Development and optimization of flurbiprofen loaded microsponges: An *in vitro* evaluation

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Abstract: Current study was designed with the aim to employ quasi emulsification, and double emulsification techniques for the development of Flurbiprofen (FLB) loaded micro sponges, followed by their physicochemical evaluation. FTIR interpretations exhibited compatibility of ingredients, while crystallographic analysis revealed crystalline nature of pure drug, which was masked upon incorporation into microsponges. Optical microscope and SEM have exposed spherical and spongy surfaces of prepared micro sponges. Micromeritics suggested that the flow properties are excellent and microsponges have remarkable drug entrapment efficiency (98.55±0.08%). *In-vitro* dissolution studies demonstrated good control over release of FLB until 8th h from the prepared microsponges. However, a difference in cumulated amount of released drug was noticed i.e. EC based formulation has released about 99.3±0.10%, while XG facilitated EC based formulations offered 92.7±2.1% release of the drug. Zeta potential indicated access of negative charge while zeta sizer has described the range of the particle size between 2.6 to 3.5µm. Conclusively the results have advocated the suitability of selected ingredients for incorporation of FLB into microsponges for its sustained delivery.

Keywords: Drug delivery**,** sustainable materials, scanning electron microscopy, micro sponges, double emulsification technique.

INTRODUCTION

To cure different pathologies, new and new approaches are being adapted and development of novel drug delivery systems having site specific, stimuli responsive and controlled release rate characteristics are in progress. FLB, a potent NSAID (non-steroidal anti-inflammatory agent), is an arylopropionic agent considered to be an effective anti-pyretic, analgesic and anti-inflammatory agent that is very much effective in rheumatoid arthritis, gout and osteoarthritis. It inhibits prostaglandin synthesis due to inactivation of cycloxygenase enzyme. However, because of its poor water solubility, its half-life decreased to 2 to 4 h, that demands its frequent administration i.e. 3 – 4 times a day to achieve therapeutic response. FLB also produce gastrointestinal associated adverse effects like peptic ulcer, dyspepsia, cramps and gastric bleeding etc. resulting in treatment failure and patient non-compliance towards therapy (Malipeddi *et al*., 2016). Microsponges are, thus, porous, micro-spherical, and highly cross-linked polymeric matrices having interconnected voids in their morphology (Chadawar and Shaji, 2007). Being larger in size i.e. 5 – 300 µm these cannot be absorbed through mucous membrane and remain safer. Presence of pores provides space for entrapment and release of active moieties. These have gained importance due to their non-collapsible, non-irritant, non-toxic, biocompatible, controlled release, self-sterilizing, stable and excellent drug entrapment properties

A number of hydrophilic and hydrophobic polymers from natural and synthetic source have been quoted in literature to be employed for controlled drug delivery. Cellulose derivatives are widely attractive for controlled release carrier systems as they are non-toxic, non-irritant, biocompatible, biodegradable, easily available as well as economical. Ethyl cellulose is a lipophilic polymer that has extensively been employed for lipophilic and hydrophilic drugs in different carrier systems(Kazlauske *et al*., 2017).

Development of FLB microsponges was aimed to achieve the stabilized drug delivery system with prolonged release and reduced side effects (Jain and Singh, 2010b, Jain and Singh, 2010a). The method selected for the preparation of microsponges was quasi- solvent emulsification technique depending upon the properties of drug and polymer. The selected method gave higher yield and pronounced drug release profile of the drug (Jelvehgari *et al*., 2006).

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MATERIALS AND METHODS

Materials

FLB was obtained as generous gift from Arson Pharmaceuticals, Lahore, Punjab, Pakistan. Ethyl cellulose (EC), Poly vinyl alcohol (PVA) and Xanthan gum (XG) were purchased from Sigma Aldrich, Germany. Double distilled water was freshly prepared in research lab of Faculty of Pharmacy, University of Lahore. All the solvents used were of analytical grade.

Method

Preparation of EC based FLB microsponges

Quasi-emulsification technique was adopted for the preparation of EC based FLB microsponges. Varying ratios i.e. drug to polymer as presented in table 1 were used to evaluate the impact of EC on various characteristics of prepared microsponges i.e. drug release, drug content and entrapment etc. Internal phase was consisted of 8ml of DCM containing weighed amount of EC. FLB was added drop-wise into the continuous phase, composed of PVA solution (1% w/v). The mixture was subjected to continuous stirring at1500 rpm speed by using overhead stirrer (GUO-HUA multi-functional) for 1 hr. afterword the mixture was pass through sartorius filter paper of 0.45µm. Obtained residual material was dried, weighed and stored for further analysis.

Xanthan gum facilitated EC based FLB micro sponges

XG facilitated EC-FLB micro sponges were developed by double emulsification technique. In this technique, 10 ml solution of 0.2% w/v XG was prepared in the mixture of acetone and water (2:8). This solution was added in the solution of FLB and EC, which was prepared using DCM as solvent. This mixture was stirred for half an hour to achieve uniform mixing; later on, this was poured into the 1% PVA solution under continuous stirring for 60 min. After that, the mixture was subjected to filtration and stored after drying for further analysis.

Chemical compatibility studies of the ingredients

FTIR studies for FLB, polymer, physical mixture and prepared microsponges were executed to observe any modification in structure and incompatibilities among ingredients on Agilent Carry 360 FTIR (United States). All the samples were precisely crushed/milled and randomly scanned at range of 4000–400 cm^{-1} and IR spectra were digitally captured (Sohail *et al*., 2014).

X-ray diffraction (XRD)

The crystalline or amorphous nature of the ingredients and fabricated micro sponges, as well as the effects of polymer on the crystallinity of the FLB was confirmed through X-ray diffractometer (Shimadzu-6000, Japan). Scanning range was kept from 5° to 35° (2θ), voltage was 40 kV and the current was 30 mA (Sohail *et al*., 2014).

Surface morphology studies

Microsponge's texture was studied using optical microscopy and scanning electron microscopy (SEM) (Hitachi, TM 3000, Japan) operated at 05 kV. All the samples were prepared after crushing and mounting the particles on aluminum stub with the help of double adhesive tape. Gold coating was performed using gold sputter coater under argon vicinity. Photomicrographs were recorded at different magnifications under scanning electron microscope (Jelvehgari *et al*., 2006).

Production yield

It is the total mass of microsponges achieved as a result of adopted process divided by the total amount of the reactants consumed. Mathematically, it was calculated by using following formula (Zaman *et al*., 2018):

$$\text{Production yield} = \frac{\text{Actual mass of microsponges}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

Encapsulation efficiency

It is estimated by taking weighed amount of microsponges and preparing their solution in their relevant buffers followed by their sonication for 4 hours at 30°C to assure complete dissolution. Sample of the solution was taken, filtered and subjected to analysis by using spectrophotometric method at 247nm for to determine the loaded contents of the drug by using following equation (Orlu *et al*., 2006).

$$\text{Entrapement efficiency yield} = \frac{\text{Actual FLB amount}}{\text{Initial FLB amount added in formulations}} \times 100$$

In vitro release studies

Dissolution properties were estimated by subjecting all prepared formulations for expected drug release pattern. FLB microsponges were treated with phosphate buffer i.e. pH 7.4 for 8 h using USP type II dissolution apparatus (Pharma Test Germany) at 37±0.5°C. 900ml buffer solution was ensured in each vessel and instrument was operated at 50rpm. Sink conditions were carefully maintained by adding 5ml fresh buffer solution on each 5ml sample withdrawal. Samples were analyzed at 247 nm using UV-VIS spectrophotometer for estimating percentage of drug release at specific time interval (Trivedi *et al*., 2014).

Zeta potential measurements

Zeta potential determination was done to determine product surface charge, which owes its stability. Particles having zeta potential value approaching – 40mV don't adhere and tend to repel each other thus ensuring stability of developed product.

RESULTS

Chemical compatibility studies of the ingredients

Results were the evident of physicochemical compatibilities of the used ingredients in the formulation of microsponges. The IR chart showed the absorption for

Table 1: Composition Table of different microsponge formulations

Ingredients	ECF1	ECF2	ECF3	ECF4	XECF1	XECF2	XECF3	XECF4
EC (mg)	1200	2400	3600	4800	1200	2400	3600	4800
XG(mg)	-	-	-	-	200	200	200	200
Acetone: water (ml)	-	-	-	-	10	10	10	10

*Constant in formulation: *FLB 1.2g, Dichloromethane (DCM) 8ml, 1% PVA 100ml*

Table 2: Results of bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)	Angle of repose (θ)
ECF1	0.2	0.24	1.2	18.1	21.8
ECF2	0.225	0.25	1.1	10	12.4
ECF3	0.32	0.34	1.06	5.5	5.7
ECF4	0.45	0.48	1.06	4.5	11.86
XECF1	0.14	0.17	1.2	17.6	7.68
XECF2	0.325	0.379	1.16	14.28	7.4
XECF3	0.31	0.33	1.06	6.5	10.98
XECF4	0.31	0.36	1.16	14.3	8.92

Table 3: Results of Kinetic models on release data

Kinetic Models		ECF1	ECF2	ECF3	ECF4	XECF1	XECF2	XECF3	XECF4
Zero order	R^2	0.960	0.936	0.921	0.877	0.984	0.985	0.891	0.854
	k_0	6.368	5.273	2.012	1.289	1.167	10.18	1.357	1.545
1st order	R^2	0.818	0.929	0.915	0.865	0.964	0.910	0.882	0.844
	k_1	4.937	5.152	4.638	4.629	4.733	5.027	4.634	4.632
Hixson-crowell	R^2	0.920	0.858	0.864	0.819	0.921	0.962	0.833	0.8003
	k_{HC}	3.629	3.126	3.56	3.513	2.897	3.300	3.434	3.602
Higuchi	R^2	0.942	0.934	0.921	0.893	0.964	0.936	0.903	0.878
	k_H	37.88	46.27	15.62	15.41	26.911	43.66	16.86	16.80
Korsmeyer-peppas	R^2	0.967	0.924	0.940	0.887	0.989	0.977	0.887	0.848
	k_{KP}	9.572	16.82	4.181	6.176	10.04	8.76	6.985	6.910
	N	1.118	0.925	1.136	0.894	1.026	1.183	0.875	0.852

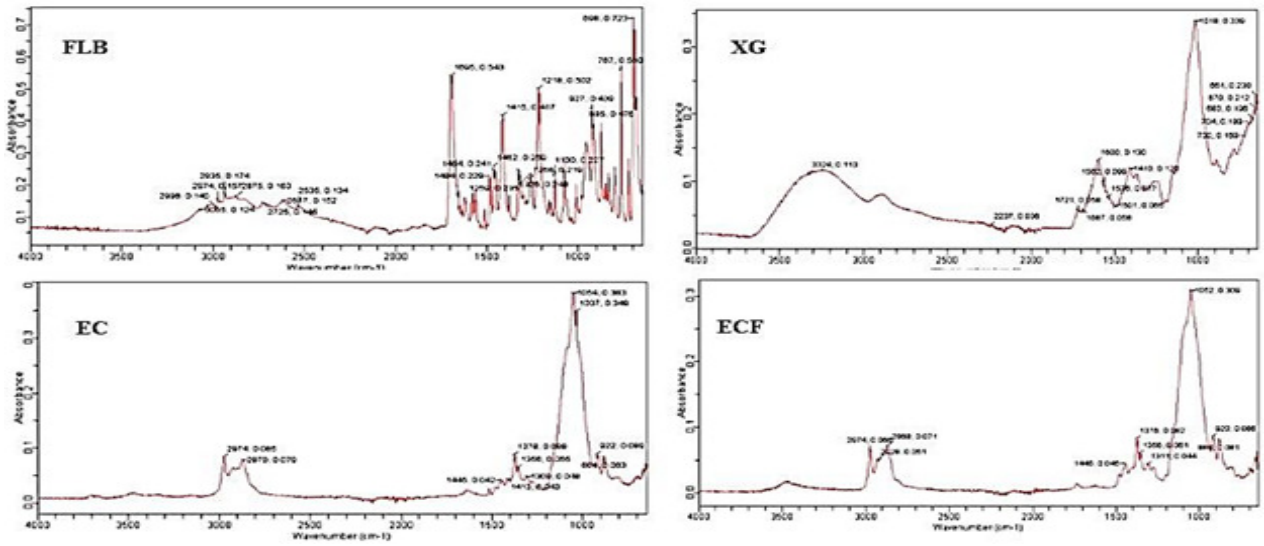

Fig. 1: FTIR spectra of FLB, XG, EC and formulation (ECF)

C=O bond at 1760-1690cm^{-1} and strong stretching occurred at this point, while the stretches shown at 3300-2500cm^{-1} indicated the mediocre bending in the –OH bond of the carboxylic group as shown in fig. 1.

Presence of two aromatic rings is also indicated from the absorption spectra. FTIR spectra of the formulation ECF showed the presence of different groups relative to the peaks were observed in individual ingredients.

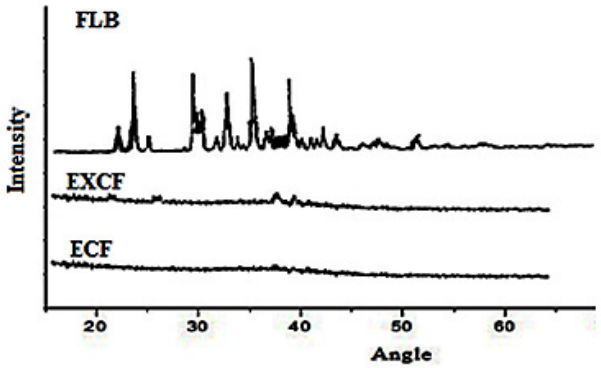

Fig. 2: XRD studies of pure FLB, formulation EXCF and ECF

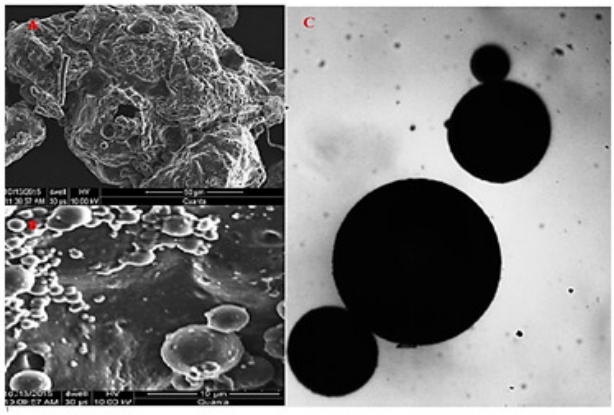

Fig. 3: SEM micrographs of A) unloaded B) loaded microsponges C) Optical microscopic image of prepared microsponge

X-ray diffraction (XRD)

XRD of the pure FLB was done to culmintae the nature of the materials. The study was conducted at room temperature and the degrees of x-ray radiations diffracted at different intensities were recorded (Varma and Pandi, 2005).

In XRD diffractogram (fig. 2), first sharp peak emerged at an angle near 23° seeking the intensity to the value of 900cps at angle of about 37°. Peaks, obtained in the resulted pattren have provided the probability that FLB is of crystalline nature (Cirri *et al*., 2005).

Optical microscopy

The microsponges were wetted with a drop of castor oil and mounted on the stage over glass slide. Outcomes have exhibited the spherical form of the prepared microparticles confirming successful attempt of FLB containing microsponges (fig. 3C) (Patel *et al*., 2010).

Scanning electron microscopy (SEM)

SEM micrographs of loaded as well as unloaded microsponges were recoreded to observe surface morphology of prepared microspnges. The results were evident of that particles have porous surfaces and spherical geomtery

Micromeritics properties

Different parameters of micromeritics studies were performed to observe the flow properties of the prepared micro sponges. The results were advocating the free flowing abilities of the particles (table 2). Prepared formulations, composed of varying concentrations of the polymer have been subjected to comparative analysis (Trivedi *et al*., 2014) (table 2).

Production yield

Results of production yield were obtained for all the formulations of FLB-containing microsponges were tabulated in table 3.

%Drug content and encapsulation efficiency

Amount of drug captured by the microsponges was less as compared to then the theoretical values in case of each formulation. Encapsulation efficiency (%) was ranged from 92.32% to 98.55%. In case of ethyl cellulose based microsponges optimum encapsulation results were observed in formulation ECF1 (97.34±0.03) while in case of xanthan gum assisted ethyl cellulose formulation XECF2 has shown promising encapsulation efficiency (%) results i.e. 98.55%.

In vitro dissolution studies

Prepared microsponges of the FLB (BCS Class II drug) were undergone through *in vitro* dissolution studies using type II dissolution apparatus(Perioli *et al*., 2011). Figure 5 showed the release profile of the EC based FLB microsponges done at pH 7.2 phosphate buffer. Trends in the graph show that ECF2 has maximum release of drug at the 8th hour while ECF3 followed by ECF4 has shown to have least release.ECF1 has comparatively less release as compared to ECF2, although having double the amount of polymer. XG facilitated EC microsponges of FLB release data shown in fig. 4B explained the trend of drug release of FLB from the polymeric carriers. It also showed XECF2 to have maximum release at the 8th h, whereas XECF1 have shown less release in comparison. XECF3 and XECF4 had shown to have approximately similar amount of drug release.

Kinetic model application on FLB microsponges

The dissolution data obtained from the in vitro dissolution studies to study the release kinetics of the different formulations prepared using different ratios of polymer to drug. Different models like zero order, first order, Hixson

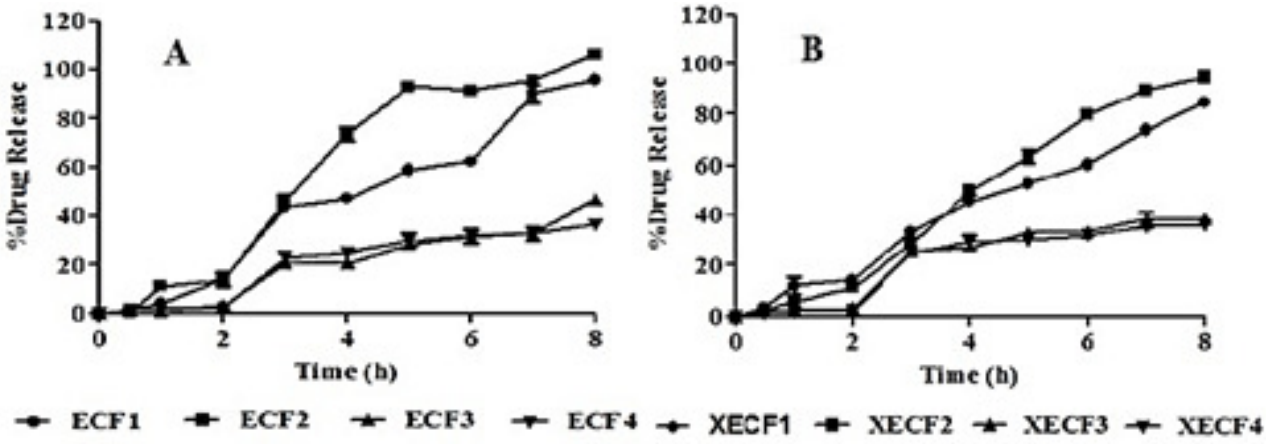

Fig. 4: Drug release profile of A) Ethyl cellulose and B) Xanthan gum facilitated Ethyl Cellulose based microsponges

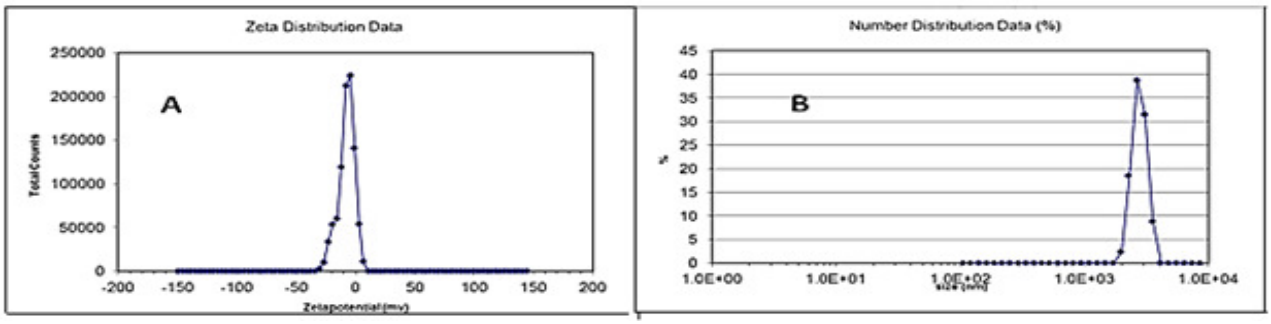

Fig. 5: Zeta potential and Zeta size results of developed formulations

Crowell, Higuchi and Korsmeyer's Peppas are applied to obtain correlation and the release constant values to estimate the best fit model for the formulation. The formulations following zero order and Hixson-Crowell model show the constant release over the time while the first order and Higuchi model show that the release of drug slows down over the time. The values obtained for each formulation applying different models are given in table 3 (Dash *et al*., 2010).

Zeta potential

It is the extent of stability of the system owing to the charge carried by the microsponges and their propensity to form aggregates. The zeta potential up to +30 or greater is the indication of that particles would be of repulsive nature, repelling each other to remain separate and -30 or below for not to flocculate and remain dispersed. Values lying between means, the flocculation will occur. fig. 5 showing the zeta distribution data for the XECF1 was evaluated using Malvern UK Nano ZS. Because of the smaller particle size of the formulation obtained due the xanthan gum incorporation and biphasic nature of the formulation process involved this formulation was evaluated through zeta potential measurements. The result showed the zeta potential to be -4.38 for the distribution of most of the particle where the range for all the particles in the formulation was from -30.45 to 6.79.

Zeta size analysis

Zeta size analysis of the formulations was done which showed the finest appearance among all fabricated ones using ethyl cellulose and xanthan gum facilitated ethyl cellulose based approaches, to estimate the size range of the particles in the formulation. This analysis was done using the Malvern instrument and size distribution data was obtained through the software in the system giving the plot of data as given in figure for XECF1. The figure 5A showed the distribution of particles for different sizes in the formulation XECF1. This analysis was done by using Malvern UK Nano ZS. The plot of data showed the 38.77 % particles of size 2.66µm (2669.04 nm) where the distribution of the data is between 1.99µm (1990.11 nm) and 3.57µm (3579.58 nm)(Tiwari *et al*., 2014).

DISCUSSIONS

Peak obtained at 1052 cm^{-1} showed the presence of alcohols, carboxylic acid, ester or ethers for the vibrations obtained in the C-O stretching. This bond was integral of FLB so the formulation showed excellent compatibility and entrapment of the FLB within the microsponges (Shah *et al*., 2009). Ahmad *et al*., 2018 developed controlled release novel microsponges of Albendazole using Eudragit RS 100. They have performed compatibility studies for polymer and the drug. FTIR

spectra confirmed no chemical interaction among ingredients during microsponge preparation of microsponges. Characteristic drug peaks were also present in the microsponge's spectra as seen in our findings (Abdellatif *et al*., 2018).

XRD results of the formulation XECF3 showed that peak intensity and sharpness was markedly reduced and numerous fused peaks were obtained, thereby confirming amorphous nature of the FLB. However, ECF diffractogram, there was complete reduction of the peaks thus confirming complete amorphous state of FLB within the microsponges. This was the reason that ECF based microsponges showed better release because maximum amount of drug was in solubilized form as compared to XECF3. It was the indication of, that drug might be existed in the form of solid solution with other excipients.

SEM studies have explored the porous surface of the particles. Pores were appeared due to removal of solvent contents. Moreover, interconnected internal cavities were observed having spherical shapes. Results are summarized in fig. 4 (Patel *et al*., 2010). Osmani *et al*., 2015 prepared diclofenac diethylamine loaded microsponges using Edragit RS 100 through Qausi emulsion diffusion technique. Present findings of topography were in good agreement with their results in terms of surface morphology and geometery of the microspnges (Osmani *et al*., 2015). The findings of flow properties have demonstrated that increased in polymeric contents may cause decrease in the flow properties of these formulations. The carr's index showed that ECF3, ECF4 and XECF3 had free flowing properties which, were further varified by results of angle of repose. The trend in the results of production yield had shown that production yield was greatly associated with polymeric contents, as increase in the polymeric contents could be the cause in increased the production yield of the microsponges (Khan *et al*., 1994). It can be seen from results that as the concentration of polymer was increased the FLB contents within the developed matrices was decreased as in ECF2 (93.12±0.01), ECF3 (94.68±0.02), ECF4 (93.3±0.02), while in XECF1, XECF3 and XECF4 encapsulation efficiency is found to be (98.19±0.03), (92.32±0.01), (94.63±0.01). Higher polymer load results in slight increase of thickness of the dispersed phase. Major or maximum part of dispersed phase was converted into the microsponges due to the evaporation of solvents. Rizkalla *et al*., 2013 prepared hydroxyzine HCl loaded ethyl cellulose based microcapsules. Their results of percent entrapment efficiency were comparable with our results(Zaki Rizkalla *et al*., 2013).

Comparing the trends in figs. 4A and 4B for both types of formulations, it was observed that XG facilitated formulations have better drug retarding ability(Orlu *et al*., 2006).

Results of zeta potential have shown that the particles have affinity for each other and they are most distributed towards negative. The negative charge on the surface indicated the dissociation of acidic groups on the surface of the microsponges' particles of the FLB. Thus the system can be stabilized by decreasing the pH(Vijay *et al*., 2010).

CONCLUSION

EC based and XG-facilitated ethyl cellulose based FLB microsponges were prepared and subsequently evaluated showing the excellent flow properties with the particle size range below 5µm and reasonable release of drug from the prepared microsponges. The results for prepared FLB microsponges showed the more fine particles of XG gum facilitated EC-FLB microsponges as compared to simple EC based FLB microsponges with more retarded and prolonged release of drug.

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