Surface modified Niosomes entrapping Minoxidil: Targeted Drug Delivery platform to treat Alopecia.

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Abstract

Background: Alopecia defined as loss of hair from the scalp and other parts of the body may be involved in some types. It is a term comes from the Greek alopex," fox" relating to manage in foxes and may be include a huge variety of conditions such as autoimmune, genetic, environmental and infectious. The appearance of clinical manifestations can diversify depend on the pathogenesis of this disease. Scaring and non-scaring are two types of alopecia. Scarring alopecia is classified into primary and secondary according to cause of destruction of hair follicle, while non scarring hair loss is classified according to the cause into: androgenic alopecia, alopecia areata, traction alopecia, effluvium (anagen and telogen), tinea capitis and trichotillomania. In 1965 scientists discovered the potent antihypertensive effect of minoxidil and since then it has been used as a treatment for hypertension, but later it was found that it could be used for treatment of alopecia "e.g. androgenic alopecia ,anagen effluvium ,alopecia areata and traction alopecia" due to its hpertrichotic effect. Minoxidil entrapped in niosomes coated with chitosan were prepared to develop targeted drug delivery systems with controlled release profile to treat alopecia

Methods: Niosomes composed of span 60 and cholesterol in molar ratio 1:1 (F2) coated with chitosan (F3) were prepared using thin film hydration method and evaluated for particle size, zeta potential using mastersizer, entrapment efficiency, morphology using scanning electron microscope (SEM), and structure by X-ray diffraction. The prepared niosomes were then incorporated in topical cream (F4) and (F5). The formed creams were evaluated for viscosity using Brookfield viscometer , spreading and irritation properties. In vitro release was also investigated for all formulae and compared to drug suspension (F1)

Results: The results revealed that particle size of (F2) and (F3) were 349.9 nm and 674.9 nm, respectively, While entrapment efficiency of (F2) and (F3) were 22.33% and 13%, respectively. Moreover, zeta potential was -40mV for (F2) and +32 mV for (F3). X- ray diffraction showed that minoxidil is crystalline in nature which didn't change and remained crystalline in all formulae. Viscosity of (F5) was 9000-9300 Cp and 6850-7600 Cp at 6 and 12 rpm respectively, with no irritation and good spreading property. In vitro release after 6 hours of F1, F2, F3, F4 and F5 were 100%, 39.11%, 33.56%, 19.66%, and 12.17%, respectively.

Conclusions: In the light of the aforementioned results, chitosan coated niosomes entrapping minoxidil incorporated in cream were successfully prepared to achieve targeted drug delivery and controlled release as well.

Introduction

Alopecia is the broad term because of any type of hair loss is a kind of alopecia. Alopecia defined as loss of hair from the scalp and other parts of the body may be involved in some types. The severity varies from a small part to the entire body.it has an effect on both males and females of all ages. Alopecia is a term comes from the Greek alopex," fox" relating to manage in foxes and may be include a huge variety of conditions such as autoimmune, genetic, environmental and infectious. The appearance of clinical manifestations can diversify depending on what the pathogenesis of this disease. In addition to the loss of hair may be temporary or permanent. Scaring and non-scaring are two types of alopecia. Scarring alopecia is classified into primary and secondary according to cause of destruction of hair follicle. For primary alopecia destruction of hair follicle is due to an inflammatory process while secondary alopecia destruction is due to an external cause as burns, infections, and radiations.(1-5). Non-scarring hair affects both males and females. Considering that any disturbances inside the hair follicle cycle may also result in hair shedding without destruction of hair follicles, Non scarring hair loss is the loss of hair without appearance of any scarring. This is in comparison to scarring hair loss. Non scarring alopecia was classified according to the cause into (6): androgenic alopecia, alopecia areata, traction alopecia, effluvium (anagen and telogen), tinea capitis and trichotillomania. In 1965 scientists discovered the potent antihypertensive effect of minoxidil and since then it has been used as a treatment for hypertension, later it was found that it doesn't only have a potent effect on lowering blood pressure but also it could be used for treatment of alopecia "e.g. androgenic alopecia ,anagen effluvium ,alopecia areata and traction alopecia" due to its hpertrichotic effect i.e. abnormal hair growth over the body(5), which was induced by conventional oral dosage form.(7)

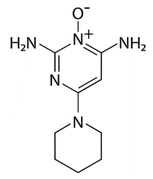


Diagram 1: structure of minoxidil

The mechanism of action of minoxidil as a treatment of alopecia: -

Minoxidil exact mechanism of action in treating alopecia (Diagram 2) is still debatable and unknown but some researches reveal that it is due to its effect on blood vessels potassium channel opening that leads to enhancing blood flow to the hair follicles carrying nutrients and oxygen to the affected area of the scalp inducing hair growth(8). Others claim that it is due to the activation of prostaglandin-endoperoxide synthase 1 (PGHs-1) by minoxidil, PGHs-1 is produced in hair follicles especially at their lower part during both anagen and catagen phases thus its activation by minoxidil will elongate anagen phase i.e. active hair growth phase, that leads to increase of hair and treatment of our disease. Also it is believed that minoxidil causes irritation in scalp thus increasing blood supply by indirect action and increase hair growth.(9)

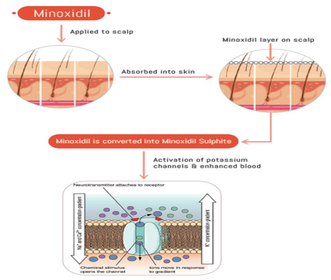


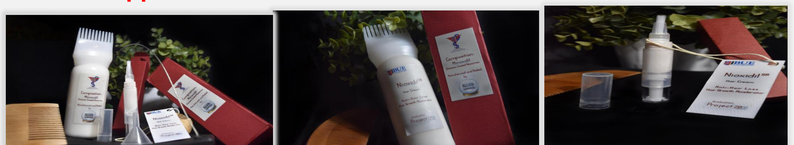
Diagram 2: The mechanism of action of minoxidil for treatment of alopecia

Carriers in nanoscale have unique physical and chemical properties that may vary from carriers in conventional size or even opposite to it. Nanocarriers have been involved in many new drug delivery systems, due to its advantages and overcoming many limitations in conventional drug delivery systems. Significant growth in using nanotechnology in treatment, research and diagnosis of diseases has opened a new way for trials and new adventure to be discovered.(10)

Niosomes are distinguished over other nanocarriers as they are chemically stable, has low toxicity, biodegradable, biocompatible, easy to be stored and handled, and finally with low production cost. Niosomes has been incorporated in many dosage forms such as; intramuscular (IM), intravenous (IV), transdermal, oral. Niosomes also increase absorption rate of some drugs, according to their nature.(11)

Chitosan is widely used in new drug delivery systems. It is a naturally occurring cationic polysaccharide, mainly obtained from marine crustaceans. It is positively charged and can cross cellular membrane. Chitosan is considered a promising therapeutic delivery system, and also in diagnosis. Back to its features which biocompatibility, biodegradability, low toxicity and structural variability. Combining chitosan with nanotechnology has been proven in new studies that can beat obstacles facing drug delivery, which improve the drug efficacy.(12)

Novel Applicators:

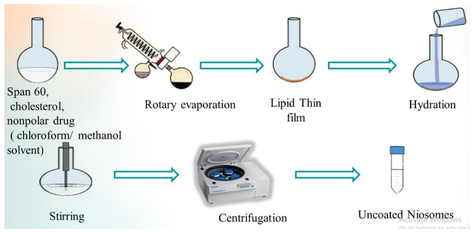


Aim of work

The aim of our study was to develop targeted drug delivery systems with controlled release profile of Minoxidil (Mn) agent entrapped in chitosan coated noisomes, to achieve targeted drug delivery and controlled release as well.

Methdology

1- preparation of niosomes: (13)



2- Coating of niosomes:

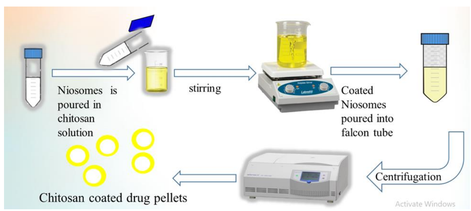


Diagram 3: Thin film hydration and coating of formed niosomes

Evaluation of niosomes

Evaluation of formed niosomes

1- Entrapment efficiency percent (EE %) : (14)

Diagram 4: Separation of entrapped and unentrapped drug.

Minoxidil entrapment efficiency (%)= Amount of minoxidil / Total amount of minoxidil used x 100, equation 1

2- Zeta potential, Particle size and polydispersty index (PDI):

- zeta potential greater than +\-30 optimum stability
- PDI 0-1 homogeneity of sample

Diagram 5:Malvern zetasizer.

3- Morphology :

Diagram 6: scanning electron microscope.

4- X-ray Diffraction:

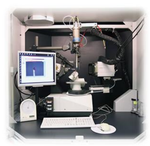


Diagram 7:X-ray diffraction device.

***In vitro* release using Franz diffusion cell**

Compare between

1. Drug Suspension (F1)
2 .Uncoated Niosomes (F2)
3. Coated Niosomes (F3)
4 .Cream Containing Uncoated Niosomes (F4)
5. Cream Containing Coated Niosomes (F5)

Evaluation of cream

Diagram 8 :Brookfield Viscometer.

2-The spreadability (S) can be calculated using the formula:-

S = M. L / T where

M = Weight tied to upper slide

L = Length of glass slide

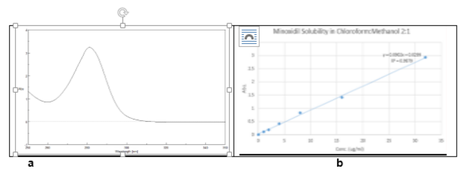
T = Time taken to separate the slides

3-Irritancy Test:

Mark the area (1sq.cm) on the dorsal surface of the left hand. The cream was applied and time was noted to the specified area. Irritation, erythema, edema were checked at regular intervals of up to 24 hours.

Results and conclusion

1- UV Absorbance and calibration curve of Minoxidil:



Figure(1): a) UV absorbance chart of minoxidil and b) calibration curve of minoxidil

2- Entrapment efficiency (EE%):

Table (1): Entrapment efficiency.

Sample	EE%
Uncoated niosomes (F2)	22.33%
Coated niosomes (F3)	13%

3-Particle size and Polydispersity index (PDI).

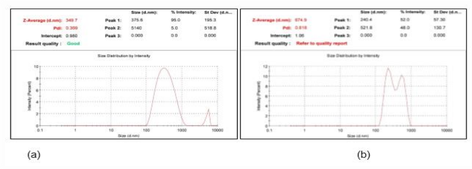


Figure (2): particle size and PDI of a) F2 and b) F3.

4- Zeta potential:

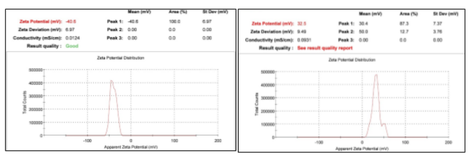


Figure (3): Zeta potential of a) F2 and b) F3.

5- X-ray Diffraction:

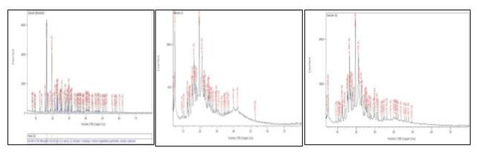
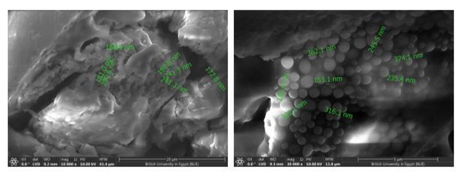


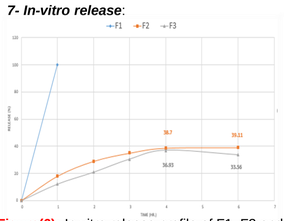
Figure (4): X-ray diffraction of a) F1, b) F2 and c) F3.

6- Morphology:

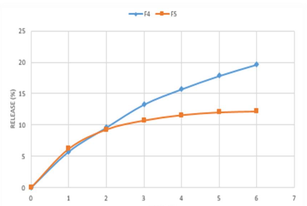


Figure(5): Scanning Electron Microscope of a) F2 and b) F3.

***7- In-vitro release*:**

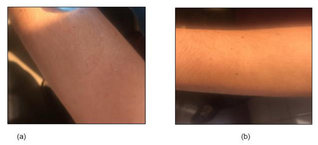


Figure(6): In vitro release profile of F1. F2 and F3.



Figure(7): In vitro release profile of F4 and F5.

8-Spreadability and Irritation test:



Figure(9): Evaluation of a) Spreadability and b) Irritation.

9-Viscosity:

Table(2): Viscosity of cream.

Rotation per minute (rpm)	Viscosity (cp)
6 rpm	9000-9300 cp
12 rpm	6850-7600 cp

Conclusion

In the light of the aforementioned results, chitosan coated niosomes entrapping minoxidil incorporated in cream were successfully prepared to achieve targeted drug delivery and controlled release as well.

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