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Design of Controlled Release System for Paracetamol Based on Modified Lignin

Mahboubeh Pishnamazi[1], Hamid Hafizi[1], Saeed Shirazian[1], Mario Culebras[2], Gavin M. Walker[1], Maurice N. Collins[2,3*]

[1] Department of Chemical Sciences, Bernal Institute, Synthesis and Solid State Pharmaceutical Centre (SSPC), University of Limerick, Limerick, Ireland

[2] Stokes Laboratories, Bernal Institute, University of Limerick, Limerick, Ireland

[3] Health Research Institute, University of Limerick, Limerick, Ireland.

[*] Corresponding author, E-mail: Maurice.Collins@ul.ie

Abstract

The influence of lignin modification on drug release and pH-dependent releasing behaviour of oral solid dosage form was investigated using three different formulations. The first formulation contains microcrystalline cellulose (MCC101) as excipient and paracetamol as active pharmaceutical ingredient (API). The second formulation includes Alcell lignin and MCC 101 as excipient and paracetamol, and the third formulation consists of carboxylated Alcell lignin, MCC 101 and paracetamol. Direct compaction was carried out in order to prepare the tablets. Lignin can be readily chemically modified due to the existence of different functional groups in its structure. The focus of this investigation is on lignin carboxylation and its influence on paracetamol control release behaviour at varying pH. Results suggest that carboxylated lignin tablets had the highest drug release, which is linked to their faster disintegration and lower tablet hardness.

Keywords: lignin; drug release; paracetamol; disintegration;

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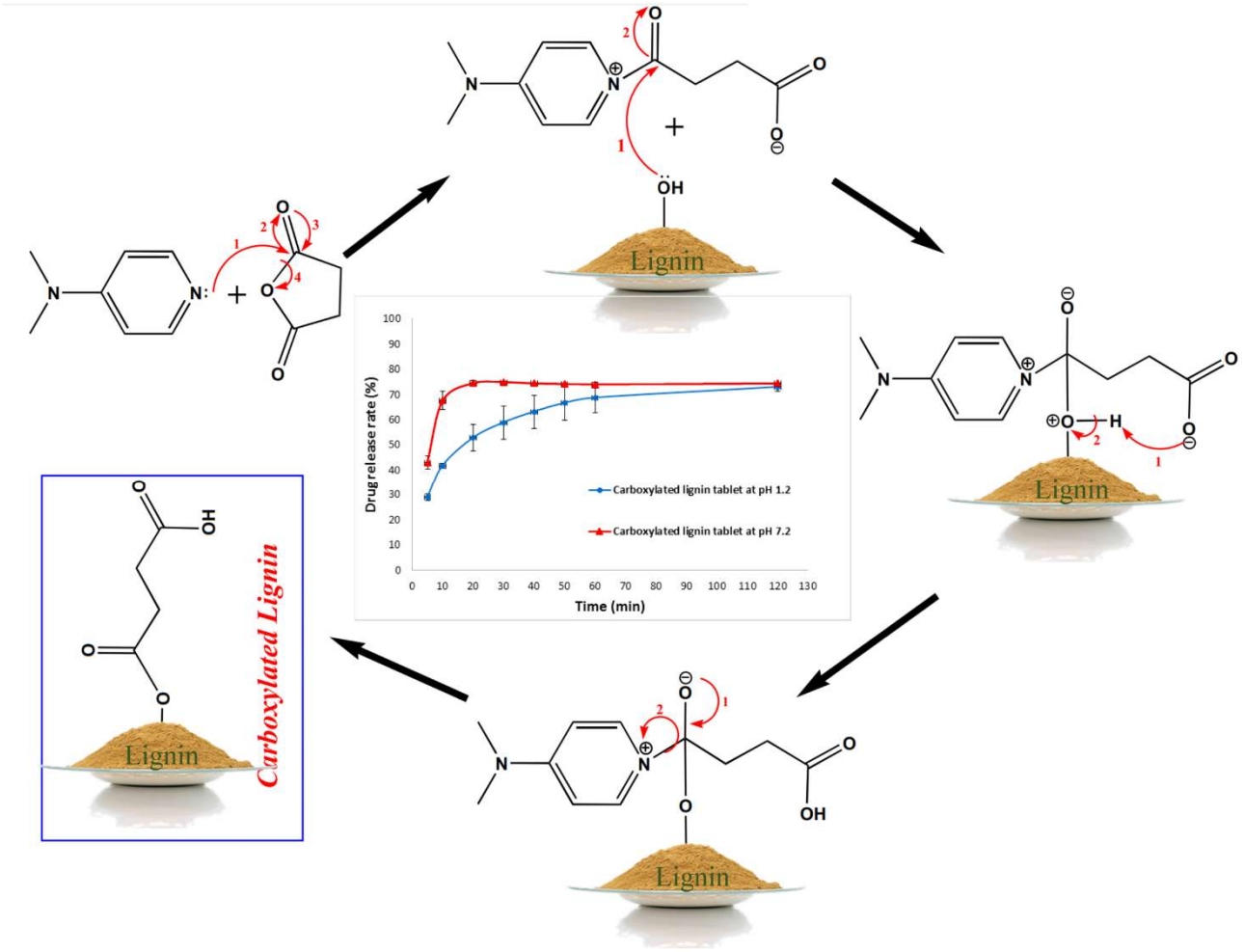
Graphical Abstract



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1. Introduction

Excipients play a significant role in the final product of pharmaceutical solid dosage forms. Variations in excipient properties influence tablet processability, hardness, disintegration and bioavailability [1-3]. Nowadays, many researchers have focused their investigations on using natural biopolymers [4] in tablet manufacturing due to their biocompatibility [5,6], also, they are cheap and widely available [7-9]. Lignin is a natural biopolymer with a number of beneficial properties including biodegradability and biocompatibility [10-14]. Recently, the use of lignin is increasing as a sustainable polymer for preparing carbon fibers [15], biofuels, bioplastics and controlled release carriers [16-21]. Due to the existence of different functional groups in the lignin structure such as; phenolic, hydroxyl and carboxyl groups, lignin can be chemically modified to enhance drug delivery and to control drug release [22-24]. Figueiredo et al. functionalized Kraft lignin nanoparticles by carboxylation in order to improve drug delivery of poorly water-soluble anti-cancer drugs which were pH-sensitive [18]. Lievonen et al. modified softwood Kraft lignin using a dialysis technique to improve its drug delivery performance [25]. Furthermore, it has been recognized that pH-responsive drug carriers provide superior drug delivery characteristics due to their ability to increase stability of API (active pharmaceutical ingredient) molecules in the stomach and release API in the intestine [26]. Li et al. investigated the release behavior of ibuprofen, using lignin-based complex micelles. The results of release tests illustrated a pH-dependent and controlled release properties due to ionization of the carboxyl groups in the lignin structure, with repulsive forces between the negatively-charged carboxyl groups of lignin and API molecules, with higher solubility of API at pH=7.4 [27]. Chen et al. synthesized lignin-based pH-responsive nano-capsules to improve controlled release of poorly water-soluble drugs by varying pH [28]. Duval et al. studied pH and light responsive behavior of controlled-release systems containing diazobenzen and modified softwood Kraft lignin [29]. Various investigation have been carried out on the effect of lignin-based polymeric nanoparticles (NPs) on the controlled release of pesticides [30,31].

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Bulut et al. studied the controlled-release behavior of paracetamol using chitosan-graft-polyacrylamide microspheres via an emulsion crosslinking technique [32]. They utilized glutaraldehyde (GA) as crosslinker to investigate the effect of that on the drug release rate. They mentioned the drug release rate was affected by some parameters such as the amount of GA, copolymer concentration and drug and polymer's composition. Their results illustrated more controlled release of drug by increasing the GA amount and copolymer, and decreasing in composition (paracetamol/polymer) ratio. Treenate et al. investigated the controlled release properties of paracetamol using a novel system composed of hydroxyethylacryl chitosan and sodium alginate in order to improve drug delivery for oral dosage forms [33]. Through improving drug water solubility, drug efficiency will be improved [34]. The current authors have evaluated the effect of lignin on the release rate of aspirin in oral dosage form, and indicated the higher release rate of drug using lignin as excipient in the tablet formulation [9].

In this study, the effect of carboxylated lignin as excipient on paracetamol release behavior was investigated. Lignin carboxylation was performed to enhance the carboxyl group content on the lignin surface in order to increase the interactions between lignin and paracetamol functional groups and allow pH triggered release. To the best of our knowledge, no studies have reported the use of carboxylated lignin in paracetamol tablet manufacturing and its effect on the release. Three different formulations have been considered, first one without lignin, second one using pure lignin and the third one contains carboxylated lignin. Paracetamol is utilized as a model drug in this research, it is a nonsteroidal anti-inflammatory [35]. Paracetamol is widely used as a pain relief drug with a fast absorption within the small intestine of the human body [36]. Drug release control is needed to overcome drug side effects associated with overdose [32,37-41]. Tablets were prepared by direct compaction and characterized using disintegration and dissolution tests. Modified lignin was verified using Fourier-Transform Infrared spectroscopy (FTIR). Drug release rates were measured using dissolution tests at pH 5.8 according to United States pharmacopeia (USP) [42]. In order to investigate

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the controlled release behaviour of paracetamol, dissolution tests were carried out at acidic condition (pH 1.2) and phosphate (pH 7.2) buffer solutions.

2. Experiments

2.1. Materials and methods

Paracetamol (4-acetamidophenol, Phion) was used as a model API to prepare three different formulations. Microcrystalline cellulose (MCC SANAQ® 101 L USP/NF/EP) and Alcell lignin (Tecnaro (Ilsfeld, Germany)) were used as excipients. More details on the lignin used in this study can be found elsewhere [2,15]. Table 1 shows the composition of the three formulations considered.

Table 1. Various formulations used in this study.

	Formulations		
Material	**A**	**B**	**C**
Paracetamol (% wt.)	20	20	20
Alcell lignin (% wt.)	0	10	0
Modified Alcell lignin (% wt.)	0	0	10
MCC 101 (% wt.)	80	70	70

2.2 Lignin modification

In order to allow conjugation reactions between lignin and paracetamol, lignin is functionalized with carboxylic acid groups. Synthesis of COOH-lignin involves ring-opening reaction of succinic anhydride with 4-dimethylaminopyridine (DMAP). 2 g of lignin, 2 g of succinic anhydride and 400 mg of DMAP were added to 250 ml of tetrahydrofuran (THF) in a 500 ml round-bottom flask, followed by stirring for 48 hr at room temperature [18]. The obtained carboxyl functionalized precipitate was filtered, and then, washed for 24 h using deionized water via soxhlet extraction system in order to remove the unreacted reagents. Finally, the modified lignin was placed in a freeze-dryer overnight. The proposed mechanism pathway [18] is presented in Fig. 1.

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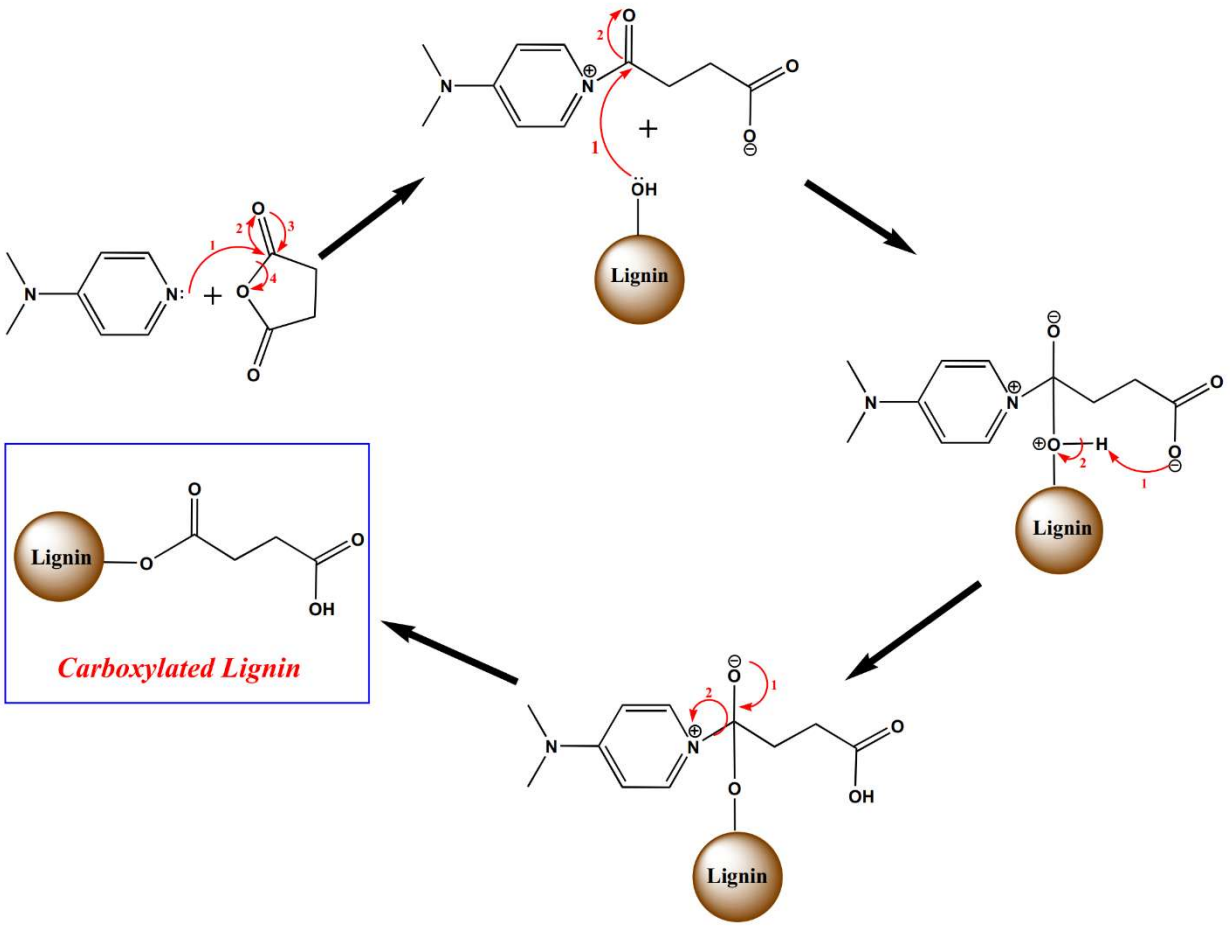

Figure 1: Mechanism of lignin carboxylation.

2.3. Tablets preparation

In order to prepare tablets, a single-punch tablet press (Gamlen Tableting GTD-1 D series) was utilized. 100 mg of each formulation were compacted to make each tablet in a 6 mm die. The tablet load was set at 400 kg, with compaction rate of 180 mm/min.

2.4. Characterisation

Fourier transform infrared spectroscopy (FTIR) measurements was carried out utilizing a Nicolet Nexus FTIR spectrometer between 450–4000 cm−1 equipped with an attenuated total reflectance accessory (ATR), a total of 60 scans with a spectral resolution of 2 cm−1. Tablet hardness was

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measured using a tablet hardness tester (Pharma Test PTB311E). Pharma Test PTZ-DIST-Disintegration Test Instrument (Hainburg, Germany) was used to measure the tablet disintegration time. 900 mL of deionized water was filled out the apparatus vessel and the peddle speed was kept constant at 100 rpm. The temperature of vessel was adjusted at 37˚C. The tests were performed for those two formulations containing pure lignin and carboxylated lignin until the tablets completely disintegrate. A Pharma Test PTWS 120D 6-Station Tablet Dissolution Testing Instrument (Hainburg, Germany) was utilized to analyse the tablets dissolution rate. For drug concentration measuring, Cary 60 UV Spectrophotometer (Agilent Technologies, Waldbronn, Germany) was used in 249 nm wavelength. All the tests were carried out in triplicate. The calibration graph can be found in Supplementary Information.

2.5. Dissolution test procedure

Phosphate buffer with pH=5.8 (according to USP 23) was used as dissolution medium [42,43]. 900 mL of medium was prepared to fill each dissolution vessel. The temperature of medium chamber and the stirrer speed were considered to keep constant at 37 ± 0.5˚C and 50 rpm respectively. For running the dissolution test, first, the temperature should reach to 37˚C. For each run, three vessels were utilized and one tablet was considered for each vessel. Five mL of sample were withdrawn at 5, 10, 20, 30, 40, 50, 60 and 120 minutes from each vessel and the same amount of medium was supplant, instantly. Afterwards, the samples were filtered applying Captiva Econofilters (PTFE membrane, 13 mm diameter, 0.2-µm pore size. Eventually, all samples were analysed to measure the drug concentration using Cary 60 UV Spectrophotometer at 249 nm wavelength, which was calibrated to find the wavelength. The cuvette type was 1/Q/10, quartz with pathway of 1cm. In order to minimize the statistical error, all the experiments were done in triplicates. For the dissolution tests of pH-responsive analysis, due to the evaluation of the controlled release behaviour of paracetamol in carboxylated lignin formulation, two different pHs were considered, phosphate buffer solution,

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pH=7.2 (intestine environment) and acidic buffer solution (0.1 N HCL), pH=1.2 (gastric environment) [44,45].

3. Results and discussion

3.1. FTIR characterization of pure lignin and modified lignin

The FTIR spectra analysis was carried out to monitor the pure lignin structure and to characterize the chemical changes in the functional groups of lignin structure during the carboxylation reactions. Fig. 2 shows the spectra of pure lignin and functionalized lignin, which have similar peaks such as; C=O (carbonyl groups) at 1600 cm-1, –OH (hydroxyl groups) which are attributed to the phenol and alcohol in the region of 3600–3100 cm-1 and aromatic ring region at 1425-1514 cm-1. Nevertheless, hydrogen-bonded hydroxyl stretching band of carboxylic acid (2250–3600 cm−1) and the stretching vibrations of C=O of the unconjugated –COOH groups at 1720 cm-1 exhibit a stronger absorption bond than the pure lignin (unmodified), proving that grafting lignin with carboxylic acid groups has been successfully done.

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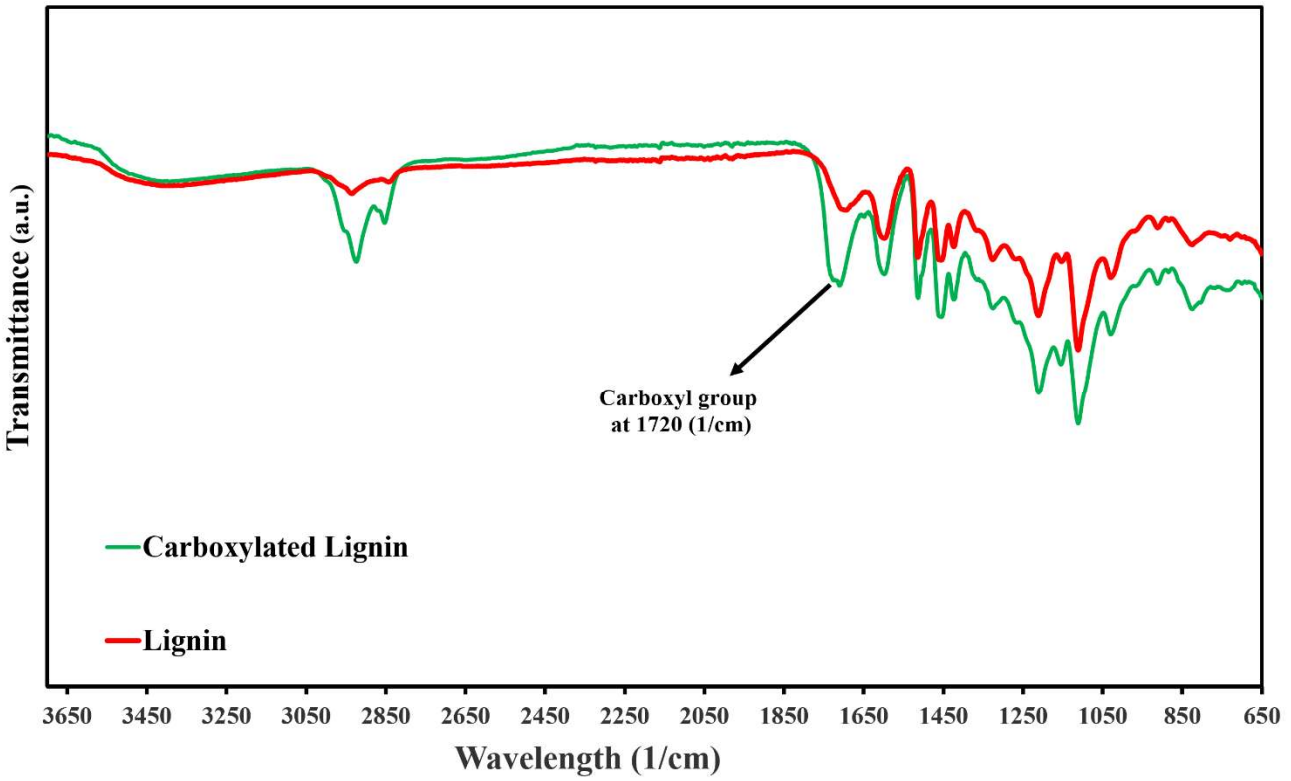

Figure 2: FTIR spectra of lignin (red) and carboxylated lignin (blue).

3.2. Effect of lignin carboxylation on the tablet disintegration time

Tablet disintegration time effect the tablet dissolution and can be used as a valuable test for solid oral dosage forms. Tablet hardness can influence tablet disintegration time, which higher hardness leading to longer disintegration times [46,47]. In order to study the effect of lignin carboxylation on the tablet disintegration time, disintegration test was performed for three different tablets, non-lignin, pure lignin and modified lignin. Fig. 4 presents the disintegration time results; in which faster disintegration time for tablets containing modified lignin is obtained. Moreover, tablet hardness is measured using a hardness tester (pharma test, PTB) for three formulations, and the results show higher hardness with the formulation without lignin (Fig. 3). Tablet hardness is affected by physical properties of materials, and interaction of drug with excipient. The tableting method is the same for each formulation, in order to mitigate its influence on tablet hardness. Generally, lower hardness equals to higher porosity, therefore, the lower hardness or higher porosity of carboxylated lignin tablet is due presumably to the structural differences in lignin after modification.

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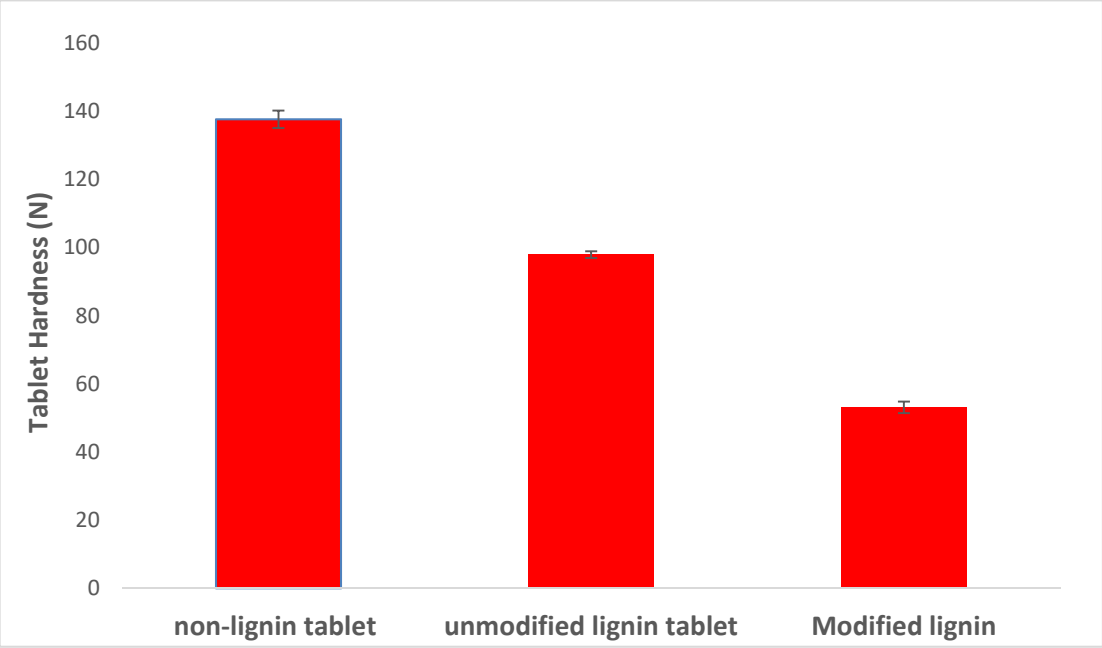

Figure 3: Hardness of tablets prepared contain pure lignin, modified lignin and non-lignin tablet.

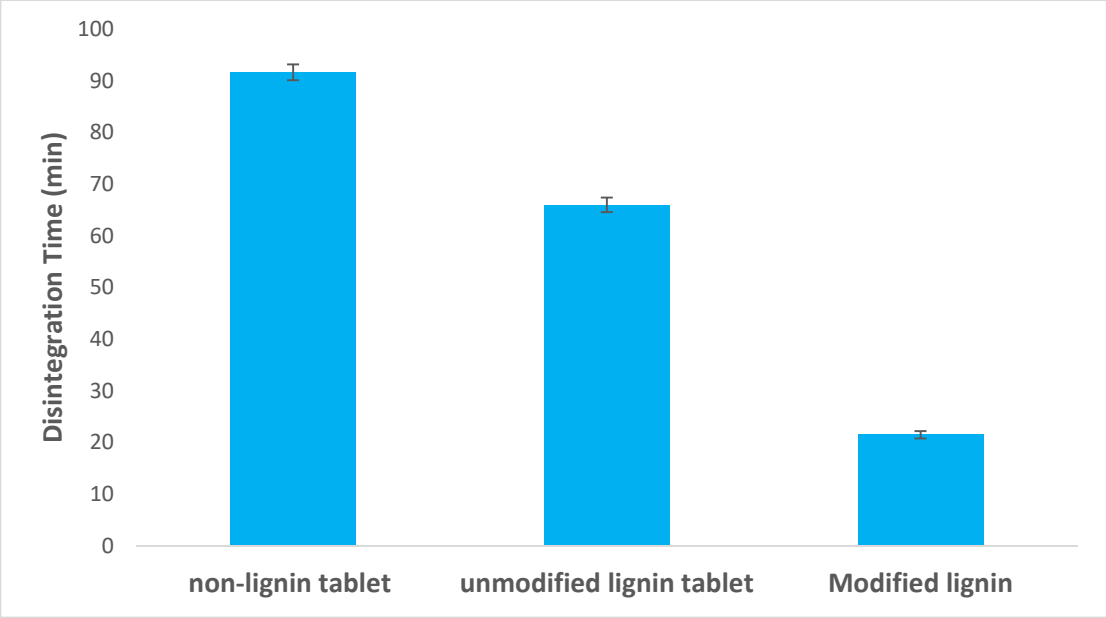

Figure 4: Disintegration time of tablets prepared contain pure lignin, modified lignin and non-lignin tablet.

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3.3. Effect of lignin carboxylation on drug release rate

Dissolution tests were performed to evaluate the effect of lignin and carboxylated lignin on the paracetamol tablet release rate. The three different formulations in table 1, were considered to study paracetamol release rate in phosphate buffer solution at pH 5.8, according to USP [42]. The release graphs of three different batches of paracetamol are displayed in Fig. 5. Interestingly, the graphs illustrate that the tablets containing functionalized lignin has the highest drug release rate and this correlates with the faster disintegration time of these formulations and lower tablet hardness.

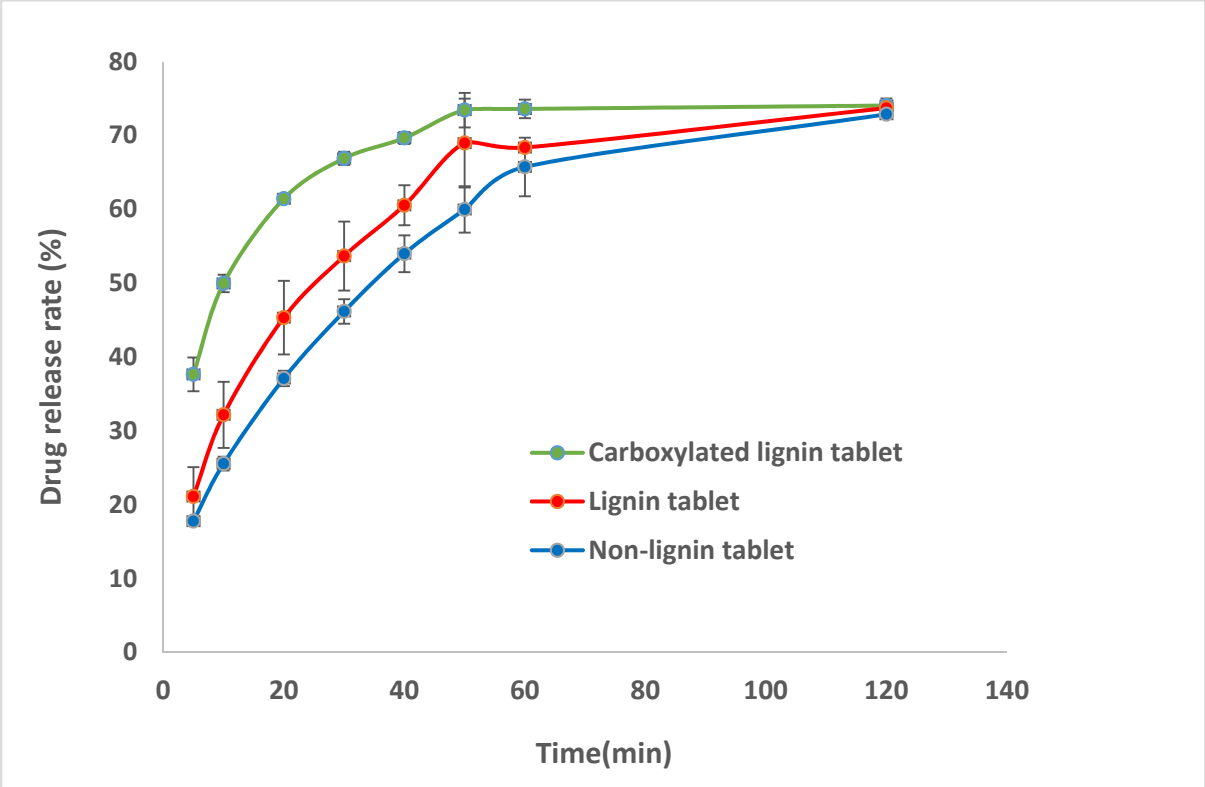

Figure 5: Drug release rate of paracetamol for the formulations at pH=5.8.

Moreover, the prepared tablets containing pure lignin have the higher drug release rate compared to formulation without lignin due to faster disintegration and lower tablet hardness [9]. Thus, Lignin functionalization improved the release properties of directly compacted paracetamol tablets.

3.4. Controlled release and pH-responsive behaviour of carboxylated lignin

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The pH-responsive behaviour of carboxylated lignin was investigated using dissolution tests in different media at various pH values, 0.1 M HCL solution (pH of 1.2, gastric environment) and phosphate buffer (pH 7.2, intestine environment) at 37˚C. The dissolution graphs in Fig. 6 presents the greater release rate of drug in buffer with pH=7.2 [44]. Increasing the carboxyl groups results to increase drug release at pH=7.2 compared to pH=1.2. In pH=1.2, the electrostatic repulsion between lignin carboxyl groups decrease due to protonation of carboxyl groups at lower pH values. However, in pH=7.2, due to ionization of carboxyl groups (Pka =4.8) of modified lignin the negatively-charged ions repel each other and presumably this leads to an swelling effect similar to how hydrogels swell on ionisation [48] and this results in higher release rates of API.

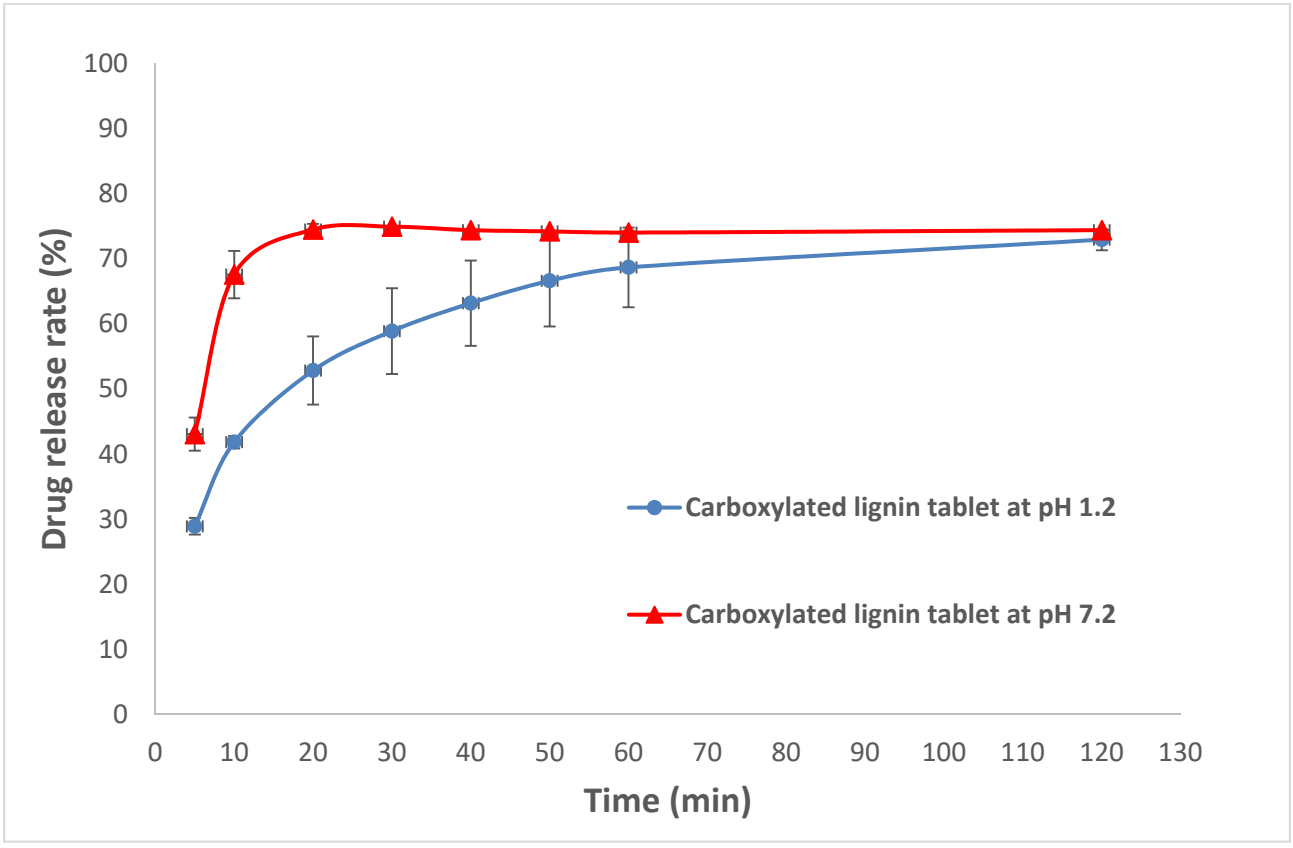

Figure 6. Drug release rate of carboxylated lignin in pH=1.2 and 7.2.

4. Conclusions

The aim of the present study was to evaluate the pH-dependent releasing behaviours of modified lignin and the effect of lignin modification on the drug release rate. Lignin modification was

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conducted via carboxylation of lignin functional groups. In order to analyse the carboxyl groups in lignin and carboxylated lignin structure, FTIR testing was carried out and the results displayed successful carboxylation. The dissolution results illustrate that there is a higher release rate of paracetamol from carboxylated lignin tablets, and this is attributed to the lower degree of interaction between lignin and the API due to the deprotonation of -COOH groups from modified lignin. Furthermore, controlled release behaviour of carboxylated lignin was performed in gastric pH of 1.2 and intestine pH of 7.2 and the release results presented a degree of controlled release. Additionally, the tablet disintegration tests showed the faster disintegration time with the carboxylated lignin tablets compared to pure lignin tablets due to lower hardness of tablets with modified lignin. Thus, these investigations presented a potential use of carboxylate[1]d lignin as an excipient in oral dosage forms.

Acknowledgements

This research was conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by SFI and is co-funded under the European Regional Development Fund under Grant Number 14/SP/2750.

The authors also would like to thank Mr. Rahmatullah Shaikh, Department of Chemical Sciences, Bernal Institute, Synthesis and Solid State Pharmaceutical Centre (SSPC), University of Limerick, Limerick, Ireland, for his useful comments on the UV calibration.

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