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Design, Development & Evaluation of Solid Dispersion Incorporated Transdermal Gel of Benzoyl Peroxide

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ABSTRACT

Benzoyl peroxide (BPO) an antiacne agent was chosen as model drug for present study is commonly used in topical formulations for the treatment of acne. The major drawback of Benzoyl Peroxide is its poor aqueous solubility. Solid Dispersion is an effective approach to improve its solubility and dissolution. To improve the permeability of Benzoyl Peroxide, the use of gel bases is a logical approach to increase the drug flux across the epithelium. Penetration rate of drugs through the stratum corneum can be increased with appropriate vehicles and transdermal permeation enhancers. Stability of the solid dispersion incorporated trandermal gel of Benzoyl Peroxide can be improved with the use of Propylene Glycol. Solid dispersion of Benzoyl Peroxide was prepared in β-cyclodextrin, PEG6000 by kneading method and were characterized for Drug Content. Out of which optimised gel showed the best *in-vitro* drug release having better dissolution, permeation and stability used for the treatment of Acne.

KEYWORDS: - Benzoyl Peroxide, Solubility, solid dispersion, dissolution, transdermal penetration enhancers, β-cyclodextrin, *in-vitro* drug release, drug content.

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INTRODUCTION

Solid Dispersion

Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in a solid state[1]. Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment and suppository bases, and improved solubility and stability[2]. Chiou and Riegelman defined the term solid dispersion as "*A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures*"[3]. The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent or the melting solvent method. It refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[4].

Solid dispersion is a unique approach which was introduced by Sekiguchi and Obi. The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi Sekiguchi. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs[5]. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. In solid dispersion method, the drug is dispersed in extremely fine state in an inert water soluble carrier in solid state. In order to achieve increased dissolution rate, sustained release of drugs and thus improve solubility and stability. A number of freely water soluble materials such as citric acid, succinic acid, bile acids, sterols and related compounds and polymers like polyvinyl pyrrolidone and polyethylene glycols are used as carrier for solid dispersions. By this approach the dissolution rate and bioavailability of poorly soluble drugs can be increased. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs.

Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in

this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersion, a first stated by Mayersohn and Gibaldi.

Solid dispersion can be prepared by fusion process, solvent process, melting solvent method, physical mixture, kneading method, supercritical fluid method. Solid dispersion is an effective technique which can easily enhance the dissolution rate of drugs[6]. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method. The technique has been used for a wide variety of poorly aqueous soluble drug. Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate.

Benzoyl peroxide (BPO) an antiacne agent was chosen as model drug for present study is commonly used in topical formulations for the treatment of acne. The major drawback of Benzoyl Peroxide is its poor aqueous solubility. Solid Dispersion is an effective approach to improve its solubility and dissolution. To improve the permeability of Benzoyl Peroxide, the use of gel bases is a logical approach to increase the drug flux across the epithelium.

Acne is the term for plugged pores (black heads and white heads), pimples and even deeper lumps (cysts or nodules) that occur on the face, neck, chest, back shoulders and even uper arms. Acne vulgaris (commonly called acne) is a skin condition caused by changes in the pilosubaceous units[7]. It is a common inflammatory disease in skin areas where sebaceous glands are largest, most numerous and active. It affects individuals of all races covers 85% of teenagers, 42.5% of men and 50.9% of women between the ages of 20 and 30 years[8]. Several hormones implicated in the regulation of sebaceous gland activity have been linked to acne. They include androgens, estrogens, progesterone, growth hormone, insulin, insulin-like growth factor, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), melanocortins and glucocorticoids. The more severe the acne, the greater the negative impact on quality of life (QOL) [9].

The term "Gel" was introduced in the late 1800 to name some semisolid material according to pharmacological, rather than molecular criteria. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. The inorganic particles form a three-dimensional "house of cards" structure[10].

MATERIALS AND METHODS USED

Benzoyl Peroxide was a gift sample obtained from Heliox Pharma. Betacyclodextrin were provided by Rouquette India Pvt. Ltd, Mumbai. PEG6000 was supplied from Central Drug House Pvt. Ltd, Delhi. Carbopol was obtained from Lubrizol Pvt. Ltd, Mumbai. All the chemicals and solvents were of analytical grade.

PREPARATION OF SOLID DISPERSIONS

- ***Preparation of Physical Mixture***

The Physical mixture of Benzoyl Peroxide prepares using PEG6000 & betacyclodextrin in 1:1, 1:2, 1:3 ratios were obtained by mixing pulverized powders of drugs and various carriers with the help of spatula.

- ***Preparation by Kneading Method***

Inclusion complex by the kneading method was prepared by geometric mixing of the drug and polymer in molar ratio. Then the mixture was kneaded with 1ml of (the minimum amount of organic solvent possible) 1:1ml of Ethanol: Water to obtain a pasty mass, which is needed for a determined time and then dried in an oven 45 to 50˚C for 24 hours. The dried mass was pulverized and passed through sieve # 100 and stored in desiccators[11].

CHARACTERISATION OF SOLID DISPERSIONS

The prepared solid dispersion were evaluated for drug carrier interaction by using: X-ray powder diffraction patterns were recorded on Xray diffractometer, Panalytical spectris Pvt. ltd. Singapore using copper as tube anode; the diffractograms were recorded under following conditions: voltage 40 kV, 35 mA, angular range 5 and fixed divergence slit. The scanning was done over 2θ range of 5º to 60ºC. FTIR spectrum was carried by KBR pellet method[12, 13].

- ***Drug Content***

Solid dispersion was taken by calculating the yield equivalent to the 5 mg then diluted to 5 ml with ethanol. After that filtering the stock solution, filtrate was diluted suitably and absorbance was measured against blank at 274 nm[14].

- ***Determination of Percent Practical Yield (PY)[15]***

To determine the efficiency of any method of production, Percentage practical yield was calculated. In this method pre-weighed solid dispersions were collected to determine practical yield (PY) from the following equation:

Percent Practical Yield (PY) = (Weight of Practical solid dispersions × 100)/ Theoretical weight (Benzoyl Peroxide + Polymer).

PREPARATION OF SOLID DISPERSION INCORPORATED GELS

Carbopol 0.25%, 0.50%, 0.75%, 1% was added to purified water with stirring. Stirring of mixture was done for 40 min. Then sodium hydroxide dissolved in water was added to mixture and stirred for 10 min. Add 10% propylene glycol to all the above compositions of carbopol gel and 5% add DMSO in 0.75%, 0.1%. The mixtures were stirred for 30 minutes till elegant and smooth gel was obtained. Optimised Solid dispersion formulation of Benzoyl Peroxide (F4) was dissolved in ethanol and added to above mixture and stirred for 15 minutes. Prepared gel was store in a suitable container[16].

PHYSICAL CHARACTERIZATION OF GELS

Physical characterization such as Homogeneity, viscosity, PH, drug content was measured.

- ***Homogeneity***

Optimized gel was properly tested for homogeneity by visual inspection after gel has been set in the container. Gel was tested for its appearance and presence of any aggregates[17].

- ***Determination of Viscosity***

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 10 rotations per minute. At each speed, the corresponding dial reading was noted. The viscosity of the gel was obtained by multiplication of the dial reading with factor given in the Brooke field Viscometer catalogues[18].

- ***Measurement of pH***

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and average values are calculated[19].

- ***In Vitro Diffusion Studies for Solid Dispersion Incorporated Gels***

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying. The dissolution release of gels through an Egg membrane. Gel sample (1gm) was taken in Egg membrane and the diffusion studies were carried out at 37±1°C using 30 ml of phosphate buffer (pH 7.4) as the dissolution medium. Three milliliters of each sample was withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample was replaced with equal volume of fresh dissolution medium. Then the samples were analyzed for drug release studies by using phosphate buffer as blank[20].

RESULTS AND DISCUSSION

Table1. Composition of Solid dispersion with different polymers

Formulation code	Drug : carrier ratio	Carrier
B1	1:1	
B2	1:2	
B3	1:3	Betacyclodextrin
B4	1:4	
B5	1:5	
P1	1:1	
P2	1:2	
P3	1:3	PEG6000
P4	1:4	
P5	1:5	
F1	1:5:1	
F2	1:5:2	
F3	1:5:3	Betacyclodextrin:PEG6000
F4	1:5:4	
F5	1:5:5	

CHARACTERISATION OF OPTIMISED SOLID DISPERSIONS

- ***Drug Content***

Table2. Drug content of optimized Solid dispersion

Optimised formulation	Absorbance	%Drug Content (Mean±S.D.)
F4	0.367	71.6±0.08

- ***Determination of Percent Practical Yield (PY)***

Practical yield = 3.510 gm

Theoretical yield =4.88 gm

% Practical yield = (Weight of Practical solid dispersions × 100)/ Theoretical weight (Benzoyl Peroxide + β-cyclodextrin + PEG 6000)

= (3.510x100)/ 4.88

= 71.92%

% Practical yield is 71.92%

- ***XRD of Optimised Solid Dispersion of Benzoyl Peroxide***

The ternary systems of all the formulations with β-CD showed some diffraction 2θ peaks with little intensity, which is attributed to a crystalline nature of β-CD. Modified and hollow pattern suggesting the formation of amorphous inclusion complex of drug with and β-CD and PEG 6000.

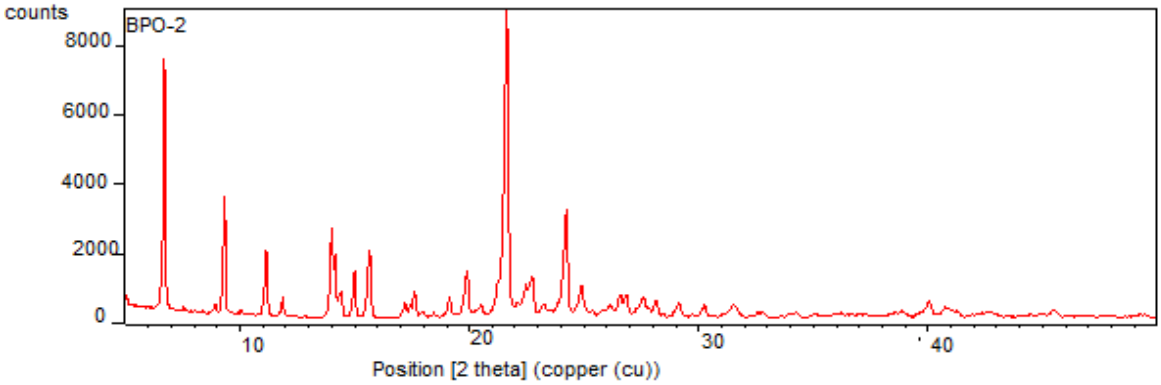

Figure1. XRD of optimised solid dispersion of Benzoyl Peroxide

PHYSICAL CHARACTERISTICS OF OPTIMISED SOLID DISPERSION INCORPORATED GELS

Table3. Physical characteristics of optimised solid dispersion incorporated gel

BATCH	pH	%Drug Content	Homogeneity	Viscosity (Cp)
G1	6.4	80 ± 0.02	Good	1015
G2	6.3	68 ± 0.04	Good	2402
G3	6.9	71.5 ± 0.06	Good	1230
G4	6.5	84.5 ± 0.08	Good	2630
G5	6.8	90 ± 0.05	Good	2166
G6	7.2	83 ± 0.03	Good	1003

Results shows that G6 solid dispersion incorporated trandermal gel has more pH than all of the

Above which matches with the pH of the skin**.**

DRUG CONTENT OF OPTIMIZED SOLID DISPERSION INCORPORATED TRANSDERMAL GEL OF BENZOYL PEROXIDE

Lack of crystallinity, i.e. amorphization, increased wettability, dispersibility and particle size reduction are considered to be important factors for dissolution rate enhancement. It is indicated β-cyclodextrin plays the role as dissolution rate promoter due to its ability to solubilize compounds via stabilization of supersaturated drug solutions presumably by inhibition of nucleation and arresting crystal growth. Therefore the formulation G5 shows higher drug content from all the gel formulations.

Table 4. Drug content of optimized solid dispersion incorporated transdermal gel of Benzoyl Peroxide

S.No.	Batch	Absorbance	%Drug Content
1	G1	0.169	80 ± 0.02
2	G2	0.145	68 ± 0.04
3	G3	0.152	71.5 ± 0.06
4	G4	0.178	84.5 ± 0.08
5	G5	0.189	90 ± 0.05
6	G6	0.175	83 ± 0.03

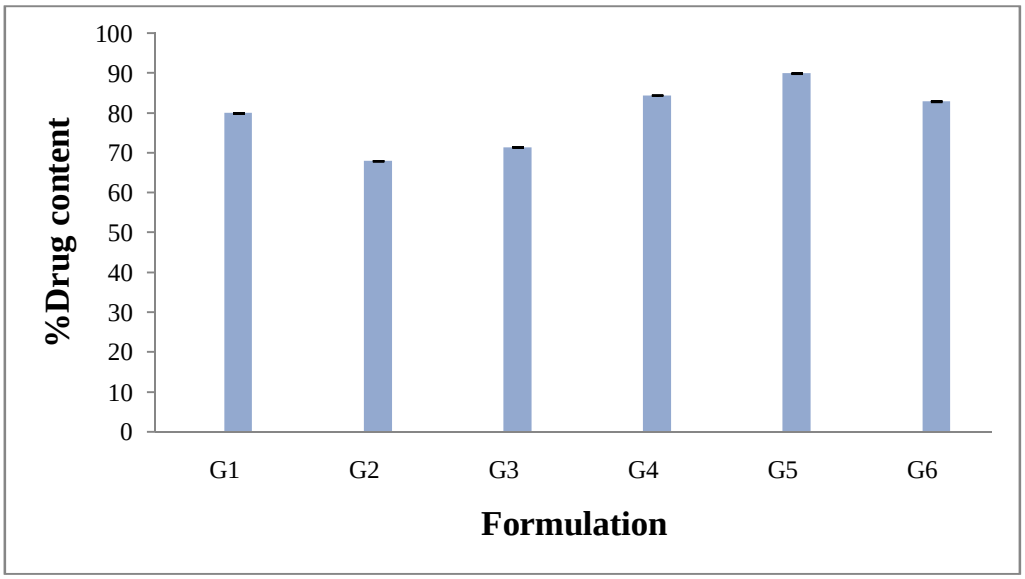

Figure2. Graph between %Drug content of optimised solid dispersion incorporated transdermal gel of Benzoyl Peroxide in various Formulations gel of benzoyl peroxide

IN-VITRO *DRUG RELEASE STUDY OF OPTIMIZED SOLID DISPERSION INCORPORATED TRANSDERMAL GEL OF BENZOYL PEROXIDE*

In-vitro drug release study was performed by Franz diffusion cell method using phosphate buffer (pH 7.4) as dissolution media. Drug release profile and a comparison of its release profile with pure drug as shown in figure.

Table 5. % Drug release of optimized solid dispersion incorporated transdermal gel of Benzoyl Peroxide

S.No.	Time (hrs)	% Drug Release (Mean ± S.D.)			
		Pure Benzoyl Peroxide	**G3**	**G5**	**G6**
1	0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	1	1.875±0.02	5.625±0.02	12± 0.02	7.5± 0.02
3	2	7.5±0.04	20.625±0.03	22.25±0.03	28.125±0.03
4	3	15±0.06	28.125±0.05	28.125±0.05	33.75±0.05
5	4	22.5±0.08	33.75± 0.08	31.75±0.08	39.375±0.08
6	5	26.25±0.07	39.375±0.06	33.75±0.06	45± 0.06
7	6	31.875±0.05	43.125±0.04	37.5±0.04	50±0.04
8	7	37.5±0.03	46.875±0.07	41.25±0.07	65.625± 0.07
9	8	43.125±0.01	50.375±0.09	45±0.09	71.25 ±0.09
10	9	45±0.09	54.875±0.12	49±0.12	80.625± 0.12

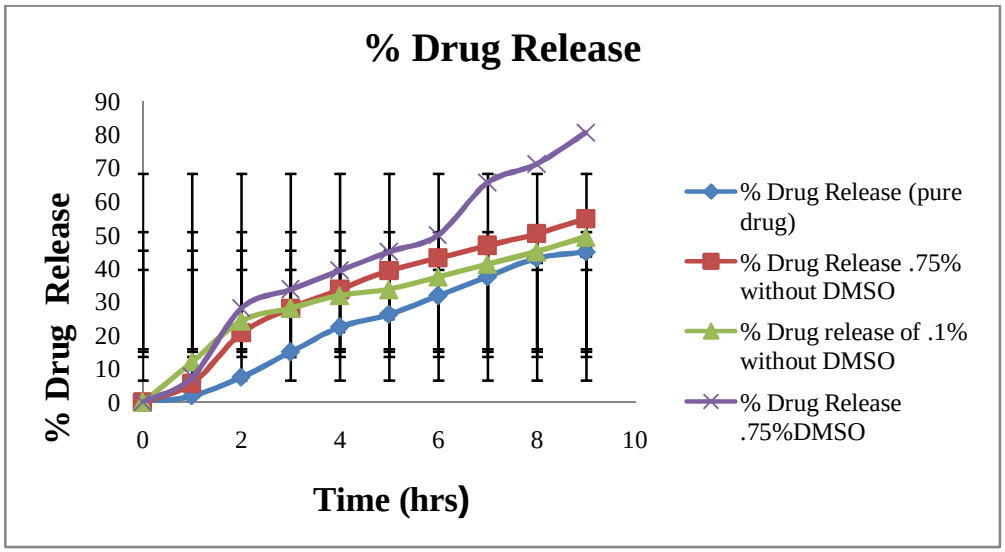

Figure3. *In-Vitro* Release study

Results shows that 0.75% Solid dispersion incorporated Transdermal gel of Benzoyl Peroxide containing DMSO as a permeation enhancer shows much higher % Drug Release as compared with the pure drug. The increased drug release of formulation G6 (0.75% optimised solid dispersion incorporated trandermal gel containing DMSO) *in vitro* release may be due to decreased viscosity of the gel.

CONCLUSION

The aim of this study was to formulate and evaluation of solid dispersion incorporated gel for better percutaneous absorption and provide stability. To improve the permeability of Benzoyl Peroxide, the use of gel bases is a logical approach to increase the drug flux across the epithelium. Penetration rate of drugs through the stratum corneum can be increased with appropriate vehicles and transdermal permeation enhancers. Stability of the solid dispersion incorporated trandermal gel of Benzoyl Peroxide can be improved with the use of Propylene Glycol. β-Cyclodextrin plays the role as dissolution rate promoter due to its ability to solubilize compounds via stabilization of supersaturated drug solutions presumably by inhibition of nucleation and arresting crystal growth. PEG was found to be the most suitable auxiliary substance in terms of superior complexation efficiency and stability constant. Higher stability constant values in the presence of PEG suggest a significant improvement in the complexation efficiency between Benzoyl Peroxide and β-cyclodextrin.

Out of the fifteen formulations, F4 showed marked increase in the solubility as well as the dissolution. The solid dispersion prepared by Kneading method showed improved dissolution. It is indicated β-cyclodextrin plays the role as dissolution rate promoter due to its ability to solubilize

compounds via stabilization of supersaturated drug solutions presumably by inhibition of nucleation and arresting crystal growth. From the above results, on the basis of drug release it may be concluded that solid dispersion incorporated Gel of Benzoyl peroxide(G6) were better for improvement of dissolution and diffusion of Benzoyl Peroxide and also to overcome acne problems and skin irritation side effects.

REFERENCES

1. Reddy D, Sivanarayana P. International Journal of Pharmacy, 2013; 3(1): 170-172.
2. Dixit AK, Singh RP. International Journal of Pharmacy & Biomedical Sciences, 2012; 3(2): 960-966.
3. Verma S, Rawat A. International Journal of Pharmacy and Technology, 2011; 3(2) :1062- 1099.
4. Luhadiya A, Aggarwal S. International Journal of Advanced Research in Pharmaceutical & Bio Sciences, 2012; 2(2): 281-291.
5. Singh S, Baghel RS, Yadav L. International Journal of Pharmacy & Life Sciences, 2011; 2(9): 1078- 1095.
6. Aejaz A, Azmail K, Sanaullah S. International Journal of Applied Pharmaceutics, 2010; 2(1):7 12.
7. Jotish M, Pranitha NC. Novel Drug Delivery System and its use in the Treatment of Acne, International Journal of Pharmacy and Technology, 2010; 2 (1): 41- 53.
8. Wankhede R, Bhalerao S. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(4): 527-531.
9. Arora MK, Yadav A. Clinical Biochemistry, “Review of Role of hormones in acne vulgaris”, Elsevier, 2011; 44: 1035–104.
10. Bhoyar N, Giri TK. Journal of Pharmacy and Allied Health Sciences, 2012; 2(2): 21-39.
11. Patil JS, Pandya NR. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(1): 71-81.
12. Chaulang G, Patil K. Research Journal of Pharmacy and Technology, 2008; 1(4): 386- 389.
13. Chadha R, Gupta S. Results in Pharma Sciences, Elsevier, 2011: 38–48.
14. Rao AB, Shivalingam MR. International Journal of Pharmaceutical Sciences and Drug Research, 2010; 2(2): 146-150.
15. Singh A, Sharma PK. Asian Journal of Pharmaceutical and Clinical Research, 2011; 4(1): 117 119.
16. Wankhede R, Bhalerao S. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(4): 527-53.

17. Ganpathi J, Laxmanan D. International Journal of Pharmaceutical and Industrial Research, 2012; 2(1): 26-29.
18. Grove J, Durr M. The effect of vehicle viscosity on the ocular bioavailability, 1990; 23–28.
19. Shivhare U, Jain K. Formulation, development and evaluation of diclofenac sodium gel using water soluble polycrylamide polymer, Digestion Journal of Nanomaterials and Biostructures 2009; 4: 285-290.
20. Thakur V, Prashar B. Drug Invention Today, 2012; 4(8): 414-419.