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Formulation and characterization of flurbiprofen loaded microsponge based gel for sustained drug delivery

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ABSTRACT

The new investigation in this present work is to develop microsponges constructed novel drug delivery system for sustained action of Flurbiprofen. Quai-emulsion solvent diffusion method was engaged using Ethyl cellulose and Eudragit RS100 with drug: polymer ratio for development of microsponges. For optimization purposes, several factors are considered in the investigation. Several evaluation studies for the formed microsponges were carried out FT-IR, SEM, DSC, X-RD, particle size analysis, morphology, drug loading and *In vitro* drug release. Finally, it was concluded that there is no drug-polymer interaction as per DSC & FT-IR. Encapsulation efficiency, particle size and drug content showed a higher impact on alteration of drug-polymer ratio. SEM studies showed that morphological microsponges are spherical and porous in nature and with the mean particle size of 38.86 μm. The gel loaded with microsponges, were followed by *In vitro* and *Ex vivo* drug release studies by modified Franz diffusion cell. Skin delivery of optimized formulation enhanced the drug residence time and maintained therapeutic concentration for an extended period of time, which is possible to show sustained action of the drug.

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INTRODUCTION

The conventional route of drug delivery is known to be regular and more traditional route. Drugs that are delivered by this route undergoes tremendously first-pass hepatic metabolism and some drugs are eliminated due to its very short half-life to overcome this difficulty topically applied medication are used to deliver the medicament in sustained way and helps in maintain constant release of drug concentration in the plasma, which are well suitable for anti-inflammatory drugs, (Osmani *et al.*, 2015b) thus an active substance projected for topical application are integrated in novel formulation which, are retained as impregnates inside the continuous network of pores of porous solid particle or microsponges that opens to the outside environment of the particle; release of drug in a sustained rate depends upon the pore size (Osmani *et al.*, 2015b).

The active ingredient (drug) can be applied directly to the skin, either in a substantially pure form or in mixture with an aqueous vehicle. Active substance can often cause toxic and/or allergic reaction such adverse reaction when applied directly these can be minimized by dilution of the active substance in a suitable vehicle, the further dilution will also reduce the efficiency of the end product for

these reasons, it would be advantageous to afford the delivery system, by applying to the skin. To enhance the performance of drug an exclusive technology for the sustained release of the drug, which consists of microsponges beads, in which active moiety is loaded (Jain and Singh, 2010).

Richard Won initially developed the microsponges technology in 1987. Its usual size ranges from 5-300μm with highly cross-linked, porous, polymeric microsponges than can entrap active ingredient and release them for a prolonged period of time (Won, 1987).

Phenylalkonoic acid derivative group of NSAIDs includes flurbiprofen which are possible inhibitors of prostaglandin synthesis. Prostaglandin sensitizes afferent nerves and potentiates the action of bradykinins in inducing pain and act as mediators of inflammation (Orlu *et al.*, 2006). The study was aimed to improve a topical formulation, which releases the drug in a sustained manner with the aid of microsponges. "We tried to develop a sustained release topical preparation of FBP by incorporating FBP into microsponges that microsponges had been loaded into gel base".

MATERIALS AND METHODS

FBP was procured from Tocris, New Delhi, India, as a gift sample. Ethyl cellulose (EC), Eudragit RS100 (ERS100), was provided by suraresha Pharma Pvt. Ltd. Rookea, Uttarakhand, India. Dichloromethane (DCM), ethanol and dibutyl phthalate were purchased from SD Fine chem. Limited, Mumbai, India. Polyvinyl alcohol (PVA) was obtained from Qualikems, Fine chemicals, Pvt. Ltd. NewDelhi, India. The other chemical used were of AR grade.

Characterization of pure drug

Melting Point

The melting point of the pure drug (FBP) was determined by the melting point apparatus (BIO TECHNICS INDIA). The drug (active moiety) was placed in a capillary tube which is sealed one end and opens other ends, then the capillary tube was fitted into the holder containing coil, gradually temperature was increased and identified for the melting point of pure drug. Average of three readings was taken and compared with the standard melting point of a drug (Osmani *et al.*, 2015a).

FTIR Spectroscopy

To verify the purity of the obtained samples like drug and excipients, FTIR spectra were verified (FTIR BRUKER) over a wavelength range of 4000-400 cm^{-1}at resolutions of 2 cm^{-1}sample were directly place on the probe and spectra were recorded (Kumar and and, 2015).

UV spectroscopy

Spectral scanning was done for the drug with 10 μg/ml concentration; the maximum absorbance was observed at 248 nm with the absorbance of 3.353.

Calibration curve of Flurbiprofen was done by using Phosphate buffer saline pH 7.4 and methanol. The drug was analyzed spectrophotometrically (biochrom Model LibraS60), and the obtained curve was contained to be linearity over a concentration range of0 to 10μg/ml with R^2 value 0.992 and 0.999.

Differential Scanning Calorimetry (DSC)

To evaluate the thermal activities of pure drug, DSC (Model 4000) studies are applied. It works under the principle of measurement of flow of heat onto the sample and reference, for a predetermined temperature cycle, crucibles of aluminum pan containing 5 mg of sample was heated at rate of 10 °C/min, starting temperature from 10-200 °C with flow rate of 10ml/min of nitrogen inert gas and thermogram was obtained (Zakirizkalla *et al.*, 2011).

Drug-excipients interaction study

Drug-excipients interaction was examined by FT-IR and DSC studies. (FTIR, Bruker) Spectra help in identification of functional groups of the compound and their interaction with excipients and DSC (Model 4000) help in evaluating physical properties of the sample as crystalline or amorphous and also assist in identifying any interaction between drug and excipients. FBP optimized batches were subjected to thermal analysis (Amrutiya *et al.*, 2009).

Preparation of FBP microsponges

Preparation of Ethyl cellulose/ Eudragit RS100 microsponges (F1-F8)

Emulsion solvent diffusion technique is employed for preparation of FBP microsponges were using an internal phase composed of ethyl cellulose/Eudragit RS100 and Triethylcitrate phthalate(1%w/v) as a plasticizer dissolved in 10ml of dichloromethane (DCM): ethanol (1:1)/6 ml of DCM, and external phase was PVA in water allowed to dissolve completely, then the internal phase was poured dropwise into the external phase under the continuous stirring at 1000rpm for 180minutes/500 rpm for 60 min. (Kumar *et al.*, 2015) . Then the microsponges were obtained due to the forced evaporation of dichloromethane and ethanol from the system, formed microsponges were then filtered washed with distilled water for several times and

Table 1: Composition of FBP microsponges

Formulation Code	Drug: polymer	Polymer used	Solvent type	% PVA	Tri ethylcitrate (%w/v)	RPM
F1	1:1	EC	DCM: Alcohol	0.2	1	1000
F2	1:2	EC	DCM: Alcohol	0.2	1	1000
F3	1:3	EC	DCM: Alcohol	0.2	1	1000
F4	1:4	EC	DCM: Alcohol	0.2	1	1000
F5	1:1	ERS-100	DCM	0.2	1	500
F6	1:2	ERS-100	DCM	0.2	1	500
F7	1:3	ERS-100	DCM	0.2	1	500
F8	1:4	ERS-100	DCM	0.2	1	500

EC=Ethyl Cellulose, ERS-100=Eudragit RS 100, DCM= Dichloromethane (Methylene chloride), PVA= Polyvinyl Alcohol, RPM= Revolution Per Minute

Table 2: composition of microsponges gel 5% w/w

Ingredients	Formulation		
	F1	F2	F3
Microsponges (g)	Equivalent to 5 g of drug	Equivalent to 5 g of drug	Equivalent to 5 g of drug
Carbopol 940 p (g)	0.25	0.5	1
Glycerin (g)	5	5	5
PBS pH 7.4 (g)	up to 100	up to 100	up to 100
Triethanolamine	3-4 drops	3-4 drops	3-4 drops
Benzyl alcohol (ml)	1	1	1

Table 3: Characteristics Peak of FTIR

Characteristic peaks	(frequency cm^{-1})		
	Drug	EC optimized formulation	ERS-100 optimized formulation
C-H Stretch (aliphatic)	2882.26	2940.45	2881.39
C-H stretch (aromatic ring)	2975.64	3075.91	3076.12
O-H stretch (carboxylic acid)	3365.76	3367.65	3363.53
C-F stretch	1361.07	1361.13	1314.19
C-O stretch	1009.87	1036.79	1059.21
C=O Stretch (carboxylic acid)	1725.27	1725.80	1722.87

left for drying under desiccator as listed in Table 1.

Evaluation of FBP microsponges

Differential scanning Calorimetry (DSC)

DSC thermogram of pure FBP and microsponges formulations was obtained using DSC (4000). Microsponges samples were kept in aluminum hermetically sealed gradually heat is supplied at a constant rate of 10 °C for a temperature of 10-200 °C by maintaining inert nitrogen gas atmosphere of a flow rate of 10 ml/min.

FTIR Spectrum

Fourier Transform Infrared Spectrophotometer (BRUKER) was used to identify the possible interaction of drug and excipient by placing the sample directly on to the probe. FTIR spectrums of pure FBP and Optimized formulation are recorded. All the ingredient used in the preparation of microsponges formulation were verified in the wavelength of 4000 to 400 cm^{-1} at a resolution of 6 cm^{-1} (Panday *et al.*, 2015).

Production yield

The microsponges production yield was determined by a formula.

Production yield = [particle mass of microsponges/ Theoretical mass (Polymer+drug)] $\times$ 100

Drug content & Encapsulation efficiency

Samples of all formulated microsponges weighted quantity equivalent to 100 mg of microsponges containing drug were dissolved in 10 ml of phosphate buffer saline (PBS) pH 7.4 under sonication for 20 min at 25°C followed by membranes filtration of pore size of 0.25 μm and evaluated for drug content spectrophotometrically at 248nm the actual drug content and encapsulation efficiency were calculated as given formula below (Osmani *et al.*, 2015b).

Actual drug content (%) = [M actual drug / M obtained] $\times$ 100

Encapsulation efficiency = [M practical / M theoretic] $\times$ 100

Scanning Electron Microscopy (SEM)

For identification of morphological features of prepared microsponges was done under SEM (LEO) maintain at 15 Kv. Samples were coated with platinum/palladium alloy under vacuum was done (Osmani *et al.*, 2015b).

Photomicroscopic Analysis

The particle size of powdered microsponges primarily carried out by binocular microscope (OLYMPUS CH20i, Model CH20iBIMF) and Photographed was done at a magnification of 10X (as shown inFigures 8 and 9), (Pawar *et al.*, 2015).

X-ray diffraction study

To study the physicochemical characteristics of initial raw material and several microsponges formulations, XRD method was applied. X-ray diffraction (X-RD) Siemens, Model D5000, the voltage 45mV and current 20 A was applied to the instrument. The diffraction pattern was carried out at 5-10 °C/min in X-ray diffractogram, sharp peak at a diffraction angle (2θ) 13° were achieved in both FBP and its microsponges formulation (Figures 9 and 10).

For identification of crystal structure modification during the raw material processing, which are subjected to thermal and mechanical stress during the formulation. X-RD pattern of FBP and final formulation were carried out. The value of relative degree was 1.24. So X-RD analysis reveals that there is no change in the crystalline nature of the drug and found to stay stable in the final formulation (Osmani *et al.*, 2015b).

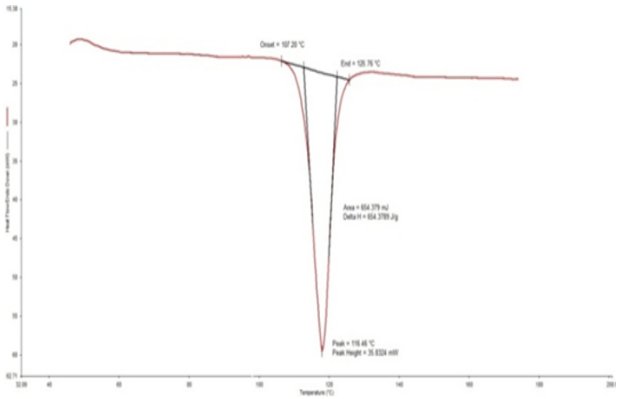

Figure 1: The DSC of Pure drug

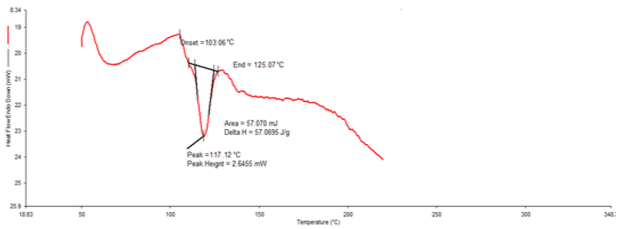

Figure 2: The DSC of Optimized formulation F2

Preparation of FBP microsponges gel

Required amount of Carbopol 940 was dissolved in 95 ml of Phosphate buffer saline pH 7.4 and allowed to swell for overnight then the mixture was stirred at 600 rpm with the help of magnetic stirrer, followed by addition of 5 g of glycerin to the above mixture, stirring was continued until the clear mixture is obtained, glycerin was incorporated for its humectant which also enhances viscosity. pH was determined and adjusted to 6.5-7.4 by using 2-3 drops of

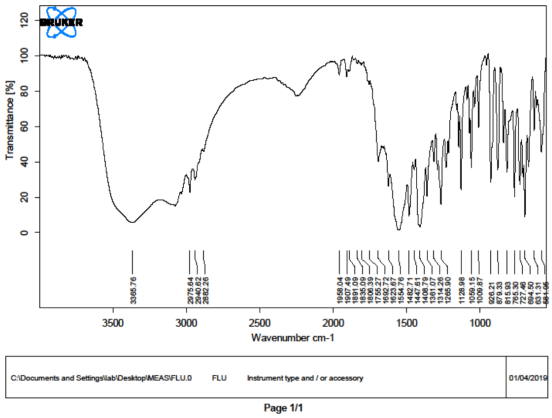

Figure 3: The FTIR spectra of Flubriprofen

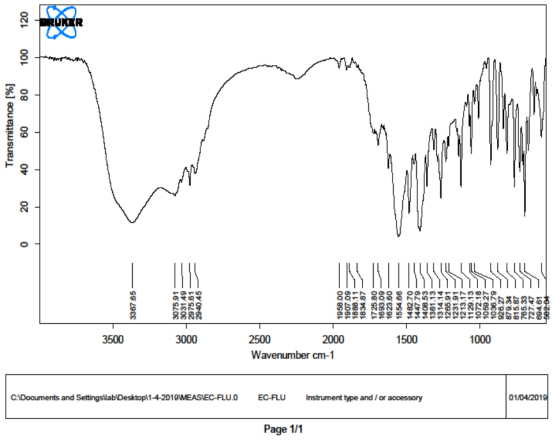

Figure 4: The FTIR spectra of Ethyl cellulose-Flubriprofen

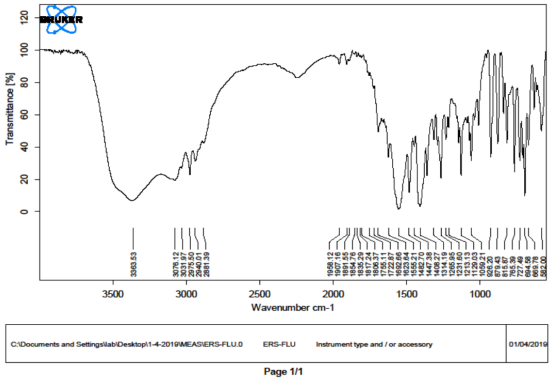

Figure 5: The FTIR spectra of Eudragit RS100 Flubriprofen

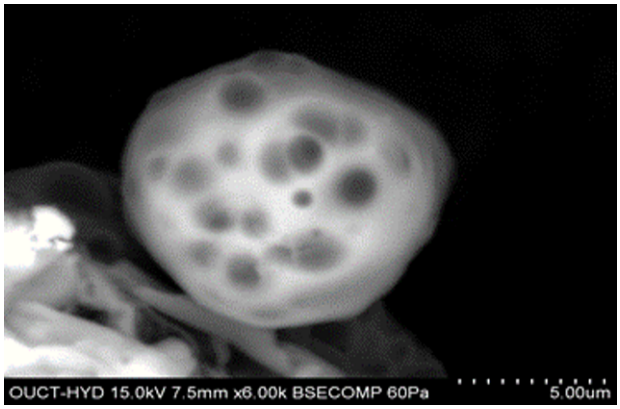

Figure 6: SEM image of Optimized formulation F2

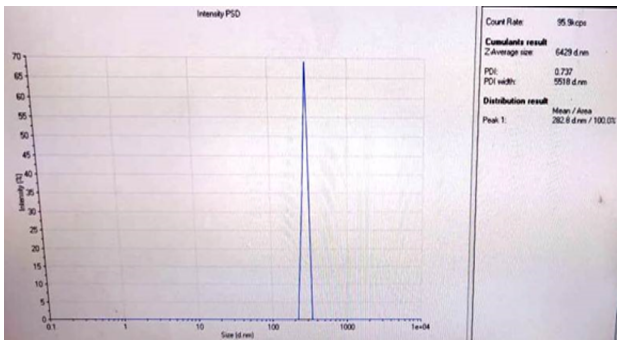

Figure 7: Particle size by Zetasizer

triethanolamine. 5 gm of equivalent microsponges containing drug was taken and thoroughly mixed with 100 gm of gel to get 5% w/w microsponges based gel, as shown inTable 2 . Which is equivalent to marketed gel (BRUGEL 5%w/w) (Panday *et al.*, 2015).

Evaluation of FBP microsponges gels

Visual inspection

Visual observation was done for the following parameters such as colour, consistency, homogeneity, and physical appearance of gel containing drug-loaded microsponges were meets the requirements (Gupta *et al.*, 2015).

pH measurement

Digital pH meter (Model MK VI) was used to record the pH of 10 g gel was dispersed in 90ml of double distilled water at room temperature, for three times and average reading was noted (Abdelmalak and El-Menshawe, 2012).

Spreadability studies

To meet the ideal characteristic of gel, spreadability studies are carried out to show the extent of the area to which gel easily spread on application to the skin. Spreadability can be calculated with respect to the time taken to separate the two slides from gel under the application of known weight (Pande *et al.*, 2015).

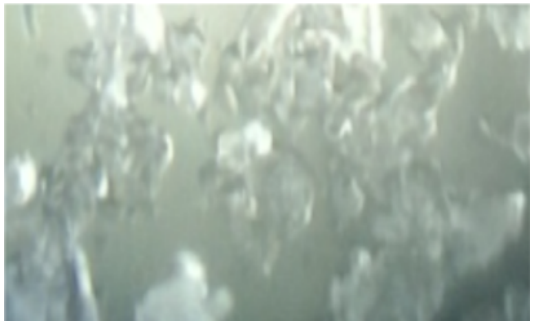

Figure 8: Before Formulation. Magnification at 10x

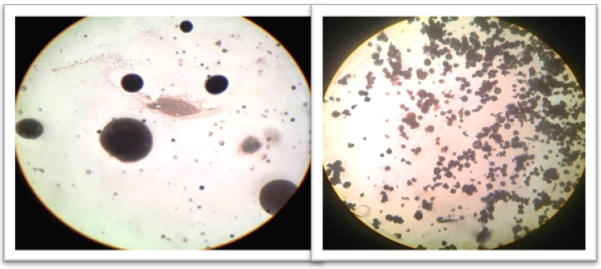

Figure 9: After Formulation. Magnification at 10x

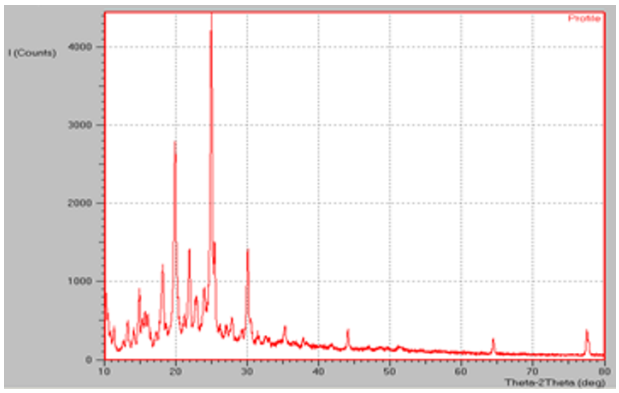

Figure 10: X-RD image of pure drug

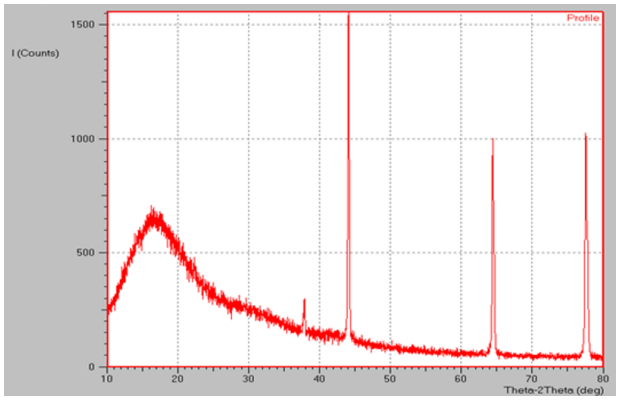

Figure 11: X-RD image of optimized formulation F2

Procedure: Wooden block-glass slide apparatus having dimensions of 15cm length & breath was used, block weight about 20 g is applied, and time for complete separation of two slides was estimated.

Spreadability calculation

S = ML/T

Where M= weight (g) applied on upper slide, L= length (slide in cm), T= time (sec) to detached the slide.

Viscosity measurement

The obtained gel formulation was measured by Brookfield viscometer (DV II+pro. Model LVDV-II+P) for its viscosity determination cone number SS64, with an angular velocity of 50 rpm at 25 °C. An average of five reading was calculated at a particular rpm & spindle number; the graph was plotted for rpm versus viscosity (Pawar *et al.*, 2015).

Tube Extrudability

Tube Extrudability test was approved by using an aluminum tube containing 15g of gel is subjected under the application of pressure of 1 kg/cm^2 for about 30 sec. The amount of gel extruded was weighted. The procedure was repeated for three times for three different positions in the tube, and average reading were documented (Kumar *et al.*, 2015).

In vitro drug release FBI microsponges gel

The *in vitro* gel diffusion was done by using Franz diffusion cells. It was covered with, previously soaked cellophane diffusion membrane was placed between the donor and recipient compartment; lower region contains 20 ml of diffusion medium as PBS at pH 7.4 was thermostatically maintained at 37±1 °C under stirring. All the formulations and marketed formulation were analyzed for drug diffusion studies, one ml of Samples were withdrawn periodically by maintain perfect sink conditions and analyzed by UV spectrophotometer at 248 nm against buffer. The cumulative % of drug release was calculated. Further various mathematical models were incorporated into release kinetics.

Ex vivo diffusion study

The selected or finalized formulation is subjected to *ex vivo* studies. For *ex vivo* studies male Wister albino rats (200-250g) were selected and sacrificed to remove skin larger than the effective surface are of the diffusion cell. The skin was formerly submerged in normal saline solution (0.948%w/v) and then fixed between the compartments of Franz diffusion cell; one ml samples were withdrawn periodically by maintaining perfect sink conditions and analyzed by UV spectrophotometer at 248 nm

against PBS pH 7.4. The drug release profile was calculated against time (Bhatia and Saini, 2018). The above experiments procedures were approved by the institution Animal Ethics committee (Registration number: 1534/PO/a/CPCSEA).

Stability studies.

Stability studies are carried out as per ICH norms; optimized gel formulation was filled in aluminum tube and are exposed to 40 °C and 75% RH in a stability chamber. Microsponges gel was evaluated for modification in appearance, pH or *in-vitro* release profile at some intervals of 0, 01, 02, 03 Months (Bhatia and Saini, 2018).

RESULTS AND DISCUSSION

Characterization of pure drug

Melting point

The melting point of FBP was in the range of 118-120 °C (actual melting point, according to IP is 117-243 °C) the procured form of an active ingredient is pure and meets the above standards.

Differential scanning Calorimetry (DSC)

As DSC thermogram are shown in Figure 2, piercing endothermic peak at 117.12 °C was observed in a finalized formulation, corresponding to melting point observed in DSC of Pure drug was 116.46 °C as shown in fig 1, but the slight difference to pure form of the drug.

FTIR spectroscopy

FTIR spectrum of pure drug sample was recorded (Figure 3), and interpretation was done. The original characteristics IR absorption peaks of pure drug (Flurbiprofen) at 2882.26 cm^{-1} ("C-H aliphatic stretching"), 2975.64 cm^{-1} ("C-H aromatic stretching"), 3365.76 cm^{-1} ("O-H carboxylic acid stretching"), 1361.07 cm^{-1} ("C-F stretching"), 1009.87 cm^{-1} ("C-O stretching"), 1725.27 cm^{-1} ("C=O carboxylic acid stretching"), these peaks are observed in formulation spectra, which reveals the purity of Flurbiprofen not interacted with polymers as showed in Figure 4 ,Figure 5.

Drug-excipients interaction study

Drug excipients compatibility was done using DSC and FTIR studies, to identify any possible reaction between drug and polymer used in the preparation of microsponges. Optimized formulation showed similar peak compare to the pure drug, but with low intensity, pure form of a drug (FBP) showed inFigure 1. However, the peak was suppressed in the optimized formulation due to its encapsulation and protection of drug as showed inFigure 2. It reveals

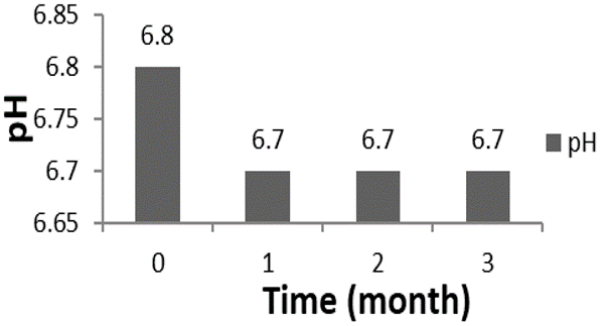

Figure 12: pH measurements instability studies

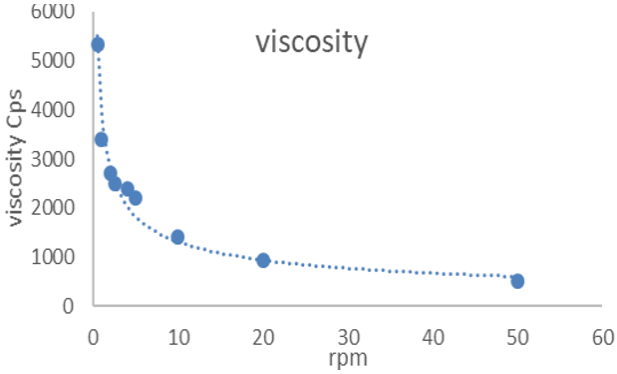

Figure 13: Viscosity studies for optimized formulation F2

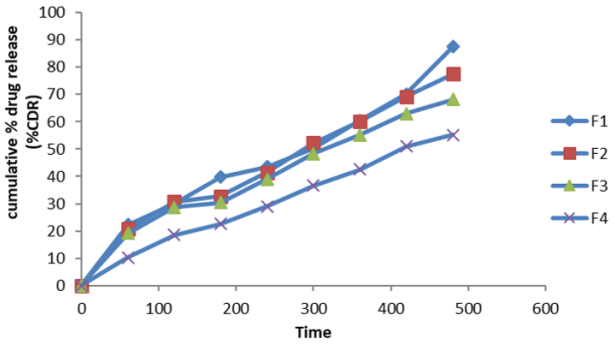

Figure 14: Comparative In vitro drug release profile of F1-F4

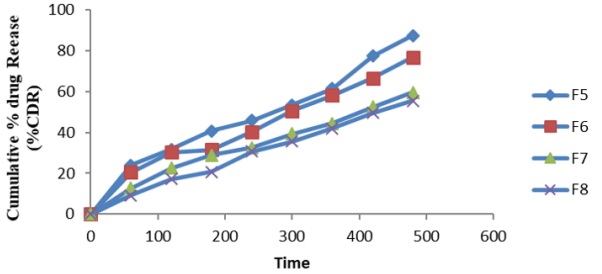

Figure 15: Comparative In Vitro drug release profile of F5-F8

Table 4: Evaluations of Microsponges

Batch	D:P	PY	%EE	%CDR	F	MTDC	MADC	PS
F1	1:1	44.90 ±1.08	98.30 ±0.125	87.43 ±0.377	0.3180	59.58 ±0.124	51.43 ±0.124	30.01 ±0.367
F2	1:2	48.42 ±0.109	93.00 ±0.496	77.45 ±0.635	0.2978	50.84 ±0.103	45.47 ±0.287	33.29 ±0.047
F3	1:4	56.36 ±0.127	88.27 ±0.443	68.16 ±0.273	0.2201	48.82 ±0.064	45.47 ±0.181	48.27 ±0.253
F4	1:8	68.42 ±0.118	86.31 ±1.53	55.19 ±0.465	0.1189	43.29 ±0.264	42.44 ±0.170	52.16 ±0.065
F5	1:1	43.36 ±1.96	98.58 ±0.352	89.52 ±0.306	0.3090	48.53 ±0.207	44.13 ±0.199	30.09 ±0.047
F6	1:2	47.26 ±0.079	96.47 ±0.265	76.81 ±0.333	0.2880	47.19 ±0.487	42.78 ±0.074	33.29 ±0.085
F7	1:4	56.08 ±0.319	91.24 ±0.157	59.52 ±0.385	0.1190	42.30 ±0.419	40.47 ±0.198	38.41 ±0.196
F8	1:8	68.16 ±0.912	89.76 ±0.317	55.42 ±0.314	0.1001	40.59 ±0.265	40.11 ±0.066	45.37 ±0.186

D: P=Drug: Polymer ratio, (PY=Production yield, (%)EE=Encapsulation Efficiency MTDC=Mean Theoretical drug content (%), MADC=Mean Actual drug content (%), PS=Particle size (μm), F=Flux(mg/cm^2 h), %CDR) All values are in Mean ± S.D n=5

Table 5: Release kinetics data of microsponges formulation

Batch Code	Zero-order	First-order	Higuchi	Peppas	Korsmeyer Peppas parameters "n" (Diffusion exponent value)	Best fit model
F1	0.966	0.853	0.935	0.957	0.6217	Zero
F2	0.976	0.961	0.956	0.962	0.6309	Zero
F3	0.972	0.983	0.967	0.970	0.6168	First
F4	0.993	0.989	0.940	0.993	0.8100	Zero
F5	0.970	0.890	0.946	0.959	0.6110	Zero
F6	0.974	0.952	0.951	0.954	0.6241	Zero
F7	0.981	0.984	0.963	0.992	0.7103	Peppas
F8	0.995	0.989	0.932	0.992	0.8662	Zero

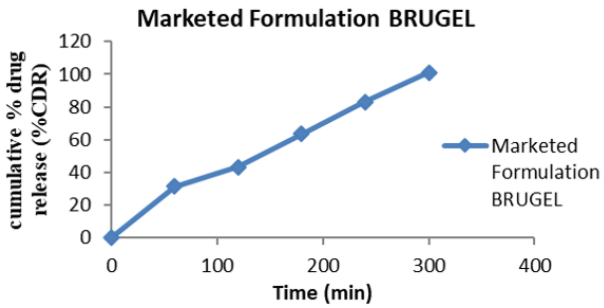

Figure 16: The in-vitro drug release profile of the marketed formulation

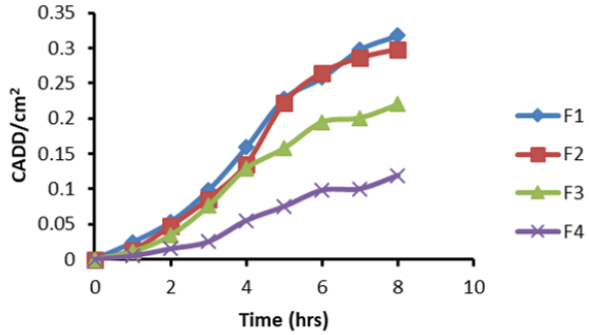

Figure 17: Comparative Ex vivo diffusion of F1-F4

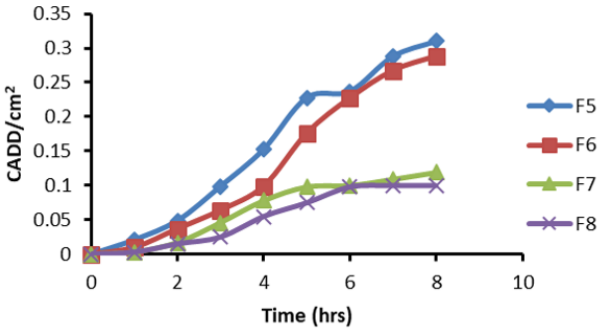

Figure 18: Comparative Ex vivo diffusion of F5-F8

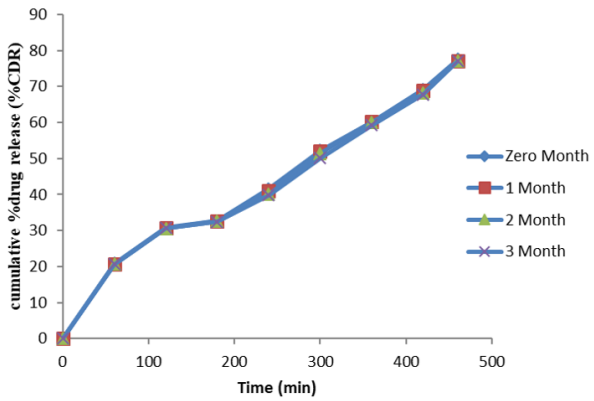

Figure 19: The in-vitro drug release profile of gel during stability study

that drug characteristic are not altered in the development of microsponges.

FTIR spectroscopic results showed desirable compatibility between drug and excipients used. The characteristics FBP at 2882.26 cm^{-1} (C-H aliphatic stretch), 2975.64 cm^{-1} (C-H aromatic stretch), 3365.76 cm^{-1} (O-H carboxylic acid stretch), 1361.07 cm^{-1} (C-F stretch), 1009.87 cm^{-1} (C-O stretch), 1725.27 cm^{-1} (C=O carboxylic acid stretch). As shown in Table 3. All characteristics peaks of FBP were obtained in microsponges formulation spectrum. Thus, IR spectroscopy reveals that FBP was highly compatible with excipients used in the preparation of microsponges.

Evaluation of FBP Microsponges

Physical appearance

The obtained microsponges are white particles with fluffy appearance compare to pure raw materials used in the preparation. The pure drug flow properties do not meet the standard and are considering as poor when compared to the obtained FBB microsponges.

Production Yield

The production yield of various batches of microsponges ranged from 44.90% to 68.42% in F1-F4 and 43.36% to 68.16% in F5-F8 (Table 4) the drug: polymer ratio was found to affect production yield considerably in both the batches for drug: polymer ratio 1:1 in F1 &F5 production yield remained very low, i.e. 44.90 % & 43.36 % for drug: polymer ratio for 1:8 (F4, F8) 68.42% & 68.16% and the concentration was kept constant for poly vinyl alcohol, which shows a clear effect of polymer in production yield. The solvent used in both the batches are different due to its solubility in the respective polymer (as given in Table 4).

Actual drug content and encapsulation efficiency

During the formulation Drug: polymer ratio in both the batches, theoretical drug content, Actual drug content and encapsulation efficiency was decreased due to the concentration of polymer increased, and the drug gets dissolved in the aqueous phase, during filtration some amount of drug is lost in the filtrate. The encapsulation efficiency in both batches were in the range of 98.30% to 86.31% & 98.58% to 89.76% (as given in Table 4).

Scanning electron microscopy

For surface morphology identification, prepared microsponges were analyzed for SEM analysis. The microsponge image is captured, as shown in Figure 6. The formed microsponges were porous in

nature, and that is induced by diffusion of solvents. Among all the batches of SEM analysis of F2 batch is selected as the optimized formulation due to its ideal spherical nature of porous microsphere.

Microsponges were also detected under the binocular microscope which discovered that particle appeared almost spherical and of single entity or groups of particles called as microsponges as shown in Figure 8 and Figure 9.

Particle size analysis

The ideal size range of microsponges is 5-300 μm. Visual inspection of various batches done using a binocular microscope, for particle size analysis in both batches, i.e. F1-F4 30.01 to 52.16 μm & F5-F8 30.09 to 45.37 μm. Due to the increase in polymer wall thickness, leads to the formulation of a larger size of microsponges. The optimized batch F2 and its corresponding particle size is 33.29 μm as shown inTable 4.

Further analysis was carried out for an optimized batch by using Zeta sizer (Malvern, Model: NanoZS90). The Z-Average size of microsponges in the diluted sample with water was 6429 (d) nm, the Poyldispersity Index (PDI) value was 0.737, which is suitable for particle size estimation (as shown in Figure 7).

X-ray diffraction study

X-ray studies are employed for determination of crystal pattern modification and polymorphism in drug crystal when diffraction pattern are alike for 2 forms of crystal, they found to have similar internal structure, and when peaks non-identical crystal have varied internal structure know as polymorphs. In this study, the finalized formation F2 peaks at a diffraction angle (2θ) 13 $^\circ$ is the same as that of a pure drug (Flurbiprofen) but with lower intensity, specifying its crystalline nature. The relative degree of crystalline (RDC)value was found to be 1.24. (as showed in Figures 10 and 11). So XPRD analysis revealed that there is no presence of polymorphs of flurbiprofen in these samples and more over complete loss of crystalline nature was not done during the formulation approach and remained to be stable.

Evaluation of FBP microsponges gel

Visual inspection

The formulated flurbiprofen microsponges gel were inspected for their colour and appearance. All the batches were appearing transparent white with uniformly distributed microsponges, with no lumps and air bubbles in the gel, former air bubbles are removed by keeping the gel undisturbed for overnight and sonication.

pH measurement

The pH of all formulated gels was measured using a pH meter. All the batches were found to be safe and non-irritating since their pH was within the normal skin pH. During the storage of gel, there was no large difference in their pH. (as shown in Figure 12).

Spreadability studies

The formulated gel get spreads easily on applying of a little amount of shear, spreadability studies of optimized formulation was found to be 2.80 g cm/s better when compared to the marketed formulation (BRUGEL) 1.89 g cm/s.

Extrudability study

The formulated microsponge gelsextrudability was found to be 98.06% as compared with the marketed formulation.

Viscosity

The viscosity of formulated Flurbiprofen microsponge gel was found to be 2200 cPs, at 5 rpm with spindle number SS63. The optimized batch showed the pseudoplastic property as evident by shear thinning, indicating the formulation was viscous in nature and found to be a desire on polymer concentration, started with increases in stress leads to decrease in viscosity, (as shown in Figure 13).

In vitro drug release

The cumulative percentage of drug release was found to decrease 87.43%-55.19% with an increase in drug: polymer ratio in F1-F4 and 87.43%-55.42% in F5-F8. The reason behind is as polymer concentration increases the thickness of the polymer wall also increased. Thus, the drug takes a longer duration to diffusion from the wall of a polymer. The highest drug release for ethyl cellulose and Eudragit RS-100 polymer was found to be merely same . F2 formulation is considered as optimized formulation due to its sustained release manner with improved morphological characters as compared with other formulated batches. Graphical representation for comparative drug release of all batches from F1-F4 and F5-F8 is shown in Figure 14 andFigure 15.

The release profile of the marketed formulation

The *In vitro* drug release of the marketed formulation was carried out to compare with microsponge formulated batches, and it was found to be a complete release of drug from marketed formulation was attained at 300 minutes (as shown in Figure 16). In contrast, formulated gel showed sustained drug delivery up to 480 minutes. So formulation F2 with carbopol concentration showed best and more

efficient to give sustained action among the all (as shown in Table 2).

Flubriprofen gel is available in the market under the brand name of BRUGEL 5%w/w.

Drug release kinetics

The above-obtained data, i.e., the cumulative percentage of drug release was fitted into various kinetic models; namely, zero-order, Higuchi, Peppas, and Korsmeyer-Peppas, n value from the above models best-fit model was determined by highest R^2(0.995) value for formulation F8. Zero-order was found to be the best model of the formulations, on the source of maximum regression value given in Table 5.

By applying a cumulative percentage of drug release data in Korsmeyer equation drug release mechanism for all formulation was inspected. For batches F1-F8, n values were found in range 0.6110-0.8662. The*n* values for Korsmeyer-Peppas model was seen to be in the range of 0.5-1, which is investigative of non-Fickian diffusion for finalised formulation F2.

Ex vivo diffusion study

The *Ex vivo* diffusion studies were done for every formulation by using rat skin, which is initially removed fat substance under the skin and several times washed with PBS (pH 7.4). From the results, it has been found that the formulation F1-F4 and F5-F8 exhibited lower drug diffusion as polymer concentration increases. The cumulative amount of drug crosses the biological membrane per unit surface of the skin from microsponges gel was plotted against time in hours, as shown in Figure 17. The sum of the drug passed through the unit area for hours is termed as flux (*J*)

The drug diffusion from biological membrane for the first hour was found to be more compared to eight hours in all the formulation; this is because of free drug is release initially followed by the trapped drug**.** Thus, the drug release was retarded from microsponges. As shown in Table 4, Figure 18.

Stability studies

During stability studies of formulation, F2 was found no change in exterior, and no significant deviation in pH,% of drug content and percentage of drug release were seen. The comparative study of drug release profile of zero month and after 3 months of stability studies are carried out and found that there is no much significant difference was observed, similarity factor (f_2) was found to be f_2= 90.96891, and Difference factor (f_1) was found to be f_1 = 1.853151. As f_2 is greater than 50 specifies good stability of the product, finally it was found that the prepared microsponges gel was stability for the period of 3 months as showed in Figure 19.

CONCLUSION

In this study, ultimately we found that the microsponges delivery of Flubriprofen are well suitable for sustained action of a drug, which is actually required for NASIDs.

The main aim behind developing Flubriprofen microsponges delivery system was to deliver an Active Pharmaceutical Ingredient (API) in a sustained manner for an extensive time period without high fluctuation in the plasma, reduced applications or intake, allergic reaction, which can be overcome by above formulations. Thus, gel bearing microsponges were designed in this approach was found to be challenging as a novel delivery system, offering in treating rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Thus formulation showed better retention of the drug (Flurbiprofen) in the skin, signifying well-improved delivery system as compared with marketed flurbiprofen gel (BRUGEL).

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