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Improving the Solubility and Absorption of the Low-Solubility Compound Aripiprazole by Electrospinning Nanofiber Formulation

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PURPOSE

In recent drug development, there is a survey report that about 70% of drug candidates are poorly soluble compounds classified as BCS Class II or Class IV[1]. Oral dosages such as tablets and capsules are effective when dissolved in the gastrointestinal tract and absorbed into the blood. Therefore, solubilization of poorly soluble compounds is an important challenge in recent drug development.

In this study, we verified the effectiveness of nano/micro fiber formulations using Electrospinning technology as a solubilization technique for a poorly soluble compound. Electrospinning is a technique in which nano/micro fibers can be obtained from mixed solutions of drugs and polymers in one step. Electrospinning has the potential to be applied to many drug substances and polymers because the sample is not exposed to heat[2].

In this study, Aripiprazole (BCS Class II) was used as a poorly soluble and low melting point (139^{O}C) compound. Nano-micro fibers were prepared using three polymer substrates. We evaluated solubility and membrane permeability using the prepared nanofibers, and confirmed that the electrospinning method is an effective method for Aripiprazole.

METHOD(S)

Perform electrospinning on Aripiprazole-polymer solution

Aripiprazole (ARI, pKa 7.46, base) and polymer were mixed and dissolved in ethanol or acetone. The amount of preparation is as follows.
0.5g ARI + 2.0g Cellulose acetate + 30mL Acetone
0.5g ARI + 2.0g HPMCAS + 20mL Acetone
0.5g ARI + 2.0g PVP K30 + 20mL EtOH
The mixtures ware processed using an electrospinning system NS1 (Inovenso, Fig.1).

Small volume dissolution test in FaSSGF

A small-volume dissolution tester µDISS (Pion) was used to evaluate the dissolution properties of Aripiprazole from nano/micro fibers in FaSSGF.

Small volume dissolution/flux test in FaSSIF

A small-volume dissolution/flux system µFLUX (Pion, Fig.2) was used to evaluate the absorption properties of Aripiprazole dissolved from nano/micro fibers.
20 mL of FaSSIF was used for the Donor chamber and 20 mL of Acceptor Sink Buffer (ASB) was used for the Acceptor chamber. The Donor chamber and Acceptor chamber were separated by a PAMPA membrane (1.54 cm^2 , PVDF).

Fig.1 Electrospinng system NS1

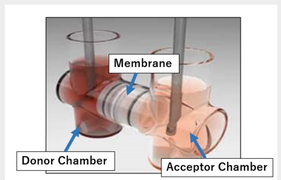

Fig.2 Dissolution/flux system µFLUX

RESULT(S)

Perform electrospinning on Aripiprazole-polymer solution

The materials after electrospinning were observed using SEM (SU8230, Hitachi High-Tech Corporation, Fig.3).

As a result of electrospinning, fibers with diameters ranging from 100 nm to several micrometers were obtained using cellulose acetate and HPMCAS based polymer solutions.
In the case of PVP-based polymer solution, no fibers were obtained, but as granules with microstructures.

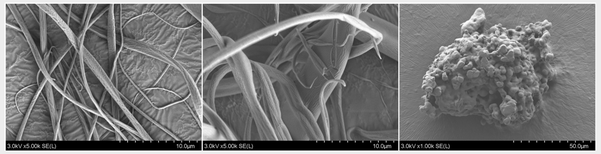

Fig.3 Materials obtained by electrospinning. (Left) Nano-micro fiber using cellulose acetate as base material, (Middle) Nano-micro fiber using HPMCAS as base material, (Right) Microstructured granule using PVP as base material

Small volume dissolution test in FaSSGF

The dissolution behaviors of Aripiprazole formulations in FaSSGF ware monitored for 60 minutes using Fiber Optics UV Probes. The results are shown in Fig.4.

Cellulose Acetate and HPMCAS-based fiber continued to slowly increase in concentration. Final concentrations were 117 µg/mL for Cellulose Acetate fiber and 136 µg/mL for HPMCAS fiber.

Granule using PVP K30 dissolved quickly, reaching 70 µg/mL in about 3 minutes, but the concentration did not increase any further.

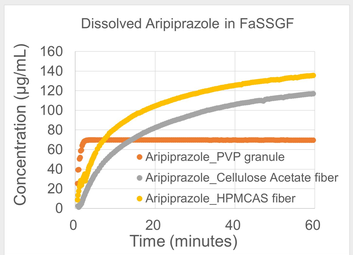

Fig.4 Dissolution profile of Aripiprazole formulations in FaSSGF

Small volume dissolution/flux test in FaSSIF

The dissolution and membrane permeation of Aripiprazole formulations were monitored for 240 minutes using a Fiber Optics UV Probe. The results are shown in Fig.5 and Fig.6.

The flux value was calculated according to Equation (1), using the concentration (c), time (t), volume (V), and membrane area (A)[3].

$$flux = \frac{dm}{A\,dt} = \frac{V}{A} \cdot \frac{dc}{dt} \qquad (1)$$

The HPMCAS fiber formulation showed the greatest improvement in solubility and membrane permeability.
In order to verify the effect of solubility and permeability by electrospinning, amorphous solid dispersions by the Hot Melt method (VCM, MeltPrep) and physical mixed powder of Aripiprazole and HPMCAS were prepared and compared.

HPMCAS fiber reached a maximum concentration of 79 µg/mL in the donor chamber 20 minutes after the start of the test. PVP granule and Cellulose Acetate fiber had a maximum concentration of about 40 µg/mL.

ASD formulation by Hot Melt had the longest supersaturation retention time. Hot Melt ASD maintained a supersaturated state even after 4 hours from the start of the test.

HPMCAS fiber showed the highest flux of 0.7 µg·cm^{-2}·min^{-1} at approximately 60 minutes in membrane permeation from the donor chamber to the acceptor chamber, and then decreased with time.

The physical mixture showed almost the same dissolution behavior as untreated Aripiprazole, but the membrane permeation was lower than untreated. Therefore, HPMCAS itself does not have the effect of accelerating membrane permeation. By forming ASD with hot melt or electrospinning fiber, the effect of solubility and membrane permeability has been confirmed.

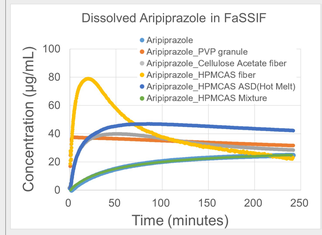

Fig.5 Dissolution profile of Aripiprazole formulations in FaSSIF (donor chamber)

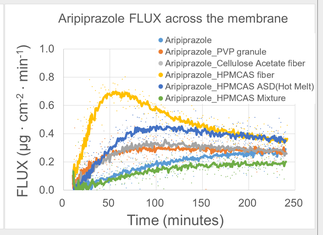

Fig.6 Flux profile of Aripiprazole formulations across the membrane

CONCLUSION(S)

In this study, we investigated the formulation of fiber preparations and evaluated the dissolution and absorption properties using a very small amount (several grams) of raw materials.

The Dissolution/Flux test is a widely used experiment to predict the absorption of drugs in vivo. The Flux value is an indicator of the amount of drug absorbed in the human gastrointestinal tract. Electrospinning technology was confirmed to be effective as a means of solubilizing the poorly soluble compound Aripiprazole and improving bioavailability.

Electrospinning is a manufacturing method that does not apply heat to raw materials, so it can be applied even when there is a difference in melting point between the drug substance and the polymer, and has the advantage of being applicable to polymers with high melting points. Moreover, in the comparison using HPMCAS as the carrier material, it was confirmed that the supersaturation concentration and flux were higher than those of the solid dispersion obtained by Hot Melt. A large surface area can be obtained by forming nano-micro fibers, which is thought to have contributed to the improvement of solubility and membrane permeation amount.

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