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Preformulation Study of Minoxidil: A Drug for Androgenic Alopecia

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Usmania[1*], Bilandi Ajay [2], Kataria K Mahesh [3]

[1]Research Scholar, M.Pharm (Pharmaceutics), Sem IV, Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar, Rajasthan, India.

[2]Assistant Professor, Dept. of Pharmaceutics, Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar, Rajasthan, India.

[3]Professor and Head, Dept. of Pharmaceutics, Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar, Rajasthan, India.

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ABSTRACT

Minoxidil, an antihypertensive peripheral vasodilator, is a prodrug converted to an active metabolite which is potassium (K) channel opener, act by hyperpolarizing smooth muscles. Minoxidil in the treatment of androgenic alopecia has led to the hypothesis that other pathways could mediate this form of hair loss, including infection and/or micro-inflammation of the hair follicles. It stimulates the growth of human hair by prolonging anagen through these proliferative and anti-apoptotic effects on dermal papillary cells. It acts by opening ATP-sensitive potassium channels in vascular smooth muscle cells thus improving the viability of hair follicles. The preformulation studies are prerequisite to ensure the development of therapeutically effective dosage form. The preformulation studies viz. identification of drug, quantitative estimation of drug, solubility determination, melting point determination, etc are carried out. This article also discussed the various characteristics of the drug i.e. pharmacodynamic and pharmacokinetic properties and others along with the mechanism of action of the drug.

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1. INTRODUCTION

Minoxidil occurs as a white to off-white, odorless, crystalline solid that is soluble in water to the extent of approximately 2 mg/ml, is readily soluble in propylene glycol or ethanol, and is almost insoluble in acetone, chloroform or ethyl acetate. Minoxidil in the treatment of androgenic alopecia i.e. baldness has led to the hypothesis that other pathways could mediate this form of hair loss, including infection and/or microinflammation of the hair follicles. [4, 11]

Minoxidil is a prodrug- converted to an active metabolite which is potassium channel opener; act by hyperpolarizing smooth muscles. [19]

1.1 Proprietary name:

Apo-Gain; Apohair; Alopexy; Alostil; Aloxidil; Folcress; Hairgain; Headway; Loniten; Lonnoten; Lonolox; Minona; Minovital; Minoxidine; Minox; Minoxigaine; Minoximen; Moxiral; Neoxidil; Normoxidil; Ralogaine; Regaine; Regro; Rogaine; Tricoxidil; Unipexil. [4]

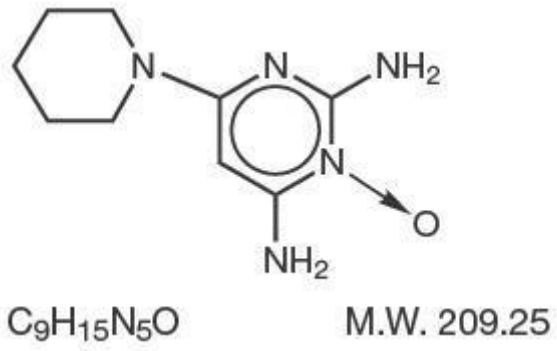
1.2 Chemical Name:

The chemical name for Minoxidil is 2,4-pyrimidinediamine, 6-(1-piperidinyl)-, 3-oxide. [4, 7, 17]

1.3 Chemical Formulae:

The chemical formula for minoxidil is $C_9H_{15}N_5O$. [2, 17]

1.4 Chemical Structure: [8, 17]



1.5 Molecular Weight: 209.25 [17]

1.6 Melting Point: 225°C

1.7 Protein Binding: In plasma, not significantly bound

1.8 Half Life: Plasma half-life, about 3 to 4 h.

1.9 Appearance: White crystalline solid [2, 7]

1.10 Solubility: Soluble in water, ethanol and propylene glycol; practically insoluble in chloroform. [2]

1.11 Dissociation Coefficient: pK_a4.6

1.12 Partition Coefficient: LogP (octanol/water), 1.2.

1.13 Dose: 5 to 50 mg daily, up to 100mg daily has been given orally. [3, 6]

1.14 Pharmacokinetics:

a. Absorption: Minoxidil is at least 90% absorbed from the GI tract in experimental animals and man.

b. Volume of distribution: Not Available

c. Protein binding: Minoxidil does not bind to plasma proteins.

d. Route of elimination: Not Available

e. Toxicity: Oral LD in rats has ranged from 1321-3492 mg/kg; in mice, 2456-2648 mg/kg.

f. Side effects: cardiovascular effects associated with hypotension such as sudden weight gain, rapid heartbeat, faintness or dizziness. [3]

1.15 Mechanism of Action:

Minoxidil increases growth of body hair. Applied topically it promotes hair growth in male pattern baldness and alopecia areata. The response is slow. The mechanism of increased hair growth is not known; may involve:

a. Enhanced microcirculation around hair follicles.
b. Direct stimulation of resting hair follicles.
c. Alteration of androgenic effect on genetically programmed hair follicles [1, 3].

Minoxidil may also cause prolongation of anagen and increases hair follicle size. Orally administered minoxidil lowers blood pressure by relaxing vascular smooth muscle through the action of its sulfated metabolite, minoxidil sulfate, as an opener of sarcolemmal KATP

channels. There is some evidence that the stimulatory effect of minoxidil on hair growth is also due to the opening of potassium channels by minoxidil sulfate, but this idea has been difficult to prove and to date, there has been no clear demonstration that KATP channels are expressed in the hair follicle. [12]

Minoxidil combined with a diuretic and β-adrenoreceptor antagonist is sometimes effective where other drugs have failed in severe hypertension resistant to other drugs. [14]

1.16 Interaction:

Medications are known to interact with minoxidil majorly are guanethidine/hydrochlorothiazide, guanadrel, tizanidine, diphenhydramine, hydrocortisone, methylprednisolone, aripiprazole, fentanyl, codeine, etc [15]

1.17 Indications:

It is used for the treatment of severe hypertension and in the topical treatment (regrowth) of androgenic alopecia in males and females and stabilization of hair loss in patients with androgenic alopecia.

1.18 Uses:

Minoxidil is used to help hair growth in the treatment of male pattern baldness. It is not used for baldness at the front of the scalp or receding hairline in men. It is also used to help hair growth in women with thinning hairs.

1.19 Storage: Stable at room temperature. [3]

General Pharmacological Properties

Minoxidil is a potent arteriolar vasodilator. 90% of the drug is absorbed from GIT. Minoxidil does bind to plasma proteins with $t^{1/2}$ of about 3-4 hrs. It is widely distributed to the body and 90% of the hepatic biotransformation occurs with no evidence of accumulation of drug when it is given chronically in patients with normal renal functions.

a. Effect on blood pressure and target organs

Blood pressure usually starts to decline after the administration of single dose. This effect is shown within one-half hour and it reaches a minimum between 2 to 3 hours and recovers at

an arithmetically linear rate of about 30% of day. If minoxidil is administered chronically, time required to achieve maximum effect on blood pressure with a daily dose is inversely related to the size of the dose. Thus it can be concluded that the blood pressure response of minoxidil is linearly related to the log of dose administered. The slope of log linear dose response relationship is proportional to the extent of hypertension.

b. Absorption

90% of minoxidil is absorbed from GIT. Plasma levels of drug reaches maximum within first hour and hypotensive effect is seen later because formation of active metabolite is delayed.

c. Metabolism

90% of the minoxidil is metabolized predominantly by conjugation with glucuronic acid at the N-oxide position in the pyrimidine ring. It also shows conversion to more polar products. It does not bind to plasma protein and does not cross blood brain barrier. Glomerular filtration rate explains its renal clearance. In the absence of functional renal tissue, metabolites can be removed by hemodialysis.

d. Cardiac lesions

Minoxidil produces several lesions that may cause tachycardia and diastolic hypotension. Its significance is not clear in humans. These lesions can be

- **Papillary muscles necrosis**

These lesions are similar to lesions produced by peripheral arterial dialators. These lesions are thought to reflect ischemia provoked by increased oxygen demand and reflects ischemia provoked by increased oxygen demand and decrease in cornory flow caused by the vasodilatory effect of these agents of these agents coupled with reflex or directly induced tachycardia.

- **Hemorrhagic lesions**

These lesions are seen in many parts of the heart, mainly in epicardium, endocardium, and walls of coronary arteries and arterioles.

- **Epicarditis**

Focal epicarditis was observed after 2 days of oral administration of minoxidil and chronic proliferative epicarditis was observed after the topical treatment twice a day.

- **Hypertrophy and dialation**

Oral and topical administration show cardiac hypertrophy and dilation. It may be due to the consequences of prolonged fluid overload but this can be reversed by diuretics.

e. Indications

Minoxidil is indicated for the treatment of hypertension that is symptomatic or associated with target organ damage. Now a days it is used in milder degrees of hypertension is not recommended but it reduces supine diastolic blood pressure by 20 mm of Hg or to 90 mm of Hg.

f. Contraindications

Minoxidil is contraindicated in pheochromocytoma because it may stimulate secretion of catecholamines in hypersensitive patients.

g. Side effects

Unwanted facial or body hairs, dizziness, fast or irregular heartbeat, fainting, chest pain, swelling of hands/ feed, unusual weigth, tiredness, etc.

h. Warnings

- **Salt and water retention**

Minoxidil must be administered with adequate diuretic to prevent the fluid water retention and further CHF. High ceiling diuretic is always required and body weight is observed regularly. If it is given without the use of diuretic then it may lead to retention of hundred milli-equivalents of salt and volumes of water which cause increased plasma and interstitial fluids (edema).

- **Tachycardia**

Minoxidil increases the heart rate. Minoxidil administration may cause increased oxygen demands with increased heart rate and cardiac output. This generally can be prevented by administration of beta adrenergic blockers or other sympathetic nervous system suppressant.

- **Pericarditis**

It has been observed that pericardial effusion occurs with inadequate or compromised renal functions in 3% of patients. In case of severe conditions withdrawal of minoxidil should be considered.

- **Interaction with Guanethine**

Administration of minoxidil does not cause orthostatic hypertension to patient already receiving guanethidine. Guanethidine should be discontinued before the use of minoxidil.

- **Hazards of Rapid control of blood pressure**

Patients with severe blood pressure elevation needs rapid control of blood pressure, especially with i.v. agents and can precipitate syncope, cerebrovascular accidents, myocardial infarction and ischemia with decrease or loss of vision or hearing.

i. Precautions

Minoxidil may reduce arterial pressure further may limit blood flow to myocardium. This can be compensated by decrease oxygen demand because of lower blood pressure. Minoxidil may cause hypersensitive reactions causing skin rashes. Patients with lower doses of minoxidil are observed for renal failure or perception of cardiac failure. Thus, patient should be monitored and withdrawal of drug is done if needed.

j. Adverse effects

- **Salt and water retention**

Use of adequate diuretic is required because of increased proximal renal tubular reabsorptiom which causes salt and water retention.

- **Dermatologic**

Hypertrichosis – elongation, thickening and enhanced pigmentation of fine body hair are seen in 80% of patients. This develops within 3 to 6 weeks after starting therapy. This effects of minoxidil is now used in the treatment of androgenic alopecia.

- **Allergic**

Rashes have been observed including bullous eruptions, toxic epidermal necrolysis and stevens Johnson syndrome

k. Overdose and Toxicity

Overdose of drug may cause toxic effects. In general a substantial increase above 2000mg/ml should be regarded as overdose. It shows toxic effects above this limit of drug like tachycardia, palpitations, angina, edema, headache, etc. [20]

2. PREFORMULATION STUDY:

Preformulation studies are required to ensure the development of a stable as well as therapeutically effective and safe dosage form. The Preformulation studies performed in this research include identification of drug, solubility analysis, identification of physical properties of drug viz. color, odor, crystallinity and hygroscopicity, identification of drug, solubility analysis and melting point of drug.

2.1 Organoleptic Properties of Drug

2.1.1 Color: By visual examination of the drug, color of drug is observed.

2.1.2 Odor: Odor of drug is judged by smelling it.

2.1.3 Hygroscopicity: Drug is kept at room temperature for some time and is further observed for gain of moisture from its surrounding environment.

2.2 Identification of Drug

2.2.1 UV spectrophotometric analysis of drug: Ultraviolet absorption in the range 200nm to 400nm of a 2 mg/ml solution in water was determined. [5, 6, 7]

2.2.2 Fourier Transform Infra-Red analysis of drugs: The FTIR analysis of the sample was carried out for qualitative compound identification. The sample was placed in ATR based Brukers Tensor 27 instrument. [7]

a. Preparation of Buffers and Reagents:

0.2 M Sodium hydroxide solution: 8.0 gm of sodium hydroxide was dissolved in distilled water and diluted to 1000 ml with distilled water.

0.2M Potassium dihydrogen phosphate solution: 27.218 gm of potassium dihydrogen phosphate was dissolved in distilled water and diluted to 1000 ml.

Phosphate buffer solution of pH 7.4: 250 ml of 0.2 M potassium dihydrogen phosphate was placed in 1000 ml volumetric flask. 112 ml of 0.2 M sodium hydroxide was added and then volume was adjusted with distilled water up to 1000 ml. pH was adjusted to 7.4 with dilute sodium hydroxide. [18]

b. Quantitative Estimation of Drug:

Determination of absorption maxima (λ max)/wavelength maxima

The standard stock solution of minoxidil was prepared by dissolving 50mg of drug in water in 100 ml volumetric flask. Stock solution of minoxidil was further diluted in water to get standard solution concentration of 100g/ml. The resulting solution was then scanned between 200 -400 nm using UV-visible spectrophotometer (Shimadzu 1601 UV Japan). [5, 10]

Standard curve of minoxidil in phosphate buffer solution (PH 7.4)

Accurately weighed 100 mg of minoxidil was dissolved in 100 ml of pH 7.4 phosphate buffer to give a solution of 1 mg/ml (1000µg/ml) concentration and this served as the first standard stock solution. From this stock solution 1 ml was taken and diluted to 100 ml using pH 7.4 phosphate buffers to get a solution of 10µg/ml concentration and this solution served as the second standard solution. Into a series of 10 ml volumetric flasks, aliquots of second standard solution (i.e.) 2 ml, 4 ml, 6 ml, 8ml, 10ml and 12 ml were added and the volume made up to 10 ml using pH 7.4 phosphate buffer. The absorbance of these solutions was measured against reagent blank at 286 nm using Shimadzu (UV-1601) UV spectrophotometer. Standard curve was plotted with concentration on x-axis and absorbance on y-axis. [5, 6, 10]

Melting point determination:

Melting point determination of minoxidil is done by using melting point apparatus. In this method, the pre-sealed capillary is filled with the small amount of drug. Then capillary and thermometer were placed in melting point apparatus. Then see capillary for melting the drug. The temperature was noted when the drug starts to melt and the drug till complete melt. [6, 10]

Solubility determination

For quantitative solubility studies, known amount of drug (1mg) was suspended in a series of different solvents and shaken for 24 hrs by wrist action shaker (York India). Solubility of minoxidil in different solvents is recorded. [11, 12]

Solubility decreases in the order: methanol > 1-propanol > 1-butanol > ethanol > 2-propanol > water. [14]

3. RESULTS AND DISCUSSION

3.1 Organoleptic Properties

Table 1: Organoleptic Properties

Sr. No.	Organoleptic property	Standard observation	Results
1	Color	White- off white	Complies
2	Hygroscopicity	Not hygroscopic	Complies
3	Odor	Odorless	Complies

3.2 Identification of Drug

3.2.1 Determination of λ max: The λ max was found to be at 286 nm.

Discussion

λ max obtained was 286 nm and thus complies with united state pharmacopoeias in USP. [8]

4.1 FT-IR Study for identification of drug:

An FT infrared (FT-IR) spectroscopy study was carried out to check the Identification of drug. The spectra obtained from FT infrared spectroscopy studies at wavelength from 4000 cm to 400-1 cm are shown Figures characteristic peaks obtained.

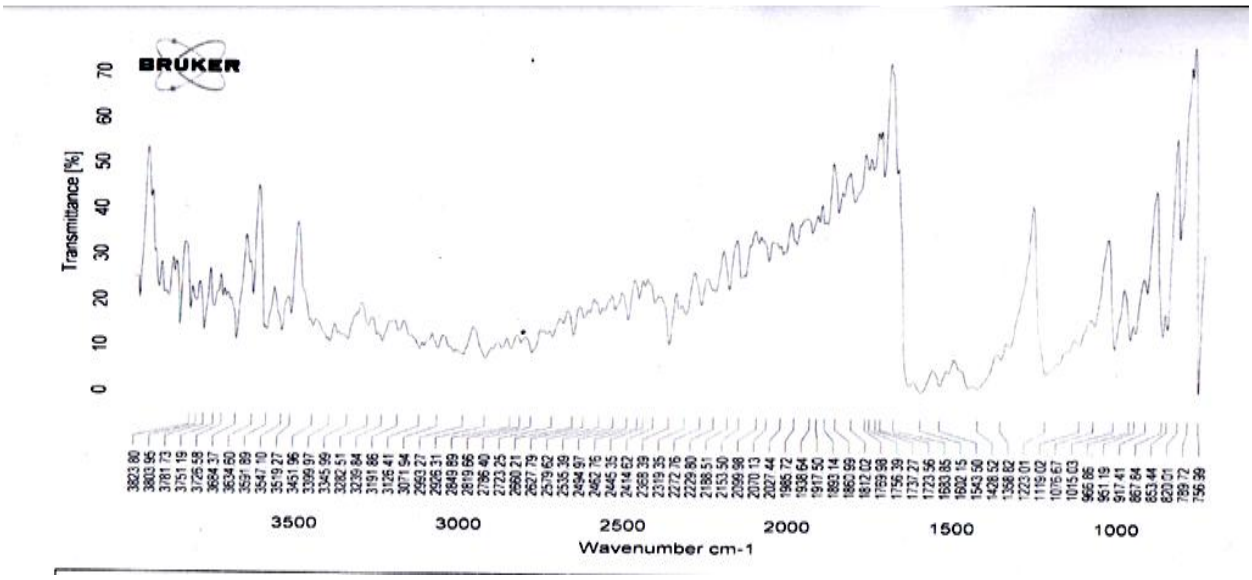


Figure 1: FTIR spectrum of minoxidil

Table: 2 Interpretation of IR spectrum of minoxidil [17]

Name of the compound	N-H	H-bonded, N-H	C-H stretch(aromatic and aliphatic)	C=N (aromatic)	Aromatic C=C stretch, N-H bending	N-O stretch, aromatic C-N stretch
Minoxidil (standard)	3470, 3445,3430, 3385	3280, 3040	2975, 2955, 2880	1650, 1618	1568, 1485, 1475, 1460, 1450	1260, 1248, 1225.
Minoxidil (drug)	3451, 3591, 3345,	3282	2926	1723	1543	1223

4.2 Calibration Curve:

Standard curve of minoxidil in phosphate buffer solution (PH 7.4)

Table 3: Absorbance value of minoxidil in PBS pH 7.4 (λmax 286 nm)

Sr. No.	Concentration(µg/ml)	Absorbance(nm)
1	4	0.149
2	8	0.32
3	12	0.502
4	16	0.624
5	20	0.82
6	24	1.016

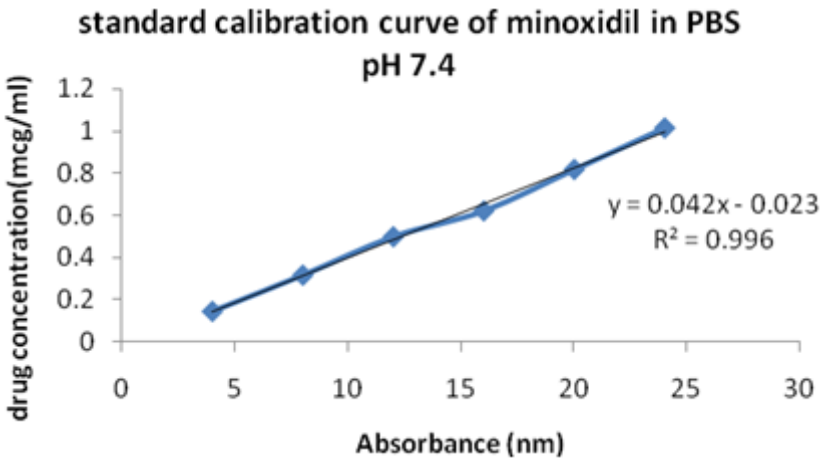


Figure 2: Standard calibration curve of minoxidil

4.3 Melting Point:

Melting Point of Minoxidil was found to be 224^{o}C.

4.4 Solubility properties:

Solubility of Minoxidil in different solvents was recorded.

Table 4: Solubility of Minoxidil in different solvents

Solvent	Solubility
Water	Soluble
Ethanol	Readily soluble
Propylene glycol	Readily soluble
Chloroform	Insoluble

CONCLUSION

Preformulation study of minoxidil was studied using various tests viz. identification of drug by UV- spectrophotometric and FTIR method along with the study of organoleptic properties of drug. This preformulation study was further carried out with the quantitative estimation of drug viz. estimation of lambda max, calibration curve melting point and solubility determination. All the results were found to be optimum and comply with standards.

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