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TOPICAL GEL FORMULATION OF DIAMINODIPHENYL SULFONE FOR ACNE VULGARIS

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ABSTRACT

Diaminodiphenyl Sulfone is chemical name of Dapsone and is a BCS Class II drug. Recently USFDA has approved Dapsone Topical Gel (ACZONE®) manufactured by Allergan for the treatment of both inflammatory and non-inflammatory acne vulgaris for the age group of 12 to 65 years. Acne vulgaris is a nearly universal skin disease afflicting 79–95% of the adolescent population. Allergan designed ACZONE® in an airless pump containing a polypropylene bottle with a high density polyethylene piston containing a consortium of solvent like Isohexane; solubilizers / surfactants like Diethylene Glycol Monoethyl Ether and Polysorbate 80; Acrylamide/Sodium Acryloyldimethyl Taurate copolymer as a polymer; Methyl Paraben as preservative and Purified Water as solvent. The aim of the present research is in cost effective manufacturing of once daily Dapsone Gel 7.5% with minimum excipients viz., Diethylene Glycol Monoethyl Ether as solubilizer, Carbomer Homopolymer type C as polymer, Methyl Paraben as preservative, Purified Water as solvent / vehicle and Sodium Hydroxide / Hydrochloric Acid as pH adjusters and packing the final product in conventional laminated tubes. The Physico-chemical properties and stability of the formulated product was found comparable to ACZONE® 7.5%. It is reported that globally about 700 million people across ages get affected by Acne Vulgaris and this research will be a boon combining the once a day dosing of 7.5% strength stabilized in a simple laminated tube packing at a reduced cost.

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INTRODUCTION

Dapsone is a BCS Class II drug[1,2]. Dapsone, a synthetic sulfone with an amino moiety linking two sulfone rings (4,4'-diaminodiphenyl sulfone; molecular weight 248.30), has had medical applications for more than 7 decades for treating various medical conditions including dermatitis herpetiformis, leprosy, and malaria. It has been used in the past for severe recalcitrant acne in doses ranging from 25–50 mg/day. The primary metabolites of Dapsone are N-acetyl Dapsone and Dapsone hydroxylamine. The most important adverse events of Dapsone result from the hydroxylamine metabolite. This compound increases oxidative stress on erythrocytes with resultant potential for dose-dependent haemolysis and methemoglobinemia. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more susceptible, as the absence of functional G6PD increases the risk of haemolysis and denaturation of haemoglobin. It was hypothesized that a topical formulation of Dapsone may be appropriate for treating acne vulgaris while minimizing systemic exposure and hematologic risk. Accordingly, a topical gel formulation of Dapsone 5% was developed by Atrix Laboratories almost a decade ago for the treatment of acne vulgaris[3]. Recently Allergan, Inc came up with a 7.5% once daily Dapsone Gel (ACZONE®) in an airless pump containing a polypropylene bottle with a high density polyethylene piston. In fact the end product is made up with consortium of solvent like Isohexane; solubilizers / surfactants like Diethylene Glycol Monoethyl Ether and Polysorbate 80; Acrylamide/Sodium Acryloyldimethyl Taurate copolymer as a polymer; methyl paraben as preservative and Purified Water as solvent[4]. Thus the rationale is in designing the once daily Dapsone Gel 7.5% with minimum excipients and packing the final product in conventional laminated tubes thereby the end product is cost-effective and also achieving the comparable transdermal delivery to that of marketed product for the treatment of Acne vulgaris.

JUSTIFICATION OF RESEARCH

For the treatment of Acne vulgaris, the marketed product with once daily application, ACZONE® 7.5% utilizes costly packaging system and also comprises a consortium of solvent like Isohexane; solubilizers / surfactants like Diethylene Glycol Monoethyl Ether and Polysorbate 80; Acrylamide/Sodium Acryloyldimethyl Taurate copolymer as a polymer; methyl paraben as preservative and Purified Water as solvent. In this research, a simple laminated tube was chosen as a packing configuration in which the end product was formulated with minimal excipients. Hence the product of research interest will be cost effective as compared to the marketed product. Moreover, the research will be designed to achieve comparable physico-chemical, drug release and stability characteristics of the designed drug product with that of the marketed product, ACZONE® 7.5%.

LITERATURE

Based on the approval history documents[4], Dapsone Gel for topical application indicated for acne vulgaris in patients 12 years of age and older is available in 5% and 7.5% strengths. 5% strength is indicated for twice daily application where as 7.5% strength is a once daily application. The marketed / reference / brand product is ACZONE®. The composition and packing details of ACZONE® 5% is 50 mg of Dapsone in a gel of Carbomer Homopolymer type C, Diethylene Glycol Monoethyl Ether, Methyl Paraben, Sodium Hydroxide and Purified Water. The gel is supplied in 30 g, 60 g and 90 g laminate tube. The composition and packing details of ACZONE® 7.5% is 75 mg of Dapsone in a gel of Diethylene Glycol Monoethyl Ether, Methyl Paraben, Acrylamide / Sodium Acryloyldimethyl Taurate copolymer, Isohexadecane, Polysorbate 80 and Purified Water. The gel is supplied in 30 g, 60 g & 90 g airless pump containing a polypropylene bottle with a high density polyethylene piston. Patents relevant to synthesis, method of uses of the drug product and composition of the drug product includes US 5863560, US 6060085, US 6620435B1 and US 9161926.

PURPOSE /OBJECTIVE

The objective is to develop a topical gel formulation of Dapsone, 7.5% w/v which would be comparable to the marketed product, ACZONE® with respect to physico-chemical properties and stability characteristics.

MATERIALS AND METHODS

MATERIALS:

Dapsone from Atul; Carbopol 980P from Lubrizol; Methyl Paraben from Spectrum; Transcutol P from Gattefosse; Hydrogen peroxide, Potassium Dihydrogen Phosphate, Sodium Hydroxide and Hydrochloric Acid from Avantor Performance Materials; Methanol, Ethanol, Acetonitrile, Anhydrous Dibasic Ammonium Phosphate and Hydrogen Peroxide from Merck Specialities; Empty laminated tubes with cap from Sorbead.

EQUIPMENTS/ INSTRUMENTS

Homogenizer of Remi motors; Colloid Mill of Cadmach; Vibrosifter of Gansons; #10 ASTM mesh & #20 ASTM mesh of Cadmach; Planetary mixer of Sams Technomech; Stirrer of Remi motors; Semi-automatic tube filling machine of Parle; Stopwatch of Casio; Micro & Ultramicro balance of Mettler Toledo; Viscometer of Brookfield; Particulate Counter of Particulate Measuring Systems; Malvern Zetasizer of Malvern Instruments; Sonicator of Fisher Scientific; Photostability chamber, 40°C / 75% RH stability chamber, 55°C Stability chamber, 30°C / 65% RH Stability Chamber, 2-8°C Stability chamber, 40°C / 75% RH stability chamber, Hot Air Oven of Thermolab Scientific Equipments; Microscopic Particle Count using SMZ-168-TP Motic Trinocular Stereomicroscope equipped with MT3i camera, PM-LED illuminator and IMT i-solution software; HPLC of Waters; UV Spectrophotometer of Shimadzu; FTIR of Thermofisher and pH Meter of Hanna Instruments.

METHODS

Topical drug products quality tests, Minimum Fill, Test For Specified Microorganisms, Microbial Enumeration Tests, Water Determination, Uniformity Of Dosage Units, Drug Release, pH, Viscosity, Particle Size Distribution – API Analysis, Preservative Effectiveness Testing, Minimum Fill, Specific Gravity, Light Diffraction Measurement of Particle Size, Anti-microbial agents content, Antimicrobial effectiveness testing, Method of Analysis of Carbopol 980P, Methyl Paraben and Transcutol P were done as per USP.

EXPERIMENTATION

API Characterization:

Dapsone API was characterized with respect to Appearance, Particle Size Distribution and Density.

Marketed Product Characterization:

The marketed product, ACZONE® (Dapsone) Gel, 5% w/w & 7.5% w/w was characterized for quantitative amounts of in-actives viz Carbomer Homopolymer Type C, Methyl Paraben and Diethylene Glycol Monoethyl Ether by HPLC and the drug product was also characterized with respect to Appearance, Fill Volume, pH, Specific gravity, Viscosity, Preservative Content, SEM, Zeta Potential, Conductivity, Particle Size, Assay and Related Substances. Apart from Physico-chemical characterization, packaging configuration was also characterized.

Prototype Formulation:

Based on physico-chemical characterization, qualitative and quantitative evaluation, pharmacokinetic details, empirical simulation and packaging characterization of the marketed product ACZONE® it was decided to develop Dapsone Gel 7.5% w/w with the composition and packaging configuration similar to ACZONE® (Dapsone) Gel 5% w/w. By this approach, the developed product combines the benefit of once daily dosing of ACZONE® Gel 7.5% and cost effectiveness of ACZONE® Gel 5% since involves the usage of essentially limited excipients to formulate as well as simple, cost-effective and comparatively environment friendly laminated tubes for packaging. Since the formulated gel is water based and drug being insoluble in water, order of addition of excipients during formulation / manufacturing process is very crucial to achieve the stable and effective dosage form. Hence in the prototype formulation much focus was emphasized on order of addition of ingredients, mixing time and characterization of the finished product under real time were evaluated and compared against the marketed product.

Manufacturing Process of Finalized Prototype:

Charge the Purified Water in the Planetary Mixer equipped with Homogenizer. Add the Carbopol 980 P slowly into the Purified Water and homogenize to disperse. In clean stainless steel vessel, charge the Transcutol P and keep under stirring. Add Methyl Paraben slowly to the stirring Transcutol P solution and dissolve. After ensuring clear solution (without any crystals of Methyl Paraben), add Dapsone slowly to the stirring solution of Methyl Paraben – Transcutol P and dissolve. After ensuring clear solution (without any crystals of Dapsone), empty the contents of Planetary mixer (Carbopol 980P dispersion) into a clean stainless steel vessel. Clean the Planetary mixer without any traces of Carbopol 980P dispersion. Charge the clear solution of Dapsone – Methyl Paraben – Transcutol P into the Planetary Mixer. Mill the aqueous dispersion of Carbopol 980 P through Colloid Mill. Charge the milled aqueous dispersion of Carbopol 980P slowly to the contents of Planetary Mixer under homogenization. Dissolve Sodium Hydroxide in Purified Water. Add the Sodium Hydroxide solution to the homogenized contents of Planetary Mixer. The final gel product is transferred to the Semiautomatic tube filling machine to fill the final product into laminated tubes and sealed.

Manufacturing Process Optimization: The following were the optimization studies taken up,

Mixing time optimization of Carbopol 980P dispersion in Purified Water.

Three (3) separate experiments were conducted to optimize the mixing time of Carbopol 980P dispersion in Purified Water. Stated quantity of Carbopol 980P was sifted through Vibrosifter (Properly earthed) equipped with #10 ASTM stainless steel mesh. The sifted material was dispersed in Purified Water in Planetary Mixer equipped with Homogenizer. The homogenizer speed was set at 1300 ± 100 RPM and the main motor speed was set at 65 ± 20 RPM. In the first experiment, mixing was done for 45 minutes and in the second and third experiment the mixing was done for 1 hour 30 min and 2 hour 15 min respectively. At the end of mixing, the dispersion was screened through #10 ASTM mesh and checked for un-dissolved polymer particles. The Mixing time where no un-dissolved polymer particles retained on #10 ASTM mesh was finalized.

Mixing time optimization of Methyl Paraben in Transcutol P.

Three (3) separate experiments were conducted to optimize the mixing time of Methyl Paraben in Transcutol P. Stated quantity of Methyl Paraben was added to Transcutol P under stirring in Lab model Remi stirrer. The stirrer speed was set at 750 ± 250 RPM. In the first experiment, mixing was done for 30 minutes and in the second and third experiment the mixing was done for 1 hour and 1 hour 30 min respectively. At the end of mixing, the solution was checked visually for crystals of Methyl Paraben. The Mixing time where no crystals of Methyl Paraben observed was finalized.

Mixing time optimization of Dapsone in Methyl Paraben – Transcutol solution.

Three (3) separate experiments were conducted to optimize the mixing time of Dapsone in Methyl Paraben-Transcutol P solution. Stated quantity of Dapsone was added to Methyl Paraben-Transcutol P solution under stirring in Lab model Remi stirrer. The stirrer speed was set at 750 ± 250 RPM. In the first experiment, mixing was done for 30 minutes and in the second and third experiment the mixing was done for 1 hour and 1 hour 30 min respectively. At the end of mixing, the solution was checked visually for undissolved Dapsone particles. The Mixing time where no undissolved particles of Dapsone observed was finalized.

Milling cycle optimization of aqueous dispersion of Carbopol 980P.

Before adding the aqueous dispersion of Carbopol 980P to the drug solution in the planetary mixer, the aqueous polymeric dispersion must be smooth without any sludge / jelly consistency. Hence to achieve uniform smooth consistency the aqueous polymeric dispersion was milled through Colloid mill. Three (3) separate experiments were conducted to optimize the milling cycle. In the first experiment, milling cycle was done for 5 minutes and in the second and third experiment the milling cycle was done for 10 minutes and 15 minutes respectively. At the end of mixing, the dispersion was passed through #5 ASTM mesh. The milling cycle time where no retention in the form of jell / sludge on #10 ASTM mesh was finalized.

Mixing time optimization of aqueous dispersion of Carbopol 980P with Dapsone – Methyl Paraben – Transcutol P solution (Pre-Gelling Stage).

The drug solution containing Dapsone – Methyl Paraben – Transcutol P was charged into the planetary mixer equipped with homogenizer and stirred. The homogenizer speed was set at 1300 ± 100 RPM and the main motor speed was set at 65 ± 20 RPM. The milled aqueous dispersion of Carbopol 980P was slowly added to the drug solution. The mixing was done up to 3 hours. Every 1 hour blend uniformity samples of 1 g to 3 g were collected in triplicate at 10 different locations in the planetary mixer. Based on the blend uniformity results the mixing time for the pre-gelling stage was finalized.

Mixing time optimization of Sodium Hydroxide in Purified Water.

Three (3) separate experiments were conducted to optimize the mixing time of Sodium Hydroxide in Purified Water. Stated quantity of Sodium Hydroxide was added to Purified Water under stirring in Lab model Remi stirrer. The stirrer speed was set at 750 ± 250 RPM. In the first experiment, mixing was done for 20 minutes and in the second and third experiment the mixing was done for 40 minutes and 60 minutes respectively. At the end of mixing, the solution was checked visually for undissolved pellets of Sodium Hydroxide. The Mixing time where no undissolved pellets of Sodium Hydroxide observed was finalized.

Mixing time optimization of neutralization (Gelling) of aqueous dispersion of Dapsone – Carbopol 980P – Transcutol P & Methyl Paraben with Sodium Hydroxide solution (Gelling Stage).

The Sodium Hydroxide solution was added slowly to the dispersion (Dapsone – Carbopol 980P – Methyl Paraben in Transcutol P – Purified Water solvent system) in planetary mixer equipped with homogenizer and stirred. The homogenizer speed was set at 1300 ± 100 RPM and the main motor speed was set at 65 ± 20 RPM. The mixing was done up to 3 hours. Every 1 hour blend uniformity samples of 1 g to 3 g were collected in triplicate at 10 different locations in the planetary mixer. Based on the blend uniformity results the mixing time for the Gelling stage was finalized.

Effect of Semiautomatic tube filling machine speed on Weight variation, Minimum fill & Content Uniformity.

The prepared Dapsone Gel, 7.5% was filled in laminated tubes and sealed using Semiautomatic tube filling machine. During filling and sealing process, samples were collected during begin, middle and end stages of process to evaluate for Weight variation and Minimum fill evaluation. Also, the complete filling operation time was divided into 30 intervals equally and at each time interval content uniformity sampling was done and evaluated.

Stability Evaluation:

The laminated tube packed drug product was stability evaluated at 40°C / 75%RH for 3 months in horizontal and vertical orientation and were characterized for Description, pH, Specific Gravity, Dissolution, Assay, Methyl Paraben Content, Related Substances, Microbial Limit Test and Antimicrobial Preservative Efficacy Test.

RESULTS AND DISCUSSION

API CHARACTERIZATION:

From the API characterization, Table.1 it is evident that the API is a coarser and free flowing powder. Since the API is going to be dissolved in solubilizer, the tabulated information is for characterization and reference purpose only.

MARKETED PRODUCT CHARACTERIZATION:

Based on the marketed product characterization tabulated in Table 2 & 3 it was decided to use the excipients viz Diethylene Glycol Monoethyl Ether (Transcutol P) as solubilizer at 37.5% w/w; Methyl Paraben as preservative at 0.20% w/w; Sodium Hydroxide as alkalizer to adjust pH; Carbomer 980 (Carbopol 980P) as gel former at 1.275% w/w; Purified Water as vehicle, quantity sufficient to 100% w/w in the formulation of Dapsone Gel, 7.5% w/w and packing of the final product will be in HDPE based laminated tubes with PP based flip closure.

PROTOTYPE FORMULATION:

In the 1st trial, the procedure followed was Carbopol 980P was dispersed in Purified Water and gel was made by adjusting the pH of the dispersion to 7.0 using sodium hydroxide solution. To the gel, Transcutol P solution containing Dapsone and Methyl Paraben was added and mixed well. The final product was not uniform with breaking gel consistency. In the 2nd trial, the procedure followed was Carbopol 980P was dispersed in Purified Water. To the polymer dispersion, Transcutol P solution containing Dapsone and Methyl Paraben was added and mixed well. Finally the gel was made by adjusting the pH of the dispersion to 7.0 using sodium hydroxide solution. The final product was not uniform, fish eye structured gel appearance observed. Drug crystallized out within 7 days of preparation. In the 3rd trial, the procedure followed was Carbopol 980P was dispersed in Purified Water. The polymer dispersion was added to the Transcutol P solution containing Dapsone and Methyl Paraben and mixed well. Finally the gel was made by adjusting the pH of the mixture to 7.0 using sodium hydroxide solution and resulted in desired gel consistency. Characterization results of the 3rd trial were tabulated in Table.4.

MANUFACTURING PROCESS OF FINALIZED PROTOTYPE:

The composition of the finalized batch made with a batch size of 10 Kg along with characterization details is tabulated in Table. 5. From the tabulated information it is evident that the Physico-chemical characteristics of the formulated product are comparable to the marketed product ACZONE® Gel, 5% & 7.5% w/w.

Manufacturing Process Optimization:

The following were the optimization studies taken up,

Mixing time optimization of Carbopol 980P dispersion in Purified Water:

Mixing time of 1 hour 30 minutes was finalized for complete dispersion (without unwetted particles) of Carbopol 980P dispersion in Purified Water in Planetary mixer with a main motor speed of 65 ± 20 RPM and homogenizer speed of 1300 ± 100 RPM. Results are tabulated in Table.6.

Mixing time optimization of Methyl Paraben in Transcutol P:

Mixing time of 1 hour was finalized for dissolving Methyl Paraben in Transcutol P using stirrer operated at 750 ± 250 RPM. Results are tabulated in Table.7.

Mixing time optimization of Dapsone in Methyl Paraben – Transcutol solution:

Mixing time of 1 hour was finalized for dissolving Dapsone in Methyl Paraben - Transcutol P solution using stirrer operated at 750 ± 250 RPM. Results are tabulated in Table.8.

Milling cycle optimization of aqueous dispersion of Carbopol 980P:

Based on the study results, aqueous dispersion of Carbopol 980P shall be subjected to 10 minutes milling cycle in colloid mill before further processing. Results are tabulated in Table.9.

Mixing time optimization of aqueous dispersion of Carbopol 980P with Dapsone – Methyl Paraben – Transcutol P solution (Pre-Gelling Stage):

Mixing time of 2 hours was finalized for the pre-gelling stage involving mixing of aqueous dispersion of Carbopol 980P with Dapsone – Methyl Paraben – Transcutol P solution in Planetary mixer with a main motor speed of 65 ± 20 RPM and homogenizer speed of 1300 ± 100 RPM. Results are tabulated in Table.10.

Mixing time optimization of Sodium Hydroxide in Purified Water:

Based on the study results, mixing time of 40 minutes was finalized for dissolving Sodium Hydroxide in Purified Water using stirrer operated at 750 ± 250 RPM. Results are tabulated in Table.11.

Mixing time optimization of neutralization (Gelling) of aqueous dispersion of Dapsone – Carbopol 980P – Transcutol P & Methyl Paraben with Sodium Hydroxide solution (Gelling Stage):

Mixing time of 2 hours was finalized for the gelling stage involving mixing of aqueous dispersion of Dapsone – Carbopol 980P – Transcutol P & Methyl Paraben with Sodium Hydroxide solution in Planetary mixer with a main motor speed of 65 ± 20 RPM and homogenizer speed of 1300 ± 100 RPM. Results are tabulated in Table.12.

Effect of Semiautomatic tube filling machine speed on Weight variation, Minimum fill & Content Uniformity:

The prepared Dapsone Gel, 7.5% was filled in laminated tubes and sealed using Semiautomatic tube filling machine. During filling and sealing process, samples were collected during begin, middle and end stages of process to evaluate for Weight variation tabulated in Table. 13-15 and Minimum fill evaluation tabulated in Table. 16-18. Also, the complete filling operation time was divided into 30 intervals equally and at each time interval content uniformity sampling was done and is tabulated in Table.19. Based on the tabulated results, it is evident that filling operation of the final product in terms of 30 g, 60 g and 90 g into laminated tubes using semi-automatic filling machine was uniform with respect to weight variation, minimum fill and content uniformity.

Stability Evaluation

The drug product packed in laminated tubes was stability evaluated at 40°C / 75%RH for 3 months in horizontal and vertical orientation. The product was tested for Description, pH, Specific Gravity, Dissolution, Assay, Methyl Paraben Content, Related Substances, Microbial Limit Test and Antimicrobial Preservative Efficacy Test. The data is presented in Table. 20-21. The results revealed that the product was found to be stable.

TABLE.1 API CHARACTERIZATION.

Description	**A white or slightly yellowish-white crystalline powder**		
Particle Size Distribution	d10 9.4 µ	d50 80.0 µ	d90 224.4 µ
Bulk Density (g / mL)	0.43		
Tapped Density (g / mL)	0.56		

TABLE.2 MARKETED PRODUCT CHARACTERIZATION.

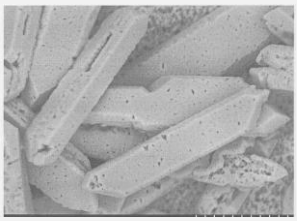
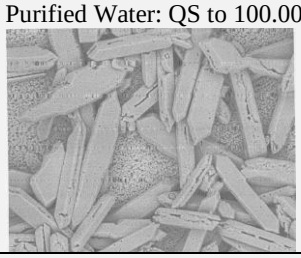
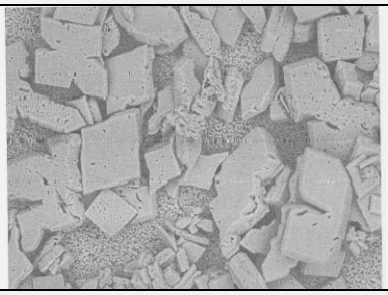
Particulars	**ACZONE® 5% w/w**	**ACZONE® 7.5% w/w**
Appearance	Gritty translucent gel with visible drug particles	Off-white to yellow gel with suspended particles
Fill Volume	30 g, 60 g & 90 g	30 g, 60 g & 90 g
pH	7.5	6.1
Specific Gravity	1.012 g / mL	0.999 g / mL
Viscosity	16,280 mpa.s	25000 mpa.s
Zeta Potential	-51.2 mV	-32.7 mV
Conductivity	0.163 mS / cm	0.213 mS / cm
Particle Size	d10 – 22.115 microns d50 – 50.915 microns d90 – 126.510 microns	d10 – 33.121 microns d50 – 80.471 microns d90 – 163.542 microns
Assay	100.8	101.8
Related Substances	Highest Unknown Impurity: 0.107 Total Impurity: 0.243	Unknown Impurity: 0.121 Total Impurity: 0.263
Excipients	Carbomer 980 Diethylene Glycol Monoethyl Ether Methyl Paraben Sodium Hydroxide Purified Water	Diethylene Glycol Monoethyl Ether Methyl Paraben Isohexadecane Polysorbate 80 Acrylamide / Sodium Acrgloyl Dimethyl Taurate Copolymer Purified Water
Packaging Configuration	High Density Polyethylene Laminated Tubes with Polypropylene Flip Closure	Airless pump containing a polypropylene bottle with a high density polyethylene piston
Quantitative Excipient Level (By HPLC)	Carbomer 980: 0.85% Diethylene Glycol Monoethyl Ether: 25.00% Methyl Paraben: 0.20% Sodium Hydroxide: To adjust pH Purified Water: QS to 100.00%	Diethylene Glycol Monoethyl Ether: 37.5% Methyl Paraben: 0.20% Simulgel™ EG: 1.275% (Consortium of Isohexadecane, Polysorbate 80 and Acrylamide / Sodium Acrgloyl Dimethyl Taurate Copolymer) Purified Water: QS to 100.00%
Scanning Electron Micrograph		
Dissolution USP-V (Paddle Over Disc Method), 50 RPM, 1000 mL, 2% HCl	**Time (min) / Mean % Drug Dissolved** 10 / 98 (86-101) 20 / 99 (91-101) 30 / 100 (95-101) 45 / 100 (98-101) 60 / 100 (100-101)	**Time (min) / Mean % Drug Dissolved** 10 / 100 (99-100) 20 / 101 (100-101) 30 / 101 (100-101) 45 / 102 (101-103) 60 / 101 (100-101)

TABLE.3 MARKETED PRODUCT CHARACTERIZATION CONT'd.

Particulars	**Role in ACZONE® 5%**	**Role in ACZONE® 7.5%**
Diethylene Glycol Monoethyl Ether (Transcutol P)	Solubilizer & Skin Permeability Enhancer	Solubilizer & Skin Permeability Enhancer
Methyl Paraben	Preservative	Preservative
Sodium Hydroxide	Alkalizer to adjust the pH of gel	Not Used
Carbomer 980 (Carbopol 980P)	Gel forming agent	Not Used
Consortium of Isohexadecane, Polysorbate 80 & Acrylamide / Sodium Acrgloyl Dimethyl Taurate Copolymer (Simulgel EG)	Not Used	Gel forming agent
Packing Configuration	HDPE based Laminated Tube with PP based flip closure	PP based bottle with HDPE based piston

TABLE.4 PROTOTYPE FORMULATION.

S.No	**Ingredients**	**% w/w**	**g / batch**
1	Dapsone	7.5	750
2	Transcutol P	37.5	3750
3	Methyl Paraben	0.2	20
4	Carbopol 980P	1.275	127.5
5	Sodium Hydroxide	QS for pH adjustment to 7 (6-8)	-
6	Purified Water	QS to 100%	QS to 10,000

Particulars	**Results**
Description	Gritty translucent material with visible drug particles
Assay	100.5%
pH	7.2
Specific Gravity	1.01 g / mL
Viscosity	18,750 mPa.s
Related Substances	Highest Unknown Impurity: 0.099 Total Impurity: 0.162
Zeta Potential	-49.7 mV
Conductivity	0.171 mS / cm
Particle Size	d10 – 27.780 microns d50 – 56.626 microns d90 – 119.764 microns
Scanning Electron Micrograph	

Dissolution USP-V (Paddle Over Disc Method), 50 RPM, 1000 mL, 2% HCl	**Time (min)**	**Mean % Drug Dissolved**
	10	99.7
	20	100.1
	30	101.5
	45	101.1
	60	100.1

Table.5 PROTOTYPE FORMULATION Vs MARKETED PRODUCT.

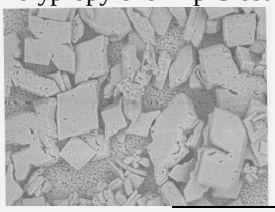
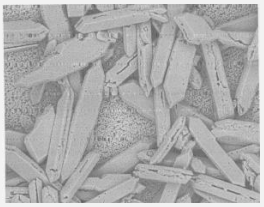
Particulars	**PROTOTYPE**	**ACZONE® 7.5% w/w**
Appearance	Gritty translucent material with visible drug particles	Off-white to yellow gel with suspended particles
Fill Volume	30 g, 60 g & 90 g	30 g, 60 g & 90 g
pH	7.2	6.1
Specific Gravity	1.01 g / mL	0.999 g / mL
Viscosity	18,750 mPa.s	25000 mpa.s
Zeta Potential	-49.7 mV	-32.7 mV
Conductivity	0.171 mS / cm	0.213 mS / cm
Particle Size	d10 – 27.780 microns d50 – 56.626 microns d90 – 119.764 microns	d10 – 33.121 microns d50 – 80.471 microns d90 – 163.542 microns
Assay	100.5%	101.8
Related Substances	Highest Unknown Impurity: 0.099 Total Impurity: 0.162	Unknown Impurity: 0.121 Total Impurity: 0.263
Excipients	Carbomer 980 Diethylene Glycol Monoethyl Ether Methyl Paraben Sodium Hydroxide Purified Water	Diethylene Glycol Monoethyl Ether Methyl Paraben Isohexadecane Polysorbate 80 Acrylamide / Sodium Acrgloyl Dimethyl Taurate Copolymer Purified Water
Packaging Configuration	High Density Polyethylene Laminated Tubes with Polypropylene Flip Closure	Airless pump containing a polypropylene bottle with a high density polyethylene piston
Scanning Electron Micrograph		
Dissolution USP-V (Paddle Over Disc Method), 50 RPM, 1000 mL, 2% HCl	**Time (min) / Mean % Drug Dissolved** 10 – 99.7 (98-100) 20 – 100.1 (99-101) 30 – 101.5 (101-102) 45 – 101.1 (100-102) 60 – 100.1 (99-101)	**Time (min) / Mean % Drug Dissolved** 10 – 100 (99-100) 20 – 101 (100-101) 30 – 101 (100-101) 45 – 102 (101-103) 60 – 101 (100-101)

TABLE.6 MIXING TIME OPTIMIZATION OF CARBOPOL 980P DISPERSION IN PURIFIED WATER.

Particulars	**Trial 1**	**Trial 2**	**Trial 3**
Main motor speed	63	65	61
Homogenizer speed	1210	1235	1295
Mixing Time	45 minutes	1 hour 30 minutes	2 hours 15 minutes
Remarks	Undissolved particles retained on #10 ASTM mesh	Clear	Clear

TABLE.7 MIXING TIME OPTIMIZATION OF METHYL PARABEN IN TRANSCUTOL P.

Particulars	**Trial 1**	**Trial 2**	**Trial 3**
Stirrer speed	611	620	617
Mixing Time	30 minutes	1 hour	1 hour 30 minutes
Remarks	Minute undissolved crystals observed	Clear	Clear

TABLE.8 MIXING TIME OPTIMIZATION OF DAPSONE IN METHYL PARABEN - TRANSCUTOL P.

Particulars	Trial 1	Trial 2	Trial 3
Stirrer speed	635	601	599
Mixing Time	30 minutes	1 hour	1 hour 30 minutes
Remarks	Undissolved Particles of Dapsone observed	Clear	Clear

TABLE.9 MILLING CYCLE OPTIMIZATION OF AQUEOUS DISPERSION OF CARBOPOL 980P.

Particulars	Trial 1	Trial 2	Trial 3
Milling cycle time in Colloid Mill	5 minutes	10 minutes	15 minutes
Remarks	Material of Jell / sludge Consistency retained on #10 ASTM mesh	No retention	No retention

TABLE.10 MIXING TIME OPTIMIZATION OF AQUEOUS DISPERSION OF CARBOPOL 980P WITH DAPSONE – METHYL PARABEN – TRANSCUTOL P SOLUTION (PRE-GELLING STAGE).

Main motor speed	**63 RPM**		
Homogenizer speed	**1238 RPM**		
S.No	**% Dapsone Assay in Pre-Gelling Stage**		
	Time (hr)		
	1.00	**2.00**	**3.00**
1	100.29	99.50	90.22
2	96.29	102.04	100.05
3	98.83	100.65	101.87
4	95.23	102.33	100.38
5	100.21	101.76	95.8
6	96.35	103.27	99.65
7	99.89	103.46	101.37
8	99.47	101.80	97.97
9	99.52	101.09	101.31
10	100.42	101.45	98.74
Average	98.65	101.74	98.74
Minimum	95.23	99.50	90.22
Maximum	100.42	103.46	101.87
% RSD	1.96	1.15	3.55

TABLE.11 MIXING TIME OPTIMIZATION OF SODIUM HYDROXIDE IN PURIFIED WATER.

Particulars	Trial 1	Trial 2	Trial 3
Stirrer speed	626	641	618
Mixing Time	20 minutes	40 minutes	60 minutes
Remarks	Undissolved particles of Sodium Hydroxide observed	Clear	Clear

TABLE.12 MIXING TIME OPTIMIZATION OF NEUTRALIZATION (GELLING) OF AQUEOUS DISPERSION OF DAPSONE – CARBOPOL 980P – TRANSCUTOL P & METHYL PARABEN WITH SODIUM HYDROXIDE SOLUTION (GELLING STAGE).

Main motor speed	**69 RPM**		
Homogenizer speed	**1215 RPM**		
S.No	**% Dapsone Assay in Gelling Stage**		
	Time (hr)		
	1.00	**2.00**	**3.00**
1	99.38	98.59	99.45
2	92.57	98.79	99.82
3	98.83	99.44	96.48
4	91.26	100.54	96.74
5	97.95	99.79	96.96
6	98.56	98.81	99.55
7	97.88	99.14	98.43
8	99.49	100.07	99.7
9	98.89	99.31	90.58
10	101.15	96.02	98.19
Average	97.60	99.05	97.59
Minimum	91.26	96.02	90.58
Maximum	101.15	100.54	99.82
% RSD	3.22	1.24	2.84

TABLE.13 WEIGHT VARIATION OF 30 g TUBE.

S.No	**WEIGHT VARIATON OF 30 g TUBE**								
	Begin			**Middle**			**End**		
	TW	GW	NW	TW	GW	NW	TW	GW	NW
1	9.16	39.71	30.55	9.15	39.59	30.44	9.15	39.16	30.01
2	9.12	39.44	30.32	9.14	38.76	29.62	9.16	38.82	29.66
3	9.10	39.36	30.26	9.15	38.80	29.65	9.17	39.02	29.85
4	9.15	39.69	30.54	9.15	39.83	30.68	9.15	39.80	30.65
5	9.15	38.71	29.56	9.14	38.83	29.69	9.15	39.96	30.81
6	9.14	38.79	29.65	9.15	39.11	29.96	9.15	39.11	29.96
7	9.16	38.50	29.34	9.16	39.68	30.52	9.16	40.17	31.01
8	9.14	38.68	29.54	9.14	39.29	30.15	9.15	39.11	29.96
9	9.15	39.14	29.99	9.16	39.33	30.17	9.15	39.04	29.89
10	9.16	39.03	29.87	9.15	40.30	31.15	9.16	38.12	28.96
Avg	9.14	39.11	29.96	9.15	39.35	30.20	9.16	39.23	30.08
Min	9.10	38.50	29.34	9.14	38.76	29.62	9.15	38.12	28.96
max	9.16	39.71	30.55	9.16	40.30	31.15	9.17	40.17	31.01

TW- Tare weight, GW - Gross weight, NW- Net weight

TABLE.14 WEIGHT VARIATION OF 60 g TUBE.

S.No	WEIGHT VARIATON OF 60 g TUBE								
	Begin			Middle			End		
	TW	GW	NW	TW	GW	NW	TW	GW	NW
1	9.95	70.21	60.26	9.92	70.44	60.52	9.96	70.31	60.35
2	9.93	70.49	60.56	9.96	70.87	60.91	9.95	69.60	59.65
3	9.94	69.56	59.62	9.94	69.80	59.86	9.93	70.45	60.52
4	9.95	69.10	59.15	9.95	69.51	59.56	9.95	70.08	60.13
5	9.93	70.19	60.26	9.96	70.47	60.51	9.96	70.11	60.15
6	9.92	70.44	60.52	9.95	70.47	60.52	9.97	69.61	59.64
7	9.96	70.22	60.26	9.96	69.58	59.62	9.98	68.14	58.16
8	9.97	70.12	60.15	9.95	70.46	60.51	9.96	69.78	59.82
9	9.92	69.78	59.86	9.94	70.15	60.21	9.97	69.48	59.51
10	9.96	69.92	59.96	9.94	69.8	59.86	9.95	70.1	60.15
Avg	9.94	70.00	60.06	9.95	70.16	60.21	9.96	69.77	59.81
Min	9.92	69.10	59.15	9.92	69.51	59.56	9.93	68.14	58.16
max	9.97	70.49	60.56	9.96	70.87	60.91	9.98	70.45	60.52

TW- Tare weight, GW - Gross weight, NW- Net weight

TABLE.15 WEIGHT VARIATION OF 90 g TUBE.

S.No	WEIGHT VARIATON OF 90 g TUBE								
	Begin			Middle			End		
	TW	GW	NW	TW	GW	NW	TW	GW	NW
1	11.36	101.92	90.56	11.35	99.91	88.56	11.35	101.58	90.23
2	11.37	100.32	88.95	11.34	101.3	89.96	11.35	101.60	90.25
3	11.35	101.00	89.65	11.36	99.32	87.96	11.36	101.05	89.69
4	11.36	99.32	87.96	11.37	99.22	87.85	11.37	100.02	88.65
5	11.35	101.00	89.65	11.38	100.00	88.62	11.36	98.10	86.74
6	11.36	102.56	91.2	11.36	100.28	88.92	11.34	100.99	89.65
7	11.35	102.00	90.65	11.35	100.97	89.62	11.36	100.05	88.69
8	11.36	98.98	87.62	11.36	102.61	91.25	11.38	101.3	89.92
9	11.35	103.45	92.10	11.37	102.62	91.25	11.35	101.58	90.23
10	11.34	102.54	91.20	11.36	99.21	87.85	11.37	101.52	90.15
Avg	11.36	101.31	89.95	11.36	100.54	89.18	11.36	100.78	89.42
Min	11.34	98.98	87.62	11.34	99.21	87.85	11.34	98.10	86.74
max	11.37	103.45	92.10	11.38	102.62	91.25	11.38	101.60	90.25

TW- Tare weight, GW - Gross weight, NW- Net weight

TABLE.16 MINIMUM FILL OF 30 g TUBE.

S.No	MINIMUM FILL OF 30 g TUBE								
	Begin			Middle			End		
	GW	ETW	NW	GW	ETW	NW	GW	ETW	NW
1	39.36	9.15	30.21	39.01	9.15	29.86	39.71	9.15	30.56
2	39.30	9.15	30.15	39.08	9.16	29.92	39.41	9.16	30.25
3	39.12	9.16	29.96	39.00	9.15	29.85	38.84	9.15	29.69
4	39.00	9.16	29.84	39.02	9.16	29.86	39.40	9.15	30.25
5	39.01	9.15	29.86	39.34	9.12	30.22	39.41	9.15	30.26
6	38.24	9.10	29.14	39.72	9.11	30.61	39.72	9.16	30.56
7	39.76	9.14	30.62	39.61	9.13	30.48	39.59	9.14	30.45
8	39.25	9.10	30.15	39.78	9.13	30.65	38.77	9.15	29.62
9	39.01	9.15	29.86	39.11	9.15	29.96	38.72	9.16	29.56
10	39.06	9.10	29.96	38.74	9.15	29.59	39.89	9.15	30.74
Avg	39.11	9.14	29.98	39.24	9.14	30.10	39.35	9.15	30.19
Min	38.24	9.10	29.14	38.74	9.11	29.59	38.72	9.14	29.56
max	39.76	9.16	30.62	39.78	9.16	30.65	39.89	9.16	30.74

ETW- Empty tube weight, GW - Gross weight, NW- Net weight

TABLE.17 MINIMUM FILL OF 60 g TUBE.

S.No	MINIMUM FILL OF 60 g TUBE								
	Begin			**Middle**			**End**		
	GW	ETW	NW	GW	ETW	NW	GW	ETW	NW
1	70.47	9.95	60.52	70.13	9.95	60.18	70.06	9.95	60.11
2	70.11	9.96	60.15	70.15	9.96	60.19	70.18	9.96	60.22
3	69.6	9.95	59.65	69.91	9.95	59.96	70.17	9.93	60.24
4	69.08	9.93	59.15	69.75	9.93	59.82	69.76	9.94	59.82
5	70.08	9.93	60.15	69.75	9.94	59.81	69.58	9.93	59.65
6	70.18	9.94	60.24	69.58	9.93	59.65	69.36	9.94	59.42
7	70.5	9.96	60.54	69.73	9.92	59.81	69.51	9.96	59.55
8	70.43	9.97	60.46	69.68	9.93	59.75	70.04	9.92	60.12
9	70.16	9.95	60.21	70.06	9.95	60.11	69.46	9.91	59.55
10	70.27	9.96	60.31	70.16	9.96	60.2	69.56	9.94	59.62
Avg	70.09	9.95	60.14	69.89	9.94	59.95	69.77	9.94	59.83
Min	69.08	9.93	59.15	69.58	9.92	59.65	69.36	9.91	59.42
max	70.50	9.97	60.54	70.16	9.96	60.20	70.18	9.96	60.24

ETW- Empty tube weight, GW - Gross weight, NW- Net weight

TABLE.18 MINIMUM FILL OF 90 g TUBE.

S.No	MINIMUM FILL OF 90 g TUBE								
	Begin			**Middle**			**End**		
	GW	ETW	NW	GW	ETW	NW	GW	ETW	NW
1	101.66	11.34	90.32	101.6	11.35	90.25	103.62	11.36	92.26
2	102.72	11.36	91.36	101.06	11.41	89.65	101.73	11.37	90.36
3	103.49	11.37	92.12	101.61	11.36	90.25	101.61	11.36	90.25
4	101.34	11.35	89.99	101.14	11.32	89.82	101.34	11.38	89.96
5	100.24	11.35	88.89	99.24	11.35	87.89	100	11.35	88.65
6	101.71	11.36	90.35	100.27	11.32	88.95	101.35	11.36	89.99
7	102.57	11.36	91.21	100.98	11.36	89.62	100.23	11.38	88.85
8	101.58	11.38	90.2	101.59	11.35	90.24	103.58	11.37	92.21
9	101.35	11.36	89.99	100.05	11.36	88.69	99.24	11.35	87.89
10	101.23	11.35	89.88	101.17	11.35	89.82	100.31	11.36	88.95
Avg	101.79	11.36	90.43	100.87	11.35	89.52	101.30	11.36	89.94
Min	100.24	11.34	88.89	99.24	11.32	87.89	99.24	11.35	87.89
max	103.49	11.38	92.12	101.61	11.41	90.25	103.62	11.38	92.26

ETW- Empty tube weight, GW - Gross weight, NW- Net weight

TABLE.19 CONTENT UNIFORMITY STUDY RESULTS.

Sample No	30 g Fill		60 g Fill		90 g Fill	
	Dapsone, USP (%)	Mean	Dapsone, USP (%)	Mean	Dapsone, USP (%)	Mean
	100.76		102.89		101.78	
1	102.33	101.67	99.02	101.64	102.08	101.52
	100.11		103.00		100.70	
	99.06		103.31		101.35	
2	101.85	100.62	102.73	100.16	102.37	101.95
	100.94		94.45		102.14	
	100.19		98.25		102.06	
3	99.01	99.33	98.33	97.86	102.06	101.17
	98.79		97.01		99.40	
	103.74		98.32		103.22	
4	100.08	101.73	106.24	101.61	100.07	102.59
	101.36		100.27		104.48	
	101.57		97.17		100.97	
5	97.51	100.24	108.88	102.08	100.79	101.17
	101.64		100.18		101.75	
	104.27		99.11		102.98	
6	103.88	100.45	97.29	97.43	100.06	101.52
	93.21		95.88		101.53	
	98.05		96.51		105.97	
7	98.08	98.56	98.91	97.57	99.52	103.26
	99.56		97.29		104.30	
	101.79		99.78		106.37	
8	101.44	100.55	98.17	98.65	100.55	101.88
	98.41		98.01		98.71	
	97.02		95.78		101.01	
9	101.50	99.75	96.55	97.26	101.96	102.00
	100.72		99.45		103.02	
	104.70		95.93		103.79	
10	98.55	101.88	107.59	99.68	100.39	103.36
	102.40		95.53		105.90	
Average		100.48	Average	99.39	Average	102.04
Minimum		98.56	Minimum	97.26	Minimum	101.17
Maximum		101.88	Maximum	102.08	Maximum	103.36
%RSD		1.08	%RSD	1.91	%RSD	0.77

TABLE. 20 STABILITY STUDY – HORIZONTAL ORIENTATION.

	Orientation - Horizontal				
Tests	**Specification**	**40°C / 75%RH**			
		Initial	**1st Month**	**2nd Month**	**3rd Month**
Description	Gritty translucent material with visible drug particles	Complies	Complies	Complies	Complies
pH	Between 6.0 to 8.0	7.1	6.9	7.1	7.1
Specific Gravity	0.85 g / mL to 1.25 g / mL	1.02	1.01	0.99	1.02
Assay	NLT 90.0% and NMT 110.0% of the labelled amount	100.1	100.7	99.8	100.1
Assay of Methyl Paraben	NLT 70%	99.8	99.7	98.5	97.9
Related Substances	Highest Unknown Impurity: NMT 0.2%	0.072	0.079	0.091	0.095
	Total Impurity: NMT 1.0%	0.169	0.181	0.194	0.207
Microbial Limit Test	Total Aerobic Microbial Count: NMT 1000 cfu / g	Absent	Absent	Absent	Absent
	Total Combined Yeasts & Moulds Count: NMT 100 cfu / g	Absent	Absent	Absent	Absent
	Specified Microorganisms:				
	Escherichia coli: Absent	Absent	Absent	Absent	Absent
	Salmonella species: Absent	Absent	Absent	Absent	Absent
	Staphylococcus aureus: Absent	Absent	Absent	Absent	Absent
	Pseudomonas aeruginosa: Absent	Absent	Absent	Absent	Absent
	Bacteria: NLT 2.0 log reduction from the initial count at 14 days.	-	6.855	6.875	6.885
Antimicrobial Preservative Efficacy Test	No Increase from the 14 days count at 28 days.	6.845	6.841	6.870	6.876
	Yeast & Molds: No increase from the initial calculated count at 14 days and 28 days.	No growth	No growth	No growth	No growth

TABLE. 21 STABILITY STUDY – VERTICAL ORIENTATION.

	Orientation - Upright				
Tests	**Specification**	**40°C / 75%RH**			
		Initial	**1st Month**	**2nd Month**	**3rd Month**
Description	Gritty translucent material with visible drug particles	Complies	Complies	Complies	Complies
pH	Between 6.0 to 8.0	7.1	7.0	7.0	7.1
Specific Gravity	0.85 g / mL to 1.25 g / mL	1.02	1.01	1.01	1.02
Assay	NLT 90.0% and NMT 110.0% of the labelled amount	100.1	99.9	100.2	99.8
Assay of Methyl Paraben	NLT 70%	99.8	99.3	99.1	98.7
Related Substances	Highest Unknown Impurity: NMT 0.2%	0.072	0.085	0.101	0.104
	Total Impurity: NMT 1.0%	0.169	0.189	0.205	0.216
Microbial Limit Test	Total Aerobic Microbial Count: NMT 1000 cfu / g	Absent	Absent	Absent	Absent
	Total Combined Yeasts & Moulds Count: NMT 100 cfu / g	Absent	Absent	Absent	Absent
	Specified Microorganisms:				
	Escherichia coli: Absent	Absent	Absent	Absent	Absent
	Salmonella species: Absent	Absent	Absent	Absent	Absent
	Staphylococcus aureus: Absent	Absent	Absent	Absent	Absent
	Pseudomonas aeruginosa: Absent	Absent	Absent	Absent	Absent
	Bacteria: NLT 2.0 log reduction from the initial count at 14 days.	-	6.829	6.863	6.877
Antimicrobial Preservative Efficacy Test	No Increase from the 14 days count at 28 days.	6.845	6.838	6.872	6.871
	Yeast & Molds: No increase from the initial calculated count at 14 days and 28 days.	No growth	No growth	No growth	No growth

CONCLUSION

The once daily topical gel of Dapsone, 7.5% w/w was successfully formulated with minimal excipients and cost-effective packaging configuration as compared to the marketed product, ACZONE®, 7.5% Gel manufactured by Allergan Inc, USA. The physico-chemical characteristics, in-vitro drug release and stability of the developed product were comparable to the marketed product. The finalized manufacturing process of the developed product was completely optimized with respect to order of addition of ingredients, mixing time, milling cycle time etc. The filling and packing trial of the formulated gel into laminated tubes using semi-automatic filling machine was found to be satisfactory. The assay and effectiveness of methyl paraben was found to be intact on stability. The developed product was found to be cost-effective as compared to the available national and international brands in the market.

COMPETING INTERESTS

The authors declare no conflict of interest.

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