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DESIGN AND EVALUATION OF CONTROLLED RELEASE CHITOSAN MICROSPHERES OF FLURBIPROFEN

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ABSTRACT

In the present investigation we developed novel controlled drug delivery of flurbiprofen using chitosan microspheres by simple emulsion and cross-linking technique by glutaraldehyde. Prepared microspheres were subjected to FT-IR, SEM studies. In the FT-IR spectrum of flurbiprofen (FBP) loaded chitosan microspheres does not shown any interaction between polymer and FBP. The size of microspheres of batch F6 was positively influenced by the proportion of polymer and was found to be spherical with occasional blisters on the surface as shown by SEM studies. In-vitro drug release studies were carried out by using pH 7.4 phosphate saline buffer solution (PBS) 12hrs at 37±0.5°C. The drug release data clearly indicate that the FBP release can be effectively controlled by varying the drug polymer ratio. Among, all batch F6 showed remarkable controlled release. Drug stability study of optimized formulation F6 was carried out at accelerated condition for two months and the dissolution profiles were not statistically different after 1 and 2 months, when compared to control (Initial month).

Keywords: chitosan, NSAID, Microspheres

INTRODUCTION:

Controlled release systems have been developed against the problems commonly associated with conventional dosage forms (dosage frequency, side effects etc.) [1, 2]. One of these systems, implant systems, enables targeting in local applications, as well as improving the treatment effectiveness [3]. Implantable controlled release systems are basically polymeric implants wherein active substance release is controlled by various polymers or polymeric membranes. Giving the active substance within a polymeric system to ensure controlled release or targeting has now been quite widespread [4-8]. Polymers used in implant systems, which are capable of controlled release, are categorized into two: synthetic and natural [9-13]. An attractive feature of polymers used in the preparation of implantable dosage forms is their being biocompatible and biodegradable [14, 15]. Although biodegradable synthetic polymers have been developed, natural polymers are widely used due to their many advantages [16]. For example, they are not antigenic, can be metabolized, have high stability and allow for high loading for water soluble active substances. Chitosan, a natural biodegradable polymer, is often used in the preparation of particular dosage forms. A cationic linear bio amino polysaccharide, chitosan, is obtained by means of alkali distillation of chitin [16-21]. Chitosan, composed of glucosamine and N-acetyl glucosamine units, is a weak base. Though it is not dissolved in organic solvents, neutral and alkali pH's, it can be dissolved in diluted acids [22]. Chitosan becomes positively charged when the free amino groups, which it naturally possesses, turn into a soluble state because of their protonation in acidic conditions, as a result of which it may react with negatively charged polymers or negatively charged surfaces such as mucosa and substrates such as fats and lipids in gastrointestinal tract that may affect lipid concentration [23-25]. Chitosan is

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an anti-allergenic polymer which is biologically compatible with living tissues and biodegradable. Its biodegradation products are harmless amino sugars that can be absorbed by the body. Chitosan is widely used to prepare particular drug delivery systems such as micro particles [27].

MATERIALS AND METHODS

A gift sample of flurbiprofen received from Natco Pharma Ltd., Hyderabad. Chitosan, heavy & light liquid paraffin, glutaraldehyde, toluene, hexane and dioctyl sodium sulphosuccinate were purchased from SD Fine chemicals, Mumbai.

Preparation of Microsphere

Microspheres were prepared by simple emulsion cross linking techniques [28-29], dispersed phase was prepared by chitosan (2% w/v) in aqueous acetic acid (5% v/v) and FBP (100 mg) in different ratios as shown in the table no. 1 was dissolved into dispersed phase. The polymer–solvent–drug solution in different ratios was added to continuous phase consisting of light & heavy liquid paraffin (each 75 ml) containing Dioctyl sodium sulphosuccinate (DOSS; 0.5% w/v) to form a water in oil (W/O) emulsion. Stirring was continued between 1000 and 1200 rpm using a 3-blade propeller stirrer. A drop-by-drop solution of aqueous glutaraldehyde (25% v/v) saturated with toluene solution was added at 15, 30, 45 and 60 minutes. Stirring was continued for 2.5 hrs to obtain microspheres, which were separated by filtration under vacuum and washed with petroleum ether followed by double distilled water. Then microspheres were dried in vacuum desiccators.

Table No. 1: Formulation Design for the preparation of flurbiprofen loaded chitosan microspheres

S. No.	Formulation code	Drug: Chitosan
1	F1	1:0.33
2	F2	1:0.5
3	F3	1:0.67
4	F4	1:1
5	F5	1:1.5
6	F6	1:2
7	F7	1:3

EVALUATION OF MICROSPHERES

Drug Content

Sample of microspheres (20 mg) were kept overnight in 40 ml of ethanol then after, the mixture was stirred for 15 minutes which is subjected to proper dilution. FBP content in the ethanol was analyzed by UV-spectrophotometer at 247 nm [30-33].

Dissolution Studies

For the in vitro release studies, the solubility of FLB was determined in pH 7.4 phosphate saline buffer solution (PBS), which is used as the dissolution environment to satisfy the sink condition [34].

Stability Studies of Microspheres

The stability study of optimized formulation F6 was carried out at accelerated condition of 40±2ºC and 75±5% R.H. for a period of two months. The microspheres were individually wrapped using aluminum foil and packed in amber colored screw capped bottle and kept at above specified condition in incubator for a period of two months. After each month microspheres sample was analyzed for the In-vitro drug release. The dissolution data was analyzed statistically.

RESULTS AND DISCUSSIONS

Controlled release microspheres of FBP were prepared by the simple emulsion method using glutaraldehyde gradually increases in polymer concentration which influence in % drug content as shown in Table no. 2. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension with diminished shearing efficiency and increased particle size. Stirring rate was kept constant in order to have uniform particle size and entrapment efficiency, particle size should not influence the rate of stirring. When increased the polymer concentration the entrapment efficiency was increased with FBP due to its poor solubility in liquid paraffin. Drug entrapment efficiency was varied in the range of 25-89%, which is observed in difference formulation as shown in Table no. 2. In-vitro drug release studies of FBP microspheres were performed for 12 hrs in phosphate buffer (pH7.4) at 37±0.5°C. The cumulative release of FBP significantly decreases with increasing the chitosan concentration as shown in Table no. 3 & Fig. 2-8. Morphology of microspheres was examined by using scanning electron microscopy. The Fig.1 shows the top view of chitosan microspheres. The top view of the microspheres showed a spherical structure. The results of stability studies after each month are as shown in table no. and fig. 9. The stability studies showed statistically significant differences in cumulative % drug release after 1 and 2 months when compared to control (Initial month) [35].

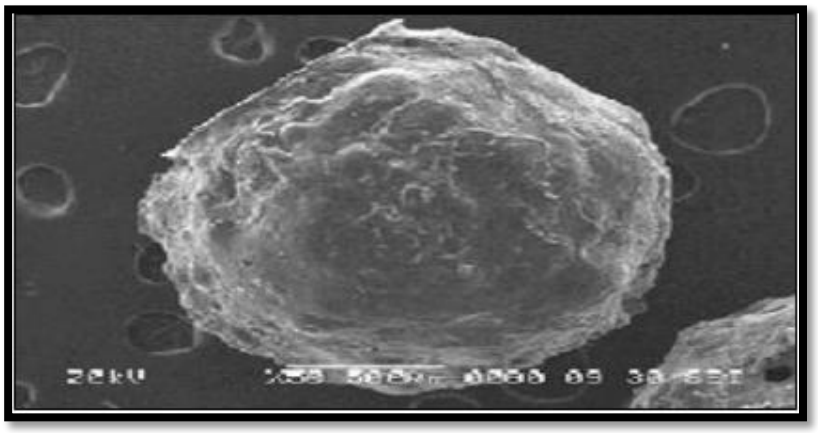

Fig. 1: Morphology of microspheres by scanning electron microscopy

Table No. 2: Percent drug content of different formulations

S. No.	Formulation	% of Drug Content
1	F1	25
2	F2	41
3	F3	56
4	F4	64
5	F5	70
6	F6	89
7	F7	38

Table No. 3: Cumulative percent of drug release of formulations F1 to F7

S. No.	Time	F1	F2	F3	F4	F5	F6	F7
1	00	0	0	0	0	0	0	0
2	1	17.32	15.5	13.46	24.12	14.14	14.14	4.01
3	2	30.29	30.2	22.26	26.6	33.2	16.12	8.12
4	3	45.3	38.92	36.37	27.7	48.14	31.61	9.01
5	4	78.9	58.58	42.12	30.01	63.23	47.04	12.01
6	5	98.55	75.09	59.23	31.12	68.32	64.04	13.22
7	6	0	97.94	75.42	35.55	74.4	68.01	18.12
8	7	0	0	82.09	57.12	76.62	74.04	23.14
9	8	0	0	97.72	68.32	79.12	75.14	28.01
10	9	0	0	0	78.01	83.02	78.14	28.12
11	10	0	0	0	92.11	82.12	79.31	29.12
12	11	0	0	0	0	86.12	83.12	35.11
13	12	0	0	0	0	94.59	94.32	42.11

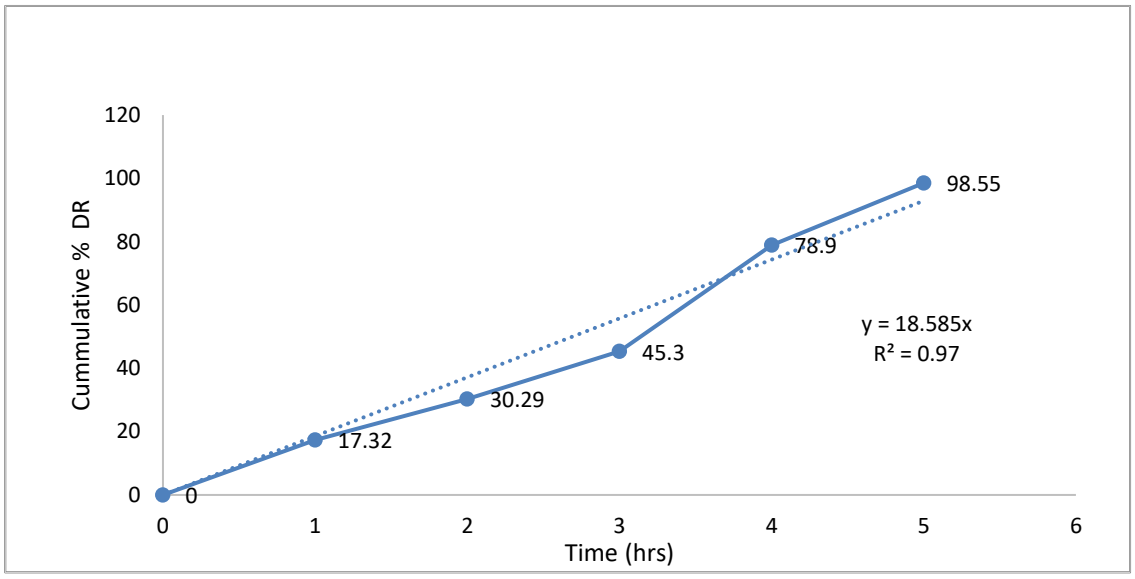

Fig. 2: Invitro drug release profile of formulation F1

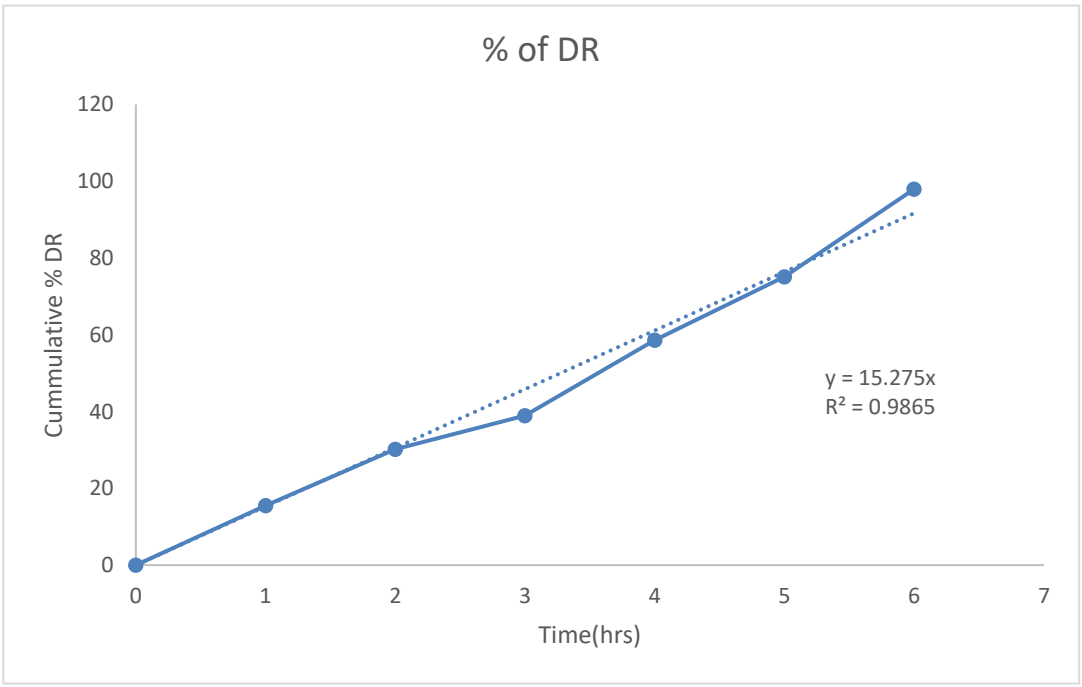

Fig. 3: Invitro drug release profile of formulation F2

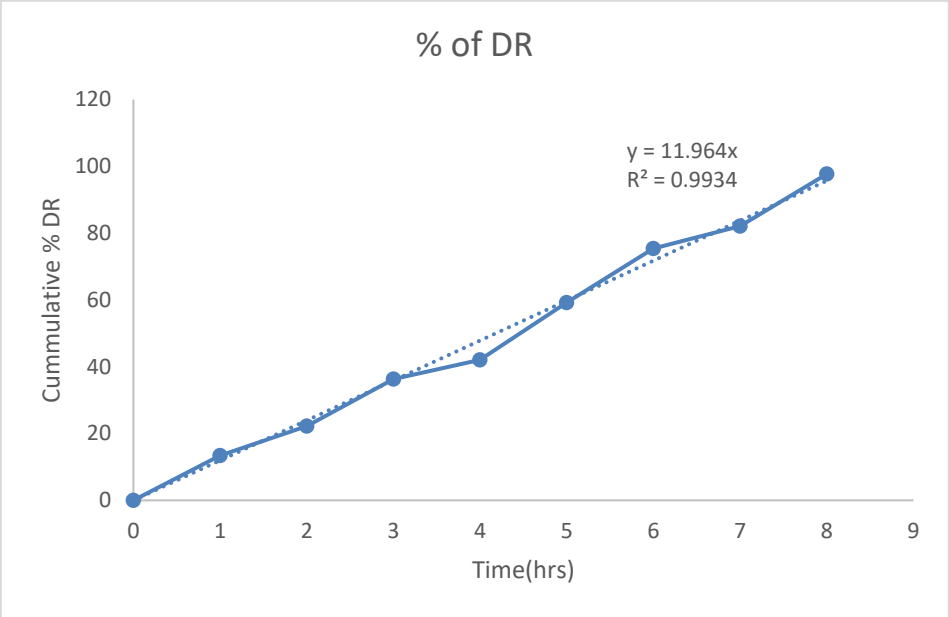

Fig. 4: Invitro drug release profile of formulation F3

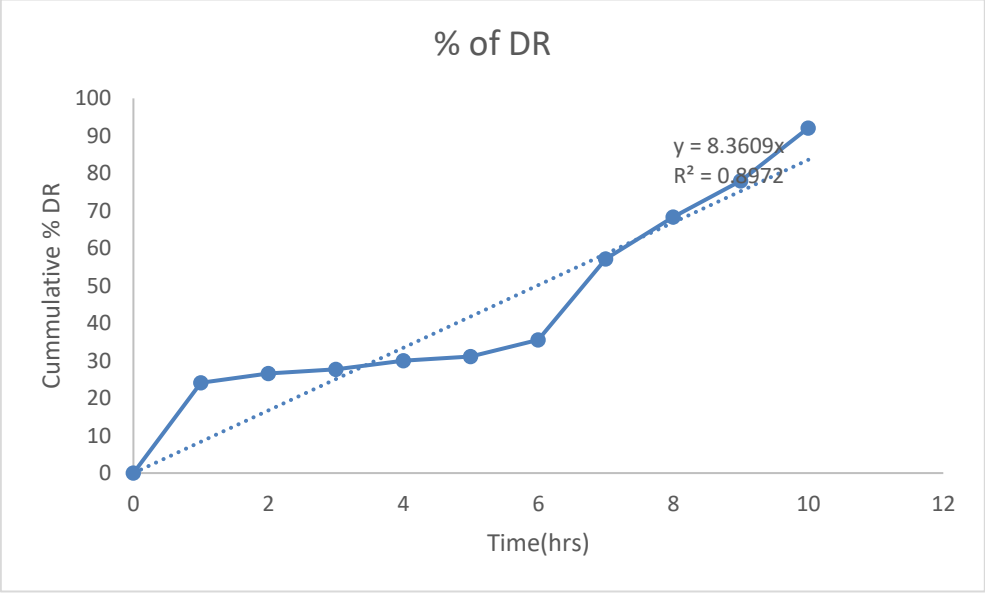

Fig. 5: Invitro drug release profile of formulation F4

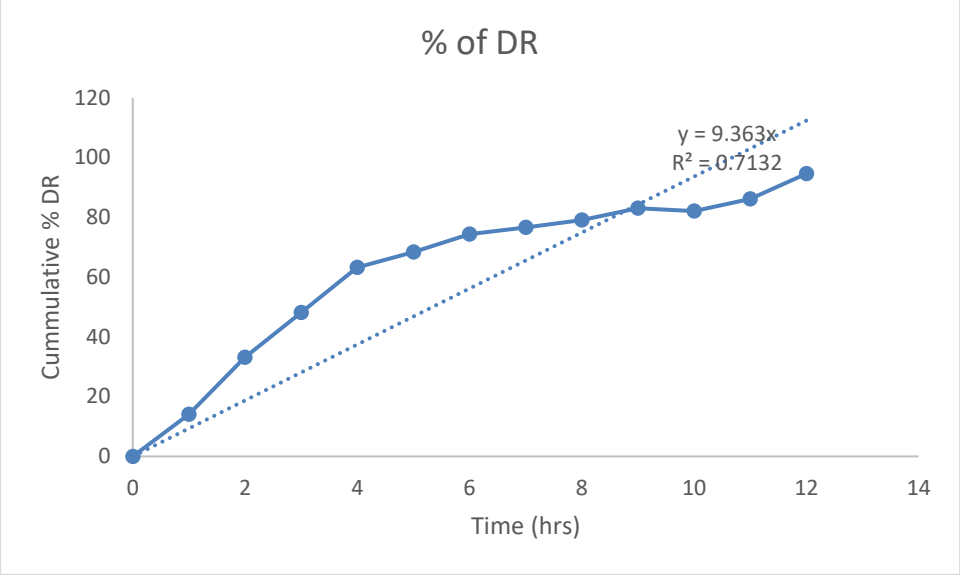

Fig. 6: Invitro drug release profile of formulation F5

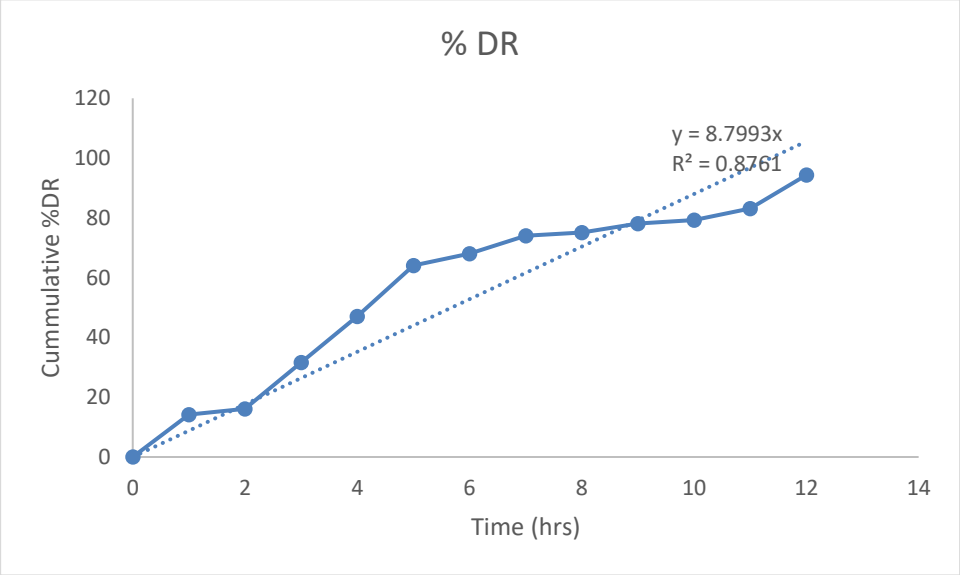

Fig. 7: Invitro drug release profile of formulation F6

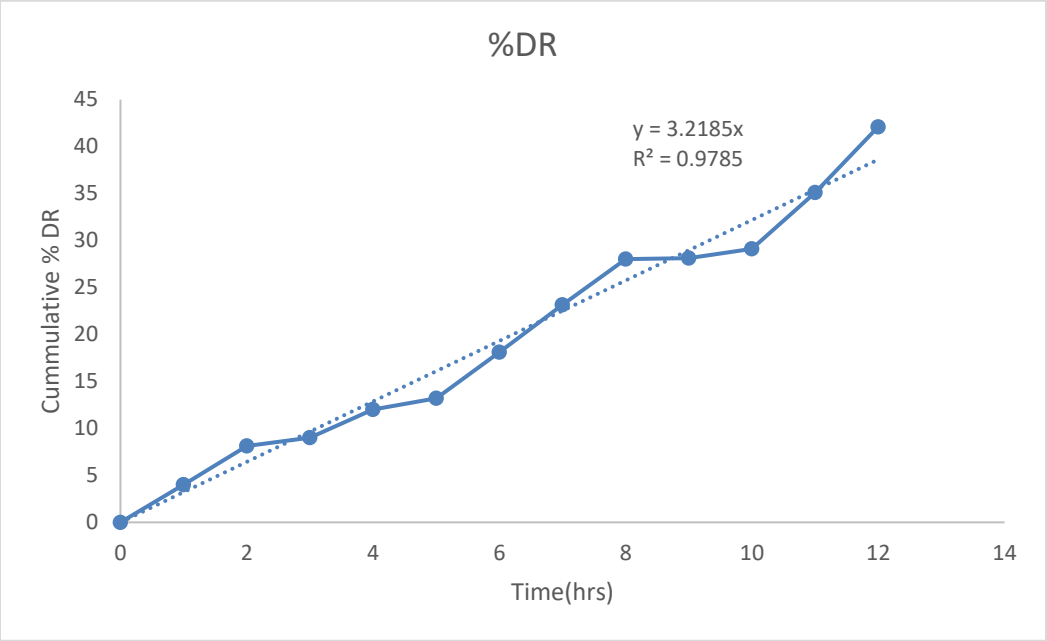

Fig. 8: Invitro drug release profile of formulation F7

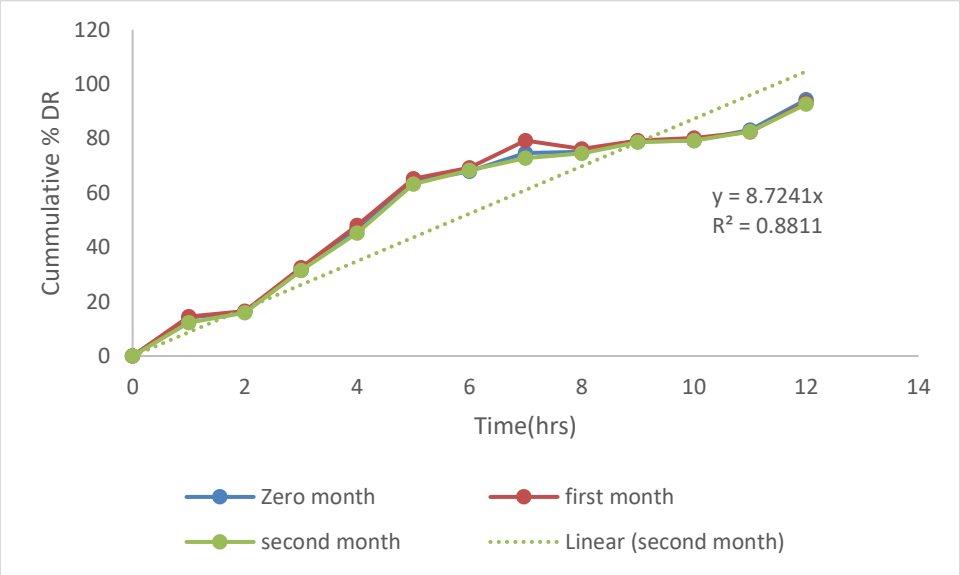

Fig. 9: Cumulative drug release profile of optimized formulation (F6) in stability studies

Table No. 4: Percent of drug release of optimized formulation (F6) in stability studies

Time (hr)	Percent of drug release		
	Initial month	First month	Second month
0	0	0	0
1	14.14	14.46	12.31
2	16.12	16.52	15.89
3	31.61	32.52	31.52
4	47.58	48.12	45.21
5	64.04	65.23	63.29
6	68.01	69.23	68.32
7	74.66	75.31	72.74
8	75.14	76.23	74.56
9	78.84	79.20	78.63
10	79.31	80.21	79.2
11	83.12	82.45	82.54
12	94.32	93.2	92.63

Fourier transform infrared spectroscopy

FTIR spectroscopy of flurbiprofen, chitosan and chitosan-FBP spheres were instructed to explain drug-biopolymer interaction. FTIR spectrums of flurbiprofen, chitosan and CS-FP spheres were compared in Fig. 10. As seen from the Figure 10a, the characteristic sharp peaks of flurbiprofen at 1694.7, 1414.7 and 1216.1 cm^{-1} were due to C=O stretching, O-H bending and C-F stretching, respectively. The characteristic band of flurbiprofen due to the hydrogen bonds of the carboxyl group appeared in the range of the 3400-2400 cm^{-1} were seen from the Figure 10b at 3290.4 cm^{-1}, 1649.0 cm^{-1}, 1586.1 cm^{-1} and 1318.9 cm^{-1} which correspond to OH and NH stretching, amide I (C=O), amide II (NH2) and amide III (C-N), respectively. Spectrum of chitosan-FBP spheres (Figure. 10c) compared with the other spectrums, there are some changes indicating the structural differences of chitosan after the encapsulation process. It is seen that the O-H and N-H stretching bands were shifted to lower wavenumbers at 3108.4 cm^{-1} due to H bonding system. Furthermore, peaks observed at 927.68 cm^{-1}, 765.27 cm^{-1}, 721.6 cm^{-1} and 697.15 cm^{-1} indicate the presence of the substitute aromatic rings of flurbiprofen. These changes greatly showed that flurbiprofen successfully encapsulated into chitosan particles. X-ray diffraction XRD patterns of chitosan, pure drug and encapsulated sample are given in Figure 11. The broad peak observed at 2θ=19° is the characteristic peak for the chitosan. The XRD pattern of flurbiprofen revealed the crystalline structure of drug observed by five sharp peaks at 2θ of 7°, 11°, 16°, 21° and 24°. The XRD pattern of flurbiprofen compared with the XRD pattern of encapsulated sample, chitosan-FBP spheres showed no sharp peaks, whereas a broad peak from 11° to 24° was observed. Mean of this broad peak is that flurbiprofen was kept in an amorphous state in the chitosan.

These results suggest that flurbiprofen successfully encapsulated in the chitosan.

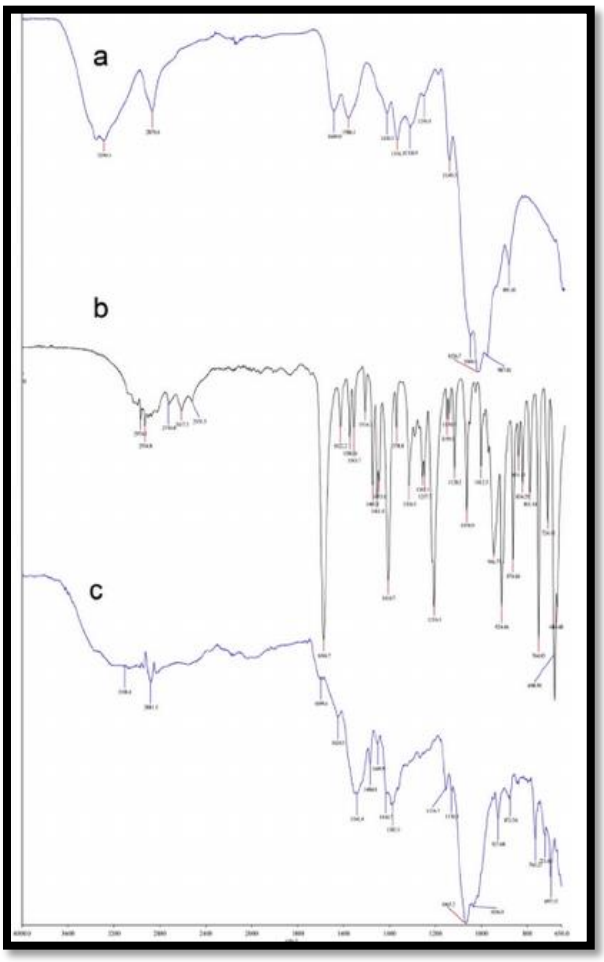

Fig. 10: Fourier transform infrared spectroscopy spectrums of (a) chitosan (b) flurbiprofen and (c) chitosan-flurbiprofen microspheres

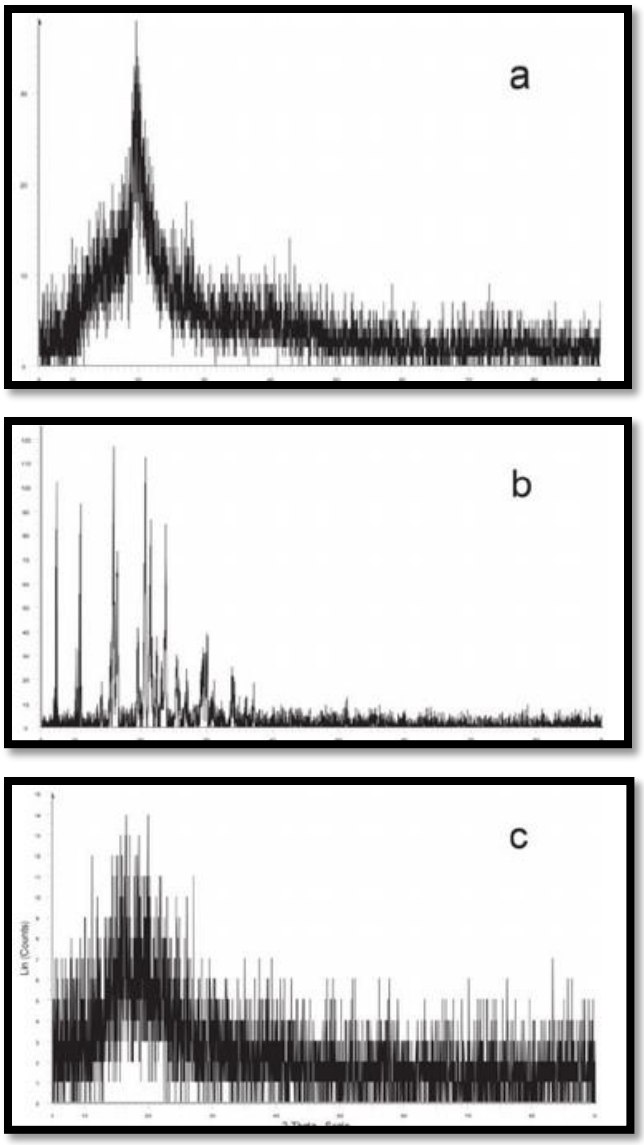

Fig. 11: X-ray diffraction pattern of (a) chitosan (b) flurbiprofen and (c) chitosan-flurbiprofen micro-nanospheres

CONCLUSION:

The simple emulsification- crosslinking technique for obtaining chitosan microspheres has proved to be useful in preparation of controlled release microsphere. Microspheres are formulated to prevent initial drug burst while modulating the controlled release dosage form, it is concluded that the controlled release FBP can be prepared. However, attempts are made to achieve nano spheres that are needed to further development.

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