Available online on 15.04.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Open Access Research Article

Formulation, development and evaluation of topical nanoemulgel of tolnaftate

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ABSTRACT

Nanoemulsion has been identified as a promising delivery system for various drugs including Biopharmaceuticals. Nanoemulsion is heterogeneous system composed of one immiscible liquid dispersed as droplets within another liquid. Aim of the present study was to investigate the nanoemulgel as transdermal delivery system for poorly water soluble drug, Tolnaftate in order to overcome the troubles associated with its oral delivery. Different nanoemulsion components (Oil, Surfactant and Cosurfactant) were selected on the basis of solubility and emulsification ability. High pressure Homogenization techninique were used for the preparation of Nanoemulsion. Carbopol 934 was added as gel matrix to convert nanoemulsion into nanoemulgel. Drug loaded Nanoemulgels were characterized for particle size, SEM, Viscosity, Spreadability, Diffusion study using egg membrane, Nanoemulgel containing 3 % Almond oil, 5.25 % Tween 80, Proplene glycol as Cosurfactant, 1 % drug, Water upto Quantity sufficient was concluded as optimized formulation (F1).

Keywords: Antifungal, Nanoemulsion, Gelling agent, Tolnaftate

Article Info: Received 20 Feb 2019; Review Completed 27 March 2019; Accepted 29 March 2019; Available online 15 April 2019

Cite this article as:

Gadkari PN, Patil PB, Saudagar RB, Formulation, development and evaluation of topical nanoemulgel of tolnaftate, Journal of Drug Delivery and Therapeutics. 2019; 9(2-s):208-213 http://dx.doi.org/10.22270/jddt.v9i2-s.2495

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INTRODUCTION

Common known skin fungal infections are caused by yeasts such as Candida and the disease name is Candidiasis or dermatophytes, such as Epidermophyton, Microsporum and Trichophyton (like Dermatophytoses, Ringworm, Tinea). Many of these fungi live only in the stratum corneum which is topmost layer of the epidermis. and do not penetrate deeper. These eruptions like dermatophytids are allergic reactions to the fungus. Fungal diseases are commonly caused by fungi that are present in the environment commonly. Most fungi are not dangerous, but some can be harmful to health. Mild fungal skin diseases symptoms can look like a rash and are very common. Fungus diseases of lungs are commonly similar to flu or tuberculosis like illness. Certain fungal diseases like bloodstream infections and fungal meningitis are less common than skin and lung infections but can be lethal.

There are various conventional routes of drug administration system namely oral, sublingual, rectal, parenteral etc. for the treatment of different kinds of disorders. Topical drug delivery system is generally used for to cure the skin infection like fungal infection. Topical drug delivery system can be defined as localized drug delivery system where drug incorporated into medication to the skin to get localizing effect of drug cure skin disorder. Topical drug delivery system have been used for treatment of both dermatological and cosmetic to their disease or healthy skin. Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption like pH changes, presence of enzymes, gastric emptying time are advantages of topical preparations. Topically applied dermal or transdermal delivery systems could replace needles required to administer many of the new biologics-based drugs and vaccines, in addition to other significant advantages such as avoiding first pass hepatic metabolism, gastric degradation and frequent dosing. However, the limited dermal and transdermal delivery of many small and large molecules is a significant challenge because of the unyielding barrier properties of the skin. A nanoemulsion can be categorized into oil-in-water (o/w) nanoemulsion and water in oil (w/o) nanoemulsion, depemding on the distribution of oil and aqueous phases. An oil-in-water nanoemulsion refers to a system having oil droplets dispersed in an aqueous phase. It is favorable delivery system for hydrophobic active substances whereas a water-in-oil nanoemulsion is suitable for hydrophilic counterparts. Nanoemulsion is a promising tool for transdermal drug delivery and is defined as a dispersion consisting of oil, surfactant, cosurfactant, and aqueous phase, which is a single

optically isotropic and thermodynamically stable liquid solution with a droplet diameter usually in range of 10-200 nm. Nanoemulsions also have attracted a great attention in delivery of therapeutically active agents since approximately 40% of new chemical entities are hydrophobic in nature and the delivery of these poorly water soluble drugs is a challenge for delivery of drugs. In pharmaceutical field, nanoemulsions have been used as a drug delivery system through various systemic routes i.e. oral, topical and parenteral. Nanoemulgel which also known as the formation of nanoemulsion-based hydrogel is the addition of nanoemulsion system into hydrogel matrix. In addition, with the gel based formulation of nanoemulgel, it exhibit upgraded properties of thixotropic, non-greasy, effortless spreadable, easily be removed, emollient, not staining, soluble in water, longer shelf life, bio-friendly, translucent and agreeable appearance. [1,2]

MATERIALS AND METHOD

Materials

Antifungal drug i.e. Tolnaftate gifted from Aarti Drugs Ltd. Mumbai, Carbopol 934, Tween 80, Propylene glycol, Almond Oil, Methyl Paraben, Propyl Paraben, BHT, was obtained from Research lab, Mumbai. Distilled water was used for all experiments. All chemicals were of pharmaceutical grade. Antifungal activity was performed on Trichophyton rubrum.

Methodology

High pressure homogenization methods are used for the formulation of nanoemulgel. There are three steps involved in the formulation of nanoemulgel which are given follows.

1. Preparation of nanoemulsion

2. Preparation of hydrogel and

3. Finally nanoemulgel will be produced by the incorporation of Nanoemulsion into gel with continuous stirring.

Formulation and development of nanoemulsion

3 [2] Full Factorial Design: For the present work 3^2 full factorial designs was selected. It has been summarized in Table 01, In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected in Table 01. The two independent variables selected were Almond oil (x1) and Speed of homogenizer (x2). [3]

Table 1: Composition of Nanoemulsion formulation as per 3^2 full factorial designs

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients			**%**						
Tolnaftate	1	1	1	1	1	1	1	1	1
Almond oil (v/v)	3	3	3	2	2	2	1	1	1
Tween 80 (v/v)	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
Propylene glycol (v/v)	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75	1.75
Methyl Paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl Paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
BHT	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Water	100	100	100	100	100	100	100	100	100

Method of preparation for nanoemulsion

Preparation of aqueous phase 'A': Accurately weighed quantity of propylene glycol was added into distilled water (80^0c).

Preparation of Oil phase 'B': Weighed quantity of Almond oil and tween 80 mixed together by maintaining hot condition, simultaneously accurately weighed quantity of Tolnaftate was added into it then addition of methyl paraben, propyl paraben and BHT in it.

Incorporation of solution 'A' in dispersion 'B': Both the phases were mixed properly with the help of High pressure Homogenizer maintaining the respective rpm. [4]

Preparation of gel

The weighed quantity of carbopol 934 was mixed in distilled water (400^0c) further addition of triethanolamine to maintain the desired pH range of the solution. The uniformity in the stirring was maintained and then the gel was kept in the refrigerator for 24 hrs.

Preparation of Emulgel

Further incorporation of nanoemulsion containing 1% drug was incorporated to obtain emulgel.

Evaluation of nanoemulsion

Scanning Electron Microscopy

The morphology of nanoemulsion can be determined by scanning electron microscopy (SEM). SEM gives a three-dimensional image of the partical. The samples are examined at suitable accelerating voltage, usually 20 kV, at different magnifications. [4]

Particle Size Analysis

Formulated Nanoemulsion should be analysed for their hydrodynamic particle size. Generally, in case of nanoemulsion dynamic light scattering method used for the measurement of particles and further particle size distribution. [4]

Zeta potential measurements

Zeta potential for nanoemulsion was determined using zetasizer hsa 3000 (Malvern instrument Ltd., UK). Samples were placed in clear disposable zeta cells and results were recorded. Before putting the fresh sample, cuvettes were washed with the methanol and rinsed using the sample to be measured before each experiment. [5]

Evaluation of Nanoemulgel

Physical Appearance

The prepared nanoemulgel formulations were inspected visually for their colour, homogeneity, consistency and pH. [4]

Determination of pH

pH of the formulation was determined by using digital pH meter. pH meter electrode was washed by distilled water and then dipped into formulation to measure pH and this process was repeated 3 times. [6, 7]

Measurement of viscosity

The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25±1ºC) before. [6, 7]

Drug content study

Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Took 1 g of the formulation into 10 ml volumetric flask added methanol in it and shake well and make up the volume with methanol. The Volumetric flask was kept for 2 hr and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered the mixer then measured absorbance by using spectrophotometer at 257 nm. [6, 7, 9]

***In-vitro* Drug release study**

The *in-vitro* drug release studies of the Emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was applied on to the surface of egg membrane dialysis membrane. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution. Total amount of gel filled in the tube to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable time interval sample were analyzed for drug content by UV visible spectrophotometer at 257 nm after appropriate dilutions. [6, 7, 10]

Antifungal study

An agar diffusion method used for determination the antifungal activity of formulation. Standard petri dish 9 cm containing medium to depth of 0.5 cm were used. The sterility of the lots was controlled before used. Incubation were prepared by suspending 1-2 colonies of Trichophyton rubrum (ATCC 28188) From 24 hr. Cultures in sabouraud's medium in to tube contain 10 ml of sterile saline. The tubes were diluted with saline. The inoculum spread over the surface of agar medium. The plate The cumulative % drug release was calculated using standard calibration curve. was dried at 35º C for 15 min prior to placing the formulation. The boars of 0.5 cm diameter were prepaid and 20 µl sample of formulation (1 % w/v) were added in the bores. After incubation at 35ºC for 24 hr. the zone of inhibition around the boars are measure. [11]

Release kinetics of selected formulation

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (cumulative % drug release v/s. time), First order (log cumulative % drug retained v/s. time), Higuchi model (cumulative % drug retained v/s. Square root of time). [6, 7]

RESULT AND DISCUSSION

Evaluation of Nanoemulsion

Scanning Electron Microscopy

Scanning electron microscopy of Nanoemulsion is shown in Fig. 01. The shape of Nanoemulsion was Spherical and the size of the Nanoemulsion was below micrometer range. Moreover, the micrograph also revealed the some agglomeration of nanoemulsion which might be due to the evaporation of water present in formulation during sample preparation prior to SEM analysis.

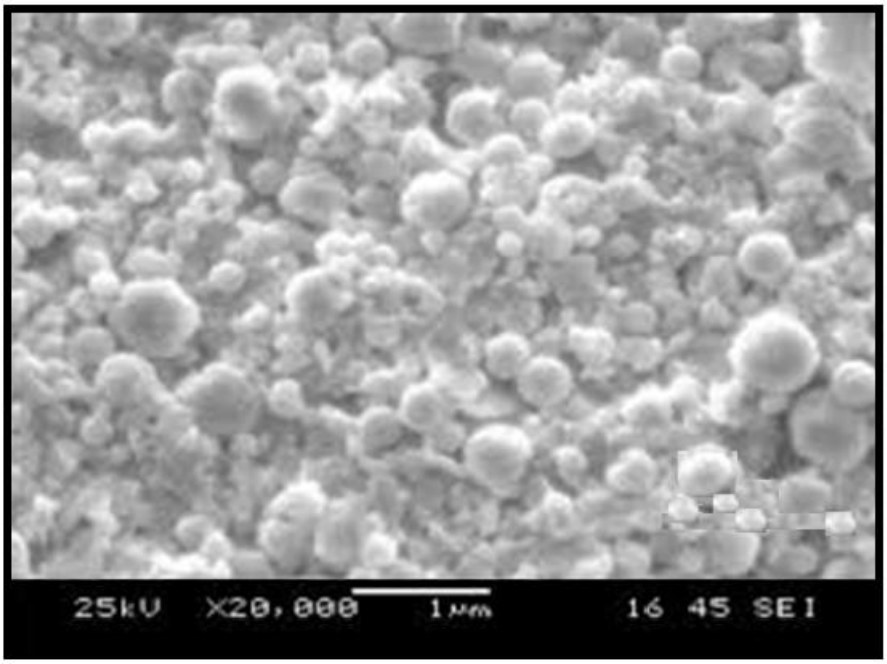

Figure 1: Scanning Electron Microscopy

Particle size and polydispersibility index

The Particle size of the Nanoemulsion of optimised batch was found to be 100 nm. It is seen with increase in concentration of Almond oil with high speed of homogenizer decrease in particle size. It is shown in Fig. 02.

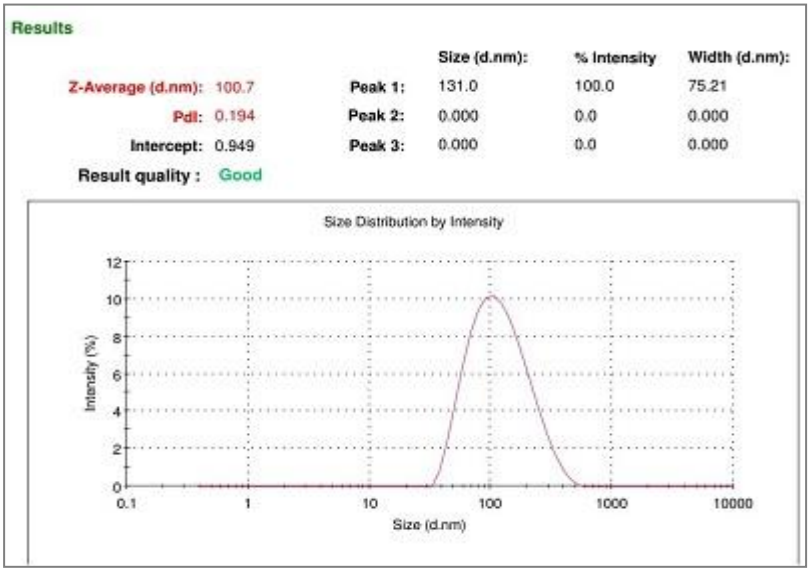

Figure 2: Particle Size of Optimized Formulation

Zeta Potential

Zeta potential shows the stability of the (colloidal dispersion) nanoemulsion under the stress testing condition according to ICH guidelines of stability studies of various pharmaceutical formulations. Zeta potential is affected by particle size, lowest particle size in nano size i.e. 100, shows -32 mV. Zeta potential which indicate thermodynamic instability of the dispersion. It is shows in Fig. 03.

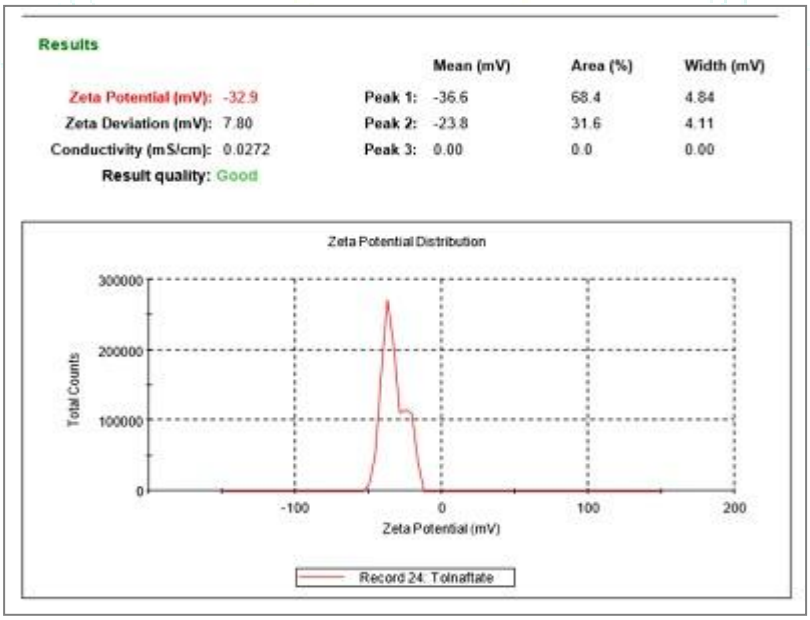

Figure 3: Zeta Potential of Optimized formulation

Evaluation of Nanoemulgel

Physical Appearance

The physical appearance of the emulgel formulation was found to be Translucent, homogeneous and consistent.

pH

pH of various emulgel are shown in the table no 02 which was found to be in range of 6.31 to 6.84.

Viscosity

The viscosity values of formulations are shown in the Table 03.

Spreadability

Spreadability shows the inverse relationship with the viscosity of the emulgel. Formulation F1, Having optimum viscosity and spreadability of this formulation is 17.77 gm.cm/sec. spreadability shows in Table 04.

Drug Content

The drug content of formulation has shown in table no.05 The percentage drug content of all prepared emulgel formulations was found to be in the range of 64 to 96%.

In-vitro drug release

The *in- vitro* release of Tolnaftate from its various emulgel formula are represented in Table 06.

Antifungal Activity

Observed value of (% Drug suspension) for Tolnaftate against Trichophyton rubrum (ATCC 28188) for zone of inhibition is 15. The study indicates that Tolnaftate retained its antifungal activity when formulated in Nanoemulsion loaded emulgel and Tolnaftate was active against selected strain of micro-organism. F1 shows a zone of inhibition of 24 mm. The results of antifungal activity of formulation have been shown in Table 07 Standard value of (Drug suspension) for Tolnaftate against Trichophyton rubrum for zone of inhibition is 24 mm.

Table 2: pH values of formulation

Sr. No.	Formulation code	Observed pH (± SD)
1	F1	6.60±0.025
2	F2	6.75±0.018
3	F3	6.55±0.011
4	F4	6.45±0.011
5	F5	6.43±0.0158
6	F6	6.33±0.011
7	F7	6.31±0.005
8	F8	6.40±0.018
9	F9	6.53±0.026

Table 3: Viscosity of formulations

Rpm	Viscosity (cP) at Room Temperature								
	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	14960	13450	14500	13750	12500	13500	14500	13500	12000
20	14200	12390	14000	13400	12250	12440	14250	12500	11709
30	13050	12050	13445	12350	11200	12203	13900	12000	10500
40	13000	11500	12230	12010	11000	11253	12750	11500	9850
50	12350	10420	11520	11250	10950	10504	12520	11200	9230

Table 4: Spreadability values of formulation

Sr.no.	Formulation code	Spreadability (g.cm/sec)± S.D.
1	F1	17.77 ± 0.025
2	F2	16 ±0.035
3	F3	15.38 ±0.028
4	F4	15.68 ±0.018
5	F5	15.09 ±0.032
6	F6	14.81± 0.012
7	F7	15.53± 0.012
8	F8	15.23± 0.011
9	F9	15.84 ±0.018

Table 5: Drug content of formulation

Sr. No.	Formulation code	Drug content (%)± SD
1	F1	96±0.5
2	F2	91.91±0.7
3	F3	95±0.7
4	F4	93.91±0.7
5	F5	94±0.7
6	F6	72±0.7
7	F7	68±1.09
8	F8	82±1.07
9	F9	64.91±1.43

Table 6: Cumulative amount of Tolnaftate diffused (%) from all the emulgel formulations through egg membrane using Modified Franz diffusion cell

Time hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	9±0.70	8.17±0.76	7.14±0.22	6.25±0.071	6.13±0.75	5.34±0.82	5.01±0.70	3.41±0.85	2.31±0.53
2	17±0.70	14.08±0.73	12.96±0.51	15.22±0.24	11.13±0.75	12.96±1.06	16.74±0.97	19.15±0.75	16.24±0.79
3	25±1.07	24.21±0.74	23.01±0.16	22.11±0.17	23.12±0.74	19.66±0.39	21.30±0.81	18.12±0.74	20.11±0.74
4	34±1.06	32.65±0.38	31.09±0.12	28.23±0.79	26.61±0.84	25.66±0.64	23.49±0.88	22.44±0.31	20.66±0.94
5	41±0.70	40.42±0.85	40.97±0.52	35.49±0.88	30.99±0.50	32.67±0.95	34.69±095	39.45±0.69	39.41±0.85
6	50±0.53	48.57±0.38	47.87±0.47	45.66±0.72	45.35±0.83	40.19±0.19	38.09±0.75	35.66±0.94	30.11±0.74
7	59±1.06	57.45±0.31	55.13±0.94	52.79±0.99	48.49±0.88	44.09±0.10	41.49±0.88	38.09±0.73	37.71±0.96
8	68±1.07	65.15±0.27	62.14±0.16	60.49±0.32	57.18±0.76	54.66±1.2	51.78±0.66	48.83±1	49.89±1.03
12	78±1.41	72.30±0.28	74.25±0.32	64.49±0.33	62.16±0.75	58.19±0.19	56.99±1.07	54.97±1.04	52.31±0.81
16	85±1.04	81.89±0.50	73.41±0.64	70.89±1.05	68.12±0.74	64.69±0.45	61.44±0.86	58.10±0.73	54.14±0.54
24	96±0.66	90±0.38	87.42±0.30	78.94± 0.50	72.09±0.73	69.99±1.0	65.05±0.72	61.19±0.76	58.45±1.21

Table 7: Antifungal Activity of Formulation F1 to F9

Sr.no.	Formulation code	*Trichophyton rubrum*
		Zone of inhibition (mm)
1.	F1	24
2.	F2	23
3.	F3	22
4.	F4	21
5.	F5	20
6.	F6	19
7.	F7	18.40
8.	F8	18
9.	F9	17
10.	1% Drug suspension	15
11.	Marketed formulation (Tinactin cream 1%)	16.40
12.	1% Formulated cream	15

Drug release Kinetics

In the present study, the drug release was analysed to study the kinetics of drug release mechanism. The results for zero order model kinetics and Higuchi model kinetics have shown in Fig. 4 and 5 respectively.

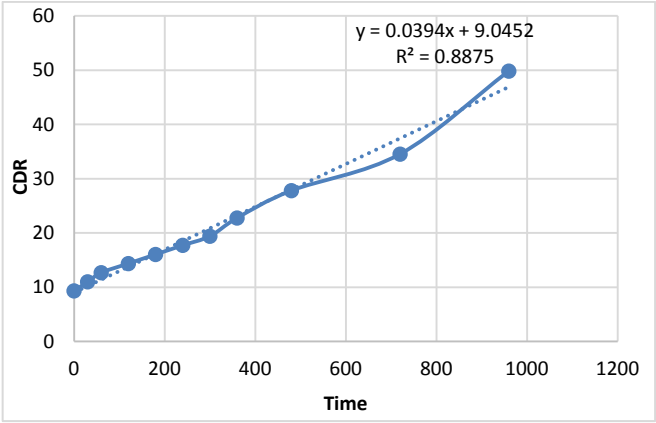

Figure 4: Model graph for comparative evaluation of Zero order Kinetics

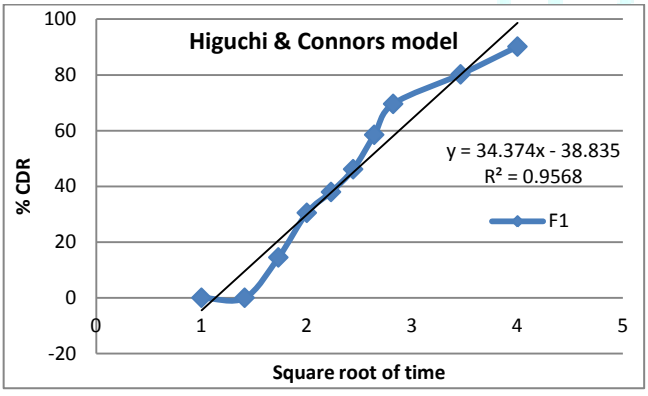

Figure 5: Model graph for comparative evaluation of Higuchi Kinetics

Comparative evaluation of Zero order kinetic model

Zero order describes the system where the release rate of drug is independent of its concentration.

Comparative evaluation of Higuchi Kinetic model

Higuchi developed model to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices.

CONCLUSION

Finally it is concluded that the Nanoemulsion loaded emulgel of Tolnaftate can be one of the promising tool in controlling the drug release via. Percutaneous mechanism for effective and longer treatment required for fungal infections with increased stability.

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