Jet dispensing of multi-layered films for the co-delivery of three antihypertensive agents

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Abstract

Three-layer thin films comprising of two polymers as substrate (ethyl cellulose and, copovidone K28) and three antihypertensive agents (hydrochlorothiazide, amiloride HCl and carvedilol) were printed using jet-dispensing technology. Two film formulations with different ethyl cellulose to copovidone K28 ratio (i.e. 90/10 and 50/50 w/w) were prepared using a three-course dispensing. The films were characterized regarding surface morphology, solid-state properties, polymer-drug interactions, drug distribution in each layer and their *in-vitro* drug release. All the components of the films were found to be in the amorphous state apart from hydrochlorothiazide which retained its crystallinity. FT-IR spectroscopy revealed hydrogen bond interactions between carvedilol and copovidone K28. Combinations of ethyl cellulose and copovidone K28 provide suitable polymeric film substrates with the ability to modify drug release. Particularly, decreased ethyl cellulose to copovidone K28 weight ratio was found to suppress the crystallization of hydrochlorothiazide and to increase the release rate of the dispensed drugs. Jet dispensing was found to be a rapid technology for the preparation of multi-layered films that can be used as personalized formulations for the delivery of combinations of drugs.

Keywords: jet dispensing, films, combination therapy, antihypertensive drugs

1. Introduction

Combination treatment has now become the standard line of treatment for cardiovascular diseases reducing the burden of morbidity and mortality associated with these pathologies [1]. Especially, for the management of hypertension, monotherapy is effective in achieving the target goal in only about 50% of patients and treatment with two or more agents from classes with different pharmacological action is often necessary to achieve adequate blood pressure control [2]. Moreover, combination therapy offers several advantages over monotherapy such as superior antihypertensive efficacy, dose strength and fewer adverse effects. For that purpose, the combination of multiple therapeutic agents into a single formulation with appropriate release profiles and doses (potentially optimized for individuals) has been suggested as an alternative approach [3].

The most recent methods for the manufacturing of multi-dosage formulations with well-defined release profiles make use of 3D printing technologies. Khaled *et al.* applied 3D extrusion-based printing for the manufacturing of multi-active solid dosage forms containing three [4] and five compartmentalized drugs [5] with independently controlled and well-defined release profiles indicating that printing technologies hold potential for the tailored manufacturing of medicines paving the way towards personalized care and treatment.

Jet dispensing is a technology that can continuously dispense liquids with a wide range of viscosities by moving the nozzle at high speeds across the x-axis and the stage across y-axis to cover all coordinates and jetting precise volume of dots. It is a highly accurate technique and can deliver nanoquantities of drugs which cannot be achieved by the current 3D printing technology. According to this technology, the jetting device operates in a continuous mode by using a pneumatic piston with a ball tip end to push fluid through a narrow orifice at the jet nozzle tip. Air pressure is used to apply force and lifts ball-needle from its seat, thereby fluid

is allowed to flow down and around the ball-needle tip. Subsequently, the air pressure is released allowing the force from the compressed spring to slam the ball-needle tip back down into its seat, separating and ejecting a dot from the fluid. As the ball returns, the force due to acceleration breaks the stream of the drug–polymer solution, which is jetted through the nozzle. The broken stream of the solution strikes the substrate from 1.0 mm to 3.5 mm above the board forming the dot. In the field of pharmaceutics, Scoutaris *et al.* [6] reported the use of jet dispensing as a rapid and reproducible technology for the preparation of taste-masked mucosal thin films with drug loadings ranging from 20 to 40% and excellent content uniformity. Recently, Scoutaris *et al.* [7] investigated the use of jet dispensing as a high-throughput screening technology for pharmaceutical cocrystals.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic that works by increasing the amount of salt and water that the kidney removes from the blood causing a decrease in blood volume. It exerts its mechanism of action by inhibiting the re-absorption of salts from the renal tubules leading to increased excretion of sodium and chloride ions and consequently of water. HCTZ is employed for the treatment of oedema and hypertension. Its usual adult dose in the case of hypertension is 25 mg orally once daily that can be increased to 50 mg daily as a single or two divided doses [8]. Amiloride HCl (AMI) is a potassium-sparing diuretic which promotes excretion of sodium and chloride while retaining potassium. AMI is prescribed as adjunct therapy to thiazide or loop diuretics for the treatment of hypertension to achieve potassium conservation and thus avoid hypokalaemia. Co-administration of AMI/HCTZ 2.5/25 mg is a common fixed dose combination for the treatment of hypertension known with the non-proprietary name co-amilozide. Carvedilol (CARV) is a non-selective β-blocking agent that has been approved for the treatment of heart failure, essential hypertension and coronary artery diseases. Controlled-release once-daily formulations of CARV are commercially available and considered as a more convenient option conferring an adherence benefit over immediate-

release formulations in conditions traditionally prone to noncompliance such as hypertension [9]. CARV and HCTZ are often administered together as a fixed dose combination for the treatment of essential hypertension particularly in cases where monotherapy cannot provide sufficient lowering of the blood pressure [10]. A combination of more than two drugs may be required for the adequate management of blood pressure. In such cases the third agent added to the medication should belong to a different pharmacological class than the initial two drugs [11].

The aim of this work is to use jet dispensing technology for the preparation of films which combine multiple drugs with different dose and independent release profiles. Two polymers (ethyl cellulose and copovidone K28) were used as substrate and hydrochlorothiazide, amiloride HCl and carvedilol as the antihypertensive agents. The films produced were characterized regarding their morphology, solid-state properties, drug-polymer interactions and distribution in each layer. The effect of the ratio of the two polymers on the *in-vitro* drug dissolution was also investigated. To the best of our knowledge this is the first study where the use of jet dispensing technology is extended to the preparation of films containing multiple drugs with independent release profiles.

2. Materials and methods

2.1. Materials

Hydrochlorothiazide (HCTZ), carvedilol (CARV) and amiloride hydrochloride hydrate (AMI) were purchased from TCI (Tokyo Chemical Industry Ltd, UK). Ethyl cellulose (EC N10 Pharm) and Kollidon® VA 64 (copovidone K28) were purchased from Hercules GmbH (USA) and BASF (Germany), respectively. The chemical structures of the antihypertensive agents and polymers used for the preparation of the films are depicted in Fig.1. Ethanol and methanol were purchased from Sigma-Aldrich (UK). All the solvent used were of analytical grade.

2.2. Methods

2.2.1. Preparation of films by jet dispensing

According to the dosage design, the multi-layered structure of the film and the presence of the polymers will allow controlling the release of each drug. Specifically, CARV and AMI are included in the top layers of the film (layers 2 and 3) in order to achieve immediate release which will be followed by controlled release of HCTZ and CARV embedded in the polymeric matrix of the bottom layer (layer 1). A schematic diagram of the film is illustrated in Fig. 2a.

Jet dispensing was carried out using a laboratory DispenseMate 583 dispenser (Nordson-Asymtek, Netherlands). The layers of the films were prepared by jetting solution of the drugs and polymers in several parallel lines. For the purposes of this study, the nozzle speed and jetting rate were set at 9 mm s^{-1} and 33 drops s^{-1}, respectively. The fluid pressure used was 11.4 bar and the nozzle 100 μm. (Fig. 2b). The size of the ball tip and the seat was 2.4 mm and 0.32 μm, respectively. For the first layer, HCTZ (7.0 mg ml^{-1}), CARV (0.7 mg ml^{-1}), EC (13.87 mg ml^{-1}) and copovidone K28 (1.54 mg ml^{-1}) were dissolved in ethanol. The same method was applied to deposit pure AMI on the surface of the first films. AMI (10 mg ml^{-1}) was dissolved in a mixture of ethanol/water (60/40 v/v). The precursor solution leading to the formation of

the third layer consisted of CARV (30.3 mg ml^{-1}) and copovidone K28 (60.6 mg ml^{-1}) dissolved in methanol. Two types of formulations were prepared which differ in the ratio of EC/copovidone K28 incorporated in the first layer of the film (i.e. 90/10 and 50/50) while layer 2 and 3 were common for both types of films. Table 1 summarizes the nominal composition of each layer for the two formulations of jet-dispensed films prepared in this study and the volume of the precursor solutions printed per film.

2.2.2. Characterization of the films

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to study the surface morphology of the films. Samples were placed on the holder with double-sided carbon tape and sputter-coated with gold (Edwards 188, sputter coater S1508) under argon atmosphere. SEM micrographs were taken using a Hitachi SU 8030 (Japan), at an accelerating voltage of 1.0 kV.

X-ray diffraction

X-ray diffraction (XRD) patterns were obtained with a Bruker D8 Advance (Germany). Cu Kα radiation at 40 mA and 40 kV with a step size of 0.02 2 theta and a speed of 0.3 s per step were used, covering a 2 theta of 5-40^{o}. The samples were rotated at 15 rpm. For the raw materials, which were in the form of powders an exit slit of 0.2 mm was used. XRD of the films was carried out using the transmission mode with a 0.6 mm exit slit. DIFFRACplus XRD Commander was the analysis software.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was performed using a Mettler-Toledo 823e (Switzerland) previously calibrated with indium. Weighed powder samples (2-5 mg) were sealed in aluminium pans with a pierced lid and heated under nitrogen flow (50 ml min^{-1}) at a

heating rate of 10 ºC min^{-1}. The heating range for the polymers and the films was from 25 to 300 ºC while for the raw drugs from 25 to 30 ºC above the melting point.

Fourier-transform infrared spectroscopy

Spectra of the raw drugs, polymers and jet-dispensed (JD) films were recorded using a Spectrum100 FT-IR spectrometer (PerkinElmer, Inc., USA) equipped with the attenuated total reflection sampling accessory. Samples were scanned at room temperature, at the transmission mode, over a wavenumber range of 4000–450 cm^{-1}, 16 accumulations and 1 cm^{-1} resolution. Before each measurement, a background spectrum of air was acquired under the same instrumental conditions. The acquired spectra were processed using the PerkinElmer Spectrum Express software.

Confocal Raman spectroscopy

Raman mapping was performed in the JD films 50/50 EC/copovidone K28 using a Jobin-Yvon LabRam 320 instrument equipped with an Olympus microscope (Horiba, Japan) by means of a He–Ne ion laser (λ = 632.8 nm) and 1800 nm^{-1}. The experimental conditions were 100 nm slit width, a 50 × Microsoft objective and 0.2 s acquisition times. Each spectrum was the mean of two. The sample profiling was performed at step increments of 8 μm in the X–Y direction over an area of 2000 × 600 μm^2. Principal component analysis (PCA) was used for analysis of the data. Prior to the analysis, all spectra were baseline corrected and normalized using the standard normal variate method (SNV) to avoid intensity deviation among the Raman spectra. The Raman chemical maps were constructed by using Solo + Mia software (Eigenvector, Research, Inc., USA).

2.2.3 Drug content and *in-vitro* dissolution studies

Drug content analysis

Jet-dispensed films were dissolved in a solution of 20% methanol in water. Solutions were filtered through a 0.45 μm PTFE syringe filters. The filtrate was analysed by HPLC-UV (Agilent 1200 Series, Agilent technologies, Germany). The stationary phase was a Waters Spherisorb® C-18 column (250 mm x 4.6 mm x 5 μm; Waters Corporation, USA). The column was maintained at 40 ºC and the injection volume was 20 μl. The monitored wavelength was 240 nm. For the simultaneous quantification of the three drugs, a gradient method was developed. The mobile phase consisted of the polar solvent A which was water with 1% triethanolamine (pH:2.2 adjusted by addition of orthophosphoric acid) and the organic solvent B which was acetonitrile. The flow rate was 1 ml min^{-1} and the gradient schedule was as follows: 0-6 min isocratic at 20% B, 6-10 min 20 → 70% B, 10-20 min isocratic at 70% B, followed by a linear change to initial conditions in 5 min of column re-equilibration. For each drug, the correlation coefficient of the calibration curve was $R^2 > 0.999$ for a concentration range of 5-100 μg ml^{-1}, indicating acceptable linearity. Drug content analysis was carried out in triplicate for each formulation (n=3).

***In-vitro* dissolution studies**

The in-vitro dissolution study of the jet-dispensed films was carried out using the USP apparatus type II (Varian 705 DS, Varian Inc., USA) at 37 ºC and 100 rpm stirring speed. To evaluate the dissolution of the formulations under conditions mimicking the gastrointestinal environment, jet-dispensed films were subjected to dissolution testing for 2 h in hydrochloric acid media (900 mL) at pH:1.2 and then were transferred for 3 h in phosphate buffer solution at pH:6.8. At specific time intervals up to 5 h, 5 ml of dissolution medium was withdrawn, filtered through 0.45 mm PTFE syringe filter and placed in HPLC vials for assay while

immediately replaced with 5 ml of fresh medium. The HPLC conditions for the assay were identical to those for drug content determination. Dissolution tests were made in triplicate for each formulation (n = 3).

3. Results and discussion

Films of 1 cm^2 were produced by jet dispensing (Fig. 3). The size of the film is close to that of a five-pence coin showing that they could be easily placed in the oral cavity and get swallowed. Jet dispensing appeared to be capable for rapid and reproducible production of thin films comprising of drugs with remarkably different water solubility in a wide dose range. Compared to the conventional method of solvent casting where a common solvent system should be selected to dissolve all drugs and polymers, in jet dispensing drug and polymer solutions in different solvents can be prepared and dispensed separately allowing greater versatility especially in the case of multi-drug films. By adjusting the film dimensions the printed drug amounts can be easily tuned and adjusted to individual patient needs [12]. Flexible manufacturing processes with adjustable dose strengths like printed films are considered particularly innovative and interesting for applications in personalized medicine or early drug development [13].

Surface morphology and solid-state characterisation

SEM images reveal the multi-layered structure of the films consisting of three layers (Fig.4a, c). Layer 1 is the bottom layer consisting of HCTZ and CARV embedded in a matrix of EC and copovidone K28, layer 2 is the middle layer consisting of AMI and layer 3 is the top layer that was formed by jetting few drops of CARV in copovidone K28. Despite the differences in the ratio of polymers used for each film formulation, the respective layers of both film formulations exhibit the same morphology. Specifically, both layer 1 and 3 are smooth and transparent indicating that the drugs are incorporated in the polymeric matrix while layer 2 consists of fine AMI particles (Fig. 4b). This shows that jet dispensing of drug solutions containing polymers (layer 1 and 3) simulates conventional film casting with drug embedded in the film, while in the absence of polymers (layer 2) it simulates ink-jet printing and the drug is resided on top of the film (Fig. 4d, [14])

XRD is a fast and straightforward method for determining basic information regarding the solid state of a material/ formulation with a limit of crystallinity detection in amorphous drug compositions around 5–10% [15]. The XRD diffractograms of the raw drugs exhibit characteristic peaks indicating their crystallinity while the patterns of both EC and copovidone K28 consist of an amorphous halo due to the amorphous nature of these polymers (Fig. 5a). The XRD diffractograms of the film formulations exhibit an amorphous halo with some characteristic peaks (2 theta: 16.7º, 19.5º, 19.9º, 21.5º, 24.8º, 28.3º) which are attributed to HCTZ (Fig. 5b, [16]). These results indicate that all the components of the film are in the amorphous state apart from HCTZ which is in the crystalline form. The reduced intensity of HCTZ peaks for the film 50/50 EC/copovidone K28 compared to those of the film 90/10 EC/copovidone K28, indicates that increased incorporation of copovidone K28 suppressed the crystallization of HCTZ.

The DSC thermographs of the raw drugs exhibit sharp endothermic peaks at 271 ºC, 118 ºC and 293 ºC due to the melting of HCTZ, CARV and AMI, respectively (Fig. 6a). Moreover, in the case of AMI, the endothermic event from 120 to 150ºC is related to the loss of water from the hydrate form of AMI. In the DSC thermographs of the jet-dispensed films, the broad endothermic peak from 40 to 100 ºC can be due to the presence of copovidone K28 while the small endothermic peaks around 230-250 ºC can be attributed to the melting of HCTZ (Fig. 6b). The melting point of HCTZ in the films has shifted to lower temperatures due to the presence of other compounds and the reduction of the size of the drug crystals which are now embedded in the polymer matrix of the first layer forming a solid dispersion. XRD and DSC are in agreement regarding the solid state of the jet-dispensed films which are partially amorphous as all the components are in the amorphous state apart from HCTZ which retains its crystallinity in the formulation.

FT-IR

FT-IR spectroscopy was implemented to identify interactions among the drugs and the polymers. The FT-IR spectra of the raw drugs, polymers and the films are illustrated in Fig. 7.

To investigate the presence of interactions between copovidone K28 and CARV, films with composition corresponding to layer 3 were prepared by jet dispensing (JD CARV/Copovidone K28). The FT-IR spectrum of CARV raw material showed a well-defined characteristic peak at 3342 cm^{-1} corresponding to the NH stretching vibration of the secondary amine. In this region, copovidone K28 demonstrated a very broad peak due to water adsorption related to the highly hygroscopic nature of the polymer (Figs. 7a, 8a). In the FT-IR spectrum of JD CARV/Copovidone K28, the peaks assigned to NH group and water have been merged and moved towards lower wavenumber indicating hydrogen bonding interaction. Also, the broadness of the peak is attributed due to the amorphous nature of CARV [17]. Moreover, the peaks of copovidone K28 at 1667 and 1661 cm^{-1} which correspond to the carbonyl peaks of aliphatic and aromatic ring have moved towards lower wavenumbers at 1658 and 1652 cm^{-1}, constituting another indication of strong hydrogen bonding interactions between CARV and copovidone K28 (Fig. 8b).

The FT-IR spectra (region: 3100-3800 cm^{-1}) of the crystalline HCTZ and the jet-dispensed films are illustrated in Fig. 9a. The most important chemical groups of HCTZ molecule are the four amino groups and the S=O groups, since these groups can interact either with other HCTZ molecules or with other compounds by means of hydrogen bonding. Specifically, HCTZ can interact with copovidone K28 via hydrogen bonding of its amino group with the carbonyl group of the polymer. HCTZ has four amino groups; two are coming from the primary sulphonamide, one from the secondary sulphonamide and finally there is one secondary amino group. In the crystalline powder, the peaks which correspond to the NH groups are at, 3392cm^{-1}, 3359cm^{-1},

3262cm^{-1}, 3166 cm^{-1} (Fig. 9a). The assignment of the NH peaks has been previously reported by Tajber *et al.* [18]. Specifically, 3392cm^{-1} corresponds to N-H secondary amines, 3362 cm^{-1} 3166 cm^{-1} at asymmetric and symmetric stretch vibration of primary sulphonamide and 3262cm^{-1} is the N–H stretch of the secondary sulphonamide. The symmetric stretching vibration of SO groups appears at 1149cm^{-1} and 1163cm^{-1}, whereas the antisymmetric stretching vibration of SO group is detected at 1347cm^{-1} and 1333cm^{-1}.

The potential hydrogen donors of HCTZ are the two amino groups of the primary sulphonamides, one from the secondary sulphonamide and one from a secondary amino group. In general, the best hydrogen bond donor will bond to the best hydrogen bond acceptor. Moreover, hydrogen bond donating abilities correlate with the acidities, as the more highly acidic group is a better donor among the similar functional groups. In the case of HCTZ, according to Adsmond *et al.* [19] the amido group is more acidic than the proton in the amino group, due to the strong electronegative character of the SO group which is able to polarize the nitrogen atom positively which in turn facilitates the release of the proton. Consequently, HCTZ will interact with the copovidone K28 via the amido group. However, the spectra did not confirm any hydrogen bonding between the carbonyl group of copovidone K28 and the amino group of HCTZ as the amino groups of HCTZ in the jet-dispensed films remain at the same position with the pure material (Fig. 9a). However, the carbonyl peaks which appeared in Fig. 9b should correspond to copovidone K28 which has moved towards lower wavenumbers at 1651 and 1657 cm^{-1}, indicating that copovidone K28 participates in hydrogen bonding interactions probably with CARV as it was mentioned previously. This is probably due to the fact that the amino groups of CARV are more electronegative than those of HCTZ.

Confocal Raman mapping

The spectra of the pure compounds in the 1000 – 1650 cm^{-1} region are illustrated in Fig.10. Carvedilol has three characteristic peaks at 1577, 1593 and at 1633 cm^{-1} and one at 1286 cm^{-1}

corresponding to CC stretching vibration and at CN sym. stretch vibration. A detailed description of the peaks has been reported by Marques *et al.* [20]. In HCTZ the strong peaks exist at 1295 cm^{-1} and at 1313 cm^{-1} while the strong peak at 1596 cm^{-1} is assigned to the NH_2 ending vibration. In terms of AMI, the two peaks at 1651 and at 1673 cm^{-1} can be attributed to C=N and C=O vibrations.

In order to investigate the distribution of the drugs on the formulation the results from confocal Raman mapping technique were analysed using principal component analysis (PCA). Based on the eigenvalues, the hyperspectral data can be described by two principal components (PCs, Fig. 11a). This is a typical observation in multivariate data analysis of Raman spectra, which leads arbitrarily to the assumption that there are only two components in the system, as the first PC corresponds to the features of the strongest spectral contributors. It can be clearly observed that the three first loadings contain characteristics peak pattern of HCTZ. Hence, for instance the strong peaks at 1149cm^{-1} and 1163cm^{-1} correspond to the symmetric stretching vibration of SO groups. It is interesting also to see in PC3 the latter peak has moved towards higher wavenumbers at 1174cm^{-1} from 1163cm^{-1}, probably due to interactions or due to different chemical environment of these HCTZ molecules. As in the case of HCTZ, characteristics peaks of CARV appear to all the PCs at 1287 cm^{-1} and at 1633cm^{-1}, indicating that both drugs are distributed across the surface (Fig.11b).

Also, the distribution of CARV in the 3rd layer was attempted. However, the PCA in the 3rd layer showed that the predominant peaks at 1288 cm^{-1}, 1388 cm^{-1}, 1510 cm^{-1} of the first PCs correspond to AMI. This can be explained by the fact that the solution of CARV/copovidone was completely absorbed by the 2nd layer.

Drug content and *in-vitro* dissolution studies

Drug content analysis of the films produced by jet-dispensing was close to the nominal values (6% relative standard deviation or less). This can be linked to the accurate dot deposition achieved by the jet dispenser which subsequently eliminates drug loss or dose variation. Moreover, jetting of solutions rather than suspensions eliminates the risk of sedimentation prior to jetting that can adversely impact drug content in each film.

The dissolution profiles of the three drugs from the two types of jet-dispensed films are illustrated in Fig. 12. For both formulations studied, complete and immediate release of AMI from the films is achieved as it expected, since it was jetted alone without any polymer in the second layer of the films. This shows that second layer manages to act as an immediate release layer following the concept of the formulation design. The release of HCTZ from the films is not complete and is delayed with the increase of EC in the polymer matrix. Unlike EC, the increase of copovidone K28 improved the release profile of all the drugs and this can be attributed to the function of this polymer as a pore former facilitating drug release from the EC matrix [21,22]. Specifically for HCTZ, when 10% of copovidone K28 was used 20% of HCTZ was released, whereas in the case of 50% of copovidone, HCTZ release increased to 60%. In the case of CARV, in both films there is an initial burst release where 20% of drug is released, attributing to the amount of drug that was deposited on the third layer and was combined with the hydrophilic copovidone K28 whereas the rest of the drug was remained trapped in the EC matrix of the first layer. The entrapment of HCTZ and CARV in the EC matrix can be attributed to the hydration of the EC and subsequent formation of a gel layer which prevents the incorporated drug molecules to migrate to the dissolution medium.

4. Conclusions

Multi-layered films containing three antihypertensive drugs were prepared by jet dispensing. The films were characterized regarding their morphology and solid-state properties while FTIR spectroscopy and confocal Raman mapping provided information on the interactions between drug and polymers and the drug distribution in the layers of the films, respectively. Combinations of EC and copovidone K28 provide suitable polymeric film substrates with the ability to modify drug release. Particularly, decreased EC to copovidone K28 weight ratio was found to suppress the crystallization of hydrochlorothiazide and to increase the release rate of the dispensed drugs. While future studies should focus on optimising drug release from each layer, this preliminary study highlights the great potential of jet dispensing as a method capable to prepare films containing drug combinations and various modes of release (e.g. immediate and sustained drug release). Multi-layered films prepared by jet dispensing can be used as flexible formulations allowing co-delivery of drug combinations and dose personalization.

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Conflict of interest disclosure

The authors confirm that this article has no conflict of interest.

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Figures

Fig. 1 Chemical structures of drugs and polymers used for the preparation of the multi-layered films by jet dispensing.

Fig. 2 Schematic illustration of (a) the formulation's design and (b) a jet nozzle.

Fig. 3 Image and dimensions of a 50/50 EC/PVP multi-layered film prepared by jet dispensing.

Fig. 4 SEM images of multi-layered films produced by jet dispensing.

Fig. 5 XRD patterns of (a) raw drugs and polymers and (b) films prepared by jet dispensing.

Fig. 6 DSC thermographs of (a) raw drugs and polymers and (b) films prepared by jet dispensing.

Fig. 7 FT-IR spectra of (a) raw drugs and (b) polymers and films prepared by jet dispensing.

Fig. 8 FT-IR spectra of carvedilol, copovidone K28 and jet-dispensed film of carvedilol-copovidone K28 in the region of (a) 3100-3800 cm-1 and (b) 1600-1800 cm-1.

Fig. 9 FT-IR spectra of hydrochlorothiazide, copovidone K28 and jet-dispensed films in the region of (a) 3100-3800 cm-1 and (b) 1600-1800 cm-1.

Fig. 10 Raman spectra of the raw drugs in the 1000-1650 cm-1 region.

Fig. 11 (a) Principal components (PCs) versus eigenvalues and (b) principal component analysis (PCA) of confocal Raman spectra for the JD 50/50 EC/copovidone K28 film formulation (red and brown arrows correspond to peaks of HCTZ and CARV, respectively).

Fig. 12 In-vitro dissolution profiles of the three drugs from multi-layered jet-dispensed films with different EC/copovidone K28.

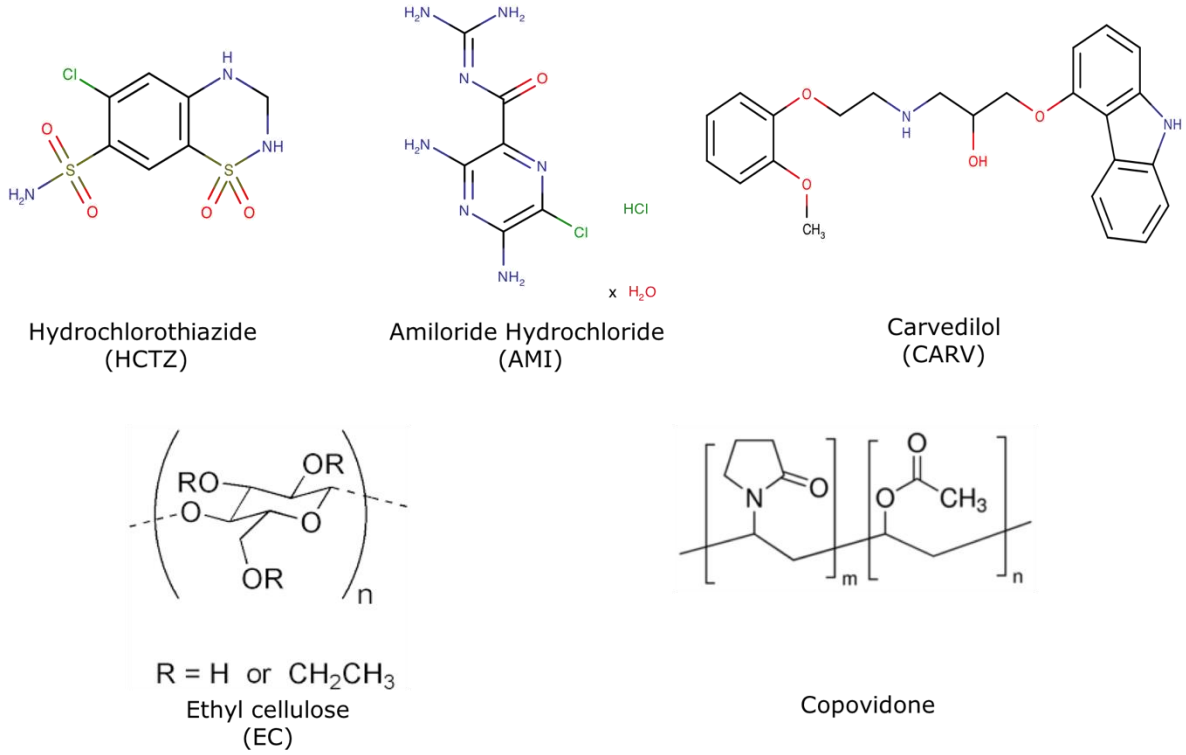

Fig. 1 Chemical structures of drugs and polymers used for the preparation of the multi-layered films by jet dispensing.

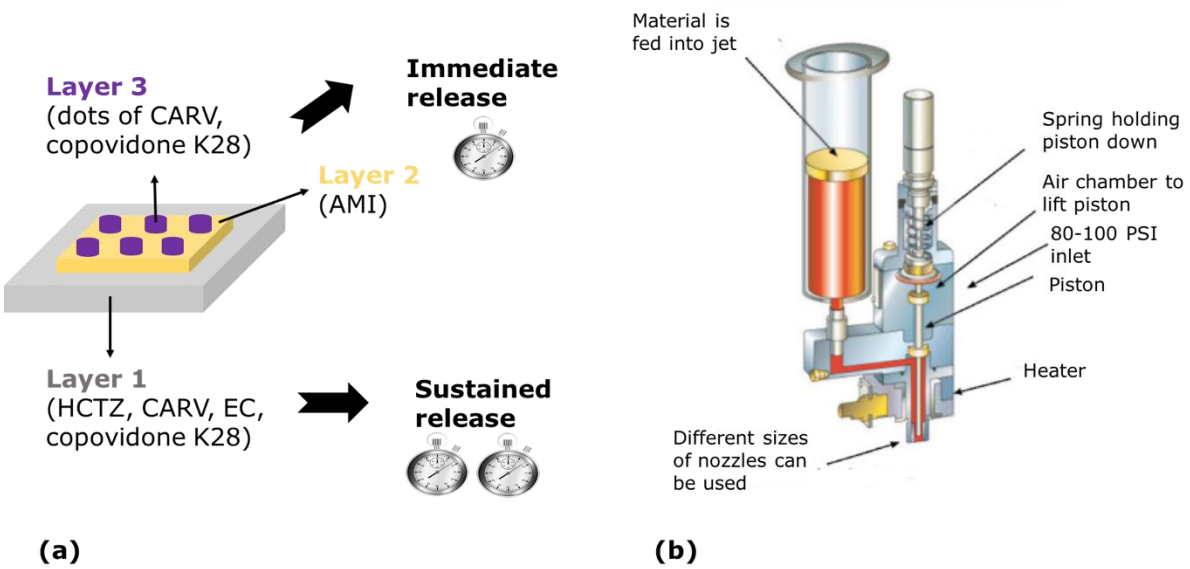

Fig. 2 Schematic illustration of (a) the formulation's design and (b) a jet nozzle.

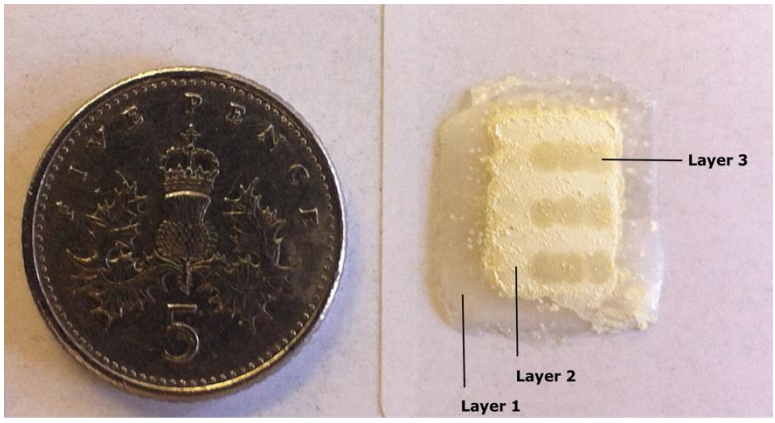

Fig. 3 Image and dimensions of a 50/50 EC/PVP multi-layered film prepared by jet dispensing.

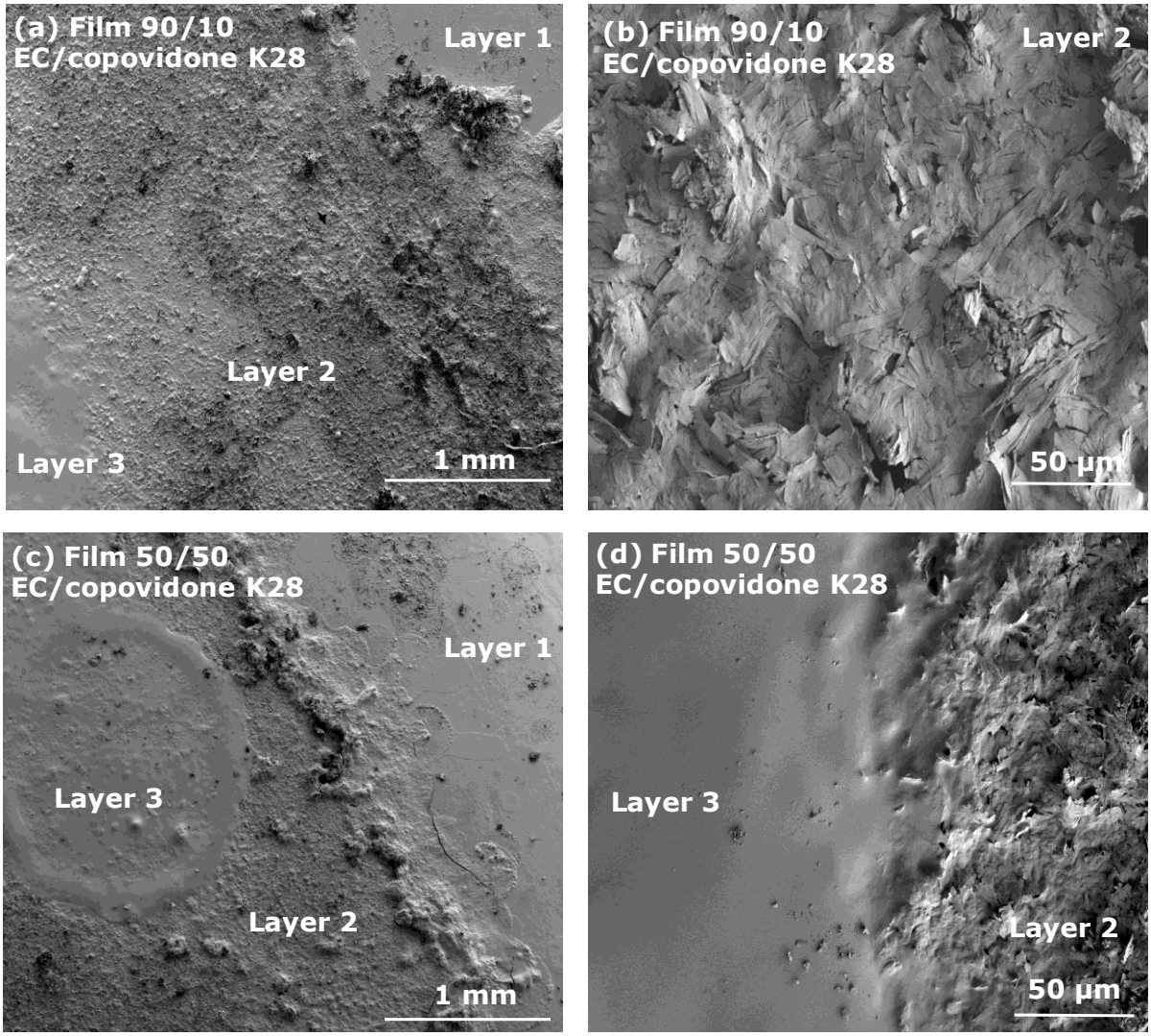

Fig. 4 SEM images of multi-layered films produced by jet dispensing.

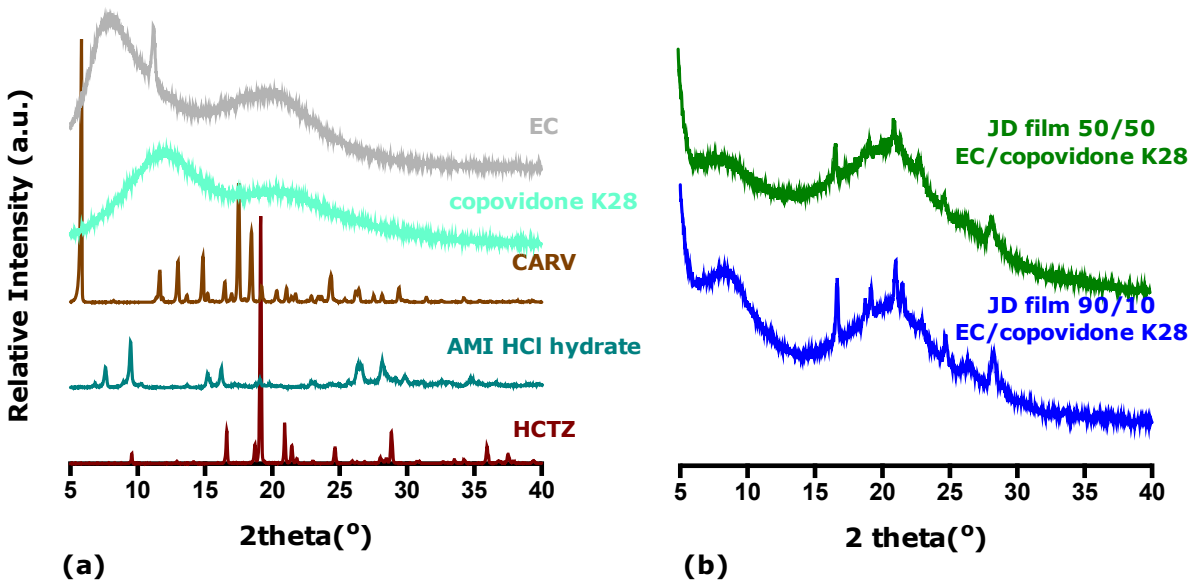

Fig. 5 XRD patterns of (a) raw drugs and polymers and (b) films prepared by jet dispensing.

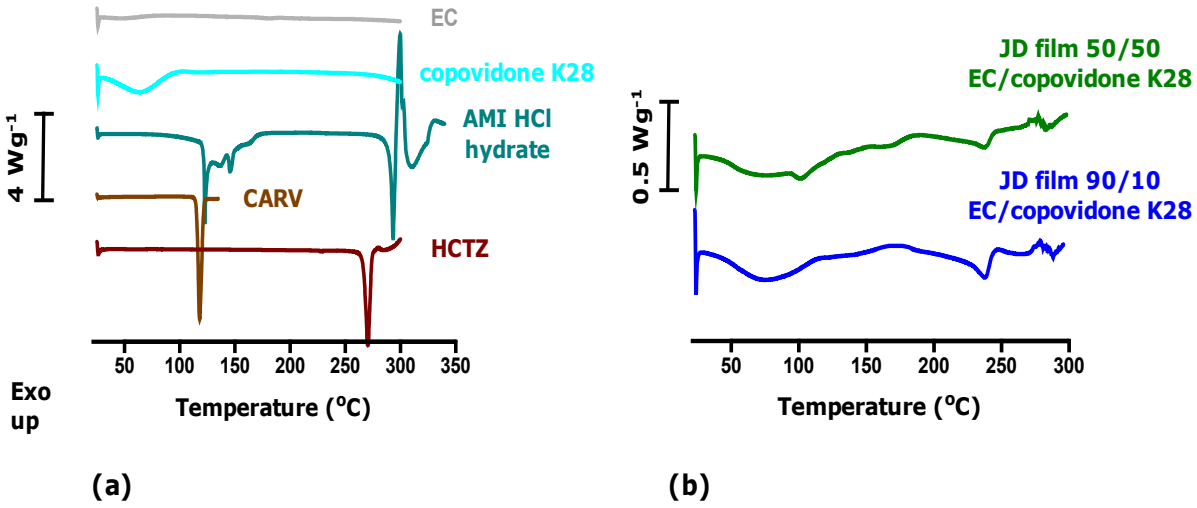

Fig. 6 DSC thermographs of (a) raw drugs and polymers and (b) films prepared by jet dispensing.

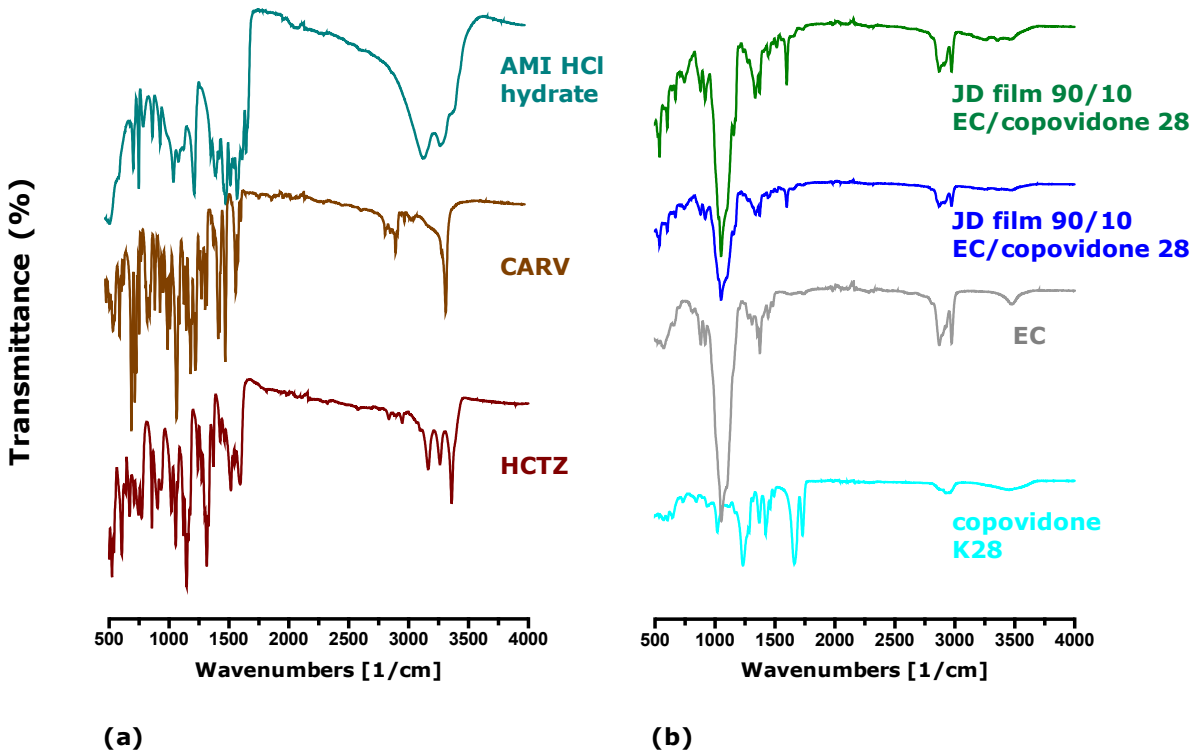

Fig. 7 FT-IR spectra of (a) raw drugs and (b) polymers and films prepared by jet dispensing.

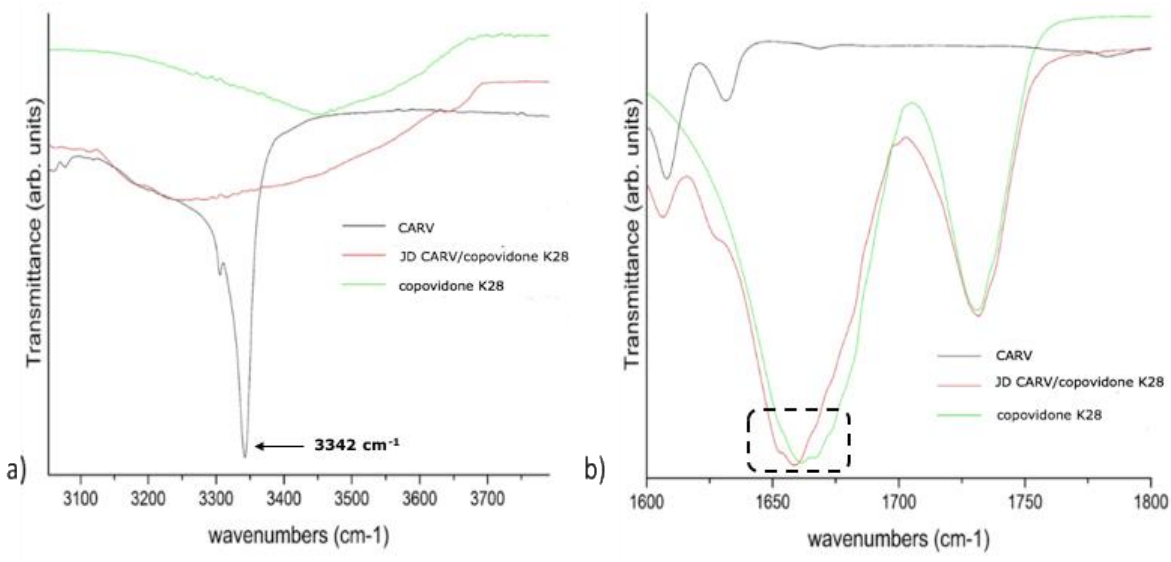

Fig. 8 FT-IR spectra of carvedilol, copovidone K28 and jet-dispensed film of carvedilol-copovidone K28 in the region of (a) 3100-3800 cm^{-1} and (b) 1600-1800 cm^{-1}.

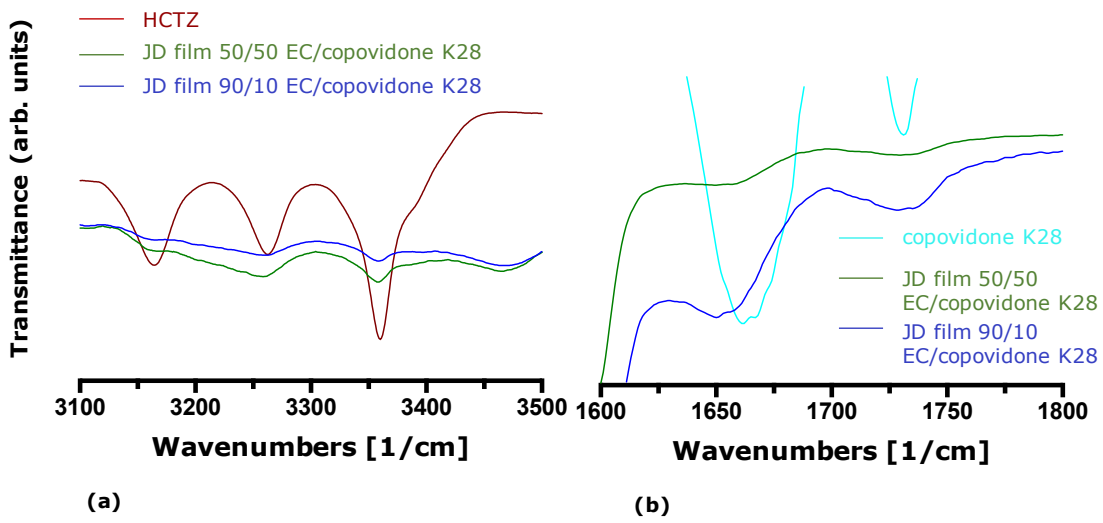

Fig. 9 FT-IR spectra of hydrochlorothiazide, copovidone K28 and jet-dispensed films in the region of (a) 3100-3800 cm^{-1} and (b) 1600-1800 cm^{-1}.

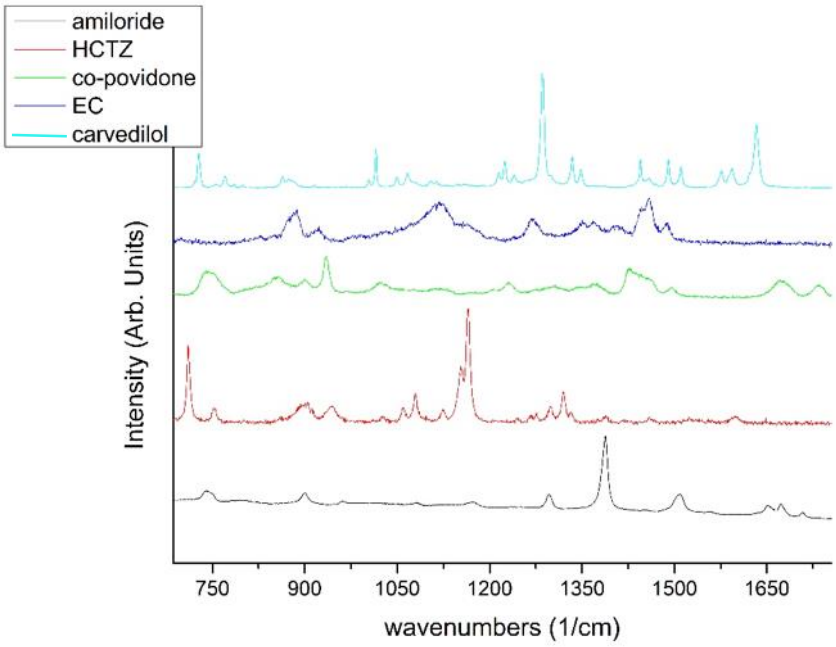

Fig. 10 Raman spectra of the raw drugs in the 1000-1650 cm^{-1} region.

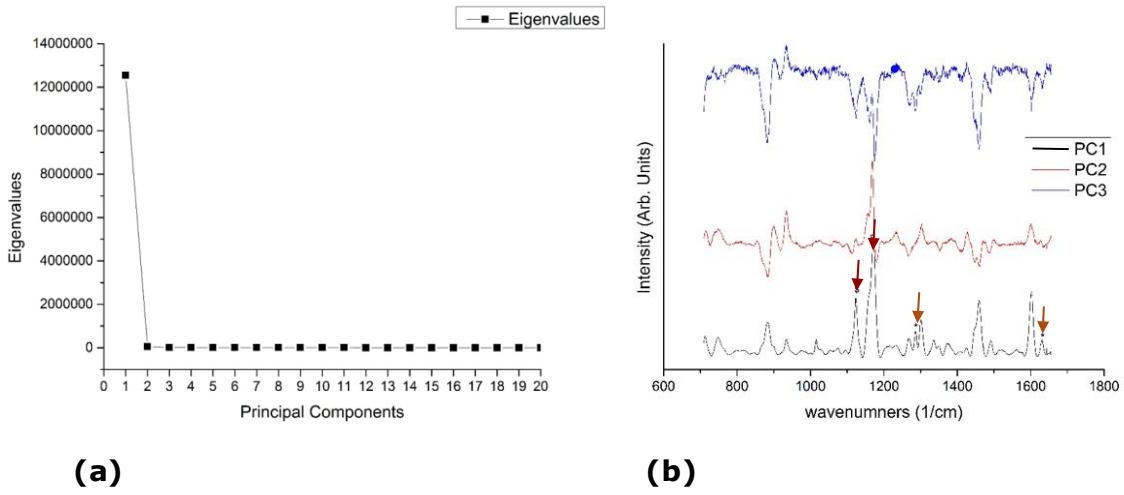

Fig. 11 (a) Principal components (PCs) versus eigenvalues and (b) principal component analysis (PCA) of confocal Raman spectra for the JD 50/50 EC/copovidone K28 film formulation (red and brown arrows correspond to peaks of HCTZ and CARV, respectively).

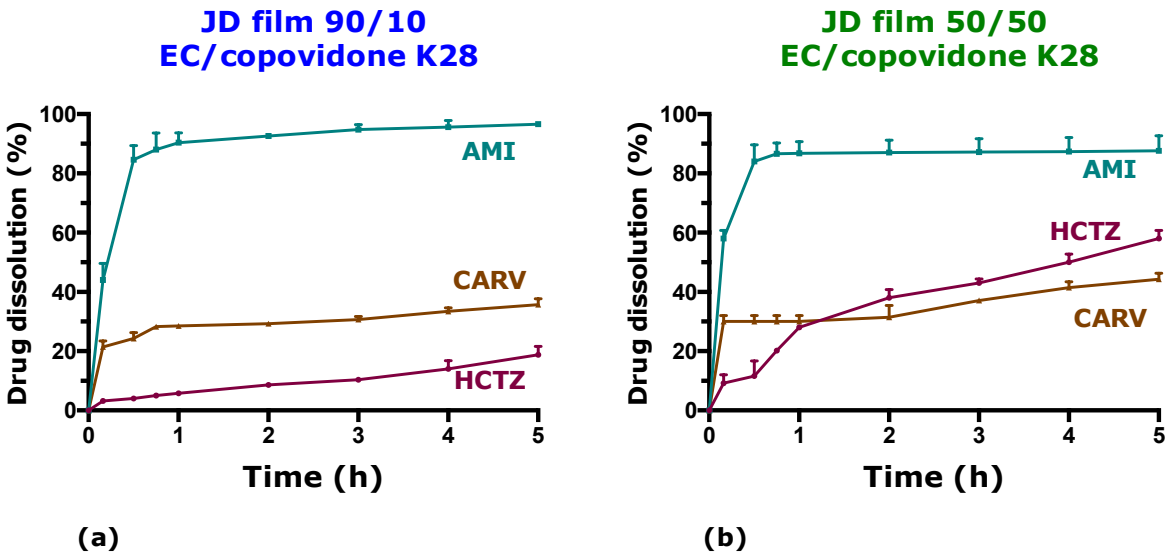

Fig. 12 *In-vitro* dissolution profiles of the three drugs from multi-layered jet-dispensed films with different EC/copovidone K28.

Table

Table 1. Nominal composition of each layer for the jet-dispensed film formulations and volume of the precursor solutions printed per film.

	Film	HCTZ (mg)	CARV (mg)	AMI (mg)	EC (mg)	Copovidone K28 (mg)	Volume printed per film (ml)
Layer 1	**90/10**	25	2.5	-	49.5	5.5	3.57
	50/50	25	2.5	-	27.5	27.5	3.57
Layer 2		-	-	2.5	-	-	0.25
Layer 3		-	1	-	-	2	0.033