ORIGINAL ARTICLE

Formulation development of topical solutions of poorly water-soluble drug indomethacin employing novel application of mixed solvency concept and their evaluation

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Abstract

Aim: Application of mixed solvency concept has been employed in the present research work to develop the topical solution formulations of poorly water-soluble drug indomethacin (as a model drug). **Material and Method:** Due to the low solubility of indomethacin in water, combination of solubilizers as mixed solvent systems was used to decrease the overall concentration of solubilizers required to produce a substantial increase in solubility and thereby resulting in enhanced permeation of indomethacin from its topical formulation. The procured sample of indomethacin was characterized by melting point, infrared, ultraviolet, and differential scanning calorimeter studies. The formulations were evaluated for various properties of a solution such as pH, viscosity, freeze-thaw study, and thin layer chromatography. Stability studies of topical indomethacin solutions were performed for 2 months at room temperature, 30°C and 40°C. **Result:** The results of stability studies of indomethacin topical solution were satisfactory. It was found that 95.07%, 93.88% and 93.45% of drug was remaining after stability study at respective temperatures in batch first and 94.89%, 94.44% and 94.32% in batch second. **Conclusion:** Mixed solvency concept successfully employed to improve the drug loading of poorly water soluble drug indomethacin.

Key words: Indomethacin, mixed solvency, nonsteroidal anti-inflammatory drug, solubility, topical solution

INTRODUCTION

Drug delivery through topical route represents a most convenient and novel approach for the application to the skin for direct treatment of cutaneous disorder (e.g., acne) or the cutaneous manifestation of a general disease (e.g., psoriasis) having the intent of containing the pharmacological or different other effects of the drug for the surface of the skin and within the skin. The major difficulty comes while delivering a drug through the skin is its action as a natural barrier. The major barrier layer of the skin is the stratum. Molecules of the drug penetrate through the skin primarily through the tortuous and continuous intercellular paths. Only those drugs can penetrate which are in the form of the molecular state through the skin.

One of the oldest dosage forms which is used in the treatment of disease and has the rapid and very high absorption of soluble medicinal products is the solution. The solution which is applied directly to the skin is called topical solution.[1] Topical formulations are made in the vehicle, which can be optimized for a particular site of the body and various types of skin conditions. The product may be designed in such a way to maximize or to moisturize the penetration of an active ingredient and medicine, into or through the skin.[2] Two major key characteristics that need to be taken into the consideration while compounding the solutions are solubility and stability.[3] Topical solution acts locally and targets at the site of allergy and inflammation

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resulting in reduced side effects and toxicity to other organs. Low aqueous solubility is the main problem for the formulation development of the various other new chemical entities as well as for various generic developments. Water is the main solvent chosen for liquid pharmaceutical formulations.[4,5] Solubility improvement techniques include derivatization, alteration of pH, cosolvency, hydrotropic solubilization, and mixed solvency.

As per the mixed solvency concept proposed by Maheshwari, each and every substance present in the universe has got solubilizing property, i.e., all the liquids, gases, and solids possess solubilizing power. As per his statement, each substance is solubilizer. A concentrated aqueous solution containing various water-soluble substances may act as good solvent for poorly water-soluble drugs. Such concentrated solutions may show synergistic or additive solubilizing actions of solubilizers present in the solution. Each and every weaker solvent (for a solute) can be made a strong solvent by proper selection of solubilizers. The concept of mixed solvency has been used to show the enhancement of aqueous solubility of a large number of poorly water-soluble drugs by employing the mixed solvency concept.[6-19]

Application of mixed solvency has been employed in present research work to develop the topical solutions of indomethacin (used as a model poorly water-soluble drug). It is white to pale yellow crystalline powder, practically insoluble in water. It is soluble in ethanol, ether, acetone, and castor oil [Figure 1]. Mixed-solvency can be employed as a tool to decrease the overall concentration of solubilizers required to produce a substantial increase in solubility and thereby resulting in enhanced permeation of indomethacin in its topical dosage form.

MATERIALS AND METHODS

Materials

Indomethacin was obtained as a gift sample from Elder Pharmaceutical Private Limited, Mumbai.

Estimation of Indomethacin

Ultraviolet (UV) spectrophotometric analysis of indomethacin

20 µg/ml solution of drug was scanned on a double-beam UV-visible spectrophotometer (Shimadzu® 1700) between wavelength ranges of 200 nm and 400 nm. UV spectrum was recorded in Figure 2.

Infrared (IR) analysis of drug sample

The IR spectroscopy of indomethacin was performed for identification of drug. About 1–5 mg of the sample

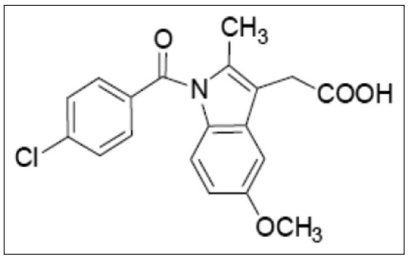

Figure 1: Structure of indomethacin

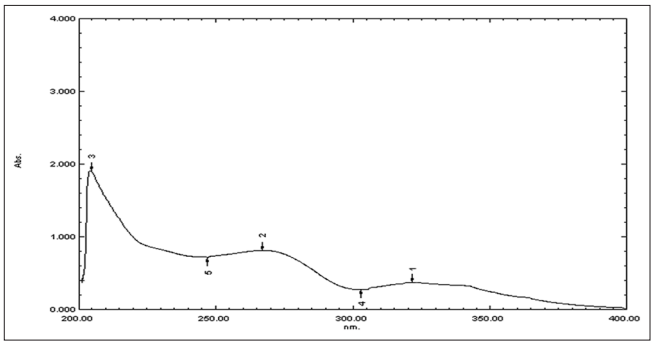

Figure 2: Ultraviolet spectra of indomethacin in demineralized water

was triturated with approximately 300 mg of dry, finely powdered potassium bromide IR and compressed as pellet and spectra were recorded on Fourier transform IR (FTIR) spectrophotometer (Shimadzu 8400 S). The IR spectrum is presented in Figure 3.

Differential scanning calorimeter (DSC) analysis of drug sample

To obtain the DSC thermograms of the drugs, a thermal analysis instrument, TA Instruments-2910 modulated DSC (USA) was employed. To carry out these studies, 1–4 mg of drug was weighed accurately and placed in one of the matched aluminum pans. The sample pan and the reference pan both were sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of 10°C/min with a continuous purge of nitrogen (45 CC/min) was done with a recording of energy changes in the sample with respect to the reference in the temperature range of 80–200°C. The DSC thermogram is shown in Figure 4.

Preparation of calibration curve of indomethacin in demineralized water

Fifty mg of drug indomethacin was accurately weighed and transferred to a 500 ml volumetric flask. To this, 10 ml of 30% w/v sodium benzoate solution was added to dissolve the drug, and the volume was made up to 500 ml with demineralized water to prepare a 100 µg/ml solution. Appropriate dilutions were made with demineralized water to obtain 5, 10, 15, 20, and 25, µg/ml solution of the drug. The absorbances of the resulting drug solutions were measured spectrophotometrically at 320 nm against the corresponding reagent blanks. The data were graphically represented in Figure 5.

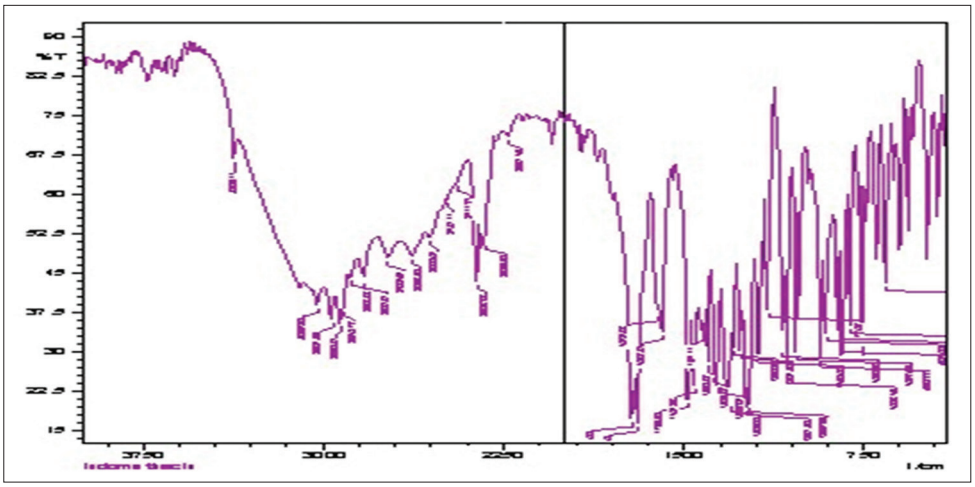

Figure 3: Infrared spectrum of indomethacin drug sample

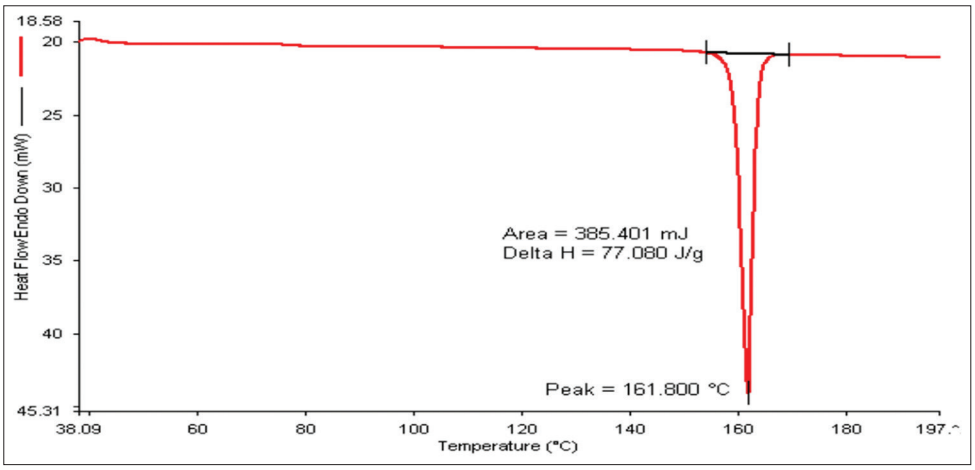

Figure 4: Differential scanning calorimeter thermogram of indomethacin drug sample

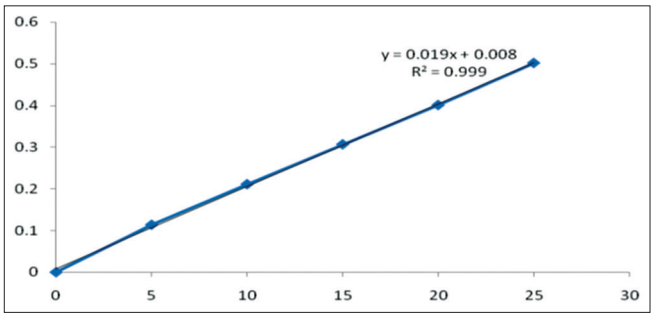

Figure 5: Calibration curve of indomethacin in demineralized water

Determination of Interference of Excipients in the Spectrophotometric Estimation of Indomethacin

Different excipients: Sodium benzoate, caffeine, niacinamide, and PEG 400 were used for the interference study. For determination of interference of excipients in the spectrophotometric estimation of indomethacin, the absorbances of the standard solutions of indomethacin were determined in DM water alone and the presence of the excipients. The absorbances were recorded against respective reagent blanks at 320 nm. Results are shown in Table 1.

Drug Solubilizers Incompatibility Studies

The different formulation components involved in the development of proposed formulations were physically mixed with the drug in 1:1 ratio and filled in glass vials properly capped and sealed. The vials of each sample were kept at room temperature and in the refrigerator and thermostatically controlled oven maintained at 40°C for 1 month period. After every week for 1 month, the vials were withdrawn, and changes in physical appearance (if any) and color of the contents were observed.

Solubility Studies

Solubility of indomethacin in distilled water and aqueous solutions of various solubilizers were determined by equilibrium solubility method. The excess drug was added to 5 ml of distilled water, and mixed solvent systems [Table 2] contained in 10 ml glass vials and vials were sealed with rubber

Table 1: Drug solubilizers interference studies in the spectrophotometric estimation of Indomethacin

Drug	Solubilizer	Drug conc. (μg/ml)	Solubilizer conc. (μg/ml)	Wavelength (nm)	Absorbance against a respective reagent blank
Indomethacin		20	-	320	0.402
Indomethacin	Sodium benzoate	20	100	320	0.408
Indomethacin	Niacinamide	20	100	320	0.406
Indomethacin	Caffeine	20	100	320	0.409
Indomethacin	PEG 400	20	100	320	0.401

closures and aluminum seals. The vials were shaken for 12 h in Orbital Flask Shaker (Khera Instruments Pvt. Ltd., Delhi, India) and allowed to equilibrate for 24 h undisturbed. The solutions containing an excess of the drug were centrifuged at 2200 r.p.m. for 5 min in ultracentrifuge and filtered through Whatman grade 5 filters. Aliquots of the filtrate were suitably diluted with distilled water, and the dilutions were analyzed on UV-visible spectrophotometer (Shimadzu 1700) against respective reagent blanks. Results are shown in Table 2.

Formulation Development of Topical Solution

Based on the solubility studies, topical solutions were prepared using blends Q and T of mixed solvent systems. Sodium benzoate, niacinamide, and PEG 400 were taken in a 50 ml volumetric flask. Distilled water (25 ml) was added to the flask, and the flask was shaken to dissolve all the excipients. Then, caffeine was added, and flask was again shaken to solubilize it. Then, indomethacin was added, and the flask was shaken to solubilize the drug completely. Sufficient distilled water was then added to make up the volume up to 50 ml. After shaking the flask for complete homogenization, the solution was filtered through the filter paper, rejecting the first few ml of solution. The prepared solution was preserved in air-tight containers. The compositions of topical solutions are presented in Table 3.

Stability Studies

Topical solutions of indomethacin of two different formulations were kept at different storage conditions. Formulations were kept at room temperature, at 30°C and 40°C. The results are shown graphically in Figures 6 and 7.

EVALUATIONS OF TOPICAL INDOMETHACIN SOLUTIONS

Thin-Layer Chromatography (TLC) Analysis

TLC analysis was done to identify any drug-solubilizer interaction [Table 4]. Methanol was used as a solvent for sample preparation for TLC of the drug.

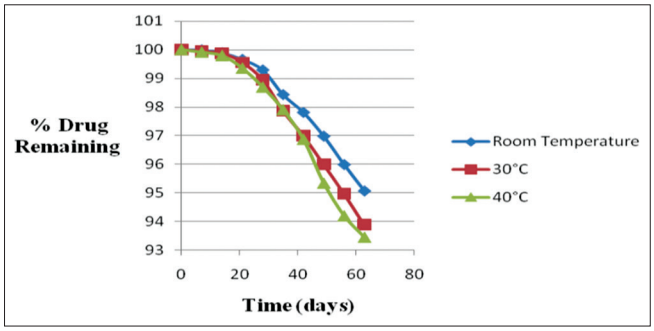

Figure 6: Graphical representation of stability of indomethacin batch first

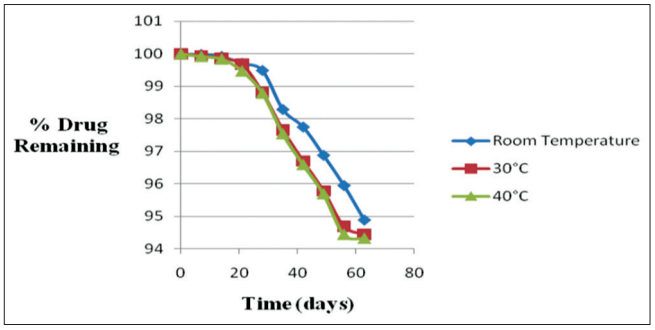

Figure 7: Graphical representation of stability of indomethacin batch second

pH of Topical Solutions of Indomethacin

Sample was taken in a dry 25 ml beaker and pH was recorded on a standardized pH meter fitted with glass calomel electrode.

Viscosity

The viscosities of the prepared topical solutions were measured by dial viscometer (Brookfield® LV). Required amount of the topical solutions was taken in 250 ml beakers individually. The dial readings were noted using all the spindles and at each spindle speed (one by one). The appropriate dial readings (10–90) were considered for calculations of viscosity in cps by multiplying the dial reading with the factor (specified according to the spindle number and the spindle speed).

Table 2: Solubility studies of indomethacin in various aqueous solutions of solubilizers

Blend	Composition of blends (w/v)	Solubility (mg/ml)
A	20% SB+5% NM+10% CF+10% UR+10% PEGFH	41.02
B	10% SB+10% NM+15% CF+10% PEGFH	15.52
C	20% SB+5% NM+5% BC+5% CF+10% PEGFH	39.47
D	15% SB+10% NM+5% UR+5% BC+10% PEGFTH	43.38
E	10% SB+10% NM+10% PEGFH	25.07
F	10% SB+15% NM+10% CF+10% PEGFH	30.87
G	10% SB+10% NM+5% BC+5% PEGFTH+10% GLY	31.98
H	15% SB+5% NM+10% PEGFTH+10% PEGFH	44.14
I	10% SB+15% NM+5% BC+5% PEGFTH	22.87
J	10% SB+10% NM+10% CF+10% PEGFH	25.49
K	5% SB+15% NM+10% UR+10% PEGFH	18.87
L	20% SB+5% UR+5% SC+10% PEGFH	29.69
M	5% SB+10% NM+5% BC+10% CF+10% PEGFH	10.87
N	15% SB+10% NM+10% GLY+5% PEGFTH	30.46
O	5% SB+10% NM+5% UR+5% CF+5% PEGFTH+10% PEGFH	13.58
P	10% NM+10% CF+10% PEGFTH+10% PEGFH	9.979
Q	20% SB+10% NM+10% CF+10% PEGFH	62.98
R	15% SB+5% NM+10% PEGFTH+10% PEGFH	28.34
S	15% SB+10% NM+5% PEGFTH+5% UR	29.78
T	20% SB+10% NM+15% CF+10% PEGFH	60.64

SB: Sodium benzoate, NM: Niacinamide, CF: Caffeine, UR: Urea, GLY: Glycerin, PEGFH - PEG 400, PEGFTH - PEG 4000, BC-β-Cyclodextrin

Table 3: Formula for indomethacin topical solution

Composition (w/v)	Batch first	Batch second
Sodium benzoate	10 g	10 g
Niacinamide	5 g	5 g
Caffeine	5 g	7.5 g
Indomethacin	1 g	1 g
PEG 400	5 ml	5 ml
Distilled water up to	50 ml	50 ml

Freeze-Thaw Testing

Two vials of each topical solution were subjected to freeze-thaw stress testing to observe any chance of precipitation. For 24 h, the vials were stored at 4°C in the refrigerator and then vials were kept at 40°C in the oven for 24 h. After this, again, vials were kept at 4°C in the refrigerator for 24 h. After 7–7 such alternate cycles at 4°C and 40°C, the vials were observed for any precipitation or turbidity.

RESULTS AND DISCUSSION

Drug Characterization

UV spectrophotometric analysis of indomethacin

The indomethacin drug sample exhibited a peak at 320 nm which was comparable to the value reported in the literature.

IR analysis of drug sample

The FTIR spectrum of drug sample had shown identical peaks as reported in a reference sample of indomethacin.

DSC analysis of drug sample

The DSC curve of the crystalline form of indomethacin showed a sharp endothermic peak at 161.8°C attributable to the melting point.

Table 4: TLC analysis of pure indomethacin and its formulations

Mobile phase	R_f value			Inference
	Drug	Batch first	Batch second	
Ethyl acetate: Hexane (7:3)	0.44	0.43	0.42	No significant change in R_f value hence no interaction between drug and solubilizer

TLC: Thin-layer chromatography

Preformulation Studies

Preparation of calibration curve of indomethacin in demineralized water

The calibration curve of indomithacin in DM water was plotted and it followed beer's lambert law.

Drug solubilizers interference studies in the spectrophotometric estimation of Indomethacin

Observing the results of drug-solubilizers interference study, it was concluded that there was no interference in UV spectrophotometric analysis of indomethacin due to excipients.

Drug solubilizers incompatibility studies

Observing the results of drug solubilizers compatibility study, it was concluded that there was no physical incompatibility between drug and selected formulation solubilizers.

Formulation Development

Solubility studies

Maximum increase in solubility of indomethacin was observed in Blend Q (20% sodium benzoate, 10% niacinamide, 10% caffeine, and 10% PEG 400) and in Blend T (20% sodium benzoate, 10% niacinamide, 15% caffeine, and 10% PEG 400) so these were selected to be used in formulation of topical solutions of indomethacin.

The solubility of the drug in distilled water was found to be 0.105 g/100 ml.

Stability studies

Stability studies of topical indomethacin solutions were performed for 2 months at room temperature, 30°C and 40°C and percentage drug remaining for first formulation (Batch First) at room temperature was 95.07%, and at 30°C was 93.88%, and at 40°C was 93.45%. Percent drug remaining for second formulation (Batch Second) at room temperature was 94.89%, at 30°C was 94.44%, and at 40°C was 94.32%. The results of stability studies of indomethacin topical solutions gave reasonably good results.

Evaluations

TLC analysis

From TLC study, it is clear that there is no significant change in R_f value indicating that there were no interactions between drug and solubilizers.

pH of topical solutions of indomethacin

Preferably the pH of topical solutions should be in the range of 5.0–5.5. pH of topical indomethacin solution batch first was 5.3 and pH of topical indomethacin solution batch second was 5.4.

Viscosity

The measured viscosities of prepared topical solutions of indomethacin were found to be 1080cps–1300cps for the first batch and 860 cps–1120 cps for the second batch.

Freeze-thaw testing

Freeze-thaw study declared that there was no precipitation and no turbidity (after 7–7 such cycles).

SUMMARY AND CONCLUSION

The main objective of the present study was to explore the mixed solvency concept in the preparation of the topical solution of poorly water-soluble drug indomethacin. The aim was to make water, a strong solvent for the poorly water-soluble drug, indomethacin for the preparation of the topical solution of drug using mixed solvency concept by the use of safe solubilizers niacinamide, sodium benzoate, PEG 4000, PEG 400, caffeine, and glycerin.

To minimize the probable toxic effects of individual solubilizers at high concentration (individually), different blends of solubilizers were tried. The blends of solubilizers of different strength were used for the solubility studies to get sufficiently high expected solubilities. The combinations of different agents were tried.

The procured sample of indomethacin was characterized by melting point, I-R spectroscopy, UV characterization, and DSC study. The melting point of the drug sample was found to be 158°C (reported 155–160°C).

Preformulation studies were performed which included solubility studies, preparation of calibration curves in demineralized water. The solubility of indomethacin drug sample in demineralized water was found to be 0.105 g/100 ml.

Different solubilizers, sodium benzoates, caffeine, niacinamide, PEG 400, and glycerin and were used for the interference study. For determination of interference of excipients in the spectrophotometric estimation of indomethacin, the absorbances of the standard solutions of indomethacin were determined in demineralized water alone and the presence of the excipients. The absorbances were recorded against respective reagent blanks at 320 nm. There is no interference in UV spectrophotometric analysis of indomethacin due to the presence of excipients.

Solubility studies were performed on 20 blends, and maximum increase in solubility of indomethacin was observed in Blend Q (20% sodium benzoate + 10% niacinamide + 10% caffeine + 10% PEG 400) and in Blend T (20% sodium benzoate + 10% niacinamide + 15% caffeine + 10% PEG 400) so these were selected to be used in formulation of topical solution of indomethacin. In Blend Q and Blend T, 2% drug concentration was used to formulate the topical solutions of indomethacin.

Stability studies of topical indomethacin solutions were performed for 2 months at room temperature, 30°C and 40°C and percentage drug remaining for the first formulation at room temperature was 95.07%, at 30°C was 93.88%, and at 40°C was 93.45%. Percentage drug remaining for the second formulation at room temperature was 94.89%, at 30°C was 94.44% and at 40°C was 94.32%. The results of stability studies of indomethacin topical solutions were reasonably good. For the evaluation, different studies were performed such as TLC, freeze-thaw study, viscosity, and pH, and satisfactory results were found.

The concept of mixed solvency was successfully employed in formulating the topical solution of poorly soluble model drug, indomethacin. In this study, there was no involvement of organic solvent to prepare a topical solution. The present study illustrates the novel application of mixed solvency concept to improve the drug loading of the poorly water-soluble drug. Pharmaceutical companies may be benefited by this concept, not only to manufacture a topical solution but also to develop other pharmaceutical formulations.

REFERENCES

1. Naik A, Kalia YN, Guy RH. Transdermal drug delivery: Overcoming the skin's barrier function. Pharm Sci Technolo Today 2000;3:318-26.
2. Available from: http://www.Dermaz.org/treatments (topical formulation.html). [Last accessed on 2014 Nov 13].
3. Available from: http://www.pharmpress.com/files/docs/PCD2E.Sample.pdf. [Last accessed on 2015 Jan 25].
4. Chaudhary A, Nagaich U, Gulatti N, Sharma VR, Khose L. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications. J Adv Pharm Educ Res 2012;2:32-67.
5. Martin A, Sinko PJ. Physical Pharmacy and Pharmaceutical Sciences. 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004.
6. Maheshwari RK. "Mixed-Solvency"-a novel concept for solubilization of poorly water-soluble drugs. J Technol Eng Sci 2009;1:39-44.
7. Maheshwari RK. "Mixed-solvency approach"-boon for solubilization of poorly water-soluble drugs. Asian J Pharm 2010;4:60-3.
8. Maheshwari RK. Solubilization of ibuprofen by mixed solvency approach. Indian Pharm 2009;8:81-4.
9. Maheshwari RK. "Mixed-solvency"–a novel concept for solubilization of poorly water-soluble drugs. Delving J Tech Eng Sci 2009;1:39-43.
10. Maheshwari RK, Shilpkar R. Formulation development and evaluation of injection of poorly soluble drug using mixed solvency concept. Int J Pharm Biosci 2012;3:179-89.
11. Soni LK, Solanki SS, Maheshwari RK. Solubilization of poorly water soluble drug using mixed solvency approach for aqueous injection. Br J Pharm Res 2014;4:549-68.
12. Maheshwari Y, Mishra DK, Mahajan SC, Maheshwari P, Maheshwari RK, Jain J. Novel pharmaceutical application of mixed solvency in the formulation development of syrups (liquid oral solutions) of poorly water-soluble drugs. Int J Pharm 2013;3:753-8.
13. Maheshwari RK, Rajagopalan R. Formulation and evaluation of paracetamol syrup made by mixed-solvency concept. Der Pharm Lett 2012;4:170-4.
14. Maheshwari RK, Rajagopalan R. Formulation and evaluation of tinidazole syrup made by mixed-solvency concept. Der Pharm Lett 2011;3:266-71.
15. Maheshwari RK, Karawande VU, Application of novel concept of mixed solvency in the design and development of floating microspheres of furosemide. Int J Pharm Pharm Sci 2013;15:167-95.
16. Agrawal A, Maheshwari RK. Formulation development and evaluation of *in situ* nasal gel of poorly water soluble drug using mixed solvency concept. Asian J Pharm 2011;5:131-40.
17. Prashant B, Rawat S, Mahajan YY, Galgatte UC, Maheshwari RK. Formulation development and evaluation of aqueous injection of poorly soluble drug made by novel application of mixed solvency concept. Int J Drug Delivery 2013;2:152-66.
18. Chandna C, Maheshwari RK. Mixed solvency concept in reducing surfactant concentration of self emulsifying drug delivery systems of candesartan cilexetil using D-optimal mixture design. Asian J Pharm 2013;7:83-91.
19. Maheshwari RK. Potentiation of solvent character by mixed solvency concept: A novel concept of solubilization. J Pharm Res 2010;3:411-3.

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