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A novel approach for follicular delivery of minoxidil for treatment of alopecia

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ABSTRACT

The recent strategy uses a distinct approach to modify diffusional barrier of the hair and utilising the pharmaceutical benefits of microemulsion to facilitate follicular permeability of Minoxidil. Various attempts were made to optimise pre-treatment and post treatment conditions, which cause the hair follicles to swell up and shrink using conventional reagents. Microemulsions prepared with oleic acid, PEG 600 and span 20 using pseudo ternary diagrams. Optimised microemulsion for topical delivery (globule size- 41.0 nm; zeta potential- +28.22 mV; transmittance- 98.1%) was considered for drug delivery. In-vitro release of 68.5% after 24 hrs was observed and ex-vivo studies showed 67.5% drug retention inside hair shaft. Prepared formulation significantly altered the follicular response in 5-Fluorouracil induced alopecia model. It opens a new avenue for delivery of drugs via transfollicular route in the treatment of follicular diseases.

1. Introduction

Alopecia, also known as spot baldness, is a kind of immune dysfunction where hair is lost from the scalp. Androgenetic Alopecia (AGA) or pattern baldness is the most common type of hair loss in human beings [1]. These are not contagious, and body immune system itself attacks the hair follicles and stops its growth. Above cases gets aggravated with the use of chemotherapy, antibiotic usage, pregnancy/hormone, allergic reaction, nutritional deficiency [2]. The use of medications in the treatment of chronic medical conditions are capable of producing a wide spectrum of hair loss, ranging from barely detectable shedding to irreversible baldness [3].

Alopecia cannot be cured, but long term therapy with appropriate medication can slow thinning of hair and increased coverage of the scalp by growing hair. Long term medication increases the risk of toxicity. Transfollicular route would be useful for the effective delivery of drugs used in alopecia as it offer site specific drug targeting even reduces the unwanted toxicity. Minoxidil is a USFDA approved medication for hair loss [4]. Further it meets all the physicochemical requirements suitable for transfollicular drug delivery. Commercially minoxidil is usually available in 2% or 5% strength in multiple topical formulations like solutions, spray, foams etc. [5].

Cosmetically available minoxidil formulation usually contains high percent of lower alcohols or alcohol based agents to achieve greater skin permeability. Further minoxidil topical formulation is recommended for thrice a day application at 12 hrs interval to the scalp. Long term exposure of alcohol and minoxidil cause several skin toxicities like; skin irritation, dry skin, redness, allergic type reaction etc. Depot drug delivery provides satisfaction to achieve possible drug targeting results in high drug concentration at the affected site and reduced drug toxicity. Present study explored the strategy involved in permanent hair dye, to promote hair shaft swelling so that the drug can penetrate better and could utilize the hair shaft as depot system to offer sustained delivery of therapeutics at the target site. In addition to this, special feature of microemulsion was also attempted to facilitate the follicular permeability of minoxidil. Surfactant present in microemulsion at sufficiently high concentration not only improves drug solubilization but also increased flux across hair. Recently Jaipakdee and Limpongsa studied the efficiency of topical microemulsion in the permeation flux of minoxidil using fractional factorial design approach. Experimental findings suggested that microemulsion systems not only increases the penetration of minoxidil but also improve drug solubility. The possible outcomes of the proposed innovation would make a substantial impact in the treatment of Androgenetic alopecia with greater patient acceptance [6]. In the present study oil

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and surfactant system having maximum solubility of minoxidil were selected and then the phase where determined and then respectively concentration were optimized using pseudoternary phase diagram. Optimized thermodynamic and transmittance conditions were considered as key variable for selection of stable microemulsion. In the present work we have studied the effect of alkaline substances like sodium carbonate or mono or tri-ethanolamine on human hair to analyze whether the drug can actually diffuse inside the hair shaft or not. Further the treatment conditions involved from pre-treatment to post-treatment were optimized to regain natural hair properties. The in-vivo efficacy of new therapeutic strategy combining the benefit of microemulsion and concept of permanent hair dye process was determined in chemotherapy induced alopecia model in rats.

2. Materials and methods

2.1. Materials

Minoxidil was obtained as gift sample from Kumar Organics, Bangalore. All the solvents used were of analytical grade. Oleic acid and Poly-ethylene glycol 600 were obtained from SD Fine-Chem Limited, Mumbai, India. Span 20 was obtained from Loba Chemie Pvt. Ltd. Mumbai, India. Ethanolamine and tartaric acid were obtained from Central Drug House, New Delhi, India.

2.2. Methods

2.2.1. Optimization of pre-treatment and post-treatment condition

Optimizing the pre-treatment and post-treatment conditions is the key features to ensure greater percutaneous drug penetration and maximum reconstruction to make safe and effective product. In general alkaline medium promotes the opening of the cuticles and acidic solutions make cuticles lie flat or “close up. Various attempts have been made to select the optimum pre-treatment and post-treatment trait based on hair morphology, physical and mechanical properties. Briefly the pre-weighed amount of human hairs were incubated in different alkaline medium (Ethanolamine and Tri-ethanolamine) at different concentration. The physical and mechanical properties of hair including microscopic observation, tensile strength and swelling index were determined at various time intervals. Similarly the concentration and exposure time of acidic medium to be used in post-treatment were determined. Briefly the pre-treated hairs were subjected to different acidic conditions (tartaric acid and citric acid) at different concentration. Physical and mechanical properties close to normal hair were considered to be the optimum post treatment conditions. Table 1 shows the conditions for different pre-treatment and post treatment scheme.

2.2.2. Preparation of microemulsion

Water in oil type microemulsion was prepared by the spontaneous emulsification method. The solubility of minoxidil in oils, surfactants and cosurfactants was evaluated to screen the components of the microemulsion. On the basis of solubility studies, oleic acid was selected as the oil phase. Span 20 and PEG 600 were chosen as surfactant and co-surfactant respectively. Various surfactants and cosurfactants were further screened for their ability to emulsify the selected oily phase using pseudo ternary phase diagram. Minoxidil loaded microemulsion was prepared by dissolving pre-determined quantity of drug in oleic acid with vortexing followed by ultrasonication. The required quantities of surfactant and cosurfactant were added and the mixture was cyclomixed to yield a homogenous solution. The aqueous phase was added gradually to oil phase with continuous stirring until a clear and transparent microemulsion was formed. Various formulation parameters including surfactant/co-surfactant, water, oil percentage and drug concentration were systematically investigated to determine their effects on particle size, zeta potential, viscosity, percentage transmittance and accelerated temperature study of Microemulsion. Table 2 enlists the composition of various microemulsion formulations prepared in this study.

2.2.3. Pseudo ternary phase diagram

Pseudo ternary phase diagram was prepared in a triangular format having three co-ordinates with the help of chemix software. Phase diagrams were prepared using different concentration of oil, S/CoS and water and the best possible combinations were selected based on the area of microemulsion region. Each co-ordinate represents one component of Microemulsion system viz. (1) Oil Phase, (2) Surfactant-Cosurfactant ratio and (3) Aqueous Phase. Each co-ordinate also represents 0 to 100% concentration of each of the phases in the increment of 10%. In the present investigation, particle size below 200 nm was employed to construct a phase diagram. The different weight ratios of surfactant to co-surfactant were mixed to an appropriate amount of the corresponding components under vigorous stirring. After equilibrium samples were visually checked and determined as being clear microemulsion. Particle size and accelerated stability were performed to select one phase clear microemulsion systems. Formulations with particle size more than 200 nm, exhibiting phase separation were considered 2 PHASE system and, formulations with particle size less than 200 nm with no sign of phase separation were considered 1 PHASE system. Accordingly phase diagram was drawn.

Table 1
Optimization of pre-treatment and post treatment conditions based on the mechanical and morphological properties of hair.

Conc. (%)	Time (mins)	Normal hair	Pre-treatment medium				Post-treatment medium			
			Ethanolamine		Tri- ethanolamine		Tartaric acid		Citric acid	
			TS (gf/cm^2)	MO	TS (gf/cm^2)	MO	TS (gf/cm2)	MO	TS (gf/cm^2)	MO
5	5	115	114	=	115	=	95	α	95	α
	10		114	=	114	=	96	α	95	α
	15		113	=	114	=	96	α	95	α
10	5		114	=	112	=	96	α	96	α
	10		114	+	112	+	98	β	97	α
	15		112	+	109	+	98	β	98	β
15	5		105	+	107	+	100	β	99	β
	10		98	+	101	++	105	γ	100	β
	15		95	++	86	+++	108	γ	103	β

(= No distortion; + Less distortion; ++ Visible and prominent distortion; +++ Permanent distortion; X Hair degradation, α No Reconstruction; β Less reconstruction; γ Prominent Reconstruction).