Research Article

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Tio2 Nanoparticles To Improve The Hair Growth Effect Of Minoxidil

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1. Abstract

Minoxidil has some problems with low efficiency of transdermal delivery and side effects like red spots and itch. In this research, TiO2 nanoparticles were developed to increase the hair growth of minoxidil even with less amount and fewer number of application than the recommended. Hollow porous TiO2 nanoparticles were made and characterized with FESEM(field emission scanning electron microscope). They had porous nanosphere structures with diameter in the range of 25 nm to 55 nm. Minoxidil-loaded TiO2 nanoparticles showed 67.7% increase of hair growth which is approximately 5 times, compared to 13.68% of hair growth got with application of only minoxidil solution after 6 months. Our results showed that minoxidil-loaded TiO2 nanoparticles improve hair growth of minoxidil even with less amount and fewer number of application than the recommended and show no significant cytotoxicity.

2. Key Words:
TiO2 nanoparticle, minoxidil, hair growth, hollow porous nanoparticle, minoxidil-loaded TiO2 nanoparticle

3. Introduction

Many people have been suffered from alopecia all over the world. Minoxidil has been very common hair growth solution applied to scalp in its treatment. However, minoxidil has some problems with low efficiency of transdermal delivery. So several attempts have been tried to enhance its penetration into the scalp and include microneedling, sonophoresis and ionophoresis [1-4]. Its delivery approaches with nanoparticles were also widely developed [5-9]. Nanoparticles with a diameter of 100-150 nm prepared using poly(L-lactide-co-glicolic acid)(PLGA) was found to deliver minoxidil to hair follicles [10]. Minoxidil encapsulated in poly(Lactide-co-glicolic acid) grafted hyaluronate nanoparticles was delivered to cells without any significant cytotoxicity [11]. A nanoparticle formulation containing 5% minoxidil enable the accumulation of minoxidil in the upper hair follicles more efficiently than a commercially available minoxidil solution [12]. PLGA, an organic polymer is expensive and difficult to synthesize homogeneously. But TiO2 nanoparticle used in this research which is an inorganic polymer, is cheap and easy to prepare homogeneously. There has been no attempt to improve the hair growth effect of minoxidil with TiO2 nanoparticles. Minoxidil also has side effects like red spots and itch. To reduce its side effect, it is important to spread less amount and fewer number of application of minoxidil than the recommended but not to decrease the hair growth effect.

In this work, hollow porous TiO2 nanoparticles were prepared with polystyrene (PS) particles as templates and minoxidil was encapsulated in them. Minoxidil-loaded TiO2 nanoparticles were examined on the effect of hair growth increase with mice, a man and a woman, compared to only minoxidil solution and confirmed on their feasibility in alopecia treatment.

4. Materials and methods

Preparation of PS template particles. The PS particles were prepared as follows [13]: 0.5 g of potassium peroxodisulfate was dissolved in 100 mL of distilled water and the solution was heated to 80°C with stirring. 10 mL of styrene solution was added to this solution, followed by addition of 0.2 g of SDS(sodium dodecylsulfate) and 0.15 g of NaHCO3 and the solution was stirred for 24 h. The reacted solution was rotary-evaporated and dried in vacuum. Preparation of porous TiO2 nanostructures. Porous TiO2 nanoparticles were prepared as follows: 90 uL of Ti(SO4)2 was added to 32 mL of distilled water and stirred at 350 rpm. 0.07 g of PS particles (50~60 nm), 1.98 mL of CTACl (cetyltrimethylammonium chloride), 200 uL of HCl and 3.6 mg of ZnCl2 were added under the stirring condition. The mixture was agitated at 70°C for 15 hrs and centrifuged. The precipitate was washed with distilled water and ethanol (1:1, v/v) and collected by centrifugation. The washed pellet was dried at 60°C overnight. The dried sample was then put into oven and kept at 300°C for 2 h and 600°C for 4 h for calcination.

Hair growth test with mice, a man and a woman. Minoxidil-loaded TiO2 nanoparticles were prepared by vigorous mixing or sonication of mixture of 0.1 g of TiO2 added to 100 ml of 5% (or 3%) minoxidil solution. Absorbance was measured at around 254 nm to know whether minoxidil was incorporated into TiO2 nanoparticles. 200 ul of a nanoparticle formulation containing 5% minoxidil was applied to a mouse whose back

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was epilated. For human test, 0.6 ml 0.7 ml of 5% minoxidil-loaded TiO2 nanoparticles had been applied to the scalp of a man and 0.6 ml 0.7 ml of 3% minoxidil-loaded TiO2 nanoparticles had been applied to the front hair line of a woman once a day after hair wash for 6 months.

5. Results and Discussion

TiO2 nanoparticles were developed to increase the effect of hair growth of minoxidil in this work. Hollow porous TiO2 nanoparticles were made by coating synthetically the surface of PS particles with TiO2 precursor like Ti(SO4)2 and removing PS templates with calcination (Fig. 1). Minoxidil-loaded TiO2 nanoparticles were prepared by vigorous mixing or sonication of mixture of TiO2 nanoparticles added to minoxidil solution.

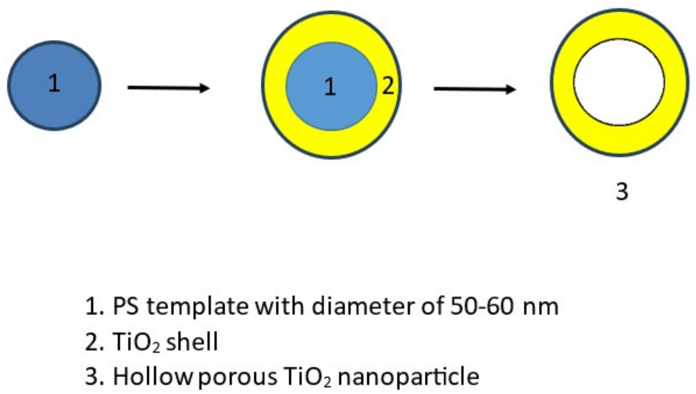

Fig. 1. Diagram explaining the preparation of hollow porous TiO2 nanoparticle. Hollow porous TiO2 nanoparticle was made by coating synthetically the surface of PS particle with TiO2 precursor like Ti(SO4)2 and removing PS template with calcination.

The FESEM image of the prepared PS particles is shown in Fig. 2. The diameters of PS particles are in the range of 50 nm to 60 nm. Porous TiO2 nanoparticles are obtained by using these PS particles as templates.

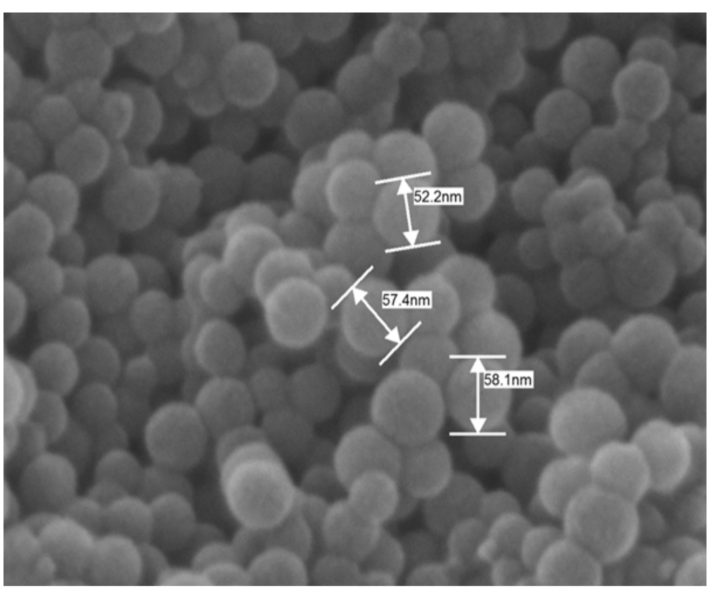

Fig. 2. FESEM image of polystyrene (PS) particles.

The FESEM image of porous TiO2 nanoparticles is shown in Fig. 3. The diameters of the prepared TiO2 nanoparticles are observed in the range of 25 nm to 55 nm, smaller than those of PS templates. This result reveals that TiO2 nanoparticles are synthesized and shrunken to small size by removing PS with calcination. PS templates were removed by calcination in air. Gradual temperature change between 300℃ and 600℃ was occurred during calcination because TiO2 nanoparticles were observed to be burst during the abrupt temperature change.

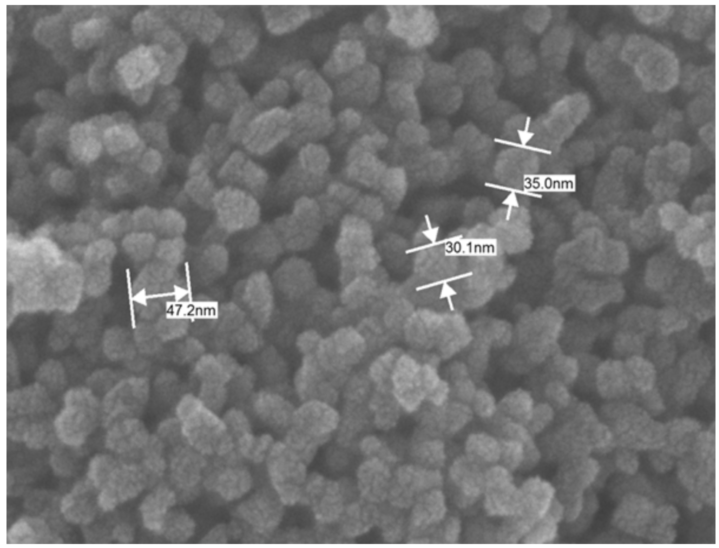

Fig. 3. FESEM image of porous TiO2 nanoparticles.

As nanoparticles less than 100 nm in size, can show the toxicity to cells, we requested to test the cytotoxicity of TiO2 nanoparticles to Korea Testing and Research Institute (KTR). According to the report of the cytotoxicity test (MTT assay) with CCD-986SK (fibroblast) cells (report number: TNK-2021-000754), TiO2 nanoparticles have no cytotoxicity at a concentration of 0.3% or less. Minoxidil-loaded TiO2 nanoparticles were prepared by vigorous mixing or sonication of mixture of 0.1 g of TiO2 added to 100 ml of 5% (or 3%) minoxidil solution. Absorbance was measured at around 254 nm, the maximum extinction wavelength of minoxidil, to know whether minoxidil was incorporated into TiO2 nanoparticles. Minoxidil was thought to be successfully incorporated into TiO2 nanoparticles from the result that the absorbance decreased from 1.70 to 1.59. 200 ul of a nanoparticle formulation containing 5% minoxidil was applied to a mouse whose back was epilated to see its hair growth effect (Fig. 4). B indicates a lane with no treatment, T indicates a lane applied with only TiO2 nanoparticles, M indicates a lane applied with only minoxidil solution and M+T indicates a lane applied with minoxidil-loaded TiO2 nanoparticles. Hair growth was observed to start after 2 weeks and occur considerably after 3 weeks in a M+T lane. On the other hand, no hair growth was observed even after 3 weeks in B, T and M lanes. This result indicates that TiO2 nanoparticles improve the hair growth effect of minoxidil.

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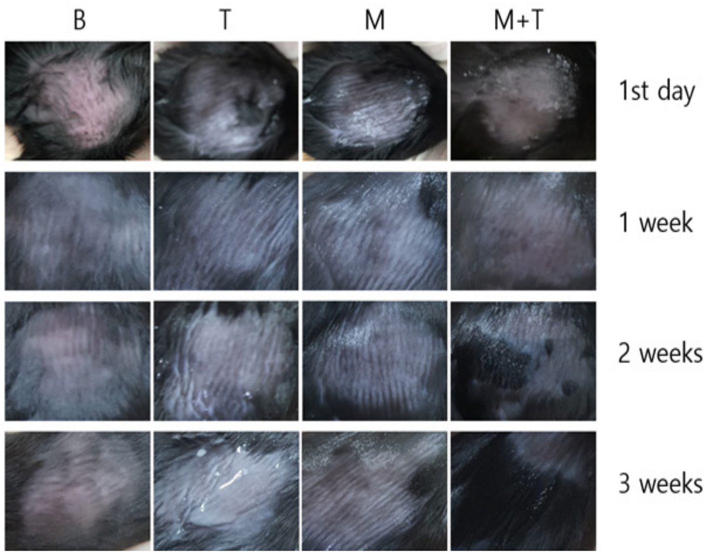

Fig. 4. Comparison of hair growth effect of each solution applied to mice whose back were epilated.

Minoxidil-loaded SiO2 nanoparticles were also prepared to know whether SiO2 nanoparticles improve the hair growth effect of minoxidil like TiO2 (Fig. 5). S indicates a lane applied with only SiO2 nanoparticles and M+S indicates a lane applied with minoxidil-loaded SiO2 nanoparticles. No hair growth was observed after 18 days in both S lane and M+S lane. This result indicates that SiO2 nanoparticles do not improve the hair growth effect of minoxidil unlike TiO2.

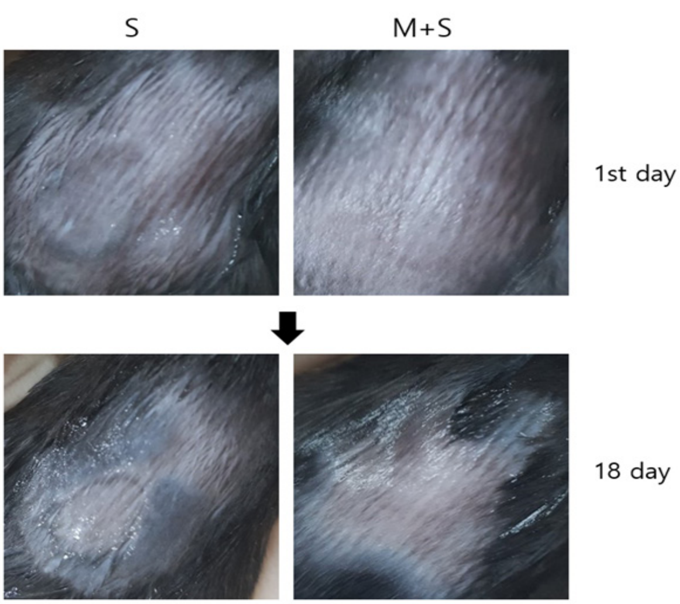

Fig. 5. Comparison of hair growth effect of each SiO2 mixture applied to mice whose back were epilated.

Hair growth effect of minoxidil-loaded TiO2 nanoparticles was also performed with a man and a woman (Fig. 6). 0.6 ml 0.7 ml of 5% minoxidil-loaded TiO2 nanoparticles had been applied to the scalp of a man and 0.6 ml 0.7 ml of 3% minoxidil-loaded TiO2 nanoparticles had been applied to the front hair line of a woman once a day after hair wash for 6 months. Overall increase of hair growth was observed on both the scalp of a man and the front hair line of a woman after 6 months, compared to start time.

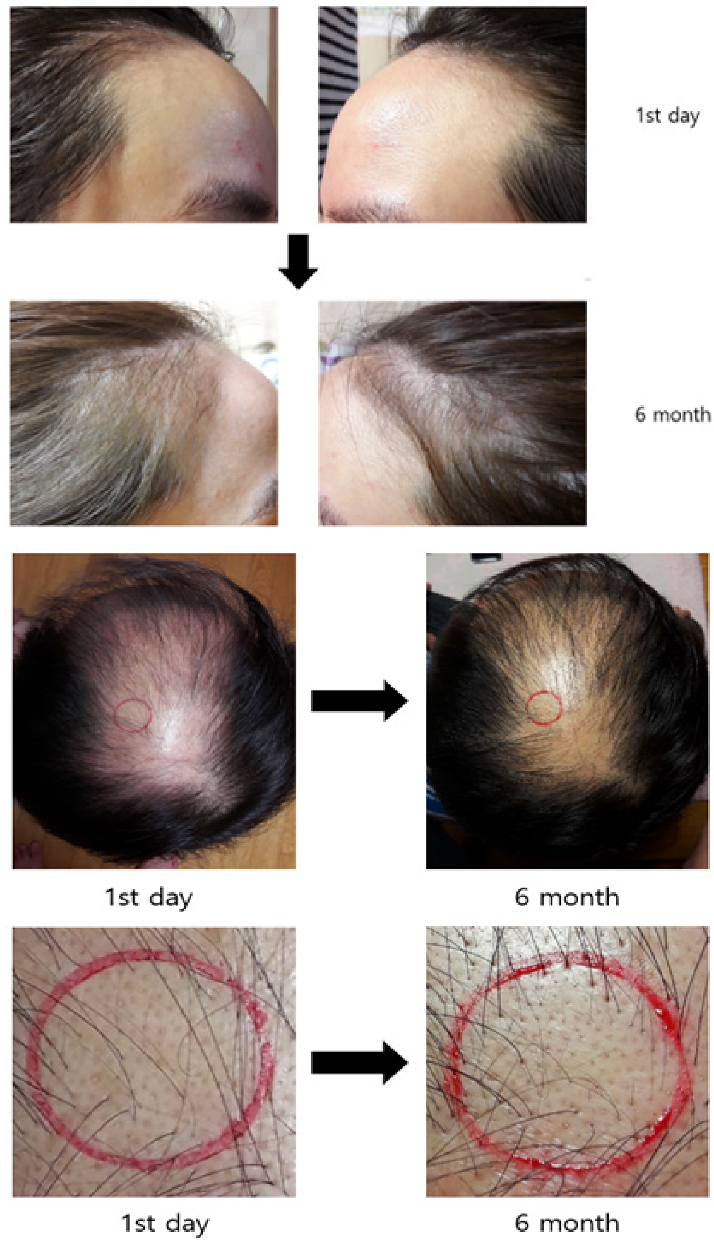

Fig. 6. Hair growth effect of (a) 3% minoxidil-loaded TiO2 nanoparticles applied to the front hair line of a woman and (b) 5% minoxidil-loaded TiO2 nanoparticles applied to the scalp of a man.

The number of hair in the circle of 1.95 cm diameter on the scalp of a man was counted versus time and shown in Fig. 7. The number increased from 31 to 50, which is 61.2% increase of hair growth after 3 months. The number increased more from 31 to 52, which is 67.7% increase of hair growth after 5.5 and 6 months. The value of 67.7% is 5 times increase, compared to 13.68% of hair growth got with application of only 5% minoxidil solution after 6 months. 0.6 ml 0.7 ml of 5% minoxidil-loaded TiO2 nanoparticles was applied once a day to get 67.7% value, on the other hand, the recommended amount and number of minoxidil application is 1 ml and twice (morning and evening) a day. It was confirmed that minoxidil-loaded TiO2 nanoparticles improve hair growth of minoxidil without any significant cytotoxicity, compared to application of only minoxidil because hair growth increased even with less amount and fewer number of application of minoxidil-loaded TiO2 nanoparticles than with the recommended those of only minoxidil solution. Minoxidil-loaded TiO2 nanoparticles are thought to deliver more minoxidil to hair follicles compared to only minoxidil, which needs the further study.

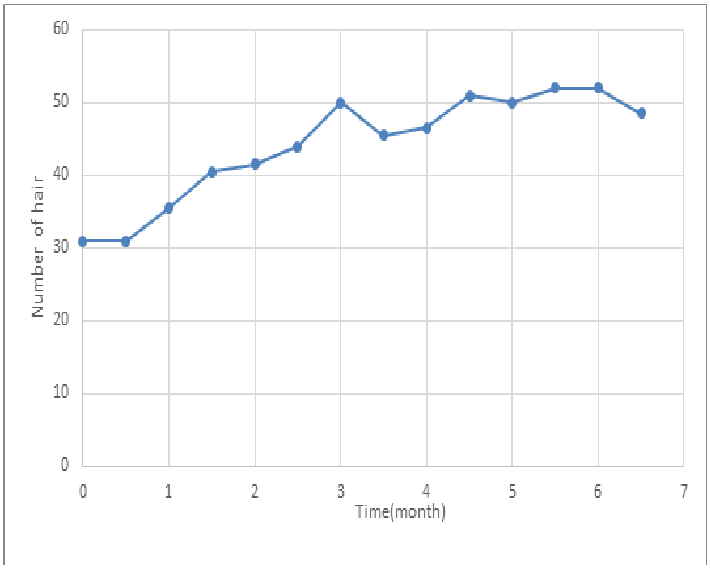

Fig. 7. The number of hair in the circle of 1.95 cm diameter on the scalp of a man versus time

6. Conclusions

TiO2 nanoparticles were developed and confirmed to increase the effect of hair growth of minoxidil. Porous TiO2 nanospheres were obtained by using PS particles as templates and characterized by FESEM. The diameters of the prepared nanoparticles were observed in the range of 25 nm to 55 nm. The increase extent of hair growth of minoxidil by TiO2 nanoparticles was assayed with mice and men. Minoxidil-loaded TiO2 nanoparticles showed 67.7% increase of hair growth which is approximately 5 times, compared to 13.68% of hair growth got with application of only minoxidil solution after 6 months. Our results showed that minoxidil-loaded TiO2 nanoparticles improve hair growth of minoxidil without any significant cytotoxicity.

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