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Formulation, Evaluation & Optimization Study of Mucoadhesive Microspheres of Flurbiprofen Prepared By Spray Dry Method

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ABSTRACT:

Utility of microspheres to delivered drugs shows various advantages, as control release of drugs, enhances bioavailability & site specific administration of the drug to the required location. In this study work showed the use of encapsulation sodium alginate, sodium carboxy methyl cellulose in micro particulate drug delivery system, which deliver orally by a capsule & gives required therapeutic action. A microsphere preparation shows merits on the conventional tablet & capsule formulations, this formulation improves surface area to enhance absorption of drug in specific area & also reduces frequency of drug dose. Flurbiprofen (NSAIDs) drug preferably use in different intestinal diseases colon ulcers, different colon cancers & infections. Flurbiprofen proved more absorption from lower GIT regions, & also showed $t_{1/2}$ 4 hrs., orally it gives less bioavailability. The microsphere preparations were characterized & evaluated as for yields of production, drug content (actual), efficiency of encapsulation, percentage Swelling Index, drug release study was done by in vitro release examination, mucoadhesive strength determination in vitro & in vivo methods.

Keywords: Mucoadhesive, Microsphere, Flurbiprofen.

INTRODUCTION

The idea of mucoadhesive system came from the requirement of to localize drug in specific site in the body for prolonged period of time. Need because of residence time of drug in the absorption site.

In oral drug delivery, absorption of drug in the absorption site is less due to the GIT transit time of the dosage form. To illustrate suppose if a drug dosage form is to deliver a drug in a sustained manner for treating some chronic disease then it is required that the dosage form should remain at the site of drug absorption which is mainly due to upper part of the intestine, for a extended period of time but this is limited because of the GI transit of the dosage form, so mucoadhesive dosage forms are formulated with the purpose of binding with the GIT mucus layer & thus improves the staying time of the drug and also providing the long time contact between a dosage form & absorbing tissue and hence enhancing the absorption of the drug[1-3].

MATERIALS AND METHODS:

Flurbiprofen provided by Teva Pharma Pvt. Ltd., also Sodium alginate & Sodium carboxy methyl cellulose gift sample from Colorcon Ltd., UK. Optimization study was done by use of Design Expert software, version 7.0.0. MS Excel, PCP disso. Pune software was used for study of drug release analysis. Also prepared microspheres were characterized & evaluated for Yields of production, drug content (actual), efficiency of encapsulation, percentage Swelling Index, and drug release study.

Preparation of Microspheres

Spray dray technique:

Spray drying technique were used to formulate mucoadhesive microspheres. An in aqueous Phase incorporating various combinations of polymers (Table 1) was formulated by dissolving sodium alginate and carboxy methylcellulose in the distilled deionized water. The drug qty (1 g), in previously dissolved 100 ml of absolute methanol & were added in polymer solution & sonicated by using sonicator (Ultra 1204 AU-Vibracell USA) to obtained a uniform mixture. Glutaraldehyde (0 – 0.30 ml) used as a crosslinking agent, , were added in the homogenized solution & produce solution were spray dried by using (LU-222 ADVANCED) lab spray drier (Labultima, In) for Formulating microspheres through nozzle of a spray-dryer (model JISL, LSD- 48 mini spray dryer, In) with at input temperature range of 115 -117 °C, & output temperature range of 80 – 85 °C at 2 % feed rate & vacuum pressure of 35 psi (2.4 kg/cm2). The prepared microsphere was collected from spray dryer & place in a desiccator including silica gel for remaining further tests[4-6].

Factorial formulations

Table.1 Combination batches by using Sodium alginate & CMC in various concentrations according to 3^2 factorial designs.

CONTENT weight (mg)	F.1	F.2	F.3	F.4	F.5	F.6	F.7	F.8	F.9
Flurbiprofen : Sodium alginate : Sodium CMC	1:2:0	1:2:1	1:2:2	1:2:0	1:2:1	1:2:2	1:2:0	1:2:1	1:2:2
Cross linking agent (%)	00	00	00	20	20	20	30	30	30

Factorial Batches [7-10]: -

A factorial design 3^2 was implanted for the optimization of oral controlled release mucoadhesive microspheres. According to this model it contains 02 independent variables at three levels as +1,0 and

-1. total nine formulations possible with this model. The content of different formulations is shown in (Table.2). The various independent variables include as drug: polymer ratio (X_1) & also % of Cross linking agent (X_2), where carboxyl methyl cellulose & sodium alginate act as an controlled release polymers. The different dependent responses include: % drug release at 8 hour (Y_1), Time taken to release 50% drug, $T_{50\%}$ (Y_2), Time taken to release 90% drug, (Y_3).

Combination Batches for microspheres: -

Table.02 Factorial Design (Preparation of Microspheres Batches)

Batch Code	Variable levels with Coded form	
	X_1	X_2
F.1	+ 1	+ 1
F.2	+ 1	0
F.3	+ 1	- 1
F.4	0	+ 1
F.5	0	0
F.6	0	- 1
F.7	- 1	+ 1
F.8	- 1	0
F.9	- 1	- 1

X_1 : drug: polymer (ratio) X_2 : Cross linking agent(Concentration)

EVALUATIONS OF MICROSPHERES:

A. Yields of production[11-14]

Production yields of microspheres for various batches was determined by using after drying mass of final product in respect with the initial total weight of the product & polymer were used for the preparation of microspheres & % production yields was determined by formula given below & results section results are reported.

$$\text{Yield of Production (\%)} = \frac{\text{Practical weight(microspheres)}}{\text{Theoretical weight (polymer \& drug)}} \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots 1$$

B. Actual drug content and encapsulation efficiency[11-14]

The $cacl_2$ solution in which the microspheres was prepared were calculated for its actual drug content by UV spectroscopy by taking its absorbance at 247nm & amount of unentrapped drug were estimated, then after determined amount of drug were deducted from total quantity of initially drug added to obtain the amount of drug which is entrapped(encapsulated). Encapsulation efficiency were estimated by using direct method in which the microspheres was added in water for 24 hrs with constant shaking with this we can extract drug from microspheres in water, which is then quantitatively determined by UV spectroscopy with taking its absorbance at 247nm & obtained used to determine encapsulation efficiency for the microspheres & using formula mentioned below & encapsulation efficiency values was shown in results section.

% encapsulation efficiency = Actual drug content(mg) X 100……..2

Total wt. of microspheres

C. Morphology of microspheres[11-14]

The microspheres size & shape for the optimized batches were determined through optical microscope and through SEM (cameca, france model-SV30). Results are reported results.

D. Swelling studies[11-14]

The swalling index of the mucoadhesive microspheres in the physiological media were determined by adding 500mg of microspheres estimated by adding in pH 6.8 phosphate buffer (100ml) of & kept for 24hrs & equation were used to determine the ability of swelling.

S.s.w = (W.s - Wo/Wo) x 100 …… 3

Where S.s.w = % swelling of microspheres,

W.o = initial wt. of microspheres, W.s = weight

of microsphere after swelling.

E. *In vitro* release study[15-19]:

In vitro release was studied for the drug by dissolution method using dissolution apparatus I (basket). The releasestudy was performed by using 900 mL (v) pH 1.2acidic buffer. The temperature was constant at 37 ± 0.5°C & speed of basket was at 100 rpm in dissolution release study. Microspheres filled in capsule and placed in dissolution medium. At an appropriate sampling time intervals, withdrawn 5 mL of the solution & filtered it taken absorbance of all samples was determinrd on UV spectrophotometer (Jasco V-630,Japan) at 224 nm, with maintaining sink condition in the apparatus. In triplicate performed this study. The % drug release was measured by PCP disso software & reported in results.

Study of release mechanism by Curve fitting:-

Release data were put into to various mathematical models to determine which release mechanism from mucoadhesive microspheres; Korsmeyer Peppas (Eq. (4)), zero order (Eq. (5)) and Higuchi release models (Eq. (6)). And reported in results.

$$\mathbf{Mt/M\infty = k_K P t^n} \quad \textbf{…… 4}$$

Where, M t/M ∞ - fraction (drug released at time‘t’)

$k_K P$ - constant(release rate)

n - release exponent.

$$\mathbf{M_t = M_0 + k_0 t} \quad \textbf{…… 5}$$

Where, M_t - Amount (drug released at time‘t’)

M_0 - concentration (drug in the solution at t=0)

k_0 - release constant (zero-order).

$$\mathbf{M_t = k_H t^{1/2}} \quad \textbf{…….... 6}$$

Where, M_t - Amount (drug release at time ‘√t’)

k_H - Higuchi release constant.

All curve fitting, simulation and plotting was carried out by using disso software (PCP V3). The mechanism of the drug release is discussed in results.

F. *In vitro* mucoadhesion strength determination of microparticles[20-22]:

A recently excised sheep's stomach were used. Before study tissue mucus surface washed with the saline normal water & tissue inclined at an 60^{o} angle using polyethane support. A glass beaker was inserted directly under polyethane for microparticles collection when they detached from tissue. A 100 mg weight of microparticles prepared in different combinations of polymers were inserted on trough of the mucus surface of & permit to hydrate for 15 minutes for interaction between the microparticle–mucin to occur. A 100 ml vol of SGF were permit to flow over tissue with rate of 40 drops/minutes. The weight of microparticle washed out determined as a % of the original weight were used as a measurement of mucoadhesion. And results are reported.

G. *In vivo* studies[23-25]:

1. Weight count method

In this technique 5 groups of 4 number of Albino rats overnight fasted & 100mg suspension of microspheres administer via needle to these rats, then after these rats sacrifies with an interval of 0, 4, 8, 12 hrs respectively. Then dissect their stomach area isolate & cut open longitudinally & note weight of microspheres adhering with stomach and intestine area, adhesive strength determined by using formula given below.

$$\% \text{ adhesive strength} = \frac{N.o - N.s}{N.s} \times 100 \quad \textbf{.....7}$$

Were, No = Weight of microspheres hydrated with small amount of H_2O
Ns = Weight of microspheres detaching from mucosal surface.
And results are reported.

RESULTS:

Table.3 Factorial batches dissolution studies of spray dry method

		Formulations				
		F1	F2	F3	F4	F5
*** Percent drug release**	1	24.753 ±0.21	26.674 ±0.21	29.548 ±1.45	21.81±0.39	27.813 ±0.54
	2	31.346 ±0.20	33.218 ±0.35	41.863 ±1.54	24.91±0.34	30.546 ±0.34
	3	39.293 ±0.28	46.423 ±0.28	57.134 ±0.46	32.74±0.33	39.293 ±0.33
	4	46.876 ±0.12	54.834 ±0.18	61.909 ±0.20	39.40±0.17	45.886 ±0.17
	5	55.592 ±0.26	61.853 ±0.19	66.800 ±0.38	45.81±0.45	56.492 ±0.45
	6	62.555 ±0.65	75.354 ±0.55	71.621 ±0.54	61.51±0.31	63.955 ±0.79
	7	**93.121 ±0.29**	83.11 ±0.54	78.383 ±1.05	77.21±1.20	67.765 ±1.49
	8	93.726 ±1.07	**93.982 ±1.28**	83.467 ±0.89	85.72±0.32	72.633 ±1.02
	9	94.035 ±0.67	94.184 ±1.40	**95.255 ±0.44**	**93.82±0.29**	82.102 ±0.99
	10	94.545 ±0.66	94.742 ±1.23	95.310 ±0.32	94.20±1.08	**94.401 ±0.42**
	11	94.931 ±1.17	94.949 ±0.74	95.422 ±0.40	94.72±1.21	94.719 ±0.18
	12	94.960 ±0.43	95.558 ±0.55	95.556 ±1.64	94.78±0.82	94.849 ±0.14
Production yield (%)		31.55	35.25	44.25	33.74	42.98
Encapsulation efficiency (%)		60.24	71.44	80.11	72.14	79.55
Swelling index (%)		204±8	212±6	260±5	158±4	169±4

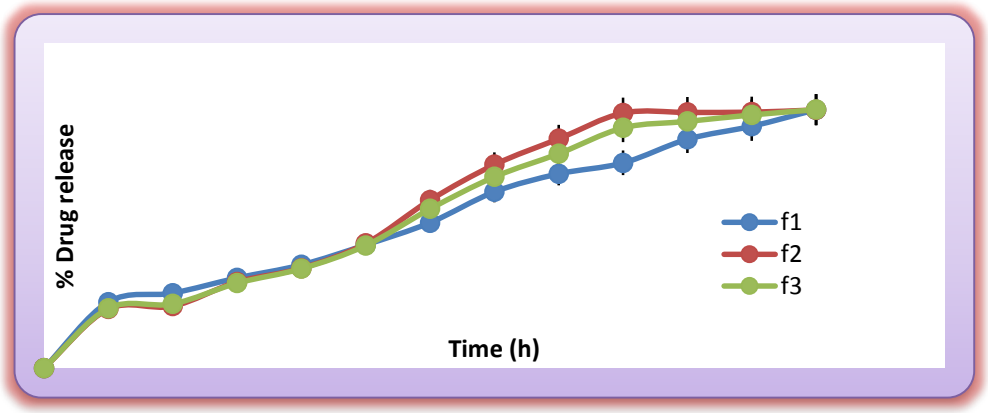
		Formulations			
		F6	F7	F8	F9
***Percent drug release**	1	25.33±0.31	26.003 ±0.14	24.512 ±1.16	24.619 ±0.45
	2	36.00±0.32	37.253 ±0.80	29.013 ±0.41	27.721 ±0.52
	3	46.81±0.34	53.213 ±1.04	33.332 ±0.25	32.561 ±1.37
	4	67.36±0.42	65.403 ±0.29	38.429 ±0.17	38.557 ±0.41
	5	71.18±0.08	76.212 ±0.23	47.391 ±0.24	46.655 ±0.65
	6	76.85±0.51	84.624 ±0.17	53.882 ±0.92	53.780 ±0.79
	7	81.83±0.31	**94.110 ±0.77**	65.778 ±1.23	65.721 ±1.49
	8	85.11±1.64	94.252 ±0.27	69.706 ±0.35	69.594 ±1.02
	9	86.71±0.59	94.457 ±0.62	77.517 ±1.06	76.741 ±0.99
	10	**95.59±0.59**	95.106 ±0.44	83.532 ±0.39	83.195 ±0.41
	11	95.66±0.54	95.553 ±0.61	**95.273 ±1.87**	88.544 ±0.24
	12	95.80±0.19	95.778 ±0.44	95.410 ±1.51	**96.146 ±0.45**
Production yield (%)		51.65	39.54	55.64	62.95
Encapsulation efficiency (%)		88.12	73.25	80.54	92.57
Swelling index (%)		175±6	118±5	130±4	148±4

Discussion: *In vitro* dissolution release study of the microspheres indicates that Formulation f1 is combination of 1:2:0 Flurbiprofen : Na-alginate : Na-CMC and gluteraldehyde 0.0 % shows 100% release upto 7.0 h. f2 is combination of 1:2:1 Flurbiprofen : Na-alginate : Na-CMC & gluteraldehyde 0.0 % shows 100% release upto 8.0 h. f3 is combination of 1:2:2 Flurbiprofen : Na-alginate : Na-CMC & cross linking agent 0.0 % shows 100% release upto 9.0 h.

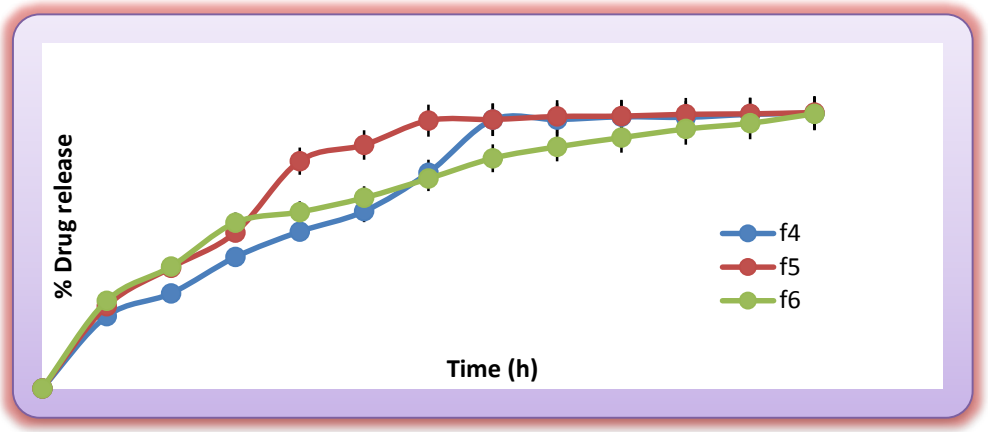
Formulation f4 is combination of 1:2:0 Flurbiprofen : Na-alginate: Na-CMC and gluteraldehyde 20.0 % shows 100% release upto 9.0 h f5 is combination of 1:2:1 Flurbiprofen : Na-alginate : Na-CMC & gluteraldehyde 20.0 % shows 100% release upto 10 h f6 is combination of 1:2:2 Flurbiprofen : Na-alginate : Na-CMC & gluteraldehyde 20.0 % shows 100% release upto 10 h.

Formulation f7 is combination of 1:2:0 Flurbiprofen : Na-alginate: Na-CMC and gluteraldehyde 30.0 % shows 100% release upto 7h f8 is combination of 1:2:1 Flurbiprofen : Na-alginate: Na-CMC & gluteraldehyde 30.0 % shows 100% release upto 11h f9 is combination of 1:2:2 Flurbiprofen : Na-alginate: Na-CMC and gluteraldehyde 30.0 % shows 100% release upto 12h. From above discussion it was clear that the as we increases the concentration of polymer & gluteraldehyde release of drug was retarded.

From above discussion formulation f9 was the optimized formulations.



A.



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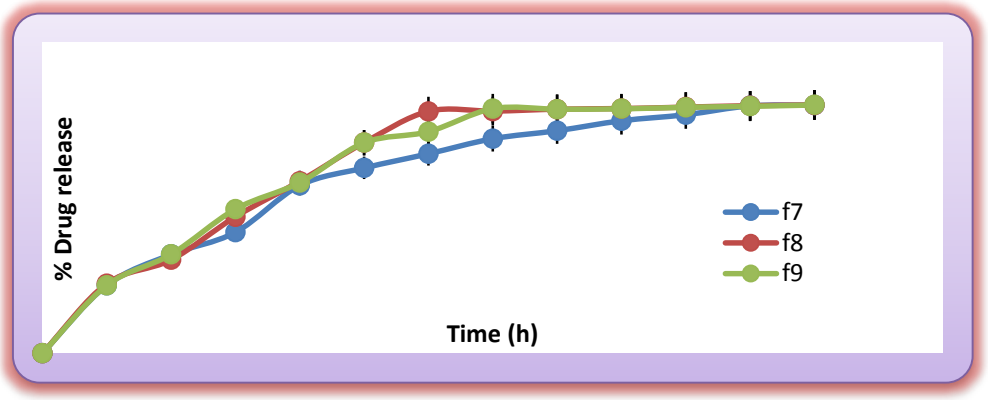

C.

Figure.1 Dissolution profile of A. F.1-F.3, B. F.4-F.6, C. F.7-F.9 formulations for factorial batches.

Yield of production, Actual drug content and entrapment (encapsulation) efficiency

The production yields of microspheres prepared through the spray dry technique is found in the range of 30-62%. Drug content (Actual) & drug encapsulation efficiency or drug entrapment efficiency of microspheres prepared by spray dry technique was found to be 60-92%.

***In vitro* mucoadhesive strength determination**

Table.4 *In vitro* data for mucoadhesive strength estimation

SR. NO	WEIGHT (mg) OF MICROSPHERES REMAINING ON GASTRIC MUCOSA				% MUCOADHESIVE STRENGTH
Optimized	3h	6h	9h	12h	
F9 (Spray dry)	44	41	35	32	76.00

In vivo mucoadhesive strength determination

Table.5 *In vivo* data for mucoadhesive strength determination

Sr.no	Weight (mg) of microspheres remaining on the rat stomach				% mucoadhesive strength
	Time (h)				
Optimized	0	4	8	12	
Spray dry	98.12	80.34	74.21	64.32	78.24

From both *in vitro & in vivo* mucoadhesive strength determination tests it was cleared that Spray dry formulation comparising of 1:2:2 ratio of flurbiprofen: Sodium alginate: Sodium CMC it reduces the release of drug up to 12 hrs due to high mucoadhesive strength

Morphology of microspheres

Morphological study of microspheres done using SEM & microspheres was studied which shows shape of microspheres almost spherical shown in fig no.2 and size shown in table no.6

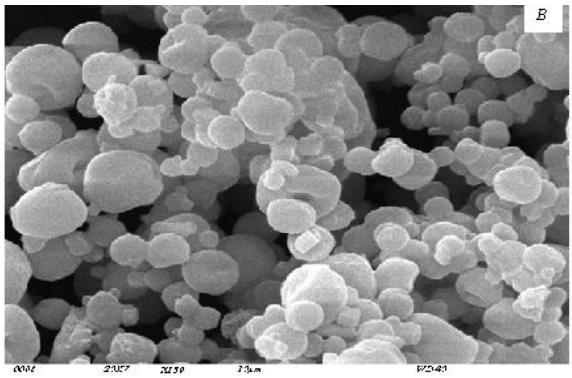

Fig.2 Morphology of microspheres prepared by Spray dry

Shape & size of optimized formulations

Table.6 Shape & size of optimized formulations.

FORMULATIONS	SIZE in µm	SHAPE
SIZE in µm(Spray dry)	11.32-12.50	Almost spherical

Results of release parameters as $T_{50\%}$, $T_{90\%}$ and flurbiprofen release at 8h for spray dry method

Table.7 Results of release parameters

Formulation	$T_{90\%}$ (h) ± SD (n-3)	$T_{50\%}$ (h) ± SD (n-3)	Flurbiprofen release at 8h (%) ± SD (n-3)
F1	5.254± 1.01	5.354 ± 0.89	93.726 ±1.07
F2	4.187 ± 1.45	4.498 ± 0.51	93.982 ±1.28
F3	5.265 ± 0.57	4.884 ± 0.78	83.467 ±0.89
F4	1.61 ± 1.21	1.65 ± 1.66	85.72±0.32
F5	3.659 ± 0.92	4.305 ± 0.45	72.633 ±1.02
F6	4.95 ± 0.78	7.006 ± 1.44	85.11±1.64
F7	3.871 ± 1.32	5.546 ± 0.54	94.252 ±0.27
F8	4.123 ± 0.78	6.45 ±1.22	69.706 ±0.35
F9	4.316 ± 0.66	6.206 ± 1.02	69.594 ±1.02

Optimization of mucoadhesive microspheres formulations

A. Effect of formulation variables.

a. Effect of formulation variables on $T_{50\%}$

Model terms for response Y_1 ($T_{50\%}$) were found to be significant with the F value of 4.88 ($p<0.0048$). All factors found significant in this study & model describing $T_{50\%}$ can be written as;

$$\mathbf{Y_1 = 2.87 + 0.51X_1 - 0.28\ X_2 + 0.26\ X_1\ X_2 + 0.48\ X_1^2 + 1.14\ X_2^2}$$

As the amount of X_1 and X_2 increases the corresponding $T_{50\%}$ also increases The **Fig 3** shows the response surface plot. It indicates at all the high levels of X_1 and X_2 the $T_{50\%}$ value is high, As discussed above this behavior is due to increase in amount of polymers (Na-alginate and Na- CMC) & cross linking agent forms a high viscous gel matrix and thus decreases the drug release and hence $T_{50\%}$ value increases, while Sodium CMC forms pores in the formed matrix and will increases the drug release thus decreases the $T_{50\%}$ value. The **Fig 4** shows the graph of predicted verses actual data.

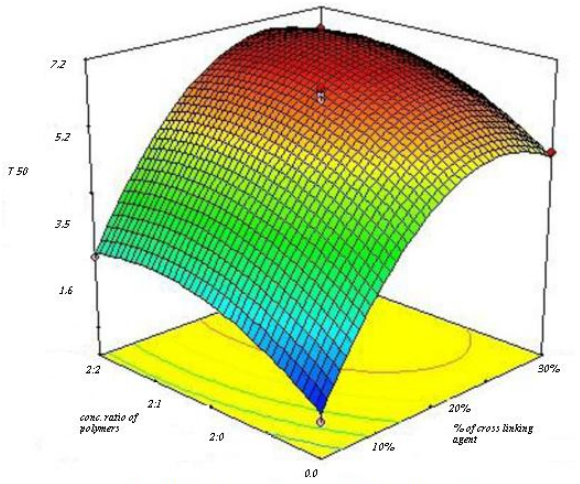

Figure 3 Response surface plot showing effect of formulation variables on $T_{50\%}$

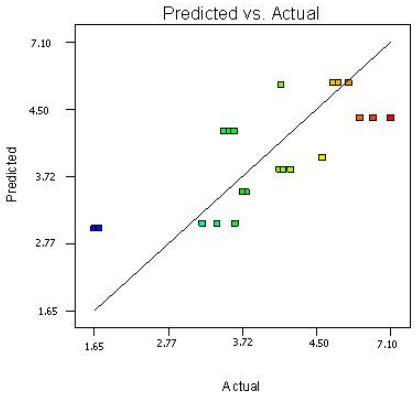

Figure 4 Linear correlation plots between actual and predicted values for $T_{50\%}$ (Y1)

b. Effect of formulation variables on $T_{90\%}$

Model terms for response Y_2 ($T_{90\%}$) was found to be significant with F value of 10.11 ($p<0.0001$). All factors found significant in this study & model describing $T_{50\%}$ can be written as;

$$Y_2 = -5.79 + 0.68X_1 - 14.83X_2 + 0.99\ X_1X_2 + 15.32\ X_1^2 + 16.12\ X_2^2$$

As the amount of X_1 and X_2 increases the corresponding $T_{90\%}$ (time required to release 90% of the drug) also increases The **Fig 5** shows the response surface plot. It indicates at all the high levels of X_1 and X_2 the $T_{50\%}$ value is high, As discussed above this behavior is due to increase in amount of polymers (Na-alginate and Na- CMC) & cross linking agent forms a high viscous gel matrix and thus decreases the drug release and hence $T_{50\%}$ value increases, while Sodium CMC forms pores in the formed matrix and will increases the drug release thus decreases the $T_{90\%}$ value. The **Fig 6** shows the graph of predicted verses actual data.

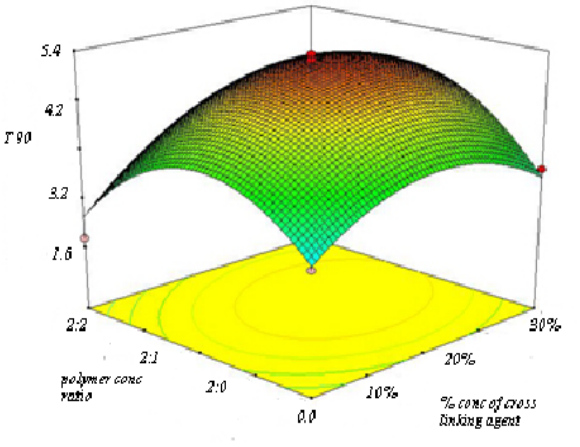

Figure 5 Response surface plot showing effect of formulation variables on $T_{90\%}$

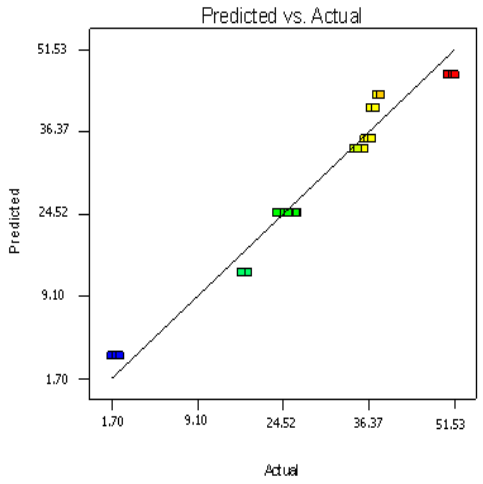

Figure 6 Linear correlation plots between actual and predicted values for $T_{90\%}$ (Y_2)

c. Effect of formulation variables on the drug release at 8 hr. (Y_3)

Quadratic model were found to be significant with the F value 28.22 (P<0.0001). In this case X_1, X_2 were found to be significant & model describes the percent flurbiprofen release at 8h can be written as;

$$Y_3 = 81.76 - 0.29X_1 + 11.45\ X_2$$

As the concentration of mucoadhesive polymer (Na-alginate and Na- CMC) enhances it causes an rise in the viscosity of the swollen matrix(gel), it contributes more hindrance in drug diffusion & thus reduces release rate. Combined effect of X_1 & X_2 shown in response surface plot (**Fig 7**) In this plots it was observed that the increasing amount of Na- CMC causes the decreases in the drug release, because of formation of gel(high viscosity)matrix. The factors X_1 & X_2 have negative effect on the drug release. The **Fig 8** Shows a graph of observed verses predicted values. The sodium alginate and Na- CMC have -ve effect on drug release, due to enhanced viscosity & gel strength. The swelling of sodium alginate may be because of uncharged –COOH group which forms H- bonds with imbibing water & also holds water inside gel matrix. Increasing amount of Sodium CMC which form a gel matrix network with sodium alginate.

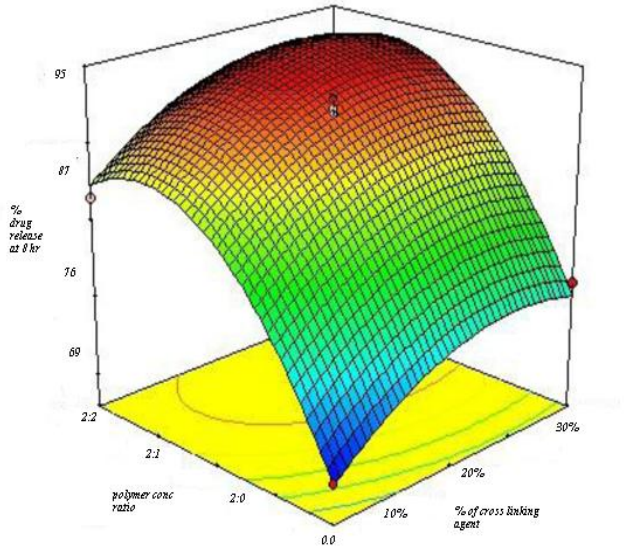

Figure 7 Response surface plot showing effect of formulation variables on percent drug release at 8 h

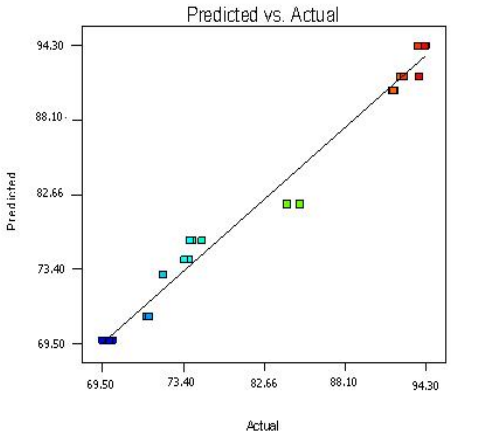

Figure 8 Linear correlation plots between actual and predicted values for percent drug release at 8 h (Y_3)

ANOVA., Pure error., Lack of fit

Results of the ANOVA shown in **Table 9** model found significant for all response(variables). Regression coefficient obtained by regression analysis.(**Table 10**) & effects are as follows; all factors was found to be significant for response Y_1, similarly only X_1, X_2 and X_1X_2 were found for Y_2, the X_1, X_2 were found significant for Y_3. The above results conveyed us that the amount of sodium alginate, Sodium CMC plays important role in formulation of mucoadhesive microspheres of flurbiprofen. Thus suitable range with these variables (yields) an optimized mucoadhesive microspheres have good strength (bioadhesive) & drug release. The predicted data of pure error & lack of fit are given in **Table 9** Residuals are the difference in observed value & predicted value. Since computed F-values was respectively less than critical F values, denotes non-significance of lack of fit.

Table.9 Data of ANOVA study for dependent variables from 3^2 factorial design

Source	d.f.	Sum square	Mean square	F value	Probability
$T_{50\%}$ (h)					
X_1	1	5.08	5.08	7.56	0.0120
X_2	1	1.48	1.48	2.20	0.1526
X_1X_2	1	0.87	0.87	1.30	0.2677
$T_{90\%}$ (h)					
X_1	1	8.28	8.28	0.060	<0.0001
X_2	1	3959.58	3959.58	28.66	<0.0001
X_1X_2	1	11.80	11.80	0.085	0.0009
NF release at 8 h (%)					
X_1	1	1.60	1.60	0.047	0.8298
X_2	1	1862.21	1862.21	54.83	<0.0001

Table.10 Data of ANOVA study for results in analyzing lack of fit and pure

Source	d.f.	Sum square	Mean square	F value	Probability
$T_{50\%}$ (h)					
Model	5	15.89	3.18	4.88	0.0048
Residual	21	14.10	0.67	-----	-----
Total	26	30.00	-----	-----	-----
Lack of fit	3	13.82	4.61	295.79	<0.0001
Pure error	18	0.28	0.016	-----	
$T_{90\%}$ (h)					
Model	5	6948.06	1389.61	10.11	<0.0001 *
Residual	21	2901.00	138.14	-----	-----
Total	26	9849.06	-----	-----	-----
Lack of fit	3	2900.00	966.67	17347.34	<0.0001
Pure error	18	1.00	0.056	-----	
NF release at 8 h (%)					
Model	2	1863.81	931.91	28.22	<0.0001 *
Residual	24	815.18	33.97	-----	-----
Total	26	2678.99	-----	-----	-----
Lack of fit	6	804.28	134.05	221.14	<0.0001
Pure error	18	10.90	0.61	-----	

Optimization

As per use of optimization technique by desirability mode were used to generate optimum solution for preparation. Process were optimized for variables (dependent) Y_1-Y_4. The optimized formula generated by targeting the Y_1 was targeted at 6 h, , Y_2 was targeted at 10 h,Y_3 was kept at range 70-80% drug release. The optimized results obtained to give 7 results out of that one formula is shown in **Table 11**. Results of optimized formula was compared with the predicted values, which showed match data between experimented & predicted values, which confirms the practicability & validity of the model.

Table.11 Composition of optimized formulation

Ingredients	**Quantities (mg)**
Drug:Sodium alginate: Sodium CMC	1:2:2
% of cross linking agent	30

SUMMERY & CONCLUSION:

The results so far obtained during this investigation encouraged us to derive the following conclusions

1. The yield of production of microspheres prepared by spry drying method was found in the range of 30-62 % which is reliable
2. The encapsulation efficiency of microspheres prepared by spry drying method was found in the range of 60-92% it is not 100% because during preparation of microspheres some drug lost in external media.
3. The *in vitro* release profile of Flurbiprofen from optimized formulations in spray drying technique were F9 shows retardation of release up to 12 hours shows good controlled release.
4. The *in vitro* Flurbiprofen release data best fitted to korsmeyer-peppas release model & also shows zero order & higuchi model.
5. The *in vitro* mucoadhesive strength of optimized formulations of spray drying technique F3 76.50% which shows good mucoadhesion.
6. The *in vivo* mucoadhesive strength of optimized formulations of spray drying technique were for F9 78.24% which shows good mucoadhesion.
7. The size of microspheres prepared by spray drying method was found for F9 11.32-12.50µm

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