CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF CLOTRIMAZOLE GEL

Ketini Bhagya Sree*[1],Dr T.K.V. Kesav Rao[1], Mrs. M.Vineela[1]

[1]Department of Pharmaceutics, Pydah College of PharmacyPatavala,Andhra University, Kakinada, Andhra Pradesh.

Article Received: May 2023 **Accepted:** June 2023 **Published:** July 2023

Abstract:

Objective: *Gel is one of the recent technologies in Novel DDS used for dual control release of emulsion and gel for topical use.*

Methods: *The method used for preparation of micro emulsion w/o was water titration method with Liquid paraffin and propylene glycol as oil phase, Tween 80 and span 80 are used as a surfactant and its concentrations were fixed based on Pseudo ternary phase diagrams. The optimized emulsion formulation was incorporated into the gel matrix that is Carbopol-934, HPMC-5 and HPMC15+ Carbopol-934 by using various concentrations.*

Results: *The prepared gel were characterized for drug content of gel for physical appearance, drug content, pH, viscosity, spreadability, extrudability and* in vitro *drug release studies. The optimized formulations showed F9 with 1:3 HPMC15+ Carbopol-934 formulations showed* in vitro *drug release of 97.82% at the end of 5 h. The optimized formulation showed good drug release within the specified limits.*

Conclusion: *Clotrimazole was proven to be a suitable candidate for formulating gel for topical delivery to achieve better patient compliance.*

Keywords: *Clotrimazole, Gel, Topical application, Carbopol-934, HPMC-5, HPMC15+ Carbopol-934, Liquid paraffin, Tween 80, Span 80 and Propylene glycol.*

Corresponding author:

Ketini Bhagya sree,
Department of Pharmaceutics,
Pydah College of Pharmacy,
Kakinada, Andhra Pradesh,
Email Id- sreebhagya482@gmail.com.

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Please cite this article in press Ketini Bhagya sree et al, ***Formulation Development And Characterization Of Clotrimazole Gel.,*** *Indo Am. J. P. Sci, 2023; 10 (07).*

INTRODUCTION:

Topical drug delivery is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal & skin as topical routes. These are applying awide range of preparations for both cosmetic and dermatological to their healthy or diseased skin. These formulations range in physicochemical nature from solid through semisolid to liquid. In semisolid preparations, the use of transparent gels has been increased in cosmetics as well as in pharmaceutical preparations. Drugs are delivered topically for their action at the site of application or for systemic effects3. The absorption of drug through the skin is improved if the drug substance is in solution,if it has a favorable lipid/water partition coefficient & if it is a nonelectrolyte. For their local action, drug applied to the skin comprise antiseptics, antifungal agent, skin emollients & protectant. The main advantages of topical delivery system areto bypass first pass metabolism. Other advantages of topical preparationsare avoidance of the risks & inconveniences of intravenous therapy & of the varied conditions of absorption like pH alterations, presence of enzymes, gastric emptying time. The topical drug delivery system is usually used where the others system of drug administration fails or it is mainly used in fungal infection. Use of topical agents needs an appreciation of the factors that influence percutaneous absorption6. Molecules can enter the skin by three routes: through intact stratum corneum, through sweat ducts, or through sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption. Rate limiting step for percutaneous absorption is the passage through this outer most layer. The main steps involved in percutaneous absorption comprise the establishment of a concentration gradient, which offers the driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient), & drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, & a high partition coefficient. Except for very small particles, water soluble ions & polar molecules do not penetrate intact stratum corneum. To manipulate the barrier function of the skin topical formulation can be used, for example, topical antibiotics & antibacterials help a damaged barrier toward off infection, sun screening agents & the horny layer protect the viable tissues from Ultraviolet radiation & emollient preparations restore pliability to a desiccated horny layer

Emulgel [1,2]:

As the name suggest they are the combination of gel and emulsion. Both oil-in-water and water-in-oil type of emulsion used as vehicle to deliver various drugs to the skin. They also have a high ability to penetrate the skin. The presence of gelling agent in water phase converts a classical emulsion into an emulgel. Emulgel for dermatological use have several favorable properties such as being thyrotrophic, greaseless, easily spreadable, easily removable, emollient, non-staining, water soluble, longer shelf life, bio friendly, transparent and pleasing appearance.

Advantages:

Incorporation of hydrophobic drugs:

Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.

Better loading capacity:

Other novel approaches like noisome and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.

Better stability:

Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.

Production feasibility and low preparation cost:

Preparation of Emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of Emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of Emulgels.

Controlled release:

Emulgels can be used to prolong the effect of drugs having shorter t1/2.

No intensive sonication:

Production of vesicular molecules needs intensive sonication which may result in drug degradation and

leakage. But this problem is not seen during the production of Emulgels as no sonication is needed.

MATERIALS:

Clotrimazole Provided by SURA LABS ,Triethanalamine Merck Specialities Pvt Ltd, Mumbai, India ,Liquid paraffin Merck Specialities Pvt Ltd, Mumbai, India ,Span 80 Merck Specialities Pvt Ltd, Mumbai, India ,Tween 80 Merck Specialities Pvt Ltd, Mumbai, India ,Propylene glycol Merck Specialities Pvt Ltd, Mumbai, India ,Methyl paraben Merck Specialities Pvt Ltd, Mumbai, India ,Carbopol-934 Merck Specialities Pvt Ltd, Mumbai, India ,HPMC-5 Merck Specialities Pvt Ltd Mumbai, India ,Alcohol Merck Specialities Pvt Ltd Mumbai, India

METHODOLOGY:

Analytical method development:

Determination of absorption maxima:

100mg of Clotrimazole pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e. 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). Scan the 10µg/ml using Double beam UV/VISspectrophotometer in the range of 200 – 400 nm

Preparation calibration curve:

100mg of Clotrimazole pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e. 100µg/ml). From this take 1, 2, 3, 4, 5 and 6ml of solution and make up to 100ml with 0.1N HCl to obtain 1, 2, 3, 4, 5 and 6 µg/ml of Clotrimazole solution. The absorbance of the above dilutions was measured at 255nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2)which determined by least-square linear regression analysis. The experiment was preformed in triplicate and based on average absorbance; the equation for the best line was generated. The results of standard curve preparation are shown in Table-and figure.

Table:1 Composition of gel formulation

COMPOSITION OF GEL FORMULATIONS (%W/W)									
Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug	1%	1%	1%	1%	1%	1%	1%	1%	1%
Carbopol-934	1	1.5	2.0	--	--	--	--	--	--
HPMC-5	--	--	--	1	1.5	2.0	--	--	--
HPMC15+Carbopol-934	--	--	--	--	--	--	1	1.5	2.0
Triethanolamine	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Liquid paraffin	4	4	4	4	4	4	4	4	4
Alcohol	2	2	2	2	2	2	2	2	2
Span 80	3	3	3	3	3	3	3	3	3
Tween 80 in ml	1	1	1	1	1	1	1	1	1
Propylene glycol	5	5	5	5	5	5	5	5	5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

RESULTS AND DISCUSSION:

A unique feature of topical drug delivery is the direct accessibility of the skin as a target organ for diagnosis and treatment. Topical drug delivery system offer several advantages over oral drug delivery systems. Oral drug delivery system produced many side effect so overcome the side effect of the oral dosage form, the drug was formulated in to topical drug delivery system i.e. gel. Gel formulation of Clotrimazole was prepared using 4 types of gelling agent: Carbopol-934, HPMC-5 and HPMC15+ Carbopol-934as polymers. Clotrimazole, used for the topical as vaginal yeast infections, oral thrush, diaper rash, tinea versicolor, and types of ringworm including athlete's foot and jock itch. In the present study, an attempt was made to formulate topical gel of DRUG for efficient delivery of drug across the skin.

Analytical Method:

Standard graph of Clotrimazole in 0.1N HCl:

The scanning of the 10µg/ml solution of Clotrimazole in the ultraviolet range (200-400nm) against 0.1 N HCl the maximum peak observed at λ_{max} as 255 nm. The standard concentrations of Clotrimazole (1-6) µg/ml) was prepared in 0.1N HCl showed good linearity with R^2 value of 0.998, which suggests that it obeys the Beer-Lamberts law.

Table No. 2: Standard Curve of Clotrimazole in 0.1 N HCl

S.No	Concentration µg/ml	Absorbance
1.	0	0
2.	1	0.138
3.	2	0.251
4.	3	0.375
5.	4	0.482
6.	5	0.587
7.	6	0.694

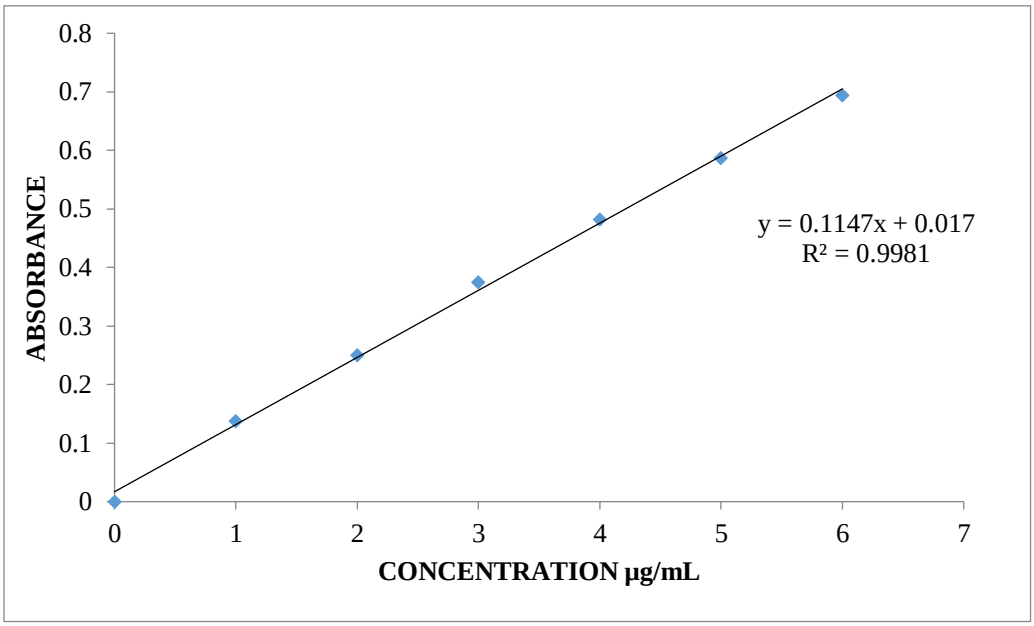

Figure No1: Standard Curve of Clotrimazole in Phosphate buffer pH 0.1N HCl

Table No. 3: Standard Curve of Clotrimazole in pH 6.8		
S. No	**Concentration µg/ml**	**Absorbance**
1.	0	0
2.	1	0.128
3.	2	0.254
4.	3	0.371
5.	4	0.482
6.	5	0.597
7.	6	0.824

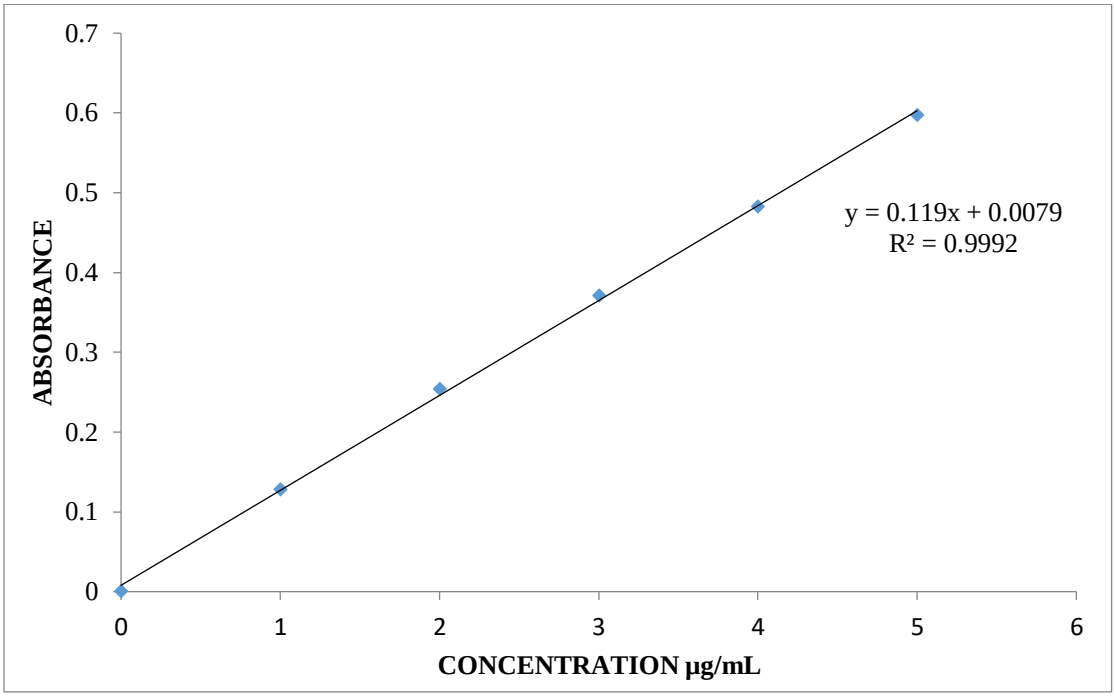

Figure No2: Calibration curve of Clotrimazole in pH 6.8 at 255nm

Preformulation parameters of powder blend

Table No. 4: Physicochemical characteristics of gel						
S.No.	**Formulation code**	**Color**	**Phase separation**	**Grittiness**	**Homogeneity**	**Consistency**
1	F1	White	None	-	Fair	+
2	F2	White	None	-	Fair	+
3	F3	White	None	-	Fair	+
4	F4	White	None	-	Good	++
5	F5	White	None	-	Good	++
6	F6	White	None	-	Good	++
7	F7	White	None	-	Excellent	+++
8	F8	White	None	-	Excellent	+++
9	F9	White	None	-	Excellent	+++

Quality control parameters for tablets:

Table No. 5: Different formulations Parameters

S. No.	Formulation code	pH	Viscosity	Spreading Coefficient	Extrudability	Drug content
1	F1	6.10	6892	16.6	10.8	98.19
2	F2	6.15	7752	18.3	11.3	99.51
3	F3	5.99	8125	16.9	13.6	98.36
4	F4	6.12	3550	21.6	9.1	97.85
5	F5	6.09	4218	28.1	10.5	98.11
6	F6	6.15	5128	32.3	11.4	99.14
7	F7	6.23	8972	33.3	12.3	99.35
8	F8	6.18	9757	35.4	15.6	98.16
9	F9	5.98	9818	39.8	17.6	100.05

***In Vitro* Drug Release Studies**

Dissolution Data of gel containing Clotrimazole by using various polymers

TIME (MIN)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	32.39	26.13	20.03	42.80	34.19	33.31	25.94	19.96	22.14
30	46.62	34.81	36.53	58.93	44.11	42.29	35.63	31.13	32.91
45	53.78	49.94	45.24	63.46	57.89	53.64	42.80	36.31	38.01
60	70.31	57.43	52.90	76.04	68.23	60.72	51.99	47.60	45.20
90	76.10	63.97	58.18	86.57	76.85	68.34	59.12	53.96	51.63
120	87.32	71.08	67.49	91.94	87.98	75.87	66.54	61.83	57.76
150	90.89	78.50	73.91		94.33	82.79	72.79	67.24	63.81
180	93.35	82.32	79.30		95.19	88.64	76.52	74.06	71.56
210		86.13	85.37			92.26	85.58	78.90	75.16
240		93.69	92.16			93.83	91.40	84.23	80.26
270		95.74	95.66				93.76	92.61	86.51
300			96.81					95.90	97.82

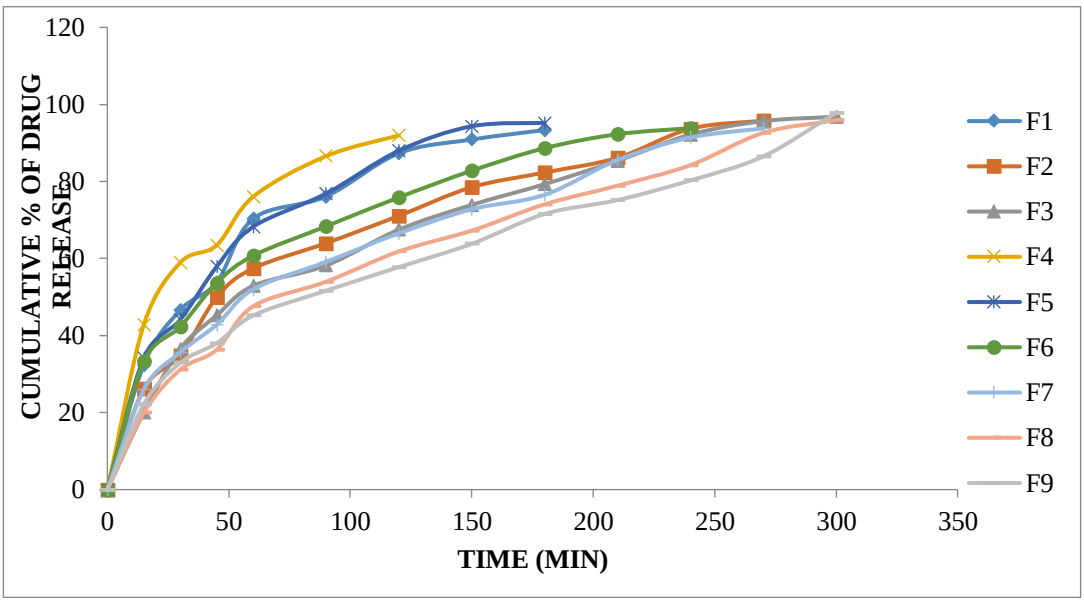

Figure No.3: Diffusion study of gel containing Clotrimazole with Carbopol-934, HPMC-5 and HPMC15+ Carbopol-934 (F1 to F9)

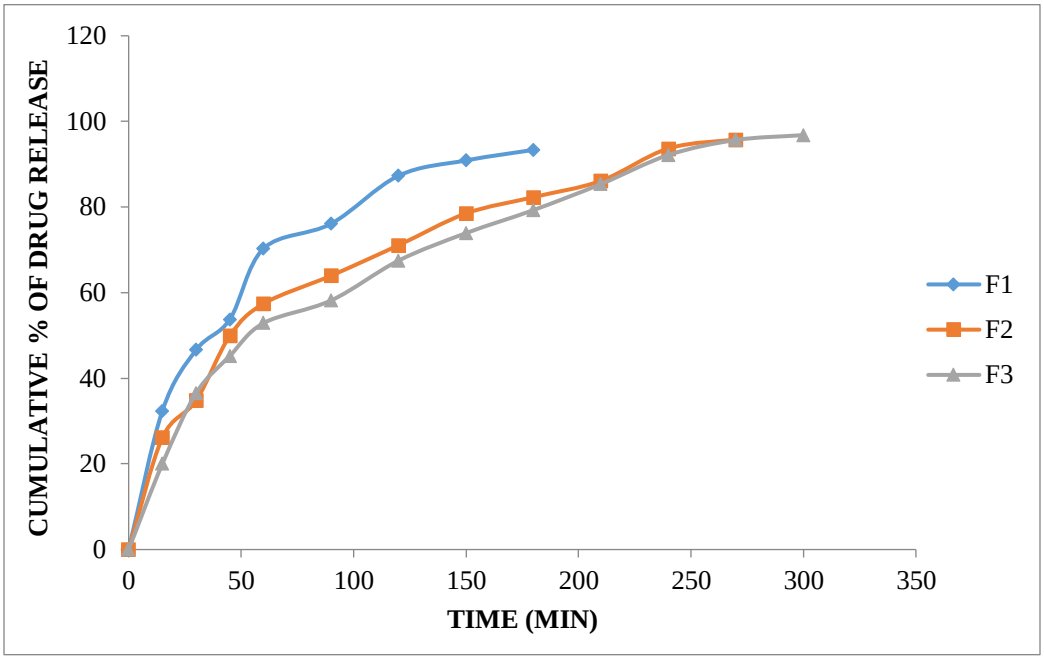

Figure No.4: Diffusion study of gel containing Clotrimazole with Carbopol-934 (F1 to F3)

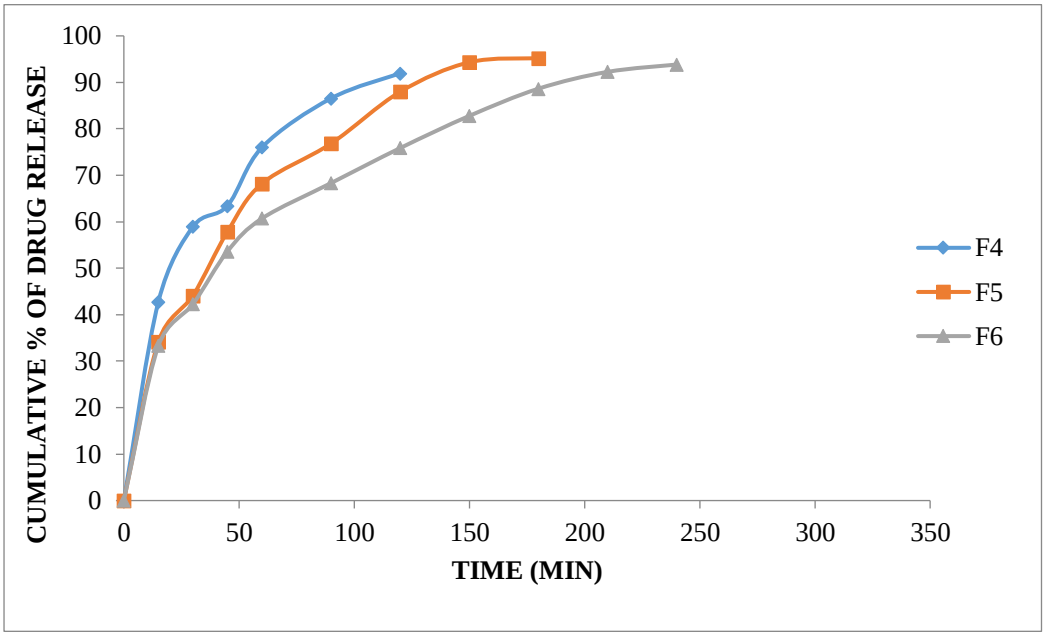

Figure No5: Diffusion study of gel containing Clotrimazole with HPMC-5 (F4 to F6)

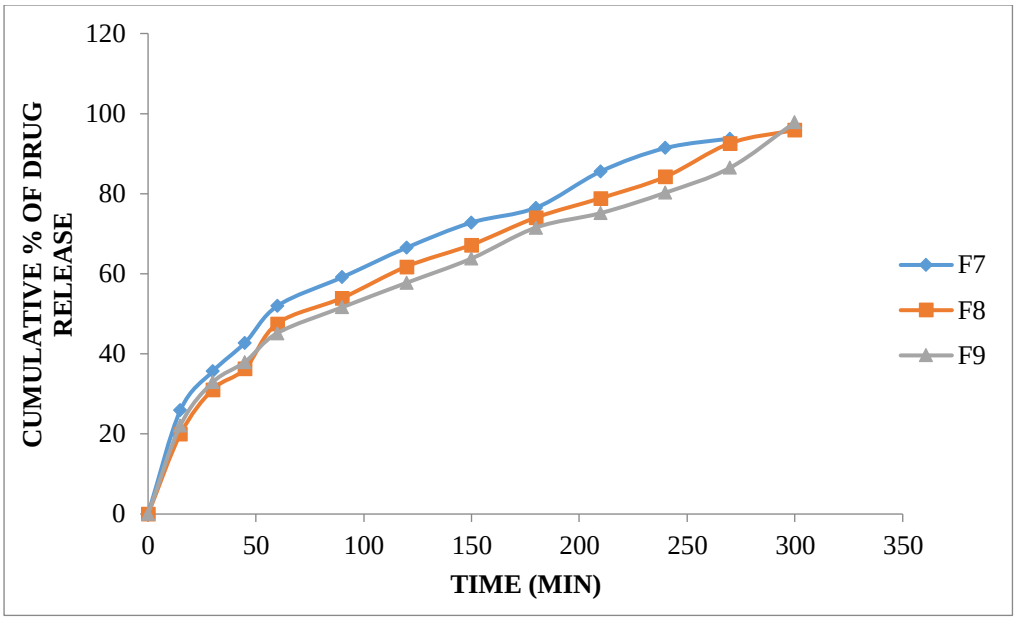

Figure No.6: Diffusion study of gel containing Clotrimazole with HPMC15+ Carbopol-934 (F7 to F9)

Table6: Release kinetics data for optimized formulation (F8)

Time (T)	Cumulative (%) Release	Root (T)	Log (%) Release	Log (T)	Log (%) Remain	RELEASE RATE (CUMULATIVE % RELEASE / t)
0	0	0			2.000	
15	22.14	3.873	1.345	1.176	1.891	1.476
30	32.91	5.477	1.517	1.477	1.827	1.097
45	38.01	6.708	1.580	1.653	1.792	0.845
60	45.2	7.746	1.655	1.778	1.739	0.753
90	51.63	9.487	1.713	1.954	1.685	0.574
120	57.76	10.954	1.762	2.079	1.626	0.481
150	63.81	12.247	1.805	2.176	1.559	0.425
180	71.56	13.416	1.855	2.255	1.454	0.398
210	75.16	14.491	1.876	2.322	1.395	0.358
240	80.26	15.492	1.904	2.380	1.295	0.334
270	86.51	16.432	1.937	2.431	1.130	0.320
300	97.82	17.321	1.990	2.477	0.338	0.326

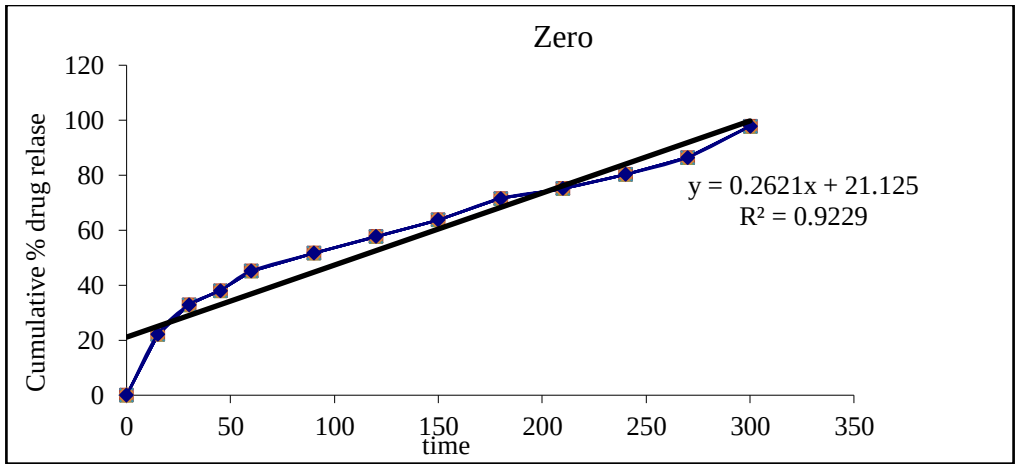

Figure No.7: Graph of zero order kinetics

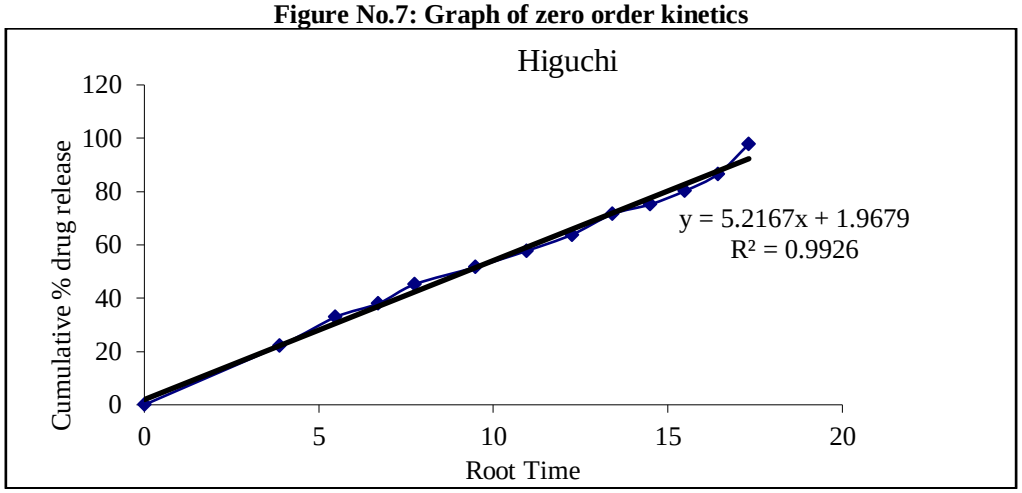

Figure No.8: Graph of higuchi release kinetics

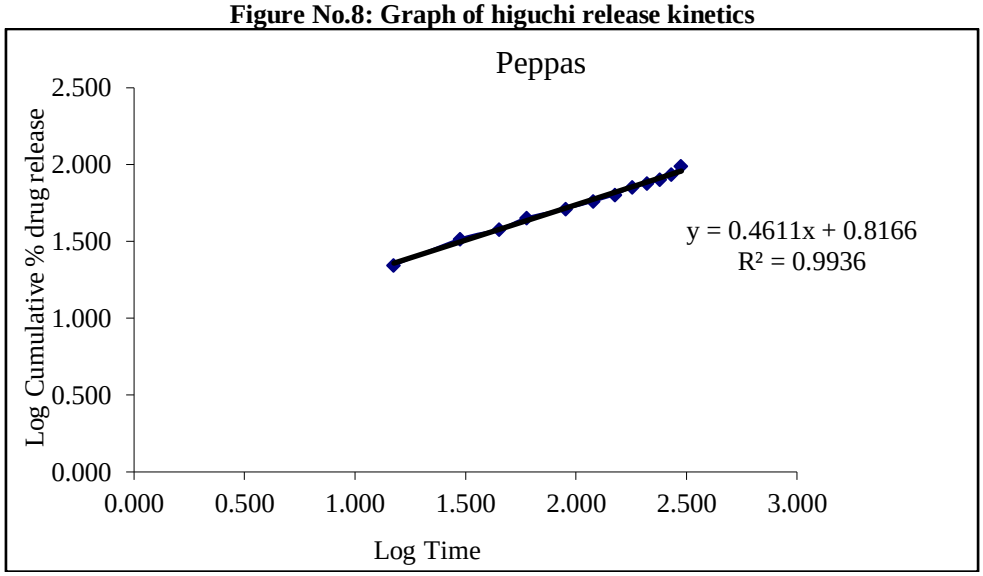

Figure No.9: Graph of peppas release kinetics

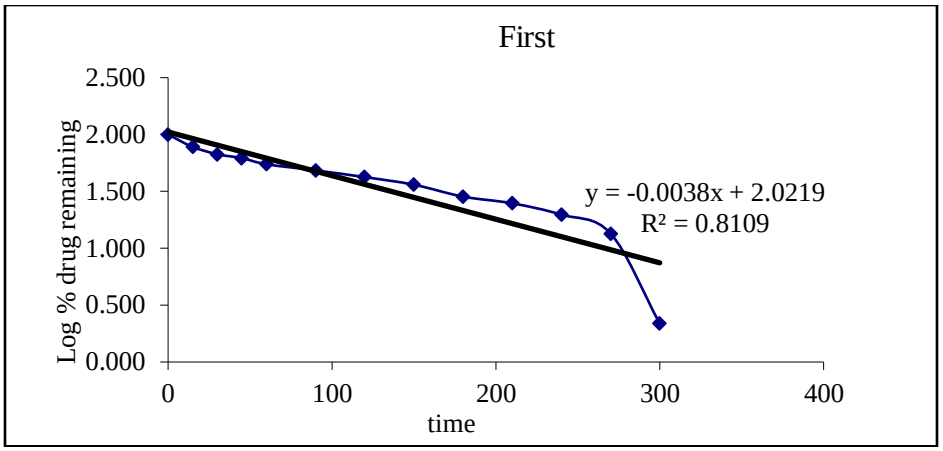

Figure No.10: Graph of first order release kinetics

Drug – Excipient compatibility studies

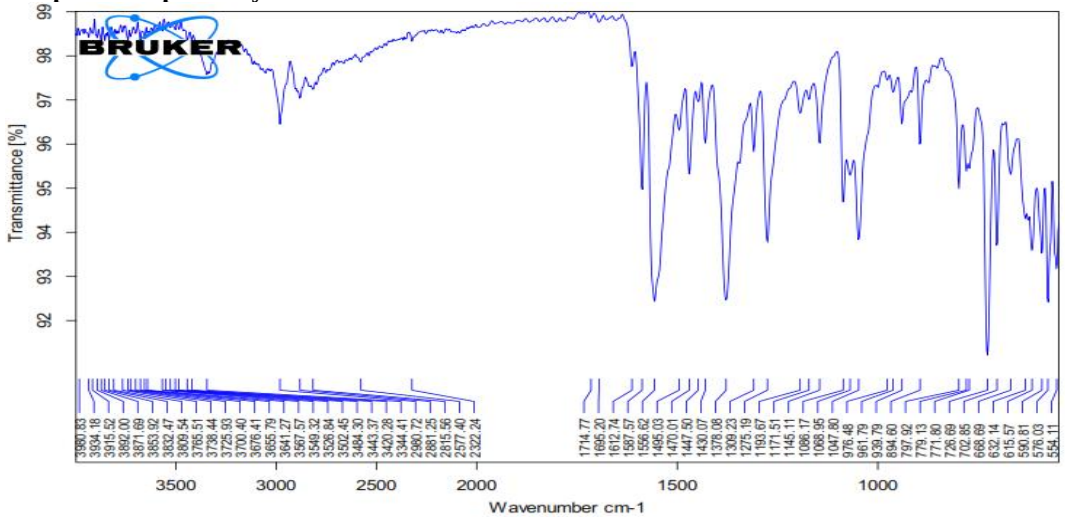

Figure No.11: FTIR GRAPH OF PURE DRUG

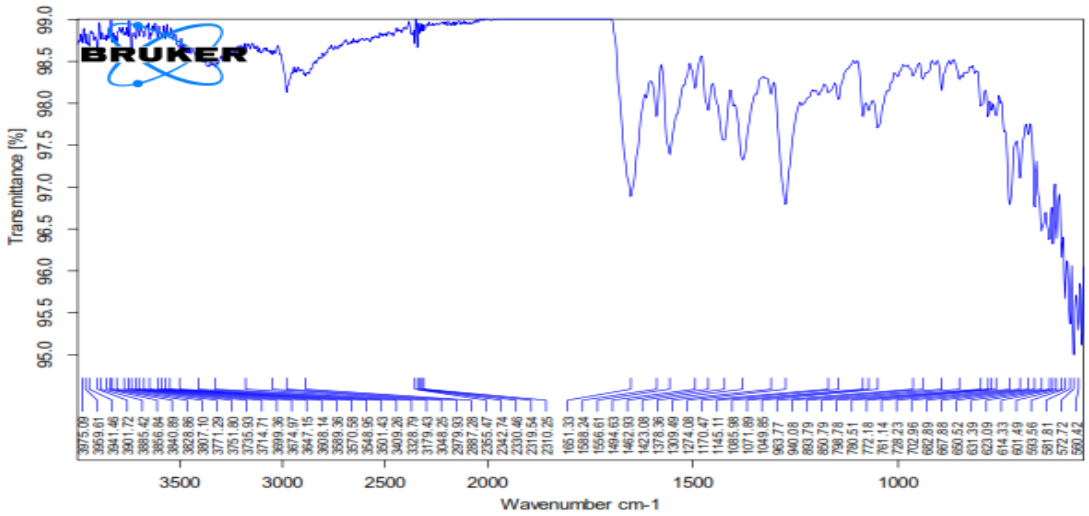

Figure No.12: FTIR GRAPH OF OPTIMISED FORMULATION

CONCLUSION:

Gel is one of the recent technologies in Novel DDS used for dual control release of emulsion and gel for topical use. Topical drug delivery generally used to impart better patient compliance. Gel is found to be helpful in enhancing spreadability, adhesion, viscosity and hence, this novel drug delivery becomes popular. The rational of the present study was to increase the penetration of drug into the skin. In the present Investigation, topical gels of Clotrimazole were formulated and subjected to various physicochemical studies such as spreading coefficient, Viscosity and *in vitro* release studies. *In vitro* release of the tests formulations were performed to determine drug release from gel. From the *in vitro* studies, formulation F9 showed maximum release of 97.82% in 300 min. So Clotrimazole gel can be used as an antifungal agent for topical drug delivery.

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