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FORMULATION AND EVALUATION OF MULTIPLE EMULSION OF CLOTRIMAZOLE

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ABSTRACT

*The main objective of present work is formulation and evaluation of multiple emulsion of clotrimazole. Multiple emulsions dosage formulation of clotrimazole which has enhanced release and bioavailability properties with less inter and intra- subject variability would be desirable. Thus, it was aimed to formulate and evaluate the multiple emulsion of clotrimazole. By the preformulation studies it is observed that clotrimazole is a white to pale yellow crystals having no odor. Solubility was determined in various solvents found that freely soluble in ethanol and methanol, slightly soluble in Distilled Water, soluble in Phosphate Buffer 6.8 pH,0.1N HCl and 0.1N NaOH. Melting point was observed in range of 147-149 ^{0}C. Partition coefficient was 1.797 obtained. Drug: Excipient Compatibility Studies at room temperature, 2^{0}C-8^{0}C and 45^{0}C-50^{0}C says it is stable. Stability also confirmed by FT-IR studies. Five different type formulations (ME-1 to ME-5) formed using fixed amount of oil phase. All five Clotrimazole multiple emulsion formulations were odorless, washable, homogeneous, stable and free from grittiness and was evaluated under the various parameters, Ph of all formulations were observed at 6.8 and viscosity between 4 0.23 to 76.38 centi poise and percentage of Drug content between 83.31 to 95.23%. In-vitro Drug Release of Clotrimazole multiple emulsion formulations were studied and found ME-1 (87.61), ME-2 (94.18), ME-3 (81.74), ME-4 (83.74) and ME-5 (78.62). Formulation **ME-2** was found excellent on the basis of cumulative percentage of drug release profile. All five formulations were also tested for stability and found formulation ME-2 was stable after 30 days against color change, creaming, creaking and phase separation. Optimized formulation **(ME-2)** drug release data were fitted into the zero order, first order, Higuchi and Peppas-Korsemeyer model of drug release kinetics. Formulation ME-2 was followed Zero Order Kinetics explained as continuous and steady release of Clotrimazole from the formulation.*

KEYWORDS: *Globules, Viscosity, Evaluation, Stability, Creaming, Cracking.*

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma (or in the site of action) and maintains it constant for the entire duration of treatment. For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosages forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables, as drug carriers. Even today these conventional drug delivery systems are the pharmaceutical products commonly seen in the prescription and over-the-counter drug marketplace. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. This results in a significant fluctuation in drug levels. Recently, there are several technical advancements which have resulted in the development of new techniques for drug delivery systems. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue. Although these advancements have led to the development of several Novel Drug Delivery Systems, that could revolutionaries method of medication and provide a number of therapeutic benefits. The sustained release dosage form has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and or prolong and its plasma profile is sustained in duration. The onset of pharmacologic action is often delayed, and the duration of its therapeutic effect is sustained**.** In the controlled release drug delivery system the release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to another. This gives high therapeutic efficacy with minimal toxicity. It gives better selectivity of pharmacological activity, and reduces patient compliance by reducing the dosing interval. Numerous attempts have been made to device clinically effective drug delivery systems. The controlled drug delivery system makes an agent to do its best when various drug carrier systems have been developed including nanoparticles, liposomes, serum albumin microbeads, erythrocytes, microcapsules, microemulsions, niosomes, multiple emulsions etc. Multiple emulsions are complex liquid description systems in which the droplets of the one dispersed liquid are further dispersed in another liquid. The inner dispersed globule/droplet in the multiple emulsions are separated from the outer liquid phase by a layer of another phase. There are mainly two types of multiple emulsions W/O/W and O/W/O emulsions. Although, w/o/w emulsions have many of the attributes of w/o emulsions, their lower viscosity, derived from water as the external phase, makes them easier to inject. Adjuvant effects have been

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reported to be improved compared to w/o emulsions or aqueous solution of antigen. Similar increase in the activity of the anticancer drug delivery using multiple emulsions has been observed. The most promising use of multiple emulsions is in the area of sustained release, drug formulation since the oil layer between the two aqueous phases can behave like a membrane controlling solute release. Liquid membrane emulsions of the o/w/o type have been used to separate hydrocarbons where the aqueous phase serves as the membrane and a solvent as the external phase. The system w/o/w on the other hand can extract contaminants from waste water, which acts as the external phase[1]. Multiple emulsions are defined as emulsions in which both types of emulsions, i.e.water-in-oil (w/o) and oil-in-water (o/w) exist simultaneously. They combine the properties of both w/o and o/w emulsions. These have been described as heterogeneous systems of one immiscible liquid dispersed in another rin the form of droplets, which usually have diameters greater than 1μm. These two liquids forming a system are characterized by their low thermodynamic stability. Multiple emulsions are very complex systems as the drops of dispersed phase themselves contain even smaller droplets, which normally consist of a liquid miscible and in most cases identical with the continuous phase. Both hydrophilic and lipophilic emulsifiers are used for the formation of multiple emulsions. In other words multiple emulsions are complex liquid description systems in which the droplets of the one dispersed liquid are further dispersed in another liquid. The inner dispersed globule/droplet in the multiple emulsions is separated from the outer liquid phase by a layer of another phase. Multiple emulsions were determined to be promising in many fields, particularly in pharmaceutics and in separation science. Their potential biopharmaceutical applications include their use as adjuvant vaccines as prolonged drug delivery systems as sorbent reservoirs in drug overdose treatments and in mobilization of enzymes. Multiple emulsions were also investigated for cosmetics for their potential advantages of prolonged release of active agent, incorporation of incompatible materials and protection of active ingredients.

MATERIALS AND METHODS

Materials

Chemicals Used: Clotrimazole, Sodiumchloride, Ethanol, Methanol, Sodiumhydroxide, n-Octanol, Capric/caprylic Triglyceride (CT), Cetyl Palmitate (CP), Cocamidopropylbetaine (CMB), Cetyldimethiconecopolyol (CDC), Sorbitanstearate (Span 60), Carbomer (TGC), Polysorbate 80 (Tween80). All chemicals should be analytical grade.

Equipments used UV-Visible spectrophotometer, Particlesize analyzer (Malvern Mastersizer 2000), Brookfieldrheometer (Model DV.III), Digital Melting point apparatus, Separating funnels, Fourier-Transform InfraRed spectroscopy, Optical microscope, Digital pH meter, Centrifuge. All the equipments should be calibrated and properly operate.

METHODS

Method of Preparation of Multiple Emulsions

Multiple emulsions (W/O/W) were prepared by two step emulsification process:

a. Preparation of primary emulsification. b. Secondary emulsification.

Primary Emulsification: Primary W_1/O emulsion was prepared by slow addition of the aqueous phase containing the electrolyte (NaCl) to the oil phase containing Clotrimazole (1%,*w*/*w*) at 80 ±2°C under continuous stirring at 250 rpm until approximately 25°C. The oily phase was prepared dissolving Clotrimazole in a combination of drug solvent and cosolvent (CT and CP) aided with the lipophilic emulsifying agents (CDC and sorbitan stearate) at 80 ± 2 °C.

Secondary Emulsification: External aqueous phase (W_2) had been prepared previously by dispersing the cross-linked TGC polymer, in a co-solvent system of deionized water and the hydrophilic emulsifying agents (CMB and/without polysorbate 80) were neutralized with 10% NaOHsolution (10%,*w*/*v*) to obtain a pH value of 6.5–7.0. The obtained primary emulsions were slowly added to the corresponding outer aqueousphases (W_2) 50:50 under 250 rpm at room temperature. After complete addition of the primary W_1/O emulsion over the external gelified aqueous phase, the resulting mix was paddle stirred for a further 10 min until a homogeneous $W_1/O/W_2$ multiple emulsion had been completely formed.

RESULTS AND DISCUSSION

Preformulating Studies

Organoleptic properties of Clotrimazole

Table no. 1: Organoleptic Properties of drug Clotrimazole

Test	Specification	Observations
Color	White to pale Yellow Crystals	Complies
Taste	Characteristic	Complies
Odor	Odorless	Complies

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Melting Point Determination

Table no. 2: Melting point of drug Clotrimazole

S. No.	Material	Melting point	Specification
1.	Clotrimazole	147-149 ^{0}C	149^{0}C

Solubility Study

Table no. 3: Solubility profile of Clotrimazole in different solvent

S. No.	Solvents	Solubility
1.	Distilled water	Slightly Soluble
2.	Ethanol	Freely Soluble
.	Methanol	Freely Soluble
4.	Phosphate Buffer 6.8 pH	Soluble
5.	0.1NHCl	Soluble
6.	0.1NNaOH	Soluble

Determination of Wavelength of Maximum Absorbance (λmax)

Table No. 4: Wavelength of Maximum Absorbance (λmax)

Conc. (µg/mL)	Scanning range (nm)	λmax
10	200-400	264.0

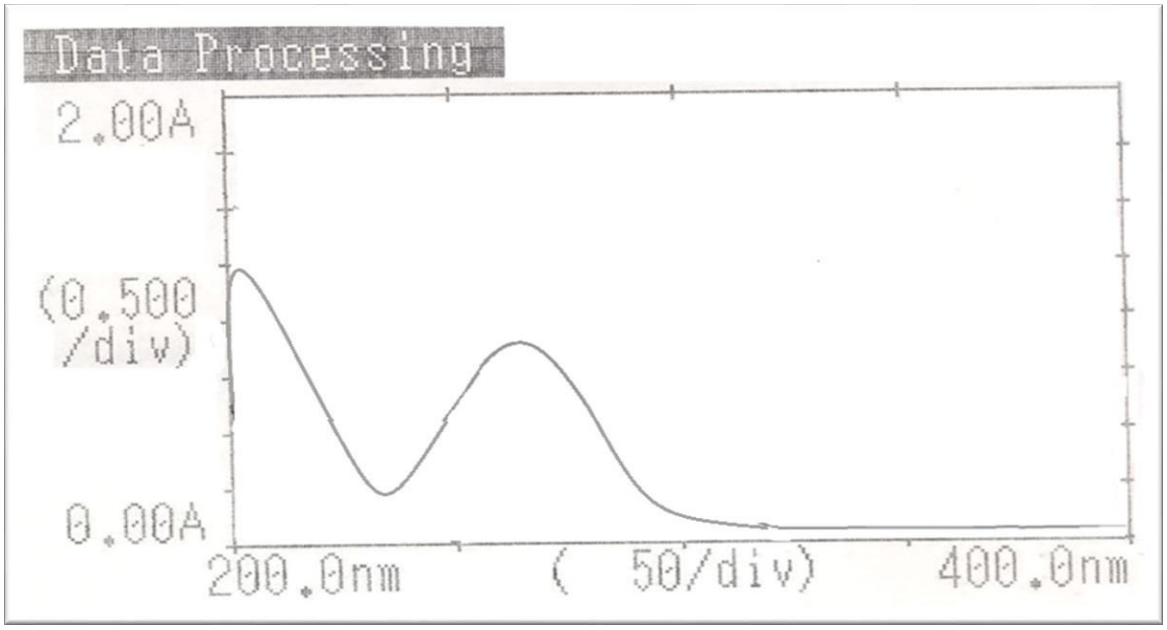

Figure no. 1: Scanning of Wavelenth of Clotrimazole

Preparation of the Calibration Curves of Clotrimazole

Table no.5: Linearity of Clotrimazole 6.8 pH buffer

Conc. (µg/ml)	0	5	10	15	20	25	30
Absorbance	0	0.109	0.228	0.352	0.472	0.605	0.727

Partition Co-efficient

Table no. 6: Partition Co-efficient

Sr. No.	Solvents	Absorbance
1.	Water	0.754
2.	n-Octanol	1.363

Partition coefficient=57.208/31.83= 1.797

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Compatibility Study

Physical Compatibility Study

Table no. 7: Physical Compatibility Study of Clotrimazole with polymer

S. No.	Material	Storage at Room temperature	Storage at 45^0C-50^0C	Storage at 2^0C -8^0C
1	Pure Drug (10mg)	Stable	Stable	Stable
2	Clotrimazole +CT+CP	Stable	Stable	Stable
3	Clotrimazole +TGT	Stable	Stable	Stable

Chemical Compatibility Study by FT-IR

Table no. 8: FT-IR Peaks of Clotrimazole

Standard Peaks (Cm^{-1})	Observed Peaks (Cm^{-1})	Peak Assigned Peaks (Cm^{-1})
3000-3500	3441	N-Hstr
3000-2840	2858	C-Hstr
1650-1600	1634	C=Cstr
1050-1000	1013	C-Clstr

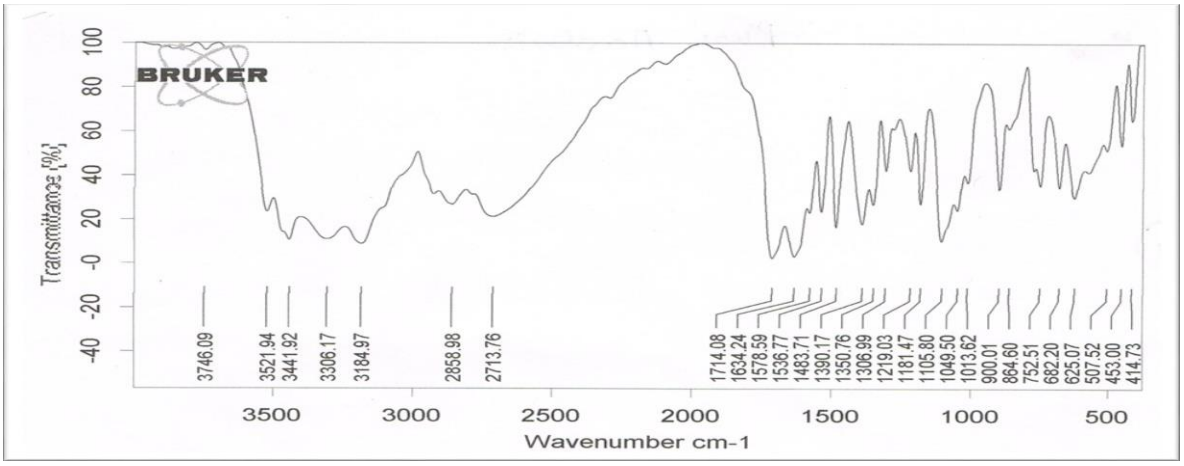

Figure no. 3: FT-IR spectrum of Clotrimazole pure

Formulation Development

Table no. 9: Formulation of Multiple Emulsions

Components	Percentage Composition (w/w)				
	ME-1	ME-2	ME-3	ME-4	ME-5
Oil phase (O)					
Clotrimazole	01.00	1.00	1.00	1.00	1.00
Capric/caprylic Triglyceride (CT)	11.00	11.00	11.00	11.00	11.00
Cetyl Palmitate (CP)	02.00	2.00	2.00	2.00	2.00
Cetyl dimethicone copolyol (CDC)	01.50	1.50	1.50	1.50	1.50
Sorbitan stearate (Span 60)	02.00	2.00	2.00	2.00	2.00
Internal Aqueous Phase (W1)					
Sodium chloride (NaCl)	0.25	0.25	0.25	0.25	0.25
Purified water at pH 6.6	32.25	32.25	32.25	32.25	32.25
External aqueous phase (W2)					
Carbomer (TGC)	0.10	0.20	0.30	0.40	0.50
Cocamidopropylbetaine (CMB)	0.70	0.60	0.50	0.40	0.30
Polysorbate 80 (Tween80)	0.00	0.50	1.00	1.50	2.00
Purified water at pH 6.6	49.20	48.70	48.20	47.70	47.20

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Evaluation of prepared Multiple Emulsion formulation

Physical evaluation of all prepared Multiple Emulsion formulation

Table no. 10: Physical evaluation of all prepared formulation

S. No.	Code of formulation	Visual observation	Phase Separation	Thermo dynamic Stability
1	ME-1	White, Cloudy	No Phase separation	Stable
2	ME-2	White, Coludy	No Phase separation	Stable
3	ME-3	White, Coludy	No Phase separation	Stable
4	ME-4	White, Coludy	No Phase separation	Stable
5	ME-5	White, Coludy	No Phase separation	Stable

Globule Size Determination

Table no. 11: Globule size determination of formulations

Formulation Code	Droplet size (µm)	Zeta potential (mV)	Poly Dispersity Index (PDI)
ME-1	2.42 ± 0.24	14.2 ± 1.42	0.402 ± 0.03
ME-2	1.94 ± 0.53	13.2 ± 1.45	0.329 ± 0.04
ME-3	1.83 ± 0.39	12.4 ± 2.66	0.424 ± 0.01
ME-4	1.99 ± 0.02	14.6 ± 1.37	0.299 ± 0.05
ME-5	2.13 ± 0.33	13.5 ± 1.86	0.443 ± 0.03

Note: All the values are mean of triple reading± standard deviation

Determination of physical properties pH, Viscosity and Drug content

Table no. 12: Physical properties, pH, Viscosity and Drug content

Formulation Code	pH	Viscosity (CP)	Drug content
ME-1	6.8	40.23	87.21 ± 1.65
ME-2	6.8	55.43	95.23 ± 1.01
ME-3	6.8	54.55	84.32 ± 1.23
ME-4	6.7	68.32	84.52 ± 1.41
ME-5	6.8	76.38	83.31 ± 2.13

***In-vitro* Release studies of Clotrimazole Multiple emulsion formulations**

Table no.13: Cumulative Percentage of drug release from multiple Emulsions

Time (hr.)	ME-1	ME-2	ME-3	ME-4	ME-5
0	0	0	0	0	0
1	06.9	15.00	12.91	11.04	08.75
2	17.9	27.43	27.78	20.55	18.37
3	30.60	40.59	35.20	31.81	26.65
4	46.20	51.45	47.60	43.01	35.91
5	58.76	61.59	59.31	51.37	42.86
6	69.84	74.02	65.93	63.08	56.71
7	80.60	86.34	74.99	74.43	67.25
8	87.61	94.18	81.27	83.74	78.62

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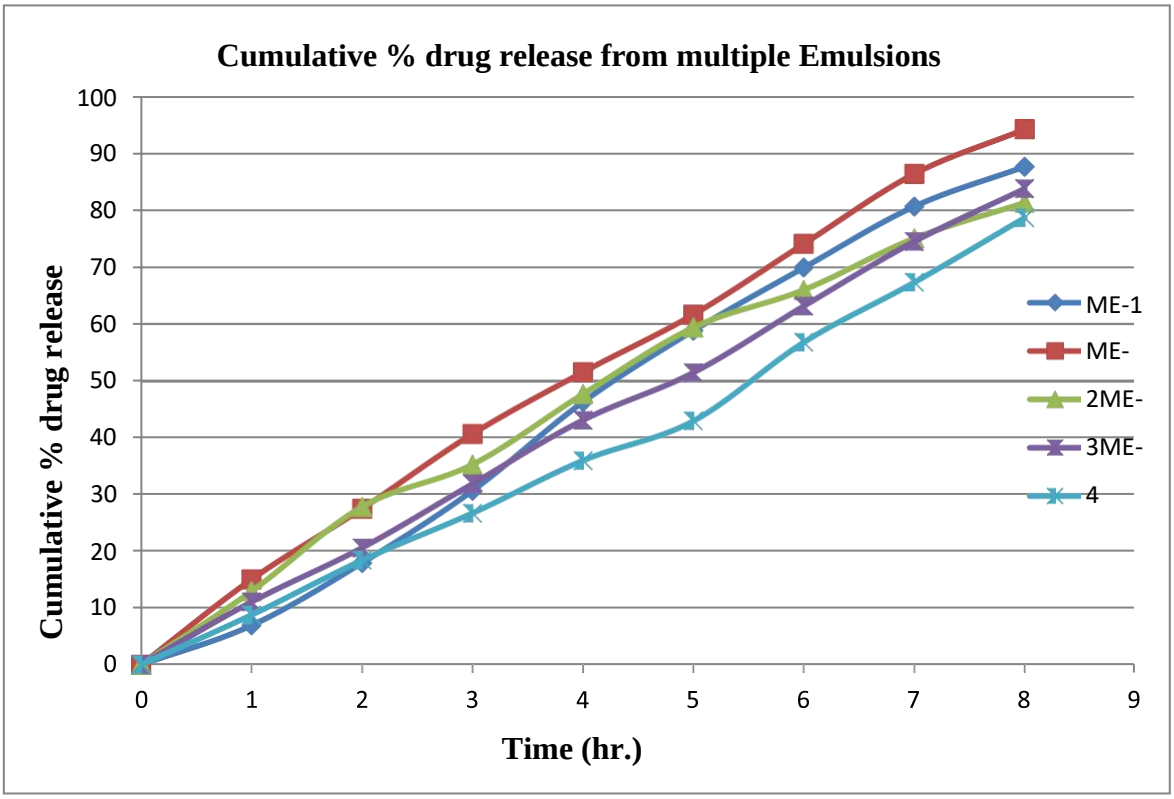

Figure no. 5 : *In-Vitro* Cumulative % Drug Release from Clotrimazole Multiple Emulsion

Stability Testing

Table no. 14: Stability testing under following parameters

Formulation Code	Stability testing after 30 days			
	Color Change	Creaming	Creaking	Phase Separation
ME-1	Observed	Observed	Not Observed	Not Observed
ME-2	Not Observed	Not Observed	Not Observed	Not Observed
ME-3	Not Observed	Not Observed	Not Observed	Observed
ME-4	Not Observed	Observed	Not Observed	Not Observed
ME-5	Not Observed	Not Observed	Not Observed	Observed

DISCUSSION

Multiple emulsions dosage formulation of clotrimazole which has enhanced release and bioavailability properties with less inter and intra- subject variability would be desirable.Thus, it was aimed to formulate and evaluate the multiple emulsion of clotrimazole. By the preformulation studies it is observed that clotrimazole is a white to pale yellow crystals having no odor. Solubility was determined in various solvents found that freely soluble in ethanol and methanol, slightly soluble in Distilled Water, soluble in Phosphate Buffer 6.8 pH,0.1N HCl and 0.1N NaOH. Melting point was observed in range of 147-149 ^{0}C. λ**max** was determined at 264 nmby scanning sample from 200-400nm and also calibration curve was obtained by absorbance of aliquots from 5-30 µg/ml with following linear equation y=0.024x-0.01R^2=0.999. Partition coefficient was 1.797 obtained. Drug: Excipient Compatibility Studies at room temperature, 2^{0}C-8^{0}C and 45^{0}C-50^{0}Csays it is stable. Stability also confirmed by FT-IR studies. Five different type formulations (ME-1 to ME-5) formed using fixed amount of oil phase having Capric/caprylic Triglyceride (CT), Cetyl Palmitate (CP), Cetyl dimethicone copolyol (CDC) and Sorbitan stearate (Span 60) and Internal Aqueous Phase contain Purified water atpH 6.6 and Sodium chloride. Different concentration of External Aqueous Phase contains Carbomer (TGC),Cocamidopropylbetaine (CMB) and Polysorbate 80 (Tween 80) in Purified water at pH 6.6. Then observed visually that all formulations were white and cloudy,there was no phase separation and Thermodynamically Stable. Characterization of all Clotrimazole multiple emulsion formulations were evaluated for Droplet size, Zeta potential and Poly Dispersity Index (PDI) all results showed in table. All five Clotrimazole multiple emulsion formulations were odorless, washable, homogeneous, stable and free from grittiness and was evaluated under the various parameters, Ph of all formulations were observed at 6.8 and viscosity between 4 0.23 to76.38 centi poise and percentage of Drug content between 83.31 to 95.23%. *In-vitro* Drug Release of Clotrimazole multiple emulsion formulations were studied and found ME-1 (87.61), ME-2 (94.18), ME-3 (81.74), ME-4 (83.74) and ME-5 (78.62). Formulation **ME-2** was found excellent on the basis of cumulative percentage of drug release profile. All five formulations were also tested for stability and found formulation ME-2 was stable after 30 days against color change, creaming, creaking and phase separation. Optimized formulation

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(ME-2) drug release data were fitted into the zero order, first order, Higuchi and Peppas-Korsemeyer model of drug release kinetics. Formulation ME-2 was followed Zero Order Kinetics explained as continuous and steady release of Clotrimazole from the formulation.

CONCLUSION

The prepared multiple emulsions of Clotrimazole had shown excellent promising results for all the evaluated parameters. On the basis of *in-vitro* drug release and drug content results, **ME-2** formulation was better drug release as compare to ME-1, ME-3, ME-4 and ME-5 which shows higher percentage of drug release. *In- vitro* release profile was applied on various kinetic models like Zero order, First order, Higuchi equation and Peppas-Korsemeyer model. The best fit with highest regression coefficient was found with Zero order. The rate constants are calculated from the slop of the respective plots the release mechanism of Multiple Emulsion. **ME-2** formulation can be further study for preclinical and clinical evaluations.

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