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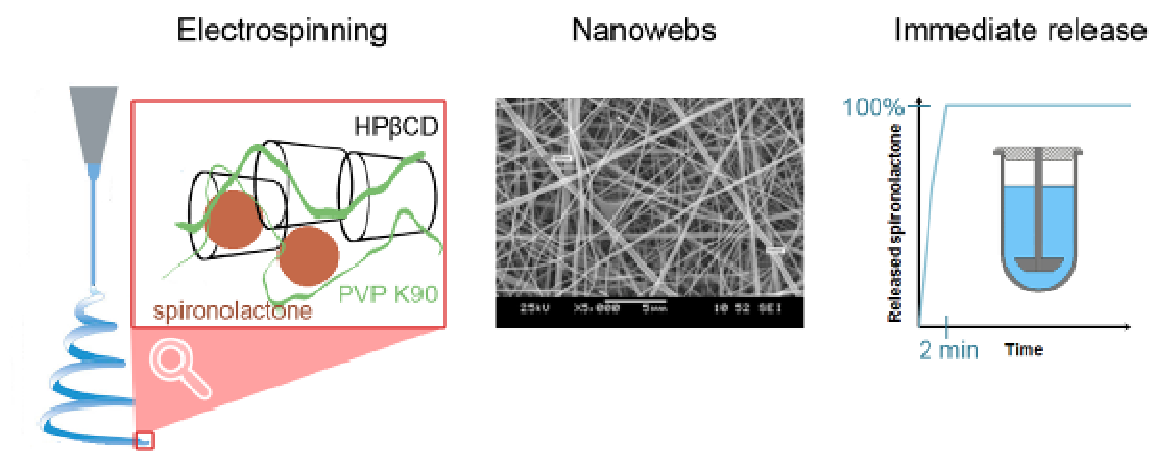
Polymer-free and polyvinylpyrrolidone-based electrospun solid dosage forms for drug dissolution enhancement

Tamás Vigh, Tímea Horváthová, Attila Balogh, Zsombor Kristóf Nagy*, György Marosi
Department of Organic Chemistry and Technology
Budapest University of Technology and Economics, Budapest, Hungary

* Corresponding author. Department of Organic Chemistry and Technology, Budapest University of Technology and Economics.
1111 Budapest, Budafoki út 8., Hungary. Tel.: +36 14631424, Fax: +36 14633648, Email: nagyzsomborkristof@gmail.com

Abstract

Fast-release nanofibres of lipophilic spironolactone were prepared in a continuous manner by electrostatic spinning, in which the application of polyvinylpyrrolidone K90 as matrix polymer enabled formation of solid solutions. However, instead of the anticipated immediate drug release, temporary precipitation was observed. The polyvinylpyrrolidone web gelled immediately after wetting, hindering drug diffusion and aiding the crystallisation of the solvated amorphous spironolactone. These local supersaturations could be successfully avoided by using hydroxypropyl- β -cyclodextrin. The oligosaccharide dissolved freely, preventing gelation and solubilising spironolactone at the place of dissolution. Transmission Raman spectroscopy, differential scanning calorimetry and X-ray powder diffraction showed that the drug was totally amorphised during processing in all formulations. High polymer content was favourable for the production of 100nm fibres, while even a small addition of hydroxypropyl- β -cyclodextrin proved enough for a dramatic release rate enhancement. Spironolactone-containing fibres were electrospun without the aid of a polymer matrix as well. This novel and still uncommon technique ensured nearly total drug release in a minute, making the system suitable for orally dissolving formulations.



Keywords: electrospinning, nanofibres, continuous pharmaceutical manufacturing, cyclodextrins, complexation, orally dissolving web, solubility, spironolactone, immediate release, transmission Raman spectroscopy

1. Introduction

Cyclodextrins (CD) and their derivatives have a rich history in pharmaceutical research and manufacture, with more than 30 CD-containing products on the global market nowadays [1]. Their reversible host-guest interaction with several drugs can enhance stability [2], mask unpleasant taste of APIs [3], decrease tissue irritation [4] and improve apparent solubility, thus helping to prevent in vivo precipitation kicsit előre szaladó gondolat, de maradhat [5]. Their solubilising effect is particularly beneficial in the case of lipophilic drugs with poor water solubility (albeit with high permeating capacity, i.e. BCS II type compounds – BCS refers to the Biopharmaceutics Classification System) – the result is a dramatic improvement in bioavailability [6]. It has been discovered that deriving CDs is important for health as well as functional reasons [7]; alkylation of –OH groups reduces secondary intermolecular interactions, resulting in higher solubility. Hydroxypropyl- β -cyclodextrin (HP β CD) is an excipient that is tolerated well by humans [8] and cited in FDA's list of Inactive Pharmaceutical Ingredients. Inclusion complexes are best formed prior to administration, during the processing of solid pharmaceuticals, in order to achieve quicker dissolution. Electrostatic spinning is a convenient process for the continuous production of drug-containing polymer nanofibres. The technique was found to be useful in many fields of pharmaceutical applications [9] – it has been used in tissue engineering [10], to manufacture wound dressings [9,11,12], transdermal [13,14] and transmembrane [15] drug delivery systems, extended release implants and textures [16,17], healthcare and surgical textiles [15] and orally dissolving immediate-release dosage forms [18,19,20,21]. The working principle is as follows: high voltage is applied between the polymer-API solution (which is pumped through a spinneret) and a grounded collector. This voltage induces the formation of an ultra-thin jet from the spinning tip, resulting in instant evaporation of the solvent. The solid API-containing polymer then builds up on the grounded collector. During the process, amorphisation takes place, elevating the free energy of API particles over that of

any crystalline forms (due to the lack of any lattice energy), resulting in the improvement of thermodynamic solubility [22]. Thus there is an increase in the dissolution driving force. Polymer matrices, which have relatively high glass-transition temperature (T_g) prevent recrystallization of amorphised compounds [23,24]. Formation of ultrafine nanofibrous solid dispersions also aids dissolution by enlarging the available surface area of the API. In addition to this, solubility also improves with decreasing particle diameter in the colloidal range [25].

Buccal absorption from electrospun webs is possible too if release from the fibres is fast enough. The novel electrospinning technique is competitive in comparison with conventional production methods of orally administered disintegrating tablets, designing of which encounters difficulties [26], and with freeze-dried batch formulations of poor strength [27]. Besides the favourable product properties, the prospect of continuous manufacture is quite attractive, as it potentiates the application of Process Analytical Technologies (PAT) and Quality by Design directives. These approaches have numerous benefits. Flexible and robust manufacturing processes can be designed [28], which can be improved continuously by building in the experience gained during production [29]. Product quality can be kept consistent over time [28], and furthermore, costs reduction can be achieved [30].

Application of the recently rediscovered and flourishing transmission Raman spectrometry (TRS) for the convenient, fast and non-invasive probing of bulk materials (tablets, capsules) has recently been reviewed by Buckley and Matousek [31]. The greatest advantage of TRS is that the technique is one of the most suitable methods to examine areas deep below the surface of the sample [32], providing accurate quantitative information, even about more complex formulations [33]. Another advantage of TRS compared to backscattering Raman spectroscopy is the suppression of surface-generated Raman and fluorescence signals [34].

The aim of this work was to investigate the applicability of electrospun polyvinylpyrrolidone (PVP), hydroxypropyl- β -cyclodextrin (HP β CD) and PVP-HP β CD nanofibres as immediate-release dosage forms and the effectiveness of TRS (as a potential PAT tool) for the detection of crystallinity in the electrospun fibres. It has been shown that PVP aids the formation of a complex with HP β CD and increases the stability constant of the complexes [35]. Furthermore, it can prolong the supersaturated state in case the complex dissolves rapidly [36]. The model drug, spironolactone (SP), was chosen from the circle of BCS II compounds with problematic dissolution properties. It is a synthetic steroid lactone, a renal competitive aldosterone antagonist. It belongs to a group of potassium-sparing diuretics, and is used primarily in the treatment of heart failure and hepatic ascites.

2. Materials and Methods

2.1. Materials

Micronised spironolactone (SP) and hydroxypropyl- β -cyclodextrin (HP β CD) with an average mw. of 1400 Da (Wacker Chemie GmbH.) were kindly provided by Gedeon Richter Plc. (Budapest, Hungary). Polyvinylpyrrolidone K90 with an average mw. of ~1000 kDa was received from BASF (Ludwigshafen, Germany).

2.2. Methods

2.2.1. Preparation of samples

As a first step, common solutions of PVP, HP β CD and SP were prepared using ethanol. Dry matter compositions are indicated in Table 1. Mixing of components to form **S1-8** was carried out at ambient temperature while warm (~50 °C) solvent was used in the case of samples **S9-13**. In order to maintain adequate viscosity for electrostatic spinning, the concentration of PVP was kept constant at 50 mg/ml

in all polymer-containing fed solutions, while in the case of the polymer-free **S8•20/80/00**, the HP β CD

concentration was set to 450 mg/ml.

Table 1

Dry matter compositions of fibres prepared by electrospinning

Sample code	SP (wt%)	HP β CD (wt%)	PVP K90 (wt%)
S1•20/00/80	20.0	0.0	80.0
S2•20/08/72	20.0	7.8	72.2
S3•20/15/65	20.0	15.0	65.0
S4•20/20/60	20.0	20.2	59.8
S5•20/30/50	20.0	30.0	50.0
S6•20/40/40	20.0	40.0	40.0
S7•20/53/27	20.0	53.3	26.7
S8•20/80/00	20.0	80.0	0.0
S9•40/20/40	40.0	20.0	40.0
S10•40/30/30	40.0	30.0	30.0
S11•50/10/40	50.0	10.0	40.0
S12•50/25/25	50.0	25.0	25.0
S13•50/40/10	50.0	40.0	10.0

Solutions showing no precipitation were loaded in 10-ml syringes and fed with a rate of 8.0 ml/h by a syringe pump (SEP-10S Plus, Aitecs, Vilnius, Lithuania). A high voltage supply (NT-35 High Voltage DC Supply, MA 2000, Nagykanizsa, Hungary) applied 25 kV between the metallic spinning tip (0.5-mm inner hole diameter) and an aluminium sheet, which was used to collect the ultrafine fibres. The horizontal distance between the aluminium sheet and the needle tip was 18 cm. All electrospinning processes were carried out at room temperature.

2.2.2. Scanning electron microscopy (SEM)

Morphology of samples was investigated with a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope. Each specimen was fixed with conductive double-sided carbon adhesive tape and sputtered with gold-palladium alloy (using JEOL 1200 instrument) in order to avoid electrostatic charging.

2.2.3. X-ray diffraction (XRD)

Samples were investigated with a PANalytical X'pert Pro MPD X-ray diffractometer (Almelo, the Netherlands) equipped with an X'Celerator detector with 0.04 sollers, using Cu K α radiation (1.542 Å) with a Ni filter. A voltage and current of 40 kV and 30 mA were used, respectively. The samples were analysed between 4° and 42° 2 θ .

2.2.4. Transmission Raman spectroscopy (TRS)

Bulk spectra of nanowebs were recorded with an AccuRA transmission Raman spectrometer (Horiba Jobin Yvon, Longjumeau, France), using 785-nm diode laser source and CCD detector.

2.2.5. Differential scanning calorimetry (DSC)

Differential scanning calorimetric measurements were carried out using Setaram DSC 92 apparatus (Caluire, France). The sample weight was between 10 and 15 mg. The temperature programme consisted of an isothermal period for 1 minute at room temperature and a subsequent linear heating from 25 °C to 300 °C with a rate of 10 °C/min, in a continuous nitrogen flow of ~30 ml/min.

2.2.6. In vitro drug dissolution

Dissolution measurements were performed on an Erweka DT6 dissolution tester (USP II Apparatus, Erweka, Heusenstamm, Germany). Electrostatically spun samples equivalent to 25 mg SP were placed in the dissolution vessel containing 900 ml distilled water maintained at (37.0 $\pm$ 0.5) °C and stirred at 100 rpm with paddles. Samples (5 ml) were withdrawn after 0.5, 1.0, 1.5, 2.0, 2.5, 5.0, 10, 15, 30, 45, 60, 90 and 120 minutes, and were not replaced with fresh water. Absorbance of spironolactone was measured at 244 nm on a Hewlett-Packard HP 8452A UV-VIS spectrophotometer (Palo Alto, USA) using a diode array detector. Concentration was calculated with the help of the calibration curve of pure spironolactone in water.

3. Results and Discussion

3.1. Preparation and visualisation of fibres

Techniques were developed which enabled the continuous manufacture of solid systems with ultrafast dissolution of the lipophilic, poor-water-solubility model drug spironolactone (SP). The hydrophilic PVP K90, being good wettable, was chosen as polymer matrix. First the active ingredient was incorporated into the pure polymer, i.e. without additional matrix components, at ambient temperature by

electrospinning (**S1•20/00/80**). In order to form fibres with uniform shape, considerable interaction was

required between molecules in the jet established during the process. Polymer concentration in the starting solution was, therefore, not negligible. Strongly interacting polymer chains orientate but do not detach from each other in the electromagnetic field, resulting in bead-free fibres. 4 to 8 wt% polymer was found to be optimal for electrospinning purposes previously [37]; accordingly, the amount of PVP was 50 mg/ml in the experiments. Morphology of the electrospun formulations was examined with

SEM (Fig. 1). In the case of **S1•20/00/80**, fibre diameters of 100 to 300nm were obtained, indicating a

high degree of entanglement and good sliding ability of oriented polymer chains. Uniform shape was found lengthwise, with no sign of beads (A).

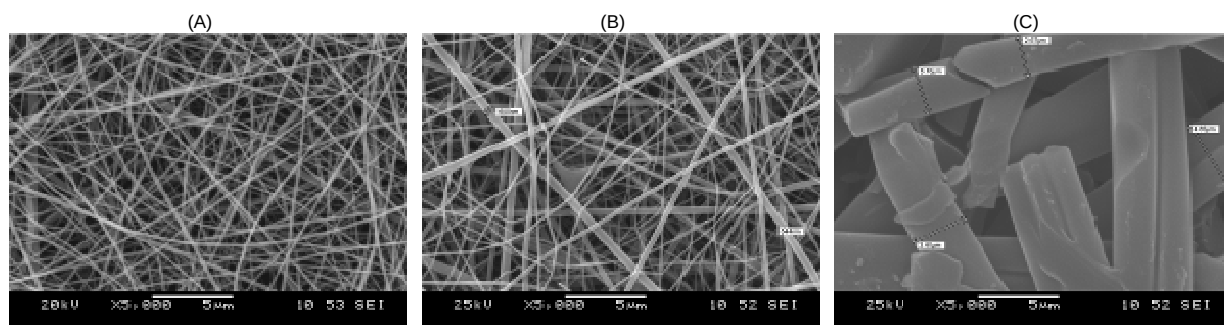


Fig. 1. SEM images of selected fibres: (A) **S1•20/00/80**, (B) **S4•20/20/60**, (C) **S8•20/80/00**

In the second phase of sample preparation it was also taken into account that the gelation of PVP K90 can retard the diffusion of the rapidly solvated API into the dissolution medium until the formulation totally disintegrates and goes into solution. Due to the low solubility of SP, this can result in local supersaturation and creates a strong driving force for precipitation as pointed out by Augustijns et al [38].

A suitable strategy to avoid supersaturation is to embed HP β CD into the fibres in different amounts (**S2-7**). One reason for the application of this additive was that its presence in the solid formulation was supposed to enable the easy disintegration of the polymer matrix and the faster diffusion of the API from the site of dissolution by loosening the network of polymer chains. The occurrence of this phenomenon is implied by the fact that the width of HP β CD-containing PVP fibres was found to be slightly greater than that of **S1**•20/00/80. For example, in the case of **S4**•20/20/60 they varied between

200-500 nm in diameter, as shown in Fig. 1 (B). Addition of the oligosaccharide, however, did not deteriorate shape uniformity. Another advantage of the application of HP β CD was that it elevated the apparent solubility of SP. This was expected to prevent precipitation. Additionally, the rate of dissolution was supposed to increase, according to Noyes–Whitney equation [39]. Common application of PVP and HP β CD was ideal, as it has been shown previously that PVP has a synergetic effect on drug complex formation and it is crucially important that the greatest possible amount of SP forms a stable complex in the dissolution medium in order to avoid precipitation.

Realisation of high drug loading in the case of immediate release formulations is often constrained by the decreased dissolution speed, which may be caused by the lower amorphisation efficiency. An attempt was made to prepare 40 and 50%-SP formulations in order to investigate the achievable drug release rate. In the case of nanofibres, poor spinnability can be another obstacle to the increase of API content. Processability of the starting solutions strongly depends on their viscosity, which is greatly influenced by polymer concentration. The percentage of PVP had to be decreased for high drug loading and the proportionally decreased fraction of ethanol could not dissolve the entire mass of SP in every case (i.e. the different samples). 40%-API mixtures could be dissolved in warm ethanol and no precipitation occurred after cooling down. Electrospinning was, therefore, robust enough in the

case of **S9**•40/20/40 and **S10**•40/30/30. On the contrary, **S11-13** could not be processed because

precipitation occurred while the solution to feed was cooling to room temperature.

While polymer chains can be easily entangled during electrospinning, it is still an engineering challenge to produce polymer-free drug-containing HP β CD fibres. Contrarily to polymers, the oligosaccharide rings can form aggregates only by secondary interactions as pointed out by Celebioglu et al. [40]. Spun HP β CD structure is held together by hydrogen bonds between the hydroxyl groups of the parallel standing rings. The lipophilic inner sides also connect with each other, forming tube-like structures. In view of the achievable advantages and lack of experience in this field, production of SP-containing polymer-free HP β CD fibres was also attempted. Starting from a viscous source solution, a stable electrified jet could be maintained without beading. As a result, continuous

fibres were obtained. Although the diameter varied between 1 and 3 μm (**S8•20/80/00**, Fig. 1 (C)),

instant dissolution could be expected owing to the highly hydrophilic oligosaccharide matrix. The high specific surface area of the examined fibres was expected to cause an extreme increase in drug release rates compared to the behaviour of crystalline SP. Moreover, ethanol evaporates rapidly during the spinning process [41,42], leaving no time for crystallisation. The obtained smooth surface and the lack of visible crystals or particles also suggested that amorphous SP was present in the fibres. This hypothesis was tested by DSC, XRD and TRS analyses.

3.2. Characterisation of physical state

Screen examinations to determine the physical state of SP in the nanofibres were carried out using differential scanning calorimetry (DSC): the melting point of crystalline SP was measured as 211 $^{\circ}\text{C}$, while no matrix components had thermic changes around the investigated temperature point, as Fig. 2 shows. No melting transition could be detected in the case of formulations, indicating that no lattice-structured SP was present in the matrix, i.e. the active ingredient had been amorphised – selected thermograms can be found in Fig. 2.

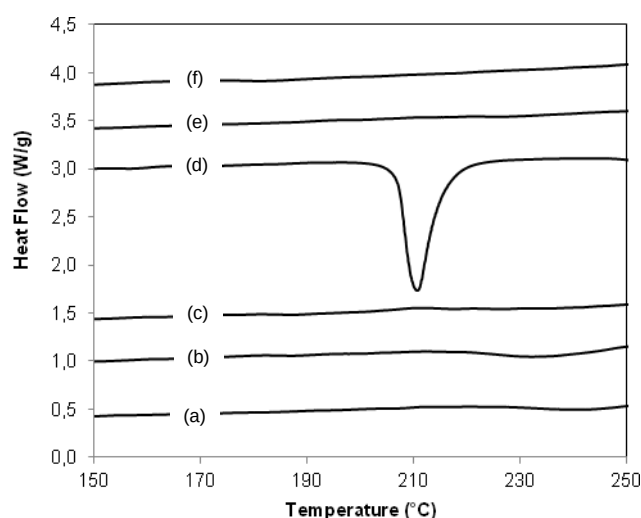


Fig. 2. DSC thermograms of (a) **S1•20/00/80**, (b) **S4•20/20/60**, (c) **S8•20/80/00**, (d) crystalline SP, (e) HP β CD and (f) PVP K90

The use of DSC for the detection of remaining crystals in SP-containing nanosystems is less appropriate than that of Raman spectroscopy or XRD as it was concluded from recent relevant experiments [42]. Hence the samples were analysed using those two techniques as well.

Transmission Raman spectra (TRS) resemble the compositions of the examined bulks and, additionally, polymorphic content of pharmaceutical formulations can be quantified [43]. The

hypothesis that TRS could be successfully employed for the detection of SP forms was confirmed by the fact that the Raman spectrum of SP changes when its physical state is changed (Fig. 3: a-b). Crystals contain molecules in an arranged and repetitive structure; neighbourhoods of Raman-active bonds are thus the same in each molecule. The peak at 1690 cm^{-1} (indicated with an arrow on Fig. 3) is assigned to the C=O bond of the thioacetyl group. If this peak is well observable, spironolactone crystals are present. Broadening or, in an extreme case, disappearance of this peak indicates that amorphisation has taken place. As amorphous bulk has no ordered structure and neighbourhoods are diverse, vibration energies are perturbed [44,45].

Raman spectroscopy confirmed, in accordance with the DSC results, that all formulations remained totally amorphised after preparation (Fig. 3). Besides the stabilisation of inordinate structure by rapid solvent evaporation, formation of SP-HP β CD inclusion complexes may also have contributed to the prevention of crystallisation during electrostatic spinning, while the high T_g of PVP K90 ($174\text{ }^{\circ}\text{C}$) ensured the stability of physical state during storage. (Our previous researches have shown that a huge fraction of totally amorphous electrosprayed SP crystallises after a day, i.e. amorphous state is fairly unstable alone.)

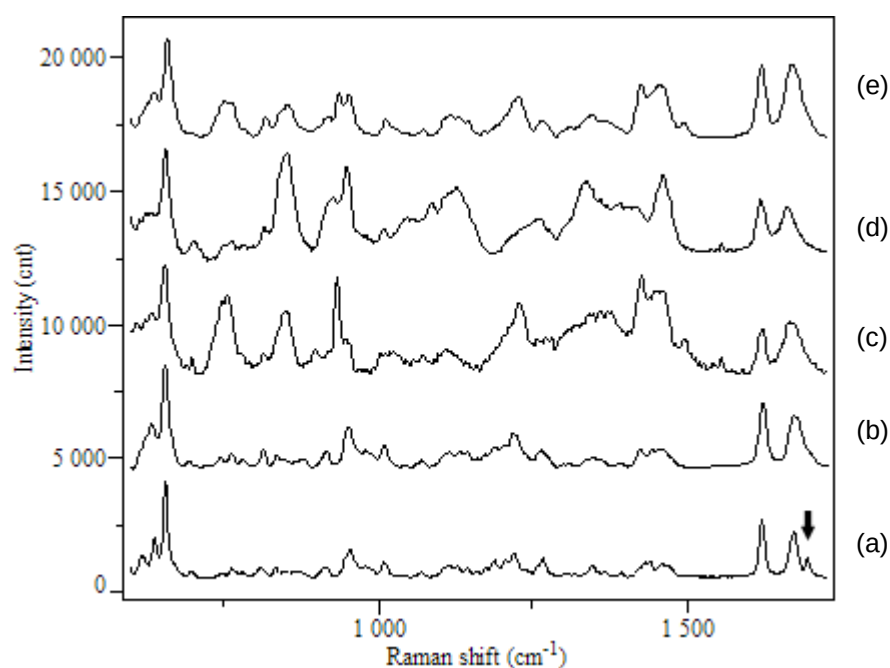


Fig. 3. Raman spectra of (a) crystalline SP, (b) electrosprayed amorphous SP,

(c) **S4•20/20/60**, (d) **S8•20/80/00** and (e) **S9•40/20/40**

The results obtained using the novel TRS technique were compared to X-ray powder diffraction (XRPD) measurements, the latter being the conventional method to detect crystallinity. Taking into account that neither PVP, nor HP β CD showed diffraction peaks, a flat XRD curve was expected in the case of nanofibres containing totally amorphised API. Fig. 4 displays the scattering curves of selected formulations and the pattern of pure crystalline SP. Disappearance of the diffraction pattern clearly proved that crystals were absent in all formulations. It must also be highlighted that TRS and XRD

results were in accordance for every sample. TRS can be used as a PAT analytical tool for the detection of physical state and provides qualitative and quantitative information about composition. Thus this novel technique proved to be competitive in comparison with XRD considering industrial applications where high-throughput multifunctional analytics is desirable.

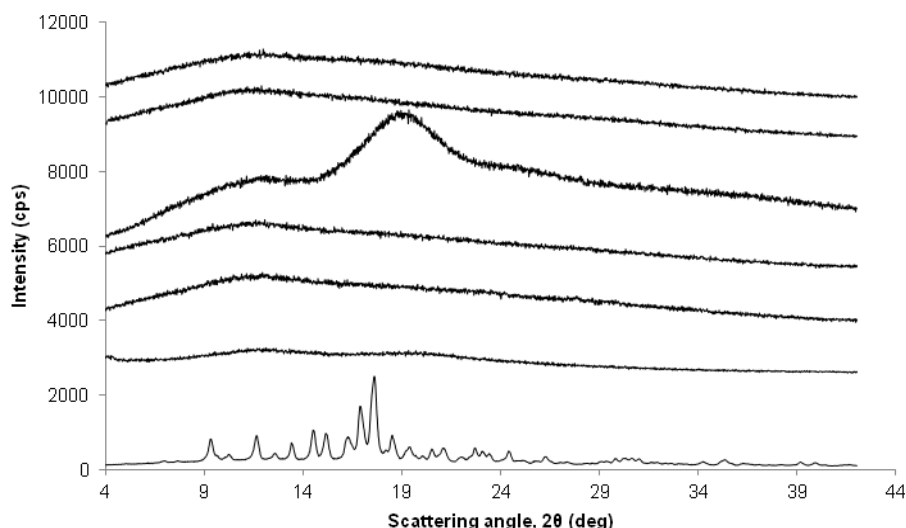


Fig. 4. X-ray scattering curves of selected formulations.

(a) Crystalline SP (starting material), (b) **S1•20/00/80**, (c) **S2•20/08/72**,

(d) **S4•20/20/60**, (e) **S8•20/80/00**, (f) **S9•40/20/40**, (g) **S10•40/30/30**

3.3. Drug release

All formulations were tested for drug release. In comparison with neat crystalline SP, initial drug

release from **S1•20/00/80** was reasonably fast: 63% of the drug content had dissolved after 30

minutes (Fig. 6). At the same time, precipitation was observed at the beginning of the measurement. Surprisingly, the precipitated SP was found to be crystalline according to the Raman spectrum recorded immediately after precipitation (Fig. 5) in spite of the fact that the API was totally amorphous in the solid formulation. SP concentration changed little after first 30 minutes, remaining around 70% of the drug content in the examined period of time. According to earlier measurements made, PVP does not cause SP solubility to decrease. Hence this observation can only be explained by local supersaturations. After wetting, the large specific surface area of the nanofibres enabled rapid release and solvation of the molecularly dispersed API at the same time as PVP underwent gelation. With the hindered diffusion from the gelled polymer matrix, local supersaturations occurred, followed by instant crystallisation.

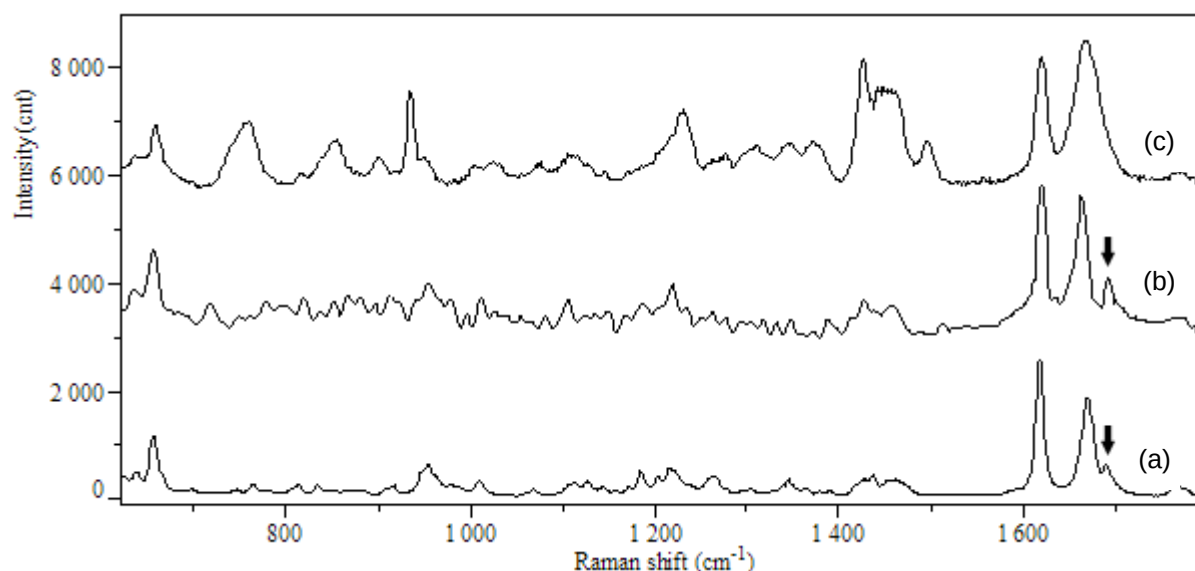


Fig. 5. Recrystallisation of SP after precipitation during dissolution – Raman spectra

(a) Crystalline SP

(b) SP precipitated during the dissolution of **S1•20/00/80**

(c) **S1•20/00/80** containing SP totally amorphised

These observations confirmed the necessity of complex formation with HP β CD posteriorly. It improves apparent solubility of SP [46] and thus hinders the formation of local supersaturations so that the benefits of amorphisation can be entirely made use of. Some precipitation occurred in the case of

S2•20/08/72 as well for the proportion of HP β CD was most probably not enough to avoid

supersaturation entirely. The phenomenon was not observed in the case of **S3-7**, which contained the complexing agent in a higher ratio (15-53.3 wt%) and, therefore, adequate solubilisation could be reached in the dissolution medium even at the beginning of dissolution.

Table 2

Average initial release rate from formulations and initial dissolution rate of crystalline SP

Sample name	Cryst. SP	S1	S3	S5	S6	S7	S8
HP β CD/PVP mass ratio	–	0	0.23	0.60	1.00	2.00	–
Initial drug release rate (mg/min) ^a	0.20	1.13	1.40	1.87	2.39	2.51	2.39

^a based on the first 10 minutes

Table 2 shows the positive correlation between initial dissolution rate and HP β CD/PVP ratio due to the improved wetting properties and less dominant gelation. An HP β CD content of 15% (**S3•20/15/65**)

was enough to ensure total drug release during the 2-hour measurement albeit at a moderate rate: 90 minutes were required (Fig. 6). Increasing the percentage of the complexing agent also increased the probability of inclusion complex formation during electrospinning, and the presumed presence of the hydrophilic SP-HP β CD complex became more dominant to the proportion of non-complexed lipophilic SP (leading to better surface wettability). In addition to this, less PVP K90 was used in these formulations, leading to less gelation and thus fast disintegration. Consequently, when there was twice as much HP β CD as SP (**S6•20/40/40**), 100% of the API was released after 20 minutes. Immediate

dissolution was achieved at 53.3% HP β CD content (**S7•20/53/27**), with 100% released in 2 minutes.

S8•20/80/00 consisted of SP and HP β CD only. PVP was left out of the formulation entirely, thus fibre

diameter increased notably. However, this had no great influence on dissolution rate, owing to the extremely good wettability and rapid disintegration of the oligosaccharide. Consequently, more than 90% was dissolved in 1 minute.

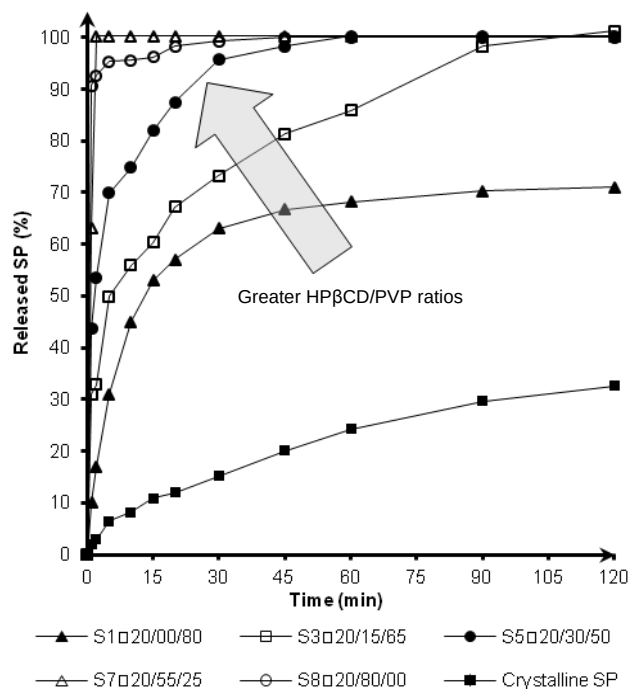


Fig. 6. Effect of HP β CD content on the dissolution rate in the case of 20% formulations

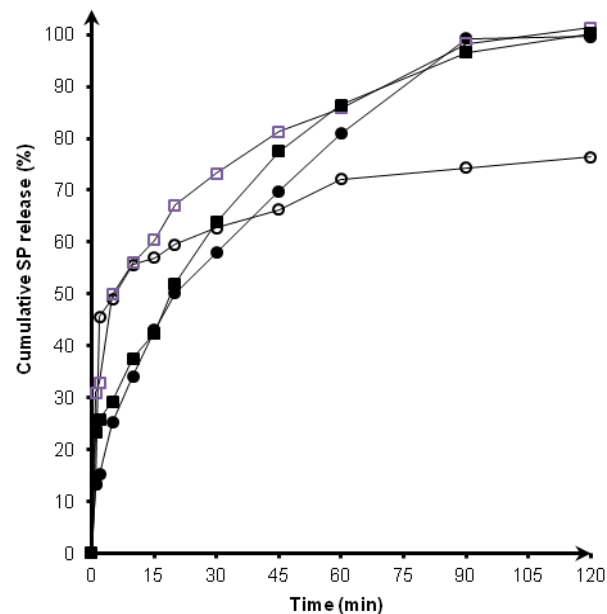


Fig. 7. Dissolution of 40%-SP formulations compared to 20% fibres of the same HP β CD to SP ratio

The influence of PVP K90 gelation on dissolution can be observed most clearly by comparing 20%-

and 40%-SP formulations of similar HP β CD/SP ratios (**S2**•20/08/72 and **S9**•40/20/40; **S3**•20/15/65

and **S10**•40/30/30). If the solubilisation power were alone responsible for the avoidance of

precipitation and the dissolution enhancement, there should have been similar curves for these parallel formulations. On the contrary, Fig. 7 shows that complete release could be achieved in the

case of **S9**•40/20/40 containing 40% API and only 40% PVP, while precipitation took place in the case

of **S2**•20/08/72 containing 20% SP and 72% PVP. It seems the PVP percentage in the fibres had a

huge impact on the outcome. At the same time no remarkable difference could be observed between **S3•20/15/65** and **S10•40/30/30**, as the matrix of **S3•20/15/65** could already disintegrate fast enough to hinder precipitation. Thus, a further decrease in PVP percentage (**S10•40/30/30**) did not result in dissolution rate increase.

4. Conclusion

In this work, immediate- and fast-release spironolactone nanowebs were prepared in a continuous electrostatic spinning process. Diameter of fibres ranged from 100 nm to 3 µm, depending on the composition.

In one part of the work, electrospinning of polymer-free HPβCD fibres was accomplished. This system ensured total drug release in a minute, demonstrating that formulations of highly lipophilic drugs that dissolve in the mouth can be developed using this technique.

Furthermore, hydroxypropyl-β-cyclodextrin was shown to have benefits beyond the acceleration of dissolution too: precipitation of released spironolactone due to local supersaturations could be successfully hindered with the complexing agent when the formulation matrix was PVP. Transmission Raman spectroscopy, in agreement with XRD, showed that the API was totally amorphised in all formulations due to rapid solvent evaporation and formation of inclusion complexes during processing. The results confirm that electrospinning is a competitive, continuous technique for the manufacture of buccal dosage forms and immediate-release solid solutions for oral administration in the case of BCS II drugs, eliminating a barrier of absorption and consequently improving bioavailability.

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