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FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELIVERY SYSTEM OF FLURBIPROFEN FOR TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT: In this present research work, the aim was to develop ileo-colonic targeted mini-tablets filled capsule system of flurbiprofen for treatment of rheumatoid arthritis. In the present study pH independent colon targeted system was developed and evaluated. SMEDDs of poorly water soluble drug flurbiprofen were prepared to enhance its dissolution rate and bioavailability. Mini-tablets of flurbiprofen were also prepared and filled in capsule. This capsule was coated with ethyl cellulose. Based on *in-vitro* dissolution studies it was noted that ethyl cellulose release takes place in colon (colon targeted). The design of formulation hence ensured colon targeted delivery of drug preventing premature drug release in stomach or small intestine and enhanced dissolution rate for enhancement of bioavailability. *In vitro* release studies were carried out in 0.1 N HCl pH 1.2, phosphate buffer pH 7.4 and phosphate buffer pH 6.8 mimicking *in-vivo* conditions for dissolution. SMEDDS exhibited a considerable increase in solubility of flurbiprofen and selected colon targeted formulation of pure drug successfully achieved colonic release of flurbiprofen with a lag time of 6 h and subsequent 75.895 % cumulative release in 11 h. Use of ethyl cellulose coated capsule efficiently delivers drug in colonic region without getting affected the SMEDDs inside for improving solubility and dissolution of drug. Thus, it was concluded that a novel ileo-colonic targeted delivery system of flurbiprofen filled by self micro emulsifying drug delivery system can be a better option for targeting early morning peak symptoms of rheumatoid arthritis and also to minimize the ulcers caused by side effects of flurbiprofen thus eliminating the use of proton pump inhibitors.

INTRODUCTION: Rheumatoid arthritis is a chronic inflammatory syndrome which causes the destruction of joints integrity. The patients with this disease have joint pain and functional disability symptoms which mainly persists in the early morning hours.

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These symptoms occur due to diurnal variations in the levels of circulating pro-inflammatory cytokines, interleukin-6 and/or tumor necrosis factor-a. The concept can be used for the better treatment of rheumatoid arthritis so that the highest amount of drug can be maintained in the bloodstream during the early morning time. In this case, colon targeting of drug or intentionally delayed absorption can be preferable in order to have a uniform therapeutic effect. Because the drug can be delivered in more amount during its greatest need as the release of drug occurs after a lag time. Thus, the peak pain and stiffness symptoms of the

disease can be overcome and good patient compliance can be achieved. Dew *et al*., developed the first colonic targeted pH responsive drug delivery system and it is most specifically referred to as 'ileo-colonic targeted drug delivery' rather than colonic targeted drug delivery system [1 – 2].

A number of approaches can be used for targeting the drugs at the colonic junction. Some of them are by using enzyme and pH dependent approaches. In the pH dependent approach, it depends on the increased pH of the gastrointestinal tract *i.e.* from stomach (pH 1.5 - 3) to terminal ileum (pH 7 - 8).

Many polymers showing pH dependent solubility are available, making it compulsory to use two polymers to retard the release in stomach and intestinal region for two and four hours respectively [3].

Normally while implementing one polymer is used on tablet or capsule for coating for preventing the drug release in stomach transit and other polymer is again coated or used in matrix form to avoid drug release in intestine. Both approaches become complicated while manufacturing urging the need for two - level coating.

Flurbiprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory agent with antipyretic and analgesic activity. Flurbiprofen is a poorly water soluble and highly permeable active pharmaceutical product belonging to BCS class II. To improve the solubility, chemical stability and oral bioavailability of several poorly water soluble drugs, self microemulsifying drug delivery systems have been successfully emerged in recent years.

Oral administration of this drug flurbiprofen is associated with severe gastrointestinal side effects like ulceration and gastro intestinal bleeding hence attempts were made to target the drug to colon to prevent the release of drug in stomach and small intestine as well as to reduce the dose of the drug by enhancing solublity implementing SMEDDS technology. Flurbiprofen is structurally and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen. So, an attempt was made to develop mini-tablets of flurbiprofen filled in a capsule for treating the early morning peak symptoms of rheumatoid arthritis [4 - 6].

The SMEEDS (self microemulsifying drug delivery system) are isotropic mixtures of oils, surfactants, co-surfactants incorporated with drug. SMEDDS mostly forms oil-in-water microemulsions whose size would be less than 100nm (*i.e.* <100nm-50nm). This droplet size can be measured when this microemulsion undergoes gastrointestinal tract**.** The large interfacial surface area is provided due to small droplet size of microemulsion which is useful for drug release and absorption [7 - 9].

Mini-tablets are very small tablets whose diameter is equal to or smaller than 3 mm that can be either placed in sachets or filled into a capsule shell for easy administration. They are having several benefits over single unit larger tablets such as consistent drug release, uniform clinical performance, more flexibility during the formulation development and maximum stability on storage.

Also mini-tablets are easier to prepare using direct compression method, which involves very less number of steps using simple equipments for their manufacture. Thus, the time and costs can be saved. Other benefits include regular shapes and excellent size uniformity.

In the present work, the reason for designing mini-tablets-filled capsule formulation is to develop a more reliable dosage form which possess all the advantages of a single unit bigger tablet and yet the problems such as danger of dose dumping and alteration in release profile of drug due to unit to unit variation can be avoided [9 - 15].

The present research has been undertaken with the aim to develop a formulation of flurbiprofen, which would attenuate the gastrointestinal related toxicities associated with oral administration and enhance the dissolution rate for enhancement of bioavailability.

Present research further focuses at achieving the colon targeting by user and manufacturing compatible technique by use of time dependent single - level coating of capsule with ethyl cellulose which will prevent premature release of the drug owing to its thickness, reducing one step in manufacturing of colon targeted drug delivery systems.

MATERIALS AND METHODS:

Materials: Flurbiprofen was purchased from Yarrow Chem Products, Mumbai, India. Microcrystalline cellulose Avicel PH 102 and Aerosil were purchased from SD Fine Chemicals, Mumbai, India. Ethyl cellulose was purchased from SD fine chem limited. Capsules of almost all sizes were obtained as gift samples from ACG Associated capsules Pvt. Ltd. Mumbai, India. Peceol, Transcutol were obtained as a gift sample from Gattefose, Mumbai. All other remaining materials used were of analytical grade.

Formulation Methods: Ethyl cellulose was found to be pH independent and slow hydrating polymer. In the view of this property there were chances that it might be able to control the release till colon if used in proper concentration.

Hence it was decided that rather than using different polymer with different thickness introducing various variables affecting the release, it is better to use a single polymer in optimized thickness as the only variable affecting the release of drug till colon. This limited variable even will ease the optimization of colon targeted formulation.

Formulation of Ethyl Cellulose Coated Capsule: 100 mg of flurbiprofen was weighed and filled in size 00 capsules. Various coating solutions were formulated and an optimized formula was selected for coating. The filled capsules were coated using dip coating technique and air dried for 12 h. The coated capsules were used for further characterization. Ethyl cellulose coating formulations are as shown in **Table 1**. Ethyl cellulose was added in 50:50 IPA and methylene chloride. Talc and titanium dioxide was used as a plasticizer [16].

TABLE 1: ETHYL CELLULOSE COATING FORMULATION

Ingredients	C1	C2	C3
Ethyl cellulose	5%	7%	9%
IPA: methylene chloride	600 ml	600 ml	600 ml
Titanium dioxide	30 g	30 g	30 g
Talc	20 g	20 g	20 g

Evaluation of Flurbiprofen Capsules:

Assay: Ethyl cellulose coated capsule containing drug equivalent to 100 mg was placed into a 100 ml volumetric flask and volume was made up using methanol to give 1000 µg/ml solution. This solution was shaken for 15 min until the drug dissolved in the solvent. Further dilutions were done suitably and drug content was determined using UV spectrophotometry.

Weight Variation: The gain in weight of capsules containing drug after coating was found out.

***In-vitro* Drug Release:** *In vitro* release of flurbiprofen from the ethyl cellulose coated capsules was carried out in 0.1N HCl pH 1.2, phosphate buffer pH 7.4 and phosphate buffer pH 6.8 and samples were withdrawn at intervals of 1 h up to 12h. Samples were analyzed spectrophotometrically at 247 nm with suitable dilution and the percentage drug release was calculated.

Preparation of SMEDDS:

Saturation Solubility of the Drugs (Flurbiprofen) in Oils, Surfactant and Co-Surfactant: In order to enhance the solubility of the drug, the SMEDDS system was prepared. The solubility studies of drug were carried out in various oils, surfactants and co surfactants for selection of SMEDDS excipient Solubility. Excess amount of drug (approximately. 25 mg) was added to 5 ml vial containing 1 ml of oil (Peceol, Maisine), Surfactant (Labrafil, Tween 20 and Tween 80) and Co-surfactant (Transcutol, Propylene glycol and Polyethylene glycol 400) and kept on an orbital shaker for 24 h at 37°C. After 24 h, solutions were centrifuged for 10 min at 3000 rpm and the supernatant was filtered. UV absorbance of Flurbiprofen was taken at 249 nm by suitable dilution with methanol[17].

Preparation of Micro Emulsion Concentrates:

Self microemulsifying concentrates were prepared by mixing required amounts of oils, surfactants and co surfactants. The concentrations of oil, surfactant and co- surfactant were varied keeping the concentration of drug constant as shown in **Table 2**.

TABLE 2: FORMULATION OF MICRO EMULSION CONCENTRATES

Formulation code	S:Cos ratio (Smix)	Oil: Smix ratio	Amount of Flurbiprofen added (mg)	Total volume of mixture(ml)
A1	1:2	1:4	100	1
A2	1:2	1:2.3	100	1
A3	1:1	1:4	100	1
A4	1:1	1:2.3	100	1

Emulsion Stability Check: [18 – 19] Upon selection of oil, surfactant and co- surfactant, Surfactant: Co-surfactant (S: CoS) ratios of 1: 1 and 1: 2 were prepared. The oil was added to the S: CoS in the ratio 1: 4 and 1:2.3. The emulsion concentrates were subjected to various stability checks for optimization of the final formulations.

a) **Freeze Thawing:** The resultant emulsions were subjected to 3 freeze thaw cycles. The emulsions were kept at a temperature of approximately - 5 °C for 24 h and immediately transferred to oven at 35 °C for next 24 h. This process was repeated 3 times and visual observation was done for any precipitation, phase separation or turbidity.

b) **Heat - Cool Cycle:** The selected emulsions were subjected to 3 heats - cool cycles where the emulsions were heated on a water bath at approximately 40 °C for 6 h, then instantly cooled in an ice bath and then kept at room temperature for 18 h. This process was repeated 3 times and visual observation was done for any precipitation, phase separation or turbidity.

c) **Centrifugation:** The prepared emulsions were centrifuged at 1000 rpm for 15 min and checked for any instability such as phase separation or turbidity.

Dispersibility Test: The efficiency of self-emulsification of oral micro emulsion is assessed by using a standard USP XXII dissolution apparatus II for dispersibility test. 1 ml of each formulation was added in 500 ml of water at 37 ± 1°C. A standard stainless steel dissolution paddle used with rotating speed of 50 rpm provided gentle agitation. The *in vitro* performance of the formulations was visually assessed using the following grading system.

Grade A: Rapidly forming (within 1 min) nano emulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion formed within 2 min.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Solubility of Self micro Emulsifying Drug Delivery System: The solubility of the drug in the selected ration of oil: S_{mix} was determined by adding fixed dose of the drug into the systems. The mixture was kept on orbital shaker for period of 24 h at 37°C. After 24 h, solutions were centrifuged for 10 min at 3000 rpm and the supernatant was filtered. UV absorbance of flurbiprofen was taken at 247 nm by suitable dilution with methanol.

Drug Content: 1ml of emulsion was taken. 1 ml of which was added to a 10 ml volumetric flask and volume was made up using methanol. Further, 1 ml from solution was withdrawn and transferred to a 10 ml flask and volume was made up using methanol. Further dilutions were done suitably and UV absorbance was taken at 247 nm. The values obtained were used to calculate the drug contents in the emulsion.

Characterization of Self Micro Emulsion: [20]

a) **Particle Size Determination:** The globule size distribution of the formulations was measured by Dynamic Light Scattering Particle Size Analyzer.

b) **Zeta Potential:** The zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. Zeta potential was measured by using Zetameter instrument. 1 ml of the micro emulsion was diluted to 10 times with distilled water and introduced in the sample container for measurement of zeta potential.

Preparation of Solid SMEDDS: Solid-SMEDDS were prepared by mixing liquid SMEDDS containing Flurbiprofen with microcrystalline cellulose (MCC) and Di-calcium Phosphate (DCP) in 1:1 proportion. Liquid SMEDDS were kept in the watch glass and weighed amount of solid carriers were mixed using glass rod to ensure

uniform distribution till a free flowing blend is obtained [21].

Mini Tablet Dosage Form:

Preparation of Mini Tablet Blends: Accurately weighed quantities of drugs and excipients were passed through sieve no. 20 and 40, respectively. Drug and excipients were added in geometric proportions in a polybag and mixed thoroughly. The lubricants were finally added to the blends to get the lubricated blend of flurbiprofen. The flow properties of the blends were evaluated.

Formulation of Flurbiprofen Mini Tablets Flurbiprofen mini tablets were formulated using direct compression method as shown in **Table 3**.

TABLE 3: MASTER FORMULAE FOR MINI TABLETS

Ingredients	MT 1	MT 2	MT 3	MT 4
Flurbiprofen	100 mg	100 mg	100 mg	100 mg
Microcrystalline cellulose	100 mg	100 mg	-	-
Dicalcium Phosphate	-	-	100 mg	100 mg
Crospovidone	2%	-	2%	-
Sodium starch glycolate	-	2%	-	2%
Talc	0.5 %	0.5 %	0.5 %	0.5 %
Magnesium stearate	0.5 %	0.5 %	0.5 %	0.5 %
Aerosil	2%	2%	2%	2%

Evaluation of Blend Flow Properties: [22]

a. Angle of repose: The angle of repose was determined by fixed funnel method. A funnel was fixed at a height of 2 cm above a flat horizontal surface. The powder was allowed to flow through the funnel and the height 'h' of the pile and radius 'r', of base was noted.

Angle of repose was determined by following equation,

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, 'h' is height of the pile; 'r' is radius of base

TABLE 4: RELATION BETWEEN ANGLE OF REPOSE AND FLOW PROPERTIES

Angle of Repose (θ)	Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

b. Bulk density and Tapped density: The blends were introduced in a 100 ml measuring cylinder and initial volume was noted as the bulk density. After the initial volume was observed, the cylinder was allowed to tap its own weight from a height of 2.5 cm. This was done using a tapped density apparatus. The tapped density was measured after 100 taps until no further change in the volume was noted.

Bulk density and tapped density were determined by the following formulae,

$$\text{Bulk density} = \frac{\text{Weight of blend}}{\text{Initial volume}}$$

$$\text{Tapped density} = \frac{\text{Weight of blend}}{\text{Initial volume}}$$

Compressibility Index: The compressibility index of the blends was determined by Carr's Compressibility index.

$$\text{Carr's index (\%)} = \frac{\text{TD - BD}}{\text{TD}} \times 100$$

TABLE 5: GRADING OF POWDERS FOR THEIR FLOW PROPERTIES

Carr's %	Flow
5 - 15	Excellent
12 - 16	Good
18 - 21	Fair to passable
23 - 35	Poor
33 - 38	Very poor
> 40	Very very poor

Hausner's Ratio: Hausner's ratio was determined by the following equation,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Hausner's ratio less than 1.25 indicated good flowability while greater than 1.25 indicated Poor flowability.

Characterization of Mini Tablets:

a) Weight Variation: The weight variation was carried out by weighing 20 randomly selected mini-tablets from each batch. The average weight was calculated and compared with the individual mini-tablet weights.

TABLE 6: PERCENTAGE DEVIATION IN WEIGHT VARIATION

Average Weight of Tablet	% Deviation
80 mg or less	± 10
More than 80 mg but less than 250 mg	± 7.5
250 mg or more	± 5

b) Thickness: Ten tablets were randomly selected from each batch and the thickness of each individual tablet was measured using a Digital Vernier Calliper.

c) Hardness: Six tablets were randomly selected from each formulation and the hardness of each tablet was determined using Pfizer hardness tester. It was expressed in kg/cm^2.

d) Drug Content: The mini tablets were powdered. Powder equivalent to the dose of one capsule was weighed accurately. Powder equivalent to the dose of flurbiprofen was weighed and transferred to a 100 ml volumetric flask and volume was made up using methanol. Further, 1 ml of this solution was withdrawn and transferred to a 10 ml flask and volume was made up using methanol. Further dilutions were done suitably and UV absorbance was taken at 247 nm.

e) *In - vitro* Release Study: The *in-vitro* drug release studies were carried out in dissolution apparatus USP type I. Mini tablets containing equaivalent dose of either of the drugs was added into 00 size capsules and placed in the basket of the dissolution apparatus containing phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5 ℃. 5 ml samples were withdrawn at intervals of 1 h. Samples were analyzed spectrophotometrically at 247 nm with suitable dilutions and the percentage drug release was calculated. Graphs of percentage drug release versus time were plotted.

Colon Targeted Drug Delivery Systems: Final colon targeted drug delivery system were formulated using C3 coating formula. Formulation C3 from coating system was selected. The selected formulations of SMEDDS (liquids SMEDDS, slurry SMEDDS) and mini tablets were filled in ethyl cellulose coated capsules(C3) to prevent the release of drug in stomach and small intestine and finally release the drug in colon. The prepared systems were then subjected to evaluation for drug content and in vitro release. Colon targeted drug delivery formulations are as shown in **Table 7**.

TABLE 7: COLON TARGETED DRUG DELIVERY FORMULATIONS

Formulations	Pure drug	A1	SMEDDS slurry	MT1	MT3
C10 Ethyl cellulose capsule (9%)	F1	F2	F3	F4	F5

Drug Content: Coated capsule containing drug equivalent to 100 mg formulation was placed into a 100 ml volumetric flask and volume was made up using methanol to give 1000 µg/ml solution. This solution was shaken for 15 min until the drug dissolved in the solvent. Further dilutions were done suitably and drug content was determined using UV spectrophotometry.

***In vitro* Dissolution Studies:** The prepared capsules were subjected to in-vitro dissolution studies using an 8 station USP (type 1) basket dissolution apparatus. The dissolution studies were carried out in 0.1 N HCl pH 1.2 for 2 hrs, in phosphate buffer pH 7.4 for 3 hrs and in phosphate buffer pH 6.8 for next 6 hours at 37±0.5°C & rotation speed was maintained at 50 rpm. At regular time interval of 1 hour, 5 ml of sample was withdrawn from the dissolution medium & replaced with equal volume of fresh medium. The sample withdrawn was subjected to UV-Visible spectrometry in shimadzu UV-1800 spectro-photometer for determination of drug release. Absorbance was measured at 247 nm for 0.1 N HCl pH 1.2, phosphate buffer pH 7.4 and phosphate buffer pH 6.8 respectively.

Release Kinetics: The rate and mechanism of release of enteric coat based capsule and ethyl cellulose coated capsule of flurbiprofen were analyzed by fitting the dissolution data into various kinetic models [23 - 25].

Zero-order Equation: Zero-order release kinetics, cumulative amount of drug released *vs* time and the release rate data are fitted to the following equation:

$$C = K_0 . t$$

First Order Equation: First-order release kinetics, log cumulative percentage of drug remaining *vs* time and the release rate data are fitted to the following equation:

$$C = 100 \times (1 - e^{-Kt})$$

Higuchi's Equation: The Higuchi release, cumulative percentage of drug released vs square root of time and the release rate data are fitted to the following equation:

$$Q = Kt1/2$$

Where, K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Korsmeyer-Peppas Equation: Log cumulative percentage of drug released *vs* log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/ M\infty = K_{tn}$$

Where Mt/M∞ is the fractional solute release, t is the release time. K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero order release**.**

Stability Studies: Stability of dosage form has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification.

Procedure: From the batches of Flurbiprofen colon targeted formulations, optimized formulation F2 and F7 were evaluated for stability studies as per ICH guidelines. Optimized formulations were stored at 40°C ± 2°C/75 ± 5% RH (accelerated stability conditions) for 3 months. The capsules were evaluated for weight variation, appearance and in vitro drug release after storage for 3 months. The values for in vitro drug release were calculated and were compared for change in dissolution profile.

RESULT AND DISCUSSION:

Formulation of Ethyl Cellulose Coated Flurbiprofen Capsules: Each size 00 capsules were filled with 100 mg of flurbiprofen powder. Coating solutions C1, C2 and C3 were prepared as per the formula in **Table 1**. The empty capsule shells were coated with C1, C2, C3 and air dried.

Evaluation of Flurbiprofen Capsules:

Assay: One capsule containing flurbiprofen powder equivalent to 100 mg was dissolved in methanol and adequately diluted to be analysed in UV spectrophotometer. Drug content was calculated and the percent drug release was found to be 98.8 %.

Weight Variation: The change in weight of capsules before and after coating was noted.

TABLE 8: WEIGHT VARIATION OF ETHYL CELLULOSE COATED CAPSULES

S. no.	Weight (capsule +drug) Uncoated (mg)	Weight (capsule + drug) Coated (mg)	% weight gain
1	199.5	222.1	11.3
2	201.4	223.6	11.0
3	199.7	221.9	11.1
4	198.3	221.3	11.5
5	198.2	220.8	11.4
6	198.9	223.7	12.4
7	196.1	219.6	11.9
8	202.7	225.2	11.1
9	197.4	218.7	10.7
10	201.5	223.3	10.8
Avg	199.37	222.02	11.360

In-vitro Drug Release:

TABLE 9: *IN VITRO* RELEASE OF FLURBIPROFEN

Time (h)	% Drug Release C1	% Drug Release C2	% Drug Release C3
60	0	0	0
120	0	0	0
180	0	0	0
240	0.718	1.629	0
300	1.25499	3.6171	3.567
360	12.31895	10.52	6.777
420	15.4404	20.0833	21.9977
480	51.3764	45.491	51.413
540	67.209	64.3591	78.9
600	70.536	80.186	80.717
660	83.8198	81.1935	83.426

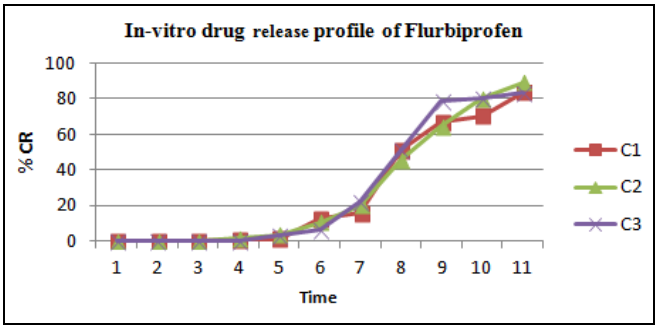

FIG. 1: *IN VITRO* RELEASE OF FLURBIPROFEN

The dissolution studies were conducted for prepared ethyl cellulose coated capsule of flurbiprofen for 12 h. Rate release profiles of the formulations C1 (5%), C2 (7%) and C3 (9%) were evaluated. All three formulations showed no release in stomach. C1 and C2 showed release in small intestine at 4th h and C3 showed negligible

release in small intestine at 5th h. Hence formulation C3 was optimized as it showed no release in stomach and retarded release of the drug in small intestine to deliver the drug in colon.

Preparation of SMEDDS:

Preliminary Studies:

Saturation Solubility of the Drug in Oils, Surfactant and Co Surfactant: For the drug to penetrate, it should be soluble in appropriate solvent. In order to screen appropriate solvents for the preparation of microemulsion, the solubility of flurbiprofen in various oils, surfactants and co-surfactants was carried out and the results were obtained. The oils used for study were Maisine 35-1 and Peceol. The solubility in Peceol was found to be the highest *i. e.* 13.231 mg/ml. From the value it was clear that Peceol solubilised the maximum amount of drug as compared to other oils used for study. The various surfactants used for solubility studies were Tween 20, Tween 80 and Labrafil M 1944 CS and co-surfactants used were PEG 400, Transcutol P and Propylene glycol. The maximum solubility among surfactants was found in the case of tween 80 *i.e.* 10.010 mg/ml. In case of co-surfactants, it was Transcutol P *i.e*. 11.7600 mg/ml.

The results of the solubility of oil, surfactant and co-surfactant solubility is depicted in graphical representation is shown in **Fig. 2, 3** and **4**. Based on the solubility, Peceol, Tween 80 and Transcutol were selected as the oil phase, surfactant and co-surfactant for the preparation of emulsion.

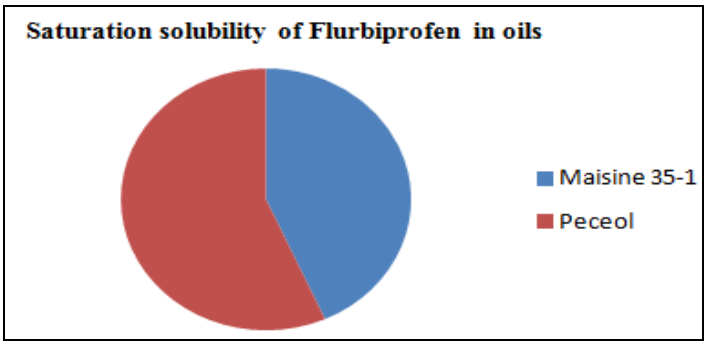

FIG. 2: SATURATION SOLUBILITY OF FLURBIPROFEN IN OILS

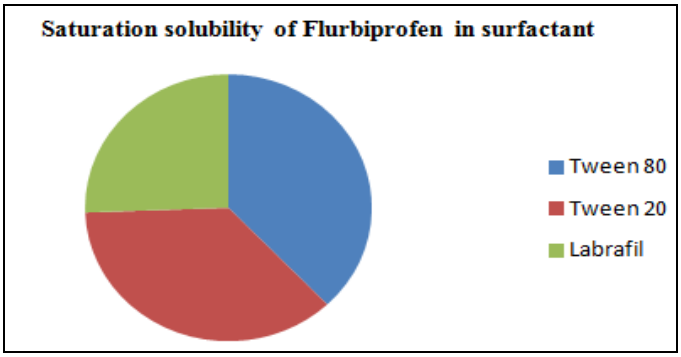

FIG. 3: SATURATION SOLUBILITY OF FLURBIPROFEN IN SURFACTANTS

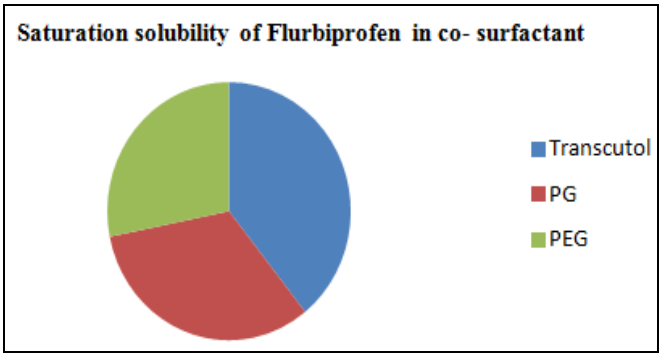

FIG. 4: SATURATION SOLUBILITY OF FLURBIPROFEN IN CO-SURFACTANT

Preparation of Micro Emulsion Concentrates: The mixture of surfactant: co-surfactant (S: CoS) and oil was prepared by adding 100 mg of flurbiprofen to the formulation based on its solubility in surfactant, co-surfactant and oil. The mixture was kept for stirring on magnetic stirrer for 24 h till the drug completely solubilized and then it was kept for 24 h to attain the equilibrium. The micro emulsions that appeared the most stable under each ratio of the surfactant and co- surfactant were then selected and evaluated for characterization studies.

Emulsion Stability Check: Three different stability checks were performed to optimize the formulations.

a) Freeze Thawing
b) Heat- Cool Cycle
c) Centrifugation

As shown in the table 10, formulation A1, A2, A3 and A4 were found to be adequately stable over a long period of time and devoid of any phase separation or turbidity. Hence, these formulations were chosen for the preparation of micro- emulsion and characterization studies.

TABLE 10: EMULSION STABILITY CHECK

Formulation code	S:CoS ratio [S_{mix}]	Oil: S_{mix} ratio	Freeze Thawing	Heat Cool Cycle	Centrifugation
A1	1:2	1:4	√	√	√
A2	1:2	1:2.3	√	√	√
A3	1:1	1:4	√	√	√
A4	1:1	1:2.3	√	√	√

Dispersibility Test: Formulation A1, A2 were categorised as grade C *i.e.* Fine milky emulsion formed within 2 min. Thus, these prototypes were used for preparation of SMEDDS.

TABLE 11: DISPERSIBILITY TEST

S. no.	Formulation Code	Grade
1	A1	C
2	A2	C
3	A3	D
4	A4	D

Solubility Testing of SMEDDS System:

TABLE 12: SOLUBILITY TESTING OF SMEDDS SYSTEM

Formulation	Solubility
A1	74.005
A2	62.097
A3	61.097
A4	57.096

Thus, based on solubility study, stability study and dispersibility test, A1 was selected as an optimized SMEDDS system and used for colon targeting of the drug.

Drug Content: The percentage drug content of all the 4 formulations of micro emulsions was determined and the percentage of drugs present was reported in **Table 13**. The drug content of flurbiprofen varied from 96 % to 99 %.The highest drug content was found in case of A1 formulation due to greater solubilisation of drug.

TABLE 13: DRUG CONTENT OF SMEDDS FORMULATION

Formulation Code	% Drug Content
A1	98.13
A2	96.31
A3	97.34
A4	97.34

Characterization of Self Micro Emulsion:

a) Particle Size Determination: The globule size of A1 formulation was evaluated on Nanotrac Particle size Analyser. The SMEDDS formulation A1 exhibited a D 90 of 94.60 nm. The particle size distribution range was found to be narrow.

TABLE 14: GLOBULE SIZE DETERMINATION OF SMEDDS

Parameters	A1
Polydispersity Index	1.213
Particle Size (nm)	94.60
Dispersion Time (min)	Less than 1 min
Zeta potential (mV)	-36.55 mV

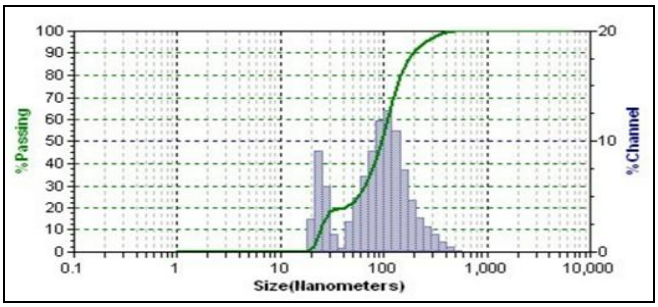

FIG. 5: GLOBULE SIZE OF FORMULATION A1

The formulations A1 was selected as optimized micro emulsion formulation based on globule size as it was ranging in micro emulsion region. So based on globule size and drug content the formulations A1 was selected as optimized formulation for further studies.

b) Zeta Potential: The Zeta potential of the formulations A1 was found to be – 36.55 mV. Thus, the zeta potential confirmed that the formulations showed good stability.

Preparation of Solid SMEDDS: The carrier was added in the liquid SMEDDS but it was very difficult to get free flowing mixture in the compressible range of tablets. In-spite of adding a large amount of carrier (1:4 ratio), bulk was not free flowing. Tablets were compressed with the same blend because addition of more carriers was uneconomical. Compressed tablets were of proper weight but very were very soft, failing in friability.

So, slurry SMEDDS were prepared and decided to compare the advantages of hydrophilic carrier material with that of liquid SMEDDS.

Mini Tablet Dosage Form:

Preparation of Mini Tablets: Flurbiprofen mini tablets were formulated using direct compression method. The prepared blends of Flurbiprofen tablets were compressed using 3 mm punches of 12 station rotary tablet compression machine.

Formulation of Flurbiprofen Mini Tablets: Minitablets were formulated as given **Table 3** and further evaluation was carried out.

Evaluation of Blend Flow Properties: The blends of different formulations were evaluated for angle of repose, bulk and tapped density, Carr's compressibility index and Hausners ratio.

The bulk density of blends was found to be between 0.2 and 0.25 g/cm^3. This indicates good packing capacity. Hausner's ratio ranged from 1.0 to 1.14, which indicated good flow ability. Carr's index was found to be between 7 and 12, showing excellent flow characteristics. The angle of repose of all the formulations was within the range of 14° to 16°, *i.e.* the blends had passable flow properties.

TABLE 15: POWDER FLOW PROPERTIES

Formulation	Angle of repose (°)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
MT1	15.64	0.244	0.270	9.6	1.10
MT2	15.24	0.244	0.277	11.9	1.135
MT3	15.98	0.244	0.263	7.22	1.077
MT4	15.22	0.239	0.27	11.48	1.129

Characterization of Mini Tablets:

TABLE 16: a) WEIGHT VARIATION, b) AVERAGE THICKNESS, c) HARDNESS AND d) PERCENT DRUG CONTENT OF TABLETS

Formulation code	Weight Variation	Average Thickness (mm)	Hardness (kg/cm2)	% Drug Content
MT1	19.95±0.176	2.68	4 - 5	97.62
MT2	19.97±0.134	2.65	4 - 5	96.37
MT3	19.96±0.094	2.67	4 - 5	97.25
MT4	20.5±0.126	2.68	4 - 5	90.104

Since, formulations MT1 and MT3 showed highest percentage of drug content compared to MT2 and MT4; they were selected as the optimized formulations for further evaluation.

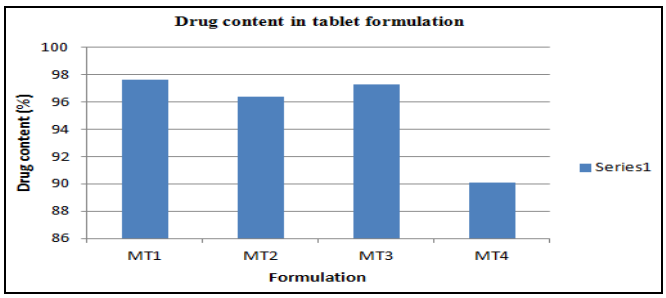

FIG. 6: PERCENTAGE DRUG CONTENT IN TABLETS

In vitro Release Study:

TABLE 17: *IN- VITRO* DRUG RELEASE OF MINI TABLETS

Time (h)	MT 1 %cumulative drug release	MT 2 %cumulative drug release	MT 3 % cumulative drug release	MT 4 %cumulative drug release
1	7.8972	5.4326	5.9749	11.456
2	20.85467	15.675	14.963305	20.564
3	56.47578	34.21	45.31355	37.455
4	79.9484	51.45	75.7558	53.545
5	81.876	65.3434	78.756	61.556

From the comparative release studies of formulation MT1- MT4, it was concluded that formulation MT1 and MT3 showed maximum in-vitro release compared to MT2 and MT4. Thus, MT1 and MT3 were selected as the optimized tablet formulations.

Colon Targeted Drug Delivery System: Colon targeted drug delivery system were prepared according to the above procedure, in which the selected coating formula, pure drug, mini tablets, SMEDDS and SMEDDS slurry were added as formulation to form a single coated capsule drug delivery system to reach the colon to see the overall effectiveness. These systems were evaluated for drug content, in vitro drug release and the results are as discussed below

Drug Content: The drug content of all the formulations is as discussed below in **Table 18**.

TABLE 18: DRUG CONTENT OF FORMULATIONS F1 – F5

Formulation	F1	F2	F3	F4	F5
Drug content	99.13	98.69	100.01	98.64	99.81

***In vitro* dissolution studies of optimised formulation:** The dissolution studies conducted for prepared ethyl cellulose capsule of flurbiprofen for 12 h. The optimized formulations of SMEDDS (A1), SMEDDS slurry, mini tablets (MT1 and MT3) and pure drug were filled in C3 formulation of coated capsules (ethyl cellulose coated capsule) and *in vitro* release studies were conducted.

TABLE 19: *IN VITRO* DRUG RELEASE OF FORMULATIONS F1 – F5

Time(h)	% cumulative drug release				
	F1	F2	F3	F4	F10
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0.008	0	0	0
4	0	0.099	0	0	0
5	0.934	2.898	5.768	0	0
6	7.675	9.349	13.867	6.8972	7.9749
7	8.227	17.088	44.811	18.85467	17.963305
8	24.255	69.376	59.01	50.47578	47.31355
9	48.755	80.115	67.255	63.6754	59.0233
10	67.974	83.791	77.015	70.4758	72.4704
11	75.895	90.499	85.9719	78.9484	77.7558
12	78.434	91.094	86.785	79.876	77.756

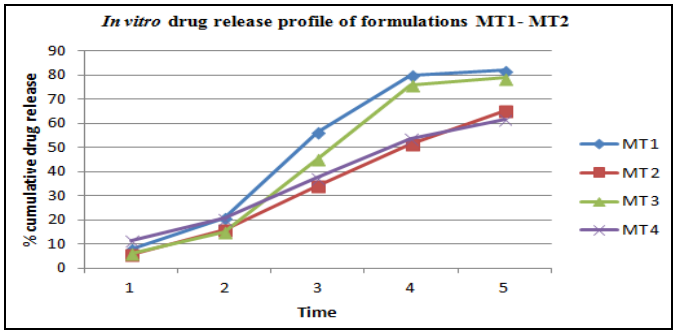

FIG. 7: *IN- VITRO* DRUG RELEASE COMPARATIVE STUDY (MINI TABLETS) OF FLURBIPROFEN

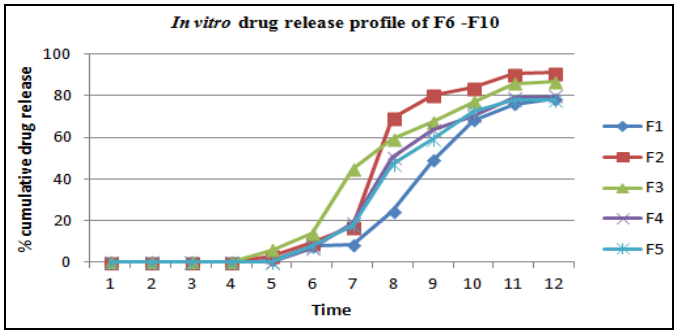

FIG. 8: *IN VITRO* DRUG RELEASE PROFILE OF F1- F5

The dissolution data reveals that the SMEDDS showed better release as compared to pure drug, SMEDDS slurry and mini tablets. Hence formulation F2 was selected. F2 formulation showed lag time of 5 h with negligible release of release of drug in small intestine. Formulation F2 showed maximum release of 91.094% after 11 hrs as compared to pure drug, SMEDDS slurry and mini tablets.

Release Kinetics: Dissolution data as further fitted in drug release kinetic to find out the best fitted model for drug release. The results of model fitting were summarized in **Table 20**. Kinetics analysis was carried out of optimized formulation F2 to analyze mechanism of drug release and order of drug release. The kinetics data of formulations F2 could be best expressed by zero order equations as the plots shows highest linearity than first order. The data was subjected to Kosmeyer-peppa's model and n values obtained from plots. The n value for formulation F2 was found to be > 0.89, which meant that the mechanism of release was Super case-II transport mechanism of drug release and best fit model was Korsmeyer-Peppas.

TABLE 20: REGRESSION COEFFICIENT VALUES OF THE FORMULATION IN VARIOUS KINETIC MODELS

Formulation	Zero order	First order	Higuchi plot	Korsmeyer peppas
F2	0.8352	0.822	0.6332	0.6339

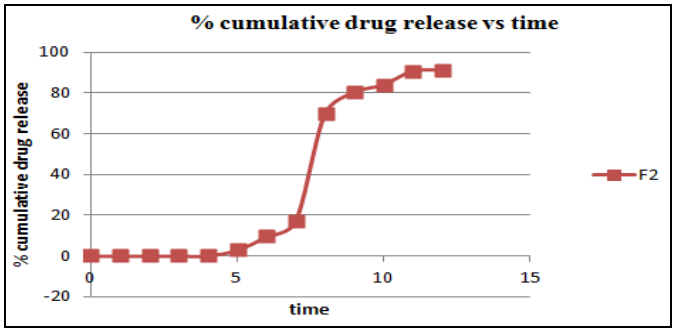

FIG. 9: ZERO ORDER DRUG RELEASE PROFILE FOR F2

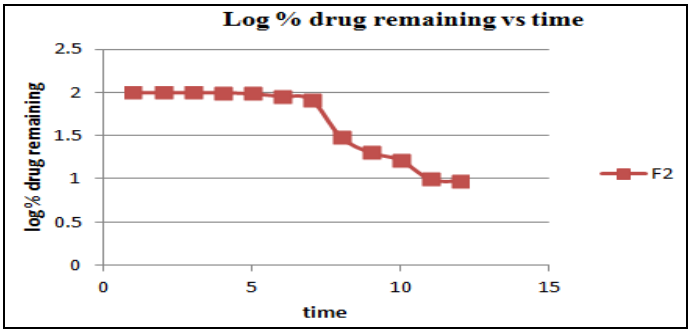

FIG. 10: FIRST ORDER DRUG RELEASE PROFILE FOR F2

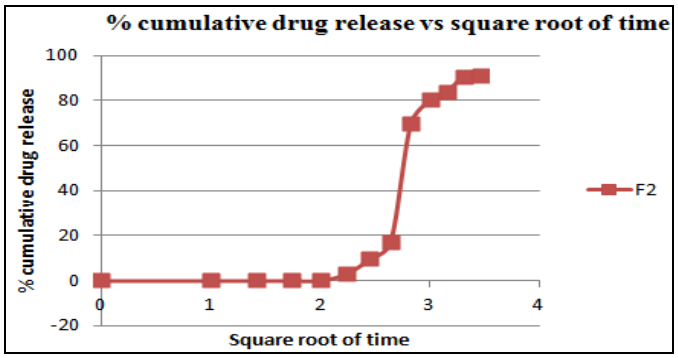

FIG. 11: HIGUCHIS PLOT FOR F2

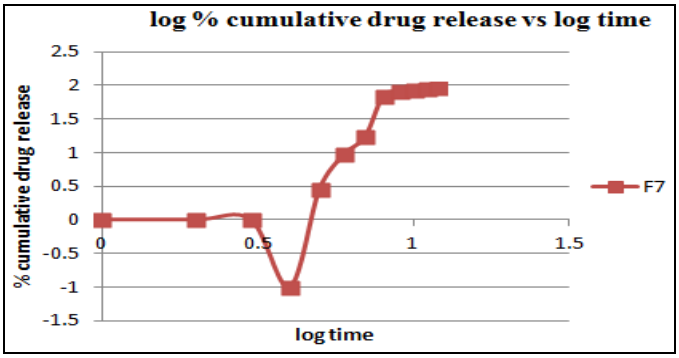

FIG. 12: KOSMEYER-PEPPAS PLOT FOR F2

Stability Studies: The accelerated stability studies were carried out according to ICH guidelines. After a period of one month, the samples were observed for any change on appearance. It was observed that capsules were devoid of any change in color or appearance of any kind. It was also noted that capsules were free of any kind of microbial or fungal growth or bad color. Hence there was no change in appearance of capsules. Similarly, no significant change was seen in drug content of both the formulations.

TABLE 21: STABILITY STUDY FOR F2 FORMULATION

Time (days)	Physical appearance	Drug content	% CRD
0	No change	97.67	94.38
30	No change	98.56	93.19
60	No change	97.54	95.23
90	No change	97.23	94.45

From the above obtained results it was concluded that, F2 was found to be stable at accelerated stability studies as per ICH for period of three months.

CONCLUSION: The present study was carried out to develop colon targeted delivery systems based on the combined approach of pH independant delivery. Flurbiprofen SMEDDS formulation was prepared and evaluated for enhanced dissolution rate & bioavailability. Colon targeting was achieved by coated capsule of flurbiprofen with ethyl cellulose to 11.360 % average weight gain. All the filled capsules were evaluated for parameters such as thickness, uniformity of weight, uniformity of content & in vitro drug release. The optimized formulation F2 has shown 91.094% percentage drug release and pure drug formulation has shown desired release profile of 78.434%. This shows that SMEDDS of poorly water soluble drug flurbiprofen enhances its dissolution rate and bioavailability. The data obtained for optimized formulations was fitted into various kinetic models. The best fitted model for optimized formulation F2 was zero order model with (r^2) value of 0.8352. The n value of formulation F2 for kosmeyer-peppa's was found to be > 0.89, which meant that the mechanism of release was Super case-II transport mechanism of drug release. From the results of the research, it was concluded that the proposed aim of stable colon targeted dosage form of flurbiprofen for the treatment rheumatoid arthritis was achieved successfully confirming the fulfillment of objectives of reduction in side effects, solubility enhancement helping in patient convenience.

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CONFLICTS OF INTEREST: Nil

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