Development & Optimization of Anti-Dandruff Shampoo by Modifying its Rheological Behavior

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Summary

Pharmaceutical product stability is an important issue in pharmaceutical industry. The rheological behavior of a pharmaceutical product affects its stability and performance characteristics such as, foaming properties and filling process during production. Ketoconazole, imidazole antifungal agent, is a weak base with two pKa-values 6.15 and 2.94. It is unstable in aqueous medium and vulnerable to degradation if not properly formulated. Oxidation and hydrolysis are the most degradation routes affecting its stability. The aim of this study to assess the effect of formulation factors such as, pH, the amount of the rheology modifier, rheological behavior and temperature on the stability of ketoconazole in aqueous media.

Different formulations of 2 gm% ketoconazole were prepared, using different percent concentrations of the rheology modifier (NaCl) as 0.8 gm%, 0.2 gm%, 0.4 gm%, 0.1 gm% at different pH values 5.5, 6.5 and 7.5. Experimental formulations were prepared at different temperature and time intervals. The measurements of pH and viscosity of the prepared shampoo were evaluated during stability. Stability studies were carried out as per ICH guidelines for 18 months and monitored by validated stability indicating HPLC method (linearity: 60-140 µg/mL; R^2=0.9995; acceptable accuracy and precision %RSD < 1.0%).

The rheological behavior of the system possess a yield point (minimum shear stress for flow to commence) and time dependency. A reduction in viscosity occurs on shearing with time and rebuilding of viscosity on standing. The key is the rate at which the structure is rebuilt. This is a function of the nature of the thixotropic agent, its concentration in the vehicle or medium, and the amount of agitation before use. The prepared ketoconazole shampoo was high stable at high pH (6.5-7.5) and at temperature < 30 °C during the manufacturing process. Furthermore, the amount of rheology modifier had a high significant effect on the stability of ketoconazole. Formulations containing 0.1 gm% NaCl showed better stability and exhibited ideal thixotropic rheological behavior.

The rheology of dispersed systems is among the most important of their physical properties, which influences not only the physical stability of the systems, but often also profoundly affects the performance features, their quality, and their utility. In dealing with rheological parameters, and in case of thixotropic systems, long shearing times should be avoided. Temperature changes can also produce spurious results, since shear stress at a constant shear rate, is also a function of temperature. It is important to consider the optimum pH for the product, since the properties of the product, particularly rheology, can be quite dependent on the pH of the system. In conclusion, the expected shelf life of the final ketoconazole formulation was stable for 18 months.

Riassunto

La stabilità di un prodotto farmaceutico o cosmetico risulta molto importante per il suo uso. Le proprietà reologiche di un prodotto ne influenzano, infatti, sia la stabilità che le caratteristiche finali, quali ad esempio le proprietà schiumogene e la rapidità di riempimento nei contenitori durante le fasi di produzione.
Il ketoconazolo è un antiinfiammatorio imidazolico caratterizzato da un pKa che va da 6.51 a 2.94. E' instabile in un mezzo acquoso e, se non propriamente formulato, facilmente degradabile. L'ossidazione e l'idrolisi sono i due fenomeni più frequenti che ne provocano la degradazione.
Lo scopo di questo studio è di controllare gli effetti provocati da alcuni parametri quali il pH, gli eventuali modificatori reologici e la temperatura sulla formulazione e sulla stabilità del prodotto finale in un mezzo acquoso.
A tal proposito, sono state controllate diverse formulazioni contenenti concentrazioni del 2% di ketoconazolo, preparate utilizzando come modificatore reologico NaCl a percentuali variabili dello 0.8 , 0,4,0, 2 e 0,1% in peso, e a diversi pH 5.5 ,6.5 e 7.5. Le formulazioni sono state preparate utilizzando diverse temperature e diversi tempi di intervallo.
Durante il periodo di stabilità sono stati verificati pH e viscosità degli shampoo formulati. Gli studi di stabilità sono stati condotti secondo le linee guida ICH per 18 mesi, monitorando la relativa stabilità per mezzo dell'HPLC/linearità (60-140ug/ml; R^2= 0,9995 accuratezza e precisione con %RSD<1,0%).
Il comportamento reologico del sistema è caratterizzato da un punto di rendimento legato al tempo. Si verifica una riduzione di viscosità durante la lavorazione ed un ulteriore incremento durante la fase di riposo. La soluzione è nel tempo dedicato alla ristrutturazione della soluzione/emulsione finale che dipende dalla natura dell'agente tixotropo, dalla sua concentrazione nel veicolo e dall'intensità del sistema emulsionante.
Durante il processo di lavorazione, la preparazione dello shampoo al ketoconazolo si è rivelata più stabile a pH più alti (6,5-7,5) ed alla temperatura di 30°C. Inoltre, la presenza del modificatore reologico è risultata importante per la stabilità del ketoconazolo. Le formulazioni contenenti 0,1% in peso di NaCl hanno dimostrato di essere più stabili e di mantenere una densità ideale.
Lo stato reologico dei sistemi risulta essere il più importante tra i sistemi fisici perche influenza profondamente non soltanto la stabilità fisica del prodotto finito, ma anche l'aspetto, la qualità ed il relativo modo d'uso. La variazione dei parametri reologico e delle temperature può provocare la formazione di sistemi poco stabili nel tempo, legati anche al loro pH.
In conclusione, tenendo presenti tutti questi parametri, la vita media del prodotto formulato con ketoconazolo è risultata stabile per 18 mesi.

INTRODUCTION

Ketoconazole, an antifungal agent, is an imidazole derivative structurally related to miconazole and clotrimazole. It possesses some antibacterial activity (1,2,3). Ketoconazole is a weak base with two pKa values 6.51 and 2.94 (Fig.1).

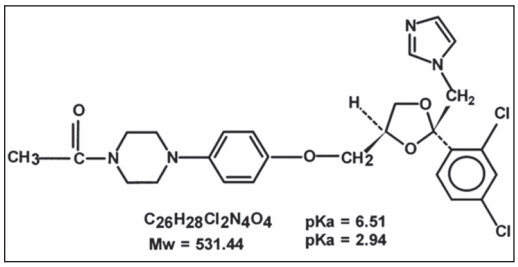

Fig. 1 *Chemical and Molecular Structure of Ketoconazole.*

It acts as antifungal by interfering with the fungal synthesis pathway of ergosterol, a constituent of cell membranes, in susceptible organisms. It has activity against yeast specially candida and cryptococcus spp., fungi, and dermatophytes (3,4,5). In animal studies, topical ketoconazole was found to be very effective on the treatment of skin dermatophytosis, skin and vaginal candidiasis (4,6). Ketoconazole is marketed in different dosage forms and routes of administration such as, orally (i.e. tablets) and topically (i.e. creams, gels, lotions and shampoos) (1,2). In fact, different topical formulations of ketoconazole have been introduced and presented in the market for antidandruff purposes with short-term stability.

Product stability is an important issue in pharmaceutical industry. A thorough knowledge of the chemical and physical stability of drugs and dosage forms is critical in the development and evaluation of pharmaceuticals. Drug products are complex mixtures of drug and excipients, and, as such, their chemical and physical stability kinetics are complex. The chemical and physical stability of these complex dosage forms, starting with pre-formulation studies and continuing through to studies of the final products, including the role of packaging. Many drugs are susceptible to physical and chemical degradation, especially in aqueous solution. Ketoconazole is vulnerable and extremely sensitive to degradation. Oxidation and hydrolysis are the most degradation pathways affecting its stability. Due to the delicate nature of ketoconazole, especially in aqueous formulations; further investigations are needed to improve the stability of ketoconazole in aqueous formulations, and elucidate the physicochemical parameters affecting its stability.

Rheology is the science of flow and deformation of matter, and describes the interrelation between force, deformation and time. In turn, fluid rheology is the consistency of different products, normally by the two components viscosity and elasticity. By viscosity is usually meant resistance to flow or thickness, and by elasticity usually stickiness or structure. Rheological behavior plays an important role on the stability of a pharmaceutical product, and determines its flow behavior and storage condition (7).

The elementary rheological properties of most products could be described in terms of shear rate and stress. In our study, the behavior of the system possessed a yield point (minimum shear stress for flow to commence) and time dependency. A reduction in viscosity occurred on shearing with time and rebuilt of viscosity on standing. During mixing, the yield stress was exceeded, and the product flowed. The structure began to re-form after cessation of shear. However, it did not re-form immediately. It took time to rebuild the order or structure that existed when the system was at rest. The key was the rate at which the structure was rebuilt (8). This was a function of the nature of the thixotropic agent (NaCl), its concentration in the aqueous medium, and the amount of agitation before use. The usage of surfactant-thickening agents' complex has shown the most stable thixotropic

system. A blend of ionic and non-ionic surfactants was preferable. The choice of surfactants was based on physicochemical characteristics of each surfactants, hydrophilic-lipophilic balance of non-ionic surfactant, critical micelle concentration of ionic surfactants; in addition to, stability and hydrodynamic of the molecules at the interfacial phase, interfacial film formation kinetics, and interactions between molecules on the surface (9).

In conclusion, the aim of this study was to assess the effect of formulation parameters such as, pH, the amount of the rheology modifier and temperature on the stability of ketoconazole in aqueous solution.

MATERIALS AND METHODS

Materials

Ketoconazole was purchased from Sigma-Aldrich, USA. Sodium lauryl ether sulphate, disodium mono lauryl ether sulfosuccinate, PEG-120 methyl glucose dioleate, coconut fatty acid diethanolamide, imidurea, hydrochloric acid, sodium hydroxide and sodium chloride were kindly supplied by Sigma Pharmaceutical Co., Egypt. All other reagents used were of analytical grade.

Method of Preparation

A vessel was charged with purified water, sodium lauryl ether sulphate and concentrated hydrochloric acid, then mixed using a mechanical overhead stirrer (IKA® RW 20 digital, Staufen, Germany) at speed 36 rpm/min. for 10 mins. Ketoconazole was added and homogenized using high-speed homogenizer (IKA® T-25 ULTRA-TURRAX Digital, Staufen, Germany) at speed 200 rpm/min. for 20 mins, followed by mixing at speed 60 rpm/min. for 30 mins.

Disodium mono lauryl ether sulfosuccinate was subsequently added and mixed at speed 60 rpm/min. for 15 mins. Temperature was controlled in all preparation steps to be 25 °C ± 2. PEG-120 methyl glucose dioleate and coconut fatty acid diethanolamide were gradually added and mixed at speed 36 rpm/min. for 10 mins. Imidurea solution, colorants and fragrances were subsequently added and mixed at speed 60 rpm/min. for 10 mins. pH was adjusted to 6.5 ± 0.5 by using sodium hydroxide and mixed at speed 80 rpm/min. for 15 mins.

Finally, sodium chloride solution was portionwisely added and homogenized at speed 200 rpm/min. for 5 mins, followed by mixing at speed 80 rpm/min. for 30 mins. The amount of sodium chloride (0.1 gm%) was necessary to obtain a stable thixotropic system.

PHYSICAL, CHEMICAL, VISCOSIMETRY AND RHEOLOGICAL CHARACTERIZATION

Physical Appearance and Visual Inspection

The prepared shampoo were evaluated in terms of clarity, transparency, homogeneity, foaming producing ability, fluidity, color intensity and stability.

Determination of pH

pH was measured at 25 °C ± 2 °C, by using pH meter (Digital pH meter, 827pHlab, Metrohm, Switzerland).

Determination of the Percentage of Solid Contents

Four grams of the prepared shampoo were placed in a dry clean previously weighted evaporating dish. The dish and shampoo were weighed

to confirm the exact weight of the shampoo. The evaporating dish with the prepared shampoo was placed on the hot plate until the liquid portion was totally evaporated and solids were precipitated. The percent weight of solids after drying was calculated.

Measurement of Surface Tension

The stalagmometric method (10) was used for measuring the surface tension of the prepared shampoo. A dry stalagmometer was filled up to the mark with 10 gm% of the prepared shampoo diluted with purified water.

Diluted shampoo were released to the weighting bottle and number of drops were calculated according to the following equation:

$$R_2 = [(W_3-W_1)n_1/(W_2-W_1)n_2] \times R_1$$

Where W_1 is the weight of empty beaker, W_2 is the weight of beaker with purified water, W_3 is the weight of beaker with diluted shampoo, n_1 is the number of drops of distilled purified water, n_2 is number of drops of diluted shampoo, R_1 is surface tension of purified water and R_2 is surface tension of diluted shampoo.

Dirt Dispersion

Two drops of the prepared shampoo and one drop of India ink were added in a test tube containing 10 ml of purified water, stoppered well and allowed to shake for ten times. The amount of ink in the foam was evaluated as none (N), light (L), moderate (M), or heavy (H) (11).

Foamability and Foaming Stability

Cylinder shake method was used for determining foaming ability of the prepared shampoo. 50 ml of 1% of the prepared shampoo was placed in a hand-closed 250 ml graduated cylinder and shaken for 10 times.

The total volume of the foam content after shaking for 1 min. was recorded. Foam stability was evaluated by shaking the volume of foam at 1 min. intervals for 4 mins (12).

Viscosimetry and Rheological Study

The viscosity of the prepared shampoo was determined at 25 °C ± 2 using Brookfield Viscometer (DV-E Viscometer, Brookfield Engineering Laboratories Inc., USA) rotated at 20 rpm, using spindle 64 and torque > 50%. The temperature and sample container's size was kept constants during measurements.

Stability Studies

Stability studies of the prepared shampoo were carried out as per ICH guidelines (13). Shampoo samples were stored at 30 °C ± 2 °C / 65% RH ± 5% RH in stability chambers for a period of 18 months. Samples were withdrawn at regular interval 3, 6, 9, 12 and 18 months for physical and chemical stability evaluation.

Analytical Method for Chemical Stability Evaluation

A stability indicating analytical method was developed for determination of ketoconazole in the aqueous shampoo.

The HPLC method was specified to separate ketoconazole, using octasilyl (C8) stationary phase column (4.6 mm x 150 mm x 5 μm) and a mobile phase composed of filtered a degassed mixture of 0.025 M phosphate buffer solution and acetonitrile in ratio of 60:40. pH was adjusted to 4.0 ± 0.5 using phosphoric acid or sodium hydroxide. Flow rate was 1.0 ml/min. UV detection was at wavelength 223 nm.

The method was linear over the range 60–140

μg/mL with R^2=0.9995. Accuracy and precision were acceptable with %RSD < 1.0%. The method was found to be specific for ketoconazole by separating ketoconazole from its degradation byproducts formed under acid and alkaline stress conditions (Fig. 2).

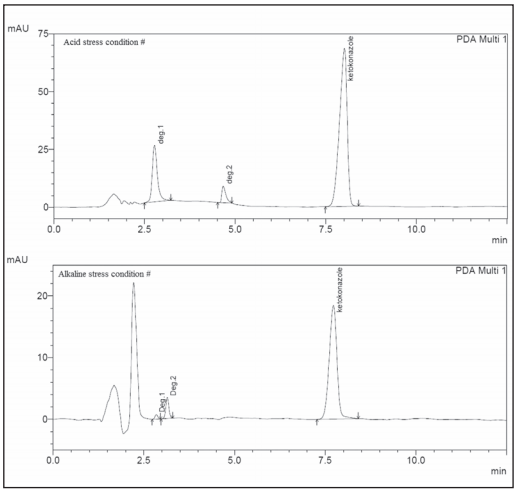

Fig. 2 *HPLC Method for Determination and Separation of Ketoconazole.*

RESULTS AND DISCUSSION

Evaluation of the Prepared Ketoconazole Shampoo

Physical Appearance and Visual Inspection

The prepared shampoo was evaluated for the physical characteristics such as clarity, transparency, homogeneity, foaming producing ability, fluidity, color intensity and stability. Our prepared shampoo was clear, transparent, homogenous, semi-viscous aqueous solution, pink in color and had characteristic odor (Table I). No significance changes were observed in physical evaluation during stability, indicating the high stability index of the prepared shampoo.

Effect of pH on Ketoconazole Stability

Most shampoos are formulated as either neutral or slightly acidic to minimize the damage to the hair. The pH of shampoo helps in minimizing irritation to the eyes, prevents swelling, promotes tightening of the scales, enhances the qualities of hair and maintain the hair, and maintains ecological balance of the scalp (14). pH-stability studies of 2% ketoconazole were conducted as per ICH guidelines (13) for 18 months at 30 °C ± 2 °C / 65% RH ± 5% RH and results are shown in (Table II). The most stable formula was at pH 6.5 as shown in (Fig. 3).

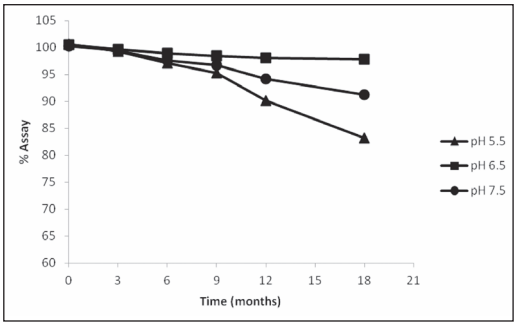

Fig. 3 *Effect of pH on % Assay of Ketoconazole during Stability.*

The Percentage of Solid Contents

In fact, if the shampoo has too many solid contents; it will not be easy to be applied and wash out from the hair. Good shampoos usually have 20 to 30% of solid contents (15). If it has low percent of solid contents; it will be too watery and wash away quickly. In turn, if it has too many solids; it will be hard to wash out. The percent of solid contents of the prepared shampoo was from 20–24% (i.e. easily washable) as shown in (Table I).

TABLE I

Physicochemical Evaluation of the Prepared Shampoo during Stability.

Parameters	0 month	6 month	12 month
Physical Appearance and Visual Inspection	Clear, Transparent, Homogenous, Pink in color	Clear, Transparent, Homogenous, Pink in color	Clear, Transparent, Homogenous, Dark Pink in color
pH	6.50±0.03	6.48±0.04	6.47±0.08
Solid Contents (%)	23.12±0.24	22.56±0.18	21.08±0.30
Surface Tension Measurement (dy./cm)	34.12±0.24	33.19±0.22	33.85±0.26
Foamability and Foam Stability (ml)	Good Foaming Foam Type: Compact, Condense Foam Volume: 86 ml	Good Foaming Foam Type: Small, Condense Foam Volume 84 ml	Good Foaming Foam Type: Small, Condense Foam Volume 90 ml
Viscosity (cp)	4700	4656	4536
% Assay of Ketoconazole	100.6±0.16	98.7±0.25	97.2±0.48
Results are mean ± SD (n = 3)			

TABLE II

Effect of pH on % Assay of Ketoconazole during Stability.

Time	pH Values		
(months)	5.5	6.5	7.5
0	100.6	100.5	100.3
3	99.3	99.7	99.4
6	97.1	98.9	97.6
9	95.3	98.4	96.7
12	90.2	98.1	94.2
18	83.2	97.8	91.2

Measurement of Surface Tension

It is an indication of the amount of surfactant required to reduce the surface tension of the shampoo. The well formulated shampoo should be able to reduce the surface tension of purified water to 40 dynes/cm (16). Reduction of the surface tension is one of the mechanisms applied to detergency. In our study, the prepared shampoo showed a good reduction in surface tension to 34.12 dynes/ cm which indicated its good cleaning and detergent actions (Table I).

Dirt Dispersion

Dirt dispersion is one of the most important parameters for evaluating the cleansing action of the shampoo. When shampoo causes the ink to concentrate in the foam, it will be difficult to wash out, then deposit on the hair. In this case, it is considered of poor quality. In our study, the prepared shampoo showed a good quality (i.e. none (N) in accordance to cleaning ability) (11).

Foamability and Foaming Stability

Foaming is an important parameter in evaluating the efficacy of the shampoo for customers. Generally, foaming of the shampoo is a result of the activity of surfactants. In our study, the prepared shampoo generated a compact, condensed and stable foam volume 86 ml. It persisted for 5 mins indicating that it has good stability (12). The higher foaming property of the prepared shampoo may result from the successful blend of non-ionic surfactants with an ionic surfactant to achieve a high HLB value (Table I).

Effect of Sodium Chloride (NaCl) Concentration on Ketoconazole Stability

Decreasing the amount of rheology modifier (NaCl) from 0.8 gm% to 0.1 gm% showed a great improvement in the stability of ketoconazole shampoo in aqueous formulations, particularly at pH 6.5. The effect of NaCl concentrations on the shelf life were compared as shown in (Table III). Results showed that formulations containing 0.8 gm% NaCl had a shorter shelf life than formulations containing 0.1 gm% NaCl that have better stability and rheological behavior (Fig. 4a and 4b).

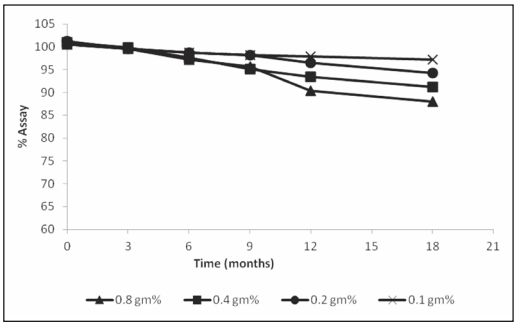

Fig. 4a *Effect of Nacl Concentration on % Assay of Ketoconazole during Stability.*

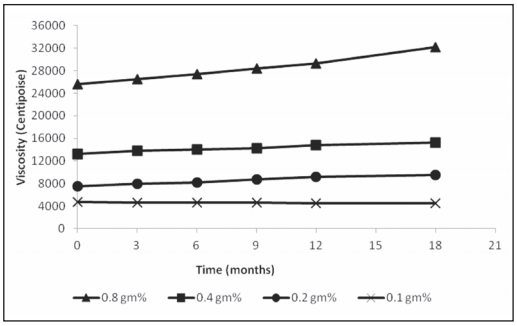

Fig. 4b *Effect of Nacl Concentration on Viscosity of Ketoconazole during Stability.*

TABLE III

Effect of Nacl Concentration on Stability and Viscosity of Ketoconazole.

Time (months)	Concentration of NaCl at pH 6.5							
	0.8 gm%		0.4 gm%		0.2 gm%		0.1 gm%	
	P	H	P	η	P	η	P	η
0	100.5	25590	100.9	13265	101.2	75.23	100.6	4700
3	99.5	26478	99.8	13825	99.6	7950	99.6	4680
6	97.2	27450	97.6	13995	98.7	8251	98.7	4656
9	95.6	28380	95.1	14256	98.2	8781	98.2	4602
12	90.3	29256	93.4	14835	96.5	9231	97.9	4559
18	87.9	32231	91.2	15235	94.2	9535	97.2	4536

P is % assay of ketoconazole; η is viscosity (Centipoise)

Effect of Temperature during Preparation on the Stability and Viscosity of Ketoconazole

Temperature is as key factor in rheology building systems. The effect of temperature on the viscosity of ketoconazole shampoo was observed during the preparation. Results indicated that while during preparation, temperature should not exceed 30°C for obtaining an ideal thixotropic system and to maintain the stability of ketoconazole.

CONCLUSION

The rheology of dispersed systems is among the most important of their physical properties, which influences not only the physical stability of the systems, but often also profoundly affects the performance features, their quality, and their utility. In dealing with rheological parameters, and in case of thixotropic systems, long shearing times should be avoided.

In turn, short shearing times at different time intervals are necessary to obtain a thixotropic system. Temperature changes can also produce spurious results, since shear stress at a constant shear rate, is also a function of temperature. It is important to consider the optimum pH for the product, since the properties of the product, particularly rheology, can be quite dependent on the pH of the system. Ketoconazole was found to undergo less hydrolysis at mild acidic pH and temperature below 30°C. Furthermore, the viscosity of the prepared shampoo was stable at the same pH and exhibited thixotrophy. Decreasing the amount of rheology modifier 0.1% gm was effective to maintain the rheological behavior of the system and stability of ketoconazole during stability. pH of the final formulation was concluded to be pH 6.5 that have been shown good physical and chemical characteristics during long-term stability studies.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to this work

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests concerning the publication of this paper.

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