



Formulation and Evaluation Thermoreversible Gel of Antifungal Agent for Treatment of Vaginal Infection

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Authors' contributions

This work was carried out in collaboration among all authors. Author RLJ designed the study. Author MVP performed the laboratory research work. Author SNS wrote the manuscript and literature survey and Author SNB performed the literature survey. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim this research work is to formulate and evaluate thermoreversible gel of antifungal agent Clotrimazole for treatment of vaginal infection.

Place and Duration of Study: Department of Biopharmaceutics, Government College of Pharmacy, Karad, Maharashtra, India, between June 2009 and July 2010.

Methodology: Different Formulations of thermoreversible gel of antifungal agent Clotrimazole were prepared by using various concentrations of ethanol, PEG 400, sodium dodecyl sulphate, polycarbophil and pluronic F 127 and pluronic F 68. The gel formulations were subjected for evaluation on the basis of rheological behaviour, mucoadhesive behaviour, *in-vitro* performance.

Results: The results indicate that Polymers such as polycarbophil, PEG- 400 in various concentrations to prepare formulations were found to release drug for period over 12 hrs. Without getting dislodged. The formulations have satisfactory rheological behavior and their diffusion profile is comparable to the marketed gel formulation. Significant difference was observed in the rheological behavior of formulations. Gel strength, spreadability, mucoadhesive strength of formulation B and C were desirable. Drug diffusion of formulation B and C were 95.2% release after

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11 hrs 98.5% release after 11 hrs, respectively which was good as compared to marketed formulation showing drug diffusion of 102.2% after 10 hrs.

Conclusion: On basis of the results we concluded that developed thermoreversible gel of Clotrimazole will be better alternative to conventional dosage form Clotrimazole & will improve patient compliance.

Keywords: Antifungal; pluronic F-127; clotrimazole; thermoreversible gel; vaginal infection; spreadability.

1. INTRODUCTION

Over the last decade, it is apparent that the human vagina remains to be a relatively unexplored route of drug delivery despite its potential as a non-invasive route of drug administration. The presence of dense network of blood vessels has made the vagina an excellent route of drug delivery for both systemic and local effect [1]. Vaginal drug delivery systems include a large variety of pharmaceutical forms such as semi-solids, tablets, capsules, Pessaries, liquid preparations, vaginal films, vaginal rings, foams, and tampons etc. Most widely used semi-solid preparations for vaginal drug delivery include creams, ointments, and gels [2]. Gels are semi-solid systems comprising small amounts of solid, dispersed in relatively large amounts of liquid, yet possessing more solid-like character. These systems form a three-dimensional, polymeric matrix in which a high degree of physical reticulation has been comprised. Gels can present several advantages over other vaginal drug delivery systems such as higher bioavailability, safety, versatility, and economical savings. Fungal infections are very common in human beings, especially in the tropical region [3].

Thermoreversible gels are systems capable of gelling in response to temperature change, generally from ambient to body temperature. Reversible gels refer to those that have the capacity to make, break and modify the bonds responsible for holding the network together. Pluronics are block copolymers which are used as thermoreversible gelling agents. Pluronic F-127 (Poloxamer 407) is a thermoreversible polymer. This characteristic has allowed pluronic F-127 to be used as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes [3]. Classes of excipient usually added to vaginal gels include gelling agents, humectants, preservatives and vehicles. Clinical usage and potential of vaginal gels are vaginal gels as

microbicides, vaginal gels as contraceptives and vaginal gels as labour inducers.

Incidence of *Candida albicans vaginitis* has been increasing since a significant number of women suffer from acute episodes and recurrent infection may frequently occur after therapy. From such a perspective, topical treatment of *Candida vaginitis* could be a rational choice for management of localized infection, while systemic therapy could be limited to patients proven to be nonresponsive or intolerant to intravaginally administered. Currently available vaginal dosage forms (such as solutions, suspension, foams, tablets and rings) have limitations, such as leakage, messiness and low residence time, which contribute to poor subject or patient compliance. Attempts are being made to develop novel vaginal drug delivery systems to enable a prolonged intravaginal residence time for administered drugs. Clotrimazole is a broad spectrum antimycotic agent effective against pathogenic dermatophytes, yeasts and several species of *Candida*, *Trichophyton*, *Microsporium*, *Epidermophyton* and *Malassezia*. Clotrimazole is known to be very effective locally and causes no major side effects [4]. Clotrimazole is incorporated in thermoreversible gel formulation. These gels are systems capable of gelling in response to temperature. These in situ gelling liquid formulations can provide the necessary vaginal and cervical coverage as a result of their fluidity before gelation and prolonged retention owing to the formation of a mucoadhesive gel [2,5].

2. MATERIAL AND METHODS

2.1 Materials

The materials used in this work comprised of following chemicals like Clotrimazole, Pluronic F127, Pluronic F68, Ethanol, Isopropyl, alcohol, Polyethylene glycol 400, Polycarbophil, Sodium dodecyl sulphate, Citric acid, Disodium hydrogen orthophosphate, Benzalkonium chloride, Tween

80, Sodium phosphate and Potassium phosphate. All these chemicals procured from Local distributor ICPA, Mumbai.

2.2 Methods

2.2.1 Optimization of gelation temperature of plain gel

Weighed accurately ethanol, Polyethylene glycol 400, clotrimazole, benzalkonium chloride, pluronic F 127 and F 68. Added PEG 400 in ethanol and dissolved clotrimazole in this mixture. Added benzalkonium chloride, pluronic F 127 and F 68 to above mixture with continuous stirring. Made the volume with distilled water with continuous stirring. Kept the resulting mixture at 4°C overnight. to obtain clear liquid. Measured the gelation temperature using water bath and thermometer. 5 gm ethanol was sufficient for drug solubility, thus other batches were discarded.

2.2.2 Formulation thermoreversible clotrimazole vaginal gel

Weighed accurately ethanol, clotrimazole, PEG, sodium dodecyl sulphate, polycarbophil, pluronic F 127 and F 68. Added PEG 400 in ethanol/isopropyl alcohol combination and dissolved drug in it. Added sodium dodecyl sulphate, polycarbophil, pluronic F 127 and F 68 with continuous stirring. Made the volume with water with continuous stirring. Measured the gelation temperature using water bath and thermometer. As concentration of polycarbophil increases gelation temperature was decreased. Thus gelation temperature of formulation B and formulation C were decreased. Large concentration of PEG 400 and pluronic combination were further decreased gelation temperature. Thus gelation temperature of

formulation D was further decreased [6,7]. Different batches of Clotrimazole Gel are shown Table 1.

2.3 Characterization of Theroreversible Clotrimazole Gel

2.3.1 Spreadability test for clotrimazole gel

Spreadability of formulation was determined by the spreadability test apparatus. It consists of wooden block provided with two glass slides. Lower slide was fixed on wooden block and upper slide with one end was tied to glass slide and other end was tied to weight pan. A gel quantity 2.5 g was placed between two slides and 1000 g weight was placed over it for 5 minutes to press the sample to a uniform thickness. Weight 80 g was added to pan. The time (in seconds) required to separate the two slides was taken as a measure of spreadability. Shorter time interval to cover the distance of 7.5 cm. indicates better spreadability [8,9].

2.3.2 Gel strength

The gel strength was determined according to a previously adopted method. A sample of 50 gm of the vaginal gel was put in a 100 ml graduated cylinder and gelled in a thermostatically controlled water bath at 37°C. A weight of 35 g was then placed onto the gelled formulation. The gel strength, which is an indication for the viscosity of the vaginal gel at physiological temperature, was determined by the time in second the weight took to penetrate 5 cm down through the gel. A range of 10-50 seconds was accepted, because less than 10 seconds the vaginal gel leaked out from the vagina and more than 50 seconds it was difficult to administer the vaginal formulation [10,11].

Table 1. Formulation batches of clotrimazole gel

Formulation No.	Ethanol/Isopropyl alcohol (gm)	Clotrimazole (mg)	PEG 400 (gm)	Sodium dodecyl sulphate (mg)	Polycarbophil (mg)	PF127/PF68% w/w	Gelation temperature °C
A	4:1	250 mg	2 gm	25 mg	50 mg	23/7	34
B	4:1	250 mg	3 gm	25 mg	100 mg	23/7	32
C	4:1	250 mg	2 gm	25 mg	75 mg	25/5	31
D	4:1	250 mg	3 gm	50 mg	100 mg	23/7	30
E	4:1	250 mg	2 gm	100 mg	50 mg	25/5	33
F	4:1	250 mg	3 gm	75 mg	50 mg	25/5	32

2.3.3 Determination of the mucoadhesive strength

The mucoadhesive strength of vaginal gel was determined by means of the mucoadhesive force-measuring device, using cut from small intestine of sheep. The pieces of tissues were stored, frozen in sorenson's phosphate buffer pH 7.4 and thawed to room temperature before use. At the time of testing a section of tissue was secured, keeping the mucosal side out, onto each glass vial using a rubber band and an aluminium cap. The diameter of each exposed mucosal membrane was 1.1 cm. The vials with the mucosal membrane were stored at 37°C for 10 min. Next, one vial with a section of tissue was connected to the balance and the other vial was fixed on a height-adjustable pan. To the exposed tissue on this vial, a constant amount of 0.1 gm vaginal gel was applied. The height of the vial was adjusted so that the gel could adhere to the mucosal tissues of both vials. A constant (preload \approx 0.5 Newton) force was placed on the upper vial and applied for 2 min. after which it was removed and the upper vial was then connected to the balance. Weights were added at a constant rate to the pan on the other side of the modified balance of the used device until the two vials were separated. The bioadhesive force, expressed as the detachment stress in dyne/cm², was determined from the minimal weights that detached the two vials using the following equation:

$$\text{Detachment stress (dyne/cm}^2\text{)} = m \times g / A$$

Where as

m = the weight added to the balance in grams.

g = acceleration due to gravity taken as 980 cm/sec².

A = area of tissue exposed and is equal to πr^2 . [12].

2.3.4 Rheological study

In this present study the Brookfield viscometer (model-Brookfield Programmable Viscometer DV- II⁺) was used to find out the rheological behaviour of gels. The gel under study was placed in a small sample holder and the spindle S64 was lowered perpendicularly into it. The spindle was rotated at speed of 60 rpm. The viscosity changes with temperature should be noted. Readings were taken from 20°C to 37°C

with increment of 2°C each time using water bath [13,14].

2.3.5 Preparation of cellophane membrane for vaginal diffusion studies

Cellophane membrane was immersed in boiling water for 2-3 hrs. It was then kept in ethanol for 12 hrs. This treatment opens up the pores of cellophane membrane. Before using, membrane was washed with distilled water and then placed in the diffusion cell for in vitro studies [15,16].

2.3.6 In vitro drug diffusion study

In the present study, *in vitro* release of Clotrimazole gel from various gel formulations were studied using Franz diffusion cell using cellophane membrane (pretreated) and compared in our studies. The cell consists of two chambers, the donor and the receptor compartment. The donor compartment is open at the top and is exposed to atmosphere. The receptor compartment is surrounded by a water jacket for maintaining the temperature at 37°C and is provided with sampling port. Diffusion media in the receptor compartment was stirred with a magnetic bead.

Diffusion medium used was citrophosphate buffer (pH 5) containing 1% Tween80. The gel formulation was kept in the donor compartment and it was separated from the receptor compartment by pretreated cellophane membrane. The donor and receptor compartments were held together using clips of strong grip. The receptor compartment containing dissolution medium (citrophosphate buffer pH 5) was maintained at 37°C \pm 1°C by circulating the water in outer jacket from organ bath. The diffusion medium was stirred with magnetic bead to prevent formation of concentrated drug solution layer below the cellophane membrane. At each sampling time 1 ml of the solution in the receptor compartment was withdrawn and replaced with 1 ml of fresh citrate buffer (pH 5) solution.

The concentration of the drug was determined by UV-spectrophotometric method. Amount of drug diffused was calculated at various time intervals by using PCP dissolution, software. In vitro drug release data for various gel bases are given in Tables 1-4 The % drug diffused Vs. time profile is shown in the graph [17,18].

3. RESULTS AND DISCUSSION

3.1 Optimization of Gelation Temperature of Plain Gel

An accepted vaginal gel formulation must have a gelation temperature in the range of 30-37°C so as to be in a liquid form at room temperature and to form a gel instantly in the vagina. Different combinations of pluronic F 127 and pluronic F 68 were prepared and checked for their gelation temperature. Results indicated that, as concentration of pluronic F127 and pluronic F 68 increases gelation temperature were decreased. From above combinations 23/7 and 25/5 combinations were taken as bases for formation of vaginal gel.

3.2 Characterization of Theroreversible Clotrimazole Gel

3.2.1 Spreadability measurement

Among the various gel formulations studied, formulation F shows better spreadability because of its less consistency it took 2.20 seconds to cover distance of 7.5 cm. Spreadability of formulation B and formulation D were 2.56, 2.55, as polycarbophil concentration was more in these formulations as compared to formulation F. The spreadability values of all formulations are given in Table 2.

3.2.2 Gel strength measurement

Formulations must have suitable gel strength in the range of 10 to 50 seconds. This would allow ease of administration for vaginal formulation and no leakage from vagina. Gel strength of formulations A to F was measured containing different concentrations of polymer. The gel strength values of formulations are given in the Table 2. Gel strength of formulation B and formulation D were found to be 55.5 & 53.5 which may be due to more polymer concentration. Since the gel strength increases as the polymer concentration increases. Gel strength measurement are given in Table 2.

3.2.3 Measurement of mucoadhesive strength

The maximum bioadhesion was recorded for formulation B (2.38 dyne/cm²) followed by formulation C (2.02 dyne/cm²). Formulation B and formulation C contain high amount of mucoadhesive polymer i.e. polycarbophil. This may be due to the reason that polycarbophil is having the carboxyl groups, which favour the establishment of, ionic and hydrogen bond between the polymer and mucin chains. Presence of PEG 400, which was used as solubilising agent for clotrimazole, added viscosity to the formulation. Mucoadhesive strength of various formulations is are given in Table 2.

3.2.4 Rheological study

Rheological studies were done from temperature 20°C to 38°C. As temperature increases from 20°C viscosity increases up to gelation temperature after which small changes in viscosity were observed. Mucoadhesive polymer causes decrease in gelation temperature of formulation. Increase in viscosity occurs as temperature increases for various formulations. Viscosity of formulation B is greater as compared to other formulations which may be due to more concentration of mucoadhesive polymer and PEG 400. Following Table 3 and Fig. 1 give rheological behavior of formulations according temperature increments. Formulations A, B, C, D, E, F shows gelation temperature 34°C, 32°C, 31°C, 30°C, 33°C, 32°C respectively. As gelation temperature reaches, there was a sharp increase in viscosity which was seen in all graphs.

3.2.5 *In vitro* drug diffusion study of gel

Drug diffusion of different formulations for definite time period (12 hrs.) is given in following Tables 1-4. Formulation B gives 101.78 average % drug release over 12 hrs. which is more sustained as compared to marketed formulation Shown in Fig. 2.

Table 2. Spreadability, gel strength, mucoadhesive strength measurement

Sr. no.	Formulations	Time in seconds for spreability	Time in seconds for gel strength	Mucoadhesive strength (dyne/cm ²)
1.	A	2.48	46.7	1.41
2.	B	2.56	55.5	2.38
3.	C	2.53	51.3	2.02
4.	D	2.55	53.2	1.95
5.	E	2.45	45	1.65
6.	F	2.20	41.3	1.23

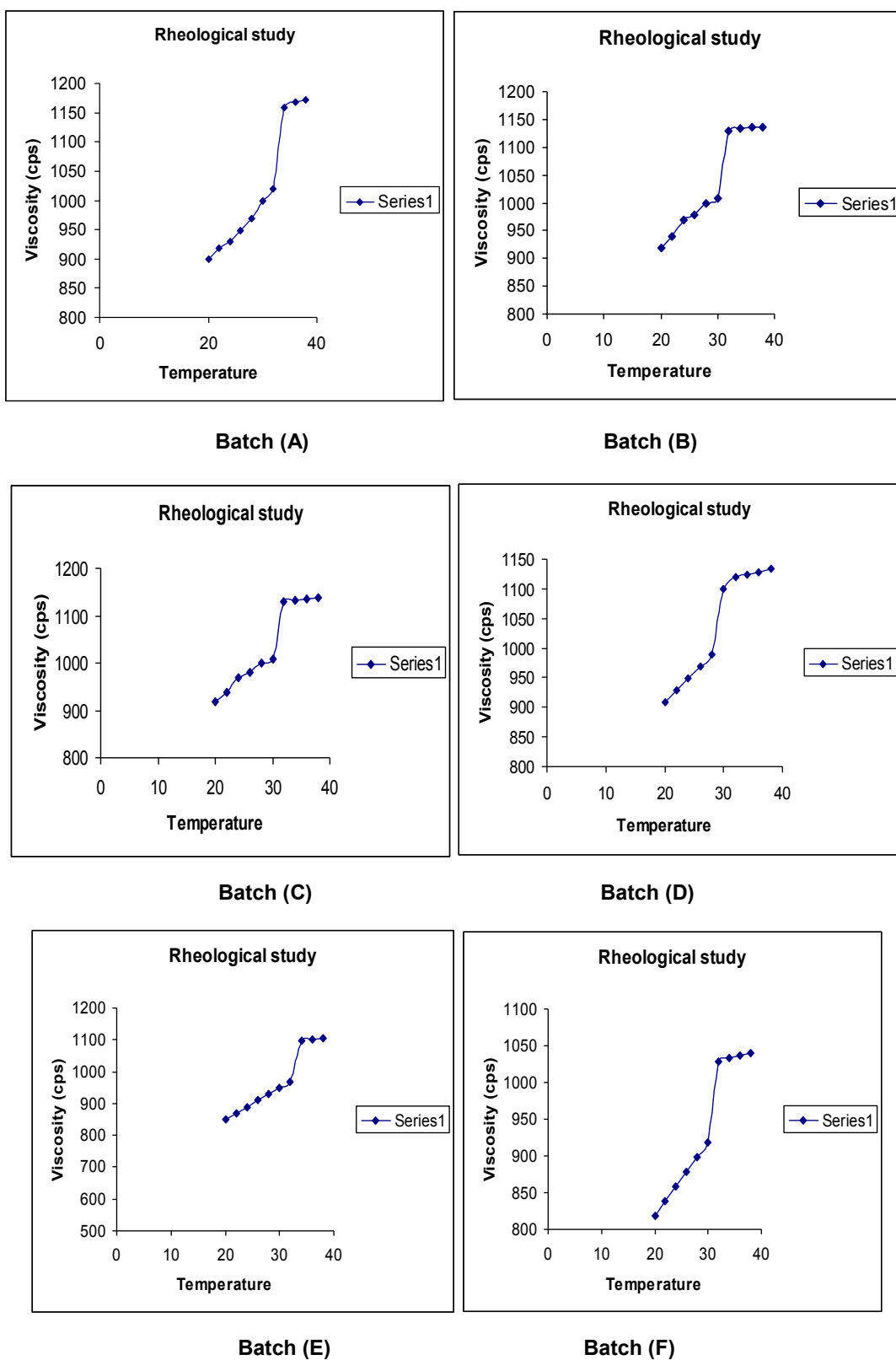


Fig. 1. Rheological study of vaginal gel

Table 3. Rheological study of thermoreversible vaginal gel

Sr.No	Temperature (°C)	Viscosity (cps) batch A	Viscosity (cps) batch B	Viscosity (cps) batch C	Viscosity (cps) batch D	Viscosity (cps) batch E	Viscosity (cps) batch F
1	20	899	949	818	909	839	819
2	22	918	969	919	923	867	833
3	24	929	989	999	949	885	859
4	26	945	1009	1090	969	909	878
5	28	968	1020	1180	988	929	899
6	30	999	1044	1279	1099	946	919
7	32	1018	1199	1323	1119	966	1021
8	34	1159	1203	1399	1123	1099	1033
9	36	1169	1223	1409	1127	1100	1037
10	38	1171	1227	1419	1133	1103	1040

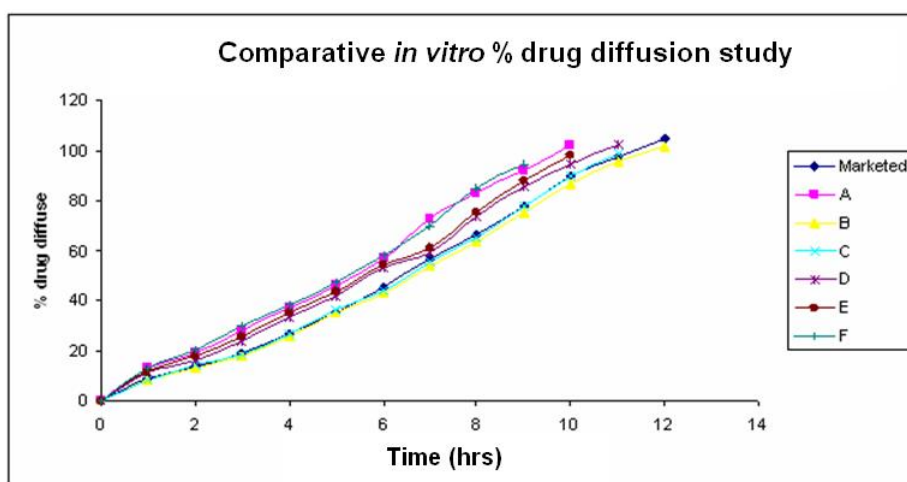


Fig. 2. Comparative *in vitro* % drug diffusion study

Table 4. Comparative data analysis of all formulations

Formulations No.	Zero order (R)	Matrix (R)	Peppas (R)	Hix.Crow (R)	Korsmeyer-Peppas Equation (n)	Korsmeyer-Peppas Equation (k)	t ₅₀	t ₇₅	f ₂
Marketed	0.9921	0.8908	0.9894	0.8809	1.0572	7.1814	6.3	9.2	-
A	0.9979	0.9193	0.9931	0.8502	0.9574	10.7644	4.9	7.6	46.76
B	0.9908	0.8866	0.9911	0.8074	1.0808	6.5987	6.51	9.47	81.55
C	0.9908	0.8869	0.9907	0.8049	1.0682	6.9893	6.3	9.2	93.50
D	0.9971	0.9102	0.9921	0.8181	0.9834	9.2259	5.5	8.4	63.06
E	0.9974	0.9132	0.9924	0.8255	0.9560	10.1103	5.3	8.13	56.19
F	0.9981	0.9203	0.9938	0.8513	0.9412	11.3472	4.83	7.43	44.54

The diffusion study of marketed preparation of the drug was carried out and was compared with our formulations. The marketed preparation gave 102.2% drug release after 10 hrs, our formulation A gave ~ 95% release after 10 hrs,

formulation B gave 95.2% release after 11 hrs, formulation C gave 98.5% release after 11 hrs., formulation D gave 102.15%, release after 11 hrs., formulation E gave 97.70% release after 10 hrs. formulation B gave 94% release after 9 hrs.

After calculating the similarity factor (f_2), the formulation C shows 93.50% similarity with marketed formulation, which was followed by formulation B- 81.85%, formulation D –63.06%, formulation E – 56.19% , formulation A – 46.76% and formulation F – 44.54% of similarity with marketed formulation.

There is retardation in the release of drug in formulations containing Polycarbophil. This may be due to the fact that Polycarbophil particles have a high concentration of ionic groups inside which causes the large influx of water by osmosis, swelling the particles until the cross-links are strained. This will lead to rapid diffusion of a soluble drug out of polymer.

2.3 Data Analysis

The release data obtained from various batches was studied with respect to effect of drug: polymers ratio & diluent ratio. To analyze the mechanism of drug release from the formulation, the release data was fitted to equations are result are shown in Table 4.

$T_{75\%}$ was found to be delayed due to the concentration of Polycarbophil. The 'n' values are more than 1.0 for marketed and formulation B & C which is an indication of super case-II transport release. For remaining formulation $0.5 < n < 1.0$ which shows anomalous type of behavior. The diffusion profile for all formulations was found to be of Peppas type. The initial faster release may be due to drug dissolution from the gel. Formulation B and formulation C showed sustained release as compared to marketed formulation. This was because these formulations contain Polycarbophil which was responsible for sustained release, also PEG 400, pluronic F 127 and F68 imparts viscosity which also affects drug release. Other formulations also contain these polymers but in small concentrations, so drug release was more.

4. CONCLUSION

Clotrimazole is a good candidate for vaginal drug delivery system so it is used in present research work. Various formulations were developed using various concentrations of ethanol, PEG 400, sodium dodecyl sulphate, polycarbophil and pluronic F 127 and pluronic F 68. The gel formulations were subjected for evaluation on the basis of rheological behaviour, mucoadhesive behavior, *in-vitro* performance. Polymers such as polycarbophil, PEG- 400 in various

concentrations to prepare formulations were found to release drug for period over 12 hrs. without getting dislodged. The formulations have satisfactory rheological behavior and their diffusion profile is comparable to the marketed gel formulation. Significant difference was observed in the rheological behavior of formulations. Gel strength, spreadability, mucoadhesive strength of formulation B and C were desirable. Drug diffusion of formulation B and C were 95.2% release after 11 hrs 98.5% release after 11 hrs, respectively which was good as compared to marketed formulation showing drug diffusion of 102.2% after 10 hrs. This system has better patient compliance because of decrease in the frequency of drug administration. This system gave large coverage area in the vagina due to thermoreversible property. So finally we conclude that developed thermoreversible vaginal gel could be promising alternative for management of skin fungal infections & formulations should be subjected for long-term stability study and *in-vivo* performance.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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