

Effect of Carbopol 934 and 940 on Fluconazole Release from Topical Gel Formulation: A Factorial Approach.

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Abstract

The aim of present research is to investigate the effect of various carbopols (934 and 940) on drug release from fluconazole gel formulation developed for topical application. Fluconazole (FCZ) is the first of a new subclass of synthetic triazole antifungal agent and it is commonly used in treatment of most fungal infections. It is available as topical powder, tablets and sterile solutions for intravenous use. In present research, full factorial design has been applied to study the effect of type of carbopols on quality attributes of FCZ gel formulation. FCZ topical gel formulation batches (F1 to F9) have been formulated as per runs obtained in factorial design and further evaluated for pH, drug content, viscosity, *invitro* drug release kinetics, etc. Fourier transform infrared spectroscopy (FTIR) study indicated no any chemical or structural changes in FCZ during formulation studies. Drug diffusion studies have shown time required for 90% of total drug release ($t_{90\%}$) from all formulations in between 28.7 ± 2.3 to 208.4 ± 3.9 min. Batch F9 showed maximum $t_{90\%}$ attributed to highest viscosity resulted in slower drug release amongst all batches (F1-F11), however, vice versa results have been observed with batch F1. These results were in accordance with concept of inverse relationship between drug release and viscosity of formulation. It has been observed that drug release from all gel formulation batches obeyed korsmeyer-peppas model. Permeation of drug through formed gel depends on viscosity and pH of gel. From present study it can be concluded that topical gel formulations of FCZ with desirable drug diffusion pattern can be successfully prepared by using carbopol 934 and carbopol 940, where both carbopols have extended the drug release at their respective higher concentrations.

Key Words

Topical gel, fluconazole, carbopol, permeability, drug diffusion.

Introduction

FCZ is the first of a new subclass of synthetic triazole antifungal agents. It is available as tablets or powder (suspension) for oral administration, and as a sterile solution for intravenous use. Additionally, FCZ is one of the commonly used anti fungal agent for most kinds of fungal infections including superficial and invasive fungal infections. In most of cases topical application of FCZ is the preferred route for treatment of such fungal infections. Presently, numerous dosage forms are available generally ingested by oral or parenteral route. Oral route is widely used, but it follows GI-side effects, first-pass metabolism and reduces bioavailability of the drug.

However, parenteral preparations are better than oral preparations as it avoid gastric metabolism and first pass effect, but formulation of parenteral preparation is costly as it requires well equipped laboratory with aseptic area. Consequently, as a replacement topical gel formulations can be used, which gives better bioavailability, avoid gastric irritation, metabolism in liver and also, because of local application delivers the drug at site of action. The transdermal entry of drug in to systemic circulation at a desired rate can be achieved by using a suitable rate controlling membrane and a drug reservoir. Gels are semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix (consisting of natural or synthetic gums) in which a high degree of physical (or sometimes chemical) cross-linking has been introduced. Some of these systems are as clear as water in appearance,

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visually aesthetically pleasing as in gelatin deserts and other are turbid. The clarity range of gels varies from clear to a whitish translucent. Gels are becoming more popular due to resistance to physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of the applied area, controlling drug release with avoidance of first pass metabolism, convenient and easy to apply. Additionally, it avoids the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time etc. Moreover, achievement of efficacy with lower total daily dosage of drug by continuous drug input and reduced fluctuations in drug levels, inter- and inpatient variations, ability to easily terminate the medications, when needed are some advantages offered by gel formulations. A relatively large area of application in comparison with buccal or nasal cavity and ability to deliver drug more selectively to a specific site with avoidance of gastro-intestinal incompatibility by gel formulations are also additional advantages to be considered.

Materials and Methods

Materials

Fluconazole was kindly gifted by Cipla pharmaceuticals ltd (Mumbai, India); Carbopol 934 and 940 were obtained from Loba chemicals (Mumbai, India) as a kind gift sample. Triethanolamine and methyl paraben were gifted by SD Fine chemicals (Mumbai, India). All other chemicals used were of analytical grade.

Methods

Preformulation Study

FTIR studies were performed to investigate the compatibility between FCZ, carbopols and other additives.

Factorial Design

A 3² factorial design was applied to study the effect of carbopol grades on quality attributes of FCZ gel formulations. In present study, carbopol 934 and carbopol 940 have been selected as independent variables. Actual and coded levels of both carbopols in design have been mentioned in Table 1. Mathematical modeling was carried out by using basic second-order 3 level full factorial design to estimate dependant variables.

Where, y is estimate of response (dependent variable); X₁ and X₂ are independent variables as content of carbopol 934 and 940 respectively; β₀ is overall mean response; β_{1,2,11,22,12} are regression model coefficients.

Formulation of Gel

As per runs obtained in 3² design (Table 2), total 9 gel formulation batches have been prepared by method described here. Additionally, separate gel formulation batches containing only carbopol 934 (F10) and carbopol 940 (F11) have been prepared to study the individual effect of two polymers. As per compositions given in Table 2, weighed quantities of carbopol 934 and carbopol 940 were allowed to soak for 24 hours in 100 ml of distilled water. FCZ was dissolved in suitable quantity of ethanol, which also acts as stabilizer and mixed with above soaked carbopol solution. Subsequently, a suitable quantity of triethanolamine was added to above drug-carbopol solution until gel with appropriate strength and transparency is formed and if required, further added to adjust the pH of gel near to the pH of skin (5.6). Formed gel formulations were further evaluated for following parameters.

Appearance

All prepared gel formulations have been observed for their visual appearance, such as transparency, colour, texture, grittiness, greasiness, stickiness, smoothness, stiffness and tackiness.

pH

The pH of the all gel formulation batches was measured by using pH meter (Mumbai, Maharashtra, India). Accurately measured quantity of gel (5 ml) was dissolved in 50 ml distilled water and the pH meter probe immersed into it. The observed pH values were recorded for all batches (F1-F11) in triplicates.

Viscosity

Viscosity of prepared gel formulations (F1-F11) was calculated by using Brookfield viscometer (Brookfield RVDV-II+P, Mumbai, Maharashtra, India) using spindle number S6. Sample holder of the Brookfield viscometer was filled with the gel sample, and then spindle was inserted into sample holder. The spindle was rotated at 100 rpm. All the rheological studies were carried out at room temperature. A viscosity measurement was done in triplicate.

$$y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{11}X_1X_1 + \beta_{22}X_2X_2 + \beta_{12}X_1X_2 \dots\dots\dots (1)$$

Drug Content

For determination of drug content, an accurately weighed quantity (1 gm) of gel equivalent to 5 mg of FCZ was dissolved in 100 ml of distilled water and analyzed by UV-Vis Spectrophotometer at 266 nm^[18] for drug content. Drug content of all gel formulation batches (F1-F11) were analysed in triplicate (Table 3).

Fourier Transform Infrared Spectroscopy

FTIR studies were carried out for drug, carbopol 934 and 940 alone, in combination and in final gel formulation (Figure 1).

In-vitro Drug Release Kinetics

In-vitro drug diffusion study was performed using Franz diffusion cell apparatus (Orchid Scientifics, Nasik, Maharashtra, India) in triplicate for every batch (F1-F11). Diffusion medium used was 25 ml of pH 7.4 phosphate buffer IP (Indian Pharmacopoeia) throughout the diffusion study maintained at 37 ± 0.5 °C^[17]. Magnetic beads were used to provide the uniform mixing of diffused drug into the receiver compartment. An accurately weighed quantity of gel (150 mg) equivalent to 0.75 mg of FCZ was taken for diffusion study. Weighed gel samples were separated from diffusion media using cellophane membrane and observed for drug diffusion kinetics. At predetermined time intervals, aliquots of 2 ml were withdrawn and analyzed by UV-Vis Spectrophotometer at 266 nm^[18]. Same amount of fresh phosphate buffer IP, pH 7.4 was used to replace the amount withdrawn from diffusion media.

Results and Discussion

As per runs obtained in 3² design, total 9 gel formulation batches have been prepared and evaluated to study the effect of carbopols on quality attributes of prepared gel.

Appearance

All FCZ gel formulation batches (F1-F11) have shown white opaque to translucent appearance with smooth and homogenous texture (Table 3).

pH

pH for all batches (F1-F11) was maintained near to pH of skin (5.6) with use of triethanolamine in small proportions. All batches have shown pH in range of 5.0 ± 0.19 to 5.9 ± 0.25 . Adjustment of gel formulations pH nearby to skin pH will avoid skin irritation and other related problems (Table 3).

Drug content

The drug content for all batches was found in narrow range of 97.45 ± 2.58 to 99.54 ± 4.62 (Table 3). Type and concentration of carbopol have shown profound effect on FCZ content of gel formulation batches. FCZ content found to be highest in F9 where both carbopol 934 and 940 were present at their highest concentrations leading to higher viscosity and entrapment of FCZ in gel structure.

From response surface plot (Figure 3), it has been clearly revealed that carbopol 940 shows predominant effect over carbopol 934, where higher drug content was observed at extreme contents of carbopol 940. Regression analysis data have shown significant effect of only carbopol 940 on drug content of gel.

A reduced model for % drug content is given as,

$$\% \text{ Drug Content} = 97.34 + 0.27X_2 + 1.29X_2X_2 \dots \dots \dots (2)$$

Viscosity

Viscosity holds a major contribution in deciding the drug content and its release from prepared gel formulation. Carbopol 934 and 940 have shown concentration dependent effect on viscosity and in turn on drug release pattern (Table 3). Batch F1 and F9 have shown least and highest viscosity amongst all batches, respectively attributed to carbopol contents. Highest viscosity of batch F9 resulted into extended drug release ($t_{90\%} = 208.4 \pm 3.9$) and lowest viscosity of batch F1 into faster rate of drug release ($t_{90\%} = 29.0 \pm 1.9$). This reveals that viscosity was the major factor controlling the release of FCZ from gel formulations.

Fourier Transform Infrared Spectroscopy

FTIR studies (Figure 1) revealed that major peaks of FCZ were retained in gel formulations also and hence, there were no any structural or chemical changes in FCZ before and after the formulation into gel. This indicates no any chemical interaction between drug, polymer and other additives used in formulation.

In-vitro Drug Release Kinetics

In-vitro drug release kinetic studies have shown Korsmeyer-Peppas best model fit for all batches (F1-F11). A plot of cumulative percent drug release against time (min) shows drug release pattern (flux) from all batches (Figure 2). It has been observed that contents of carbopol 934 and 940 contributed in

deciding gel viscosity and in turn drug release pattern from prepared gel formulations (Table 3). Time required for 90% of total drug release ($t_{90\%}$) ranges from 28.7 ± 2.3 to 208.4 ± 3.9 mins for all the batches (F1-F11). Batch F9 have shown highest $t_{90\%}$ (208.4 ± 3.9 min) attributed to its highest viscosity amongst all the batches, however, vice versa results have been observed for batch F1 (28.7 ± 2.3 min). It has been observed that carbopol 934 have shown profound effect in presence of carbopol 940 in extending FCZ release from gel formulations (F1, F4 and F7; F2, F5 and F8; F3, F6 and F9). However, individually carbopol 940 have shown profound effect over carbopol 934 in extending FCZ release from gel formulations (F10 and F11). Therefore, simultaneous use of both grades of carbopol (934 and 940) in formulation of gel would result in extended drug release for longer time with reduction in dose and dose dependent toxicity if any.

Response surface plot (Figure 4) has shown higher and lower $t_{90\%}$ at extreme carbopol contents where extended drug release was clearly seen towards higher carbopol contents. Regression analysis data have shown significant effect of both carbopols (934 and 940) on $t_{90\%}$, where carbopol 934 have shown predominant effect over carbopol 940.

A reduced model for $t_{90\%}$ is given as,

$$t_{90\%} = 87.31 + 58.07X_1 + 45.48X_2 + 31.4X_1X_2, \dots \dots \dots (3)$$

Conclusion

From present investigation it can be concluded that FCZ topical gel formulation can be successfully formulated by using combination of carbopol 934 and carbopol 940. Selection of carbopol type and content is the major key factor in deciding viscosity and in turn FCZ release from gel. Therefore, both grades of carbopol (934 and 940) can be preferred in extending drug release where reduced dose of drug/s is favoured. However, if desired carbopol 940 can be used alone for extending drug release but not as much as used in combination with carbopol 934.

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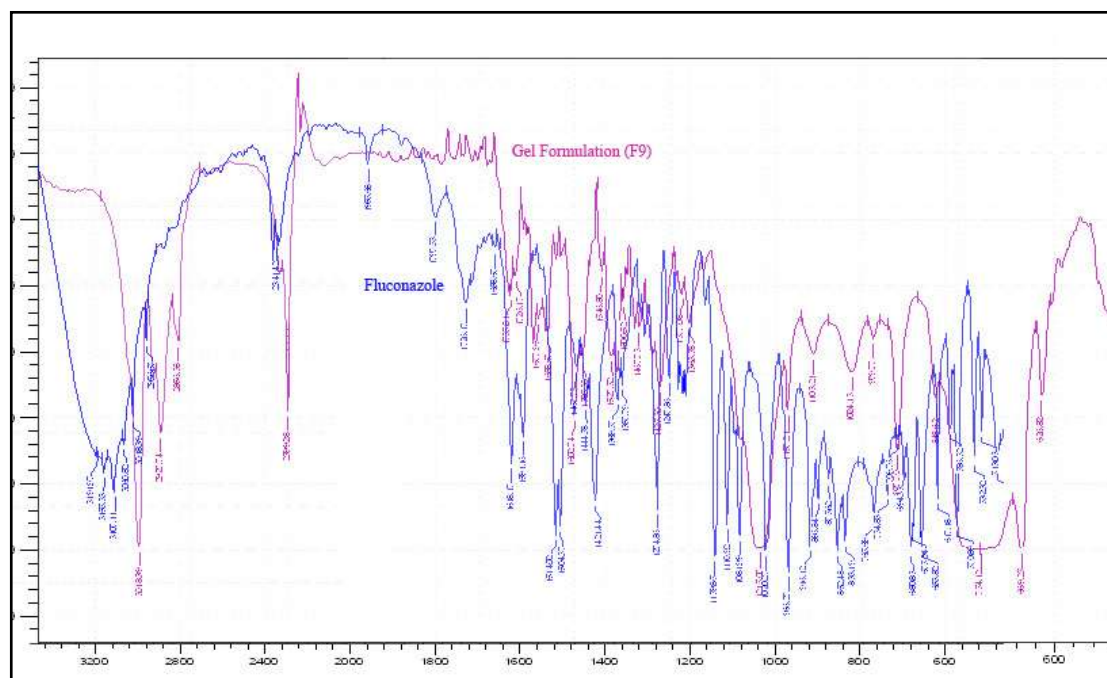


Fig. 1: FTIR in final gel formulation.

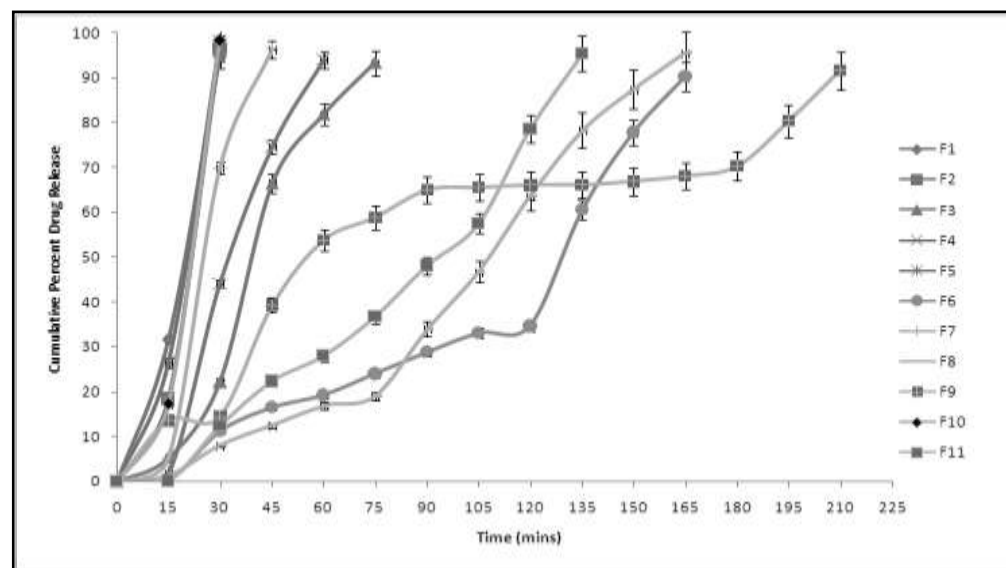


Fig. 2: Cumulative percent drug release.

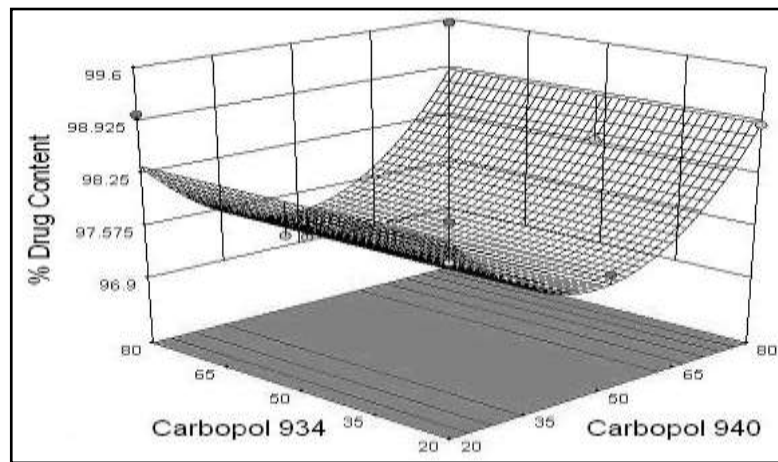


Fig. 3: Response surface plot.

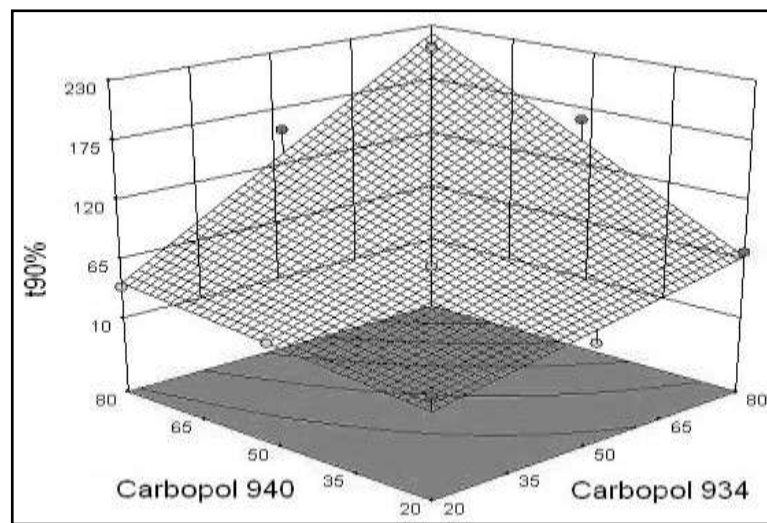


Fig. 3: Response surface plot.

Table 1. Actual and coded values of independent variables.

Independent variables	Coded values			Actual values (mg)		
	-1	0	+1	20	50	80
Carbopol 934 (X ₁)	-1	0	+1	20	50	80
Carbopol 940 (X ₂)	-1	0	+1	20	50	80

Table 2. Composition of FCZ gel formulation.

Formulation Batch Code	Carbopol 934 (mg)	Carbopol 940 (mg)	Water (ml)	FCZ (mg)	Ethanol (ml)	Triethanolamine (ml)
F1	20	20	100	75	3	q.s.
F2	50	20	100	75	3	q.s.
F3	80	20	100	75	3	q.s.
F4	20	50	100	75	3	q.s.
F5	50	50	100	75	3	q.s.
F6	80	50	100	75	3	q.s.
F7	20	80	100	75	3	q.s.
F8	50	80	100	75	3	q.s.
F9	80	80	100	75	3	q.s.
F10	100	-	100	75	3	q.s.
F11	-	100	100	75	3	q.s.

Table 3. Evaluation parameters for FCZ of gel formulations*.

Batch code	Appearance	pH	Percent drug content	Viscosity at 100 rpm (cps)	t_{90%} (min)	Model fit
F1	White opaque	5.2 ± 0.21	98.12 ± 3.36	very less	28.7 ± 2.3	Korsmeyer-Peppas
F2	White opaque	5.0 ± 0.19	97.94 ± 2.58	30 ± 2	29.1 ± 2.2	Korsmeyer-Peppas
F3	White opaque	5.5 ± 0.45	99.01 ± 2.95	125 ± 6	72.2 ± 4.1	Korsmeyer-Peppas
F4	Creamish white	5.0 ± 0.25	97.45 ± 2.78	9 ± 2	29.0 ± 1.9	Korsmeyer-Peppas
F5	Opaque	5.7 ± 0.63	97.63 ± 5.51	56 ± 3	59.1 ± 2.1	Korsmeyer-Peppas
F6	Translucent	5.4 ± 0.41	96.94 ± 4.87	664 ± 12	164.8 ± 4.8	Korsmeyer-Peppas
F7	White opaque	5.6 ± 0.34	98.88 ± 2.65	38 ± 4	39.3 ± 1.5	Korsmeyer-Peppas
F8	Translucent	5.8 ± 0.48	98.30 ± 3.84	280 ± 8	155.2 ± 2.9	Korsmeyer-Peppas
F9	Translucent	5.9 ± 0.25	99.54 ± 4.62	3200 ± 18	208.4 ± 3.9	Korsmeyer-Peppas
F10	White opaque	5.4 ± 0.57	99.22 ± 3.01	27 ± 2	29.0 ± 2.4	Korsmeyer-Peppas
F11	Translucent	5.6 ± 0.62	98.15 ± 2.96	230 ± 5	131.3 ± 3.1	Korsmeyer-Peppas

* All values indicate Average ± SD (n = 3).
