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RESEARCH ARTICLE

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Abstract

Novel medicated straws were developed based on drug-loaded electrospun fibers prepared by direct current electrospinning (DCES) and high-speed electrospinning (HSES) of scaled-up productivity. Good quality micro- and nanofibers were electrospun using both techniques despite the multiple times higher throughput rate of HSES based on the scanning electron microscopic imaging (SEM). Solid state analyses revealed that the poorly soluble model drug carvedilol (CAR) was dispersed in an amorphous form in the electrospun polyvinylpyrrolidone (PVPK30) fibers. In vitro dissolution studies revealed ultrafast drug release from the prepared fibrous formulations inserted into plastic straws. Based on the results the developed drug delivery system is suitable for storing the formulation in a solid dosage form and in situ turning it into liquid form when administered.

Keywords

high speed electrospinning, amorphous solid dispersions, medicated straws, novel drug delivery system

1 Introduction

Due to the increasing number of poorly water-soluble drugs in the field of pharmaceutical industry, the urge for the development of novel methods aiming the enhanced dissolution of these substances is growing [1–3]. Among the various techniques the preparation of amorphous solid dispersions (ASDs), which are solid state formulations containing a drug dispersed in an amorphous form in a carrier (mostly a polymer), are proven to be an excellent way of enhancing the dissolution properties, thus, advancing bioavailability [4, 5]. Oral solid dosage forms also have significant advantages over liquid dosage forms, for instance increased stability of the active pharmaceutical ingredient (API) and higher dose precision, therefore EMA (European Medicines Agency) recommends the development of solid dosage forms over liquid formulations [6].

For the preparation of ASDs electrospinning (ES) is one of the most appealing methods combining the advantages of amorphous drug formulations and huge surface area of the fibers, therefore greatly improving dissolution properties. The main challenge of ES is the scale-up of the productivity to industrial scale [7, 8], for which HSES seems to be the most promising solution so far in the pharmaceutical arena [9]. HSES combines the drawing force of the electrostatic field and the high frequency rotation of the spinneret with sharp edges enabling multiple orders of magnitude higher productivity while maintaining the fibrous morphology.

Solid dispersion products are marketed mainly in tablet form due to its proper patient compliance and easy administration [10]. However, there are many cases in which the administration of tablets is not the most suitable medication. Dysphagia has been reported as a main reason of challenging the administration of APIs in tablet form. For instance, dysphagia occurs at different stages of Parkinson's disease [11], Huntington's disease and there are other conditions causing swallowing difficulties like muscle weakness [12, 13]. With aging there could also appear changes in the swallowing ability [14]. Nevertheless the application of tablets can be even more challenging for pediatric use since children need different dosing and their compliance is usually worse than adults' [15].

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In order to overcome the described challenges other ways making the administration easier also have to be considered such as the application of orally disintegrating tablets, oral thin film technology [16] and medicated straws. In these cases the storage of the active agent is implemented in solid state. Patient compliance can be further improved if undesired sticking of the dosage form on the oral mucosa can be avoided and adequate taste masking is also achievable which is especially important in the case of children. Medicated straws have the potential to fulfil these requirements. However, only a few medicated straws have been reported so far which contained pellets and granules as primary formulation and neither of those studies provided details about the *in vitro* dissolution of the drug [15, 17, 18].

In this study the first attempt is described of combining the medicated straw technique and ASD formulations based on fibers with ultrafast drug release. The model drug CAR is a widely applied antihypertensive BCS II drug usually applied in a poorly water-soluble crystalline form in the distributed tablets in the doses of 6.25 mg, 12.5 mg and 25 mg [19]. Due to its weak basic nature its solubility can be enhanced by complexation with cyclodextrins [20], however, the preparation of CAR-loaded amorphous solid dispersions has served even better results [21, 22]. For the dose of CAR 6.25 mg was chosen. Conventional DCES and scaled-up HSES were used to prepare CAR-loaded fibers [9]. For the matrix the popular polymer carrier in ASDs, PVP was chosen [10, 23], however applied solely it is a poor complexing agent [24]. Besides constructing the straws with electrospun fibers, solid state analyses were applied to explore the physical state of the drug in the solid dispersions and *in vitro* dissolution studies were carried out on the newly developed drug delivery system.

2 Materials and methods

2.1 Materials

Polyvinylpyrrolidone K30 (PVPK30, 50.000 Da) was purchased from BASF. Carvedilol (CAR) from Sigma-Aldrich (Budapest, Hungary) was used as API. Absolute methanol (MeOH) was purchased from Molar Chemicals (Budapest, Hungary). For the development of medicated straws commercial plastic straws were purchased.

2.2 Direct current electrospinning (DCES)

The DCES tests were conducted using an NT-35 high voltage direct current supply (MA2000; Unitronik Ltd, Nagykanizsa, Hungary). The electrical potential applied on the spinneret electrode was 25 kV. A grounded aluminum plate covered with aluminum foil was used as collector. The distance of the spinneret and the collector was 20 cm. Solutions of the polymeric excipient and the drug were prepared for ES using a magnetic stirrer (600 rpm). The solutions were dosed by a SEP-10S Plus type syringe pump through a needle spinneret (1 mm ID, 2 mm OD) at 5 mL/h rate.

2.3 High speed electrospinning (HSES)

The HSES experiments were performed by using a SEP-10S Plus type syringe pump similarly to the case of the DCES experiments. The solutions were dosed at 1500 mL/h to the HSES device (Quick 2000, Tiszavasvári, Hungary) with a rotating spinneret (40.000 rpm). The applied electrical potential was 60 kV. The distance of the spinneret and the collector was 35 cm.

2.4 Scanning electron microscopy (SEM)

Morphology of the samples was investigated by a JEOL 6380LVa (JEOL, Tokyo, Japan) type scanning electron microscope. Each specimen was fixed by conductive double-sided carbon adhesive tape and sputter-coated with gold prior to the examination. Applied accelerating voltage and working distance were 20 kV and 10 mm, respectively.

2.5 Differential scanning calorimetry (DSC)

Differential scanning calorimetry measurements were carried out using a Setaram (Calure, France) DSC 92 apparatus (sample weight: ~10-15 mg, open aluminum pan, nitrogen flush). The temperature program consisted of an isothermal period, which lasted for 1 min at 25 °C, with subsequent linear heating from 25 °C to 220 °C at the rate of 10 °C/min. Purified indium standard was used to calibrate the instrument.

2.6 X-ray powder diffraction (XRPD)

X-ray powder diffraction patterns were recorded by a PANanalytical X'pert Pro MDP X-ray diffractometer (Almelo, The Netherlands) using Cu-K α radiation (1.542 Å) and Ni filter. The applied voltage was 40 kV while the current was 30 mA. The untreated materials and the fibrous samples as spun were analyzed for angles 2 θ between 4° and 42°.

2.7 Raman microspectroscopy

Raman spectroscopy measurements were carried out using a Horiba Jobin-Yvon LabRAM (Longjumeau, France) system coupled with an external diode laser source (785 nm, 80 mW) and an Olympus BX-40 optical microscope. The fibrous samples were gently compressed into a flat tablet (Camilla OL95; Manfredi, Torino, Italy) and the spectra were recorded with an objective of 10 \times magnification.

2.8 *In vitro* dissolution tests

The dissolution studies were performed using a Harvard Apparatus 33 type syringe pump (Artisan Technology Group, Champaign, USA). Each straw containing 62.5 mg fibers equivalent to 6.25 mg CAR dose was vertically fixed in a lab stand and 100 mL of distilled water was fed through in 20 mL portions at 6 mL/s (21.6 L/h) dosing rate from bottom to top modeling the sipping of a person with a straw. The solution fractions were collected in 20 mL volumetric flasks containing 168 μ L 37 w/w% HCl solution in order to set the

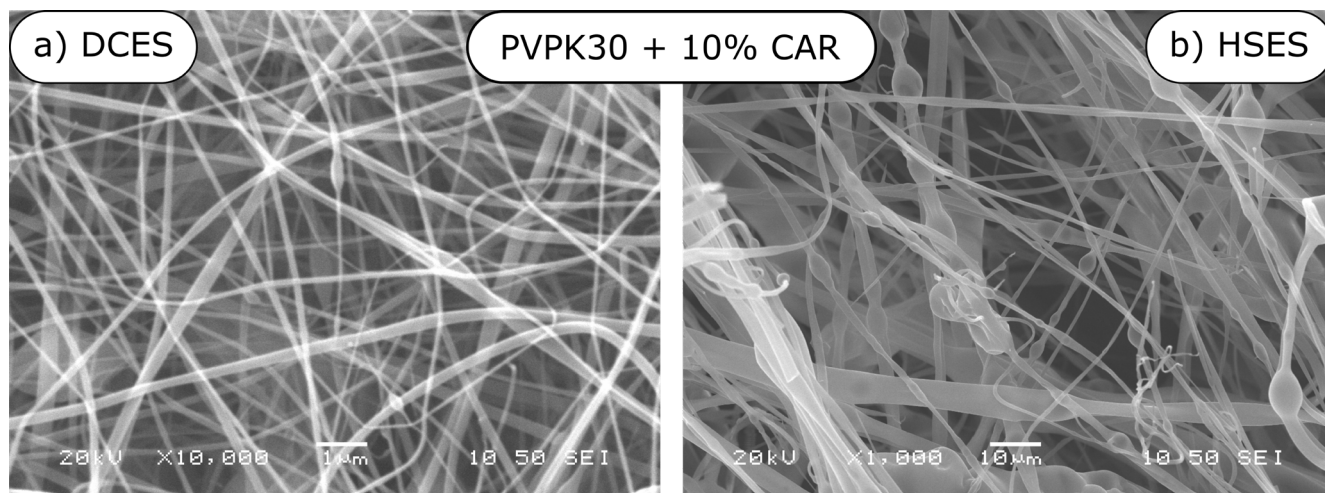


Fig. 1 a) SEM images of drug-loaded DCES fibers; b) SEM images of drug-loaded HSES fibers.

pH of the solutions to the gastric pH. An Agilent 8453 UV-Vis spectrophotometer (Palo Alto, California) was used to measure the concentration of the dissolved CAR at a wavelength of 242 nm. Percentage of dissolution was readily calculated according to the calibration curve of CAR due to the lack of absorption peaks of the applied excipients in this range.

3 Results and Discussion

3.1 Optimization of ES and preparing drug-loaded PVPK30 fibers

Firstly, the concentration of PVPK30 in MeOH had to be optimized for ES in order to prepare good quality electrospun fibers preferably free from beads and droplets. Previous studies with PVPK30 have reported the production of defect-free, good quality nanofibers from PVPK30/EtOH solutions [25, 26], however, when MeOH was applied instead of EtOH during the DCES process, 2.7 g PVPK30 in 10 mL MeOH was required to produce fibers suitable for further experiments. At a dosing rate of 5 mL/h smooth operation of ES could be achieved without drying or spattering of the liquid jet. Based on the optimized composition HSES was also tested with scaled-up productivity. The same solution could be electrospun with HSES at an increased 1500 mL/h providing a dry fibrous fabric in good agreement with previous studies reporting no need of change in solution properties to conduct HSES [9]. As it can be seen in Fig. 1 the incorporation of the drug into the matrix at 10% weight ratio did not deteriorate fiber morphology, however, the average diameter of the HSES fibers was one order of magnitude larger than that of the DCES nanofibers. The SEM images of the HSES product show fibers with diameters ranging ~1 μm-10 μm while DCES mat comprises of ~90 nm-400 nm nanofibers. Moreover, there are slightly more beads on the HSES fibers. The observed differences can be attributed to the 300 times higher feeding rate and the more intense forces of HSES exerted on the polymeric liquid compared to the laboratory scale DCES [9].

3.2 Solid state analyses with DSC, XRPD and Raman spectroscopy

The physical state of the drug in the fibers was firstly investigated with DSC. The melting point of the pure crystalline CAR at 117 °C is clearly detectable as a sharp peak (Fig. 2). In the case of PVPK30 only the wide peak of water loss can be observed below 100 °C, i.e., the matrix is fully amorphous. The drug-loaded DCES and HSES samples show no sign of crystalline traces at 117 °C, thus, according to the DSC measurements CAR turned into amorphous with both DCES and HSES.

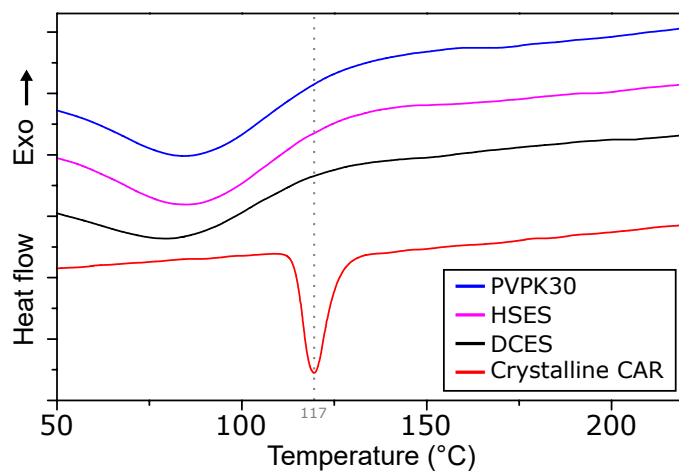


Fig. 2 DSC thermogram of the crystalline CAR, PVPK30 and the drug-loaded electrospun fibers.

Additional analysis was carried out with XRPD as an effective method to investigate the crystallinity of drug-loaded formulations [27]. The results of the XRPD measurements can be seen in Fig. 3. Sharp diffraction peaks of crystalline CAR are also easily identified, the most intense peaks are at around $2\theta = 6^\circ$ and 17° . PVPK30 was found to be amorphous as well as the formulated drug-loaded electrospun fibers in good accordance with the results of the DSC measurements.

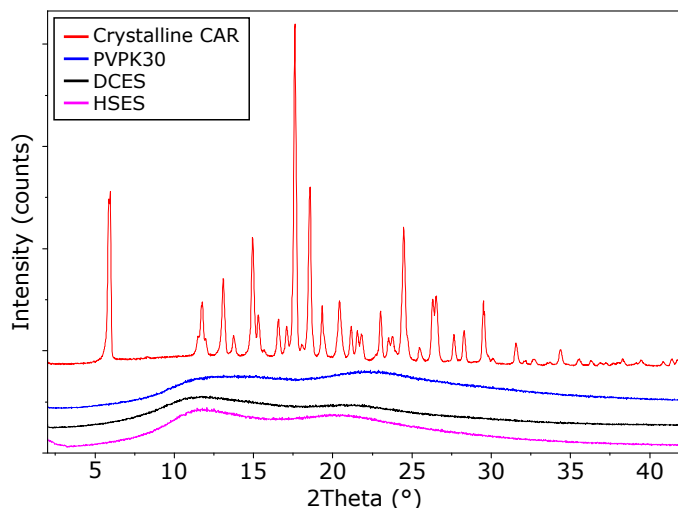


Fig. 3 X-ray powder diffraction of crystalline CAR, PVPK30 and the drug-loaded electrospun fibers.

Another sensitive method - Raman spectroscopy - was used to verify the presumably molecularly dispersed state of the drug in the electrospun fibers since the Raman peaks of amorphous and crystalline carvedilol distinctly differ allowing the identification of the presence of small crystalline particles in the formulation [28, 29]. The Raman spectra of the examined materials are shown in Fig. 4. The spectrum of crystalline CAR shows sharp peaks among which the most intensive - the C-C and C-N symmetric stretchings - are centered around 1290 cm^{-1} [30]. PVPK30 rather has broad characteristic peaks referring to its amorphous state and also has a sharp peak at around 930 cm^{-1} reported to display the ring breathing of the pyrrolidone function [31]. The characteristic peaks of CAR is detectable in both DCES and HSES fibers, however, in a more broadened and less intense form signifying the transformation of CAR from crystalline to a fully amorphous form.

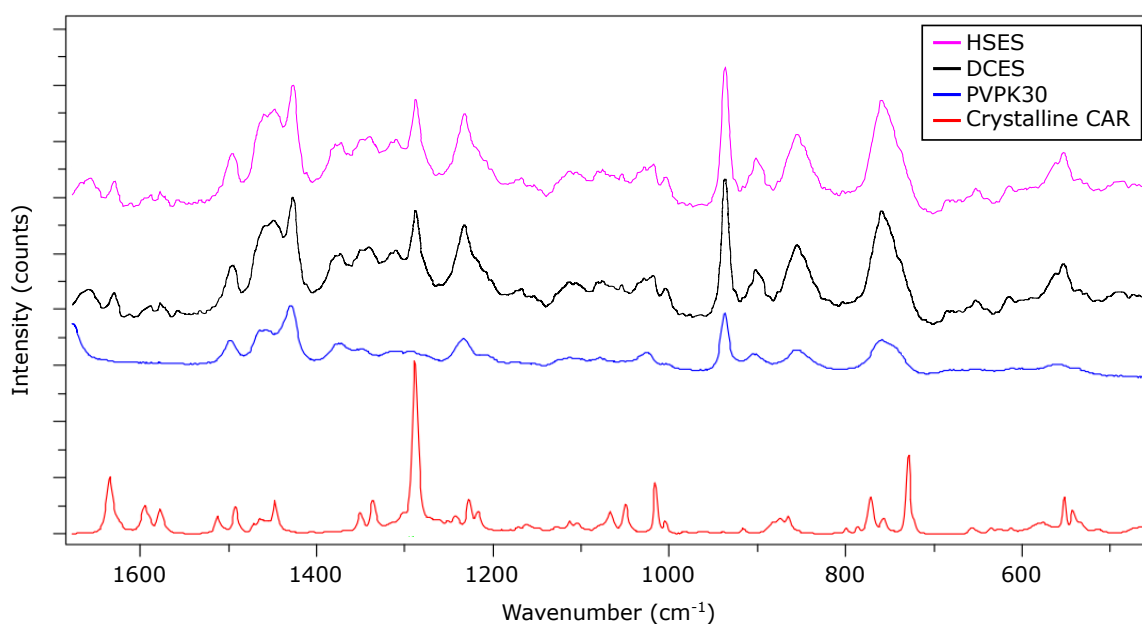


Fig. 4 Raman shifts of crystalline CAR, PVPK30 and the drug-loaded electrospun fibers.

3.3 Development of novel electrospun web-loaded medicated straws

Micro and nanofibers of 62.5 mg with the composition of PVPK30+10%CAR were loaded into transparent plastic straws with an inner diameter of 6 mm using a clip (Fig. 5 a). To avoid the slipping of the fibers out of the straw during the administration by the patients barriers made of plastic tubes (5 mm long, Fig. 5 b, c) were placed before the fibers 40 mm from the upper end of the straws. This way the tubes closed up together and pressed up against the plastic wall, thus, mechanically fixing their position without the need for any other additives (e.g., glue).

Instead of using a clip to manually load the fibers a possible quicker way could be sucking the fibers into the straws with vacuum. However, in this case care must be taken since the more wrinkled fibrous web can lead to slower dissolution of the product due to the higher pressure drop on the straw. Therefore, the intensification of the production process requires further developments.

3.4 *In vitro* dissolution tests

In vitro testing the dissolution of the electrospun web-loaded medicated straws necessitated the determination of the throughput of human sipping. A group of 15 adults (6 females, 9 males) was examined to sip tap water from a glass for 5 seconds with the same straws used for our experiments. The sipping processes was conducted with each subject in triplicate. The average sipping speed was calculated after weighing of the remaining water. The grand average sipping speed of the participants was determined to be $6.0 \pm 1.3\text{ mL/s}$. The dissolution tests were executed by feeding the water at the obtained dosing rate, 5 sips of 20 mL solutions were sampled which equals to an average sip with a straw for adults [32].

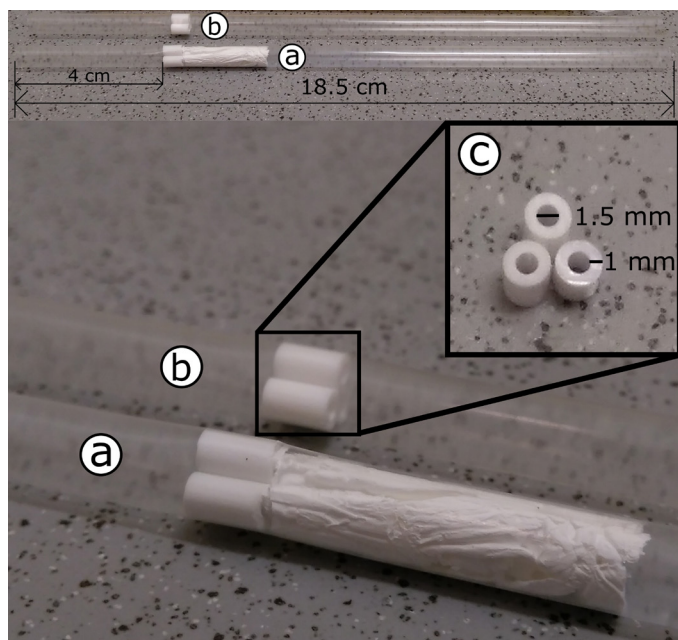


Fig. 5 a) Developed medicated straw with drug-loaded fibers; b) Plastic tubes in a straw; c) Plastic tubes in detail.

The results of the dissolution tests are shown in Fig. 6. Both DCES and HSES fibers exhibited ultrafast drug dissolution since the drug release in the first 20 mL samples was close to 80% and exceeded 95% in cases of straws with DCES and HSES fibers, respectively. The drug release was practically complete within the first two sips with both types of electrospun formulation due to the huge surface areas and the amorphously dispersed drug in the fibers. The better drug release profile of the HSES mat compared to DCES fibers could make one wonder since the scaled-up technique produced fibers with significantly larger diameters and more beads as shown in Fig. 1. This phenomenon can be explained by the better accessibility of the loosely collected HSES fibers leading to faster drug release

despite the thicker average diameter. A similar conclusion has been drawn when the drug release from fine yet tightly packed DCES fibers and loose melt-blown fibers with one order of magnitude larger fiber diameter was compared [33].

4 Conclusions

Micro- and nanofibers loaded with a poorly soluble API were prepared for the development of a medicated straw formulation using laboratory scale DCES and scaled-up HSES at an increased throughput rate of 1500 mL/h. Various solid state analyses (DSC, XRPD and Raman microspectroscopy) revealed no crystalline traces of CAR in the fibrous fabrics prepared with both techniques. A medicated straw was developed for the first time based on electrospun fibers by which the formulation could be stored in solid state maintaining stability and precise dosing and the administration of the drug can be implemented in liquid state providing better compliance. The *in vitro* dissolution tests were conducted at a sipping speed of 6 mL/s based on measured sipping speeds of a 15-member group. The HSES product showed slightly better dissolution compared to DCES fibers making the developed drug delivery system feasible for advancing patient compliance of geriatric and pediatric uses.

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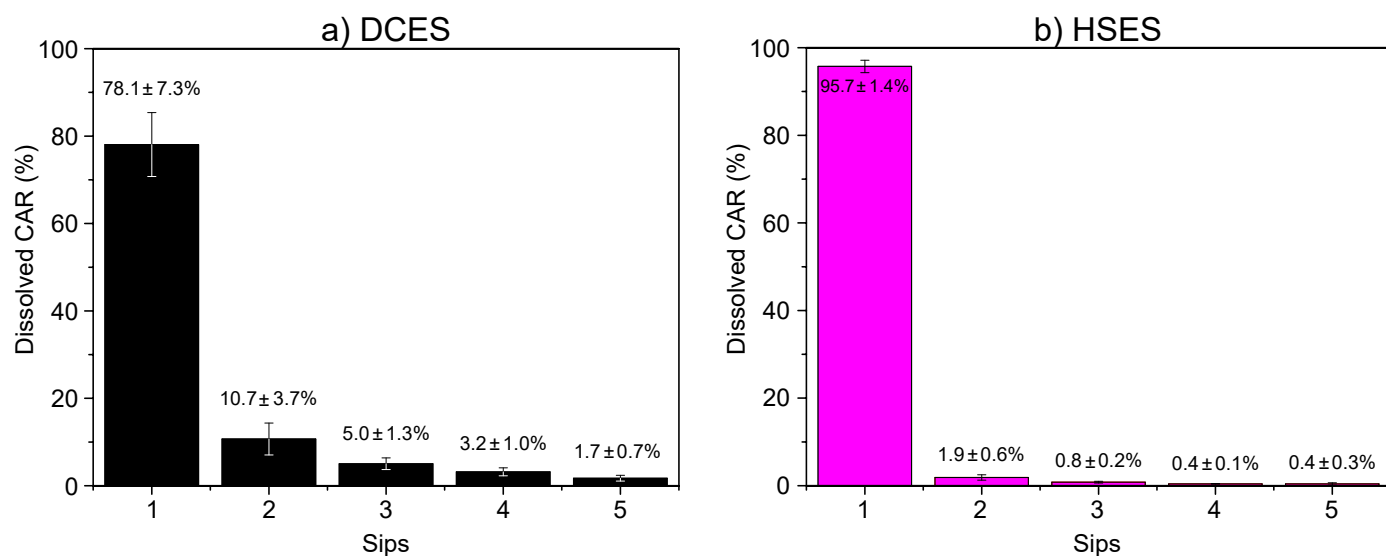


Fig. 6 a) Dissolution results of DCES samples; b) Dissolution results of HSES samples; The error bars indicate the standard deviations (n=3).

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