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Evaluating the role of lactose anomeric composition in tablet disintegration and dissolution: a hidden variable in pharmaceutical formulation

Thamer Alzoubi,[a,b] Gary P. Martin,[a] Kendal Pitt,[c] Hetvi Triboandas,[c] Fangyi Chen,[a] Abhimata Paramanandana[a] and Paul G. Royall [ID] *[a]

Lactose, a chiral excipient, is widely used in the pharmaceutical industry as a diluent because it is safe and has developable physical properties. However, there are stability issues; β lactose powder stored at 40 °C/ 75% RH will epimerize from the β to the α chiral form within 7 days. The influence of lactose chiral composition on medicine stability is poorly understood but is likely to be valuable when ensuring the safety and effectiveness of the finished pharmaceutical product (FPP). Therefore, the aim of this study was to investigate the effect of the anomeric composition of lactose on tablet properties. Tablets with a higher α lactose content (79.5/20.5 α/β % w/w (α79%)) demonstrated faster disintegration times when compared to tablets formulated with a higher β content (13.5/86.5 α/β % w/w (α13%)), *i.e.*, 27 s compared to 220 s. Differences in tablet hardness ($p \leq 0.05$) were also observed, with tablets containing a higher α composition exhibiting higher hardness (*i.e.*, 207 N as opposed to 170 N under a 40 kN compression force). The release of acetylsalicylic acid was found to be faster from tablets that were formulated with 'aged' or epimerised lactose (α79%) compared to those produced using β lactose, as received (α13%), the respective T_{90} values being 60 and 91 min. To conclude, it is apparent that the stereoisomeric effects of lactose excipients on tablets are evident, and therefore, the measurement of anomeric content is advised prior to tablet manufacture.

1. Introduction

Ensuring the safety and quality attributes of finished pharmaceutical products is essential for maintaining therapeutic performance throughout their shelf life. While the influence of active pharmaceutical ingredients on product stability is well recognized, the role of excipients remains comparatively underexplored. Excipients are often considered inert; their physicochemical properties are selected to optimise the dosage form, for example, tablet hardness, disintegration, and dissolution, thereby influencing drug bioavailability.[1,2] Regulatory guidelines acknowledge that excipient characteristics impact formulation performance, yet stereochemical variability in chiral excipients is rarely addressed.[3,4]

Lactose is one of the most widely used excipients in solid dosage forms, primarily as a diluent.[5] This excipient is chiral

and has two stereoisomers. It exists as two anomeric forms, α and β, which differ in solubility, crystallinity, and propensity to form hydrates.[6] These anomers can interconvert under certain manufacturing and storage conditions, such as elevated temperature and humidity, leading to changes in the α/β ratio.[7,8] For example, anhydrous β-lactose stored at 40 °C and 75% relative humidity undergoes epimerization to the α form within seven days, with a reported half-life of approximately 32 days.[9] Despite the prevalence of lactose in pharmaceutical formulations, the implications of its anomeric composition for tablet performance have received little attention. Current compendial standards do not specify limits for anomeric content, and manufacturers typically do not quantify this parameter, even though variability between batches is common.[10] For instance, lactose powders labelled as α-lactose monohydrate may contain up to 6% w/w β-anomer, while β-lactose samples may include up to 5% w/w α-anomer.[9–12]

The subtlety of this stereochemical effect represents an overlooked source of variability in formulation performance. Previous studies have compared tablets composed of pure α or β lactose, but systematic evaluation across a range of anomeric ratios is lacking.[8,13–16] This study addresses this gap by investi-

[a]*Institute of Pharmaceutical Science, King's College London, London SE1 9NH, UK.*
E-mail: paul.royall@kcl.ac.uk
[b]*Department of Pharmaceutical Sciences, College of Health Sciences, PAAET (Public Authority for Applied Education and Training), Kuwait*
[c]*Leicester School of Pharmacy, De Montfort University, Leicester LE1 9BH, UK*

gating the impact of lactose anomeric composition on key tablet properties, including disintegration, hardness, and drug release. Tablets formulated with a higher α-lactose content (79.5% α/20.5% β w/w (α79%)) demonstrated markedly faster disintegration times (27 s) compared to those with a higher β-lactose content (13.5% α/86.5% β w/w (α13%)), which disintegrated in 220 s. Differences in tablet hardness were also observed (207 N *versus* 170 N at 40 kN compression force), and acetylsalicylic acid release was faster from tablets containing epimerized lactose (T_{90} = 60 min) compared to those formulated with β-lactose as received (T_{90} = 91 min), Fig. 1.

The aim of this paper was to evaluate the role of lactose anomeric composition in tablet disintegration and dissolution, highlighting the complexity of common excipients used in pharmaceutical formulations. Lactose powders with defined α/β ratios were formulated into tablets and characterized using thermal and non-thermal analytical techniques, followed by compendial physical testing. The findings highlight the importance of monitoring anomeric composition as a critical quality attribute in pharmaceutical manufacturing.

2. Methods

2.1 Sample preparation

Lactose powder samples with four different ratios of α-anomer contents were used as specified in Table 1. Lactose samples II and III were produced as described previously,[9] and powder batches of anhydrous β lactose (α13) (ACROS Organics (80% β and 20% α labelled content), Lot A0416062, Germany), α lactose monohydrate, α·LMH (Sigma Aldrich (≥99% α labelled content, L3625, Lot SLBX8370, USA)) and microcrystalline cellulose (MCC) (Alfa Aesar, UK, Lot 10227760) were used as received. Each lactose batch (I, II, III and IV) was placed inside a 50 mL plastic container (2.5 cm diameter and 6.5 cm height) along with 4% w/w MCC. The container was filled to less than half the volume, and the contents were mixed for 15 min using a Turbula® mixer (Glen Creston, Stanmore, UK). Each container contained 3.3 g of total powder weight, which was sufficient to produce 10 tablets + a 10% overage, to allow for possible powder loss during tablet production.
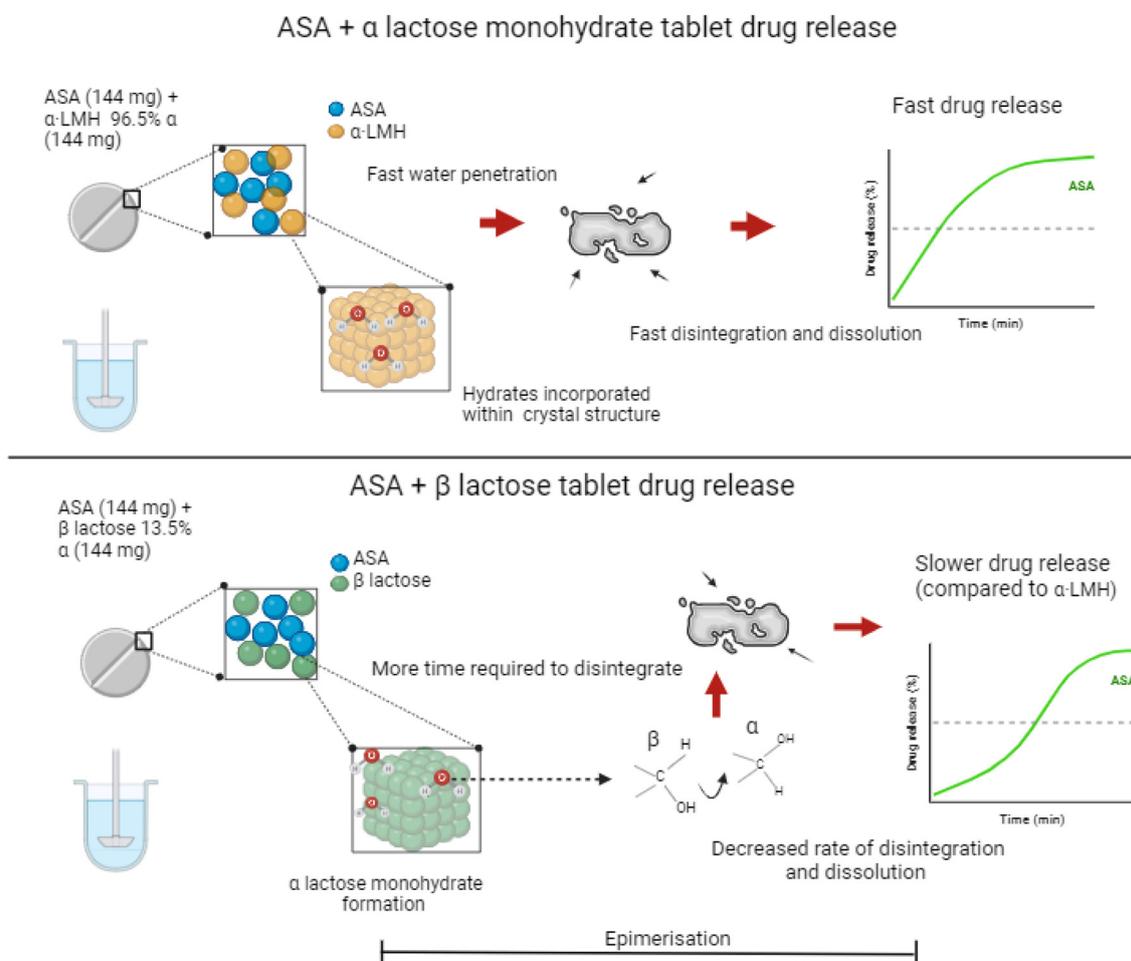

Fig. 1 The proposed hypothesis illustrating the difference in the mechanism of disintegration and dissolution of tablets containing ASA + α lactose monohydrate, α·LMH 96.5/3.5% α/β (α97%) and ASA + anhydrous β lactose, 86.5/13.5% β/α (α13%), created with BioRender.com. Epimerisation proceeds as water penetrates the ASA + β lactose tablet, converting β lactose to α·LMH.

Table 1 The anomeric composition (α/β) of the lactose powders used in tablet manufacture with a summary of the applied stress conditions and time that were necessary to induce the epimerisation to the received lactose sample. The full methods, characterisation, and statistical differences have been reported previously[9]

Lactose powder	α-Anomer content (% w/w)	β-Aanomer content (% w/w)	Designation	±SD (%)	Applied modifications
I (anhydrous β-lactose)	13.5	86.5	α13%	0.4	As received
II	50.2	49.8	α50%	0.1	35 days storage (40 °C/75% RH)
III	79.5	20.5	α79%	0.3	60 days storage (40 °C/75% RH)
IV (α-lactose monohydrate)	96.6	3.4	α·LMH	0.7	As received

2.2 Tablet production

Tablets were prepared individually using a manual hydraulic press (PerkinElmer, UK) by adding 300 mg (weighed using a Sartorius electronic balance to the nearest 0.001 mg) of each lactose/MCC mixture into a 10 mm (diameter) die punch which was assembled using alignment plates. Each tablet was flat in shape with a 10 mm diameter and 3 mm thickness (for further visual description, refer to SI 1). Four different batches of tablets were produced containing different anomeric content as specified in Table 1 under 3 different compression forces. Apart from the anomeric differences, all tablets were manufactured under the same conditions. For each batch of tablets, the compression forces used were 10, 20 and 40 kilo Newtons (kN). Upon reaching the designated force, the pressure valve was opened, minimizing dwell time. The die and punches were lightly lubricated with magnesium stearate, after the production of every 10 tablets using a small application brush.

2.3 Tablets for ASA dissolution

Tablets were produced as described in section 2.2 but comprising of a 1 : 1 weight ratio of aspirin (ASA) (Lot A0334368, Acros Organics) and lactose powders (α·LMH as received, α13, α50 and α79% α anomer) combined with 4% w/w MCC (i.e., 12 mg per tablet). Each tablet contained 144 mg of ASA, and every tablet weighed a total of 300 mg.

2.4 Appearance and dimensions

Each tablet produced was visually examined for unusual characteristics. These included changes in colour, shape and chipping of tablets. The average dimensions (diameter and height) of 3 randomly selected tablets taken from every batch were recorded using a digital calliper (Duratool, Taiwan). No more than 10% deviation was deemed acceptable as per the previous study criteria.[17]

2.5 Weight uniformity

Each tablet was carefully weighed using an electronic balance (to the nearest 0.1 mg) prior to testing. The mean weight (±SD) for each batch was calculated (Table S2) with no more than 5% deviation from the average weight being acceptable for any tablet.[18]

2.6 Thermal analysis

2.6.1 Differential scanning calorimetry. Tablets were crushed using a mortar and pestle (n = 6) until the composite powder was generated, and the composition was analysed ≤10 min of post-crushing. DSC 2500 (TA Instruments, USA) was calibrated with indium, tin and lead (TA instruments, USA). All DSC analyses followed the method described previously.[9] All tablets were left for a 24 h post-production period before conducting the analysis.

2.6.2 Thermogravimetric analysis (TGA). Mass loss measurements of the tablets were performed following crushing and mixing as described in section 2.6.1. A thermogravimetric analyser (TGA Q500, TA Instruments, USA) was employed to measure the loss of mass between 80 and 160 °C, and this was taken to be indicative of the loss of water of hydration. The sample preparation and analysis method followed those reported in an earlier study.[9]

2.7 Nuclear magnetic resonance

Sample preparation and the method for measurement of anomer composition were described previously.[9] ASA + lactose tablets (n = 6) were dissolved in DMSO + 0.03% TMS (tetramethylsilane) % v/v (VWR Chemicals, USA, Lot: 210020 Batch: 0121D) and analysed 24 h after preparation using 5 mm Wilmad NMR sample tubes (Batch: 112619A). Each sample was analysed in triplicate (n = 3).

2.8 Hardness testing

Hardness testing was conducted in accordance with the methods detailed in the BP (2001)[19] and USP (2012).[20] 10 individual tablets were weighed to ensure uniformity of weight, and each, in turn, was placed in the compartment of a C50 hardness tester (Engineering Systems, Nottingham, UK). Between measurements, the jaws of the instrument were brushed to remove any residual powder or fragments. The weight (kg, converted to Newtons) causing each tablet to break was recorded. This procedure was repeated for each of the 10 tablets (n = 10) that had been prepared using 3 different compression forces (10, 20 and 40 kN) and for tablets containing lactose with different anomeric content (Table 1). The mean, minimum and maximum results for each test batch were recorded.

2.9 Disintegration

Disintegration testing was carried out (DTG 4000, Copley Scientific, Nottingham, UK) in accordance with BP (2021) and USP (2019) testing procedures.[21] For each batch of tablets, 6 separate tablets were carefully placed inside individual open-

ended tubes (height: 75 mm, diameter: 25 mm). The tubes were enclosed within a water bath containing 800 mL of purified water at 37 °C, which served as the disintegration medium. The vertical frequency of the tubes was 30 cycles per min, and the disintegration time for each tablet was recorded as the time at which the last fragment of the tablet was lost through the mesh at the base of each tube. No plastic disks were employed in any of the tubes, in accordance with the specifications of the compendial monograph.[21]

2.10 Scanning electron microscopy

A self-adhesive carbon disc was applied to an aluminium stub. Lactose-only tablets were broken in half manually, placed on a carbon disc and coated with a 5 nm gold layer. Samples were examined using Phenom ProX software, version 4.6.4 (Thermo Scientific, USA) at a voltage of 10 kV and applying a full back-scattered electron detector.

2.11 Dissolution, UV and RI analyses

2.11.1 Lactose-only tablets. *In vitro* dissolution testing was conducted using paddle apparatus 2 (USP, 2011) fitted to a 708-DS dissolution apparatus (Agilent Technologies, Inc., USA). The vessels were filled with 900 mL of water for HPLC as dissolution media. The temperature was maintained at 37 ± 0.5 °C, and the paddle was rotated at 50 ± 0.5% rpm. Sampling cannulas were fitted with 10-micron external filter tips (Lot 110AJD821-10K, Quality Lab Accessories, USA). The tablets were produced as described in section 2.2, using powders α13 and α79 only. The compression pressure was 20 kN ($n = 6$ for each batch). Each tablet was subjected to the tests as described in sections 2.4 and 2.5. The samples from the dissolution testing were collected into HPLC vials using a fraction collector (Agilent, serial number MY19380089) and analysed using an HPLC-Refractive Index (RI) detector. After removal of every sample (1.5 mL), the medium was replaced with the same amount of water for HPLC. The samples were collected at 1, 5, 10, 15 and 20 min, and the dissolution procedure was carried out 6 times for each tablet batch. The HPLC vials containing the released lactose were then measured using the method described in section 2.11.3 to measure the % release of lactose.

2.11.2 Dissolution of tablets containing ASA. Tablets produced as described in section 2.3 were tested for dissolution using the procedure and instruments outlined in section 2.11.1 but using 0.1M HCL as the dissolution medium. However, the dissolution apparatus in this case was equipped with a UV spectrophotometer (Cary 60, Agilent Technologies, Inc., USA), and single-reading absorbance measurements were recorded at a wavelength of 265 nm. Sampling points were at min 1, and then at 5 min intervals up to 120 min, to obtain a comprehensive dissolution profile. Measurements were conducted on 6 tablets from each batch ($n = 6$). A calibration curve was constructed by UV analysis using the same spectrophotometer at concentrations of 1, 5, 10, 20 and 40 µg mL^{-1} ASA, using 0.1 M HCL as a solvent (pH 1.2). Absorbance was measured at a wavelength of 265 nm using Scan software

(Agilent Technologies, Inc., USA). Each calibration sample was analysed in triplicate ($n = 3$).

2.11.3 Quantification of lactose using HPLC-refractive index. HPLC analysis was performed using a 1260 Infinity II HPLC system (Agilent, USA) equipped with a refractive index detector (RID) and a C-18 column (150 × 4.6 mm, 5 µm). The mobile phase comprised 100% water for HPLC (Lot 2352724). The sample injection volume was 50 µl, and the flow rate was established at 0.5 mL min^{-1} flow rate with the binary pump pressure set at 0.4 bar. The column and RID temperatures were set at 50 °C. Lactose solution samples were prepared by dissolving 20 mg of the powder in 50 mL of water for HPLC and diluting this solution to produce 400, 200, 100, 50, and 10 µg mL^{-1} lactose solutions to enable the construction of a calibration curve. Under these conditions, the lactose was eluted with a retention time (RT) of 3.4 min. The analysis was identically repeated for α·LMH and α13 powders to investigate possible differences in RT or peak area. Two calibration curves were therefore constructed. Once it was established that the anomeric content did not interfere with the RID ability to detect total lactose or affect R_t, then the method was used to quantify lactose at each dissolution time-point, and it was removed as described in section 2.11.1.

2.12 Similarity dissolution factor (f_2)

A model-independent approach using the similarity factor (f_2) was implemented, also known as the fit factor method,[22] to verify the changes in dissolution profiles. This approach is recommended by the USP and FDA[19,23] and is summarised in eqn (1) as follows:

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

where n is the number of dissolution time points, R_t is the reference (*i.e.*, tablets incorporated with as received β lactose) cumulative percentage dissolved at the selected n time (t) points, and T_t is the test sample (tablets containing stored lactose) cumulative percentage dissolved at the selected time points. As standardised by the FDA, for the dissolution profiles to be considered similar or equivalent curves and performance, the f_2 value must fall between 51 and 100. Should the f_2 value be 0–50 then it can be considered that no similarities exist between the curves.[24] Therefore, the higher the value, the more similar the performance of the drug (a value of 100 corresponds to identical performances). Overall, 6 time points were used, and no more than 1 measurement above 85% was employed.

2.13 True density and porosity

The true density (g cm^{-3}) and pore volume (cm^3 g^{-1}) of the powder were obtained using a helium pycnometer (Micromeritics, US). Prior to analysis, the chamber O-ring was gently greased using Dow Corning® high vacuum grease (Micromeritics Instrument Corporation, USA) to prevent gas leakage. Each powder sample was weighed (1.6 ± 0.1 g) inside

the 3.5 cm^3 chamber insert (AccuPyc™ Multi-Volume Calibration Standard, Micromeritics, US). The samples were subjected to 10 helium gas purges followed by 10 gas pressure cycles (19.5 psig cycle fill pressure). True density and pore volume were calculated by taking the average of the 10 cycles. Each sample was analysed in triplicate (AccuPyc II, Version 4.0 software, Micromeritics, USA).

2.14 Statistical analysis

To determine statistical differences in the data, un-paired Student's *t*-tests were applied using Microsoft Excel 2016®. The level of significance was determined, and a significant difference was accepted if *p* was ≤0.05.

3. Results

The results section begins with the properties of the prepared tablets and lactose powders to evidence that they were suitable to explore the complexity of lactose's anomeric composition and its effect on disintegration and dissolution. A minimum of 4% w/w microcrystalline cellulose (MCC) was mixed into all lactose powders before tableting to act as a binder and prevent lamination, which had been observed in tablets containing high levels of β-lactose without MCC[25,26] (SI S1).
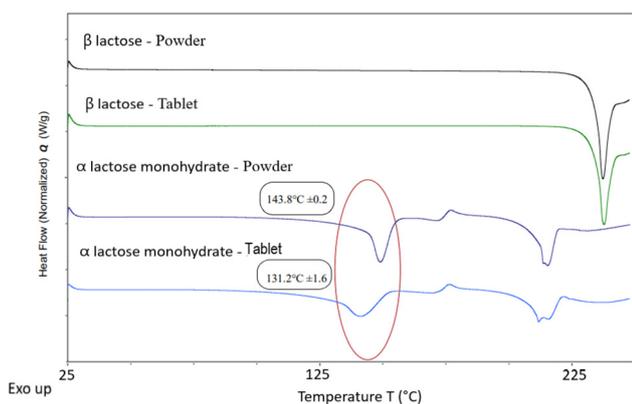

Fig. 2 DSC curves of BL powder (β lactose as received, α13%), β lactose tablet (α13%), α·LMH powder (α·LMH as received α97%) and α·LMH tablet (*n* = 3). NB: normalised heat flow was 0 at the beginning of each run. All samples contained 4% w/w MCC.

3.1 Anomeric composition and tablet properties: weight uniformity, thermal behaviour and hardness

The tablets produced complied with compendial BP specifications for weight uniformity, remaining within the acceptable range of 95–105%, with the exception of two that were only slightly outside this limit. All tablets were entirely within the specified range for dimensions (SI S2). H^{1}NMR and DSC analyses recorded no alteration in the anomeric content of lactose following tableting, indicating that tablet compression did not influence the anomeric composition of the original lactose powders (SI S4, Fig. 2 and Table 2). No changes in melting points were observed; however, the onset temperature for hydrate release from tablets containing α·LMH was significantly lower (*p* ≤ 0.05) than that of the uncompressed powder. Water loss from α·LMH occurred at 143.8 ± 0.2 °C in the powder and 131.2 ± 1.6 °C in the tablets (highlighted in red in Fig. 2, and supported by the TGA results, SI S3).

Hardness measurements further highlighted the complex influence of anomeric content on the properties of tablets containing lactose (Fig. 3a). For example, at a compression force of 20 kN, the hardness of tablets comprising β lactose (as received α13%) and α·LMH (as received α97%) was 123 ± 21 N and 78.8 ± 10.4 N, respectively (*p* ≤ 0.05) (SI S5). Differences in hardness were also seen for tablets prepared using β lactose powders that had been stored for different lengths of time at 40 °C/75% RH (Table 1). These batches of lactose powders contained different ratios of the α and β anomers and allowed investigation of tablets which contained 13% α anomer, 50% α anomer and 79% α anomer as determined by H^{1}NMR (Table 1). At a compression force of 20 kN, the hardness of the tablets increased from 122.9 ± 21 to 142.1 ± 6 N, as the α anomer content increased from 13% to 79% (*p* ≤ 0.05). At 40 kN compression force, α13% and α79% exhibited hardness properties of 170.2 ± 16 and 207.4 ± 19 N, respectively (*p* ≤ 0.05). Lactose powders, α·LMH as received (α97%), and α·LMH stored at 40 °C/75% RH for 35 days (α98%) and 60 days (α98%), respectively, were also used to produce tablets. There were no significant differences between the hardness of the tablets produced using any of these lactose samples (SI S5).

3.2 Disintegration

Higher compression forces produced harder tablets, which prolonged disintegration time. However, among tablets compressed at the same force, variations in anomeric composition

Table 2 Thermal and chemical analysis of different anomeric forms (β-lactose and α·LMH, as received), *n* = 3 (±SD). To determine the peak integration and temperature values, the limits were set at 220–247 °C for β-lactose samples and 120–160 and 200–220 °C for α·LMH

Sample	Loss of hydrate (°C)	Enthalpy of hydrate loss (J g^{-1})	Melting point (°C)	Enthalpy of melting (J g^{-1})	αAnomer content (%)
β-Lactose powder	—	—	235.1 ± 0.3	122 ± 8.75	13.5 ± 0.4
β-Lactose tablet	—	—	233 ± 0.6	121.3 ± 5	14.5 ± 0.7
α-LMH powder	143.8 ± 0.2*	150.24 ± 12.2	213.7 ± 1.5	77.02 ± 3	96.6 ± 1.5
α-LMH tablet	131.2 ± 1.6*	139.9 ± 11.6	211.7 ± 0.9	82.6 ± 3.2	97.1 ± 0.1

* Indicates a statistical difference (*p* ≤ 0.05) between the powder and tablet.
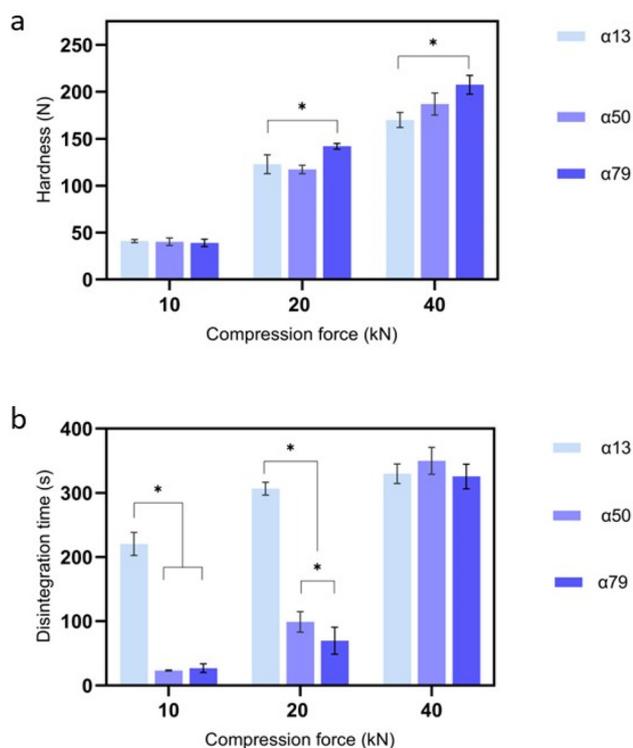
Fig. 3 The hardness properties (a) and disintegration times (b) of tablets containing three different ratios of lactose anomers (produced after timed storage of the received β lactose, α13%, at 40 °C/75% RH). The β lactose powder (as received) was stored for 35 and 60 days to obtain powders with the increased α-contents (*i.e.*, α50% and α79%, respectively). The powders were subsequently used to make tablet batches. The tablets were prepared by different compression forces: 10, 20 and 40 kN. Error bars represent SD between samples (*n* = 10 for hardness and (*n* = 6) for disintegration). Significant differences between batches are marked by * ($p \leq 0.05$).

influenced disintegration time (Fig. 3b). For example, tablets produced with β lactose (α13%) were found to disintegrate in 220.4 ± 18 s compared to tablets containing α50% and α79%, where both disintegrated markedly faster ($p \leq 0.05$) in 23.5 ± 1

and 27.8 ± 6.4 s, respectively (Table 3). In contrast, when comparing the hardness properties of these three batches of tablets (which were identical other than in the different anomer contents of lactose), no change in hardness was observed (Fig. 3(a), at a compression force of 10 kN). However, α79% containing tablets produced at 20 kN demonstrated higher crushing strength compared to β lactose (α13%) tablets but considerably shorter disintegration times, and therefore, tablet hardness was not directly correlated with disintegration time, when compression forces of 10 and 20 kN were applied.

When a 40 kN compression force was applied, there were no differences in disintegration times between the batches of tablets that contained lactose of different anomeric compositions. A similar investigation was conducted using tablets of α·LMH stored under conditions identical to the former lactose tablet batches. Table 3 shows the time taken for every batch to disintegrate. No differences ($p > 0.05$) were observed in the disintegration times of tablets containing α·LMH, after the tablets were stored under higher humidity.

3.3 Dissolution

3.3.1 Dissolution of lactose-only tablets. The dissolution of lactose-only tablets was examined to understand the effect of anomeric content on lactose release without the inclusion of API, using tablets produced with α13% and α79%. Initially, two calibration curves were constructed using HPLC-RI for α13% and α·LMH (α97%) for comparison purposes with R^2 values of 0.9984 and 0.9982, respectively. The differences in peak area (SI S6) were attributed to the monohydrate content in α·LMH (4.8%). Therefore, for example, 10 mg of α lactose monohydrate is equivalent to 9.5 mg of lactose. Refractive index peaks with an RT of 3.4 min were detected for both samples (Fig. 4). The tablets containing higher α content (α79%) showed faster lactose release compared to β lactose (α13%). This difference was observed as early as the first minute, for example, 19.4 ± 3.9 and 11.1 ± 3.2% of the lactose present were released from the α79% lactose and α lactose (α13%) tablets, respectively ($p \leq 0.05$). However, after 5 min,

Table 3 Disintegration times in seconds (s) of tablets produced using three compression forces containing lactose composed of powders with different α/β ratios (*n* = 10 ±SD). The tablets containing α·LMH were subjected to identical stress conditions (0, 35 and 60 days at 40 °C/75% RH). Mean of *n* = 6 ±SD

Compression force (kN)	α13% disintegration time (s)	α50% disintegration time (s)	α79% disintegration time (s)
10	220 ± 18	23 ± 1*	27 ± 6.4*
20	306 ± 10	98 ± 16*	69 ± 21*,+
40	329 ± 15	349 ± 36	325 ± 19

Compression force (kN)	α·LMH as received (α97%), disintegration time (s)	α·LMH – 35 days (α98%), disintegration time (s)	α·LMH – 60 days (α98%), disintegration time (s)
10	25 ± 4	23 ± 3	21 ± 3
20	21 ± 2	19 ± 3	20 ± 5
40	41 ± 9	32 ± 11	46 ± 18

*Statistical differences ($p \leq 0.05$) observed between α13% and tablets containing α50% and α79% lactose. +Statistical difference between all three samples.
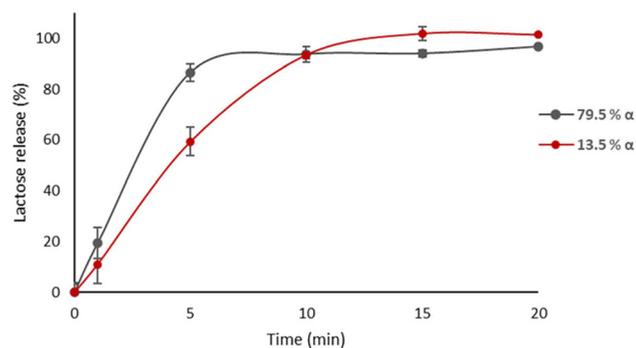
Fig. 4 The dissolution profiles between α79% and α13% lactose-only tablets compressed with 20 kN force (mean ± SD, $n = 6$).

86.5 ± 6% was released from the α79% tablets compared to 59.2 ± 7.6% from α13% lactose tablets ($p \leq 0.05$). After 20 min, lactose release reached a steady amount of 96.5 ± 1.3 and 101 ± 2.6% for α79% and α13% tablets, respectively. SEM analysis of the different tablets showed no obvious changes within their interior (SI S7). Similar internal structures were seen, indicating that the variation in dissolution was due to anomeric content rather than changes in the particles' packing and morphology within the compressed tablets.

3.3.2 Dissolution of ASA tablets. Studies on drug-free tablets demonstrated how lactose anomeric complexity influences tablet properties (sections 3.1 to 3.3.1). To further illustrate the role of anomeric content, acetylsalicylic acid or ASA, a BCS Class I drug,[27] was incorporated into lactose-based tablets using the lactose powders of differing anomeric content discussed in the earlier sections. Calibration of the HPLC assay yielded a good linear relationship between absorbance at 265 nm and ASA concentration (Abs = 0.0049(conc) + 0.0018, $R^2 = 0.9997$). All dissolution ASA profiles complied with the FDA and EMA guidelines; however, within this compliance, variations in lactose anomeric content affected dissolution times. The longer β-lactose powder (α13%) was exposed to 40 °C/75% RH, the higher the resulting α anomer content and the faster the release of ASA. This was observed as early as 10 min after the start of dissolution, where the drug release of tablets containing as-received β lactose (α13%) was 9.12 ± 1.7%, whereas 18.6 ± 4.8% drug release was recorded for ASA tablets containing α79% lactose content ($p \leq 0.05$). The amount of ASA released during all the dissolution profiles was dependent on the anomeric lactose composition present in the tablets (Fig. 5(a) & Table 4). For example, after 15 min, a significant difference ($p \leq 0.05$) was recorded between α13% + ASA, α50% + ASA and α79% + ASA, whereby the drug release
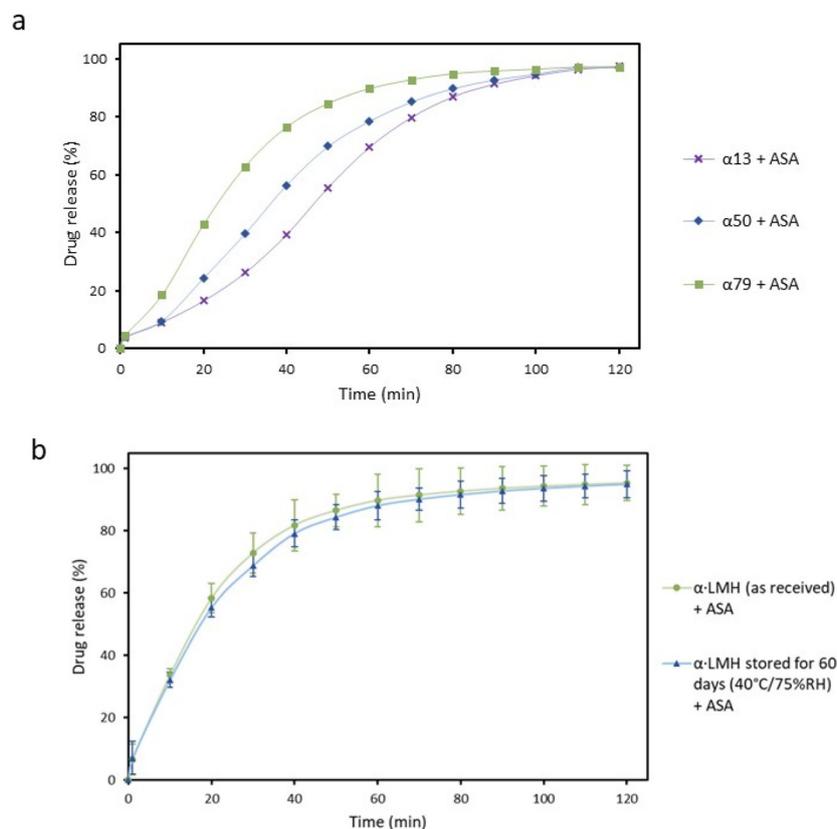

Fig. 5 (a) Dissolution profiles of ASA from tablets containing different anomeric ratios of lactose produced using a compression force of 20 kN. (b) Dissolution rate (mean ± SD, $n = 6$) for ASA from tablets containing α·LMH (as received 97% α anomer) and tablets produced from α·LMH powder stored for 60 days at 40 °C/75% RH (98% α anomer) using a compression force of 20 kN. Data were recorded every 5 min; for illustrative purposes, only data gathered every 10 min are shown. Statistical analysis of variance is addressed in (a).

Table 4 The parameters ($T_{25\%}$, $T_{50\%}$ and $T_{90\%}$) used to characterize the drug release equivalent time required to release 25, 50 and 90% of ASA, respectively

Tablet matrix	T_{25} (min)	T_{50} (min)	T_{90} (min)
α13% + ASA	29	46.5	91
α50% + ASA	20*	36*	80*
α79% + ASA	12.5*	23*	60*
α·LMH (as received α97%) + ASA	7[+]	16[+]	60[+]
α·LMH (stored for 60 days at 40 °C/75% RH 98% α) + ASA	7.5[+]	17.5[+]	67[+]

* Indicates statistical difference between the starting material of α13 + ASA and tablets comprising of epimerised lactose. α·LMH samples were used as control measures to compare the storage effect on α·LMH. [+] Indicates a statistically significant difference ($p \leq 0.05$) between tablets produced using α13%, α50%, α79% with α·LMH tablets (as received and stored α97%).

was 12.6 ± 2.1, 15.1 ± 1.4 and 31 ± 7.7%, respectively. The rate of dissolution continued to increase as the α lactose content increased. The time taken to release 25, 50 and 90% of ASA (T_{25}, T_{50} and T_{90}) is shown in Table 4. After 120 min, the release of ASA from each of the three different batches of tablets reached a steady state of 97.3, 97.2 and 97% release, respectively (Fig. 5(a)). In contrast, the rate of dissolution from tablets containing ASA

mixed with α·LMH (as received α97%) and α·LMH (60 days storage at 40 °C/75% RH α98%) was similar with no statistical differences being recorded (Fig. 5(b)).

3.3.3   Independent model of the similarity factor approach. ASA tablets containing α50% and α79% lactose showed differences in drug release at 15, 30 and 45 minutes (Fig. 6(a)). To explore the impact of anomeric content, these dissolution profiles were compared to ASA + α13% tablets (Fig. 6(b)). f_2 values for the α50% and α79% containing tablets were determined to be 48 and 23, respectively, with the lower value indicating greater dissimilarity. The obvious dissimilarity was also observed between α·LMH (as received α97%) + ASA and α13% + ASA ($f_2 = 18$). Nevertheless, when comparing tablet matrices comprising α·LMH α97% + ASA and α79% + ASA, an f_2 value of 50 was recorded, suggesting an average of 10% difference in all the processed time points. Tablets containing ASA + α·LMH (as received α97%) and ASA + stored α·LMH (60 days; 40 °C/75% RH α98%) exhibited similarity in dissolution profiles with an f_2 value of 79.

3.4   Effect of tabletting and ASA incorporation on anomeric content

The hardness and disintegration tests conducted on the tablets containing ASA indicated that there were significant
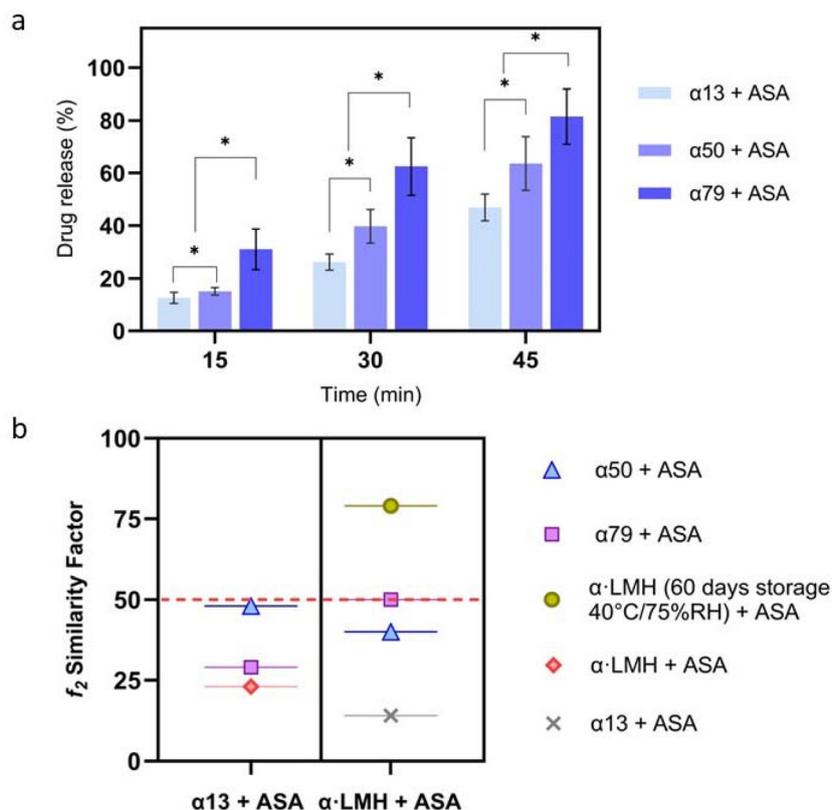

Fig. 6 (a) Mean ± SD of acetylsalicylic acid (ASA) ($n = 6$) dissolved in 0.1M HCl from tablets manufactured from lactose containing different anomeric ratios at selected time points (15, 30 and 45 min). (b) Similarity factor (f_2) showing the similarity between reference tablets of α13% + ASA and α·LMH (α·LMH as received 97% α anomer) + ASA with lactose stored for 35 days (α50%), 60 days (α79%) and α·LMH for 60 days (98% α anomer) + ASA, at 40 °C/75% RH.

differences between the batches, which may be attributable to differences in the anomeric ratio of the lactose content. Initially, it was necessary to investigate whether tabletting lactose with ASA had any effect on the anomer content of lactose. H^1NMR was conducted for a 24 h post-tablet production period. The NMR analysis of the tablets and pure ASA shows no effect of the API on the chemical stability of lactose ($p > 0.05$), as depicted in Fig. 7. Slight changes in the signals indicated that there may have been a limited alteration in the anomeric content of lactose of the tablets and the starting feed material. However, this could have been related to the presence of ASA causing the chemical shifts, which typified the lactose anomers, to become less separated (instead of doublet NMR peaks, as seen previously).[9] Nevertheless, the anomeric content (%) from the starting material and post-tabletting proved to be similar, indicating chemical and anomeric stability.

3.5 True density and pore volume

The pore volume observed for α50% and α79% lactose powders was 0.355 and 0.353 cm^3 g^{-1} compared to 0.367 cm^3 g^{-1} for the starting material, α13% (as received β-lactose), with a significant statistical difference recorded ($p \leq 0.05$). This was also the case for the true density, which was 1.552 and 1.546 g cm^{-3} (α50% and α79%, respectively) compared to 1.589 g cm^{-3} for α13% ($p \leq 0.05$), respectively. True density and total pore volume decreased as the α content of α lactose increased due to epimerisation, as compared to β-lactose as received.

4. Discussion

This study demonstrated the role of anomeric composition on the dissolution rate of aspirin tablets formulated with lactose.
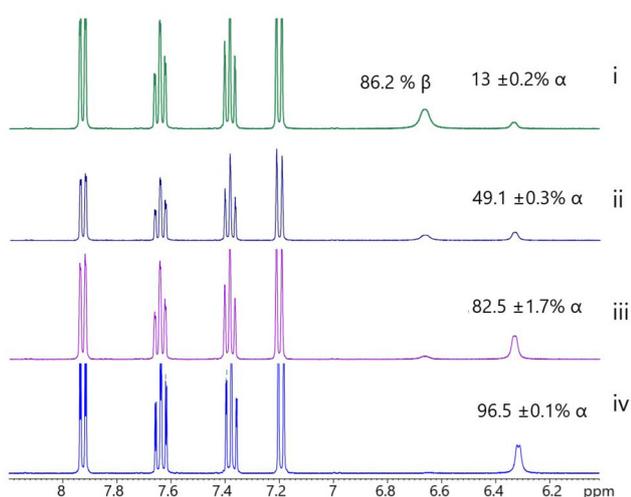

Fig. 7 Enlarged region (6–8 ppm) of the H^1NMR spectra of tablets containing (i) β lactose as received (α13%) + acetylsalicylic acid (ASA), (ii) 50.2/49.8% α/β (α50%) + ASA, (iii) 79.5/20.5% α/β (α79%) + ASA and (iv) α·LMH (α97%) + ASA. The chemical shifts due to ASA can be seen between the regions of 7–8 ppm.

The following discussion explores the complexity of this behaviour, and where possible covers potential mechanisms for how anomeric content influences tablet formation, hardness, disintegration and ultimately dissolution.

The 4% w/w of MCC was added to all formulations to consistently remove the potential for lamination, which was observed in the tablets containing β anhydrous lactose (α13%). The inclusion of small amounts of binders in lactose-containing tablets is common.[28–30]

Tablets manufactured at a low compression force (10 kN) showed no differences in hardness properties between β lactose (as received) α13%, α50%, and α79%. The force used was insufficient to cause extensive deformation of the lactose powdered particles, whereas a higher compression force would be expected to induce greater particle deformation and further stronger contact between particles within the powder.[31] This assumption is supported by the data obtained from tablets prepared at higher compression forces. For example, when the tablets were compressed using forces of 20 and 40 kN, significant differences in crushing strength were recorded ($p \leq 0.05$) between α13% and α79% at both forces, mirroring previous tabletting studies.[8,32] Specifically for lactose tablets, anomeric composition has been observed to influence hardness, partially attributable to cohesive energy.[33] Anhydrous α lactose has been observed to have a higher cohesion between its molecules which has been argued to lead to a higher tensile strength within its tablets.[34] In our study (at 20 & 40 kN), the more α lactose present, the harder the tablets (Fig. 3), implying an increase in cohesion. Thermal analysis shows that this is not anhydrous α as no dehydration of α·LMH is observed as a consequence of tabletting (Fig. 2).

Tablets manufactured using α·LMH powders that were stored under identical conditions to those of the tablets produced from epimerised β lactose demonstrated no difference in hardness, suggesting that the effect is caused only by the hydrate-driven epimerisation process. This justifies the assumption that the ingress of water into the as received anhydrous β lactose powder stored at 75% RH caused a shift in anomeric content and the higher α·LMH generated as a function of time results in stronger lactose tablets. It has been speculated previously that, as the compaction force is increased, the pore size within particles is diminished, with the largest pores being reduced in size first.[35,36] However, using epimerised lactose, there was no evidence from the SEM images of defined pores within the powder particles[9] and pore-volume data demonstrated only a slight decrease in pore volume between as received material (β lactose) and epimerised lactose powders (SI S8). Therefore, the incorporation of water molecules within the crystal structure of lactose (α79%) may have contributed to harder tablets by promoting interparticle bonding within the lactose powders and thus increasing cohesion. This suggested mechanism is supported by the related literature.[32,37]

Tablets containing a higher α content due to epimerisation (α50% and α79%) disintegrated more rapidly than anhydrous β lactose tablets generated by compression forces of 10 and

20 kN. Wicking may promote disintegration,[38] but a potentially more convincing explanation for the influence of epimer content on disintegration is the 'competition for water theory'.[24,39] Such a mechanism also supports the observed dissolution results. At the highest compression force, there was no influence of anomer content; at this compression, penetration of water was restricted, leading to slower disintegration. The disintegration times given in section 3.4 are comparable to the times reported in the limited number of previous studies.[34,40,41] For example, Patel *et al.*[40] found that α·LMH tablets disintegrated in 45 (s), whereas van Kamp *et al.*[41] showed that the disintegration of α·LMH and β anhydrous tablets took 14 and 205 (s), respectively, at 20 kN (using 13 mm diameter tablets). Here, the rapid disintegration of tablets α·LMH has been attributed to their ability to take up water, leading to faster disruption of bonds between lactose molecules that hold the tablet together.[42] These are primarily hydrogen bonds that are weakened because of the penetration of water, with this process being dependent on the dielectric constant of the solvent.[42] Such bonds are present between the lactose particles as well as the lactose molecules. Faster disintegration rates were observed with higher α content, even with increased hardness properties (SI S9). This indicated that the mechanisms discussed earlier are responsible for the tablets' disintegration, and not the hardness properties. Nevertheless, when extremely high compression forces were used (40 kN), large differences were apparent between tablets containing α·LMH and α79%. This complex finding could be attributed to the remaining β content present in α79% contributing to the strength of the bonds formed between powder particles at extremely high compression forces (especially at the surface), promoting less elastic deformation of the β lactose particles within the α79 tablets.[43]

An acidic medium was used for dissolution testing, since this is viewed by Official Compendia as simulating the typical pH of gastric fluid and is regularly used for ASA tablets.[44,45] Based on the hardness and disintegration data, it was decided that tablets prepared with a compression force of 20 kN might show the best differentiation between different lactose grades incorporated as an excipient in the ASA tablets.

The release of ASA might be expected to be fastest from tablets containing the highest proportion of β lactose. For example, Xiang *et al.* developed pollen-shaped anhydrous lactose particles with different α/β ratios, but this was based on the composition of the feed lactose grades and not the final product.[46] Particles were prepared by adding an ethanolic solution of the drug which may have also induced some epimerisation (which does not appear to have been tested for). Acetaminophen release into simulated gastric fluid was recorded as being faster for tablets with a higher β anhydrous content. This was attributed in part to the higher solubility of the β analogue compared to α lactose[47,48] and to the different surface structure (*e.g.*, porosity) of the different particles produced using differing lactose anomer ratios. Confirmation of the anomeric composition of the particles prior to dissolution is required to support this conclusion. In our study, α·LMH as

received produced tablets with the fastest ASA release and quickest dissolution, followed in turn by ASA tablets containing lactose with 79%, 50% and 13% α-anomer, respectively. The anomeric composition of these samples was confirmed by NMR. Xiang *et al.*'s lactose particles had complex structures, and the storage conditions were not reported, which further complicates the applicability of their work to the data reported in this paper.[46]

The principal factors affecting API dissolution from immediate-release tablets include the particle size of the tabletted powder[49] as well as tablet hardness,[50] although tablet hardness does not necessarily correlate inversely with the dissolution behaviour of tablets.[51,52] Data for the particle size distribution (PSD) of the lactose powders obtained from[9] and used in this current study showed no significant changes in this parameter, and these compared favourably with those reported previously.[53,54] For example, Sebhatu and Alderborn[54] reported a particle size range of 50–100 μm and a medium particle diameter of 47 μm for crystalline lactose monohydrate. Smaller particle sizes of API usually provide a faster rate of drug release because of their larger surface area.[55] However, the particle size of ASA powder used in this study was identical for the starting materials prior to the tableting process. In addition, the particle size of the epimerised lactose (α50% and α79%) in the composite powders remained broadly the same as that of the β analogue, while the dissolution rate of the tablets increased as a function of increasing α lactose content. Moreover, the hardness of tablets containing ASA in a 1 : 1 ASA + lactose powder (ranging in α/β content) did not show significant differences (SI S10), indicating that the ASA amount had no effect on the tablet strength. It was therefore concluded that particle size and tablet hardness had little influence upon the dissolution rate: lactose anomeric content controlled dissolution.

A competition for water mechanism may be a route to explaining the differences in ASA release from tablets containing different amounts of α and β lactose. This starts with the concept that epimerisation may take place (from β to α) upon water interaction with the tablet in the dissolution bath, for tablets containing higher β content, causing slower disintegration and dissolution at the start of the experiment (Fig. 1).

This hypothesis is based on the competition-for-water and the blockage of pores caused by recrystallisation, a theory already proposed in the literature of other tablet systems.[39,56] In the case of tablets with high β lactose content (see Table 4), in the layer of aqueous dissolution media touching the surface and within tablet pores, β lactose with its higher solubility will rapidly enter solution, nearing a saturation concentration.[24,39] This β lactose will epimerise and form α lactose, producing a supersaturated solution[56] and resulting in the recrystallisation of α lactose monohydrate because of its lower solubility. Thus, α lactose competes for water, forming the solid monohydrate on the tablet surface and blocking further β lactose from entering the solution. The penetration of water into the β lactose tablet is reduced compared to the α lactose monohydrate tablets, because in the case of β, the activity of water, its

effective concentration is reduced at the tablet surface as the water molecules are being removed to form the monohydrate. For α lactose monohydrate tablets, more water is available at the surface for penetration and to contribute to disintegration, because the hydrate is already formed. This mechanism explains the observation of higher disintegration and dissolution times for tablets prepared from lactose powders containing a high ratio of the β anomer.

The true density and pore volume data reported in section 3.5 do not appear to contradict the competition-for-water and pore blockage mechanism and are not necessarily factors causing faster disintegration and dissolution for the tablets with more α·LMH present. The β-lactose as received (α13%) had significant but only slightly higher values for density and pore volume. All values reported here (section 3.5) broadly concurred with the literature density and pore volumes for lactose powders. For example, true density values of 1.42,[57] 1.55, 1.55 (for a particle size range of 20–45 μm),[58] 1.53 (for a particle size of 45–63 μm)[58] and 1.54 g cm^{-3} for various lactose powders[59] are documented. For comparison, values of 1.38 and 1.43 g cm^{-3} are typical for ASA.[60] Moreover, the total pore volumes of 0.35 cm^3 g^{-1} measured here for samples containing α50% & α79% were found to be almost identical to the values reported.[61] The lack of influence of density and pore volume on disintegration and dissolution reflects the proposed mechanism, as once water-induced epimerisation occurs, surface hydrate forms, reducing any influence of the powders' original density and pore volume.

Stereoactivity and epimerisation of APIs and possible effects on the dissolution of dosage forms have been previously addressed and investigated by a number of authors, with most reporting that enantiomeric or racemic forms influence dissolution.[62–64] For example, (±)-verapamil exhibited a slightly higher dissolution rate when measuring -*R* compared to the -*S* enantiomer.[65] The work reported here is unusual as the dissolution of a non-chiral API has been shown to be influenced by the chirality and the complexity of the anomeric composition of an excipient frequently included in tablet formulations.

6. Conclusion

The study fulfilled the aim by evaluating how lactose anomeric composition affects tablet disintegration and dissolution. The behaviour of this common excipient was complex, and the observations were well explained by a mechanism involving competition for water between the anomers during disintegration and dissolution.

Measurement of lactose anomeric composition before pharmaceutical manufacturing is advisable. Tablets prepared with different anomeric contents showed distinctive differences in tensile strength, disintegration and lamination. In tablets containing anhydrous β lactose, higher α anomer content increased hardness, while disintegration time decreased markedly as the α fraction increased. The dis-

solution behaviour of tablets containing ASA differed significantly with varying α content, and higher α content produced faster drug release. The similarity factor f_2 between tablets made with β lactose (α13%) and α79% lactose was 23, indicating high dissimilarity. Changes in ASA release were clearly dependent on the storage of the anhydrous β lactose powders used to manufacture the tablets, with conditions such as ≥40 °C and 75% RH producing marked differences in dissolution.

Conflicts of interest

There are no conflicts to declare.

Data availability

The raw data are not currently stored in an open source – but can be made available upon request to the first author.

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d4pm00256c.

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