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Effect of lignin as natural polymer on the release rate of acetylsalicylic acid tablets

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Abstract
The main focus here is on the improvement of formulations utilising non-conventional bio-based excipients to improve tablet release rates. Two different formulations were considered. The first formulation contains Alcell lignin, lactose monohydrate and microcrystalline cellulose as excipients and acetylsalicylic acid (aspirin) as active pharmaceutical ingredient (API). The second formulation contains lactose monohydrate and microcrystalline cellulose as excipients and aspirin as API. The prepared formulations were roller compacted followed by milling, sieving, and tableting. The tablets were then characterised in terms of dissolution rate in order to compare the release rates. Results indicated that tablets containing Alcell lignin have quicker release, faster disintegration times and higher tablet hardness for all samples with differing process parameters. Higher API dissolution has been attributed to the amorphous structure of lignin and its interaction with aspirin, which increases dissolution of the API.

Keywords: Lignin; Dry granulation; Roll compaction; Drug dissolution; Drug release; Hydrolysation; Acetylsalicylic acid
1. Introduction

Three different methods are considered for tablet manufacturing in the pharmaceutical industry, i.e. direct compaction, dry, and wet granulation. Recently, there has been focus on direct compaction due to cost and time effectiveness as less number of processing steps are involved. Moreover, the tablets produced by direct compaction have faster dissolution rates [1]. However, in order to improve powder flowability and bulk density, especially for poor flowing materials, granulation has proved useful. Dry granulation is continuous and is the preferred method for moisture and heat sensitive materials as no binder is used [2-6].

Today, one of the major challenges facing the pharmaceutical industry is to enhance the bioavailability which play a crucial role in drug development [7]. Tablet release rate has a significant effect on tablet bioavailability [8] in which higher release rates result in higher bioavailability and lower side effects. Currently, the most common method for enhancing the bioavailability of drugs is preparation of amorphous solid dispersion. In an amorphous solid dispersion (ASD), the API is transformed to amorphous phase from crystalline by various techniques, and then API is dispersed in a polymeric carrier, which enhances the dissolution of API molecules.

Excipients are inert substances used in drug production to assist manufacturing and control the dosage, quality, stability, bioavailability, toxicity and efficacy [9-11]. For example, sugar compounds such as lactose and cellulose derivatives such as MCC are the most commonly used excipients in tablet manufacturing [10, 12, 13]. In this study, in order to investigate the effect of excipient on tablet release rate, disintegration and dissolution tests have been extensively studied [14-19]. Several researchers have illustrated that the influence of excipients on release of oral dosage drugs is significant [20]. The type of excipient, its physical and chemical properties, and interaction with API can effect processability and stability of tablets as well as overcome the drug side effects [21]. Therefore, tablet formulation can be considered as a critical factor in
pharmaceutical production due to its considerable effect on disintegration, dissolution and drug release rate [7, 20, 22-24].

Various researchers have focused on improved tablet release rate and drug absorption, etc. by developing novel excipients. Due to some issues in relation to side effects and release rates of solid dosage forms [25], use of materials with desired functionality as excipient in tablets are increasing. In tablet manufacturing, amorphous materials are showing great promise as excipients as they exhibit higher dissolution compared to crystalline equivalents due to disordered structure and higher free energy [25-29]. On the other hand, the thermodynamic instability of amorphous excipients used in tablets, might result in relaxation and crystal growth of crystalline API molecules over time which is not favourable for bioavailability [30].

Recently, biological macromolecules have attracted attention for use as excipient in tablet production to enhance drug dissolution and bioavailability. A number of studies have been carried out on lignin to improve chemical modification [31-33], and to develop new pharmaceutical formulations with increased functionality [34, 35] because of lignin structure which contains phenolic and aliphatic hydroxyl groups [35]. Lignin has a high potential to be used in tablet manufacturing either with chemical modification or without chemical modification [32]. Furthermore, some researchers have investigated the ability of lignin’s nanoparticles (NPs) in drug delivery due to its non-toxicity, biodegradability and stability. Lignin has also been used to transport hydrophobic drugs [36]. Lignin is an amorphous polymer and non-amphiphilic in nature, and displays high chemical stability due to 3D network structure [37]. As lignin is rich in phenolic and aliphatic hydroxyl groups [38], it interacts with most API molecules through π-π stacking and hydrogen bonding, and this makes lignin potentially useful as a drug carrier to enhance bioavailability [16, 17, 21, 26, 28, 34, 37, 39-43].

Aspirin, which is known as a delayed-release drug is utilised as a model API in this work [44]. In fact, the dissolution rate of aspirin is the rate-limiting step, which controls the absorption and
bioavailability. Moreover, another challenge associated with aspirin is that it hydrolyses to salicylic acid upon exposure to aqueous solutions, which should be taken into account during the dissolution tests [8, 15, 41, 45-47]. Wang et al. have investigated aspirin hydrolysis during dissolution tests, and found out that the hydrolysis of aspirin occurs during dissolution [47]. Sumirtapura et al. studied the dissolution of different types of acetylsalicylic acid products, and distinguished time lags for differing aspirin tablets [46]. Peltonen et al. utilised three different tablets containing aspirin for dissolution tests. The first type of tablets contained aspirin and MCC; the second ones consisted of aspirin and lactose, while the third ones included aspirin, lactose and MCC. They investigated the effect of pH on aspirin release rate and found higher release at higher pH. Moreover, they reported that adding lactose to aspirin in the formulation leads to increased release rate. On the other hand, adding MCC results in decreased release rate [15].

In comparison with other literature, the authors have tried to analyse the dissolution of different formulations containing aspirin as API and various excipients. Lignin was used as a new excipient to evaluate its performance in tablet manufacturing in order to improve drug release rates. Indeed, the purpose of this study is to investigate the effect of Alcell lignin on tablet properties including hardness, disintegration time and drug release rate. The main aim is to explore the possibility of using lignin as natural material to enhance bioavailability of poorly water-soluble drugs. Two different formulations are utilised, one formulation containing Alcell lignin and another one without lignin. First, two different blends are roller compacted to produce ribbons. Then, the produced ribbons are milled to make granules. Afterwards, these granules are used to produce tablets. Different tablet characterisation tests including; disintegration, hardness and dissolution tests are carried out to understand the effect of lignin as natural polymer on drug release rate.

2. Experimental procedure

2.1. Materials and methods
In order to prepare the formulations, acetylsalicylic acid (Alfa Aesar, 99% C$_9$H$_8$O$_4$) was utilised as a model API. Different excipients were utilised including microcrystalline cellulose (MCC SANAQ® 102 L USP/NF/EP), lactose monohydrate (Lennox USP, NF, BP, Ph, pure pharma grade) and Alcell lignin (Tecnaro (Ilsfeld, Germany)). More details on the lignin used in this study can be found elsewhere [33, 48]. To prepare the mixtures, 1% w/w magnesium stearate (Sigma-Aldrich, Ph. Eur., BP, ≥90% stearic and palmitic acid basis), as lubricant and croscarmellose sodium (CCS) (IMCD NF, PH.Eur.,JP) as disintegrant were used in the formulations. Table 1 illustrates the two different formulations considered; in the first one; 5 wt. % of aspirin was mixed with 20 wt. % of lactose, 20 wt. % of lignin, 3 wt. % of CCS and 1 wt. % MgSt, and the rest is MCC 102. The second formulation was prepared with 5 wt. % of aspirin, 20 wt. % of lactose, 3 wt. % of CCS, 1 wt. % MgSt, and the rest is MCC 102. All components were mixed using a Morphy Richards Stand Mixer. Ortho-phosphoric acid (analytical reagent grade, Fisher Scientific UK) and acetonitrile, HPLC grade, 99.7+% min Liquid (Alfa Aesar) were mixed to prepare mobile phase for HPLC analysis.

Table 1. Characteristics of different formulations used in this study.

<table>
<thead>
<tr>
<th>Material</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid (% wt.)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Alcell lignin (% wt.)</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Lactose (% wt.)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>MCC 102 (% wt.)</td>
<td>51</td>
<td>71</td>
</tr>
<tr>
<td>Croscarmellose sodium (% wt.)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Magnesium stearate (% wt.)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

2.2. Equipment and instruments

2.2.1 Dry granulation by roll compaction and milling process

To prepare the tablets, the dry granulation method was used for the entirety of this work in a series of ribbon production, milling, and tableting. The ribbons were produced using a roller compactor
(Freund TF-MINI) integrated with a vertical screw feeder for feeding the formulations. The rollers' dimensions are 100 mm in diameter and 25 mm in width. The considered process parameters included screw speed (SS) and roll pressure (RP), while roll speed was kept constant at 4 rpm. The screw speed was changed between 10-14 rpm, and roll pressure was changed between 30-50 bars in the ribbon production experiments. The density of produced ribbons were measured using GeoPyc density analyser (Micrometrics Instrument Corp., Norcross – USA). The produced ribbons were then milled using a conical mill (Laboratory Comil 193 AS) with mesh size of 813 µm, and impeller speed of 3000 rpm. The particle size distribution (PSD) of fine powder and granules were measured using Microtrac S3500 particle size analyser.

2.2.2 Tablet preparation and characterisation

A benchtop single punch tablet press (Gamlen Tableting GTD-1 D series) was used to produce the tablets with different formulations. 100 mg of two different formulations of produced granules were pressed to make tablets in a 6 mm (diameter) die. The tablet compression was carried out at 180 mm/min speed under fixed load of 400 kg. Croscarmellose sodium was used as a super disintegrant in tablet preparation experiments [23].

Hardness of the produced tablets was measured using a tablet hardness tester (Pharma Test PTB311E). To measure the disintegration time, Pharma Test PTZ-DIST- Disintegration Test Instrument (Hainburg, Germany) was used. The apparatus chamber was filled with 900 mL of deionized water and the apparatus paddle was adjusted at 100 rpm. Three samples were tested in deionized water at 37 °C for each process parameters and for two different formulations. All the disintegration tests were conducted until the tablets completely disintegrate. The dissolution of produced tablets was performed using a Pharma Test PTWS 120D 6-Station Tablet Dissolution Testing Instrument (Hainburg, Germany).

The concentration of the API in each sample was measured using High Performance Liquid Chromatography (HPLC). Chromatography was performed using an Agilent (Agilent Technologies,
Waldbronn, Germany) 1260 Infinity II HPLC system. The HPLC system consisted of a quaternary pump G1311B, a diode array detector G1315D set at wavelengths of 200 nm for acetylsalicylic acid and salicylic acid, auto-sampler G1329 B and a thermostated column compartment G1316A set at 25 °C. The system operated under isocratic flow at 0.75 mL/min using mobile phases consisting of A) 0.1 % Ortho-phosphoric acid; B) acetonitrile; A/B =50/50, v/v. The injection volume was 10 mL. The total run time was 10 minutes, and the type of column used was Kromasil 5C18 (250×4.6 mm).

2.3. Dissolution test procedure
The dissolution chamber was filled with 500 mL of prepared medium 0.1 N HCl (ACS, ISO, Reag. Ph Eur, Hydrochloric acid fuming 37% wt.) at pH=1.2. The medium temperature was kept constant at 37 ± 0.5°C and the stirrer was adjusted to a speed of 75 rpm [45]. When the temperature reached 37°C, one tablet was placed in each dissolution vessel to run the dissolution test for 120 minutes. Three mL of the dissolution medium were withdrawn at 5, 10, 20, 30, 40, 50, 60 and 120 minutes, then medium was replaced with the same amount, immediately. Then, the samples were filtered using Captiva Econofilters (PTFE membrane, 13 mm diameter, 0.2-µm pore size) syringes to prepare for the analysis by HPLC at 200 nm wavelength, immediately, due to hydrolysis of acetylsalicylic acid.

In order to prepare the buffer solution (pH = 1.2) for the dissolution tests, 2 g sodium chloride was dissolved in 200 mL deionized water. Then, it was diluted with deionized water in a 1000 mL volumetric flask and 7 mL HCl was added. In order to prepare the calibration solutions for HPLC analysis, 5 mg of acetylsalicylic acid and 5 mg salicylic acid were dissolved in 20 mL of buffer solution, separately. Then, they were mixed to prepare the calibration solution. Afterwards, the prepared solutions were diluted with buffer solution 6 times. The standard curves of drug concentration vs peak area were drawn for different formulations giving $R^2=0.99$.

3. Results and discussion
3.1. Dissolution profiles for two different formulations

Two different formulations were evaluated to find the effect of Alcell lignin on the aspirin tablet release rate. One formulation contains Alcell lignin, MCC 102 and lactose as excipients and the other one contains lactose and MCC 102 as excipients. Both formulations contain aspirin as API. Fig. 1 illustrates the graphs of drug release rate for tablets prepared at various process parameters. As seen, different levels of screw speed and roll pressure were considered in this study. Interestingly, the results show that the tablets containing Alcell lignin have higher release rate than the tablets without lignin for all prepared samples. In addition, the equilibrium dissolution for the tablets containing lignin is greater which is attributed to the enhancement of solubility of ASA with addition of lignin. It is also seen that faster release kinetics is obtained for the tablets containing lignin such that the majority of the API are dissolved in the first 10 minutes of the dissolution test. Moreover, the tablets prepared with lignin indicated less variability in the dissolution measurements. The data is provided in the Supplementary file for both formulations.

In other words, tablets containing lignin with very high release rate acts as a disintegrating agent in the dissolution chamber, facilitate the dissolution kinetics, and accelerate to equilibrium release. Moreover, due to amorphous nature of lignin, it may be concluded that lignin enhances the solubility of API due to its disordered structure and higher Gibbs free energy of the amorphous phase in the dissolution media. The cross-linked structure of lignin is likely to have an effect on dissolution and disintegration as well. Peltonen et al. [15] studied the effect of pH on the release rate of aspirin tablets with different formulations (B (aspirin & lactose), A (aspirin, lactose &MCC) and C (aspirin &MCC)). They illustrated in pH 1.2 the release rate of aspirin with the different formulations are low and it does not show 100% release rate after more than 200 minutes. Maximum release rates of the formulation B was around 90% after 200 minutes. For formulation A, the release rate was around 80% after 500 minutes and for formulation C was around 70% after 500 minutes.
The roll compaction process parameters affect the release rate of aspirin also in which the effect of roll pressure is more significant compared to screw speed. For the tablets without lignin, increasing roll pressure (at constant screw speed of 14 rpm) results in reduction of API dissolution, which could be attributed to the particle size of granules, which produce the tablets. In the roll compaction process, increasing the roll pressure results in enhancement of granule size. However, the effect of process parameters on the API dissolution is not significant, because the dissolution depends mainly on the chemical structure of API and interaction with the dissolution medium. In fact, the granulation improves the flowability of particles in the manufacturing.

Screw speed=14 rpm - Roll pressure=30 bar

![Drug release vs. Time graph](image_url)
Drug release (%)

Screw speed=14 rpm - Roll pressure=40 bar

Lignin tablet
Non-lignin tablet

Screw speed=14 rpm - Roll pressure=50 bar

Lignin tablet
Non-lignin tablet

Screw speed=12 rpm - Roll pressure=30 bar

Lignin tablet
Non-lignin tablet
Figure 1: Dissolution release rate of acetylsalicylic acid for different lignin and non-lignin tablets at different process parameters.

3.2. Effect of process parameters on tablet disintegration time

The effect of roll pressure and screw speed as the main process parameters of dry granulation on the tablet disintegration time for the two formulations is shown in Fig. 2. In terms of the effect of roll pressure as process parameter on disintegration time of tablets, the results illustrate that increasing the roll pressure while keeping the screw speed constant, results in decreasing the disintegration time for both formulations. Increasing the roll pressure results in higher densify of ribbons during the roll compaction process, and subsequently produce larger granules because higher mechanical
energy is required to break up the ribbons during the milling step. The tablets made with larger granules will be more porous, and subsequently leads to faster disintegration time. It is also observed from Fig. 2 that the tablets containing lignin have faster disintegration time than non-lignin tablets due to the amorphous and inherent structure of lignin, which has higher affinity towards the solution media compared to MCC and lactose.

Moreover, the particle size of raw materials used as excipients are shown in Fig. 3. As observed, lignin has smaller particle size compared to MCC 102, and introducing lignin as an excipient results in better compaction behaviour. In fact, smaller particles provide better particle-particle contact during the roll compaction and denser ribbons are produced, which in turn results in larger granules in the milling stage [49]. Furthermore, the size distributions of the used granules for tableting are shown in the Supplementary file. It is seen that the formulation containing lignin has slightly larger granule size, which results in faster disintegration time.
Figure 2: Disintegration time of tablets prepared with and without lignin as function of process parameters.
Figure 3: Particle size distribution of materials; MCC 102, lactose and lignin.

3.3. Effect of process parameters on tablet hardness

Fig. 4 illustrates the hardness of the tablets prepared using the two formulations as a function of process parameters. The results reveal that the lignin tablets have higher hardness than non-lignin tablets for all samples. Also, it can be seen that increasing the roll pressure leads to reduction of tablet hardness due to larger granules being obtained at higher roll pressure which in turn leads to weak physical bonds between particles. The results also indicate that by increasing screw speed, the tablet hardness decreases; however, the change is not considerable. In addition, the standard range of tablet hardness is between 39-79 N, therefore the lignin tablets are within the standard range of hardness. The reason why tablets containing lignin display higher hardness can be attributed to the interaction between lignin and other constituents of the formulation where lignin acts as a binder thereby increasing tablet hardness.
The main aim of this study was to investigate the effect of lignin-based excipients on release of oral dosage aspirin tablets. Lignin was selected as an excipient to evaluate its influence on release rate and tablet properties at varying processing conditions due its chemical structure. Results illustrated that lignin tablets compared to non-lignin tablets have higher hardness, faster disintegration time, and higher release rate. Indeed, the critical quality attributes of the tablets were improved by introducing the lignin. Higher release rate of tablets with lignin formulation are due to amorphous structure of lignin and interaction with the API, which improves drug solubility and therefore

Figure 4: Hardness of tablets prepared with and without lignin as function of process parameters.

4. Conclusions
bioavailability, the key factor in oral dosage development. On the other hand, higher roll pressure leads to more densified ribbons associated with lignin blends and consequently, larger granules are produced. These larger granules result in porous tablets, which leads to faster disintegration times as solute diffuses faster into the tablets. Also, the greater hardness for the tablets containing lignin are attributed to better affinity between lignin and MCC which leads to lignin acting as a tablet binder.

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References

Graphical abstract
Research highlights

- Preparation of tablets containing lignin using dry granulation method
- Investigations on the effect of lignin on the API (ASA) release rate
- The tablets containing lignin showed quicker release and faster disintegration