



# Formulation, Characterisation & Evaluation of Flurbiprofen Mucoadhesive Microspheres by Spray Drying Method

Prashant Patil<sup>1,2\*</sup>, Santosh Singh<sup>1</sup>, Girish Kashid<sup>1</sup>

## Abstract

spray dry methods for formulation of microspheres to deliver medications have numerous other benefits over one another, including controlled drug release, increased bioavailability, and targeted drug delivery to the desired place. In order to achieve the required therapeutic effect, this research demonstrates the usage of encapsulating sodium alginate and sodium carboxy methyl cellulose in biodegradable microsphere delivery system, to be administered orally via a capsule. The benefit of microsphere formulations over traditional tablet or capsule formulations are that they increase the surface area exposed to the absorption site, boosting medication absorption and reducing drug dose frequency. An non-steroidal anti-inflammatory drug called flurbiprofen is used to treat infections and intestinal diseases such ulcerative colitis, Crohn's disease, and carcinomas. Flurbiprofen has a half-life of 4 hours, a poor bioavailability when taken orally, and its highest absorption occurs in the lower gastrointestinal system. The production yields, actual drug content, encapsulation effectiveness, percentage Swelling Index, in vitro release analysis, mucoadhesive strength assessment, and in vivo procedures of the microsphere formulations were all assessed.

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**Key Words:** Microsphere, Mucoadhesive, Flurbiprofen

**DOI Number:** 10.14704/nq.2022.20.8.NQ55753

**NeuroQuantology 2022; 20(8):804-811**

## Introduction

The requirement to localize drugs at specific body sites resulted in the development of mucoadhesive systems, as medication absorption is frequently constrained by the length of time it spends at the absorption site. The gastrointestinal transit time of the dose form limits medication absorption in oral drug delivery. For example, suppose a drug dosage form needs to stay at the site of absorption, which is primarily the upper side part of the gut over an extended period of time to administer the medication in a sustained manner for treating some chronic disease. However, this is limited by the dosage form's gastrointestinal transit, so mucoadhesive dosage forms are necessary. intended to be formulated to connect with the mucus layer of the GIT and extend the drug's stay in the body as

well as to provide close contact between a dosage form and the absorbing tissue, which will increase the drug's absorption.1-3.

## Materials And Methods

TevaPharma (Pvt.) Ltd. offers free samples of flurbiprofen, while sodium alginate and sodium carboxy methyl cellulose (Colorcon Ltd., UK). The State-Ease, Inc., Minneapolis-based Design Expert software, version 7.0.0, was successfully used to implement the central composite design. For the evaluation of drug release data, SPSS 17.0 (SPSS Inc.), DD solver, and Microsoft Excel were utilised. Microspheres formulations were assessed for encapsulation effectiveness, real drug content, % yield, and release research.

**Corresponding author:** Prashant Patil

**Address:** <sup>1</sup>School of Pharmacy Suresh Gyan Vihar University Jaipur - 302017, Rajasthan, India, <sup>2</sup>R.G Sapkal College of Pharmacy Nashik

**Email:**

pprashant32@yahoo.com



**Spray dray technique**

Mucoadhesive microspheres were prepared by spray drying technique. An aqueous solution containing different combinations/ratios of the polymers (Table 1) were prepared by dissolving sodium alginate and carboxy methylcellulose in distilled deionized water. The drug (1 g), previously dissolved in 100 ml of absolute methanol, was added to the polymer solution and sonicated using Ultra sonicator (1204 AU-Vibracell, USA) to obtain a homogeneous mixture. A crosslinking agent, glutaraldehyde (0 – 0.30 ml), was added to the

homogenized solution and The resultant solution was spray dried using LU-222 ADVANCED lab spray drier (Labultima, India) for preparing microspheres through the nozzle of a spray-dryer (JISL, LSD- 48 mini spray dryer, India) at input temperature of 115 -117 °C, output temperature of 80 – 85 °C at 2 % feed rate and vacuum pressure of 35 psi (2.4 kg/cm<sup>2</sup>). The resulting microspheres were collected from the spray dryer and kept in a desiccator containing silica gel pending further tests4-7.

**Factorial formulations**

**Table 1: Combination batches by using Sodium alginate & CMC in various concentrations according to 32 factorial design.**

CONTENT (Wt in mg.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
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**

A 32 factorial design was implanted for optimization of oral controlled release tablet tablets. According to the model it contains two independent variables at three levels +1,0 and -1. According to the model total nine formulations possible. The composition of different formulations is shown in (Table.1). The different independent

variables include: drug: polymer ratio (X1) & percentage of Cross linking agent (X2), Where carboxyl methyl cellulose & sodium alginate act as an controlled release polymers. The different dependent responses include: % drug release at 8 hour (Y1), Time taken to release 50% drug, T50% (Y2), Time taken to release 90% drug, (Y3 )8-13.

**Combination Batches for microspheres**

**Table 2 Factorial Design for Preparation of Batches**

Batch Code	Variable levels in Coded form	
	X1	X2
F1	+1	+1
F2	+1	0
F3	+1	-1
F4	0	+1
F5	0	0
F6	0	-1
F7	-1	+1
F8	-1	0
F9	-1	-1

X1 : drug: polymer ratio X2 : Concentration of Cross linking agent



**Characterization and Evaluation of microspheres14-24**

**Yields of production**

The yields of production microspheres of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microspheres and percent production yields were calculated as per the formula mentioned below and results are reported in results.

$$\text{Production yield} = \frac{\text{Practical mass(microspheres)}}{\text{Theoretical mass(polymer+drug)}} \times 100 \dots\dots\dots 1$$

**Actual drug content and encapsulation efficiency**

Wherein the calcium chloride solution in which the microspheres were prepared was estimated for its drug content through UV spectroscopy by taking its absorbance at 247nm and the amount of unloaded drug was estimated, then determined amount of drug was deducted from the total quantity of drug added initially to obtain the amount of drug which is encapsulated. Encapsulation efficiency was determined by direct method wherein the microspheres were immersed in the water for 24 hours with constant shaking which would result in the extraction of drug from the microspheres in water, which is then quantitatively estimated through UV spectroscopy by taking its absorbance at 247nm and the value thus obtained is used to determine the encapsulation efficiency of the microspheres using the formula mentioned below and encapsulation efficiency values were reported in results.

$$\text{Percent encapsulation efficiency} = \frac{\text{Actual drug content(mg)}}{\text{Total mass of microspheres}} \times 100 \dots\dots\dots 2$$

**Morphology of microspheres**

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

**Swelling studies**

The swelling ability of the uncoated microspheres in physiological media was determined by

immersing an accurately weighed amount (500 mg) of microspheres in a little excess of 100 ml of phosphate buffer (pH 6.8) and kept for 24 h. equation was to compute the degree of swelling.

$$S_{sw} = \frac{(W_s - W_o)}{W_o} \times 100 \dots\dots\dots 3$$

where  $S_{sw}$  = percent swelling of microspheres,  $W_o$  = initial weight of microspheres,  $W_s$  = weight of microsphere after swelling.

**In vitro release study**

Apparatus I (basket) I was used to study in vitro drug release utilizing the dissolution method. The dissolution was carried out in an acidic buffer with a pH of 1.2 & 900 mL (v). During the dissolution investigation, the temperature was held at 37 0.5°C and the basket's speed was held at 100 rpm. Capsules are packed with microspheres and set in a dissolution media. The solution was withheld for 5 mL at predetermined intervals, filtered, and samples' absorbance was measured at 247 nm using a UV spectrophotometer (Jasco V-630, Japan) as an equal volume of new dissolution medium was poured into the apparatus. Dissolution tests were carried out three times. PCP Disso programme calculated the drug release percentage and provided the results.

**Study of release mechanism by Curve fitting**

Release data were fitted to the Korsmeyer-Peppas (Eq. (4)), zero-order (Eq. (5)), and Higuchi release models (Eq. (6)) mathematical models used to describe the mechanism of release from microspheres. and findings were reported.

$$kKPt^n = \frac{M_t}{M_\infty} \dots\dots\dots 4$$

Where  $kKP$  is the release rate constant,  $n$  is the release exponent, and  $M_t/M_\infty$  is the percentage of the drug released at time  $t'$ .

$$M_t = M_0 + k_0t$$

$$\dots\dots\dots 5$$

Where  $M_t$  is the quantity of the drug released at time  $t'$ ,  $M_0$  is the amount of the drug in the solution at time  $t'$ , and  $k_0$  is the zero-order release constant.

$$M_t = k_H t^{1/2} \dots\dots\dots 6$$

Where  $k_H$  is the Higuchi release constant and  $M_t$  is the amount of medication released at time  $\sqrt{t}$ .

Using the disso software, all curve fitting, simulation, and charting was done (PCP V3). The results address the drug release mechanism.



		Formulations
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Factorial batches dissolution studies spray dry

Table 3  
Data of release

		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	93.221 ±0.29	83.11 ±0.54	78.383 ±1.05	77.21±1.20	67.765 ±1.49
	8	93.726 ±1.07	93.282 ±1.28	83.467 ±0.89	85.72±0.32	72.633 ±1.02
	9	94.035 ±0.67	94.184 ±1.40	95.155 ±0.44	93.72±0.29	82.102 ±0.99
	10	94.545 ±0.66	94.742 ±1.23	95.310 ±0.32	94.20±1.08	94.501 ±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

**in vitro dissolution study flurbiprofen from factorial batches**

\*Represents mean ± S.D. (n = 3)

**Discussion**

In vitro dissolution study of the microspheres indicates that Formulation F1 is a 1:2:0 mixture. Flurbiprofen with sodium alginate, sodium CMC, and cross-linking agent at a concentration of 0.0% exhibits 100% release for up to 7.0 hours. F2 is a 1:2:1 combination. Flurbiprofen with sodium alginate, sodium CMC, and cross-linking agent at a concentration of 0.0% exhibits 100% release for up to 8.0 hours. F3 is a 1:2:2 combination. Flurbiprofen with sodium alginate, sodium CMC, and cross-linking agent at 0.0% demonstrates 100% release for up to 9.0 hours.

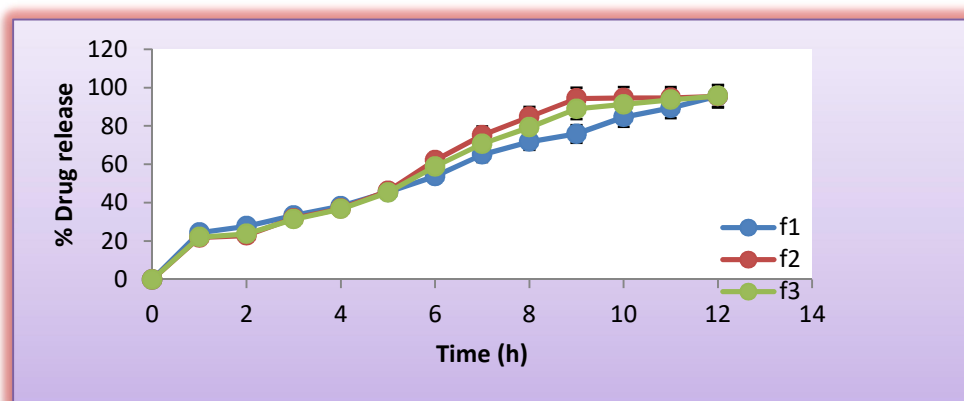
Formula F4 is a 1:2:0 combination. Flurbiprofen: Sodium alginate: Sodium CMC & cross-linking agent 20.0% demonstrates 100% release for up to 9.0 hours F5 is a 1:2:1 combination. Flurbiprofen: Sodium CMC & cross linking agent 20.0%

demonstrates 100% release for up to 10 hours F6 is a 1:2:2 combination. Flurbiprofen: 20.0% sodium alginate, 20.0% sodium CMC, and cross-linking agent exhibits 100% release for up to 10 hours.

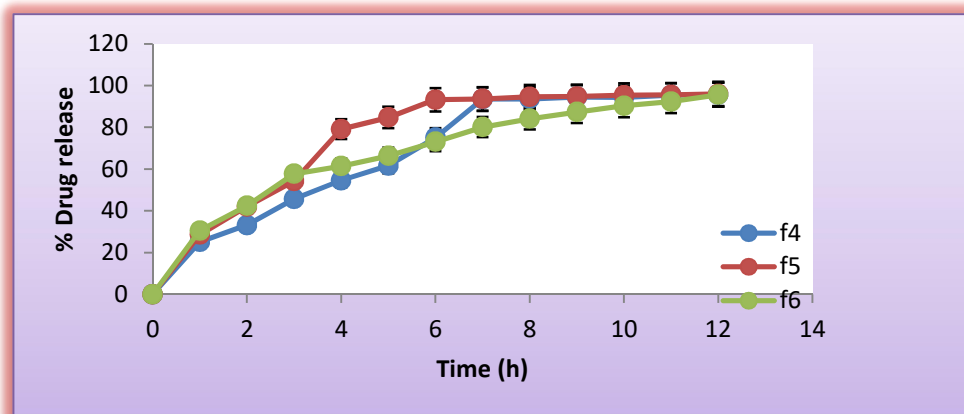
The formula F7 is combination of 1:2:0 Flurbiprofen : Sodium alginate : Sodium CMC & cross linking agent 30.0 % shows 100% release upto 7h F8 is combination of 1:2:1 Flurbiprofen : Sodium alginate : Sodium CMC & cross linking agent 30.0 % shows 100% release upto 11h F9 is combination of 1:2:2 Flurbiprofen : Sodium alginate : Sodium CMC & cross linking agent 30.0 % shows 100% release upto 12h. From above discussion it was clear that the as we increases the concentration of polymer & cross linking agent release of drug was retarded. From above discussion formulation f9 was the optimized 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	94.210 ±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	95.49±0.59	95.106 ±0.44	83.532 ±0.39	83.195 ±0.41
	11	95.66±0.54	95.553 ±0.61	95.173 ±1.87	88.544 ±0.24
	12	95.80±0.19	95.778 ±0.44	95.410 ±1.51	96.246 ±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

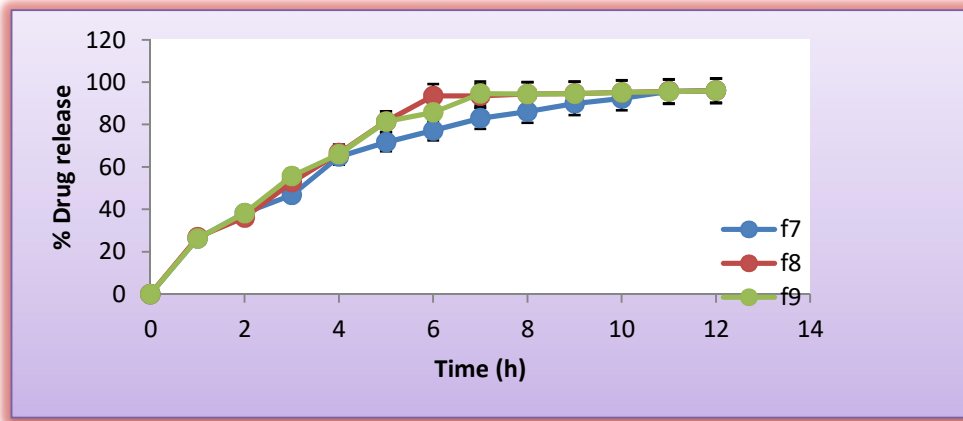


A.



B.





C.

Figure.1 Dissolution profile of A. F1-F3 B. F4-F6 C. F7-F9 formulations for factorial batches

**Yield of production, Actual drug content and encapsulation efficiency**

The production yields of microspheres prepared through the spray dry technique is found in the

range of 31-60%. Actual drug content and encapsulation efficiency or drug entrapment efficiency of the microspheres prepared by spray dry technique was found to be 61-93%.

**In vitromucoadhesive strength determination**

Table 4 In vitro data for measuring the strength of the mucoadhesive.

Sr.No.	Weight (Mg) (Microspheres) Remaining On Gastric Mucosa				% Mucoadhesive Strength
	3h	6h	9h	12h	
F9 (Spray dry)	43	40	35	31	75.00

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**Ex vivomucoadhesive strength determination**

Table 5 In vivo data for mucoadhesive strength determination

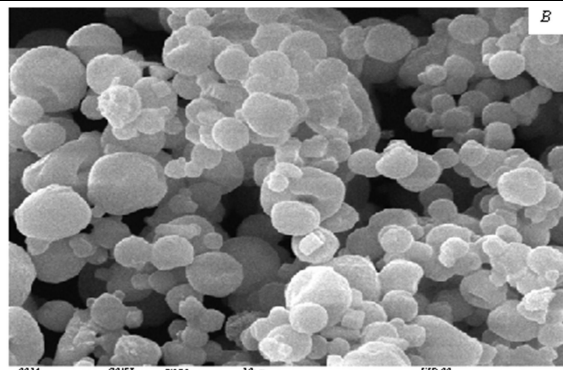
Sr.No	Weight (mg) of microspheres remaining on the rat stomach				% mucoadhesive strength
	Time (h)				
Optimized	0	4	8	12	
Spray dry	98.12	80.34	74.21	64.32	78.41

From both in vitro and in vivomucoadhesive strength determination tests it was cleared that in Spray dry technique optimized formulations shows 78.41 mucoadhesive strength respectively. Spray dry formulation comparing of 1:2:2 ratio of flurbiprofen: Sodium alginate: Sodium CMC it retard the release of drug up to 12 hours 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**

**Table 6 Size of optimized microspheres**

Formulations	Size In $\mu\text{m}$	Shape
SIZE in $\mu\text{m}$ (Spray Dry)	11.31-12.52	Almost spherical

**Summery & Conclusion**

The results so far obtained during this investigation encouraged us to derive the following conclusions The production yield of microspheres prepared by spry drying technique was found in the range of 31-60 % which is reliable

The encapsulation efficiency of microspheres prepared by spry drying technique was found in the range of 61-93% it is not 100% because during preparation of microspheres some drug lost in external media.

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.

The in vitroFlurbiprofen release data fitted to korsmeyer-peppas release model also shows zero order and higuchi model.

The in vitromucoadhesive strength of optimized formulations of spray drying technique were for F9 75.00% which shows good mucoadhesion.

The ex vivomucoadhesive strength of optimized formulations of spray drying technique were for F9 78.41% which shows good mucoadhesion.

The size of microspheres prepared by spray drying technique was found for F9 11.31-12.52 $\mu\text{m}$

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