IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
May 2020 Vol.:18, Issue:2

Development of Generic Miconazole Nitrate Cream 2% Using QbD Technique

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ISSN 2349-7203
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Submission: 21 April 2020
Accepted: 29 April 2020
Published: 30 May 2020

Keywords: Generic, Quality by Design, Topical Product, Orange Book, Miconazole Nitrate

ABSTRACT

Miconazole nitrate is a commonly used antifungal agent primarily in the treatment of Candidiasis. The present study aims to demonstrate the generic development of miconazole nitrate cream 2 % using Quality by Design (QbD) technique and to ensure the generic drug product has similar desired quality attributes to the reference-listed drug (RLD). This includes the concept of reverse-engineering to copy the RLD as a strategy during product development to ensure qualitative (Q1, same components) and quantitative (Q2, same components with same concentration) formulation similarity, as well as similarity in formulation microstructure (Q3). The present study employs in vitro skin permeation studies as a tool to justify similarities in the formulation between the formulated generic product and the RLD to ensure a successful bioequivalence study.

INTRODUCTION

A generic formulation is comparable to an innovator drug product in all aspects like dosage form, strength, route of administration, quality, performance characteristics, and intended use. All drug products that are approved including innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (*Orange Book*) [1]. ANDA applicant must include a patent certification in the application and this certification must make one of the following statements: No patent information on the drug product that is the subject of the ANDA has been submitted to FDA [PARA I], that such patent has expired [PARA II], the date on which such patent expires [PARA III], that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted [PARA IV] [2]. Generic applications are termed as "abbreviated" since they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product performs in the same manner as the innovator drug. To ensure pharmaceutical and therapeutic equivalence, generic drug product has similar desired quality attributes of the RLDs (Reference Listed Drug) [1].

Formulation development of generic topical drug products: The major goal while formulating a generic topical drug product is quantitative sameness (Q1, same components as the RLD) and qualitative sameness (Q2, same components in the same concentration as the RLD) to the RLD and same arrangement of matter (Q3, same microstructure). However, even with Q1/Q2 similarity, special attention needs to be directed towards the excipient grade, because different grades of an excipient can have a significant impact on drug product quality attributes. Apart from excipients used in the generic formulation design, the delivery of drug substances into the skin from a topical drug product can be very sensitive to differences in the manufacturing processes. This is attributable to the fact that the manufacturing process can have a profound impact on the formulation microstructure (Q3). Thus the goal of process development of generic drug products should be to achieve a similar arrangement of matter as the RLD (Q3, same components in same concentration with the same arrangement of matter (microstructure) as the reference-listed drug), which assures similar critical quality attributes to those of the RLD. Q3 microstructure sameness includes identical rheology, type of emulsion (O/W emulsion, W/O emulsion, and globule size), and physical state of the drug in

the semisolid system (Solubilized drug vs. dispersed solid drug, the particle size of drug particles) compared to those of the RLD [3].

Quality by design: Quality by Design (QbD) is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control [4-9]. QbD involves several steps which are depicted in Figure no. 1.

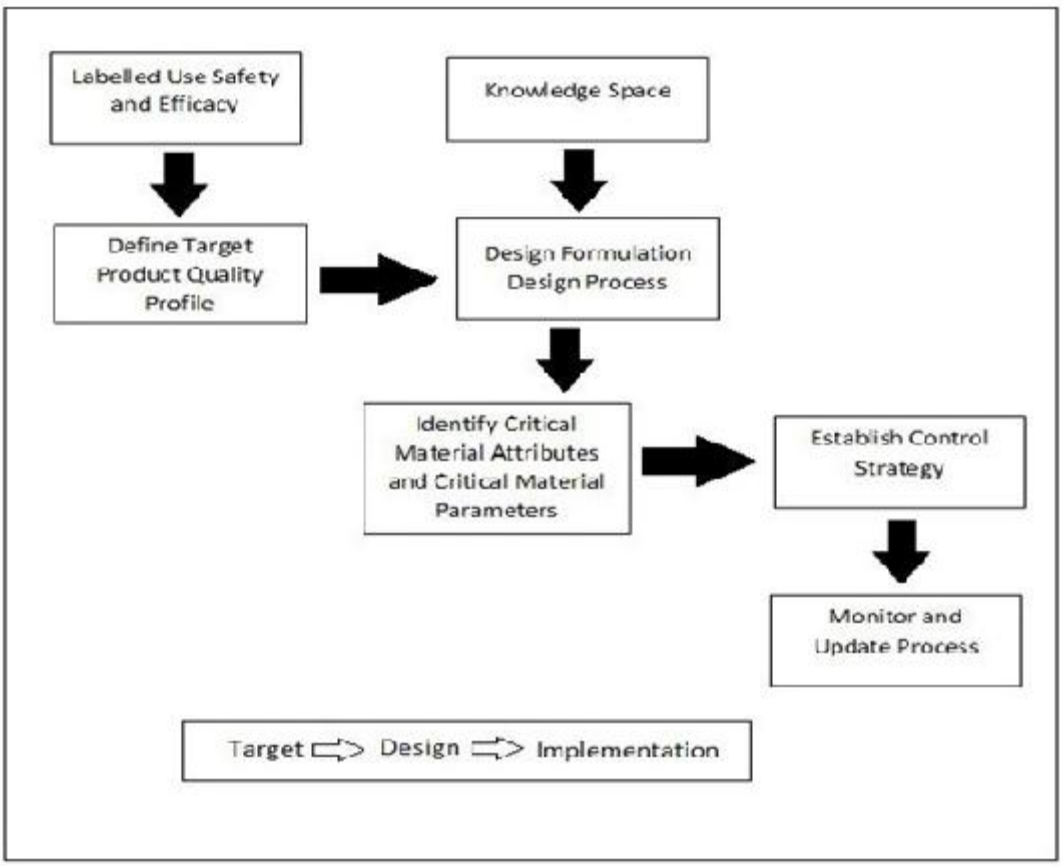

Figure No. 1:- Overview of QbD

The following pharmaceutical development report summarizes the development of Generic Miconazole nitrate cream 2%, a generic version of the reference listed drug (RLD) using principles of QbD. The RLD is an anti-fungal cream used primarily in the treatment of Candidiasis. We used Quality by Design (QbD) to develop generic Miconazole nitrate cream that is therapeutically equivalent to the RLD.

MATERIALS AND METHODS

Miconazole nitrate was obtained as a gift sample from Glenmark Laboratories, Mumbai, India. Marketed Miconazole nitrate cream 2% was purchased from the local wholesale shop, Pune. Solvents used were of analytical grade. All other chemicals were procured from local sources and were of analytical grade.

Analysis of RLD:

The miconazole nitrate cream 2% purchased from the market was treated as and its analysis was carried out for the parameters like viscosity, hardness, oil globule diameter, assay, *in vitro* drug release, *in vitro* permeation and antifungal activity by experimentation.

Quality Target Product Profiling:

Based on the physical characteristics as well as the *in vitro* diffusion studies and physicochemical characteristics of the RLD, a quality target product profile (QTPP) was defined for Generic Miconazole nitrate cream 2%.

Characterization of Drug:

Assay:

Preparation of Calibration curve [10-11]:

Standard stock solution (1000 µg/ml) of Miconazole nitrate was in methanol was suitably diluted to produce concentrations (5, 10, 15, 20, 25, 30 µg/ml). The analysis was done using Agilent HPLC at 232 nm at a 1 ml/min flow rate using a C18 column.

Analysis of RLD cream [11]:

RLD cream (2.2 g) was dissolved in 15 ml of acidic methanol and added to beaker covered by a watch glass and placed in a water bath at 90 º with agitation until the cream components were melted. The contents were stirred for 5 min on a magnetic stirrer and stored at room temperature until the specimen resolidified. The heating shaking cooling procedure was repeated twice to guarantee the complete solubilization and extraction of miconazole nitrate from the matrix components. The obtained suspensions were then transferred to a 25 ml volumetric flask, washing the vessels with acidic methanol aliquots that were collected in the

same flasks. Suspensions were then made up to volume with the same solvent, centrifuged at 2000 rpm kept at −20 º for 20 min, and then centrifuged at 2000 rpm for 15 min. After that, 4 ml of the supernatants (at room temperature) were transferred to a 10 ml flask and made up to volume with acetonitrile The solutions were poured again in new centrifuge tubes and kept at −20 º in the freezer for 20 min. Remaining lipophilic components completely precipitated in this step, were separated by centrifugation at 2000 rpm for 15 min. Suitable aliquots of the solutions were filtered through a 0.45 µ nylon filter and analyzed using HPLC.

Risk Assessment of Drug Substance Attributes:

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQA's.

Excipient Compatibility Studies:

The excipients used in Miconazole nitrate cream were selected based on those used in RLD, excipient compatibility studies, and prior use in approved products. The Miconazole nitrate was mixed with cetostearyl alcohol, polysorbate 60, and isopropyl myristate in ratio likely to be used in formulation stored for 2 weeks at 40ºC. Later the samples were subjected to IR spectrophotometry.

Formulation development Miconazole nitrate cream 2%:

Initial Risk Assessment of the Formulation and Process Variables:

In initial risk assessment, the risks were rated assuming the impact of each formulation attribute and manufacturing process that changed.

DOE (Design of Experiments) Formulation:

Based on initial risk assessment the quantity of the material attributes of cetostearyl alcohol, polysorbate 60, and process attribute shear rate of the stirrer was decided to be critical. DOE methodology was employed to get a formula that will have characteristics of RLD. The Box Behnken design was employed and the levels of factors were chosen based on those reported in the literature [12-14]. The responses were chosen were CQA's which indicated drug quality.

Table No. 1: Design of experiments for formulation development

Variables		Levels		
		+1	**0**	**-1**
A	Cetostearyl alcohol concentration (%)	7	5.5	4
B	Polysorbate 60 concentration (%)	2	1.5	1
C	Shear rate (rpm)	500	300	100
Responses		**Goal**	**Acceptable Ranges as per RLD**	
Y1	Viscosity (cps)	Similar to RLD	8700-8800	
Y2	Hardness (g)	Similar to RLD	50-55	
Y3	Oil globule diameter (nm)	Similar to RLD	450-475	
Y4	*In vitro* release rate (%)	Similar to RLD	11.80	

Formulation of cream:

The oil phase consisting of cetostearyl alcohol, isopropyl myristate, and polysorbate 60 was accurately weighed and heated to 75ºC. Aqueous phase consisting of propylene glycol, benzoic acid, and water was weighed and heated to 75º C. Oil and aqueous phase were mixed under mechanical stirrer and cooled to 40º C followed by the addition of slurry of miconazole, polysorbate 60, and water. Finally, pH was adjusted to 6.5-7 with a 1% NaOH solution [15].

Evaluation of cream [16]:

Viscosity: Brookfield digital viscometer (model LV-DV-II), equipped with S 07 spindle was used to determine viscosity (cps) of the formulations. The viscosity was measured at 60 rpm after 30 seconds. Measurements were performed at ambient temperature and in triplicate.

Hardness: The Spreadability of all the formulations was determined by using Brookfield Texture Analyzer (CT 100). Cream (20 gm) was taken in the cup of the texture analyzer, previously aligned with the probe. The hardness values obtained were recorded.

Oil globule diameter: The globule diameter of 1% dispersion of formulations in water was measured by using Malvern Zetasizer ZS 90 UK.

***In*-vitro drug release rate:** *In vitro* release rate of formulations was measured by using Franz Diffusion cell (Model: FDC03 Make: Orchid Scientifics), across cellulose acetate membrane of 0.45 µ. Cream (300 mg) was applied to the membrane and the release of miconazole nitrate to phosphate buffer pH 6.8 was determined by using HPLC. The study was carried out at 37° for 6 hours and sampling was done every hour. The mobile phase used was acetonitrile: methanol (60:40) at the flow rate of 1ml/min with retention time (RT) of 4.2 min.

Updated Risk Assessment:

Updated risk assessment was carried out based upon the findings of the formulation development.

Control Strategy:

The control strategy for Generic Miconazole nitrate 2%, was built upon the outcome of extensive product and process understanding studies.

Comparison of optimized formulation with RLD:

***In vitro* Permeation Test (IVPT) [17]:**

After Successful application, a comparison of the permeation of the newly formulated generic cream and RLD was carried out. The comparison was done by the determination of the rate of permeation of both RLD and optimized cream formulation. Receptor medium used was phosphate buffer: methanol (7:3) and samples were suitably diluted with the mobile phase (acetonitrile: methanol 60:40) and analyzed using HPLC.

***In vitro* antifungal activity [18]:**

Antimicrobial efficiency studies were determined in the agar diffusion medium employing the Cup plate technique. The RLD and the developed formulation (test) solutions (25 µl) were taken into cups bored into sterile soybean casein digest agar previously seeded with 100 µl broth containing *Candida albicans* MTCC 4748. After allowing diffusion of formulation for 20 min., the plates were incubated for 24 hours at 37 ° C. The zone of inhibition was compared with that of the standard (RLD).

RESULTS AND DISCUSSION

Analysis of RLD:

Mode of Action: Miconazole nitrate interacts with 14-α demethylase, a cytochrome P-450 enzyme necessary to convert lanosterol to ergosterol. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in increased cellular permeability causing leakage of cellular contents.

Physicochemical Characterization

The physicochemical characterization of the RLD cream is summarized in Table 2.

Table No. 2: Physicochemical characteristics of RLD cream (n=3)

Test	Result
Description	White smooth cream
Strength (%)	2
Weight (gm)	15
Texture	Smooth
Viscosity (cps)	8800±0.013
Hardness (g)	51.50±0.1
pH	6.9±0.001
Oil globule diameter (nm)	472.7±0.3
Assay (%)	98.67±0.02
In vitro release rate (/h)	11.80±0.25

In vitro release rate:-

The release profile of miconazole from RLD is shown in fig. 2. The equation of best fit line was $y = 11.80x – 7.586$ ($R^2 = 0.977$), hence the release rate determined over 6 h was found to be at 11.80/h.

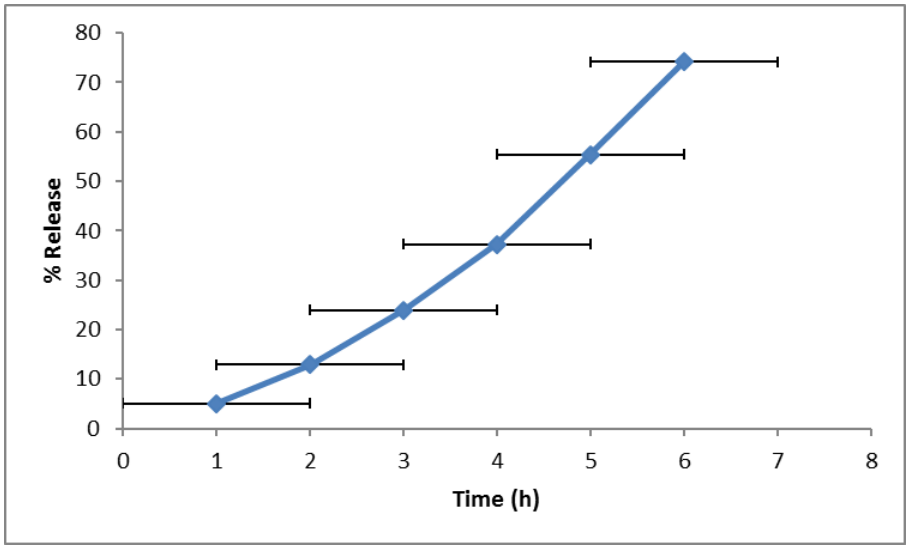

Figure No. 2: *in vitro* drug release of miconazole nitrate cream

Quality Target Product Profile:

Based on the physical characteristics as well as the in vitro release rate studies and physicochemical characteristics of the RLD, a quality target product profile (QTPP) was defined for Generic Miconazole nitrate cream 2% in Table 3.

Table No. 3: Quality target product profile for generic cream

QTPP Elements	Target	Justification
Dosage form	Cream	Pharmaceutical equivalence requirement: same dosage form
Route of administration	Topical	Pharmaceutical equivalence requirement: same route of administration
Dosage strength	2 %	Pharmaceutical equivalence requirement: same strength
Dosage design	O/W emulsion cream with Miconazole nitrate dispersed in the cream base	Equivalent to RLD
Stability	At least 24-month shelf-life at RT	Equivalent to or better than RLD shelf-life
Appearance	White smooth cream with dispersed Miconazole nitrate API	Match RLD and for patient acceptability
Identification	Positive for Miconazole nitrate	Needed for clinical effectiveness
Assay	90–110 %	Needed for clinical effectiveness
Container closure system	Identical to the primary packaging of RLD	Needed to achieve the target shelf-life
Drug product quality attributes	Physical attributes: Rheological behavior, Oil globule size, hardness, pH	Needed for clinical effectiveness and patient acceptability, Required to demonstrate Q3.
	Identification	
	Assay	
	In vitro release rate	
Preservatives content	Methyl Paraben: 80.0–110.0 %, Propyl Paraben: 80.0–110.0 % label claim	Needed to ensure protection from microbial contamination.

The critical quality attributes (CQAs) of the drug product are summarized in Table 4. The attributes of generic Miconazole nitrate cream 2% such as viscosity, hardness, oil globule diameter, *in vitro* drug release which is critical to the quality of drug products were identified. These CQAs have the potential to be impacted by the formulation and/or process variables and, therefore, were investigated in the formulation and process development studies.

On the other hand, CQAs including identity, preservative content, and microbial limits which are unlikely to be impacted by formulation and/or process variables were not discussed in detail. However, these CQAs are still targeting elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy.

Table No. 4: Critical quality attributes for generic cream

Quality Attributes of Drug Product	Target	CQA	Justification
Identification	Positive for Miconazole nitrate	No	Formulation and process variables are unlikely to affect this attribute. Therefore, this CQA will not be discussed during formulation and process development.
Assay	90-110 % w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product.
Viscosity	Match RLD	Yes	Needed for clinical effectiveness and patient acceptability. To demonstrate a similar arrangement of matter to RLD (Q3)
Hardness (Spreadability)	Match RLD	Yes	Ensures the spreading of the formulation to the site of application. Needed for clinical effectiveness and patient acceptability.
Oil globule diameter	Match RLD	Yes	Variability in globule size will affect viscosity and efficacy.
In vitro drug release	Match RLD	Yes	Failure to meet drug release specifications can impact bioavailability. Both formulation and process variables affect the release profile. This CQA will be investigated throughout the formulation and process development.

Assay:

Calibration curve:

The linearity equation was found to be y = 568322x + 196691 and the regression coefficient (R^2) was found to be 0.994 (fig. 3).

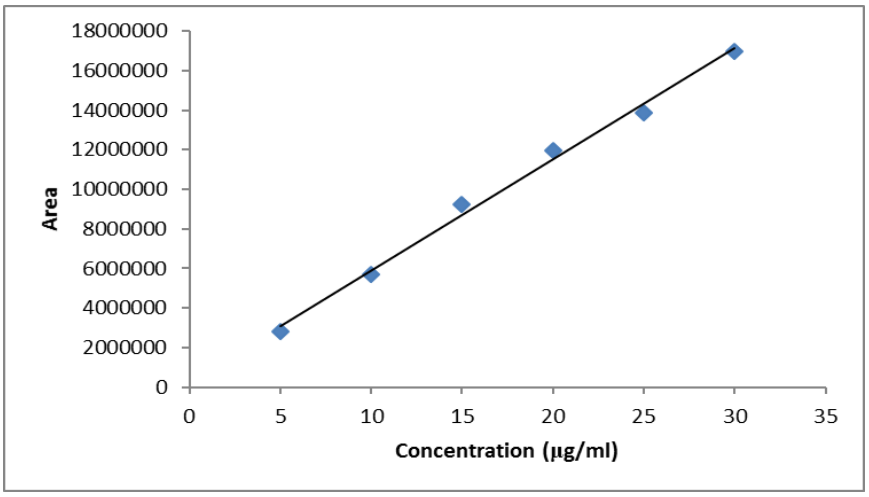

Figure No. 3: Calibration curve of miconazole nitrate in methanol (n=3)

Assay of RLD cream:

The area of filtrate having a concentration of 10.56µg/ml was found to be 6120993 and % assay was found to be 98.67% which is between the limits. Assay value according to USP should be between 95-110%.

Risk Assessment of Drug Substance Attribute:

Drug substance attributes are important as they directly influence the product properties and therefore it was very necessary to assess the risks associated with drug substance properties and is stated in table 5.

Table No. 5: Initial risk assessment for drug substance attributes

Drug Product CQA's	Drug Substance Attributes			
	Solid State Form	Particle size	Assay	Solubility
In vitro release rate	Low	Low	Low	Low
Viscosity	Low	Low	Low	Low
Hardness (Spreadability)	Low	Low	Low	Medium
Oil globule diameter	Low	Low	Low	Low

Excipient Compatibility Studies:

Figure 4 shows the peak observed in both the IR graphs. All the significant peaks shown in the figure are characteristic for Miconazole Nitrate and were also seen in the drug excipient blend stored at 40°C, as well as there was no new peak observed. The characteristic peaks observed for Miconazole Nitrate were for-C-H Stretch at 3072.71 cm^{-1}, Aromatic combination band at 1932.74, aliphatic –C-H Stretch 2891.39 cm^{-1}, -C-H bending 1363.72 cm^{-1}, N-H Stretch 3396.76 cm^{-1}, Ether C-O-C Stretch 1105.25 cm^{-1}, -NO2 bending 1354.07 cm^{-1}, C-Cl stretching 727.19 cm^{1} the peaks were observed in blends along with the characteristic peaks of the excipients. No changes in IR spectra were seen this amounted to the conclusion that the miconazole nitrate was compatible with selected excipients.

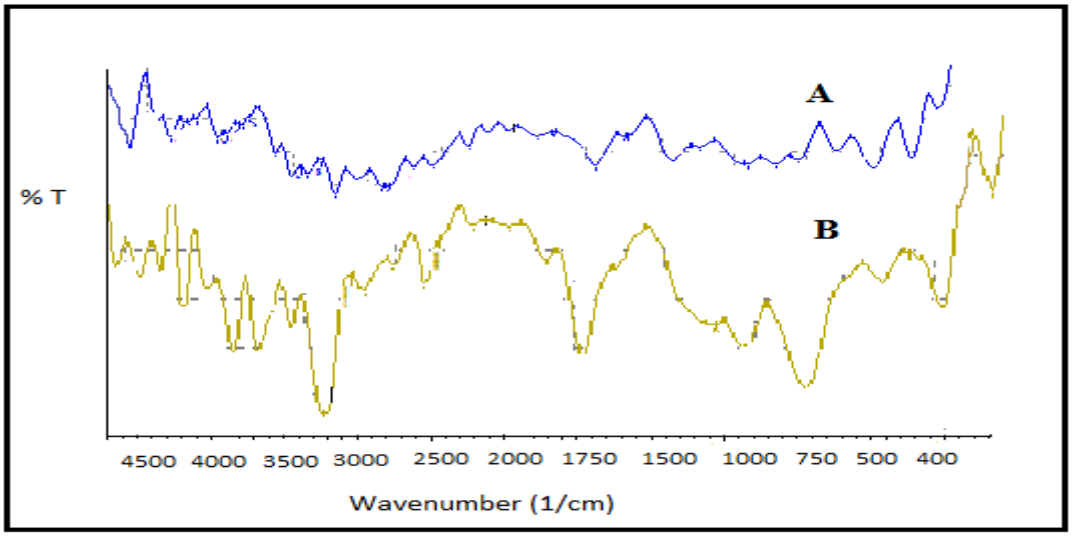

Figure No. 4: IR Spectrum A) Miconazole Nitrate, B) Miconazole Nitrate cream blend

Formulation development of Miconazole nitrate cream 2%

Initial Risk Assessment of the Formulation and Process Variables:

Initial risk assessment for formulation and process variables was done and listed in table 6. The effect of cetostearyl alcohol concentration, polysorbate 60 concentration, the shear rate on viscosity, hardness, oil globule diameter, *in vitro* drug release rate was assessed and the level of risk associated was assigned through color code.

Table No. 6: Initial risk assessment of the formulation and process variables

CQA's	Cetostearyl alcohol concentration	Polysorbate 60 concentration	Shear rate (rpm)
In vitro drug release rate	High	High	Medium
Viscosity	High	High	Medium
Hardness (Spreadability)	Medium	High	Medium
Oil globule diameter	High	High	High

Design of Experiment:

The Box Behnken design was chosen which gave 15 sets of experiments with randomized runs (Table 7). Another advantage is that this design avoids treatment combinations that are extreme in terms of the region in which we are doing our experiment.

Table No. 7: Box Benkhen design and responses of the trial runs for formula optimization

	Factor 1	Factor 2	Factor 3	Response 1	Response 2	Response 3	Response 4
Std	A: Cetostearyl alcohol concentration	B: Polysorbate 60 concentration	C: Shear rate	Viscosity	Hardness	Oil globule diameter	*In vitro* release rate
	%	%	rpm	cps	G	nm	/h
1	8	2	300	3100	45.65	710.8	11.67
2	14	2	300	7800	75.25	700.7	8.653
3	8	4	300	5400	49.66	313.6	8.182
4	14	4	300	9010	79.32	239.2	8.133
5	8	3	100	3250	39.25	586.7	10.68
6	14	3	100	9004	79.1	410.7	9.003
7	8	3	500	3425	49.0	639.5	9.68
8	14	3	500	10010	81.536	356.5	9.02
9	11	2	100	7621	60.38	796.4	10.43
10	11	4	100	8542	65.21	367.7	8.965
11	11	2	500	7562	62.44	763.2	10.15
12	11	4	500	8516	65.73	210.6	8.132
13	11	3	300	7950	65.45	388.2	9.752
14	11	3	300	7948	63.14	343.1	9.254
15	11	3	300	7960	64.75	380.4	8.165

DoE Evaluation:

Response surface Fig. 5 for viscosity which gives the equation.

$$\text{Viscosity} = +7952.67 + 2581.12A + 673.12B + 137.00C - 272.50AB + 207.75AC + 8.25BC\ 1631.58A^2 + 6.42B^2 + 101.17C^2$$

According to the equation, there is a significant increase in viscosity of cream as the concentration of cetostearyl alcohol increases as it acts as a co-surfactant which lowers the oil globule diameter and in turn increases viscosity. The concentration of polysorbate 60 also has a slightly positive impact on the viscosity as polysorbate 60 acts as an emulsifier which lowers oil globule diameter and increases surface area and in turn increases viscosity. Shear

rate directly influences viscosity by decreasing oil globule diameter, so it has a positive effect on viscosity.

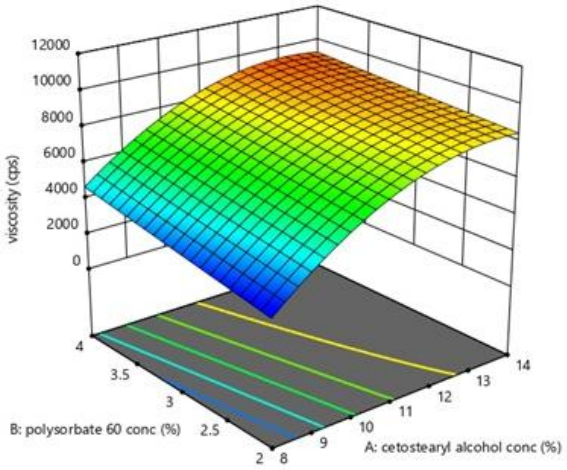

Figure No. 5: Response surface curve for viscosity

Response surface Fig. 6 for hardness which gives the equation.

$$\text{Hardness} = +64.45 + 16.46A + 2.02B + 1.85C + 0.0150AB - 1.83AC - 0.3850BC - 1.60A^2 - 0.3791B^2 - 0.6276C^2$$

According to the equation, there is a significant increase in hardness as the concentration of cetostearyl alcohol and polysorbate 60 increases as they reduce oil globule diameter by acting as co-emulsifier and emulsifier. As the oil globule diameter decreases, the surface area increases, and in turn, there is an increase in hardness. Shear rate shows a slightly positive effect on the hardness by decreasing oil globule diameter.

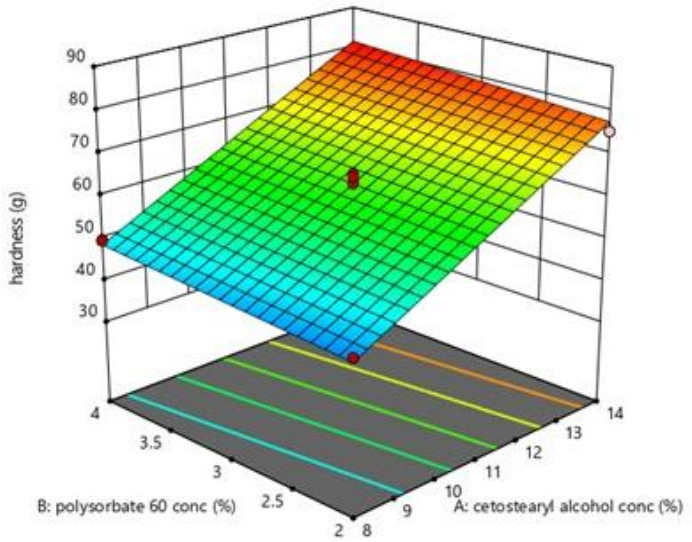

Figure No. 6: Response surface curve for hardness

Response surface Fig. 7 for oil globule diameter which gives the equation.

$$\text{Oil globule diameter} = +370.57 - 67.94A - 230.00B - 23.96C - 16.08AB - 26.75AC - 30.98BC + 42.19A^2 + 78.32B^2 + 85.59C^2$$

According to the equation, there is a significant increase in oil globule diameter as the concentration of polysorbate 60 decreases as it acts as an emulsifier, while the other two variables i.e. concentration of cetostearyl alcohol and shear rate have slightly negative impact on the oil globule diameter.

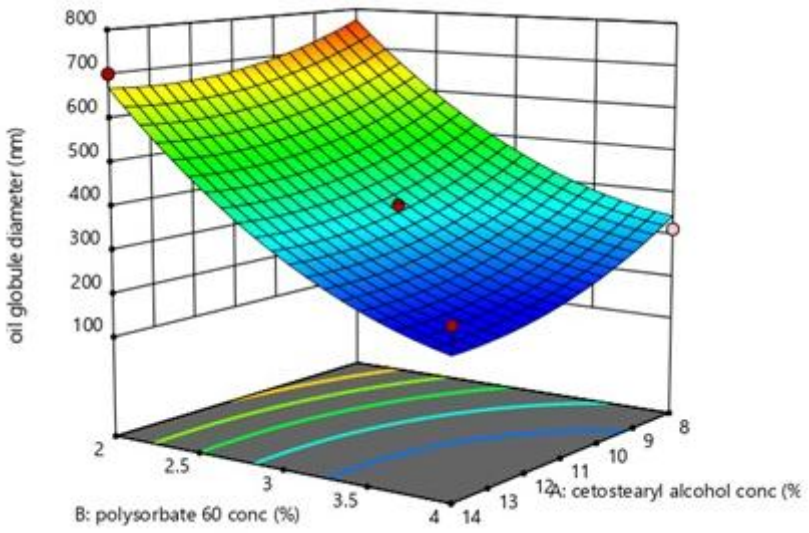

Figure No. 7: Response surface curve for oil globule diameter

Response surface Fig. 8 for *in vitro* release rate which gives the equation.

$$\textit{In vitro}\ \text{release rate} = +9.06 - 0.6754A - 0.9364B - 0.2620C + 0.7420AB + 0.2543AC - 0.1383BC + 0.1395A^2 - 0.0370B^2 + 0.3993C^2$$

According to the equation, there is a significant increase in *the vitro* release rate of cream as the concentration of polysorbate 60 and cetostearyl alcohol decreases. A higher concentration of polysorbate 60 and cetostearyl alcohol, decreases globule diameter, and increases viscosity and in turn decreases the release of miconazole nitrate from the cream matrix. The shear rate has a slightly negative impact on the *in vitro* release rate.

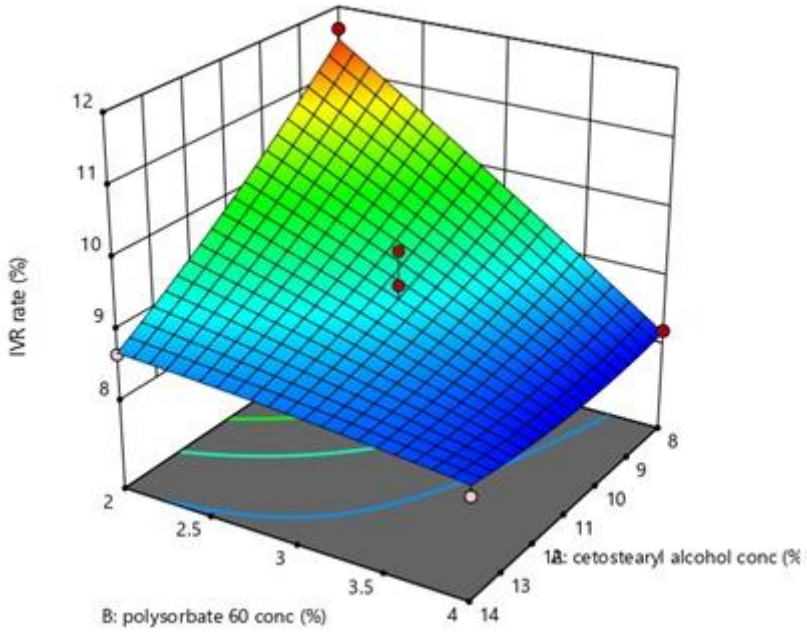

Figure No. 8: Response surface curve for *in vitro* release rate

Updated Risk Assessment of the Formulation Variables:

After optimizing the formulation variables an updated risk assessment is done to check whether all the risks are reduced and being taken care of from the initial risk assessment (Table 8).

Table No. 8: Updated risk assessment for formulation and process variables

CQA's	Cetostearyl alcohol concentration	Polysorbate 60 concentration	Shear rate (rpm)
Viscosity	Low	Low	Low
Hardness (Spreadability)	Low	Low	Low
Oil globule diameter	Low	Low	Low
In vitro release rate	Low	Low	Low

Control Strategy:

The control strategy for the commercial manufacture of Generic Miconazole nitrate cream 2%, is proposed and presented in Table 9. The control strategy includes Miconazole nitrate and excipient material attributes to be controlled, in-process controls, high-risk process

parameter ranges studied during development, and the proposed operating ranges for commercial manufacture.

Table No. 9: Control strategy for the formulation of miconazole nitrate cream

Factor	Attributes or Parameters	Range studied (lab scale)	Purpose of control
Cetostearyl alcohol concentration	Range	9.7-9.8%	To ensure proper viscosity and spreadability of cream
Polysorbate 60 concentration	Range	2.9-3.1%	To ensure the formation of proper emulsion and viscosity.
Shear rate	Range	100-140 rpm	To ensure proper mixing and emulsification

Comparison of optimized cream with RLD:

***In vitro* Permeation Test (IVPT)**

The results of the comparison between RLD and generic cream (fig. 9) showed that the flux of generic cream is similar to that of RLD. Table 10 shows the values of flux for RLD and generic cream.

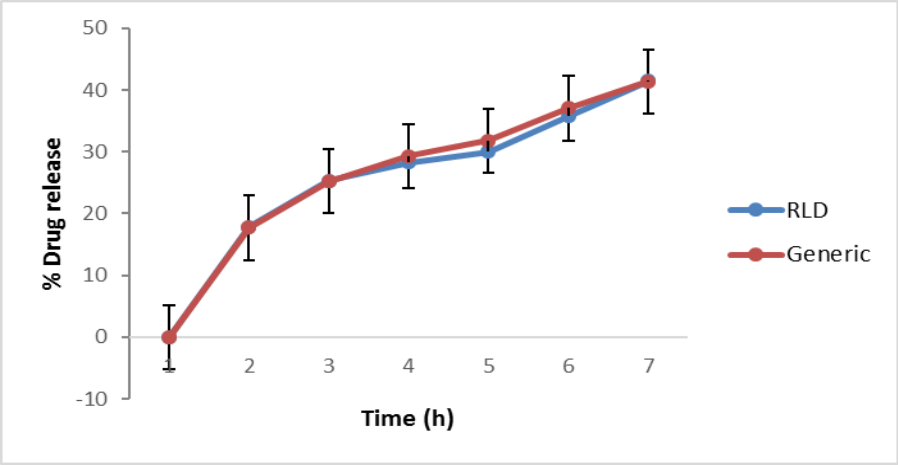

Figure No. 9: Comparative drug permeation profile of RLD and generic cream

Table No. 10:- *In Vitro* permeation test for comparison (n=3)

Sr. No.	Formulation	Flux (mg/h/cm^2)
1	RLD	43.49±0.32
2	Generic Miconazole nitrate cream	43.55±0.27

***In-vitro* antifungal activity:**

The results of the study showed that the cream indicates the presence of antifungal activity (Fig. 10); antimicrobial activity was based on the measurement of inhibition zones formed around the disc. From the observation of the agar plate containing generic Miconazole nitrate cream against Candida albicans gave a similar zone of inhibition similar to that of the marketed RLD cream (Table 11).

Table No. 11:- Comparison of antifungal activity (n=3)

Formulation	Concentration (µg/µl)	Zone of inhibition (mm)
Test (Generic)	30	14±0.33
	50	12±0.41
Marketed (RLD)	30	13±0.36
	50	12±0.46
Solvent (methanol)	-	0

The anti-fungal activity of generic cream and RLD was compared and found to be significant using a one-sample t-test. There is no significant difference in the antifungal activity of generic cream and RLD with a p-value of less than 0.0003.

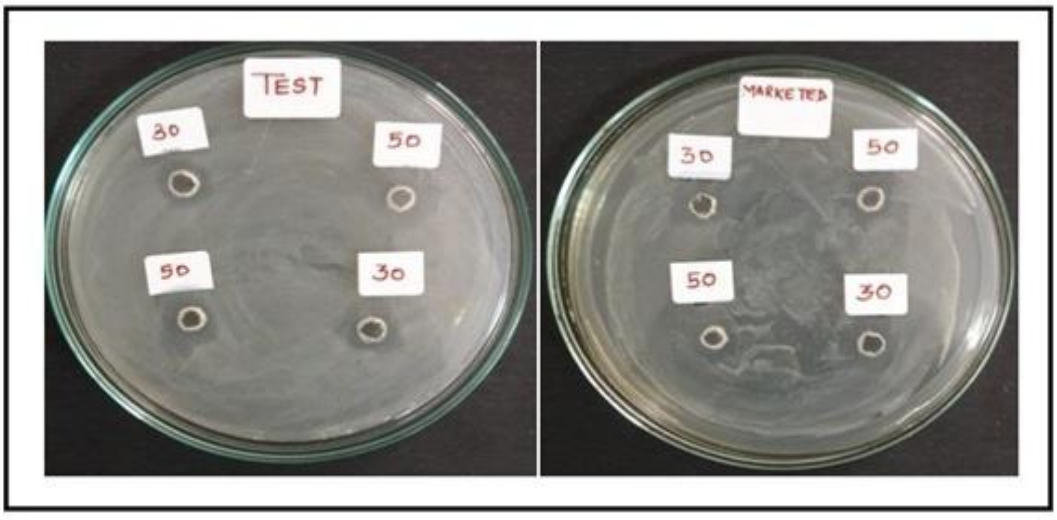

Figure No. 10: MIC of test and marketed cream

A comparison of RLD with an optimized batch is shown in table 12.

Table No. 12: Comparison of the optimized batch with RLD (n=3)

Formulation	Viscosity (cps)	Hardness (g)	Oil globule diameter (nm)	*In vitro* drug release rate (/h)	Assay (%)	*In vitro* permeation test (mg/h/cm^2)	*In vitro* antifungal activity (mm)
RLD	8800±0.013	51.50±0.19	472.7±0.39	11.80±0.25	98.67±0.02	43.49±0.32	12±0.41
Optimized batch	8805±0.019	51.45±0.13	473.1±0.32	11.77±0.31	98.78±0.04	43.55±0.27	12±0.46

The QbD approach taken during the pharmaceutical development of Generic Miconazole nitrate cream 2% facilitated product and process understanding. During the formulation development, the optimized formula which performs similar to RLD was developed using Design of Experiments. Proper risk management was done before any development which gave an idea about where the product could fail and these risks were addressed in the later development stages. During the formulation and manufacturing process development, the manufacturing process was defined based on knowledge gained through development and optimization, and a strategy for process control was developed.

ACKNOWLEDGMENTS

The authors are thankful to Glenmark Laboratories, Mumbai for providing Miconazole nitrate drug as a gift sample for this work. They also thank Principal Dr. Ashwini Madgulakar of AISSMS College of Pharmacy, Pune for providing the required facilities to carry out this research work. They also thank Mrs. Shivani Rao of AISSMS College of Pharmacy, Pune for providing guidance to conduct microbial studies.

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