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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF NAPROXEN USING DIFFERENT CARRIERS BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

In the present study an attempt has been made to increase the *in vitro* dissolution rate of poorly water-soluble drug naproxen, by employing novel solid dispersion methods are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drug. Naproxen formulations were prepared by using melting-solvent method, and using carrier like urea and PEG4000. The formulation were prepared with the above mentioned carriers in three different drug-carrier (w/w) ratios of 1:1, 1:2 and 1:3. The prepared solid dispersion was subjected for percentage practical yield, drug content, and FT-IR and DSC studies. Absence of significant drug-carrier interaction was confirmed by FTIR and DSC data. In-vitro release profiles of all solid dispersions (F-1 to F-6) were comparatively evaluated and also studied against pure naproxen. The drug release from all the solid dispersion displayed nearly zero-order release kinetics with (r) values ranging from approximately 0.993. Solid dispersion of formulation (F3) naproxen and urea combination prepared in (1:3) ratio showed excellent solubility and the dissolution rate was found to be 98.32% drug release at 30 min was selected as the best formulation in this study. Solubility of naproxen was increased as the concentration of carriers increased.

KEYWORDS: Naproxen, Urea, PEG4000, Enhancement dissolution, Solid dispersion, Melting- solvent method, Dissolution rate, structure, Pharmacokinetic, metastable form.

1. INTRODUCTION

The solubility of drug is one of the most important criteria in formulation development. Oral bioavailability of drugs depends on its solubility and dissolution rate, these drugs having very

low solubility in biological fluids, which results into poor bioavailability after oral administration.[1] Solid dispersion is one of the techniques to improve solubility and hence bioavailability of poorly water soluble drugs. Solid dispersion methodologies are have attracted considerable interest of enhancing the dissolution rate of highly lipophilic drugs thereby increasing their solubility by reducing drug particle size, improving wettability and forming the amorphous particles.[2] The term solid dispersion defined to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier and a hydrophobic drug.[3] Naproxen is NSAID drug under the BCS class II. Drugs having the low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.[9] In case of solid dispersion, drug is dispersed in the matrix generally a hydrophilic matrix and a hydrophobic drug, thereby forming a solid dispersion.[10]

1.1 Solubility

Solubility can be defined as qualitatively as well as quantitatively. Quantitatively solubility can be defined as the solute concentration in a saturated solution at a particular temperature. Whereas qualitative it can be defined as the spontaneous interaction of two substances to produces a homogenous molecular dispersion.[11]

Solubility is of the Consideration of the modified Noyes-Whitney equation provides some hints as to how improve the dissolution rate of even very poorly soluble compounds and to minimize the limitations to oral bioavailability of substance.[13]

$$dC/dt = AD (Cs - C)/h$$

Where,

dC/dt = The rate of dissolution,

A = The surface area available for dissolution,

D = The diffusion coefficient of the compound,

Cs = The solubility of the compound in a dissolution medium,

C = The concentration of drug present in the medium at a time t

h = The thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.[14]

Table 1: Biopharmaceutical Classification System (BCS).

Class	Permeability	Solubility
Class I	High	High
Class II	High	Low
Class III	Low	High
Class IV	Low	Low

2. MATERIALS AND METHODS

2.1 Materials

Naproxen is taken as Gift sample from Medreich limited Bangalore, Urea is taken as S S R Enterprises Pvt Ltd., PEG 4000 is taken from S S R Enterprises Pvt Ltd.

2.2 Method

The crystalline or amorphous forms of formulation were produced by using Melting-solvent method.

Naproxen and urea and polyethylene glycol 4000 were taken as drug and carrier systems. The drug and different carriers with different ratios are dissolved in particular solvent together in a china dish and mixed thoroughly both ingredients. Put on the dish on hot plate to evaporate the solvent. The finally obtained mass was passed through mesh no#60 and like this, other formulations with different proportion were prepared in various ratio of drug: excipients such as 1:1, 1:2, and 1:3.

Table 2: Formula for Naproxen Solid Dispersion.

Batch Code	Method	Ratio	Drug (g)	Excipients (g)
F_1	Melting solvent method	1:1	Naproxen (1g)	Urea (1g)
F_2		1:2	Naproxen (1g)	Urea (2g)
F_3		1:3	Naproxen (1g)	Urea (3g)
F_4		1:1	Naproxen (1g)	PEG 4000 (1g)
F_5		1:2	Naproxen (1g)	PEG 4000 (2g)
F_6		1:3	Naproxen (1g)	PEG 4000 (3g)

Melting Solvent Method (Melt Evaporation)

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polymers either urea and

polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 4000 without significant loss of its solid property. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg and particularly useful for drugs that are thermolabile or have high melting points.[57-60]

3. RESULTS

3.1 Characterization of Active Pharmaceutical Ingredient

In Preformulation studies, characterization of API was performed and it was found that all are within the range specified in the pharmacopoeia. Physical appearance of drug was examined by various organoleptic properties.

Color : White amorphous powder;

Odor : Odorless;

Taste : Tasteless;

State : Fine to granular powder.

Melting point

Melting point of the Naproxen was determined by Capillary Fusion method. It was found to be 153^{o}C.

Preparation procedure for calibration curve of Naproxen

The absorbance of the solutions was measured at 330nm using UV-visible spectrophotometer. A graph of concentration vs. absorbance was plotted.

Table 3: Calibration curve of Naproxen.

S.No	Concentrations (µg/ml)	Absorbance at 330nm
1	0	0
2	2	0.178
3	4	0.356
4	6	0.534
5	8	0.712
6	10	0.890
7	12	0.97

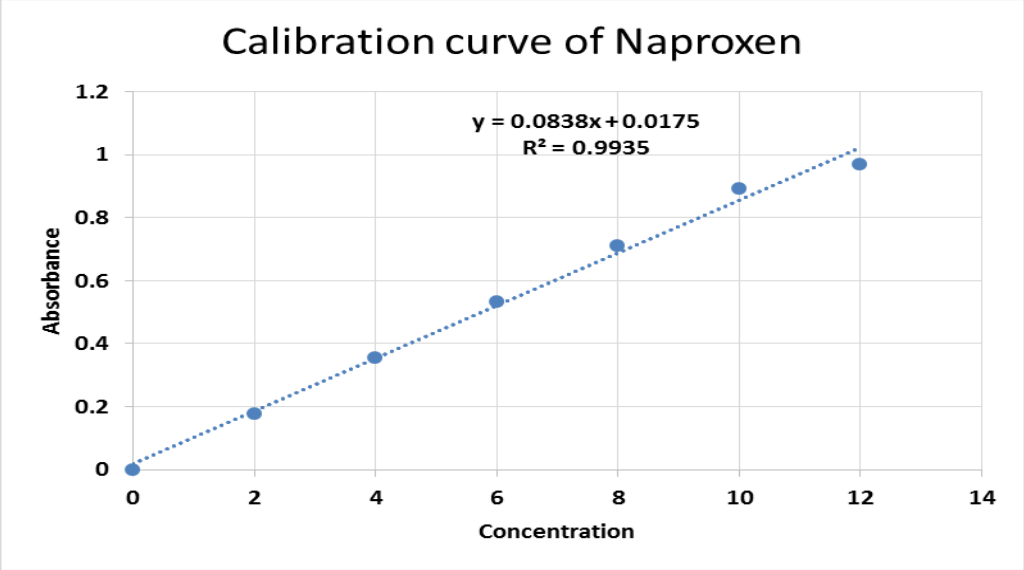

Figure 1: Calibration curve of Naproxen.

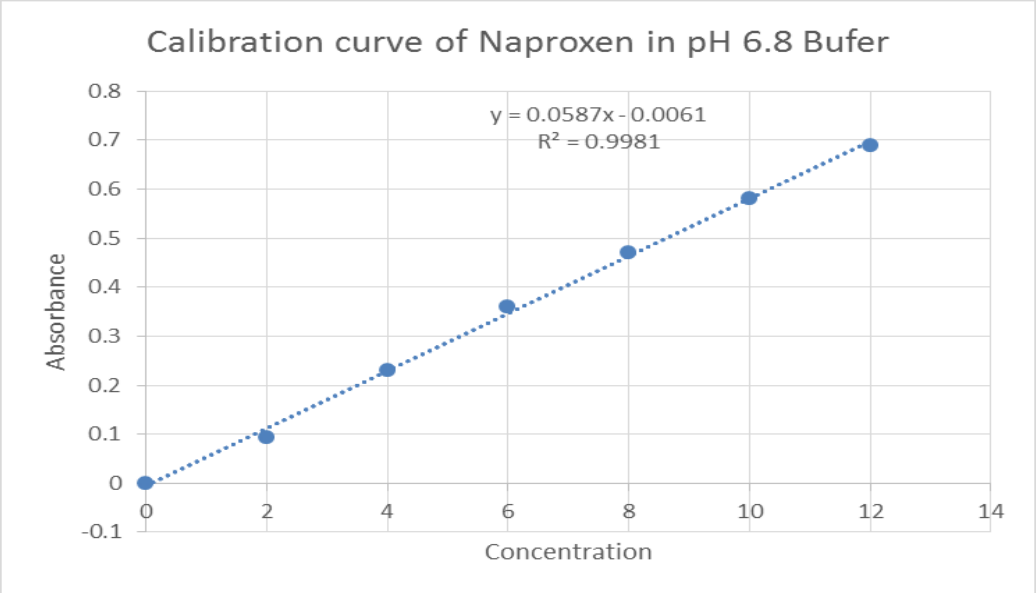

Figure 2: Calibration cure of Naproxen in Ph 6.8 Buffer.

Precompression Parameter of Powder Blend

Table 4: Precompression parameter of powder blend.

Batch code	Bulk density (gm/cm3)	Tapped density(gm/cm3)	Carr's Index (%)	Hausner's ratio	Angle of Repose θ)
F_1	0.191	0.303	36.9%	1.58	25.24
F_2	0.255	0.298	14.4%	1.16	27.47
F_3	0.259	0.280	7.5%	0.08	23.57
F_4	0.364	0.568	35.9%	1.56	26.2
F_5	0.390	0.550	29%	1.41	25.74
F_6	0.427	0.613	30.3%	1.43	23.62

FTIR Compatability Studies

Agilent Technologies

Sample ID:Naproxene pure
Sample Scans:8
Background Scans:8
Resolution:4
System Status:Good
File Location:C:\Program Files (x86)\Agilent\MicroLab PC\Results\Naproxene pure_2018-01-19T16-51-41.a2r

Method Name:DEMO
User:research
Date/Time:01/19/2018 4:51:41 PM
Range:4000 - 650
Apodization:Happ-Genzel

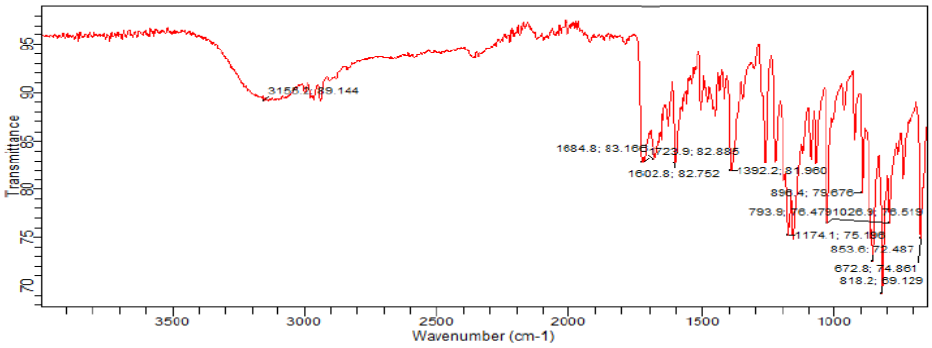

Figure 3: FTIR graph of Naproxen pure drug.

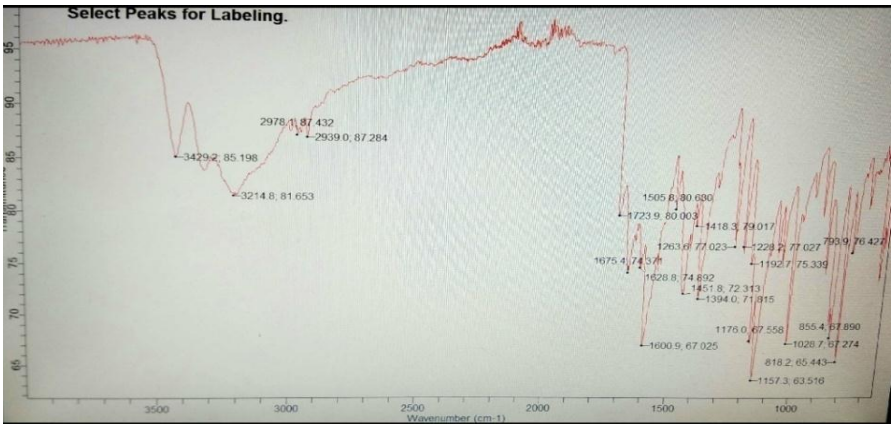

Figure 4: FTIR graph of Naproxen: Urea- 1:3.

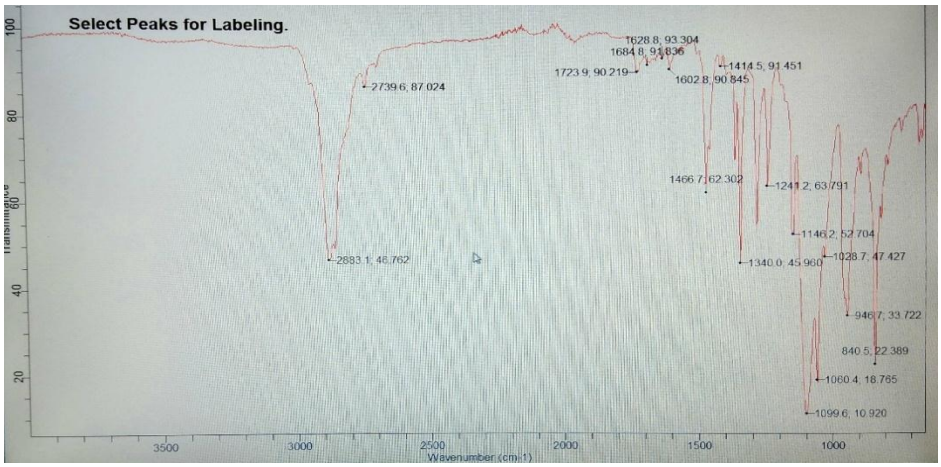

Figure 5: FTIR graph of Naproxen: PEG 4000- 1:3.

Interpretation of FTIR Studies

Table 5: Interpretation of FTIR peaks present in Naproxen.

S.No.	Wave number in formulation ($cm^{-1)}$	Characteristic Wave number range cm^{-1}	Bond nature and bond attributed
1	3155	3000-3700	O-H Stretching
2	1684	1600-1700	C-C Stretching
3	793	600-900	C-H Rocking
4	3429	3300-3600	C-O Stretching
5	2978	2700-3300	C-H Stretching
6	1600	1600-1900	C=O Stretching
7	1466	1200-1500	O-H Bending
8	3205	2700-3300	C-H Stretching
9	2739	2700-3300	C-H Stretching
10	3429	3300-3600	C=O Stretching

3.2 Premormulation Studies

Solubility

Solubility of Naproxen was determined in different solvent systems and buffers.

Table 6: Solubility of Naproxen in different solvents.

S. No	Solvents	Solubility
1	Distilled water	-
2	Methanol	++
3	Di ethyl ether	+
4	Benzene	-
5	Phosphate buffer 6.8	+

Partially soluble (-), slightly soluble (+), Soluble (++).

% Practical yield and Drug content uniformity studies

Table 7: Percentage practical yield in all formulations.

S.No	Formulation Code	% Practical yield	Mean% Drug Content*SD(CV)
1	F_1	86.00%	97.23± 0.46
2	F_2	88.00%	98.14±1.23
3	F_3	96.16%	99.56±0.67
4	F_4	92.25%	101.45±0.89
5	F_5	93.00%	102.65±1.02
6	F_6	94.75%	103.99±1.21

Solubility study

Phase solubility study was carried out in order in to ascertain effect of carriers on the solubility characteristics of naproxen. Solubility of naproxen was increased as the concentration of carriers increased. The results of saturation solubility studies are given in

(Table 3). The solubility of pure drug in water, in PBS (pH 7.4) and methanol was found to be 26.04 ± 0.5, 55.77±0.4 and 68.42±0.5 µg/ml respectively. The solubility of solid dispersion of naproxen prepared by melt method in water, in PBS (pH 7.4) and methanol were found in the range of 45.03±0.84, 77.63±0.87, 73.63±0.71µg/ml and The solubility of solid dispersion of naproxen prepared by melting- solvent method in water, in PBS (pH 7.4) and methanol were found in the range of 52.73 ± 2.65, 89.65 ± 2.03 and 78.50± 2.00 µg/ml respectively.

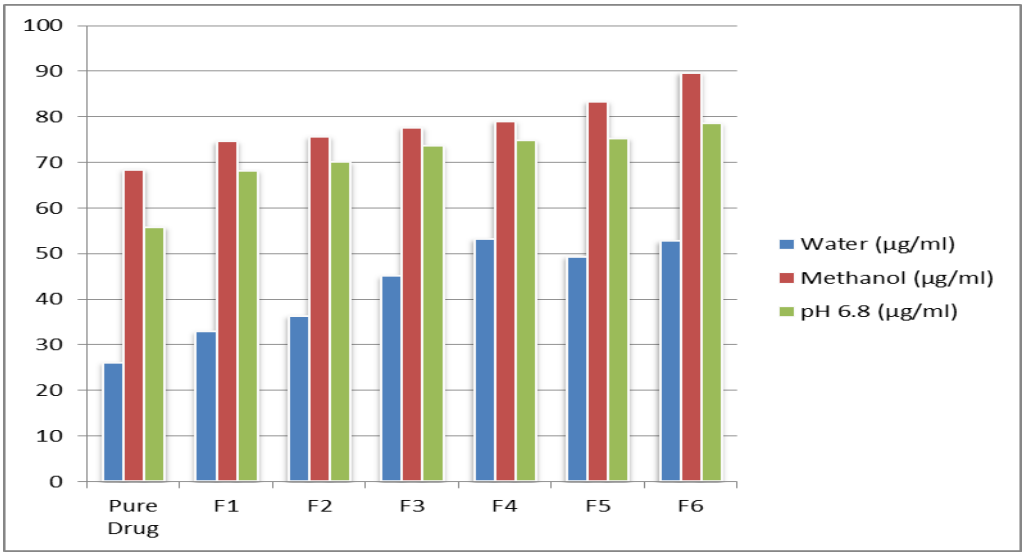

Figure 6: Solubility studies of drug in all dispersions formulation.

DSC Evaluation for Formulation

Accurately weighed samples (pure and treated naproxen, carriers, physical mixtures and solid dispersions) were placed in the sealed standard aluminum pans with lids. The thermogram analysis of the naproxen formulations was conducted using the differential scanning calorimetry (DSC60, Shimadzu, Japan) method. The heating rate was 20°C/min and the heat flow was recorded from 25°C to 300°C. Aluminum oxide was used as a reference. DSC is a well-known technique that measures heat flow into or out of a material as a function of time or temperature. Crystallinity can be determined with DSC by quantifying the heat associated with melting (fusion) of the material. The thermal curves of naproxen and of the different examined binary combinations are collected in Figures 22, 23, 24 and 25. The DSC curve of naproxen was typical of a crystalline anhydrous substance, showing a sharp endothermic peak (*T*onset= 153˚C, *T*peak= 156˚C), corresponding to the drug melting. The peaks were showing sharp ends at 158.2^{o}c, 135.4^{o}C, 133.6^{o}C, 60.2^{o}C of Pure Naproxen, physical mixture, Naproxen: Urea (1:3), and Naproxen: PEG4000 (1:3) respectively.

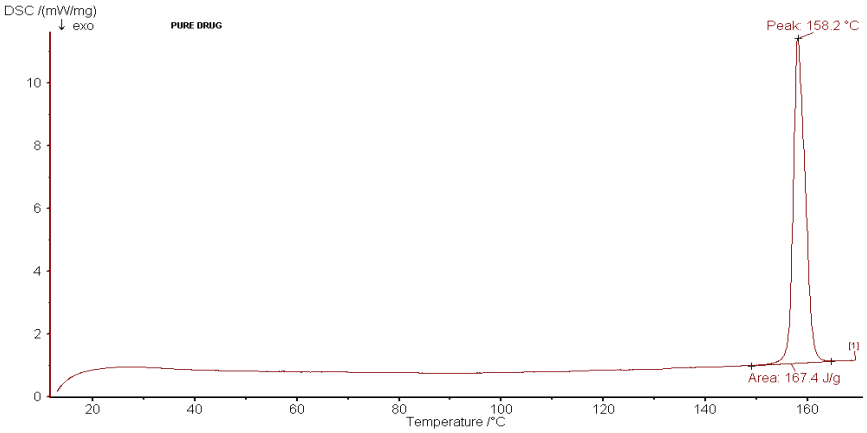

Figure 7: DSC for Pure Naproxen.

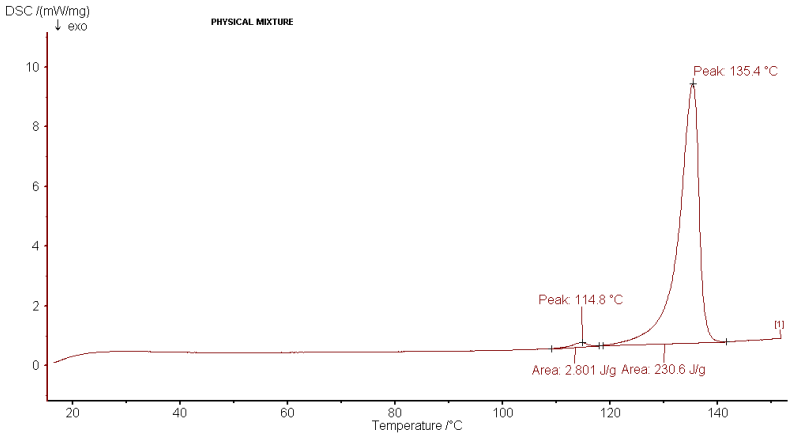

Figure 8: DSC test for Physical mixture.

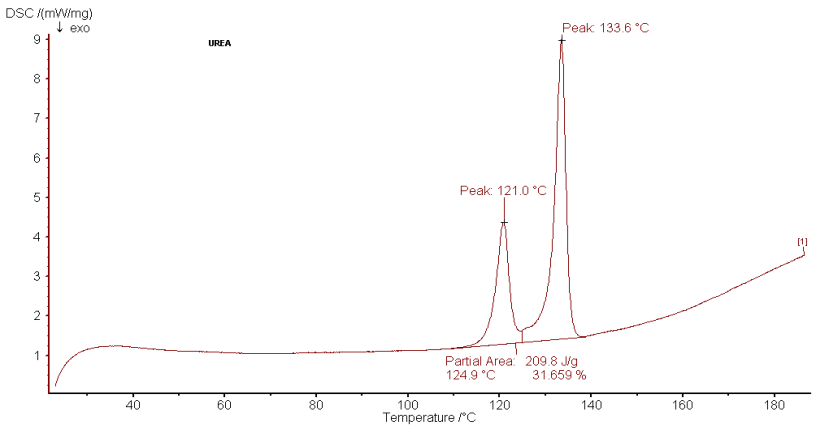

Figure 9: DSC for Naproxen: Urea (1:3).

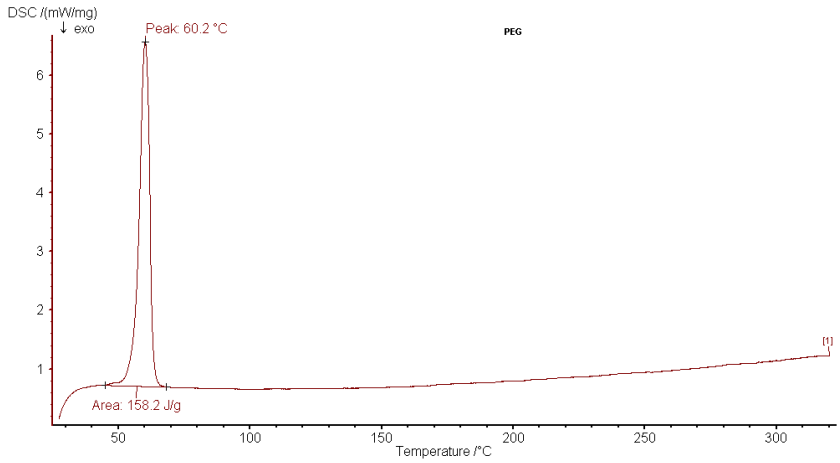

Figure 10: DSC for Naproxen: PEG 4000 (1:3).

3.3. Capsule Characterization

Weight variation

Weigh 20 capsules individually and calculate the average weight. It should vary with pulse or minus 10. If the capsules are does not passes this test, can carried out another 20 capsules.

% Weight variation = Individual weight- Average weight/ Average weight X 100.

Table 8: Percentage weight variation for all solid dispersions.

S. No	Formulations	% Weight variation
1	F1	8.1%
2	F2	8.6%
3	F3	8.8%
4	F4	8.9%
5	F5	9.0%
6	F6	9.2%

Disintegration Test

It is perform to determine the disintegration rate of capsules. Disintegration means breakdown of layer or complex molecules to smaller molecules. In six tubes capsules are placed, they are in 3 inches top is opened and to the bottom 10 mesh screen is placed at one liter apparatus. The apparatus is filled with 500ml of disintegration fluid and temperature maintained at 37+-2^{O}C and 28-32 cycles/min, the distance between up and down is 6-7cm.

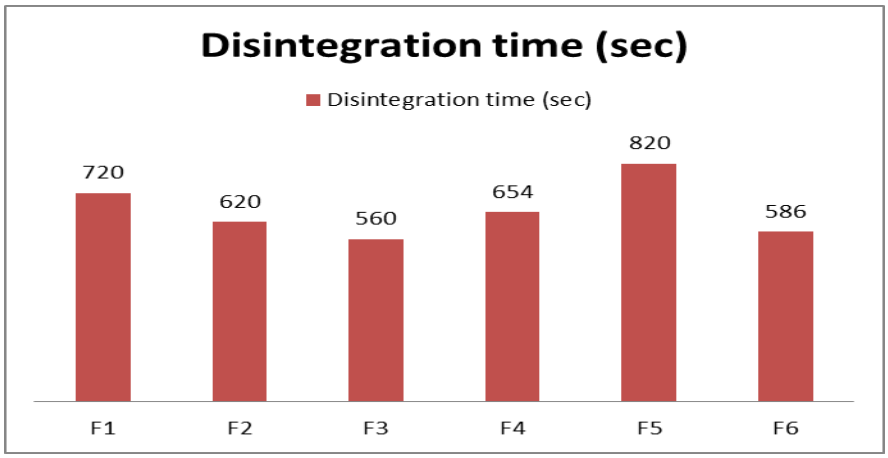

Figure 11: Comparison on In vitro Disintegration time of Naproxen solid dispersions.

***In-vitro* drug release profile**

The dissolution studies were carried out with Dissolution apparatus USP Type II. The Temperature and paddle speed were maintained at 37.0±0.5°C at 75 rpm for one hrs. The dissolution medium consisted of 900 ml of having pH (6.8) buffers. At predetermined time, 5 ml samples were withdrawn filtered through 0.45µm Whatman filter paper, diluted suitably and analyzed spectrophotometrically at 271 nm. An equal volume of fresh dissolution medium maintained at the same temperature was added to maintain the sink conditions. The polymers did not interfere with the UV analysis of the drug. The mean of three determinations was calculated.

Table 9: *In vitro* drug release study for drug and first three solid dispersions formulation.

S.No.	Timing (min)	Pure drug	F1	F2	F3
1	5	4.71%	18.9%	37.61%	69.87%
2	10	5.46%	23.78%	47.54%	77.54%
3	15	8.45%	38.91%	58.91%	80.63%
4	20	11.81%	43.76%	65.43%	83.89%
5	25	13.04%	57.32%	76.12%	85.41%
6	30	15.83%	61.45%	81.34%	98.32%

Table 10: *In vitro* drug release study for drug and last three solid dispersions formulation.

S.No.	Timing (min)	Pure drug	F4	F5	F6
1	5	4.71%	14.17%	33.47%	67.71%
2	10	5.46%	22.30%	40.71%	75.86%
3	15	8.45%	24.87%	44.23%	82.38%
4	20	11.81%	36.70%	51.64%	85.13%
5	25	13.04%	39.78%	55.09%	88.76%
6	30	15.83%	45.34%	57.12%	96.06%

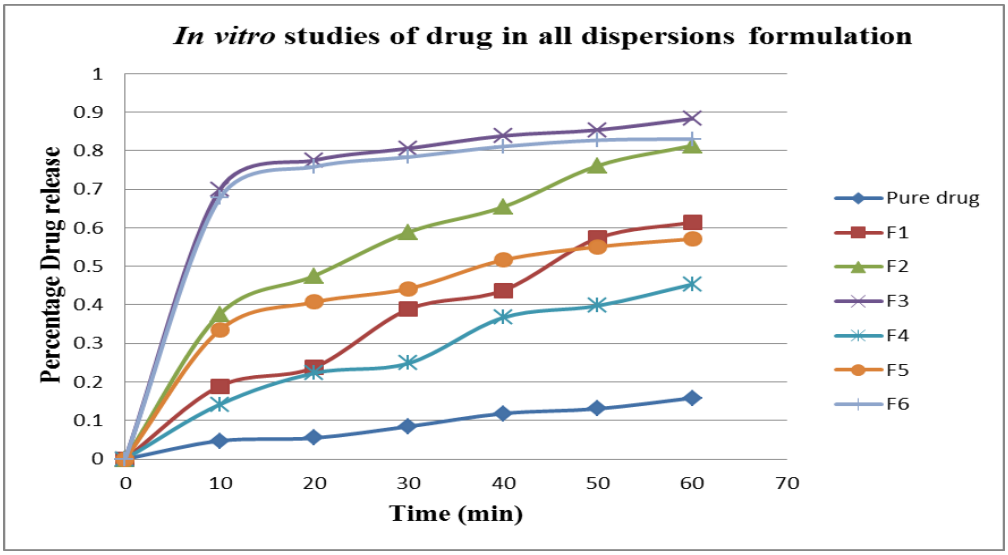

Figure 12: In vitro Drug release study for all solid dispersions.

Mechanism of Drug Release

The in vitro drug release data obtained from all the formulations were tabulated and fitted into three popular models of data treatment as follows.

- Cumulative percent drug released versus time plots (zero-order).
- Log cumulative percent drug remained verses time plots (first-order).
- When the data was plotted as log cumulative percent drug remaining versus time, the plots obtained were linear indicating first-order release kinetics. Cumulative percent drug released versus time plots (zero-order) the plots obtained were linear (Tables 14-15) and figure-27).

CONCLUSION

The data obtained from the study of " Enhancement of Solubility and Dissolution rate of Naproxen using Different carriers by Solid Dispersion Technique" revels following conclusion:

- The solid dispersion prepared by solvent- melting evaporation method were found to be white in color, fine and free flowing powders with uniform drug content.
- IR spectroscopic studies indicated that there was no drug-excipients interaction.
- In vitro dissolution studies indicated that, an increase in drug-Excipients ratio showed an increase in drug release rate.
- In their 6 formulation (F1-F6) the Percentage practical yield for all formulations of solid dispersions were prepared among F3 found to be promising 96.16%.
- Solubility of naproxen was increased as the concentration of carriers increased.

- The drug release from all the solid dispersion displayed nearly first-order release kinetics with r values ranging from approximately 0.993 to 0.998.
- Formulation F3 prepared with a drug-carrier ratio of 1:3 (naproxen: urea) showed promising results in enhancing the dissolution rate of poorly water-soluble naproxen (98.32% drug release in 30 min).
- The comparison between pure drug and formulations is done through solubility study and In-vitro study. The formulations are shown as better solubility and bioavailability, in that Urea Containg formulations better solubility than PEG formulation.

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