. In this context, tomography is defined as the “cross-sectional imaging of an object from either transmission or reflection data collected by illuminating the object from many different directions” [8]. MRI is considered a tomographic technique in the context of this review even though the three-dimensional imaging methodology is not necessarily associated with the reconstruction of two-dimensional cross-sectional images. In addition to their ability to provide non-destructive tomographic information, all four techniques are able to resolve the internal structure of typical pharmaceutical excipients that are opaque at visible frequencies. Other imaging techniques that can also image at depth, such as confocal imaging, are not part of this review as they have only a limited ability to penetrate typical excipients used for the formulation of pharmaceutical solid dosage forms. Techniques that require large central facilities such as synchrotrons are also excluded from consideration.

2. Computed Tomography

2.1. Introduction to Computed Tomography

In contrast to a two-dimensional projection image, which is typically acquired by propagating a collimated beam either through the object of interest or reflecting it off its surface at normal incidence, a full three-dimensional image is not recorded directly but is obtained through reconstruction of two dimensional image cross-sections and subsequent stacking of the reconstructed slices.

In traditional computed tomography (CT), data for one slice in the xy plane is acquired at different angles, the object is moved in the z-direction and the process is repeated until the area of interest has been covered. The corresponding slices are reconstructed and a three dimensional image is obtained by stacking all slices on top of one another. In this approach the resolution in z-direction is mainly limited by the beam diameter, the dimensions of the detector and scattering of the radiation.

The slice images are reconstructed by mathematical algorithms using a number of projections at different angles through the sample in the xy plane. The projections can be acquired in transmission, reflection or from scattered radiation; however, for clarity the remainder of this section will only discuss tomography in transmission. Further details of the development of computed tomography and the image reconstruction techniques can be found in section 1.1 in the electronic supplementary materials (available online).

An important further advance in CT was achieved by the development of setups that are capable of providing three-dimensional images without the need of acquiring sequences of two-dimensional slices and subsequent stacking of the slices. This was realised by using a diverging cone beam rather than a two-dimensional fan or collimated beam together with a scintillator screen coupled to a 2D CCD detector array for detection (see next section for details). The image reconstruction requires the implementation of algorithms such as the Feldkamp algorithm [9] which is capable of reconstructing the three-dimensional image from the cone beam data. The details of the reconstruction techniques are out of the scope of this article and the reader is referred to the literature [8, 10, 11].

Even though computed tomography is most frequently employed using X-rays, the principle of tomographic image reconstruction can be applied over the whole range of the electromagnetic spectrum as long as the radiation can, at least partially, penetrate the object of interest. Due to their high energy, X-rays have the advantage that they are able to penetrate easily all pharmaceutically relevant excipients, exhibit negligible diffraction and as a consequence of the short wavelength allow for very high resolution images. However, tomography with X-rays will not always be the method of choice to investigate the internal structure of solid dosage forms. The image contrast is dependent on either relatively high density differences in the material, which often is not the case for a standard tablet, or the presence of atoms with different mass, which again is not necessarily common. In cases where X-rays do not lead to sufficient contrast it can be advantageous to use different types of radiation to acquire tomographic images. Examples of such experiments will be introduced later in this review.

2.2. X-Ray Microtomography (XµCT)

X-Ray microtomography (XµCT) evolved from medical CT with the aim to image small objects with high resolution. In 1982 the principle of XµCT was first demonstrated by Elliott and Dover [12] at the example of a tomographic image through
the shell of a freshwater snail on a setup similar to a CT scanner used by Hounsfield. In this experiment the spatial resolution of the reconstructed cross section was better than 20 \( \mu \text{m} \). There is no clear distinction at what resolution conventional CT ends and where X\( \mu \)CT starts but it is suggested that any results with higher spatial resolution than 100 \( \mu \text{m} \) should be regarded as X\( \mu \)CT [13].

In contrast to conventional CT, where X-ray source and detector are rotated around the sample object, the equipment used for modern X\( \mu \)CT typically rotates the sample object while source and detector are kept stationary (Fig. 1). Starting from the experimental setups used by Elliott and Dover more advanced instruments have been developed that use a collimated beam of X-rays combined with a matching 2D array detector [14]. By restricting the dimensions of the sample object to sizes smaller than the diameter of the X-ray beam such systems are able to acquire tomographic data of whole 3D objects in one rotation scan without the need of iterating the sample in \( z \) direction after the acquisition of a single \( xy \) slice. Unfortunately, only synchrotron facilities provide bright enough light sources for the operation of these parallel beam setups.

Almost all experimental work on X\( \mu \)CT which has been published in the pharmaceutical field is performed on instruments that use a cone beam in combination with a 2D array detector. As in the parallel beam setups it is possible to image a whole three-dimensional object by just rotating the object through 180° and recording the projection images using the cone-beam configuration. Higher resolutions have been possible through the development of X-ray tubes with very small apertures providing point like sources. The major limitation of these setups is that there is a trade-off between sample size and magnification. The shadow of the projected object must not exceed the size of the scintillation screen.

![Figure 1: Cone beam X\( \mu \)CT setup. A point source emits a diverging beam of X-rays. The X-rays penetrate the sample object and are attenuated. The transmitted radiation, or shadow image, of the object is projected onto a scintillation screen which typically uses a layer of phosphor to convert the X-rays to visible light. Optical lenses or fibre optics coupled to the scintillator (not shown) are used to project the image from the scintillation screen to a 2D CCD array detector. After the shadow image is acquired the object is rotated. The magnification is set by adjusting the distance between the sample object and the X-ray source.](image)

For the operation of these parallel beam setups. Only synchrotron facilities provide bright enough light sources. The development of X-ray tubes with very small apertures provide three-dimensional object by just rotating the object through 180° after the acquisition of a single \( xy \) slice. Unfortunately, only synchrotron facilities provide bright enough light sources for the operation of these parallel beam setups.

The work by Farber, Tardos and Michaels on the porosity and morphology of granules is the first example of X\( \mu \)CT being used in a pharmaceutical context [19]. The results for the porosity measurements by X\( \mu \)CT were compared to mercury porosimetry and gas absorption measurements. However, the resolution of the measurement is limited to pores bigger than 4 \( \mu \text{m} \). The pore size distribution is also strongly dependent on the contrast between pores and the material. As the density of typical pharmaceutical excipients is not very high, the contrast between the material and the air in the pores is not always unequivocal in the reconstructed images. In order to calculate the pore size the images need to be converted from greyscale (different densities) to binary (material or air) images. During this process a threshold of what density is regarded as air and what as sample material has to be defined which has a very strong impact on the resulting pore size. The authors concluded that the precision of X\( \mu \)CT for the determination of pore sizes is inferior to mercury porosimetry, yet X\( \mu \)CT gives additional information in terms of the pore morphology, spatial distribution and connectivity. Furthermore, the true pore size distribution is obtained rather than only the size distribution of the pore “necks” as is the case in mercury porosimetry.

Ansari and Stepanek used X\( \mu \)CT for the characterisation of the granule microstructure during the development of a fluid bed melt granulation process [20]. They were able to show the formation of hollow core granules by X\( \mu \)CT depending on the formulation composition and particle size of the excipients used. Based on the results obtained by X\( \mu \)CT they were able to develop a mathematical model to aid the formulation development.

Yang and Fu studied compaction and mixing processes of powders using X\( \mu \)CT [21]. For their study Yang and Fu developed a lead labelling method to trace highly spherical microrystalline cellulose (MCC) particles during compaction and blending experiments. The MCC particles were separated into different fractions and impregnated with varying amounts of view on the detector. In order to achieve magnifications of 120x and higher the object has to be restricted to a maximum size of about 2 mm. A further disadvantage of instruments based on the setup shown in Fig. 1 is that they are inherently susceptible to ringing artefacts. This is due to the fact that each detector element is used for the same projection in all shadow images and subtle differences in the sensitivity between the individual array elements, which are unavoidable in CCDs, will lead to ringing artefacts in the reconstructed images.

One elegant solution to overcome both problems is to use time-delay integration methods as introduced by Davis and Elliott [15]. The same authors have also published a very clear overview about the different artefacts in X\( \mu \)CT [16] and how to use the technique quantitatively for chemical element analysis [17]. Stock has provided an excellent comprehensive review of X\( \mu \)CT in a materials science context and the reader is referred to this review for more details on the details of the technique [13]. A first thorough overview of pharmaceutical applications for X\( \mu \)CT was compiled by Hancock and Mullarney [18].

2.3. Pharmaceutical Applications

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lead (II) acetate trihydrate. Lead (atomic number 82) is strongly absorbing at X-ray energies and the impregnation with the lead solution provides an excellent contrast between the different particle fractions. By tracing the relative positions and movements of the lead impregnated particles, die compaction and mixing in a model V-blender on the particulate level was investigated. The authors concluded from the compaction experiments that the local strains within one region of the compact are not identical with the global strain. In a miniature V-blender Yang and Fu studied different mixing processes using two fractions of MCC particles, one labelled with lead acetate and the other fraction unlabelled. The particle size distribution for both fractions was identical. For the mixing experiments, the analysis was performed using the shadow images rather than reconstructed cross sections. Different loading configurations for the blender were investigated. It was possible to study the mixing process both qualitatively and quantitatively using 1D profiles. This is a valuable first step in developing XµCT for process applications. However, one arm of the model mixer used for the study only measures 18 mm and the particles used for the study had a size of around 200 µm. Given the small scale of the mixer required for the XµCT experiments, it remains to be seen whether the results can be transferred to the conditions in an industrial mixer.

The first application of XµCT to investigate entire pharmaceutical dosage forms is a study by Ozeki et al. [22]. Tomographic cross sections of dry coated tablets were used qualitatively in order to investigate differences in density between the different tablet components and to detect exfoliation between these structures. At a compaction pressure of 100 MPa the contrast between the tablet core and the dry coating was very weak while it was much stronger at a compaction pressure of 200 MPa. No exfoliation was detected.

One of the early applications of XµCT in the materials science community was the measurement of density variations in compacts [23]. Following up on these studies compaction of pharmaceutical powder mixtures was investigated. Sinka et al. used direct compressed tablets of different geometry and embossing made of MCC [24] to assess the applicability of XµCT for the quantitative measurement of density variations within tablets. The model tablets were compressed at two different compaction forces. Considerable density differences within the tablets were detected (Fig. 2).

Busignies et al. studied localised density variations in tablets of the form of flat faced cylindrical compacts of MCC by XµCT [25]. The tablets were compacted over a range of pressures between 40 and 280 MPa and the linearity of the X-ray attenuation as a function of density was validated over the range of samples. The greyscale of the reconstructed image slices was calibrated to the material density and this calibration was used to produce false-colour maps of the spatial density distribution within the tablets (Fig. 3A). Significant density variations within the tablets of more than 10% were detected. It was found that the tablets are denser at the surface compared with the centre which was attributed to wall friction during the compaction process. This effect was more pronounced with increasing compaction pressure. In addition, the thickness of the ring of higher density along the central band of the tablet was found to decrease with increasing compaction pressure (Fig. 3B). It was suggested that this property is important with regards to the friability of the tablet, in particular, when the tablet is embossed with structures at length scales comparable to the density gradient. The density distribution along the z axis was found to be much more uniform for the cylindrical model tablets studied.

Fu et al. investigated the packing structure in granular systems [26]. Two model systems of packed powders were used: glass beads and spherical MCC particles ranging from 180 to 300 µm in diameter. An algorithm was developed, and applied to reconstructed XµCT slices of both systems, to automatically identify and locate the absolute position of individual particles in a three dimensional coordinate system. The identification was based on the unique particle morphology and thus no tracer particles were required for the experiments. The experimental results were found to be in quantitative agreement with simulations for the packing using a discrete element modelling (DEM)
In addition to the previous study Fu et al. used the same approach to study the displacement of marker particles in a powder bed in situ during compaction [27]. For the experiments the authors designed a compression rig made of polycarbonate and flat faced metal punches that was suitable for XµCT image acquisition. In this rig only the upper punch was lowered during compression while the lower punch was kept stationary. A mixture of spherical sugar particles and glass ballotini (n < 100, as marker particles) was loaded into the rig. The powder mixture was compacted in discrete steps outside the XµCT setup using a universal testing machine. After each compression step the position of the upper punch was fixed and the rig was transferred into the XµCT instrument for image acquisition. Fu et al. used their watershed algorithm to locate the glass ballotini in the powder bed and trace their position between the different compaction steps (Fig. 4). Even though the tracer particles exhibit different mechanical and surface friction forces compared to the sugar spheres it was assumed that they followed the local motion of the surrounding material. The results of the compaction experiments were promising. By quantitative analysis of the tracer particle positions with increasing compression force the authors were able to detect wall friction effects at the die-wall boundary (Fig. 4B).

Traini et al. used XµCT to qualitatively study drug release from a modified drug release tablet [28]. In this osmotic release oral system (OROS) the tablet is coated on the outside with a semi-permeable membrane and divided internally into two compartments separated by a further impermeable membrane. One of the compartments contains a polymer matrix while the other compartment contains the drug formulation. Driven by osmotic pressure the polymer matrix swells upon water uptake and actively pushes the contents of the drug containing second compartment through a small hole in the tablet coating. This system can be used for zero order drug release products. In their study Trani et al. imaged tablets before dissolution and at 14 and 24 hours during dissolution. The samples from the dissolution study were dried at 50°C for one hour before characterisation by XµCT (Fig. 5). It was possible to distinguish the two compartments of the tablet before dissolution as well as after 14 hours into the dissolution process. However, no membrane between the two compartments was reported. Based on the reconstructed cross-sections the authors modelled the void space that was observed in the tablet shell after drying the samples from the dissolution experiments. However, the void space observed in the tablet in these experiments is not representative of the structure of the tablet during dissolution. It is very likely that the morphology of the internal tablet structure has changed over the drying period. No quantitative data recording the evolution of observed void volume over dissolution time was presented.

The first example of in situ imaging of a pharmaceutical dosage form during dissolution by XµCT was reported in a paper by Karakosta et al. [29]. Model tablets of diltiazem hydrochloride and Eudragit RSPO (3 mm in diameter) were compressed and imaged over a total of 5 hours while exposed to distilled water. The acquisition of each sample took 40 minutes and the resulting image resolution was $10 \times 10 \times 10 \, \mu m^3$. The results obtained by XµCT, which is sensitive to the electron density distribution in the sample, was compared to the results of the same experiments performed by $^1H$ MRI (see next section), in which the signal was dominated by hydrogen species with sufficiently long relaxation time for imaging experiments. Even though the contrast between water and the polymer matrix in the XµCT images was found to be rather poor the technique was found to be well suited to study the evolution of air voids within the tablet matrix during water ingress (Fig. 6A-H).
ff imaged in the dry state and after they were exposed to distilled prepared by compacting spray-dried powder of the excipient, we re
and electron microscopy [30]. The pellets, which were pre-
and the core of the pellet was observed. This membrane could
with a razor blade, a membrane between a porous outer layer
images, which were acquired after cutting through the pelle ts
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µCT were freeze-dried. In all experiments using wet pellets, as the contrast between the membrane and the water was insufficient. The authors assume that the freeze-drying process preserves the real texture in the pel-
lets by preventing a collapse of the structure and does not lead to artefacts itself. It is concluded that upon dissolution water initially quenches the pellet surface while water is continuing to penetrate into the core. In a second step the membrane, formed during the quenching, develops into a hydrogel and the water movement becomes diffusion controlled. Similar samples were also analysed by MRI (see next section).

Among other techniques XµCT was used by Inman et al. to characterise fracture in bilayered MCC tablets [31]. Wedges of fractured bilayer structures were analysed and it was possible to localise cracks in the tablet matrix. Based on the results from XµCT the authors concluded that stress relaxation during the two stage compression of bilayered tablets occurs most likely in the radial direction immediately after ejection of the tablets from the die.

3. Magnetic Resonance Imaging (MRI)

As outlined in the last section, the contrast in XµCT is achieved by the attenuation of photons as a result of absorption, refraction or scattering when a collimated beam of X-rays is used to illuminate the sample specimen. As a consequence of their photon energy it is through the interaction with the electrons of the sample material that X-rays are attenuated. In contrast, in nuclear magnetic resonance (NMR) the magnetic moments of certain nuclei in the sample, which is placed in an external magnetic field B₀, align with this field and then can be excited with a pulse of radiation. The excitation of the nuclei leads to absorption of photons and subsequent re-emission which is measured as the NMR signal. A short introduction to nuclear magnetic resonance in the context of this review is provided in section 1.2.1 which is available in the online supplementary materials.

3.1. Tomographic Imaging Principles

The concept of generating a spatially resolved NMR signal for tomographic experiments was first demonstrated by Lauter-
bur by imaging two test tubes of water surrounded by D₂O [32]. At the same time Mansfield and Grannell published their findings of NMR ‘diffraction’ in solids which made use of the same concept [33]. Lauterbur referred to this technique as zeug-
matography but despite the impact of his paper, he was awarded the Nobel Prize for this work in 2003 together with Sir Peter Mansfield, this term did not prevail. In magnetic resonance imaging (MRI), as the technique is now commonly refereed to, spatial resolution is introduced to the NMR experiment by applying one or multiple magnetic field gradients G in addition to B₀.

\[ \omega_r = \gamma (B_0 + G_x y) \]  

(1)

Here Gₓ refers to a gradient in the y direction (γ is the gy-
romagnetic ratio and ω is the frequency as detailed in sec-
tion 1.2.1 of the online supplementary materials). The addi-
tional gradient has the effect that it slightly shifts the resonance

Figure 6: The central coronal slice extracted from a three-dimensional XµCT data set. Slice A) is the dry matrix. Air appears dark and the side grey stripes are part of the polymer tube supporting the sample. Slices B)-H) show the same slice exposed to water for the following times: 45, 90, 135, 180, 225, 270, and 315 min. Water appears as light grey, comparable to the tablet. I) The increase in the mean air-void volume in μm³ with respect to time. (modified from [29]).

Using the image data for the different time points during disso-
lution it was possible to quantify the air-void size distribution in the whole tablet volume (Fig. 6I). The results of the air-void evolution were discussed in terms of two diffusion coarsening models: Ostwald ripening and diffusion of droplets into contact followed by coalescence. Based on the distribution function of the air voids and the fact that sudden collapse of some voids was observed experimentally it was concluded that the coalescence model describes the observations best. The authors suggested that the air voids might play a role in the initial wetting of the porous medium and its structural integrity.

Chauve et al. analysed the changes in morphology upon disso-
lution of small pellets made of high-amylose starch by XµCT and electron microscopy [30]. The pellets, which were prepared by compacting spray-dried powder of the excipient, were imaged in the dry state and after they were exposed to distilled water for different amounts of time. For the XµCT experiments the pellets which had been in contact with water were either im-
aged directly or freeze-dried prior to the acquisition, while all pellets analysed by electron microscopy were freeze-dried. In both the XµCT cross sections as well as the scanning electron images, which were acquired after cutting through the pellets with a razor blade, a membrane between a porous outer layer and the core of the pellet was observed. This membrane could not be distinguished from the hydrating water in the XµCT ex-
3.2. Pulse Sequences

In order to acquire the information that is required to reconstruct MR images a number of different so-called pulse sequences are used. The pulse sequence describes the timing, strength and sequence of the r.f. pulses and gradient pulses that are applied, and usually repeated for a large number of cycles, for the MRI experiment. The pulse sequence is usually described in an abstract schematic as it needs to be adapted to the specific conditions of different magnets, coils, amplifiers and software on each MRI instrument.

A large number of pulse sequences have been developed which allow MR images to be acquired under a variety of conditions and acquisition speeds and which also allow us to measure a number of different properties, such as the spatial distribution of velocity of flowing liquids in a sample. The pulse sequences also enable the operator to enhance the contrast within MR images depending on the physico-chemical properties of the samples, e.g. the $T_1$ or $T_2$. The sequences are distinguished by a tremendous number of acronyms such as RARE, GERSV and SPRITE and whole books have been dedicated to the topic [39]. Most often basic pulse sequences such as the spin echo sequence have been used for pharmaceutical MRI applications so far and the reader is referred to the literature for further details of specific pulse sequences [40].

So far, MRI has been widely applied for quantitative analysis of chemical products and processes [41] and in chemical processes and reaction engineering [42]. Melia et al. and Richardson et al. provided first overviews of different applications for MRI to characterise controlled release pharmaceutical dosage forms [43, 44].

3.3. Pharmaceutical Applications

The majority of the research activities in the field of imaging pharmaceutical dosage forms with MR techniques have focused on studying the hydration of polymers of matrix tablets. Only a few groups have studied pellets or other dosage forms and only one study on film coated tablets has been reported so far. Typically a flat faced tablet with a diameter of less than 1 cm and a thickness of several millimetres is used as a model tablet system and a standard spin-echo imaging sequence is employed for the image acquisition. Table S.1 in the electronic supplementary materials of this article (available online) gives the full details of the work published to date [29, 45–65, 65–77]. Due to the amount of work in the field and the restriction in space we will only highlight some select studies in more detail in this section.

The first application of MRI to study pharmaceutical tablets was published by Nebgen et al. [45, 78]. By immersing tablets in silicon oil spiked with a gadolinium complex it was possible to image the three-dimensional void space, filled by the oil, within the tablets. Three different types of tablets were analysed: placebo tablets made of MCC, drug loaded MCC tablets and compression coated tablets. The spatial distribution of porosity as a function of the compaction used for the MCC tablets was analysed and compared to the bulk porosity as determined by gas pycnometry. In the compression coated tablets it was possible to detect hairline cracks running from the core through the entire erosion matrix coat to the tablet side faces.

Rajabi-Siahboomi et al. studied the formation and growth of a hydrate pseudogel layer on the surface of flat faced hydroxypropylmethylcellulose (HPMC) tablets as a function of immersion time in water [46]. The tablets were fixed onto a sample mount during the immersion and imaging experiments and the water was removed prior to the image acquisition. Uniform growth of the gel layer was observed in the radial and axial planes of the tablet. The dimensions of the tablet core exhibited an anisotropic change: while the tablet core shrank in the radial plane of the tablet, expansion was observed in the axial plane. This behaviour was tentatively assigned to a release in compression stress along the axial direction of the tablet as a result of water uptake. The edges of the tablets were found to hydrate to a greater extent than at the centre of the tablet faces.
Figure 8: Quantitative MR imaging of the buffer uptake in a monolithic implant of poly(glycolic acid-co-DL-lactic acid) (PGLA) unloaded (A and B) and loaded with API (C to E). A) Radially averaged water concentration profiles acquired during the penetration of PBS buffer into the placebo implant between 12 and 80 min. B) Weight uptake of PBS in the placebo samples (gravimetric data • and NMR data □). C) Radially averaged water concentration profiles of the drug loaded PGLA implant between 1.5 and 234.3 h. D) Corresponding weight uptake of PBS (gravimetric data • and NMR data □). E) Images of the PBS ingress into the drug-loaded implants (modified from [50]).

While all the previous MR imaging work on pharmaceutical dosage forms was qualitative, Hyde et al. published the first quantitative study investigating the ingress of water in PBS buffer into monolithic implants made of poly(glycolic acid-co-DL-lactic acid) (PGLA) produced by an extrusion process (Fig. 8) [50]. The results of the spatially resolved MRI method were compared to the gravimetric determination of water uptake and excellent agreement was found between the two techniques. Depending on whether API was loaded into the polymer matrix or pure polymer (placebo) was exposed to the buffer solution, the kinetics of the PBS ingress was very different. While the unloaded PGLA matrix was saturated with PBS after 80 min, the process took more than 74 h in the presence of goserelin, a large peptide molecule used as the model API for this study. This effect was attributed to changes in the physical structure of the polymer by the API molecule. Along with this strong increase in penetration time a change in the transport mechanism was detected by the quantitative analysis of the MR images.

The erosion of a soluble API containing tablet cores embedded in a much more slowly disintegrating polymer matrix by dry coating was the subject of a study by Fahie et al. [53]. MRI was used to elucidate the mechanism of erosion of the API containing compartment in two different formulations of the in controlled release tablets. The formulations were different in composition and processing of the outer “scaffolding shell”, which covered the top and bottom surface of the tablet but not the central band (see Fig. 10 for a similar system). A strong dependency of the drug release profile on formulation was observed by dissolution testing. The MRI experiments revealed distinct qualitative differences in the porosity of the release rate controlling coating barrier on the top and the bottom of the tablet. The formulation that exhibited higher porosity of these areas correlated with faster release of the drug. Based on the MRI images the authors were able to dismiss an alternative mechanism of accelerated drug release that had been suggested based on destructive visual inspection of samples during dissolution testing. All experiments in this study were performed under static dissolution conditions.

Narasimham et al. investigated the distribution of molecular mobility during dissolution in poly(vinyl alcohol) (PVA) tablets [58]. The ingress of water into model tablets was imaged by one-dimensional imaging of the water distribution and the self-diffusion coefficient of the water molecules in the polymer. Depending on the molecular weight of the PVA and the location within the tablet, differences were found in the kinetics of the hydration and the diffusion mechanism (Fig. 9). The experimental results were compared to predictions based on a mathematical model of polymer dissolution. Good consistency between the experimental results and the theoretical predictions was found.

The first example of an in situ imaging study of tablet dissolution under non-static conditions was performed by Fyfe et al. [60]. For the imaging experiment a modification of a commercial flow through cell (USP apparatus IV) was developed that could be fitted within the diameter of an MR imaging coil. Three different controlled release dosage forms were investigated with this setup: a HPMC placebo tablet, a dry-coated tablet and an osmotic pump tablet similar to the one investigated by Traini et al. [28]. The imaging experiments were per-
formed both under static and flow conditions with flow rates up to 16 ml min$^{-1}$ and the images were purely qualitative. While fast flow rates can lead to distortions and artefacts in the images, the authors found that the flow rates used for their experiments were too low to cause such effects. Differences in HPMC dissolution were found upon comparison of the images acquired under static and flow conditions. Mechanical shear at the surface of the dissolving HPMC caused decreasing thickness of the gel layer as the flow rate increased. These experiments highlight the importance of performing the MRI experiments under the same conditions as those used in traditional dissolution testing, if the results are to be compared.

Sutch et al. used MRI for the investigation of pulsatile release capsules [67]. Pulsatile release capsules consist of a capsule body, which is coated with a water insoluble polymer, and a release controlling plug that seals the capsule and erodes with time. Once the dissolution medium penetrates into the capsule it contacts an excipient that leads to expulsion of the API content upon hydration. In this study, the performance of capsules that were coated using either aqueous or organic coating processes was analysed. The capsules with the aqueous coating were found to exhibit premature and erratic drug release. Coating formulations based on organic solvents showed the desired pulsatile release profile. Based on the MR images it was proposed that the early release of the capsules based on the aqueous coating formulation was caused by the poor seal between capsule and plug of this capsule and subsequent premature hydration of the expulsion agent. For the studies a combination of two-dimensional spin-echo images and images acquired with the RARE sequence was used.

Djemai and Sinka have quantified density variations in tablets [71]. In an approach similar to Nebgen et al. [45], tablets were immersed with mineral oil under vacuum. A saturation of 95% of the pore space by the oil was estimated. A set of flat faced cylindrical MCC tablets of uniform density was prepared and their density was determined by their weight and dimensions. This set of tablets was used as a calibration set such that the MRI signal from the pore space of the tablet could provide a measure of tablet density (Fig. 11). Different sets of production tablets were analysed using the MRI method and the density distribution within the dosage form was determined. The results of the MRI experiment were compared to a previous study on the density distribution is tablets measured by X$\mu$CT by Sinka et al. [24] and good agreement was found between the two techniques.

4. Terahertz Imaging

4.1. Measurement Principles

Terahertz radiation has excellent potential in the advancement of our understanding of pharmaceutical solid dosage forms but is, as yet, under-explored. Recent developments in semiconductor physics and ultrafast laser technology have made it possible to provide light at terahertz frequencies (a frequency of 1 THz equals a wavelength of 0.3 mm) in a relatively
when researchers at the Bell labs developed the photoconductive antenna technology on which modern terahertz emitters and detectors are based [80]. This technology combines approaches from both optics and electronics in order to bridge the gap of the electromagnetic spectrum where only very weak sources and detectors were available previously.

The breakthrough for the generation and detection of coherent terahertz radiation only dates back to as far as the late 1980s when researchers at the Bell labs developed the photoconductive antenna technology on which modern terahertz emitters and detectors are based [80]. This technology combines approaches from both optics and electronics in order to bridge the gap of the electromagnetic spectrum where only very weak sources and detectors were available previously.

The emitter and receiver devices used to generate and detect terahertz radiation are made of GaAs, a III-V semiconducting material, with a band gap of 1.42 eV. Pulses of terahertz radiation are generated when charges are accelerated across this material. In order for this to happen, two electrodes with a gap in between are patterned onto a flat wafer of the semiconductor. A DC electric field is then applied between the two electrodes. As the electrodes are connected through a semiconductor, no charges can move between the electrodes, a configuration comparable to an open switch. This setup is called a biased photoconductive antenna. The photoconduction occurs when a short pulse of light with a photon energy $h\nu$ ( Planck constant and $\nu$ frequency) exceeding the band gap of GaAs, that corresponds to a wavelength of less than 873 nm, is directed onto the gap between the electrodes. Electrons and holes form on the surface of the device as the electrons in the semiconductor are excited from their valence band into the conducting band. Due to the DC bias voltage between the electrodes, the photo-injected charges are then accelerated towards the electrodes and as a result of the charge acceleration an electric field is emitted – the terahertz pulse.

The detection of the terahertz pulse is achieved through the reverse process (Fig. 12). Rather than applying a bias voltage across the semiconductor, during detection the sub-picosecond terahertz pulse is focused onto the device using a hemispherical lens with a similar refractive index to the GaAs. Simultaneously, a femtosecond pulse of NIR light is focused onto the gap between the electrodes on the opposite face of the semiconductor. The NIR pulse, which is derived from the same NIR laser beam used to generate the terahertz pulse, is called the probe pulse and is used to optically gate the semiconductor switch by generating charge carriers in the device. These charge carriers are then accelerated by the terahertz pulse. The resultant photo-induced current, which is proportional to the terahertz electric field, is measured between the electrodes. By sweeping the delay of the NIR pulse relative to the terahertz pulse, the electric field of the pulse can be sampled. The repetition rate of the pulses is typically around 80 MHz and with fast optical delay lines and fast data acquisition interfaces the whole terahertz waveform can be acquired within milliseconds. Using this coherent detection scheme, no cryogenic cooling is required to distinguish the terahertz radiation from the thermal background.

The development of terahertz technology was facilitated by substantial advances in laser technology over the last decade leading to a reduction in size, cost and availability for femtosecond lasers. Typically titanium sapphire lasers operating at 800 nm central wavelength with a pulse duration between 10 and 100 fs are used for the generation and detection of terahertz radiation.

Terahertz time-domain spectroscopy (THz-TDS, often also referred to as terahertz pulsed spectroscopy, TPS) is an ideal probe for the physical characterisation of pharmaceutical solids [82, 83]. It is non-destructive and interacts with vibrational

Figure 11: Quantitative imaging of tablet density by MRI A) Calibration of the MRI technique using a stack of flat faced model tablets of MCC compressed with 1 to 4.9 kN. Values in brackets refer to the theoretical relative density from weight and dimension measurements. B) Relative density maps of cross sections through the three principal axes in a tablet. All densities are stated in g cm$^{-3}$ (compare (a) to the results from X$\mu$CT in Fig. 2, modified from [71]).

Figure 12: Principle of coherent photoconductive detection of the terahertz electric field in time-domain terahertz spectrometers using a low-temperature grown GaAs antenna. Using a delay line the NIR gating pulse is systematically delayed with respect to the terahertz pulse (simplified as measurements 1-6 in this illustration) and the electric field of the terahertz pulse is measured in consecutive measurements.
modes that extend across large domains of the lattice in organic molecular crystals [84]. The ability to probe the lattice dynamics which represent interactions between molecules in their crystal structure makes terahertz spectroscopy a very powerful tool for the analysis of complex solid-state materials properties [85, 86]. In terms of imaging applications of terahertz radiation, a detailed overview of different techniques and applications has been published recently by Chan et al. [87].

4.2. Time-resolved Terahertz Pulsed Reflection Imaging

In addition to tomographic imaging using reconstruction algorithms, it is also possible to explore the structure of a pharmaceutical dosage form using time-resolved analysis of the back reflections of a pulse of radiation that is able to penetrate into the dosage form. To date, this imaging technique, called terahertz pulsed imaging (TPI), is the most commonly used terahertz imaging approach for the characterisation of pharmaceutical solid dosage forms.

In TPI terahertz light can be used to probe the internal structure of a solid dosage form [88]. Most of the excipients that make up the bulk of a tablet are transparent to terahertz light, whereas the drug and interfaces from different coating layers or substructures within the tablet lead to a contrast in the images due to a change in their refractive index. When ultrashort pulses of coherent terahertz radiation are directed onto the surface of a coated tablet, part of the pulse is reflected from the surface of the coating while the remaining photons are propagating into the coating (Fig. 13). With an average power of the terahertz radiation in the µW range there is no thermal stress induced in the sample. The concept of structural imaging is based on the experiment by Mittleman et al. [89] and was subsequently applied to image pharmaceutical dosage forms by Fitzgerald et al. in 2005 using the example of a sugar coated tablet [90].

The ratio of the reflected to the transmitted radiation is given by the dielectric properties of the coating material. As the terahertz pulse propagates deeper into the dosage form further reflections occur whenever there is a change in real refractive index, such as at the interfaces of coating layers. Time-resolved detection of the reflected pulses is performed to record the time-domain waveform of the reflected terahertz pulse (Fig. S.3 and S.4 in the online supplementary materials). The thickness of all coating layers that the pulse has propagated through can be determined non-destructively using the time-of-flight between the pulses and the refractive index of the coating material.

A single terahertz time-domain waveform, which contains the information characterising the coating structure at one specific point on the surface of the dosage form, can be acquired in about 50 ns. In order to examine the whole solid dosage form in detail, it is necessary to acquire the terahertz waveforms over the surface of the tablet. For the measurement of the waveform at each spot the tablet has to be presented to the terahertz optics at an angle of normal incidence. Fortunately, this task can be achieved conveniently by using an automated terahertz tablet scanner. As a first step the instrument generates a model of the three-dimensional surface dimensions of the entire tablet (Fig. S.5 in the online supplementary materials). The tablet is held by a robot arm that is able to present any point on the surface of the tablet at an angle of normal incidence to the terahertz optics. The surface model is stored and can be used as the basis for the subsequent terahertz mapping. For the imaging of multiple tablets of identical geometry the same surface map can be used, thus reducing the acquisition time by a factor of two.

By mapping over the entire surface of the tablet, the statistical distribution of the coating thickness and its quality can be quantified (Fig. 14). Even though the lateral spatial resolution of terahertz images in the x and y direction is diffraction limited to about 50 to 200 µm due to the long wavelength of terahertz radiation, the axial resolution in z direction, a function of the pulse duration, is better than 40 µm [88].

The first example of how TPI can be used to study film coated tablets was demonstrated by Zeitler et al. [88]. In this study the potential of the technique to characterise a wide range of commercially available pharmaceutical dosage forms such as film coated tablets, layered tablets and soft gelatine capsules...
was investigated. In the same study the TPI instrument that is capable of performing the fully automated terahertz mapping experiment of all surfaces of a dosage form was introduced. Depending on the overall surface area of the dosage form an acquisition time between 20 and 50 minutes was required for modelling the surface and recording a three-dimensional terahertz map of a film-coated tablet.

In application to sustained-release tablets, TPI was further evaluated for pharmaceutical applications by Ho et al. [91]. The thickness measurements obtained non-destructively by TPI were validated against measurements of cross sections through the same sample specimens by optical microscopy. Very good agreement was found between the two techniques. While the microscopy technique provided a very limited number of data points over the surface of the sample and the technique is inherently destructive, TPI was found to provide much greater statistical usefulness as the number of sample points over the surface of the tablet was higher by several orders of magnitude than that associated with optical microscopy. The ability to detect and quantify the extent of coating defects by TPI further highlighted the rich information content provided by terahertz structural images to assess the reproducibility, uniformity and distribution of film coating layers. Important insights to aid process development have been obtained. For example, in development of film coating technology, weight gain data during coating are used and it is assumed that a uniform distribution of the film exists over the whole surface of the tablet. Ho et al. demonstrated that this is not always an appropriate assumption (Fig. 15).

In a study by Spencer et al. the coating thickness was measured by TPI of three different enteric coated tablets was correlated with the mean dissolution time (MDT) of the respective tablets [92]. The results of the film thickness measurements revealed that the mean coating thickness varied between 57 and 109 µm between the different tablets. The inhomogeneity in thickness is surprising given that the tablets used for this study were marketed products that had been sourced commercially. As the TPI experiments are non-destructive it was possible to perform dissolution testing on the same samples that were used for the coating thickness determination. A modest correlation was found between mean coating thickness and MDT. However, it was acknowledged that the delayed-release system was more complex and coating thickness was only one factor contributing to the dissolution performance amongst others. The authors speculated that the exposure of the tablets to media of different pH under different shear stress conditions as required by the modified USP procedure for dissolution testing of delayed-release tablets (50 rpm stirring in 500 ml at pH 1.2 for 2 h; followed by 100 rpm stirring in 900 ml at pH 6.0 for 1 h; followed by 50 rpm stirring in 900 ml at pH in the range between 6.5 and 7.2 until dissolution) will have an impact on the dissolution behaviour beyond the factors that are solely affected by the coating thickness and further work is required to understand this process in more detail.

For the case of sustained-release tablets produced under lab and pilot scale conditions Ho et al. further investigated the applicability of TPI to correlate coating parameters obtained by TPI with the dissolution performance of the dosage form [93]. Even though the tablets from lab and pilot scale batches were coated to the same weight gain the MDT was found to be significantly longer for the pilot scale tablets. TPI was able to discriminate the two batches based on significant differences in the coating thickness even though the weight gain was identical. In addition to the coating thickness the authors highlighted that changes in coating density, which can be extracted from the relative reflectivity of the coating compared to a reference mirror, form a very important parameter that can be used to assess the quality of film coatings by TPI. The correlation between coating thickness and MDT was very clear and much stronger than in the study by Spencer et al.

The effect of material density on the refractive index of a tablet has been demonstrated previously by Pore et al. [94]. For example, for two different filler excipients an increasing refractive index was found with increasing tablet hardness due to changes in compaction force and speed. It was possible to detect concealed cracks in tablets by TPI and the results were validated by XμCT. While the combined acquisition and data processing time in TPI was about 30 to 45 min the process took several hours in XμCT with the same samples. By combining the data acquired with TPI on a set of model tablets of different density with a partial least squares calibration Palermo et al. were able to map density differences on the surface of tablets [95]. The increase in refractive index with increasing compaction force which was reported in the study by Palermo et al., based on tablets made from a mixture of four excipients, agree with the findings of Pore et al. which are based on single component compacts.

Ho et al. evaluated the applicability of TPI for understanding of process scale up [96]. 190 sustained-release tablets were sampled during the scale-up operation of a film coating process from the lab to the pilot scale and analysed by TPI. Dissolution testing was performed on the same tablets and the results from TPI analysis and dissolution testing were correlated. In terms of the amount of polymer applied, the traditional parameter that is used for process control and to assess the coating quality, no significant differences between the lab and pilot scale were found. However, the MDT of the pilot scale batch was twice as long compared to the lab scale batch. It was found that within a batch, variations in film layer thickness were most strongly correlated to the MDT. The significant difference in MDT between lab and pilot scale correlated to differences in film density as...
measured by TPI. The results of this study suggest that TPI not only can be used for the non-destructive evaluation of the film thickness but that the information obtained from the imaging experiment contains much more quantitative information on the physico-chemical properties of the coating that can be used to assess its quality.

Shen et al. showed examples of how the reflected terahertz pulses can not only be used to study the structure of a dosage form, but to investigate its chemical composition [97]. Using the reflection from a mirror as a reference, the absorption coefficient $\alpha$ and refractive index $n$ can be extracted from the sample reflection:

$$n(v) + i\frac{\alpha(v)}{4\pi v} = \frac{1 - P_s(v)/P_m(v)}{1 + P_s(v)/P_m(v)},$$

(2)

where $P_s(v)$ is the Fourier transform of the sample reflection and $P_m(v)$ is the reference reflection from the mirror. Shen et al. recorded the chemical distribution of lactose and sucrose over the surface of a sample pellet. It was possible to distinguish the chemicals and determine the spatial distribution of the composition within the samples.

Based on these results Cogdill et al. developed a more advanced signal processing technique for terahertz chemical mapping in real pharmaceutical tablets rather than a polyethylene matrix [98]. The tablets were direct compressed mixtures of MCC, lactose and theophylline. By using the terahertz maps of a set of calibration samples it was possible to build different multivariate models for quantitative image analysis. The quantitative models were tested using tablets made of two spatially separated segments of different mixing ratios. No comment was made with regards to the effective sampling depth in the imaging experiments.

The first three-dimensional chemical mapping experiment using pulsed terahertz radiation was performed by Shen et al. [99]. Using the example of a flat faced model tablet that contained well confined domains of lactose and tartaric acid the authors demonstrated how the spectral signature of the materials can be extracted non-destructively at depth (Fig. 16). A time-partitioned Fourier transform of the reflected terahertz waveform with a fixed window width was then employed to produce depth-resolved spectral components of the pulse [100]. While it was possible to extract the spectral information at depth in the sample tablet which was made of polyethylene, this material is almost transparent to terahertz radiation and thus not quite representative of a realistic pharmaceutical tablet.

In a next step Shen and Taday demonstrated the technique in a pharmaceutical excipient matrix [101]. This paper also contains a detailed description of the technique together with the underlying theory for the pulse propagation in a multilayered sample and data on the validation of the spatial resolution at different frequencies. From their experimental results Shen and Taday conclude that, in principle, TPI provides the necessary penetration depth and specificity for non-destructive chemical mapping in a three-dimensional matrix.

The spectral resolution at depth is influenced strongly by scattering and refraction caused by the tablet matrix and further work will be necessary to develop a robust method to routinely perform three-dimensional chemical mapping experiments. First steps have been made to address this issue [102]. So far, in the experiments by Shen et al. the sample only exhibited one layer of chemical at any point over the surface of the sample. To date no example has been published of a system where a sequence of multiple or overlapping layers was spatially resolved at depth. There are a large number of potential applications for this experiment in the context of pharmaceutical dosage forms: investigating the spatial distribution of different polymorphic forms in a dosage form as a result of compaction or coating, moisture uptake during storage of a tablet, drug stability over storage time in the final product, etc.

At present, the pulsed terahertz sources are not powerful enough to image entirely through large pharmaceutical dosage forms. Attenuation due to absorption and scattering limits the range of the terahertz pulse in tablets to about 2 mm [88]. With further developments in more powerful emitters it is quite possible that this limitation will be overcome within the next few years. With the terahertz pulse propagating through the dosage form twice in order to be detected, there is significant interaction with the dielectric over the path length. For the future development of TPI one challenge will be the incorporation of dispersion and diffraction effects into the data analysis. So far these effects are not accounted for and will have a strong impact on the reconstruction of the internal structure leading to distortions and increasing uncertainties at increasing depth or at interfaces with a strong curvature. For coating thicknesses below 150 µm, such as the typical film coating layer on a tablet, these effects are negligible, however, for the resolution of internal structure in layered tablets the effects will be significant.

4.3. Transmission Terahertz Tomography

In analogy to tomographic experiments with X-rays as discussed in section 2 it is possible to perform computed tomography at terahertz frequencies. To date, no example of applying this technology to pharmaceutical samples has yet been re-
ported. The following section gives an outlook of possible future developments in this field and a discussion of the limitations in the context of pharmaceutical dosage form characterisation.

4.3.1. Pulsed Setups

A good overview on tomography using pulsed terahertz systems is provided in the review by Wang and Zhang [103]. The first report of terahertz tomography by Ferguson et al. demonstrated the principle of a three dimensional terahertz transmission tomography experiment using the example of a turkey bone fragment [104].

In contrast to the reconstruction technique outlined in section 2.1, the frequency dependent absorption and phase shifts need to be considered for terahertz pulsed tomography. The analogous equation to Eq. S-7 in X-ray CT for terahertz tomography, gives the expression for the line integral of the parallel projection of the transmitted terahertz pulse \( P(\omega, \theta, l) \) as

\[
P(\omega, \theta, l) = P_l(\omega) \exp \left[ \int_{\alpha(\omega)} \frac{-i\omega \delta(x)}{c} dx \right]. \tag{3}
\]

where \( \omega \) is the frequency of the terahertz signal, \( \theta \) the projection angle, \( l \) the horizontal offset from the axis of rotation, \( L \) the straight line between source and detector (see Fig. 2A), and \( c \) the speed of light [104]. \( \delta = n + ik \) is the complex refractive index of the object along \( L \). Here, \( n \) denotes the real refractive index and \( k \) is the extinction coefficient. The absorption coefficient \( \alpha \) is related to the extinction coefficient as \( \alpha = (2\omega k)/c \). Without going into further details on the reconstruction of these complex datasets it is clear that this technology allows the extraction of additional information from the sample matrix. It is possible to reconstruct tomographic cross sections that represent the attenuation of a particular frequency component or to specifically enhance the contrast between interfaces based on their differences in real refractive index. The ability to use subtle differences in the refractive index of the sample for image contrast is very powerful as demonstrated in the previous subsection on TPI.

The increase in information content of the imaged object compared with X-ray CT due to phase sensitive detection and the use of a wide range of frequencies are significant advantages of terahertz tomography. However, the relative disadvantages are the much lower spatial resolution, strong dispersion and relatively weak light sources of terahertz CT compared to X\( \mu \)CT. Scattering effects in terahertz measurements also need to be fully understood and considered [102]. The data analysis is further complicated by the fact that the different frequency components in a broadband terahertz pulse have different spatial distributions in the beam profile and will therefore propagate through different volumes of the sample. Further research will have to explore the full potential of this technique and address the outstanding challenges before this technique can be widely applied.

4.3.2. Terahertz Quantum Cascade Lasers

Quantum cascade lasers (QCL) are a novel source of terahertz radiation which can provide high power terahertz radiation either at a single frequency [105] or at multiple frequencies [106]. Rather than lasing from the bandgap transition between the conduction and valence band, a QCL is a semiconductor laser that is lasing from transitions between sub-bands. In a QCL the conduction band is split into sub-bands by quantum confinement [107] and it is these so-called inter sub-band transitions that are used for lasing. The whole QCL device measures only a few millimetres and has the potential to be built very cheaply. Even though the development of THz-QCLs is in its early phase and the present designs require operation at temperatures below 160 K, the technology has already been employed for proof-of-principle tomographic imaging applications.

Nguyen et al. have used a THz-QCL operating at 2.9 THz combined with a Golay cell for detection in a CT setup analogous to that shown in Fig. 1A [108]. The pulse power of the THz-QCL was 70 mW (250 ns pulse duration, 80 kHz repetition rate). The results from this approach are very promising (Fig. 17), yet it remains to be seen whether it will be possible to resolve fine internal structures of less than 1 mm. The spatial resolution of the setup is limited by the diameter of the terahertz beam.

5. Optical Coherence Tomography (OCT)

The development of optical coherence tomography, a contact-free non-invasive imaging technology that can be applied to both transparent and turbid media, originates from optical coherence-domain reflectometry (OCDR). OCDR is an interferometry technique which was initially developed in order to detect defects in structures such as fibre-optic cables [109, 110]. Huang et al. developed the first OCT setup and

Figure 17: Tomography of a polystyrene phantom off a head using a THz-QCL. Visualisation of the reconstructed 3D image. A) The hole inside the phantom is revealed, B) the shape of the phantom is reconstructed, C) the top view shows the nose and cheek features. The data integration time was 15 minutes per image slice. (modified from [108]).
structures of the sample. These photons still exhibit coherence and can be detected by the interferometer. Interference between the sample and the reference mirror is observed when the optical path difference between the two arms of the interferometer is less than the coherence length of the source radiation. By scanning the reference mirror of the interferometer depth information from the sample is obtained (Figs. 18 and 19). In analogy to TPI (Sec. 4.2), in OCT the axial \((z)\) resolution is decoupled from the lateral resolution in the \(xy\) plane. The OCT measurement can be performed in the time-domain by moving the reference mirror but it is also possible to acquire the data in the frequency-domain. For frequency-domain OCT two main configurations are in use. In both cases the mirror is kept stationary. One method is to directly measure the spectrum at the detector while the alternative approach is to use a narrow bandwidth light source that can be rapidly swept over a broad frequency range instead of the broad bandwidth light source. In frequency-domain OCT significantly higher acquisition rates can be achieved with scan rates as fast as 5 MHz and no moving parts are required. The acquisition speed in time-domain OCT is similar to TPI for a single point measurement. In contrast to TPI however, 2D array detectors are available for OCT experiments, most commonly performed at near-infrared frequencies. Even though the data acquisition rates in frequency-domain OCT can be much higher than in time-domain the measurement is limited by the data processing time for the fast Fourier transform.

OCT is widely applied to study the microstructure of biological tissues. Depending on the tissue type, imaging depths between 1 mm and up to 2 cm with an axial resolution below 1 \(\mu m\) have been demonstrated. A review of the technology by Schmitt gives a summary of the technical aspects of OCT in biological tissues and the associated theoretical issues involved in imaging highly scattering tissues with partially coherent light [112]. Applications of OCT outside the biomedical field have been recently reviewed by Stifter [113].

To date, there have been no reported applications of OCT in the pharmaceutical literature. However, the results of varnish layer analysis on paintings and structural characterisation of ceramics and porcelain in art conservation imply that the technology should be in principle applicable to the film coatings on pharmaceutical dosage forms as well [114–117].

Wiesauer et al. demonstrated the high axial resolution that can be achieved by more advanced OCT configurations (so-called UHR-OCT, ultra-high resolution OCT) [118]. In contrast to standard OCT, here a Mach–Zehnder interferometer and a femtosecond laser is used rather than a Michelson interferometer and a cw source. The resolution and contrast that can be achieved on this setup was highlighted on samples of polymer film, wooden floor laminate and polymer foam (Fig. 20).

Kastner et al. have compared OCT and \(X\)-\(\mu\)CT for applications in non-destructive materials testing [119]. The study involved a comparison of the performance to resolve the internal structures in samples of fibre reinforced materials, polymer foams, composite floor panels, multilayered foils, the geometry of complex plastic shapes made by injection moulding and the dimensions of very fine holes in a polyamide phantom. While both techniques are suitable to study such materials it was concluded that the advantages of OCT were its higher resolution for contact free measurements of dimensions on surfaces of objects and in thin layers and its suitability for in-line applications in an industrial quality control context. The major advantages of \(X\)-\(\mu\)CT were the broad range of materials that can be studied with the technique and the ability to obtain a full 3D model of the object – in contrast to OCT which, as a reflection technique,
often cannot penetrate the whole object. Compared to TPI, OCT has a potentially higher axial and lateral resolution and can achieve faster data acquisition due to the availability of array detectors at near-infrared frequencies. However, OCT measurements at near-infrared frequencies, which is the frequency range in that the current equipment is almost exclusively operating in, is problematic for imaging pharmaceutical solid dosage forms. A number of very common excipients, such as titanium dioxide, are strongly absorbing in the near-infrared. In addition, the particle size of pharmaceutical formulations is often on a similar length scale as the wavelength in the near-infrared which will lead to very strong scattering and hence reduced signal in OCT. Even though the recent work in the field of non-destructive material characterisation is encouraging and provides some indications that OCT might be useful for the characterisation of pharmaceutical solid dosage forms, further work is required in order to evaluate the potential of this technique.

6. Conclusions

Modern in vitro tomography techniques can be employed to reveal unique insights into the structure and performance of pharmaceutical solid dosage forms, information which is not directly accessible by means of surface imaging techniques or measurements of bulk properties. The rich information content that can be extracted from tomographic experiments is crucial for the development of a better scientific understanding of how solid dosage forms work and how their quality and performance can be improved for optimal treatment of specific diseases and reduction of side effects. The developments in technology over the last two decades provide the scientists and engineers involved in both R&D and manufacturing with very powerful new tools that can improve the understanding and better development of robust processes to manufacture such solid dosage forms with consistent quality. All techniques are non-invasive and, with the exception of MRI, when using liquids to image indirectly the solid fraction, non-destructive. This is a big leap forwards in terms of understanding what processes are going on inside a dosage form during production, storage and dissolution. It makes a lot of the, often elaborate and time-consuming techniques — that were developed in attempts to infer these properties from indirect observations or by cutting the dosage form — redundant. Nebgen et al. provide a good overview of some of these techniques in the introduction of their seminal study [45]. The information contents accessible through the four techniques introduced in this review not only span a wide range of length and time scales but also very different specificity to changes in the chemical and physical characteristics of the sample.

There is little doubt that the invention of the tablet press and the subsequent patent on the ‘pill and lozenge’ press by William Brockedon in 1843 has revolutionised the quality, stability and convenience with respect to how medicine is administered to the patient [120]. While engineers were able to transform the production process of tablets within a few decades from the compaction of simple powder mixtures by local pharmacists to fully automated tabletting machines capable of producing up to 500 tablets per second on an industrial scale, the development of a thorough scientific understanding of the dosage form itself and how the API is released still eludes us. This difference in development of time-scales is not too surprising given the already existing state of the art in compaction engineering in other industries at the time compared to the scientific understanding of the dissolution of solids which was only emerging roughly at around the same time [121–123]. Further advances in the fundamental physical chemistry of disintegration and compaction were achieved over the last century, yet the lack of experimental techniques to study such processes not only in a simple powder but also directly in tablets themselves, optically opaque compacts of often quite chemically heterogeneous particles, limited the development of a better understanding of the dosage form. While in the past this imbalance could be tolerated to a certain extent [124], the quality requirements of today’s medicines and the economical costs associated with pharmaceutical production make it imperative to move on from the commonly employed empirical and indirect characterisation methods, such as weight gain during coating or the amount of released drug during dissolution testing, and aim at achieving a full understanding of solid dosage forms through scientific first principles which in turn can provide the solid foundation for process optimisation and control. Process understanding can only be developed when the formulation scientist and the process engineer both know how changes in formulation and processing conditions impact on the performance of the end product.

Pharmaceutical solid dosage forms are complex systems which provide a number of challenges with regards to their physical and chemical properties. In terms of physical dimensions, “[t]ablets made of compressed powders contain structure over length scales from ångströms, the interfaces between particles and the surrounding air or water, to many micrometers, the air voids and large particles, to millimetres, the size of individual tablets.” [29] The differences in length scales have a direct impact on the release characteristics of the dosage form: “For example, the rate of dissolution of the soluble component potentially depends on the dissolution rate at the interface between water and its crystalline particles; on its overall solubility and concentration-dependent diffusion constant; on any potential swelling of the insoluble matrix; as well as on structure on larger length scales, for example the porosity, which may well evolve with time.” [ibid.] Not only huge variations in length scales but also in time scales need to be accounted for. Modern
formulations are produced with a variety of different release kinetics. The time scales of dosage form disintegration and drug release can range between a few seconds in evanescent or sublingual tablets; a few minutes in immediate release; several hours in enteric coated dosage forms, sustained or controlled release tablets; and up to several months for subcutaneous implants. There is also some preliminary evidence in the literature that even for tablets where drug release is only observed after a few hours, much more rapid processes may contribute to the performance of the dosage form. Strübing et al. for example recently observed evidence for rapid water ingress into tablets coated with a sustained release barrier within a few minutes [125], however, the implications of this observation, which could be due to absorption of the dissolution medium into the open pore voids, are yet not understood. Apart from the challenges due to the vast range of length and time scales present, a number of changes in the physico-chemical properties of the drug and excipient molecules during processing, storage and contact with the release medium complicate the rational understanding of solid dosage forms: drug-excipient interactions, polymorphism, hydrate formation, crystallisation, supersaturation, precipitation, formation of complexes and other interactions of the drug or excipient molecules on the surface of the dosage form with molecules in the dissolution medium all have an effect on the performance of the medicine. In addition, the quality of the medicine is influenced by photo- and temperature induced chemical degradation during storage and many other factors that can only be assessed in the final dosage form.

Quantitative experimental observations of the solid dosage form and the changes induced by contact with the dissolution medium can form the basis for the development of reproducible \textit{in-vitro} dissolution models, which in turn would provide a robust platform for rational product development in the future. To date, a lot of knowledge is generated by understanding pure compounds and their bulk properties; however, a holistic approach that takes the whole dosage form into account is necessary to acknowledge the strong complexity on different physical and chemical levels as outlined above. The pharmaceutical scientist responsible for the formulation of the dosage form is likely to be confronted with a number of new techniques, such as the ones introduced in this review, and it is important to understand the basic physics behind tomographic techniques in order to make an adequate choice of which technique to employ, how to interpret the results and how to identify and eliminate artefacts in the measurements.

Table S.2 in the online supplementary materials gives an overview of the key characteristics of the different techniques. In comparison with the other techniques, the advantages of $X\mu$CT are in the high spatial resolution that can be achieved with this technique. In addition, X-rays are able to penetrate typical pharmaceutical samples easily and are not significantly scattered or refracted. The technique is very useful to study the microstructure of e.g. the tablet matrix and depending on the contrast of the images it can even be possible to quantify the pore size distribution. The major limitations of $X\mu$CT are due to the size restriction of the sample for high resolution measurements. Only fragments of samples with dimensions of up to $2 \cdot 2 \cdot 2 \text{ mm}^3$ can be imaged at the highest resolution. An additional restriction for the measurement of large objects is that the reconstruction algorithms require the whole area of interest to be present in the field of view at any time throughout acquisition of the different projection images. This requirement makes it impossible to select small volumes of a larger object to be imaged at high resolution. However, new developments in the instrumentation now allow larger objects to be imaged at high resolution using connected scans where the detector is moved and the field of view is extended. Such setups are able to image whole tablets for instance with an isotropic resolution of $2 \mu m$ by sequentially acquiring four connected scans, yet the acquisition time is then also four times longer than for a normal scan. The data processing and image reconstruction requires substantial computational resources. Using parallel computing strategies it is possible to process the acquired data on the time scale of a couple of hours. Besides the difficulties of imaging larger objects at high resolution, the contrast of the internal structure of solid dosage forms in $X\mu$CT is often not very strong. It is typically not possible to distinguish between API and excipient and hence the API distribution within the tablet matrix cannot be analysed. Further, the contrast between water and the tablet matrix is not very high which, together with the relatively long acquisitions times, limits the applicability of $X\mu$CT for \textit{in situ} dissolution studies. The lack in contrast is due to the very similar electron density of the different polymers, API and water.

To date, MRI is the most established technique for the characterisation of pharmaceutical solid dosage forms out of the four techniques introduced in this review. It has been mostly applied to study diffusion processes in matrix tablets, a field of research that emerged from previous applications of MRI in the materials science community to study diffusion in polymers. MRI has a unique ability to study transport processes and it is possible to perform \textit{in situ} imaging experiments of tablet dissolution. It has a high chemical sensitivity and at the same time is able to provide spatially resolved quantitative information from within the entire volume of any dosage forms of arbitrary geometry (as long as it fits into the imaging coil). This makes MRI potentially more powerful than $X\mu$CT, which has only low chemical sensitivity, and both terahertz imaging and OCT which may struggle to provide consistent image quality throughout the whole volume of a dosage form. Scattering losses or diffraction of the pulse of electromagnetic radiation used to perturb the magnetic field within the magnet, are both no problem for MRI experiments. MRI is different to the other techniques in that it typically images the aqueous phase surrounding and penetrating into the dosage form rather than the solid directly. A large variety of different properties can be imaged or emphasised by making use of the different pulse sequences that have been developed. MRI is the only technique of the four that provides strong contrast between the liquid and solid phase while the dosage form is immersed in an aqueous liquid. Some of the limitations of MRI are the sample size restrictions due to the dimensions of the magnet, the restrictions that result from the fact that no paramagnetic objects can be present in the magnet, and the relatively long image acquisition time required to acquire images with high resolution and high
signal-to-noise.
Compared to the other three techniques, terahertz tomography is the most recent development. Due to this disparity in development time not all aspects of the technology are fully exploited yet. The area of tomographic imaging through an entire dosage form using terahertz quantum cascade lasers is only at an experimental stage and only preliminary feasibility studies have been performed that show the great potential for this technology for the future. However, with respect to TPI and the area of structural imaging of pharmaceutical dosage forms there is one big exception where terahertz technology has matured much faster. While X\text{µ}CT, MRI and OCT were all developed in other research communities and only later introduced to the characterisation of pharmaceuticals, the pharmaceutical sciences have served as the core field for the development of TPI.

The role of pharmaceutics for the development of TPI is comparable to the biomedical field and the development of OCT. Commercial instrumentation that is specifically designed to image the coating structure over the whole surface of film coated tablets has been on the market for more than three years. Factors that limit the rapid development of novel applications for terahertz radiation in process research are its strong absorption by water, the need for more powerful sources, the lack of array detectors and waveguiding technology, and the limited understanding of the exact contrast mechanisms in terahertz imaging. More research is required into the fundamental physics of the interaction of terahertz radiation with matter. Effects such as strong scattering and diffraction of the radiation by the tablet matrix need to be investigated before the technology can be developed for routine tomography applications. In terms of the image acquisition speed terahertz imaging can be operated much faster than X\text{µ}CT and MRI. While the strong absorption of terahertz radiation by water can be a limitation of the technique when studying processes in an entirely aqueous environment, it is very advantageous for studying the interaction of solids with liquids as it provides excellent contrast between the two phases [126].

Of the four techniques discussed, OCT stands out in that it has not yet been applied for the characterisation of pharmaceutical solid dosage forms. However, based on the high resolution that can be achieved in the characterisation of the layer structure in plastic foil, the technique has a clear potential for future impact in the pharmaceutical field. The high axial resolution and the rapid data acquisition are major advantages of OCT. In order to overcome the problem of strong absorption by typical pharmaceutical excipients further developments in photonics are required to expand OCT into different frequency regimes. Most of the available instruments operate in the visible or NIR regions of the electromagnetic spectrum where strong scattering is taking place on the length scales of pharmaceutical solids and only low penetration of the solid dosage form can be achieved. While considerable advances in scattering theory have been made in the OCT research community, the technology will benefit from sources and detectors that are able to operate at lower frequencies. The low absorption of pharmaceutical excipients at terahertz frequencies would make OCT a particularly attractive technique to bring together high resolution, high penetration and strong contrast. However, such development will be far from trivial due to the coherence length characteristics of the currently available THz-QCL and the remaining challenges for the development of more powerful detectors.

This review highlights the rapid developments in the field of tomographic imaging techniques, how such techniques have already impacted in pharmaceutical research and development and what the potential of performing non-destructive three-dimensional imaging brings into pharmaceuticals. There is an increasing research activity into the characterisation of solid oral dosage forms by tomography and the research applications diversify both in terms of what techniques are applied and which problems are explored (Fig. 21). As with all solid state characterisation work, there is no one ideal technique to solve all problems but we hope that this review gives a good insight into the basic working principles of the different types of tomographic approaches and provides some rational as to which techniques to chose for a specific sample.

Acknowledgements

The authors would like to acknowledge Ms Gentiana Shiko and Ms Ya Ying Chen for help with the literature review and both the RCUK Basic Technology Programme and St Gobain plc for funding.

References


\[ I_{\theta,l}(d) = I_0 \exp[-\mu_{\theta,l}d], \quad (S-1) \]

where \( I_{\theta,l} \) is the attenuated intensity at angle \( \theta \) and horizontal offset from the axis of rotation \( l \), \( I_0 \) is the source intensity, \( \mu \) is the absorption coefficient and \( d \) is the thickness of the object. Any additional losses e.g. due to scattering are omitted for simplicity. The absorption coefficient can also be expressed in terms of mass attenuation which reflects explicitly that the attenuation of the beam is directly dependent on the number of atoms along \( d \)

\[ I_{\theta,l}(d) = I_0 \exp\left[-\left(\frac{\mu_{\theta,l,0}}{\rho_{0,0}}\right)\rho_1 d\right], \quad (S-2) \]

here \( \rho_1 \) is the real local density, \( \mu_{0,0} \) is the normal absorption coefficient and \( \rho_{0,0} \) the normal density of material \( i \). In mixtures of different chemicals along \( d \) the absorption coefficient is the sum of the local absorption coefficients

\[ \mu_{\theta,l}(d) = \sum_i \left(\frac{\mu_{\theta,l,0}}{\rho_{0,0}}\right)\rho_i. \quad (S-3) \]
Consequently, for a monochromatic beam propagating along \( \mathbf{L} \) the intensity at position \( L \) is attenuated by \( \mu(L) \) and the Beer-Lambert law for monochromatic radiation can be written as
\[
I_{\alpha} = I_0 \exp \left[ -\int \mu_\alpha(L)dL \right]. \tag{S-4}
\]

In addition to the attenuation of the intensity, which is the squared amplitude of the electric field, the phase of the propagating electromagnetic wave also changes due to refraction. However, the change in phase has no effect on the image reconstruction in this type of computed tomography as the detectors used for these experiments are not generally phase sensitive. There has been recent progress in the development of phase sensitive tomography but this area is outside the scope of this review as, so far, it has not been applied to the tomography of pharmaceutical dosage forms.

The central problem in CT is to resolve the spatial variation of \( \mu \) based on the line integrals of \( \mathbf{L} \) at varying angles \( \theta \) and horizontal offsets from the axis of rotation \( l \),
\[
\int \mu_\alpha(L)dL = \ln(I_0/I_\alpha). \tag{S-5}
\]

As Eqn. S-5 shows, in mathematical terms the attenuation of the radiation due to the interaction with the sample object is a line integral. The projection of the object is the set of line integrals along \( l \) at each rotation angle \( \theta \) (Fig. S.2).

A mathematical reconstruction algorithm forms the basis of all tomographic imaging techniques. Early work by Radon, the so-called Radon-transform [127], and later work by Cormack including a proof-of-concept study [128] and others [129] implementing mathematical image reconstruction algorithms formed the basis for the first successful tomographic experiments with \( \gamma \)- and X-rays [130], the subsequent introduction of the first commercially available CT scanner by Hounsfield [131] and the 1979 Nobel prize in Physiology or Medicine for Hounsfield and Cormack “for the development of computer assisted tomography”.

For the reconstruction the projections at different angles through the object of interest are used. In general, the projections over the whole range of 180° are required, even though reconstruction is possible with less data using more advanced methods. A number of different approaches can be used to achieve the reconstruction of the image: iterative reconstruction, backprojection, Fourier-based approaches, and the filtered backprojection technique. The most widely used reconstruction method is the filtered backprojection algorithm where Fourier filter techniques are applied prior to the backprojection step.

For the case of parallel rays that propagate along a straight line \( L \) between source and detector the line integral \( P_\theta(l) \) for each projection at angle \( \theta \) and horizontal offset from the axis of rotation \( l \) (see Fig. S.2A) can be written as:
\[
P_\theta(l) = \int_{\theta,0} f(x,y)ds \tag{S-6}
\]
\[
P_\theta(l) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x,y)\delta(x \cos \theta + y \sin \theta - l)dxdl \tag{S-7}
\]

The function \( P_\theta(l) \) is the Radon transform of the function \( f(x,y) \) (Fig. S.2B). The matrix of all projections over \( \theta = 0 \) to 180° is referred to as the sinogram (Fig. S.2C). To reconstruct the object based on \( P_\theta(l) \) the projection is initially Fourier transformed
\[
S_\theta(w) = \int_{-\infty}^{\infty} P_\theta(l)e^{-j2\piwl}dl. \tag{S-8}
\]

In the next step the inverse Fourier transform of the product of \( S_\theta(w) \) and a filter function \( T(w) \) is calculated. The filter function is used to filter out statistical noise and improve the signal-to-noise (SNR)
\[
Q(x \cos \theta + y \sin \theta) = Q(l) = \int_{-\infty}^{\infty} S_\theta(w)T(w)e^{-j2\piwl}dw. \tag{S-9}
\]

\( Q(l) \) is then backprojected into the space domain in order to reconstruct the original object \( f(x,y) \) (Fig. S.2D-E).

\[
f(x,y) = \int_{-\infty}^{\infty} Q(x \cos \theta + y \sin \theta)dl. \tag{S-10}
\]

1.2. Magnetic Resonance Imaging
1.2.1. Introduction to Nuclear Magnetic Resonance

In the presence of \( B_0 \) the nuclear spin energies of all nuclei in the sample with a non-zero nuclear spin quantum number (such as \( ^1\text{H}, ^1\text{C}, ^19\text{F} \) ) become non-degenerate, which means that they split into different energy states. This phenomenon, called the Zeemann effect, forms the basis for NMR experiments. For a nucleus such as hydrogen, which exhibits only two different spin energy states (+1/2 and −1/2), the nuclear spin can either align to precess with the field or opposite to the field. The energy state that corresponds to an alignment parallel with the field has a slightly lower energy compared to the spin aligned opposite (or anti-parallel) to the field. The distribution of spins between the two states follows the Boltzman distribution and as a consequence of the very small energy difference between the spin states at room temperature compared to \( kT \) only a small excess in the number of spins are in the ground state, aligned with the field, at equilibrium. This makes spectroscopic observations difficult, as a difference in populations between ground state and excited state is required to measure the transition between the states. However, with increasing field strength of \( B_0 \) the energy gap between the states increases linearly and with it the excess population of the lower energy level – which explains the advantage of performing NMR experiments with stronger magnetic fields \( B_0 \). The alignment of the nuclear spins in the static magnetic field leads to the formation of a net magnetisations vector \( \mathbf{M}_s \) along the field \( B_0 \). The magnitude of \( \mathbf{M}_s \) is directly proportional to the number of resonant spins in the sample.

The equilibrium magnetisation vector associated with the nuclear spin system can be perturbed by pulses of electromagnetic radiation that are generated in coils within the static magnetic field. When the photon energy \( E = h\omega \) of an excitation pulse with a frequency component \( \omega_0 \) matches exactly the energy difference between the states, photons are absorbed from the lower
Figure S.2: The sample object and corresponding projections at different angles using the plane-parallel collimated source setup. A) Sample object orientation, B) corresponding absorption of the object which is linear to the spatial dimensions of the object. C) Sinogram obtained from projections at 1° increments over the range of θ = 0 to 180°. D) Reconstruction of the image using filtered backprojection based on the four projections shown in A) and B). Note that the lines cross at points corresponding to the edges of the sample object. E) Reconstruction using the projection of the range of θ = 0 to 180° at 1° increments. F) Reconstruction using the projection of the range of θ = 0 to 180° at 1° increments.
energy state (spins precessing parallel to $B_0$) to the higher energy state (spins precessing anti-parallel to $B_0$):

$$\Delta E = \omega_0 = \gamma B_0,$$

(S-11)

where $\gamma$ is the gyromagnetic ratio, which is takes a specific value for each nucleus. For hydrogen the gyromagnetic ratio is highest, which is the reason for the particular attraction to study hydrogen nuclei in NMR studies. The excitation photon energy falls in the radio frequency (r.f.) range of the electromagnetic spectrum. After a finite time photons are re-emitted by transition of the nuclear spin system to the lower energy state. When the aligned nuclei are perturbed by a pulse of r.f. radiation, they are subject to a torque on their magnetic moment and start to precess about the direction of $B_0$ in the $xy$ plane at a frequency called the Larmor frequency (which equals $\omega_0$). During the return to equilibrium conditions, the precession of the nuclei leads to the induction of a voltage in the receiver, an additional coil around the sample, which is measures as the NMR signal.

Beyond the mere discrimination of different isotopes by their Larmor frequency, NMR has very high chemical sensitivity. The precise splitting of the energy levels for the different nuclei of the same isotope in a molecule is influenced by its electronic environment. Rather than a single energy, and hence resonance frequency, the energies of the different nuclei in the sample exhibit a subtle shift relative to the nominal level depending on the molecular structure or chemical environment. This variation is called the chemical shift and forms the basis of NMR spectroscopy.

Further information on the physico-chemical properties of the sample can be extracted from NMR experiments by quantifying the time it takes for the bulk magnetisation in the sample to return to equilibrium after excitation, a process called relaxation in NMR terminology. Two different relaxation processes are commonly used to characterise a sample: the time it takes the net magnetisation to build up along the field $B_0$ in the $z$ direction (called $T_1$, spin-lattice or better longitudinal relaxation time) and defined as $dM_z/dt = (M_z - M_0)/T_1$; and the time it takes for the magnetisation in the $x$ and $y$ directions to decay to zero (referred to as $T_2$, spin-spin or transversal relaxation time), defined as $dM_{xy}/dt = -M_{xy}/T_2$.Again, the exact details of these processes and the underlying quantum mechanics would be far beyond the scope of this review and the reader is referred to introductory texts on the topic such as the excellent texts by Levitt [132] and Keeler [133].

From a technical perspective, NMR experiments are usually carried out by placing the sample in the static magnetic field of a superconducting magnet. Commercial equipment is available with magnetic field strengths up to 22.31 T (this is equivalent to an resonance frequency of 950 MHz in the case of the hydrogen nucleus). The sample is positioned at the centre of the homogeneous magnetic field inside the bore that runs through the magnet. For the perturbation from equilibrium r.f. pulses are applied using oscillating currents in one or more coils around the sample inside the magnet. After excitation, the induced NMR signal is typically measured by the same coil which then acts as a receiver. The NMR signal, which is measured in the time-domain and is also referred to as the free induction decay (FID), is then separated into its frequency components by Fast Fourier transformation.

A good overview of applications of NMR spectroscopy in a pharmaceutical context is provided by the reviews by Holzgrabe et al. [134], Harris [135] and Geppi et al. [136].

1.2.2. Overview of the Pharmaceutical Applications of MRI

Tab. S.1 provides a summary of the research published on the analysis of pharmaceutical solid dosage forms by MRI.

1.3. Additional Figures

This section provides additional figures to supplement the illustration of the article.
Figure S.5: Automatically measured three-dimensional surface model of a tablet used for TPI mapping. The terahertz waveforms are acquired for the data points highlighted as black dots starting from the centre of the tablet. The projections plotted in red show the trajectories of the scan over the surface of the tablet. Alternatively the terahertz waveforms can also be acquired in a point-to-point raster over the surface of the tablet.

1.4. Comparison Between the Different Tomographic Techniques

Tab. S.2 provides a comparison of the different tomographic techniques discussed in the review.
Table S.1: Overview of the publications applying MR imaging techniques to characterise solid dosage forms. All studies use $^1$H except where stated. The field strength of the magnet is given as the corresponding $^1$H resonance frequency. MRI methods are referred to as follows: FLASH fast low angle shot; SE spin-echo imaging sequence; SPI single point imaging; MSS multi-slice sequence, number in brackets refers to the number of slices imaged simultaneously; PFG pulsed field gradient; PGSE pulsed gradient spin echo; RARE rapid acquisition with relaxation enhancement; PGSTEBP pulsed field gradient-stimulated echo sequence with bipolar gradients. Details of the sample and its dimensions are referred to as: CAPP capsule plug, ETAB elongated tablet, EXT extrudate, IMP implant, PEL spherical pellet, TAB circular tablet; $d$ specifies the diameter of the sample $t$ is the corresponding sample thickness or length.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Magnet / MHz</th>
<th>Experiment / sample</th>
<th>Details of MRI method</th>
<th>Sample / mm</th>
<th>Slice thickness (axial resolution)</th>
<th>In-plane (lateral resolution)</th>
<th>Acquisition time</th>
</tr>
</thead>
<tbody>
<tr>
<td>[45]</td>
<td>300</td>
<td>porosity imaging of tablets penetrated by gadolinium-doped silicon oil; different excipients were compared and cracks and delamination was studied in layered / compression coated tablets</td>
<td>3D-SE</td>
<td>TAB, $d$: 12, $t$: 7</td>
<td>654-95 $\mu$m</td>
<td>327-95 $\mu$m</td>
<td>4-4.5 h</td>
</tr>
<tr>
<td>[46]</td>
<td>500</td>
<td>qualitative study on the hydration of HPMC tablets; tablets were immersed in water for different time intervals; imaging was performed after taking tablets out of water</td>
<td>2D-SE</td>
<td>TAB, $d$: 5, $t$: 2.9 to 3.3</td>
<td>650 $\mu$m</td>
<td>100 $\mu$m</td>
<td>2 min</td>
</tr>
<tr>
<td>[47]</td>
<td>500</td>
<td>samples and methodology of immersion similar to [46]; measurement of self-diffusion coefficient and $T_2$ weighted images; imaging of hydrated tablet loaded with insoluble particles and API</td>
<td>2D-SE</td>
<td>TAB, $d$: 5</td>
<td>650 $\mu$m</td>
<td>70 $\mu$m</td>
<td>2 min</td>
</tr>
<tr>
<td>[48]</td>
<td>400</td>
<td>hydration of HPC tablets; determination of the water penetration rate; correlation of the MRI results to dissolution testing; water penetration is not the only rate-limiting step in drug release from hydrophilic matrix system</td>
<td>2D-SE</td>
<td>CAPP, $d$ &lt; 6.5</td>
<td>2 mm</td>
<td>78 $\mu$m</td>
<td>4.25 min</td>
</tr>
<tr>
<td>[49]</td>
<td>500</td>
<td>hydration of HPMC and poly(vinyl alcohol) (PVA) tablets; $T_2$ weighted images; PVA forms a gel that restricts the movement of water molecules stronger than the HPMC gel</td>
<td>2D-SE</td>
<td>TAB, $d$: 6, $t$: 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[50]</td>
<td>200</td>
<td>extruded monolithic zero-order release kinetics implant; first fully quantitative MRI study; water concentration profiles, transport kinetics and weight uptake; characterisation of the liquid in polymer by $T_2$ maps</td>
<td>2D-SE</td>
<td>IMP, $d$: 1.2, $t$: 1 mm</td>
<td>32 $\mu$m</td>
<td>12.5</td>
<td>1 h</td>
</tr>
<tr>
<td>[51]</td>
<td>500</td>
<td>samples and methodology of immersion similar to [46]; measurement of spatial distribution of self-diffusion coefficient and $T_2$ relaxation times in gel layer; water mobility was found to differ between tablets with different degrees of polymer substitution; gradient of water mobility across the gel layer</td>
<td>2D-SE</td>
<td>TAB, $d$: 5</td>
<td>650 $\mu$m</td>
<td>100 $\mu$m</td>
<td>2 min</td>
</tr>
<tr>
<td>[52]</td>
<td>200</td>
<td>in situ quantitative study of water and polymer concentration measured simultaneously in a sample of poly(ethylene oxide); quantitative measurement of the swelling kinetics; use of deuterated water to discriminate hydrogen atoms in the polymer from nuclei of the water</td>
<td>1D-SE / 1D-$T_1$</td>
<td>TAB, $d$: 2.7, $t$: 3</td>
<td>500 $\mu$m</td>
<td>29 $\mu$m</td>
<td>4 min$^1$</td>
</tr>
<tr>
<td>[53]</td>
<td>400</td>
<td>qualitative imaging study of the erosion of the drug containing compartment of a dry coated controlled release tablet; dissolution was performed in simulated gastric fluid in USP apparatus II</td>
<td>2D-SE</td>
<td>TAB, $d$: 12.5</td>
<td>900 $\mu$m</td>
<td>80 $\mu$m</td>
<td></td>
</tr>
<tr>
<td>[54]</td>
<td>400</td>
<td>NMR spectroscopy experiments on HPMC in aqueous solution; in situ study on the hydration of HPMC tablets with only one tablet face exposed to water</td>
<td>1D-SE</td>
<td>TAB, $d$: 12.8, $t$: 1.3-2.7</td>
<td>156 $\mu$m</td>
<td>3 min$^2$</td>
<td></td>
</tr>
<tr>
<td>[55]</td>
<td>400</td>
<td>short communication about the influence of trapped air in a compact of HPMC on the MR imaging experiments; vacuum treatment method in order to get rid of any air in the tablet medium</td>
<td>2D-SE</td>
<td>TAB, $d$: 12.8, $t$: 1.4</td>
<td>300 $\mu$m</td>
<td>70 $\mu$m</td>
<td>2.5 h</td>
</tr>
<tr>
<td>[56]</td>
<td>200</td>
<td>measurement of the dimensional changes in hydroxypropylcellulose tablets of different polymer grades upon hydration; $T_2$ measurements and self-diffusion coefficient</td>
<td>2D-SE</td>
<td>TAB, $d$: 10</td>
<td>5 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^1$per image, 30 min for the whole sequence
$^2$per image, 30 min for the whole sequence
<table>
<thead>
<tr>
<th>Paper</th>
<th>Magnet / MHz</th>
<th>Experiment / sample</th>
<th>Details of MRI method</th>
<th>Sample / mm</th>
<th>Slice thickness (axial resolution)</th>
<th>In-plane (lateral resolution)</th>
<th>Acquisition time</th>
</tr>
</thead>
<tbody>
<tr>
<td>[57]</td>
<td>500</td>
<td><em>in situ</em> dissolution of PVA tablets of varying molecular weight polymer grades; solvent concentration and diffusion-weighted profiles are acquired; reptation at the interface between glassy and rubbery polymer during dissolution</td>
<td>1D-SE</td>
<td>TAB, d: 4.2, r: 2</td>
<td>28 µm</td>
<td>40 s (^3)</td>
<td></td>
</tr>
<tr>
<td>[58]</td>
<td>500</td>
<td><em>in situ</em> dissolution of PVA tablets; theoretical polymer dissolution model; solvent concentration and diffusion-weighted profiles are acquired</td>
<td>1D-SE</td>
<td>TAB, d: 4.2, r: 2-2.5</td>
<td>29 µm</td>
<td>see [57]</td>
<td></td>
</tr>
<tr>
<td>[59]</td>
<td>200</td>
<td>Measurement of water distribution in lipid/MCC extrudates processed at different speed and different water content in the formulation (40-45% m/m); samples were placed in hermetically sealed tube; no dissolution medium was added, the extrudates were measured as such</td>
<td>1D-SE</td>
<td>EXT, d: 2, r: 8</td>
<td>78 µm</td>
<td>109 µm</td>
<td>10 h</td>
</tr>
<tr>
<td>[60]</td>
<td>400</td>
<td>First experiment of <em>in situ</em> qualitative measurements of drug dissolution in a custom designed flow through cell (USP apparatus IV); hydration of HPMC tablets; dissolution of controlled release tablets similar to [53] and osmotic pump tablets</td>
<td>2D-SE</td>
<td>TAB, d: 8.8, r: 1.7</td>
<td>500 µm</td>
<td>100 µm</td>
<td></td>
</tr>
<tr>
<td>[61]</td>
<td>400</td>
<td>Drug release upon hydration of HPMC tablets loaded with two F containing model API; (^1)H/(^19)F study; (^1)H imaging as in [55]; quantitative (^19)F 1D images; strong differences in the kinetics of the drug diffusion out of the tablet matrix were observed and explained in terms of the API diffusion coefficient and its relation to the tablet matrix expansion</td>
<td>1D-SE</td>
<td>TAB, d:12.8, r: 1.3</td>
<td>200 µm</td>
<td>22-86 min</td>
<td></td>
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<tr>
<td>[62]</td>
<td>600</td>
<td>Drug release from different formulations of API loaded lipid matrix pellets; ingress of dissolution solution; diffusion measurements using PGSE sequence</td>
<td>2D-SE</td>
<td>MSS (8)</td>
<td>250 µm</td>
<td>22 µm</td>
<td>60 min</td>
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<td>[63]</td>
<td>200</td>
<td>3D imaging of the distribution of liquid within the pellets</td>
<td>3D-SE</td>
<td>PEL, d: 0.8-0.10</td>
<td>47 µm</td>
<td>47 µm</td>
<td>49 h</td>
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<tr>
<td>[64]</td>
<td>300</td>
<td>Quantitative imaging experiment of the liquid concentration, T2 distribution and self-diffusion coefficient within poly(glycolic lactic acid) controlled release drug delivery system</td>
<td>2D-PFG-SE</td>
<td>CYL, d: 1.3</td>
<td>500 µm</td>
<td>78 µm</td>
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<tr>
<td>[65]</td>
<td>300</td>
<td>Disintegration of immediate release tablets under static conditions using a very fast image acquisition pulse sequence; disintegration kinetics measured by image analysis of MR images</td>
<td>SPI, FLASH</td>
<td>TAB</td>
<td>2 mm</td>
<td>0.5 s</td>
<td></td>
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<tr>
<td>[66]</td>
<td>300</td>
<td>Swelling and water uptake of high-amylose starch (0.7 amylose : 0.3 amylopectin, gelatinised and cross-linked) tablets; depending on the temperature different swelling and diffusion behaviours were observed</td>
<td>2D-SE</td>
<td>TAB, d: 8.6, r: 2.7</td>
<td>500 µm/78/59 µm</td>
<td>35 min</td>
<td></td>
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<tr>
<td>[67]</td>
<td>300</td>
<td>Dimensional changes and amount of water uptake in different sized tablets similar to [65]</td>
<td>2D-SE</td>
<td>TAB, d: 4.8-8.6, r: 1.2-2.7</td>
<td>78 µm</td>
<td>35 min</td>
<td></td>
</tr>
<tr>
<td>[68]</td>
<td>400</td>
<td>Dissolution study of coated pulsatile release capsules; release is triggered by swelling hydrogel plug; the reasons for the failure of one coating formulation in dissolution testing was evaluated against samples of a well performing formulation</td>
<td>2D-SE</td>
<td>CAP, d:7.6, r: 18.4</td>
<td>500 µm</td>
<td>50 µm</td>
<td>3-8 min</td>
</tr>
<tr>
<td>[69]</td>
<td>200</td>
<td>3D imaging of the porosity of a tablet; using a vacuum pump tablet was saturated with inert poly(dimethyl) siloxane prior to imaging; 2D self-diffusion maps were acquired; tablets were imaged before dissolution and after partial dissolution; the effect of different compression forces on the porosity was compared</td>
<td>3D-SE</td>
<td>TAB, d: 46, r: 19-21</td>
<td>195 µm</td>
<td>195 µm</td>
<td></td>
</tr>
</tbody>
</table>

\(^3\)for each 1D profile, diffusion images were acquired in 6 min

Continued on next page
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<td>[69]</td>
<td>100</td>
<td>quantitative measurement of the polymer concentration during the hydration of tablets made of different cellulose ether polymers (hydroxyethylcellulose, hydroxypropylcellulose and two different grades of HPMC); $T_1$ weighted images</td>
<td>2D-SE</td>
<td>TAB; $d$: 12, $r$: 4.3-5</td>
<td>3 mm</td>
<td>200 $\mu$m</td>
<td>4 min</td>
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<tr>
<td>[70]</td>
<td>300</td>
<td>swelling and water diffusion was studied in samples of high amyllose starch tablets; while swelling was anisotropic, the diffusion process was almost isotropic; the effect of temperature on the swelling and diffusion was studied (see also [66])</td>
<td>2D-SE</td>
<td>TAB; $d$: 9.1, $r$: 3.7</td>
<td>1 mm</td>
<td>156 $\mu$m</td>
<td>8.5 min</td>
</tr>
<tr>
<td>[71]</td>
<td>400</td>
<td>placebo tablets made of MCC were immersed with mineral oil; MRI signal was calibrated for density using flat faced disks of known density; density distribution in tablets of different shape was measured by MRI</td>
<td>2D-SE</td>
<td>TAB, $d$: 9, $r$: 6-9; eTAB, $d$: 8, $r$: 4</td>
<td>500 $\mu$m</td>
<td>40 $\mu$m</td>
<td>1 h</td>
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<tr>
<td>[29]</td>
<td>400</td>
<td>study into the formation of air bubbles during hydration of Eudragit polymer tablets loaded with API; MRI results are compared to X\textmu CT</td>
<td>2D-SE</td>
<td>TAB, $d$: 9, $r$: 3</td>
<td>1 mm</td>
<td>29 - 188 $\mu$m</td>
<td>34 min</td>
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<tr>
<td>[72]</td>
<td>400</td>
<td>samples similar to [29]; water penetration into the tablets is studied experimentally and the results are compared to a mathematical dissolution-diffusion model that is sensitive to particle size</td>
<td>2D-SE</td>
<td>TAB, $d$: 9, $r$: 3</td>
<td>1 mm</td>
<td>29 - 375 $\mu$m</td>
<td>9 min</td>
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<tr>
<td>[73]</td>
<td>300</td>
<td>investigation of the pore structure evolution in pellets during dissolution; pellets were made of lactose and MCC and the porosity of the pellets with and without API was studied; $T_2$ derived pore size distribution; surface to volume ratios, tortuosity and pore ratios were quantified over immersion time</td>
<td>PGSTEBP</td>
<td>PEL, $d$: 1-2</td>
<td>n/a</td>
<td>n/a</td>
<td>5 min</td>
</tr>
<tr>
<td>[74]</td>
<td>400</td>
<td>water uptake and swelling in tablets made of mixtures of high-amylose starch and API; self-diffusion coefficient weighting; drug loading accelerated the kinetics of tablet hydration in both cases of API studied; evidence for the formation of a membrane in the starch matrix during dissolution was found, findings agree with X\textmu CT study [30]</td>
<td>2D-SE</td>
<td>TAB, $d$: 8.8, $r$: 3</td>
<td>500 $\mu$m</td>
<td>117 $\mu$m</td>
<td>17 min</td>
</tr>
<tr>
<td>[75]</td>
<td>100</td>
<td>porosity measurement of tablets made of three different excipients (MCC, lactose and anhydrous calcium phosphate) compressed at different pressures; tablets were immersed in silicone oil prior to the measurement; measurement of self-diffusion coefficient perpendicular and parallel to compression axis</td>
<td>PGSTE</td>
<td>TAB, $d$: 8.8</td>
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<tr>
<td>[76]</td>
<td>20</td>
<td>qualitative characterisation of the internal structure of film-coated floating tablets during dissolution augmenting the measurements of the floating strength</td>
<td>2D-SE</td>
<td>TAB, $d$: 11</td>
<td>10 mm</td>
<td>312.5 $\mu$m</td>
<td>10 min</td>
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<tr>
<td>[77]</td>
<td>200</td>
<td>dissolution study of capsules formulated from HPMC and L-dopa using an in situ flow through cell in a horizontal magnet; experiments in simulated gastric fluid</td>
<td>2D-SE</td>
<td>CAP, $d$: 7.7</td>
<td>35 mm</td>
<td>137 $\mu$m</td>
<td>5-10 min</td>
</tr>
<tr>
<td>Technique</td>
<td>µCT Acquisition time</td>
<td>MRI Acquisition time</td>
<td>TPI Data acquisition time</td>
<td>THz tomography Data acquisition time</td>
<td>OCT Data acquisition time</td>
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<tr>
<td>X-ray CT</td>
<td>5-20 min (10 · 10 · 10 µm³ resolution)</td>
<td>5-60 min</td>
<td>40 min</td>
<td>120-300 min</td>
<td>10 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>20-80 min (5 · 5 · 5 µm³ resolution)</td>
<td>20-80 min</td>
<td>5-10 min</td>
<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
<td>1-4 h</td>
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<td></td>
</tr>
<tr>
<td>TPI</td>
<td>480-960 min (2.5 · 2.5 · 2.5 µm³ resolution)</td>
<td>480-960 min</td>
<td>60-120 min (5 · 5 · 5 µm³ resolution)</td>
<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
<td>1-4 h</td>
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<td></td>
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<tr>
<td>THz tomography</td>
<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
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<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
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<tr>
<td>OCT</td>
<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
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<td>1-4 h (2.5 · 2.5 · 2.5 µm³ resolution)</td>
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</tr>
</tbody>
</table>

Data processing time

30-60 min (5 · 5 · 5 µm³ resolution) | < 1 min | 1-10 min | 1-10 min |

Spatial resolution

1.3 · 1.3 · 1.3 µm³ to 5 · 5 · 5 µm³ instrument dependent | 20-1000 µm³ to 5 · 5 · 5 µm³ | 150 · 150 µm² lateral, 30 µm axial | 0.5 to 2 mm axial | axial 1 > z > 10 µm¹³

Maximum sample size

at maximum resolution 1-2 mm, using connected scans | 5 mm to 30 cm³ | 21 mm | no data available | n/a¹³

Contrast mechanism

electron density | change in optical constants (mainly refractive index) | change in optical constants (mainly absorption coefficient) | change in optical constants (mainly refractive index) |

Chemical sensitivity

low sensitivity due to very similar electron densities of API, excipients and water | high | high | high | low |

Continued on next page

¹to cover the entire volume/surface of a tablet (10 mm diameter, 5 mm thick)

²The acquisition time includes the time that is required to build a 3D model of the tablet. When scanning multiple tablets of the same dimensions the acquisition time for subsequent tablets is half of stated time.

³It is also possible to image only select areas of the tablet in much shorter time intervals.

⁴This is an estimate, as there is no equipment on the market that is capable of automatically scanning all surfaces of the tablet using connected scans it is possible to image larger objects

⁵single PC workstation, dual core processor

⁶Data processing can be performed on clusters. Algorithms are currently under development that will allow a dramatic reduction in reconstruction time down to less than 30 min at 2.5 · 2.5 · 2.5 µm³ resolution

⁷Two offset camera positions and two levels of scanning along the short axis of the object are required to achieve this resolution. The scanning and reconstruction time increase by a factor of 8 compared to 2.5 · 2.5 · 2.5 µm³ resolution.

⁸the voxel size is usually not isotropic

⁹depending on the instrument configuration; the lateral spatial resolution is diffraction limited and depends on the frequency of the light source used for the experiment

¹⁰the maximum sample size is restricted by the diameter of the magnet bore and the coil used for the experiments. 89 mm refers to a typical bore in a 500 MHz system while 30 cm refers to an 85 MHz system. See Tab. S.3 for details

¹¹the maximum sample size at maximum resolution 1-2 mm, using connected scans is possible to image larger objects

¹²probe head can be applied to samples of arbitrary shape. No equipment is commercially available that can image pharmaceutical dosage forms in a fully automated fashion
**Table S.2 – continued from previous page**

<table>
<thead>
<tr>
<th>Technique</th>
<th>X(\mu)CT</th>
<th>MRI</th>
<th>TPI</th>
<th>THz tomography</th>
<th>OCT</th>
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<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>– high resolution</td>
<td>– chemical specificity</td>
<td>– strong contrast</td>
<td>– strong contrast in pharmaceutically relevant excipients</td>
<td>– very fast acquisition</td>
<td></td>
</tr>
<tr>
<td>– no limitations on sample geometry</td>
<td>– in situ dissolution studies are possible</td>
<td>– high dynamic range</td>
<td>– imaging through entire dosage form is possible</td>
<td>– good spatial resolution and extremely high axial resolution</td>
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</tr>
<tr>
<td>– high penetration power</td>
<td>– quantitative technique</td>
<td>– chemical sensitivity</td>
<td>– potential for 3D chemical imaging</td>
<td>– real time imaging is possible</td>
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<tr>
<td></td>
<td>– ability to study flow and diffusion processes</td>
<td>– wide range of imaging sequences is available to specifically emphasise certain properties of the sample</td>
<td>– it is not possible to image through a whole tablet</td>
<td>– point mapping techniques, no array detectors available yet</td>
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<tr>
<td></td>
<td>– strong contrast in pharmaceutically relevant excipients</td>
<td>– difficult reconstruction due to scattering and diffraction effects</td>
<td>– experimental technique</td>
<td>– strong absorption and scattering at currently available imaging frequencies (NIR)</td>
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<td></td>
<td>– strong contrast in pharmaceutically relevant excipients</td>
<td>– point mapping techniques, no array detectors available yet</td>
<td>– further developments in source and detector technology required</td>
<td>– point mapping techniques, no array detectors available yet</td>
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<tr>
<td></td>
<td>– quantitative technique</td>
<td>– scattering and refraction effects</td>
<td>– point mapping techniques, no array detectors available yet</td>
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**Limitations**

- Long acquisition and data processing time
- Poor contrast between typical pharmaceutical matrix and water
- Only some solids can be imaged directly; the experiments are usually destructive as they require the interaction of a liquid phase with the sample
- Operation of strong magnetic fields requires special safety precautions
- Restricted sample size in magnetic more
- Paramagnetic materials (such as most metals) have to be eliminated from the sample setup
- Commercial availability

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<tr>
<td>Commercial availability</td>
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<td>yes</td>
<td>yes</td>
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Additional References in the Supplementary Information


