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ABSTRACTBOOK

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Novel fenofibrate-gelatin microcapsules with improved solubility and excellent flow property: preparation, physicochemical characterization and pharmacokinetic evaluation

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INTRODUCTION

Fenofibrate, a BCS Class II drug, is a very hydrophobic drug [1]. It is frequently prescribed to treat hypercholesterolemia and hypertriglyceridemia [2]. However, it has a very low oral bioavailability due to its poor aqueous solubility. Bioavailability of fenofibrate can be improved by enhancing its aqueous solubility. Microencapsulation with gelatin is a promising way to promote the aqueous solubility of numerous BCS Class II agents [3]. In present research, fenofibrate-gelatin microcapsules were developed and characterized for solubility, dissolution, flowability, crystallinity, drug-gelatin interaction, morphology and bioavailability.

METHODS

Preparation of fenofibrate-gelatin microcapsules

Fenofibrate-gelatin microcapsules, at the weight ratios of 1/1, 1/2, 1/4, 1/8, 1/10, 1/15 and 1/20, were developed by the solvent-evaporation method using the spray-drying technique. Fenofibrate and gelatin were completely dissolved in 40% ethanol at 50°C. The resultant clear solution was spray-dried using Buchi B-290 spray-dryer at the following optimized conditions: inlet temperature, 110°C; outlet temperature, 65°C; flow rate, 3 ml/min; aspirator setting, 100%; spraying-gas pressure, 4 kg/cm^2.

Determination of flow property

The flow property was assessed by the angle of repose, Carr's index and Hausner ratio. The angle of repose was determined using ABD-72 powder peculiarity testing equipment. The bulk and tapped densities was measured using KYT-4000 instrument.

Aqueous solubility

An excess of sample was vortex-mixed with 1 ml water in 2 ml microtube. Then, it was placed on a shaker (100 rpm) in a water-bath (25°C) for 7 days. Afterwards, the sample was centrifuged (10,000 xg), diluted and filtered (0.45 μm). The filterate (50 μl) was assayed by the HPLC method using a C18 column (4.6 mm x 250 mm, 5 μm) at 30°C, a mobile phase (acetonitrile: 0.1% w/v phosphoric acid; 75:25, v/v) at 2 ml/min flow rate, and a 286 nm wavelength.

Dissolution

Dissolution test was performed in 900 ml of Tween 80 at 37°C using USP dissolution apparatus II (at 75 rpm paddle rotation). The periodically taken samples (1 ml) were filtered (0.45 μm) and analyzed (50 μl) by the HPLC method described above.

Solid state characterization

The solid state characterization was accomplished by PXRD, DSC, SEM and FT-IR spectroscopy.

The PXRD analysis was conducted in the range of 10-80 °C using Rigaku diffractometer (Model D/MAX-2500 PC) at 40 mA current, 40 kV voltages, 0.02°/second step size and 5°/min scanning speed.

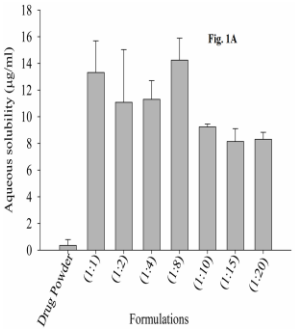
The DSC analysis was executed in the range of 30-130°C at 10°/min speed using a differential scanning calorimeter (Model Q20, TA instruments).

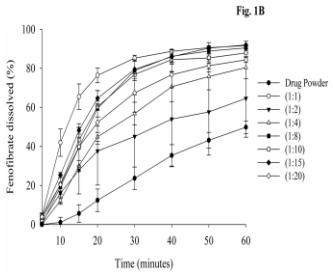
The FT-IR spectroscopy was done in the range of 400-4000 cm^{-1} using a Nicol-6700 spectrophotometer.

The SEM was performed using a scanning electron microscope (Model S-4800).

Pharmacokinetics

Twenty-four hours fasted Sprague-Dawley rats (~300 g) were orally given the samples at the drug dose of 20 mg/kg. The blood samples (0.4 ml) were withdrawn from the cannulated carotid artery periodically. Plasma (0.2 ml) was isolated from blood by centrifugation (10,000 xg, 5 min), acidified with HCl and clofibric acid was added as an internal standard. The extraction was performed using diethyl ether (liquid liquid extraction). The organic layer





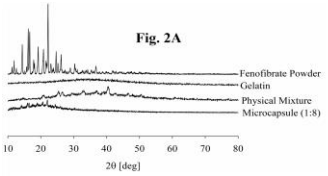
was evaporated in another clean microtube at 40°C. The residue was reconstituted with 0.2 ml acetonitrile and 100 µl was assayed by the HPLC method using a C18 column (4.6 mm x 250 mm, 5 µm) at 30°C, a mobile phase (acetonitrile: 0.1% w/v phosphoric acid; 54:46, v/v) at 2 ml/min flow rate, and a 285 nm wavelength. All the procedures were conducted in accordance with the guidelines of International Animal Care and Use Committee (IACUC) adopted by the Institute of Laboratory Animal Resources of Hanyang University. The pharmacokinetic parameters were calculated using non-compartmental analysis (WinNonlin software).

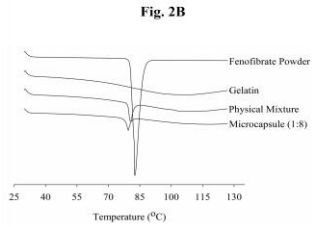
RESULTS AND DISCUSSION

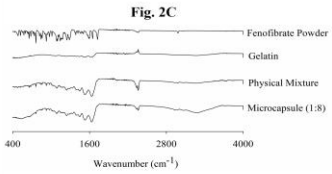
All formulations furnished improved solubility, dissolution and flowability as compared to the drug powder. However, gelatin microcapsule containing fenofibrate/gelatin (1/8, w/w) was selected because it showed the most improved drug solubility (~ 14.9 µg/ml) [Fig. 1A], good dissolution (~ 90% at 40 min) [Fig. 1B] and excellent flowability (angle of repose, ~30; Carr's index, ~14; Hausner's ratio, ~1.16) [Table 1]. The PXRD [Fig. 2A] and DSC [Fig. 2B] results confirmed the presence of crystalline drug in this microcapsule. The FT-IR [Fig. 2C] spectra of the physical mixture and microcapsule were exactly the same, confirming the absence of strong interaction between fenofibrate and gelatin. The SEM showed the crystalline irregular shaped drug [Fig. 2D] and smooth-surfaced spherical microcapsules [Fig. 2E]. Moreover, the bioavailability enhancement was ~ 5-fold compared to that of the drug powder (88.80 ± 25.42 vs. 17.72 ± 1.52 h.µ/ml) [Fig. 3]. Thus, our results suggested that the enhanced aqueous solubility and bioavailability of the drug was due to improved wetting because of close contact between the drug and surrounding hydrophilic gelatin; resulting in the decreased hydrophobicity of the drug.

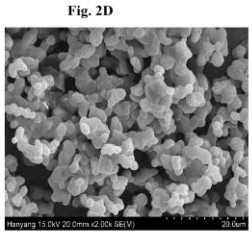
Composition (w/w)		Angle of repose (degrees)	Carr's index	Hausner's ratio
Fenofibrate	Gelatin			
-	-	47.111 ± 0.929	33.364 ± 0.834	1.501 ± 0.028
1	1	43.283 ± 2.575	27.641 ± 0.478	1.382 ± 0.012
1	2	39.648 ± 1.854	26.950 ± 0.700	1.369 ± 0.019
1	4	37.671 ± 1.713	19.250 ± 0.500	1.238 ± 0.011
1	8	29.833 ± 1.902	13.546 ± 1.338	1.157 ± 0.023
1	10	34.876 ± 2.871	16.239 ± 1.519	1.194 ± 0.029
1	15	35.759 ± 1.557	17.063 ± 1.499	1.206 ± 0.028
1	20	35.068 ± 3.318	15.653 ± 1.470	1.186 ± 0.027

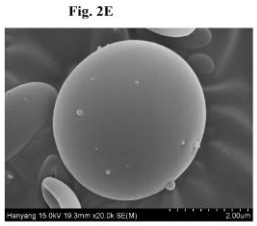
Table 1. Compositions and flowability of fenofibrate gelatin microcapsules (n=3).











CONCLUSION

The free-flowing fenofibrate-gelatin microcapsule (1/8, w/w) could be a promising drug delivery system to administer fenofibrate with improved aqueous solubility and oral bioavailability.

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