JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and Development of Minoxidil Loaded Microspheres for Topical Drug Delivery System Using DoE Approach

Pandey Vivek J[1]*, Hardeep Banwait[2], Sahjesh Rathi[2], Pragnesh Patni[3]

1. **Student of Master of Pharmacy, Department of Pharmaceutics, A- One Pharmacy College, Enasan, Ahmedabad, Gujarat, India**
2. **Assistant Professor, Department of Pharmaceutics, A- One Pharmacy College, Enasan, Ahmedabad, Gujarat, India**
3. **Professor, Department of Pharmacology, A- One Pharmacy College, Enasan, Ahmedabad, Gujarat, India**

Article history:

Received 07 March 2017
Accepted 14 April 2017
Available online 15 Jun 2017

Citation:
Pandey V., Banwait H., Rathi S. Patni P. Formulation and Development of Minoxidil Loaded Microspheres For Topical Drug Delivery System Using DoE Approach **J Pharm Sci Bioscientific Res**. 2017. 7(3):257-261

For Correspondence:
Pandey Vivek J

Student of Master of Pharmacy, Department of Pharmaceutics, A- One Pharmacy College, Enasan, Ahmedabad, Gujarat, India.

(www.jpsbr.org)

ABSTRACT: Many marketed conventional topical dosage forms may absorb quickly drug and hence increase dosing frequency through skin. Conventional marketed gel proposed to act on outer layers of skin which may release API an application and produce a very much concentrated layer which may be quickly absorbed. Hence the necessity subsists to exploit on quantity of period that drug which can present inside epidermis with lessening transdermal penetration keep on body. Minoxidil is a potent direct-acting peripheral vasodilator that reduce peripheral resistance and produces a fall in blood pressure having adverse effect like cardiovascular effects associated with hypotension such as sudden weight gain, rapid heartbeat, faintness or dizziness. The major remarkable side effect of Minoxidil is unnecessary hair growth in various part of the body known as hirsutism on continue prolong oral use of it. Minoxidil while applying topically promotes the survival of human dermal papillary cells (DPCs) by activating both extracellular signals regulated kinase (ERK) & Akt so use topically in human baldness or alopesia. Minoxidil loaded Microspheres was prepared by using solvent evaporation method and evaluated. Minoxidil loaded Microspheres based topical drug delivery system to capitalize on the measure of time which presents active ingredients at least dose, lessen side effects due to localized drug within epidermis by reducing transdermal penetration that delivering the drug at fungal infection site and give drug release profiles.

KEY WORDS: Minoxidil, Microspheres, DoE, Topical gel

1 INTRODUCTION

1.1 Introduction to DoE Method:

A design of experiment (DoE) is a structured, organized method for determining the relationship between factors affecting a process and the output of that process. A design of experiment is conducted to evaluate whether the variables in a process are feasible or not. The variables ranked as high risk are evaluated by conducting DoE studies to gain process understanding. Design of experiments (DoE) can efficiently screen and optimize formulation variables and identify the desired combination of excipients within the design space. DoE is also used to understand if and how changes in one or more of the process inputs have an effect on the product quality and/or if a process input is independent of changes in other inputs. DoE studies are conducted to optimise the critical process parameters and their ranges in a design space

1.2.1 FACTERS AFFECTING TRANSDERMAL PERMEABILITY:

1.2.1.1 Physicochemical Properties of the Penetrant.

- Partition co-efficient

- PH condition
- Drug concentration

1.2.1.2 Physicochemical Properties of the Drug Delivery System

- The affinity of the vehicle for the drug molecules
- Composition of drug delivery system
- Enhancement of transdermal permeation.

1.2.1.3 Physiological and Pathological Condition of the Skin

- Skin age
- Lipid film
- Skin hydration
- Skin temperature
- Cutaneous drug metabolism
- Species differences
- Pathological injury to the skin

1.3 Topical Gel

Gel defined as semi rigid systems in which movement of the dispersing medium is restricted by an interlacing three dimensional network of particles or solvated macromolecules in the dispersed phase. The rigidity of gel due to presence of the network formed by the interlinking of particles gelling agent. The nature of the particles and type of the force that is responsible for the linkages, which determines the structure of the network and the properties of the gel. Physical and chemical cross linking may be involved. The individual particles particles of hydrophilic colloid may consists of either spherical or single macromolecules. There are two types of force responsible for linkage between gelling agent that is Wander Waals forces and weaker hydrogen bonds. Slightly increase in temperature due to weaker hydrogen bond so liquefaction of gel.

1.4 Introduction to Microspheres Drug Delivery System

A controlled release drug delivery system can overcome some of the problem of the conventional therapy and enhance therapeutic efficacy of a given drug. To achieve maximum therapeutic efficacy that necessary to delivery the agent to target tissue or cell in the optimal amount in the true period of the time there by causing little toxicity and minimal side effects. One most important of microspheres is that act as carrier for drug. Microspheres can be described as a small particles (1-1000 micrometre size) for use as a carriers of the drug and other therapeutic agents distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles. Microspheres are matrix system that contains drug throughout their structure. Thin coatings to small particles of solids or liquids with. It provides the means of converting the liquids to solids of altering the colloidal and surface properties. Very tiny droplets of liquid or solid material are coated with a continuous film of polymeric material for providing environmental protection. The product obtained by this process is called as microparticles or microspheres.

1.5 Alopacia and its treatment:

Hair loss is one of the most common complaints among all patients consulting a dermatologist and is usually associated with severe psychological disturbances, distress and symptoms of depression.

Diagnosis is based on detailed clinical history, physical exam, clinical diagnostic tests, laboratory testing, and scalp biopsy, which may be necessary to confirm some diagnosis.

The pathophysiology of such disorders may include infectious, nutritional, con- genital, autoimmune, or environmental causes. The most common forms of nonscarring alopecia are androgenic alopecia, telogen effluvium, and alopecia areata. Scarring alopecia is caused by trauma, infections, discoid lupus erythematosus, or lichen planus. Other disorders include trichotillomania, traction alopecia, tinea capitis, and hair shaft abnormalities.

Molecular formula of Minoxidil is $C_9H_{15}N_5O$,molecular weight is 209.25 gm/mol, A potent Direc-Acting Peripheral Vasodilator category Mechanism of Action of minoxidil Orally used for the hypertension by vasodilation. Topically promote the survival of human dermal papillary cells or Hair cells by Activating both extracellular signal regulated Kinase(ERK) & Akt, Its Bioavailability of 1.4 of a 2% of a topical solution, Half Life 4.2 Hour, Log P 1.24, pKa value 4.61.

2. MATERIALS

Minoxidil was obtained from GBSL, Kabilpore, Navsari, Ethyl cellulose and PVA from Astron Research Limited, Ahmadabad. Ethanol from Lobachemi Private Limited, Mumbai, Liquid Paraffin and Petroleum Ether from Merck Specialties Private Limited, Mumbai. Carbopol 934 P from Ethicare Pharmaceutical PVT. LTD, Por. Propylene Glycol and Triethanolamine Astron Research Limited, Ahmadabad.

3. Preparation and Characterization of Minoxidil Microspheres loaded Topical gel

3.1 Method of Preparation Minoxidil Microspheres loaded Topical Gel:

Weigh accurately Carbopol 934-P and liquefied in 100 mL of water for 2 hours soaking with 600 RPM agitation then penetration enhancer will be added to the formulated gel which may prevent drying of gel. To this aqueous solution of Triethanolamine was added with slow agitation with continuous stirring. The Minoxidil Loaded Microspheres was be add in the gel.

3.2 Preliminary Trial batches of Topical Gel

Preliminary trials will be undertaken to develop Minoxidil loaded Microspheres gel. The various concentrations of Carbopol 934 was taken.

3.3 Characterization of Topical Gel

3.4 Skin Permeation Study (Ex- vivo Study)

Albino rat skin will be carefully excised. After removing the hypodermal adipose tissue the skin will be used as a barrier membrane for the studies. The best formulation from in vitro studies will be selected for this study, the rat skin was used as membrane between donor and receptor compartment. The receptor compartment will be filled with phosphate buffer pH 7.4 and will be stirred using a magnetic stirrer at 37 ± 1c.the samples were analyzed using UV spectrophotometer at 275 nm against a blank

Figure 1: Solubility Profile of Minoxidil

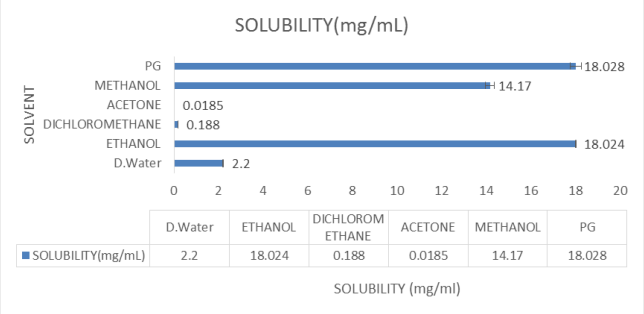


Figure 2.Calibration Curve of Minoxidil

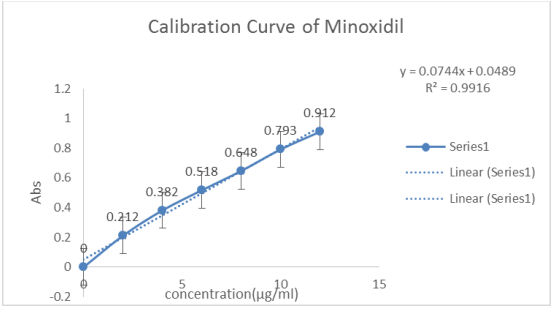
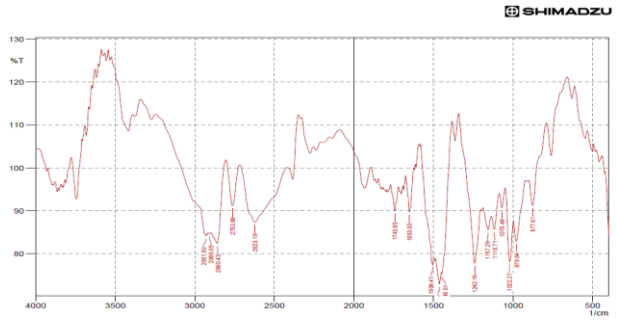


Table1: Summary Report of calibration curve for Minoxidil

Sl. No.	Parameters	Minoxidil
1	Wavelength (λmax)	285
2	Beer's limit (µg/mL)	0-50
3	Corrélation coefficient (R^2)	0.996
4	Slope	0.074

Figure 3: Identification of Minoxidil by FT-IR Spectroscopy



4 .Factorial Design for Minoxidil Microspheres

Various batches of Minoxidil microspheres by DoE Using QbD approach were prepared according to 2^3 factorial designs which are as shown in table.

Table 2: Factorial Design

Independent Variables of Formulations		
Independent Variables	**Low(-)**	**High(+)**
Drug:Polymer ratio (X_1)	1:1	1:2
Internal Phase volume (X_2)	10	15
Speed (RPM) (X_3)	1500	2000
Dependent Variables		
Y1 = Particle size		
Y2 = % Entrapment efficiency		
Y3 = % CDR		

5. Check point analysis of Validation Batches

MNXMS5 & MNXMS7 was designed and evaluated as check point formulation using pooled t-test at 95% confidence interval, degree of freedom 4 and $p < 0.05$. MNXMS5 & MNXMS7 shown no significance difference and hence establish validity of the generated model.

Table 3: Validation Batches: Predicted Response

BATCH NO	POLYMER CON.-MG (X1)	INT. PHASE VOL.-ML (X2)	SPEED-RPM (X3)	P.SIZ-µm(Y1)	E.E.-% (Y2)	CDRT8-% (Y3)
MNXMS5	100.01	13.70	1925	15.42	79.73	81.27
MNXMS7	98.53	13.70	1975	10.42	83.73	89.27

Table 4: Validation Batches: Actual Response

Batch No	Polymer Con.-mg (X1)	Int. Phase Vol.-mL (X2)	Speed-RPM (X3)	P.SIZ-µm (Y1)	E.E.-% (Y2)	CDRT8-% (Y3)
MNXMS5	100.01	13.70	1925	15.48	79.40	81.18
MNXMS7	98.53	13.70	1975	10.46	83.78	89.12

6. % Cumulative Drug Release profile Dissolution:

Table 5: % Cumulative Drug Release profile Dissolution of MNX Microspheres (MNXMS5 and MNXMS7)

Time (hr)	MNXMS5 (Mean ± S.D.) (n = 3)	MNXMS7 (Mean ± S.D.) (n = 3)
0	0.00	0.00
1	13.5±0.87	14.9±1.14
2	21.5±1.08	32.2±1.77
3	31.9±1.73	41.2±0.86
4	39.7±1.24	49.8±1.43
5	52.2±1.52	62.3±1.97
6	61.4±0.96	71.6±1.28
7	71.2±1.35	80.99±1.63
8	84.18±1.67	92.12±1.39

From the above table 5 indicated that faster drug release from batch MNXMS7 Compared to batch MNXMS5. MNXMS7 was selected as validated optimized Batch and further consider for loading into gel.

From the result table 6 data we have found that Minoxidil Microspheres Topical Gel prepared from Ethyl cellulose having greater drug content and spreadability mostly MNXMS7 containing MNX -Ethyl cellulose. Table 6 shows the data for the drug content, spreadability, clarity, pH, Skin Irritation Activity of various Minoxidil Topical Gel.

Figure 4:% Cumulative Drug Release profile of MNX microspheres (MNXMS5 & MNXMS7

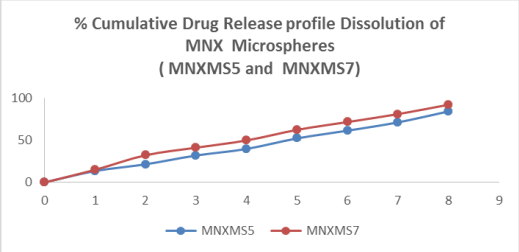


Table 6. Result of MNX Topical Gel

Parameter	Pure Drug Gel	Marketed Minoxidil Gel	Optimized MNX Microspheres (MNXMS7) Gel
Dose	100mg	2%	**100 mg**
Strength	15 gm	15 gm	**15 gm**
Clarity	Transparent	Transparent	**Transparent**
Odour	Odourless	Odourless	**Odourless**
Colour	Red	Colourless	**Red**
pH (Mean ± S.D.) (n = 3)	6.71±0.58	6.21±0.02	**6.79±0.03**
Spreadability (Mean ± S.D.) (n = 3)	11.3±0.79	12.28±1.03	**12.43±0.78**
Viscosity (Mean ± S.D.) (n = 3)	9471±123 cps	9888±43 cps	**9593±23 cps**
% Drug content (Mean ± S.D.) (n = 3)	85.33±0.78	84.77±1.57	**88.88±0.81**
Skin Irritation	Nil	Nil	**Nil**

7. CONCLUSION

Drug delivery via polymer systems has been proposed to be the prevailing type of controlled drug delivery devices both in present and future. For scientific as well as economic reasons, such delivery systems have potential advantage which includes enhanced therapeutic response, predictable rate of release and extent of absorption, topical retention and improved patient acceptance.

In the present work a topical polymeric microspheres formulation of a locally acting antifungal agent, Minoxidil has been developed. The study includes formulation and development of Minoxidil microspheres by DoE method of QbD approach. The idea behind developing a topical

polymeric microspheres delivery system was to deliver Minoxidil in a Control release pattern for an extended period which will lower application frequency and improve patient compliance. To begin with, the variables involved (viz. Selection of internal and external phase, selection of the type and concentration of emulsifier, selection of speed and time of stirring required for preparation) in the preparation of the microspheres were identified CQAs to develop a QbD approach.

A topical polymeric microspheres formulation of Minoxidil was formulated using Ethyl cellulose.

The internal phase suitable for the preparation of microspheres was found to be Ethanol and the external phase was found to be Liquid Paraffin by solubility analysis of drug and poymer.

The concentration of the polymer required to produce microspheres with good physical and morphological characteristics.The volume of internal and external phase required to prepare good microspheres was found to be 10mL of internal and 50mL of the external phase. The minimum concentration of the emulsifier PVA required to produce microspheres was found to be 0.75% w/v.

The minimum speed and time of stirring was found to be 2000rpm for 60 Min. The ratio of drug: polymer required to produce microspheres with good encapsulation efficiency was found to be from 1:1 to 1:2, further increase in the Polymer concentration also increase in particle size. Hence, it was concluded that 1:1 were optimum ratios of drug: polymer to produce good spherical with small in particle size of microspheres. To begin with, the variables involved (viz. Selection of internal and external phase, selection of the type and concentration of emulsifier, selection of speed and time of stirring required for preparation) in the preparation of the microspheres were identified CQAs and their effect on the physical and morphological properties of the microspheres was to develop a QbD approach. In factorial design, the amount of drug (MNX): polymer (EC) ratio (X1), Internal Phase volume (X2) and Speed (X3) were taken as independent variables while % Yi. Particle sizes (Y1), E.E (Y2) and % CDR (Y3) were selected as dependent variables for both factorial designs. The microspheres after check point analysis which gave better physical, morphological and % encapsulation in the polymers were selected for incorporation into the gel formulations.

The release profile of the Minoxidil in the form of microspheres loaded Topical Gel was compared with that of the pure Minoxidil Topical Gel. From the results it can be concluded that the microspheres Topical Gel could control the drug release over a period of 8 hours and with compared the pure Minoxidil . By model fitting of the data obtained from the drug release profile we can conclude that drug release mechanism was Higuchi (Matrix) Model.

The formulations Optimized Minoxidil Microspheres (MNXMS7) loaded Gel were subjected to stability studies for 1 months and significant changes observed.

Finally, we may conclude that Optimized Minoxidil Microspheres (MNXMS7) loaded Gel were best formulated among the class of Ethyl cellulose as a matrix polymer.

8. REFERENCE

1. Sandipan R, “Quality by design: A holistic concept of building quality in pharmaceuticals.” *International Journal Pharm Biomed Research,* **2012,** *3*(2), 100-108.
2. Dr.Reddy’s, “quality by design (qbd) in pharmaceuticals”, *International Journal of Pharmacy and Pharmaceutical Sciences,* **2011**, 4.
3. Lawrence X. *Pharmaceutical Research* **2007,** 25(4), 1-6.
4. Chowdary KP, “Recent research on QbD approach in formulation development-a review”, *International Journal of Chemical Science and Technology,* **2014,** 4(1), 282-92.
5. Ramteke K.H, “Transdermal Drug Delivery System:Review”, *Journal Of Advanced Scientific Research,* **2012,** 3(1), 22-35
6. Katlein F, “Comprehensive Overview and Treatment Update on Hair loss”, “*Journal of Cosmetics*, *Dermatological Sciences and Application”*, **2013**, 3, 1-8.
7. Parhi R, “Formulation and in-vitro evaluation of Minoxidil topical gel”, “*turk J. Pharma Science”,* **2014**, 11(2), 153-162.
8. George E, “Formulation and Evaluation of Topical gel containing Hair Growth Promoters for the Treatment of Alopesia”, “*Bulletin of pharmaceutical research”,* **2014**, 4(1), 1-8.