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Formulation, Development and Evaluation of Controlled Release Film Forming Gel for Antiseptic Activity.

Tulsidas Nimbekar*, and Shishupal Bodhankar.

Bajiraoji Karanjekar College of Pharmacy, Sakoli, Dist. Bhandara, Maharashtra, India -441802.

ABSTRACT

The suitability of drug with respect to lower dose, solubility, lower molecular weight and short half-life makes this drug as a suitable candidate for administration by transdermal route. The effectiveness of topical therapy depends on the physicochemical properties of the drug and adherence of the patient to the treatment regimen as well as the system's ability to adhere to skin during the therapy so as to promote drug penetration through the skin barrier. Conventional formulations for topical and dermatological administration of drugs have certain limitations like poor adherence to skin, poor permeability and compromised patient compliance. In the present study povidone-iodine transdermal films were prepared by various methods using polymer Eudragit L-100. The prepared transdermal films were evaluated for Appearance, thickness, folding endurance, weight variation, flatness, moisture absorption, moisture loss, moisture content, Folding endurance, water vapor transmission, and in vitro drug diffusion study. Drug polymer interactions were determined by FTIR. The transdermal films prepared by using Eudragit L 100 showed good physical properties. The formulation batch (F5) containing Eudragit L 100 showed maximum Antiseptic activity byfilm which was prepared by spray method & solvent casting method.

Keywords: Film forming polymers; Topical drug delivery; Antiseptic activity; povidone-iodine.

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Corresponding author

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INTRODUCTION

The skin is a very attractive organ for the application of pharmaceutically active substances due to its considerable size and easy accessibility. The skin is the largest organ of the human body with a surface area of approximately 1.5 – 2.0 m^2 and an average thickness of 0.5 mm (ranging from 0.05 mm to 2 mm). [1] As interface between the body and the outside world the skin fulfils important protective as well as sensory functions. It contains a variety of receptors to receive different impulses such as pressure, touch, temperature and pain for the communication between the body and the environment. Through its capillary system and the subcutaneous fatty tissue the body temperature is regulated. The mechanical strength of the skin protects the body against mechanical stress. Its low permeability for a broad range of substances shields the body against chemical and microbiological noxes and prevents the dehydration of the body by limiting the transepidermal water loss. [2]

The approach chosen for the new dosage form is a in-situ film forming polymeric formulations. On the skin surface the solution solidifies into a film which is able to deliver the active moiety to the skin. In-situ Film forming preparations are defined as non-solid dosage forms that produce a substantial film in situ after application on the skin or any other body surface. Such compositions can either be liquids or semisolids with a film forming polymer as basic material for the matrix. The formed film is sufficiently substantial to provide a sustained drug release to the skin and prevent the deposition of dust particles and reduces the chances of further infection. The polymerisation of the monomers takes place in situ and is catalysed for example by the presence of water on the skin. A wide variety of other ingredients such as fragrances, glycerol, petroleum jelly, dyes, preservatives, proteins and stabilizing agents are commonly added to polymeric formulations and can be used for the delivery of medication such as Antibiotics, Antiseptics, Antifungal, Anti-acne agents, Corticosteroids, Moisturizing or Protective agents (such as calamine) related to skin disorders and/or injury. [3, 4]

MATERIALS AND METHODS

Synthesis of povidone-iodine powder

The Synthesis of povidone-iodine powder was carried out as per the Procedure & Evaluation of povidone-iodine powder given by Lorenz et al. [5]

Identification Tests

A. Add 0.005 ml of a 10% w/v solution to a mixture of 1ml of starch indicator and 9ml of water, a deep blue colour is produced.

B. Spread 1ml of a 10% w/v solution over an area of about 20cm x 20cm on a glass plate and allow it to dry in air at room temperature and in an atm. Of low humidity overnight; a brown, dry, non-smearing film is formed which dissolves readily in water.

C. **Colour -** By visual inspection

Determination of "Free" Iodine in Povidone-iodine

The amount of uncomplexed, or free Iodine in a sample of povidone –iodine is determined using heptane as the solvent in a solid-liquid extraction procedure. The distribution coefficient of iodine between heptane and a given povidone-iodine complex is calculated using the equation:

$$K = (\{Ah-Ih\})\ (25) / Ih$$

Where K is the distribution, Ai is the available iodine in ml of povidone-iodine solution, and Ih is the number of milligrams of iodine in heptanes

Stability determination of povidone iodine[5]

The following calculation steps are performed to deduce the 6-hour stability of the povidone iodine sample. The available iodine value from bottle 2 is used to deduce the amount of iodine blank:

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Iodine blank = (Vb) (N) (12.692)/50 = Ib

Where Vb is the volume (in ml) of thiosulfate TS (having a normality of N) used in this titration . The available iodine value from bottle 1 is used to deduce the incubated amount of iodine:

Incubated sample Iodine = (Vb) (N) (12.692)/50 = Is

Where Vs is the volume (in ml) of thiosulfate TS used in this particular titration. The percent iodine loss incurred over the 6-hour stress test is calculated using:

Iodine loss = ({Ib-Is})(100)/Ib

Evaluation of Antiseptic activity [6]

Make two test tube of nutrient broth containing 9ml of broth in each test tube . add 1ml of water into each test tube and plug with cotton then incubate at 37 °C for 2 days. After two days the sterile NA pour it into petri plates it was form semi solid mass then pread culture all over the plate. Keep it into refrigerator for some time. After solidifing agar make cups into it add sample to boar and put it into incubator for 24hr.

Fourier Transform Infrared (FTIR) Spectral Studies

Fourier transform infrared (FTIR) spectral data were taken on Shimadzu instrument model to find out the functional group. Povidone- iodine powder crushed with potassium bromide to get the mixture which was then used for taking IR- spectra.

Selection of in situ-film forming polymers [6]

Not all the polymers having property to form a film so the following methods are chosen for preformulation study of polymer and to check the film forming property of polymers and form a film using various concentrations. The methods are taken into consideration such as **Measurement of pH**, **Density, Melting point**, **Solubility, etc.**

Optimization of formula

From the study of polymers it was concluded that Eudragit L-100 was selected as best film forming polymer and following table shows the optimized using different concentrations of Eudragit L-100.

Table 1- Optimization of formula

Formula	Eudragit L-100 (%)	PEG-400 (%)	Povidone-Iodine powder (%)	Iso propyl Alcohol (ml)	6.8 phosphate buffer (ml)
F1	1	2	5	75	25
F2	1.5	2.5	5	75	25
F3	2	3	5	75	25
F4	2.5	3.5	5	75	25
F5	3	4	5	75	25
F6	3.5	4.5	5	75	25

Selected formula

Based on the evaluation of above following formula was selected.

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Table 2 - Optimized formula

formula	Eudragit L-100 (%)	PEG-400 (%)	Povidone-Iodine powder (%)	IPA (ml)	6.8 phosphate buffer (ml)
F5	3	4	5	75	25

Method of prepration – Weighed given quantity of Eudrgit L-100 and transferred into the beaker containing IPA and 6.8 Phosphate buffer and dissolve the polymer. Then add prepared povidone-iodine powder and also dissolved them into the polymeric solution then add plasticizer.

Evaluation of above In-situ film forming polymeric solution[7]

Density - The density by using following formula:

$$\text{Density} = \text{Mass/volume } (g/cm^3)$$

Viscosity – Determined by Oswald viscometer & calculated by using following formula:

$$n_1/n_2 = p_1t_1/p_2t_2$$

Iodine content - Weighed 3g of povidone-iodine solution transfer to a beaker and add 200 ml of water .cover the beaker and stirred with a mechanical stirrer at room temperature for not more than 1 hour to dissolve as completely as possible. Titrate immediately thereafter with 0.1 M sodium thiosulphate using 3ml of starch solution, added towards the end of the titration, as indicator.

Spreadability - Spredability of the formulation was determined by using ROLEX ointment slab method. Spredability is given in unit gm.cm/sec. Spredability of the formulation determined by the following formulation.

$$S = M \times L/T$$

Where, L-length moved by glass slide, T- Time in seconds, M- Weight in pan .

Antiseptic activity

Make two test tube of nutrient broth containing 9 ml of broth in each test tube. Add 1ml of water into each test tube and plug with cotton then incubate at 37 °C for 2 days. After two days the sterile NA pour it into petri plates it was form semi solid mass then spread culture all over the plate. Keep it into refrigerator for some time. After solidifying agar make cups into it add sample to boar and put it into incubator for 24hr.

Solvent Casting method- Film were produced by solvent evaporation on a glass slide. Into this slide pour 15 ml of the polymeric solution were cast and left to dry at room temperature for 24 hours.

Evaluation of film which was prepared by solvent casting method and by spray method [8,9, 10]

Appearance- All prepared films were evaluated for their appearances i.e. if they are transparent or opaque.

Thickness of film- The thickness of film was measured by vernier caliper. The thickness uniformity was measured at five different sites of film and average of five reading was taken with standard deviation.

Drying time- For the assessment of the drying time the formulation was applied to the inner sides of the forearm of a human volunteer. After 2 minutes a glass slide was placed on the film without pressure. If no remains of liquid were visible on the glass slide after removal, the film was considered dry. If remains of liquid were visible on the glass slide the experiment was repeated until the film was found to be completely dry.

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Moisture absorption studies- The moisture absorption study was carried out at 75% RH at 25 ± 1°C using saturated solution of sodium chloride. The pre-weighed samples of film were kept under the humidity condition as mention above and weighed the film after 24 hours. The increase in the weight indicates the moisture absorption by samples which can be calculate by using the following formula,

$$\% \text{ moisture absorption } = \frac{W2 - W1}{W1} \times 100$$

Where, W1 = initial weight of film. W2 = weight of film after 24 hours placed in desiccators.

Water vapor transmission rate (WVTR)- The WVTR study was carried out in desiccators maintained at 43% and 75% RH at 25 ± 1°C using saturated solution of potassium carbonate and sodium chloride respectively. Film were placed on the mouth of glass vials containing fused calcium chloride and sealed using silicon wax. These vials were accurately weighed and placed in desiccators at 43% and 75% RH. The weight of the vials was recorded after 24 hours. The water vapor transmission rate was calculated by using the following formula,

$$WVTR = \frac{W2 - W1}{W1} \times 100$$

Where, **W1** = initial weight of vials sealed with film. **W2** = weight of vials after 24 hours placed in desiccators

Folding endurance of film - The folding endurance was measured manually for the prepared film. A strip of film (4×3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

Weight variation test of film -The three disks of 2×2 cm^2 of film was cut and weighed on electronic weigh balance for weight variation test.

The test was done to check the uniformity of weight and thus check the batch-to-batch variation.

In-vitro drug diffusion study of film -The drug diffusion study through film were conducted by using vertical type diffusion cell (Franz type) having receptor compartment 15ml volume with 2cm^2 area. The receptor compartment was filled 15ml of phosphate buffer pH 7.4; the activated dialysis membrane was mounted on the flange of the diffusion cell receptor compartment. The prepared film placed on center of membrane with sufficient quantity of drug, the donor compartment was then placed in position and the two valves of the cell clamped together. The whole assembly was kept on a magnetic stirrer and solution in the receptor compartment was constantly stirred using a magnetic bead at 32°C maintained.

RESULTS AND DISCUSSION

Evaluation of povidone-iodine powder: Assay-Iodine content

As per BP 1ml of 0.1 M sodium thiosulphate is equivalent to 0.01269 g of I.

Theoretical yield = 6 %
Practical yield = 5 %

So available iodine in 5% povidone-iodine powder was **0.833 %**

The only available iodine shows the antiseptic activity so that its necessary to determined the available iodine in povidone-iodine complex.

Identification

A. A deep blue colour is produced.
B. A brown, dry, non-smearing film is formed which dissolves redily in water.

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The above identification test (**A&B**) confirms that the synthesized povidone-iodine powder was same as standerd povidone-iodine powder.

C. Colour- The colour of povidone-iodine powder was observerd visually and it was brown in colour.

Determination of "Free" Iodine in Povidone-iodine

The amount of uncomplexed or free Iodine in a sample of povidone–iodine was determined as described in previous section**.** The result was shown in table **4.** The value of k (Distribution coefficient) within range. i.e K value must be greater than 100-150. Because distribution coefficient greater than 100-150 indicates that no iodine odor was detected and therefore satisfactory iodine-polymer complexing was assumed to be present.

Stability determination of povidone-iodine

The stability of a given povidone-iodine sample was determined as described in previous section and calculate the value using formula**.** The result was shown in table **4.** Iodine is hygroscopic in nature and sublimes in atmosphere hence stability determination of povidone-iodine powder was necessary to performed and result shows that only 18% iodine loss after 6 hours at 75^0c.

Antiseptic activity

Antiseptic activity was performed and the sample plate of antiseptic activity shown below:

Zone of Inhibition = **2.8 ± 0.2 cm**

The zone of inhibition indicates that the area where the growth of micro-organisams does not took place and the povidone-iodine powder shows the antiseptic activity.

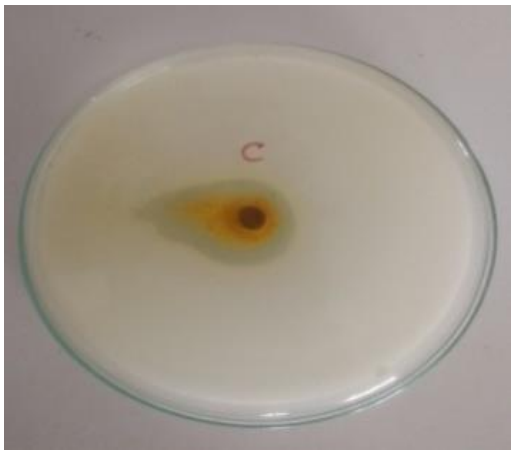

Figure- sample plate (Povidone-iodine powder)

Fourier Transform Infrared (FTIR) Spectral Studies

Interpretation of FT-IR graph of povidone-iodine powder were given in **3** which was interpreted from figure.

Table 3- details of FT-IR of povidone-iodine powder

Sr. no	Frequency (cm^{-1})	Assignment
1	2949	Aliphatic –CH- stretching mode
2	2884	Aliphatic –CH- stretching mode

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3	1678	Carbonyl stretching mode
4	1453	Hetrocyclic ring mode
5	1420	-CH2 scissors derormation mode
6	1373	-CH2 and –CH wagging mode
7	1283	-CH2 bending mode

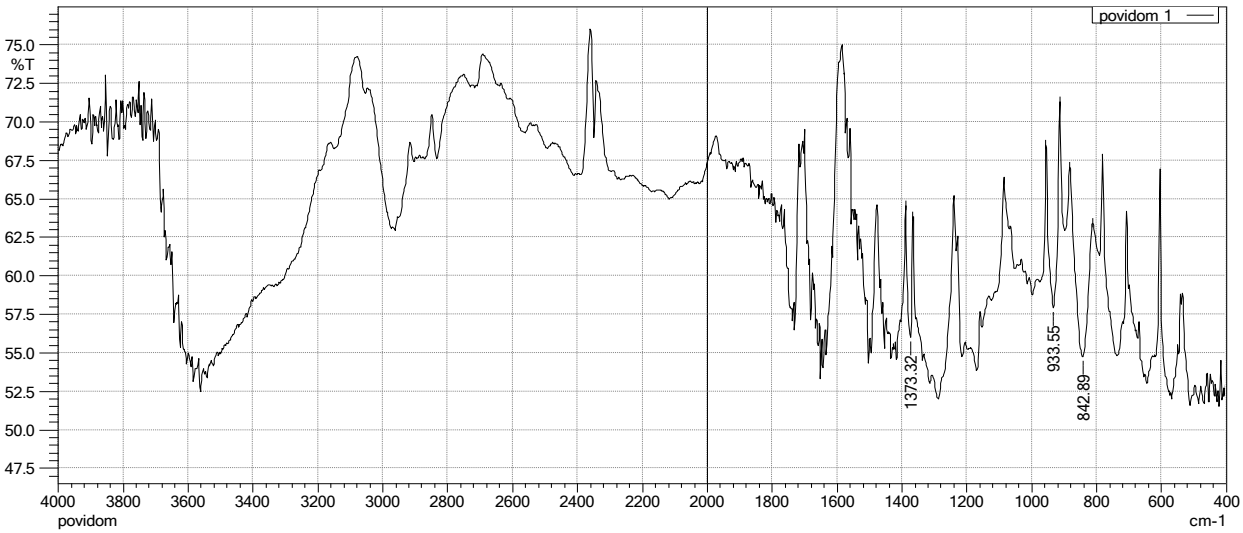

Figure- Fourier Transform Infrared (FTIR) Spectral graph of povidone-iodine powder.

Table 4- Evaluation of povidone-iodine powder

Parameters	Assay	Identification	Colour	Determination of "Free" Iodine in Povidone-iodine	Stability determination of povidone iodine	Antiseptic activity
Result	Practical yield 5% = available iodine 0.833%	A- A deep blue colour . B-A brown, dry , non-smearing film is formed which dissolves readily in water	Brown colour	K=121	Iodine loss = 28%	Area of inhibition =2.8±0.2cm

Selection of In situ-film forming polymers

Table 5- Selection of In situ-film forming polymers

Sr. no	Polymers	pH	Density g/cm^3	Melting point	Solubility
1.	Hydroxy propyl cellulose	5.0-8.5	0.5	120-130^0	Ethanol and methanol
2.	Hydroxy propyl methyl cellulose-	5.5-8.0	1.39	190-200^0	cold water
3.	Polyvinyl alcohol-	5.0-6.5	1.19-1.31	228-230^0	water and in organic solvents
4.	PVP-K-30	3.0-7.0	1.2	150-180^0	Water
5.	Sodium alginate	6-8	1.601	300^0	Water
6.	Eudragit L-100	6.0-6.5	1.062	216-220^0	IPA, ethanol

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Optimization of polymer and plasticizer concentrations

Table 6- Optimization of polymer and plasticizer concentrations

Sr. no	Polymers	(gm)	Plasticizers	(gm)	Solvent	(ml)	Result
1	HPC	0.5	Triethyl citrate	0.2	Ethanol	20	Film not formed
2	Eudragit l-100	2	Triethyl citrate	0.5	IPA	20	Thick film formed
3	PVP-K 30	2	Dibutyl phthalate	0.8	Ethanol	20	No film formed
4	Eudragit L-100	1.5	Glycerol	1.5	Ethanol	20	No film formed
5	Eudragit L-100	2	Propylene glycol	1	IPA	20	More plastic film formed
6	Eudragit L-100	2	PEG- 400	0.75	IPA	20	Good film
7	Sodiumalginate	2	Propylene glycol	0.5	Ehanol	20	Not film formed
8	PVA	2	Triethyl citrate	0.5	Ethanol	20	Good film

Evaluation of In-situ film forming polymeric solution

Table 7- Results of Evaluation of In-situ film forming polymeric solution

Parameters	Batch1	Batch2	Batch3	Batch4	Batch5	Batch6	Mean± SD
Density g/cm^3	0.836	0.7170	0.948	0.883	0.934	0.901	0.86±0.084
Viscosity cps	40.32	33.42	29.51	37.90	39.15	34.45	35.79±4.077
Iodine content %	0.801	0.790	0.731	0.811	0.781	0.776	0.78 ±0.02
Spredability (gm cm / sec)	12.2	12.6	13.1	14	13.5	14.3	13.28±0.808
Antiseptic activity (zone of inhibition cm)	2.3	2.6	3.1	3	2.8	3.5	2.88 ±0.41

Evaluation of film which was prepared by solvent casting method

Table 8 -Evaluation of film which was prepared by solvent casting method

Parameter	F1	F2	F3	F4	F5	F6	Mean ±SD
Appearance	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent	
Thickness	1mm	1mm	1mm	1mm	1mm	1mm	
Drying time in min.	5.43	3.45	5.23	5.55	4.45	6.35	5.07±1.00
Moisture absorption	2.20	4.33	3.16	3.78	4.41	4.90	3.79±0.98
Water vapor transmission rate(WVTR)	3.83	3.91	2.10	3.45	2.9	4.3	3.41±0.79
Folding endurance	37	27	33	38	21	40	32.66±7.33
Weight variation(avg.)	0.292	0.286	0.285	0.290	0.285	0.275	0.285±0.005

in gm							
% drug release	68.34	72.39	69.12	76.90	74.27	71.85	72.14±3.19

Table 9 -Evaluation of film which was prepared by spray method

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**Mean ±SD**
Appearance	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent	
Thickness	1mm	1mm	1mm	1mm	1mm	1mm	
Drying time in min.	6.34	5.54	5.12	7.00	6.33	6.45	6.13±0.67
Moisture absorption	2.45	4.14	3.25	4.55	2.90	4.56	3.64±0.89
Water vapor transmission rate(WVTR)	4.45	3.78	2.89	3.45	3.47	4.19	3.70±0.56
Folding endurance	31	29	33	26	21	23	27.16±4.66
Weight variation(avg.) in gm	0.281	0.286	0.285	0.290	0.280	0.275	0.282± 0.005
% drug release	71.34	72.39	68.45	76.56	74.23	73.85	72.88±2.77

SUMMARY AND CONCLUSION

Aim of present research work was to developed in-situ film for skin injury. In-situ polymeric film intended to sustained release of drug and cover the skin injury to prevent the deposition of dust particles.

In market most of the antiseptic lotions, creams are available but problem with this type of dosage form is that they washed off along with the fluid present on skin injury. And most of the skin injury /wounds are necessary to remains open. So that to overcome this drawback the present study was carried out to formulate and evaluate film forming polymeric solution.

In the beginning synthesized the povidone-iodine powder as an antiseptic agent i.e API and evaluated. The API evaluations showed satisfactory result.

The film forming polymer Eudragit L-100 was selected from preformulation study and optimized the formula by evaluating for various parameters. Prepared film using solvent casting method and in-situ film by spray method and films were evaluated for appearance, thickness, folding endurance, drying time, moisture absorption , water vapour transmission, in-vitro diffusion study.

From the above studies it can be concluded that in-situ film can be successfully prepared for sustained release of a drug for local action on skin like skin injury. Along with cover the skin injury and protect it from deposition of dust particles and prevent further infection and improved patient compliance.

REFERENCES

[1] P. Patil, S. Shrivastava, Fast dissolving oral film: An innovative drug delivery system, International journal of sciences and research (2012).
[2] A. Arya , A. Chandra , K. Sharma , K. Pathak , Fast dissolving oral film an innovative drug
[3] delivery system and dosage form, International journal of chem. Tech research, (2010), 2(1).

[4] A. Tucker, Z. Chik, L. Michaels, K. Kirby, M. Seed, A. Johnston, C.A.S. Alam, Study of a combined percutaneous local anaesthetic and the TDS system for venepuncture, Anaesthesia 61 (2006) 123-126.

[5] Kashmira Kathe, Harsha Kathpalia, Film forming systems for topical and transdermal drug delivery, Asian Journal of Pharmaceutical Sciences, Volume 12(6), 2017, Pages 487-497

[6] Lorenz et al. Patent US4128633 Process for preparing povidone-iodine complex page no. 4&5

[7] Indian pharmacopoeia 1996 volume 11 page no 645.

[8] M. Aquil , A.Ali , Fabrication and evaluation of polymeric films for transdermal delivery of pinacidil: Pharmazie. 2004; 59: 631-635.

[9] M. Leichtnam, H. Rolland, P. Wüthrich, R. Guy, Formulation and evaluation of a testosterone transdermal spray, J. Pharm. Sci. 95 (2006) 1693-1702.

[10] Shivhare U.D., Dorlikar V.P., Bhusari K.P., Mathur V.B., Mirani B.N. Effect of polymeric compositions on pharmacotechnical properties of Carvedilol transdermal film. Int. J. Pharm. Sci. Nanotech.2009; 2:457-459.

[11] B. Mikari, K. Mahadik, Formulation and evaluation of topical liposomal gel for fluconazole, Indian J.Pharm Sci (2010) 44(4), 324-325.