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# ENHANCEMENT OF SOLUBILITY OF BCS CLASS II DRUG VIA TOPICAL DELIVERY FROM SUPERSATURATED DRUG DELIVERY SYSTEM: A NEWER APPROACH FOR THE TREATMENT OF OSTEOARTHRITIS

**Dipika Chavda*[1], Atindra Shukla[2]**

[1]*Department of Pharmaceutics, Anand Pharmacy College, Anand, Gujarat, India*

[2]*Shah-Schulman Center for Surface Science and Nanotechnology, Dharmsinh Desai University, Nadiad, Gujarat, India*

**Corresponding author: dchavda3@gmail.com*

## ABSTRACT

The present research was aimed to develop topical supersaturated spray formulation for delivery of naproxen (BCS class II drug) for the treatment of osteoarthritis. From saturated solutions of topical formulations, maximum drug flux is achieved under ideal circumstances, therefore, the enhanced drug penetration through diffusion would expect from supersaturated drug delivery systems. Nevertheless, upon penetration into skin, these supersaturated formulations tend to crystallize because of the characteristic lack of stability, which might be overcome by adding anti nucleant polymers. To delay or inhibit crystallization, Hydroxypropyl methylcellulose (HPMC) has been used in this study, which has also been found effective in maintaining the high activity state at a high degree of saturation (DS). The solubility behavior of naproxen in ethanol-propylene glycol (PG) mixtures was carefully evaluated by calculating the dielectric constant, as well as various other physical properties. Supersaturated topical spray-on system for Naproxen was formulated by using the co-solvency method, where 9:1 ethanol: PG ratio was used as a solvent. The prepared system was checked for all physicochemical evaluations including stability and in vitro drug diffusion. In vitro study showed 99.95% drug release at 6 minutes. The optimized formulation passed stability study over a year. The supersaturated spray formulation developed with ethanol/PG and HPMC E5 consequently epitomizes a boosting methodology targeting to increase stability as well as the permeability flux of a BCS class II drugs.

**Keywords:** Supersaturation, Topical drug delivery, Propylene glycol, Ethanol, Spray

## 1. INTRODUCTION

Osteoarthritis (OA) prevails to elderly persons aged more than 55 years which leads to disability. It is the most common joint disease occurs worldwide in which, patients experience limitations in movement and even cannot perform their daily activities. In this chronic arthropathy, prevention of occurrence is not possible and quality of life is reduced because of entire joint lead to pain and disability [1-4]. Amongst non-pharmacological, pharmacological, and surgical treatment,the most affordable and efficacious treatment option is pharmacological treatment including analgesics, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs) [5]. Oral NSAIDs lead to morbidity and mortality because of GIT adverse events including nausea, vomiting, diarrhea, dyspepsia, ulcer and bleeding [6, 7]. Topical NSAIDs are an attractive substitute for oral therapy in reducing the symptoms of OA, with minimal adverse side effects [5-9]. According to the American Geriatric Society, all localized non-neuropathic pain in geriatric patients should be treated with topical analgesics [4, 8]. NSAIDs may be either selective or non-selective cyclooxygenase (COX-2) inhibitors. Topical NSAIDs reduce synthesis of prostaglandin which is involved in pain, vasodilation and decreased the sensitivity of blood vessels to bradykinin and histamine [3, 5, 10, 11]. In the present era, the pharmaceutical formulations for the treatment of OA are most commonly occupied with BCS class II drugs which necessitating novel formulations to overcome barriers in treatment as well as biopharmaceutical properties [12]. One such promising approach is the supersaturated drug delivery system, in which the concentration of a solute exceeds the saturated system. This phenomenon makes it thermodynamically unstable which leads to the formation of spontaneous crystals which is known as a labile state. If the compound remains in solution under supersaturated conditions, it is called a metastable state,

and the addition of any foreign particles, external force, ultrasound, and nucleation results in crystallization [11-13]. The frontier between the metastable and labile states is known as critical degree of supersaturation (DS), which depends on drug concentration as well as temperature [5, 6, 11, 12, 14, 15]. The complex interaction occurs between the skin, drug candidate, and the drug delivery system upon application to the skin. This can be explained well with the help of Fick's first law of diffusion where the rate of penetration of API into the skin is affected by the surface area of treatment, the concentration of different excipients, and permeability of the skin [16, 17]. Topical spray-on systems (TSSs) can effectively deliver drugs across the skin while retaining skin integrity in a noninvasive manner.TSS has many advantages over other skin formulations like flexibility in dose deliverance, less irritation as compared to semisolids due to no rubbing and ease of application. Moreover, it is a promising tool as compared to traditional transdermal drug delivery systems because of the ease of development and manufacturing on a large scale. TSS provides a unique in situ supersaturated drug delivery mechanism [11, 18]. The drug is stable in the initial formulation in a sub-saturated state, but when applied to the skin the volatile solvent evaporates resulting in an increase in the thermodynamic activity of the drug on the skin surface, to the extent that a supersaturated state exists. As the drug saturates the solvent system on the SC, the SC will become saturated with the drug and as a supersaturated system exists on the surface of the SC, the same will occur in the SC [17, 18]. For a supersaturated drug profile to remain for a significant time, the thermodynamic drug state on the skin must remain constant with minimal drug crystallization and precipitation. Once the drug on skin precipitates, the system returns to a saturated state. For this reason, the use of anti-nucleants in volatile topical preparations is to reduce the drug precipitation rate. The inclusion of an anti-nucleants is believed to possibly increase the duration of the supersaturated state on the skin surface [4, 9]. With deep insight into the literature search, it was observed that none of the formulations was aimed to overcome both problems regarding osteoarthritis treatment such as poor solubility and patient compliance. Moreover, even the systematic development of a supersaturated drug delivery system for naproxen is also not reported. Due to larger dose, naproxen was not able to incorporate into a semisolid or liquid formulation which was also tried to overcome in the present research by having the aim of developing and optimizing the topical supersaturated spray-on system to overcome the problems of the low solubility of the drug and to improve more patient compliance.

## 2. MATERIAL AND METHODS

### 2.1. Material

Naproxen was received as a gift sample from Baroque Pharmaceutical Ltd. Gujarat, India. Alcohol, Propylene glycol (PG), Poly Vinyl pyrrolidone (PVP), Poly Ethylene Glycol (PEG), and Hydroxy Propyl Methyl Cellulose (HPMC) were purchased from Astron chemicals, Ahmedabad, India. Ultipore® N66 nylon membrane was purchased from Pall life science, Pune, India. Double distilled water was used throughout the study and all other reagents were of analytical grade.

### 2.2. Preliminary screening of formulation parameters and development of supersaturated topical spray on system

Ethanol, PG, PEG400, PEG 300, PEG 200, and water were used as solvents for screening by using the shake flask method [19, 20]. To enhance the solubility of the drug, the binary co-solvent approach was applied and saturation solubility of the drug was measured [20]. Based on the literature survey, the solvent shift method was chosen for anti-precipitants screening. HPMC E3, HPMC E5, HPMC E15, and PVP K25 and PVP K30 were chosen as precipitation inhibitors for the study [18, 22-24]. The degree of supersaturation (DS) is expressed as the concentration of the drug in the solution divided by the equilibrium solubility of the drug. It is expressed as a ratio of the concentration of drug in solution after 5 minutes post drug addition to the equilibrium solubility of naproxen in the solvent.

$$DS = \frac{C}{Ceq} \quad \text{.....Equation (1)}$$

Where C is the drug concentration and Ceq is the equilibrium drug concentration. It also represents the state of the drug in solution [25]. The data indicates the state of supersaturation. Where, DS=0 indicates drug is in a saturation state, DS<1 shows drug is in an unsaturated state and DS>1 reflects drug is in a supersaturated state. In this study, the supersaturated spray-on system was prepared followed by screening and preformulation. Accurately measured anti-nucleants HPMC E5 was first dissolved in the different ratios of ethanol/PG mixture; which was subsequently saturated

with naproxen. Methyl Salicylate was subsequently added. All the ingredients were uniformly mixed into it using bath sonication for 3 minutes. Prepared formulations (Table 1) were then characterized by different evaluation parameters.

**Table 1: Composition of naproxen spray by the layout of $3^2$ full factorial designs**

| Batch No. | Concentration of HPMC E-5 (mg) X1 | Ratio of Ethanol:PG X2 | Concentration of HPMC E-5 (mg) X1 | Ratio of Ethanol: PG X2 | Naproxen (mg) | Ethanol (ml) | PG (ml) | Methyl salicylate (ml) |
|---|---|---|---|---|---|---|---|---|
| | Coded value | | De-Coded value | | | | | |
| F1 | 1 | 1 | 150 | 9:1 | 680 | 9 | 1 | 0.5 |
| F2 | 0 | 1 | 100 | 9:1 | 680 | 9 | 1 | 0.5 |
| F3 | -1 | 0 | 50 | 8:2 | 680 | 8 | 2 | 0.5 |
| F4 | -1 | 1 | 50 | 9:1 | 680 | 9 | 1 | 0.5 |
| F5 | 1 | 0 | 150 | 8:2 | 680 | 8 | 2 | 0.5 |
| F6 | 0 | -1 | 100 | 7:3 | 680 | 7 | 3 | 0.5 |
| F7 | -1 | -1 | 50 | 7:3 | 680 | 7 | 3 | 0.5 |
| F8 | 0 | 0 | 100 | 8:2 | 680 | 8 | 2 | 0.5 |
| F9 | 1 | -1 | 150 | 7:1 | 680 | 9 | 1 | 0.5 |
| F10* | 0.114 | 0.9815 | 102.85 | 84:16 | 680 | 8.4 | 1.6 | 0.5 |

**Batch F10 was the checkpoint batch of the present study*

### 2.3. Full factorial design

The formulated spray-on systems were optimized by using a three-level ($3^2$) full factorial design by using Design-Expert software [26]. For this optimization, selected independent variables were concentration of HPMC E5 (X1) and ethanol: PG ratio (X2) and degree of supersaturation (Y1) and % cumulative drug release at 6 minutes (Y2) were chosen as dependent variables. The variables conforming to each factor were included with qualitative levels corresponding to each excipient. The prepared formulations were filled into spray bottles and clarity of the formulation was observed with the naked eye on a black and white background. The sprays were analyzed to determine the pH, the viscosity, the refractive index, the specific gravity, the spray pattern, the average weight per actuation, the drug content for each spray, and the in vitro diffusion study [20, 21, 27-30]. By applying the optimization tool, after measuring response for each batch, quadratic model was fitted by performing multiple regression analysis and was validated by ANOVA and formulation of checkpoint batch. For validation, practical and experimental responses must be same with minimum relative error [26].

### 2.4. Evaluations

#### *2.4.1. Physico-chemical evaluations*

The clarity of the solutions was checked by the naked eye by observing the formulations against light and dark background. The pH and viscosity of the prepared formulations were determined at 25°C using a digital pH meter and Brookfield viscometer (10 rpm, spindle C16-1) respectively. The pH value must fall within the physiological range. The refractive index of the prepared formula was observed and calculated using an Abbe refractometer by placing a drop of solution on the slide and relative to water (1.333). If the system refractive index is similar to the respective water value (1.333), the preparation is transparent [31, 32].

#### *2.4.2. X-ray diffraction (XRD) study*

X-ray diffraction is a non-destructive analytical technique used for the identification and quantitative analysis of various crystalline forms of molecules. The physiochemical change in the drug resulting from the solvent evaporation technique was analyzed. XRD patterns are recorded with D8 Advance from Bruker AXS. Scatterable, interchangeable X-ray detectors: NaI luminosity type detector with a low bottom (0.4 cps), high dynamic range (up to 2x106), and a Brown placement sensor. Quantification of crystallization at the same value of 2θ indicates the degree of crystallization of the drug in the composition concerning the degree of crystallization of the pure drug [21].

#### *2.4.3. In-vitro diffusion study*

The study of drug release through the Ultipore® N66 nylon membrane (0.2 µm poresize and 145 µm

thickness) was studied using Franz diffusion cells. The nylon membrane was selected because it has the least rate-limiting effect on drugs though it is a thicker membrane [34]. The receptor compartment was filled with 15 ml of phosphate buffer at pH 7.4 to guarantee the state of the sink and the temperature was maintained at 37±0.5 °C. A uniform mixing of the receptor medium was carried out using magnetic agitation. At predefined time intervals, 1 ml aliquots were removed from the receptor compartment and the samples were analyzed in a UV spectrophotometer at 231 nm. After each sampling, the same amount of fresh dissolution medium was replaced to maintain the sink condition. Each experiment was repeated three times [33].

#### *2.4.4. Spray pattern*

The spray pattern was assessed by delivering the spray through the spray bottle. 10 mg Sudan Red was dissolved in prepared formulations to facilitate visualization and then was sprayed on a piece of paper to check spray pattern [26, 39].

#### *2.4.5. Average weight per actuation*

To measure average weight per actuation, the weight of spray bottle before and after five successive deliveries of sprays were recorded. The calculation was done by dividing the weight difference by number of deliveries. The experiment was repeated thrice and the average volume was reported [39].

#### *2.4.6. Drug content per each spray*

The drug content of the formulations was determined by mixing 1 ml formulation with the appropriate solvent for complete drug extraction. The solutions were filtered through 0.45 µm membrane filters and subjected to spectrophotometric analysis (SHIMADZU UV-1650 PC (E) 230V, Japan). The drug content was calculated from the linear regression equation. Samples from drug- free spray were used as a blank solution during analysis [39].

#### *2.4.7. Stability studies*

Short-term stability study was performed to check crystal growth and clarity of the supersaturated solutions and for that; they were placed at ambient (25 °C) as well as 5 °C for one week. Crystal growth by microscopy and particle size determination method was determined daily for 7 days. For long term stability study, the optimized formulation was stored for 12 months as per ICH guidelines (Q1A (R2)30±2 °C /65% RH±5% RH). The chemical stability of the formulation was assessed at 15 days, 1 month, 3 months, 6 months, 9 months, and 12 months by the estimation of the physical evaluation of crystal growth, pH, clarity, and drug release pattern [31, 32].

## 3. RESULTS AND DISCUSSION

The solubility was checked in phosphate buffer at different pH 1.2, 5.8, 6.8 and 7.4. It was also checked in ethanol and water. The results shown in Table 2 show that ethanol and phosphate buffer pH 7.4 has a high solubilizing capacity and was chosen as dissolution media for further study. The results also reveal that the drug may get better penetration at this pH which mimics the human skin condition. Screening of solvents was done based on the solubility of naproxen in different solvents. Out of the selected solvents from the literature search, the solubility of naproxen was found highest in Ethanol and Propylene glycol (PG). To enhance the solubility further; the co-solvency approach was adopted. Ethanol and PG were combined in different ratios as per Table 3 and effects of co-solvency were measured to check the saturation solubility of naproxen. The solubility may found to be correlated with dielectric constant. From the literature search, it can be derived that the degree of interaction between polymer and drug molecules decreases and it also decrease dielectric constant, since the decrease in dielectric constant typically increases drug solubility. Moreover, solubility data shown in Table 4 indicates that the mixture of ethanol and PG in 9:1 ratio enhance the solubility. From the study, it was shown that the HPMC family gave the best anti-precipitant effect that the PVP family because HPMC may prevent nucleation for crystal growth also change bulk property and from the survey as concentration increases degree of supersaturation was found to be lower. As shown in Table 5, the degree of supersaturation after 5 minutes were calculated in different precipitation inhibitors and HPMC E5 shows the best results in all concentrations. The degree of supersaturation study was continued up to 2 hours to check the change in DS per time. For that data of HPMC E5 in all concentration 0.01%, 0.1%, 1% and 2% was measured and calculated. The data shown in Table 6 reveals that less reduction in DS was observed in 1% concentration HPMC E5 hence 1% concentration of HPMC E5 was selected for the study. 1% HPMC E-5 was able to maintain supersaturation for a longer duration. The observed solutions were clear against light and dark background when observed

through naked eyes which were confirmed by the refractive index results of the prepared formulation. They were found to be 1.326± 0.01 and as compared with water (1.333); which indicates the transparent nature of the formulation. The prepared formulations had an appropriate observed pH value of 6.4- 6.95 which is best suitable for topical application. The mean viscosity of prepared formulation was found 4.32±0.5 cps. The low viscosity indicates easy spray ability. The degree of crystallinity of a given sample was measured by using powder X-ray diffraction spectroscopy. As shown in Figure 1, it can be concluded that when upon physical mixing of drug and excipients, overall crystallinity is reduced and the number of amorphous structures is increased. Consequently, the optimized formulation sample demonstrates fewer and less intense peaks. This illustrates that the overall crystallinity of the optimized formulation is decreased because of more amorphous nature and which leads to more solubility [40]. XRD patterns are shown in Fig. 1 where the powder X-ray diffractogram of pure Naproxen showed numerous distinctive peaks that indicated a high crystallinity. The diffractograms of the physical mixture were found to be more diffuse compared to drugs, while there is no characteristic peak *i.e.* formation of amorphous solid-state (Physical mixture). The naproxen diffusion data obtained for formulations F1 to F9 were shown in Figure 2. The study was performed for 20 minutes, the total amount of naproxen (approximately 100 %) transported from formulation to dissolution media was in the time limit of 5 to 12 minutes from all batches F1 to F9. It was detected that naproxen transport from all formulations was highly influenced by the amount of HPMC E5 and the ratio of ethanol: PG. The increased concentration of anti nucleant gave a decrease in drug release as viscosity was also increased by a high amount of HPMC E5. The higher amount of ethanol was responsible for the high solubility of drugs which consequently increased the drug release up to 100%within a shorter period. In diffusion study of batch F1, F2, F3, F4, F5, F6, F7, F8, F9 were shown transport of naproxen 96.03, 99.95, 88.21, 96.03, 86.83, 81.36, 80.62, 91.02 and 83.96 % respectively at 6 minutes. In a design matrix of $3^2$ full factorial design, from all the design level (0, 1) was found to be more effective and gave the highest reaction in both responses. Polymer and co-solvents gave an immediate release of drug and Batch F2 were further evaluated for 8 h and it showed impressive constant sustain release effect up to 8 h. From the in-vitro study, it was concluded that there was a significant enhancement of diffusion observed in the prepared formulations Figure 2. The main and confounding effects of the independent variable were observed on dependent variables Y1 DS and Y2 % Drug release at 6 minutes. The evaluation of the full model embodies all significant and less significant statistics however the reduced model offered merely significant ($p < 0.05$) parameters. The screening of the most significant parameters affected by the response was done by the reduced model. It was specified a confounding effect nevertheless it was capable to filter out noteworthy parameters. Contour plots of both responses are shown in Fig. 3 (a) and 3(b).Y1 (DS) was influenced byan increased concentration of polymer HPMC E5 as a positive effect as shown in equation 3. Increased ratio of Ethanol: PG from 7:3 to 9:1 increase more drug release in 6 minutes (Y2) as shown in equation 4.

$$Y1 = 2.42 + 0.3367X1 - 0.0250X2 + 0.0175X1X2 - 0.1967X1^2 - 0.0117X2^2 \ (R^2 = 0.9945) \ \ldots \text{Equation 3.}$$

$$Y2 = 83.17 - 1.60X1 + 10.11X2 - 2.72X1X2 - 4.25X1^2 + 4.76X2^2 \ (R^2 = 0.9682) \ \ldots \text{Equation 4.}$$

The adequacy of the obtained response was checked by using the check-point batch (Fig.4). As per equations 3 and 4, the experimental and predicted value was 2.37 and 2.41 for DS, and % drug release in 6 minutes was 98.83 and 98.51 respectively. They were found to be statistically acceptable because the relative error for the check-point batch was found to be less than 8%, which was in the range of -1.65% and 0.32% respectively. The experimental and predicted values reflect the worthy agreement between each other. The good spray pattern of prepared formulations was found in terms of uniform and spherical spots. The average volume per actuation was found 0.73±0.004 and dose per actuation was also calculated. The concentration of Naproxen found per dose was 49.64±0.17 mg/ml. There was not any variation in the amount expelled out per actuation indicating the effectiveness of the pump system in delivering reproducible amounts of the formulation per actuation. In short-term stability studies, physical appearance and crystal growth were observed for 1 week, it was found that there was no visible crystal growth and it was also confirmed through a refractometer and microscopy. The stability study of the optimized batch was conducted at 30±2°C and 65%±5% RH for 1 year. At different time intervals, the

optimized batch was exposed to several assessments like clarity, pH, crystal growth by microscopy, and in vitro drug release at 6 minutes. The methods in employment for the study were similar to those explained above. Measured parameters and their results are shown in Table 7, which concluded that the formulation was stable over the study period.

**Table 2: Phase solubility study**

| Solvents | Solubility (mg/ml) |
|---|---|
| Water | 0.02±0.001 |
| Ethanol | 49.334±0.02 |
| pH 1.2 | 1.638±0.004 |
| pH 5.8 | 5.216±0.02 |
| pH 6.8 | 7.168±0.02 |
| pH 7.4 | 9.033±0.04 |

**Table 3: Screening of Solvents**

| Solvents (5 ml) | Appearance | Actual Drug added (mg/5ml) | Solubility found (mg/5ml) |
|---|---|---|---|
| Propylene Glycol | Clear | 132 mg | 131.44 |
| Ethanol | Clear | 247 mg | 246.67 |
| PEG 400 | Slightly Opaque | 78 mg | 66.01 |
| PEG 300 | Opaque | 72 mg | 57.325 |
| PEG 200 | Milky White | 69 mg | 43.08 |
| Water | White | 2 mg | 0.857 |

**Table 4: Saturation Solubility study of naproxen (mixtures of Ethanol, PG and water in different ratios)**

| Batch | PG (ml) | Ethanol (ml) | Saturation Solubility (mg/ml) | Dielectric constant |
|---|---|---|---|---|
| EP1 | 0.1 | 0.9 | 39.03 | 31.25 |
| EP2 | 0.2 | 0.8 | 41.92 | 30.5 |
| EP3 | 0.3 | 0.7 | 54.08 | 29.75 |
| EP4 | 0.4 | 0.6 | 56.05 | 29.06 |
| EP5 | 0.5 | 0.5 | 57.56 | 28.25 |
| EP6 | 0.6 | 0.4 | 60.68 | 27.5 |
| EP7 | 0.7 | 0.3 | 63.23 | 26.75 |
| EP8 | 0.8 | 0.2 | 65.20 | 26.02 |
| EP9 | 0.9 | 0.1 | 68.09 | 25.25 |
| E0P1 | - | 1 | 26.29 | 32.01 |
| E1P0 | 1 | - | 49.33 | 24.5 |

**Table 5: Screening of precipitation inhibitors**

| Concentration (%) | Degree of supersaturation (after 5 min.) | | | | |
|---|---|---|---|---|---|
| | HPMC E3 | HPMC E5 | HPMC E15 | PVP K25 | PVP K30 |
| **0.01** | 1.85 | 1.90 | 1.74 | 1.34 | 1.32 |
| **0.1** | 1.81 | 1.85 | 1.60 | 1.13 | 1.11 |
| **1** | 1.74 | 1.81 | 1.37 | 1.05 | 1.04 |
| **2** | 1.62 | 1.63 | 1.23 | 1.02 | 0.98 |

**Table 6: Degree of supersaturation at 2 h**

| HPMC E-5 for naproxen (At 2 Hr) | | | | |
|---|---|---|---|---|
| DS (N=3)±SD | | | | |
| TIME (min) | TIME (min) | TIME (min) | TIME (min) | TIME (min) |
| 5 | 5 | 5 | 5 | 5 |
| 30 | 30 | 30 | 30 | 30 |
| 60 | 60 | 60 | 60 | 60 |
| 120 | 120 | 120 | 120 | 120 |

**Table 7: stability study of optimized formulation**

| Time Parameter | Initial value | 15 days | 1 month | 3 month | 6 month | 9 month | 12 month |
|---|---|---|---|---|---|---|---|
| Clarity | Clear | Clear | Clear | Clear | Clear | Clear | Clear |
| pH | 5.7 ± 0.3 | 5.7 ± 0.6 | 5.8 ± 0.2 | 5.8 ± 0.5 | 5.6 ± 0.1 | 5.6 ± 0.4 | 5.6 ± 0.7 |
| Crystal Growth | Not observed | Not observed | Not observed | Not observed | Not observed | Not observed | Not observed |
| Drug release at 6 min. | 99.95± 0.2 | 99.94± 0.5 | 99.83 ± 0.4 | 99.74 ± 0.3 | 99.67 ± 0.6 | 99.62 ± 0.2 | 99.53 ± 0.6 |

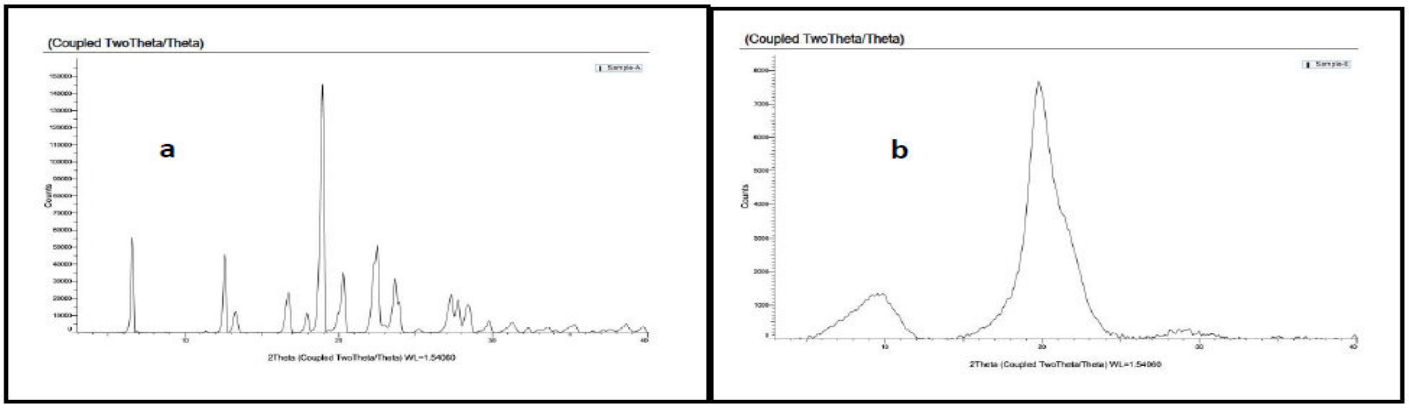


**Fig. 1: X-ray diffractogram of (a) drug (b) formulation**

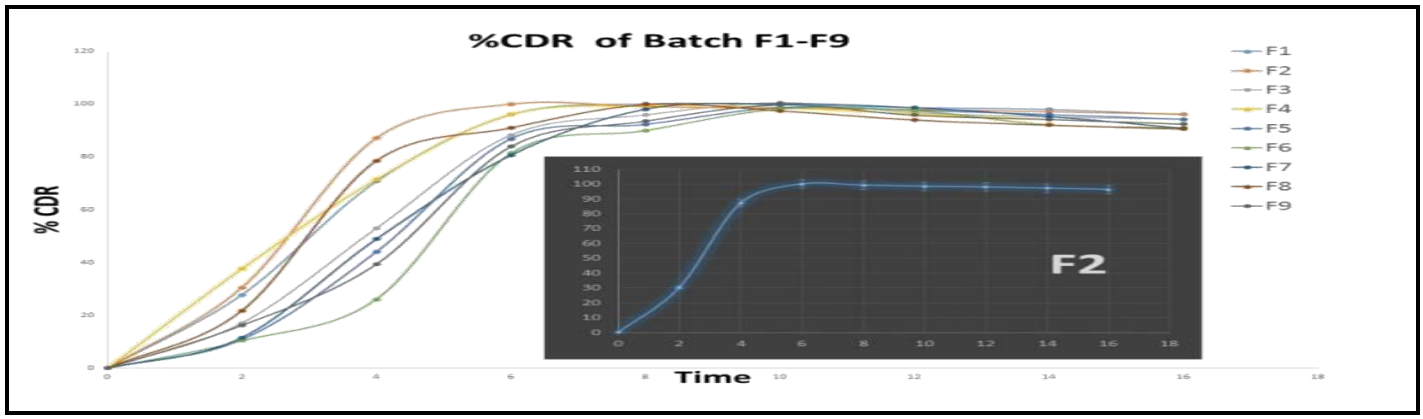


**Fig. 2: Drug release study**

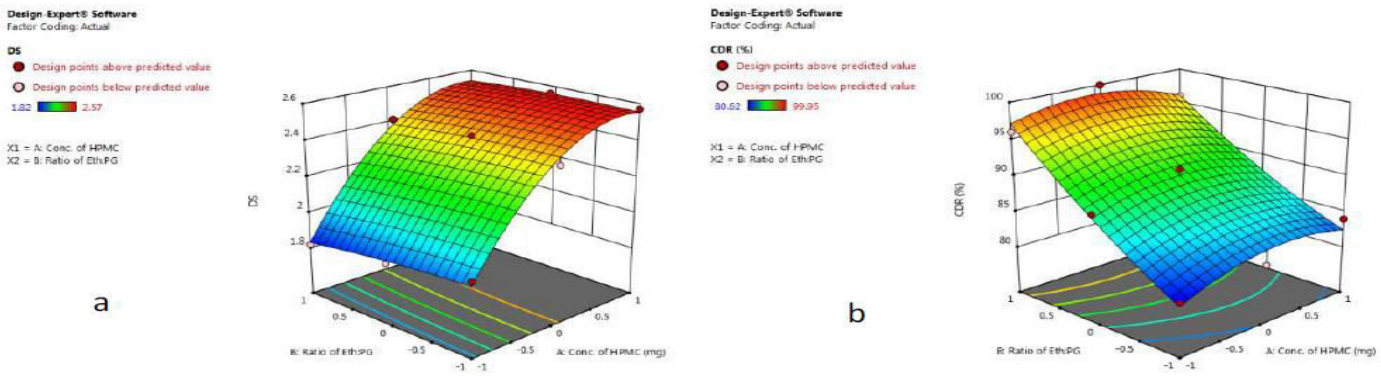


**Fig. 3: (a) contour plot of DS (b) contour plot of Drug release at 6 minutes**

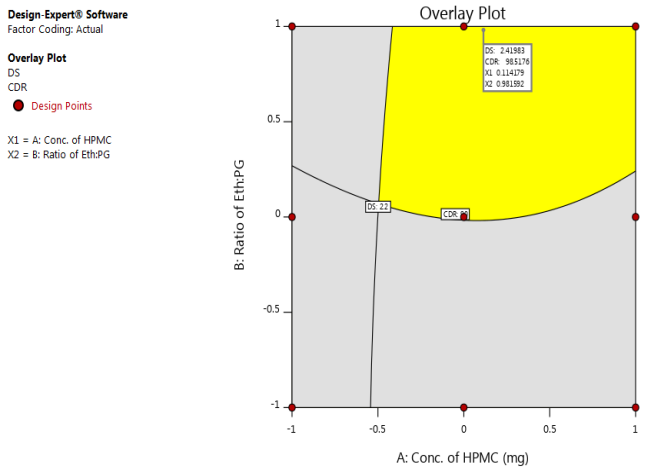


**Fig. 4: Overlay Spectra**

## 4. CONCLUSION

The outermost skin layer, known as stratum corneum, is the major barrier for permeation of Naproxen. Incorporation of ethanol and PG would be advantageous to attain a good percutaneous spray-on system for adequate dermal penetration and higher drug flux. This study has shown that in a single co-solvent vehicle of ethanol/PG flux is directly proportional to the degree of supersaturation whilst alone the vehicle did not give an impressive result. HPMC E5 was chosen as an anti nucleant to delay the onset of crystallization in the formulation. During stability study, it had shown excellent inhibition in crystal growth. The supersaturation of the drug in formulation gave higher drug flux which increases in vitro diffusion rate. The novel topical spray on the system was designed and evaluated where it was found that ethanol/PG in 9:1 ratio was showing the best results.

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