J. Pharm. Res. 2019;18(1):20–26

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

ORIGINAL ARTICLE

Development of a Novel Emulsified Oral Dosage form of an Antifungal Drug in a Quality by Design Framework and Verifying its Critical Quality Attributes

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ARTICLE INFO

Article history:
Received 18.12.2018
Revised 22.03.2019
Accepted 10.03.2019

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https://doi.org/10.18579/jopcr/v18.1.roopesh

ABSTRACT

Objectives: The aim of this study was to formulate a novel BCS class II antifungal formulation of itraconazole and optimise its critical quality attributes (CQAs) using a Quality by Design (QbD) approach.
Methods: Material attributes and CQAs were identified using risk assessment according to the International Conference of Harmonization (ICHQ9) quality guidelines. The material attributes were found to be the ratios of surfactant (Tween 80) and co-surfactant (Transcutol). The CQA selected for optimization was dissolution. A screening design was performed on the surfactant and co-surfactant to fix the ratio of Smix, resulting in four optimized ratios: 1:1, 1:3, 5:3, and 5:1. Pseudo ternary phase diagrams were constructed, and ranges for excipients were fixed. Based on the results of the screened ratios, a Mixture Design – Design of Experiment (DoE) was used for optimization.
Findings: Optimized runs of ten runs for dissolution were achieved by the application of the mixture design, with formulation F2 showing a maximum release of 93.35%.
Novelty: Quality by Design (QbD) can be utilized to optimize the CQAs of a novel BCS class II antifungal formulation, itraconazole.

Keywords: QbD; Screening design; Mixture design; Extreme vertices; SEDDS; Itraconazole

INTRODUCTION

Quality by Design (QbD) has supported both industry and the FDA to achieve scientific, risk-based, and proactive approaches to pharmaceutical product development [1]. QbD is a systemic approach for pharmaceutical product development which leads to formulations and manufacturing processes with desired quality attributes [2]. Pharmaceutical QbD may include achieving a meaningful control strategy based on clinical performance to increase process capability by enhancing the product and process design [3]. The theme of QbD is Quality cannot be tested in the product but should be built into it [4,5].

The first and one of the most important steps when using QbD is to predefine the QTPP. The nano-based QTPP comprises quality parameters that should ideally be achieved to ensure final product quality, considering product safety and efficacy. The second step of QbD-based development is to identify CQAs. CQAs are product quality attributes derived from the QTPP that have an impact on the final product quality, and for this reason, they must be studied and controlled (Q8, 2009). Any change in formulation or process variables might be a threat to CQAs, so such parameters must be ensured during development and production to achieve the required quality [6,7].

The development of a novel emulsified oral dosage form for antifungal drugs represents a significant advancement in pharmaceutical formulation. Antifungal drugs are crucial for treating a variety of fungal infections, but their effectiveness is often limited by poor solubility and bioavailability. Emulsified oral dosage forms can address these challenges by improving drug solubility and facilitating better absorption in the gastrointestinal tract. By developing an emulsified oral dosage form, this project aimed to create a more effective antifungal treatment with enhanced bioavailability and therapeutic efficacy, ultimately leading to better patient outcomes in the management of fungal infections.

Cryptococcosis is a global fungal systemic infection caused by the yeasts Cryptococcus neoformans and Cryptococcus gattii, which mainly affect immunocompromised patients [8]. Pulmonary and central nervous system infections

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are the most common disease manifestations, and meningitis is a primary clinical complication[9].

The current therapeutic arsenal for cryptococcosis is restricted to amphotericin B, fluconazole, and 5-flucytosine. In addition, fungal resistance to these conventional drugs has become a global challenge for the health system. Therefore, developing new antifungal drugs that are more effective, safe, and active against resistant strains is highly relevant for treating current fungal infections[9].

The development of an effective and safe oral formulation of Amphotericin B would have significant applications in the treatment of disseminated fungal infections and would dramatically expand access to visceral leishmaniasis treatment. However, the bioavailability of Amp B is negligible because of its low aqueous solubility, poor membrane permeability, and instability at low pH in gastric fluid. Recently, attention has been focused on the use of oral lipid excipients to enhance the solubility and bioavailability of poorly water-soluble lipophilic drugs[10]. Oral lipid excipients consisting of (A) medium-chain triglycerides, fatty acids, and nonionic surfactants designed to achieve self-nano-emulsification drug delivery systems (SEDDS) in aqueous media[11] or (B) glycerol monooleate with poly (ethylene glycol) (PEG)-phospholipids were explored as solubilizing agents for Amp B, followed by the characterization of stability in simulated gastric fluid and simulated intestinal fluid[12].

METHODOLOGY

Materials

The materials used in the development of the novel emulsified oral dosage form of an antifungal drug include a range of specific components sourced from various suppliers. The primary drug used was itraconazole, which was obtained from Radiant Pharma, Mumbai. To stabilize the emulsion, the surfactant Tween 80 was used, sourced from S.D. Fine Chemicals Ltd., also located in Mumbai. The co-surfactant employed in the formulation was Transcutol, procured from Vasa Scientific Co. in Bangalore. The oil phase of the emulsion consisted of Caproyl 90, which was supplied by Vasa Scientific Co. Methanol, which was utilised as a solvent in the formulation process, was acquired from S.D. Fine Chemicals Ltd., Mumbai. Additionally, 0.1N HCl, used as the dissolution medium, was provided by S.D. Fine Chemicals Ltd., Mumbai. Purified water, another solvent in the formulation, was also utilised.

Equipment used

The equipment used in the development of the novel emulsified oral dosage form of an antifungal drug includes several key instruments from various reputable sources. A digital electronic balance (ATY234) was sourced from Shimadzu Corporation, Japan, to ensure precise measurements of the materials. A UV/visible spectrophotometer (model 1700, Shimadzu Corporation, Japan) was used to analyse the samples. Dissolution testing was conducted using a Dissolution Apparatus D58000 supplied by Lab India, Mumbai. The mixing processes were facilitated using a Magnetic Stirrer from REMI INDIA. Additionally, an ultra-sonicator from Sidilu Renewable Pvt., Bangalore, was used to ensure thorough mixing and emulsification of the components.

Determination of melting point

The melting point of the obtained sample was determined as it is the first indication of sample purity. The melting point of the drug was determined by taking a small amount of drug in a capillary tube closed at one end and placing it in a melting point apparatus, with the temperature at which the drug melts. The averages of triplicate readings were recorded.

Analytical profile of itraconazole

Determination of lambda max of the drug:

A 10 μg/ml solution of itraconazole in methanol was scanned in the UV range 200–400 nm. The λ_{max} value of Itraconazole was found to be 260 nm.

Construction of the calibration curve

Standard calibration curve of itraconazole in methanol: Stock Solution.

Stock 1. The standard stock solution was prepared by dissolving 100mg of Itraconazole in methanol in 100ml volumetric flask and the volume was made up to the mark with methanol to get 1000μg/ml concentration and this solution was used as standard stock solution (SS)

Stock 2. 4 ml of the solution was pipetted out from stock I and further diluted with 100 ml of methanol. (It gives 40 μg/ml solution)

From stock solution II, aliquots of 1, 2, 3, 4, and 5 ml were transferred to a 10 ml volumetric flask and diluted with methanol up to the mark. The absorbance of these solutions was measured at λ_{max} 260 nm and a graph of concentration versus absorbance was plotted.

Formulation

Excipient Screening – Saturation Solubility studies

The solubility of itraconazole in various oil phases, surfactants, and co-surfactants was determined by separately dissolving an excess amount of drug in 2 ml of each selected individual oil, surfactant, and co-surfactant contained in stopper vials (5 ml capacity). The liquids were mixed using a vortex mixer at 37°C±1°C for 72 h to reach equilibrium. The equilibrated samples were then removed from the mixer. and centrifuged (3000 rpm) for 15 min. The supernatants were removed and filtered through a membrane. Aliquots

of the supernatant were diluted with methanol, and the drug content was quantified using a UV spectrometer at λ_{max} 260 nm. Surfactants and co-surfactants which showed the highest solubility of the drug were selected for the formulation.

The selected surfactant and co-surfactant were then given a range of 1-5 and 1-3 respectively and the appropriate ratios of the surfactant and co-surfactant were determined by screening design using the JMP 11SAS software.

Development of pseudo-ternary phase diagram

Pseudo-ternary phase diagrams were designed using the PROSIM ternary diagram software. To construct the ternary phase diagram, the ratios of surfactant and co-surfactant were selected. In this study, five different ratios of surfactant (Tween 80) to co-surfactant (Transcutol) were studied: 1:1, 1:3, 5:3, and 5:1. These mixtures (S/Cos) were mixed with the oil phase to obtain weight ratios of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. These mixtures were mixed thoroughly on a magnetic stirrer and titrated against distilled water until the system became cloudy to determine the maximum water uptake. A tendency to emulsify spontaneously was also observed.

Preparation of liquid SEDDS formulation

The formulations were prepared by dissolving itraconazole in a mixture of surfactants, co-surfactants, and oil. The final mixture was vortexed to obtain a clear solution. The lipid formulations were assessed visually for their rates of emulsification, clarity, drug-loading capacity, and dissolution profile.

Application of DOE

Once the formulations were prepared, the required ranges of surfactant, co-surfactant, and oil were fixed based on the points obtained from the pseudo ternary phase diagram. The obtained ranges were then uploaded to the DOE, which provided optimized runs for dissolution.

Evaluation studies

Phase separation

The diluted SEDDS was maintained for 24 h and observed for phase separation.

Clarity

1 g of SEEDS preparation was diluted 1:10 and 1:25 with distilled water and 0.1N HCl and checked for percentage transmittance at 400 nm and 650 nm.

Self-emulsification time

1 g of the SMEEDS preparation was diluted in 250 ml of distilled water, and this mixture was placed on a magnetic stirrer at 50 rpm. The time required to form a clear emulsion was determined.

Cloud Point determination

The cloud point is generally determined by gradually increasing the temperature of the water bath in which the formulation is placed.

Drug content

The SEDDS (10 mg) was diluted to 10 ml with methanol. 0.2 ml was pipetted out from this solution and further diluted with 4.8 ml methanol and HCl (5 ml, 0.1N) to make up the volume to 10 ml.

In vitro drug release studies

Drug release studies from SEDDS were performed using USP dissolution apparatus II with 900 ml of 0.1 N HCL as a medium at 37 $\pm$ 0.5°C. The paddle speed was adjusted to 50 rpm. An itraconazole-loaded liquid SEDDS (equivalent to 10 mg of itraconazole) was placed in a dissolution tester (LAB INDIA). At predetermined time intervals of 5, 10, 15, 30, 45, and 60 min, an aliquot (5 ml) of the sample was collected, filtered, and analysed for itraconazole content by UV spectroscopy. An equivalent volume (5 ml) of fresh dissolution medium was added to maintain sink conditions.

RESULTS AND DISCUSSION

Performance studies, construction of a pseudo-ternary phase diagram, and evaluation of liquid SEDDS for phase separation, self-emulsification time, cloud point determination, and drug content are shown in Tables **??**, **??** and 3. The melting point of itraconazole was found to be 170°C $\pm$ 0.5, which meets the standards specified in the official limits. The UV spectrum scans of itraconazole in methanol showed a maximum absorbance λ_{max} at 260 nm. Most drugs suffer from solubility or permeability problems, which add to the poor bioavailability of drugs. Most drugs are structurally optimized during drug discovery studies to increase their solubility, efficiently penetrate biological barriers, and easily reach their target receptors. Although an increase in lipophilicity helps in better absorption, their delivery to aqueous physiological media becomes difficult. On the other hand, some drugs have good water solubility but lack sufficient lipophilicity to effectively penetrate lipoidal tissues, and absorption becomes a rate-limiting factor for such drugs.

SEDDS due to their unique structure and dynamics, SEDDSs afford efficient delivery of both lipophilic and hydrophilic drugs through aqueous and lipoidal environments. Hence, they are ideally suited to attempt to alleviate absorption-related problems for drugs with low solubility, low permeability, or both.

Table 1: Performance studies

Melting point studies			
Reported value with SD	**Observed value**		
170 °C ± 0.5	Trail 1	Trail 2	Trail 3
	170 °C	170.3 °C	170 °C
Calibration of Itraconazole in methanol			
Sl. No	**Concentration (μg/ml)**	**Absorbance at 260nm**	**± SD**
1	5	0.151	0.0047
2	10	0.311	0.0081
3	15	0.423	0.00047
4	20	0.617	0.00047
5	25	0.740	0.00047
Solubility profile of Itraconazole			
Oil /Surfactant	**Solubility (mg/mL)**		
Isopropyl myristate	0.206 ± 2.07		
Captex 200	1.008 ± 2.08		
Captex 355	2.127 ± 1.97		
Tocopherol acetate	5.22 ± 1.87		
Capryol 90	22.132 ± 1.58		
Tween 80	3.709 ± 1.04		
Labrasol	7.147 ± 1.65		
Transcutol	4.6 ± 1.48		

The model drug is a typical antifungal drug that belongs to BCS class II, with good permeability, but suffers from low water solubility. Hence, in the present work, an attempt was made to enhance the dissolution rate by increasing the solubility of the model drug with the aid of the SEDDS.

Preliminary methods

The preliminary methods for the study included several key steps. The solubility test revealed that the drug was soluble in Capryol C 11. In the wavelength scan, a 10 μg/ml drug solution in methanol was scanned in the UV range between 200 and 400 nm, with maximum absorbance at 260 nm. For the calibration curve, drug concentrations between 5-20 μg/ml were plotted, resulting in a linear plot with an R^2 value of 0.9957. Screening was performed on the surfactants and co-surfactants to obtain specific ratios for preparing the liquid SEDDS formulation. The ratios obtained after screening were 1:1, 1:3, 5:3, and 5:1, respectively. Pseudo ternary phase diagrams were constructed for the screened ratios, and evaluation tests were performed, as mentioned in Table **??**. Following the screening design, a mixture design was conducted with ten experimental runs. Among these, F2 exhibited a drug release rate of 93.35%.

Evaluation studies

Clarity

All four ratios were clear, transparent, and yellowish to pale yellow in colour. The clarity is represented in terms of % transmission, where absorbance and % transmission are noted at 650 nm and 400 nm, respectively. The best results were reported for all ratios at 650 nm compared to 400 nm. The percentage of transmission was greater than 90%. The best results were reported for a ratio of 1:3 (99.55%). A Higher transmittance should be obtained with optically clear solutions, because cloudier solutions scatter more of the incident radiation, resulting in lower transmittance. Aqueous dispersions with small absorbances are optically clear and oil droplets are thought to be in a state of finer dispersion.

Phase separation

Diluted SEDDS ratios of 1:1, 1:3, 5:3, and 5:1 was maintained for 24 h and observed for phase separation**.** Except for the 5:3 ratio, all other ratios showed good stability without any phase separation, as shown in Table 3.

Cloud Point determination

The cloud point is generally determined by gradually increasing the temperature of the water bath in which the formulation is placed. The cloud point is the temperature

Table 2: Construction of pseudo ternary phase diagram

Concentration of oil, Smix & water used for constructing phase diagram for 1:1 ratio

Sl. no	Oil (g)	Smix (g)	Water (g)	Total	% Smix	% Oil	% Water
1	0.1	0.9	3.91	4.91	18.32	2.03	79.6
2	0.2	0.8	1.59	2.59	30.88	7.72	61.38
3	0.3	0.7	0.47	1.47	47.61	20.40	31.97
4	0.4	0.6	0.31	1.31	45.80	30.5	23.66
5	0.5	0.5	0.27	1.27	39.37	39.37	21.25
6	0.6	0.4	0.19	1.19	33.61	50.42	15.96
7	0.7	0.3	0.19	1.19	25.21	58.8	15.96
8	0.8	0.2	0.12	1.12	17.85	71.42	10.7
9	0.9	0.1	0.1	1.1	9.09	81.81	9.09

Concentration of oil, Smix & water used for constructing phase diagram for 1:3 ratio

Sl. no	Oil (g)	Smix (g)	Water (g)	Total	% Smix	% Oil	% Water
1	0.1	0.9	2.14	3.14	28.6	3.18	68.15
2	0.2	0.8	0.86	1.86	43.01	10.75	46.23
3	0.3	0.7	0.60	1.60	43.75	18.75	37.5
4	0.4	0.6	0.41	1.41	42.55	28.36	29.03
5	0.5	0.5	0.18	1.18	42.37	42.37	15.25
6	0.6	0.4	0.19	1.19	33.61	50.42	15.96
7	0.7	0.3	0.20	1.20	25	58.33	16.66
8	0.8	0.2	0.16	1.16	17.24	68.96	13.79
9	0.9	0.1	0.09	1.09	9.1	82.56	8.2

Concentration of oil, Smix & water used for constructing phase diagram 5:3 ratio

Sl. no	Oil (g)	Smix (g)	Water (g)	Total	% Smix	% Oil	% Water
a 1	0.1	0.9	3.61	4.61	19.25	2.16	78.3
g 2	0.2	0.8	1.62	2.62	30.53	7.63	61.83
r 3	0.3	0.7	0.43	1.43	48.95	20.97	30.06
a 4	0.4	0.6	0.34	1.34	44.7	29.85	25.37
m5	0.5	0.5	0.26	1.26	39.68	39.69	20.63
6	0.6	0.4	0.27	1.27	31.49	47.24	21.25
f 7	0.7	0.3	0.18	1.18	25.42	59.32	15.25
o 8	0.8	0.2	0.21	1.21	16.52	66.11	17.35
r 9	0.9	0.1	0.03	1.03	9.7	87.37	2.91

Concentration of oil, Smix & water used for constructing phase diagram 5:1

Sl. no	Oil (g)	Smix (g)	Water (g)	Total	% Smix	% Oil	% Water
g 1	0.1	0.9	3.26	4.26	21.12	2.34	76.52
r 2	0.2	0.8	1.09	2.09	38.27	9.56	52.15
a 3	0.3	0.7	0.34	1.34	52.23	22.38	25.37
m4	0.4	0.6	0.2	1.2	50	33.33	16.66
5	0.5	0.5	0.2	1.2	41.6	41.6	16.66
f 6	0.6	0.4	0.23	1.23	32.52	48.78	18.66
o 7	0.7	0.3	0.19	1.19	25.21	58.82	15.9
r 8	0.8	0.2	0.09	1.09	18.34	73.39	8.25
: 9	0.9	0.1	0.08	1.08	9.2	83.33	7.40

Table 3: Evaluation of liquid SEDDS for, phase separation, self-emulsification time, cloud point determination and drug content.

Evaluation of liquid SEDDS

Ratios	Phase separation	Self-emulsificationtime (min)	Cloud point(°c)	Drug content (mg)	%Drug content
1:1	-	< 1	75	4.64	92.8
1:3	-	< 1	70	4.92	98.5
5:3	+	>1	90	5.07	90.4
5:1	-	< 1	80	4.21	84.2

Drug loading in 1ml of SEDDS formulation

Ratios	Drug loading / ml formulation(mg/ml)
1:1	134.59
1:3	152.00
5:3	138.63
5:1	130.30

Dissolution profile data

SL. No	Smix	Water	Oil	% release
1	0.9	0.01	0.09	85.89
2	0.87	0.05	0.08	93.06
3	0.9	0.02	0.08	88.09
4	0.7	0.03	0.27	88.68
5	0.8	0.01	0.19	83.72
6	0.885	0.035	0.08	87.21
7	0.78	0.05	0.16	84.06
8	0.7	0.05	0.25	84.16
9	0.7	0.01	0.29	85.99
10	0.9	0.015	0.085	89.03

In vitro drug release profile - Percentage cumulative drug release of SEDDS formulation

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	58.96	64.56	56.54	62.78	55.43	58.98	63.44	62.76	54.44	65.32
15	72.43	77.32	72.38	79.25	70.98	65.43	79.26	75.44	64.32	78.98
30	86.38	93.56	88.45	89.66	82.35	79.63	84.55	83.68	84.44	89.66
45	85.92	93.288	88.26	88.83	84.68	87.55	84.32	84.88	86.32	89.45
60	85.89	93.06	88.09	88.68	83.72	87.21	84.06	84.16	85.99	89.03

above which an aqueous solution of water-soluble surfactants, especially nonionic surfactants, becomes turbid. This indicates the successful formation of a stable emulsion. When the temperature is higher than the cloud point, irreversible phase separation occurs, and the cloudiness of the preparation would have a negative effect on drug absorption because of the dehydration of the polyethylene oxide moiety. Hence, the cloud point for SEDDS should be above 37°C, which will prevent phase separation occurring in the gastrointestinal tract. The cloud point for all four ratios was above 70°C, indicating that the formulations were stable at the body temperature.

Drug Content

1 g of SMEDDS was taken and diluted to 100 ml with methanol. Further dilutions were performed with methanol followed by 0.1N HCl, and the absorbance was recorded at 260 nm. The drug content of the selected SMEDDS formulation at a ratio of 1:3 was found to be the maximum, that is 98.5% $\pm$ 0.304.

In vitro drug release studies

The % drug release after 1 h for formulations F1-F10 varied from 83.04% to 93.35% (Table 3). The formulation F2 showed a maximum release of 93.35% among the other nine formulations.

CONCLUSION

The combination of Capryol, Tween 80, and Transcutol is a potential lipid combination for self-emulsification. The amounts of surfactant and co-surfactant were identified as critical quality attributes (CQAs) that significantly affected the drug dissolution. The critical ratios of the surfactants and co-surfactants were determined using a definitive screening design. Optimized dissolution runs were achieved through the application of a mixture design, resulting in a release rate of 83–93% for the formulations. Thus, Quality by Design (QbD) was successfully used to optimize the formulation.

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