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NMR imaging of density distributions in tablets

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Abstract

This paper describes the use of ^{1}H nuclear magnetic resonance (NMR) for 3D mapping of the relative density distribution in pharmaceutical tablets manufactured under controlled conditions. The tablets are impregnated with a compatible liquid. The technique involves imaging of the presence of liquid which occupies the open pore space. The method does not require special calibration as the signal is directly proportional to the porosity for the imaging conditions used. The NMR imaging method is validated using uniform density flat faced tablets and also by direct comparison with X-ray computed tomography. The results illustrate (1) the effect of die wall friction on density distribution by compressing round, curved faced tablets using clean and pre-lubricated tooling, (2) the evolution of density distribution during compaction for both clean and pre-lubricated die wall conditions, by imaging tablets compressed to different compaction forces, and (3) the effect of tablet image on density distribution by compressing two complex shape tablets in identical dies to the same average density using punches with different geometries.
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Keywords: NMR imaging; Tablet; Compaction; Density distribution; Die wall friction

1. Introduction

Die compaction is a unit operation employed in pharmaceuticals, powder metallurgy, ceramics and other industries. During compaction complex movement takes place within the powder bed and interactions occur between the powder and tooling, i.e. die wall and punch faces. As a result distinct density patterns develop in the volume of the compact due to the combined effect of the main contributing factors (Sinka et al., 2003) such as: compaction behaviour of powder, friction between powder and die wall and powder and punches, geometry of die and punches, sequence of punch motion, and initial conditions of the powder before compaction, which relate to the state of the powder in the die after filling. The density distribution in tablets is important because it affects the local material properties, which in turn can influence the bioavailability of the drug and the mechanical properties of the tablets.

Density measurements in powder compacts have been carried out since the early 1900s as reviewed by Train (1957) and include techniques based on differential machining, hardness tests or X-ray shadow of lead grids placed in the compact. Macleod and Marshall (1977) have presented autoradiography experiments using ceramic compacts possessing natural radioactivity and the density distribution patterns were discussed in the context of die wall friction. Various experimental procedures have been used for characterising the density distribution in compacts made of a wide range of powders, including pharmaceutical materials (Hersey and Train, 1960; Kandeil and De Malherbe, 1977; Sixsmith and McCluskey, 1981; Charlton and Newton, 1985; Ozkan and Briscoe, 1996; Sinka et al., 2003; Eiliazadeh et al., 2004). More modern techniques available to characterise compact microstructure were reviewed by Lannutti (1997) and include X-ray CT which was also applied to characterise density distributions (Sinka et al., 2004) and defects (Wu et al., 2005) in pharmaceutical tablets.

Nuclear magnetic resonance imaging has been applied to characterise the internal structure of various materials, such as: ceramic samples, composite materials, extruded gel pastes, and tablets (Ellingson et al., 1987, 1989; Götz et al., 2002; Mantle et al., 2004; Nebgen et al., 1995).

The objective of this paper is to present the NMRI method for generating quantitative relative density maps for pharmaceutical tablets and examine the effect of tablet geometry and die wall friction on the relative density distribution at various

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stages during compaction. The relative density is defined as RD = 1 − ϕ where ϕ represents the porosity.

2. NMR imaging method

NMR imaging is an inspection technique which provides cross-sectional images in planes through a component. The theory of nuclear magnetic resonance is well documented in texts on the subject (Callaghan, 1991) and is summarised as follows. Nuclear magnetic resonance occurs when nuclei possessing a magnetic moment μ are placed in an external magnetic field B_0, and irradiated with radio-frequency (RF) radiation B_1 perpendicular to B_0. Nuclei having a magnetic moment also possesses 'spin', a form of angular momentum characterised by the spin quantum I which for the hydrogen nucleus is equal to 1/2. When a sample containing nuclei with a magnetic moment is placed in a static magnetic field B_0 (pointing along the laboratory z-axis), the nuclear moments populate themselves between two distinct energy levels. The population difference between these two levels is governed by the Boltzmann distribution (Harris, 1986) and gives rise to a net magnetisation vector $\mathbf{M}_0 = (\mathbf{i}M_x, \mathbf{j}M_y, \mathbf{k}M_z)$. Transitions between these two energy levels may then be induced by irradiating the system with electromagnetic irradiation whose frequency is proportional to the difference of the energy level spacing:

$$\Delta E = \gamma h B_0 = h\omega_0 \quad (1)$$

where γ is the gyromagnetic ratio for ^{1}H, h is Planck's constant and ω_0 is known as the Larmor frequency. In modern NMR spectroscopy and imaging a pulse of electromagnetic radiation in the RF region is used to perturb the distribution of spins between the two energy levels. After the pulse, an RF NMR signal is detected as the equilibrium distribution between the two levels is restored. The time dependence of the signal is then monitored from which a frequency spectrum is obtained via Fourier transformation. A single sharp line in the frequency domain results if the sample contains a single proton chemical species, e.g. water. Key parameters with this technique are the spin–lattice relaxation time T_1, the spin–spin relaxation time T_2 of the sample, and the strength of the magnetic field gradient B_0, determining the image resolution, contrast, and measuring period.

NMR relaxation time has an important effect on the imaging process. T_1 is the characteristic time for the build-up of magnetic polarization of a nucleus, and directly affects the rate at which data can be accumulated from successive acquisitions of NMR signals during the production of an image. It therefore controls the total time to acquire an image and the signal-to-noise (*S*/*N*) ratio achieved per unit time. T_2 is the characteristic time for the decay of the transverse precessing magnetic moment which is detected as the NMR signal. T_2 affects the achievable spatial resolution and *S*/*N* ratio. Long T_2s are desirable, and are found in compounds which have minimal spin–spin coupling and which form non-viscous solutions. T_2 should be significantly greater than the echo time TE in order to avoid limiting spatial resolution and *S*/*N* ratio.

3. Materials and tablet preparation

3.1. Tablet compression

The tablets were compressed using a press where the bottom punch was stationary with respect to the die. Round and capsule shaped tablets were manufactured from microcrystalline cellulose (grade Avicel PH102, manufactured by FMC BioPolymer, Cork, Ireland). The nominal mean particle size of the powder is 100 μm and the full density of the material is 1520 kg m^{-3}. The bulk density of the powder is around 300 kg m^{-3}.

The characteristics of the round tablets are presented in Table 1. The tablets were compressed using curved faced tooling having a cup radius of 8.03 mm, which is commonly referred to as deep concave tooling. In order to generate snapshots of density distributions at various stages of compaction, series of tablets were compacted to different compaction forces.

The effect of friction between powder and tooling was examined by compressing tablets using clean and pre-lubricated tooling as follows:

- In order to achieve high friction between powder and tooling the die and punches were degreased prior to compaction: this is referred to as "clean" tool condition.
- In order to achieve low friction the die and punches were preconditioned by compressing pure magnesium stearate (a common pharmaceutical powder lubricant): this is referred to as "lubricated" tool condition.

In order to study the effect of geometry for complex shape tablets, two tablets were compressed in identical dies using tooling with different cup geometries. The top surfaces of the tablets had different break-lines while on the lower surfaces the letters

Table 1
Characteristics of round tablets

Tablet	m (g)	D (mm)	H (mm)	Compression force (N)	RD	Condition
NMR_01	0.314	8.78	9.11	500	0.435	Clean
NMR_02	0.324	8.78	7.88	1000	0.533	Clean
NMR_03	0.320	8.76	6.59	2000	0.655	Clean
NMR_04	0.320	8.76	6.08	3000	0.724	Clean
NMR_05	0.320	8.77	7.68	1000	0.543	Lubricated
NMR_06	0.327	8.76	6.01	3000	0.751	Lubricated
NMR_07	0.335	8.74	5.59	4950	0.845	Lubricated

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