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Mucoadhesive Pentoxyfylline Microsphere for Non-Invasive Nasal Drug Delivery

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Abstract: The aim of this study was to formulate and evaluate mucoadhesive sodium alginate microspheres for nasal administration of Pentoxifylline to avoid first-pass metabolism. Microspheres were prepared using an ionic gelation process using a 2^3-factorial design. We investigated the effects of several factors on particle size and *in vitro* mucoadhesion, including drug-to-polymer weight ratio, calcium chloride ($CaCl_2$) concentration, and cross-linking time. Particle size of the mucoadhesive microsphre was found in the 27.01 to 33.78 µm range, were the in-vitro mucoadhesive result showed in the range 76.14 to 87.58 %. The microspheres were characterized by SEM to study the shape and distribution of drugs within the microspheres. The surface morphology studied by SEM showed spherical shape and smooth surface of pentoxifylline sodium alginate loaded microsphere containing 2% w/v of Carbopol prepared by ionotropic gelation method. F6 formulation shows highest percentage of in-vitro diffusion 84.78 %. In vitro dissolution tests were performed in pH 6.2 phosphate buffer indicated non- Fickenian type of transport for the diffusion of drug from the Pentoxyfylline mucoadhesive microsphere. It has been shown that the Hixson-Crowell model best describes the release of Pentoxyfylline from Carbopol. The F6 formulation utilized use of the Hixson-Crowell diffusion model of drug release, which wasdetermined to be the model that best fit the data (r^2=0.9697). The formulation showed that the Fickian mechanism of drug release was acting when the n value was less than 0.5.

Keywords: Mucoadhesive microsphere; cross-linking time; SEM; Surface morphology

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1. Introduction

Conventional formulations of hemorheological agents are well absorbed from the gastrointestinal tract but undergo substantial first-pass hepatic metabolism. Its absolute oral bioavailability is approximately 25%. Therefore, multiple doses are recommended to maintain effective plasma concentrations. However, conventional dosage forms have shown disadvantages due to the inability to retain and localize the system within the gastrointestinal tract. Therefore, an alternative route of administration was decided. The nasal route has attracted the attention of many researchers and developers due to its high potential for drug delivery. The nasal cavity offers many advantages as a drug delivery site because it underlies a large surface area for absorption and a highly vascularized epithelial tissue [1,2] .

Mucoadhesive microcarriers systems are an interesting topic in the development of drug delivery systems to increase residence time at the site of application or absorption. Microspheres have excellent bioadhesive properties and readily swell when in contact with the nasal mucosa, thus increasing drug bioavailability and residence time after intranasal administration, and thus can be used for long-term drug localization.[3] The use of suitable mucoadhesive polymers on the surface of the microcarriers has other advantages

due to more intimate contact with the nasal mucosa. The result is efficient absorption, increased drug bioavailability, improved patient compliance, and targeting to the site of absorption [3, 4].

2. Material and Method:

Pentoxyfylline was obtained as a gift sample from Zydus, Ankleshwar, sodium al ginate procured from Yarrow Chemical, Mumbai, all other chemicals & reagents used in this investigation were of research grade.

2.1. Preparation of Pentoxyfylline sodium alginate microspheres:

Experimental designs were employed to prepare Pentoxyfylline microsphere. The details of factorial designs are shown in table 1. Microspheres were prepared using the ionotropic gelation method. The required amount of sodium alginate was accurately weighed and dissolved in distilled water using a mechanical stirrer. Drugs were added after a while. A mechanical stirrer was used to thoroughly mix the above solutions.

The solution was then sonicated for about 30 minutes to remove air bubbles. After sonication, the solution was left for 30 minutes. Using a 23-gauge syringe needle, the resulting solution was added dropwise to 50 mL of 8% calcium chloride ($CaCl_2$) solution containing 10% v/v acetic acid. The microspheres were washed three times with distilled water [5-7].

2.2. Experimental Design:

Table 1. 2^3 Factorial design of Pentoxyfylline microsphere.

Name	Units	Low	High	-alpha	+alpha
Sodium Alginate	Gm	1.95	2.05	1.92929	2.07071
Carbopol	Mg	450	550	429.289	570.711

*1% Pentoxyfylline use in all formulation

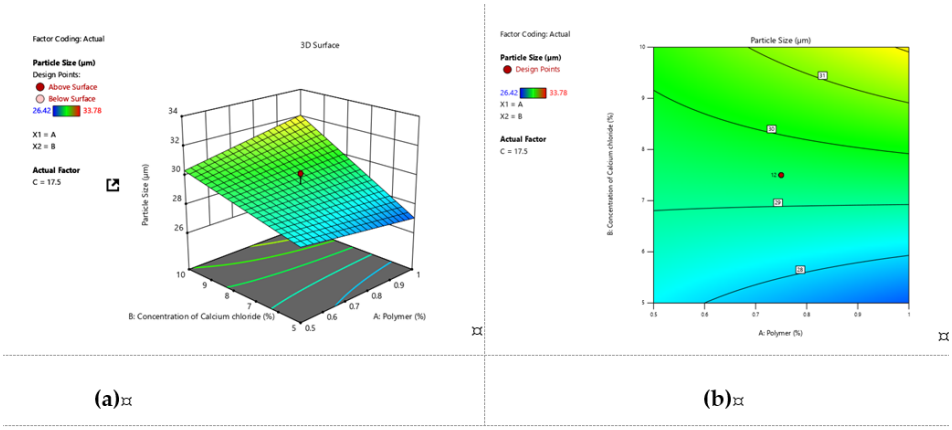
3. Result and Discussion:

3.1. Particle size:

Particle size determinations of microspheres from all the batches were performed, and the results, shown in Table 2, were found to be in the range of 27.01 to 33.78 μm. which is suitable for intranasal absorption. The figure 1.(a) and (b) depicates, the particle size of the microsphere increased as the polymer concentration increased, owing to an increase in polymer concentration, which increased the viscosity of the polymeric solution, and thus the microsphere with a larger particle size was formed. On this basis, it was decided to optimize the polymer concentration prior to preparing microspheres. As the polymer concentration increases, so does the concentration of $CaCl_2$, and increasing the time of cross-linking results in the formation of larger microspheres [8,9].

Table 2. Particle size of Pentoxyfylline microsphere.

Formulation Code	Particle size, μm
PM1	27.01±0.08
PM2	30.48±0.02
PM3	29.11±0.05
PM4	33.78±0.03
PM5	32.74±0.07
PM6	31.45±0.03



(a) **(b)**

Figure 1. Particle size of pentoxyfylline microsphere: (a) 3D graph of Particle size; (b) Contour graph of Particle size.

3.2. Surface morphology:

Surface morphology Figure 2, shows SEM photographs of pentoxifylline loaded sodium alginate microsphere. The surface morphology studied by SEM showed spherical shape and smooth surface of pentoxifylline sodium alginate loaded microsphere containing 2% w/v of Carbopol prepared by ionotropic gelation method. Whereas further increase in Carbopol concentration above 2% w/v leads to formation of aggregated, and form smaller and discrete particles [10].

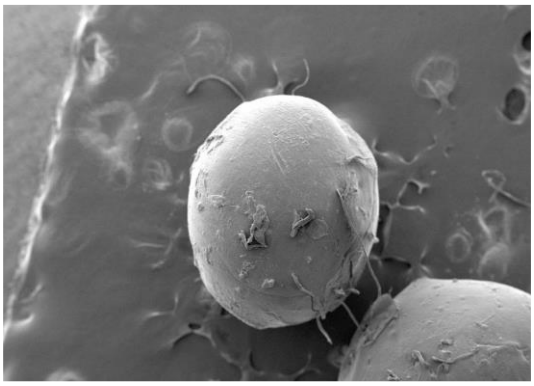


Figure 2. Scanning Electron Microscopy of Pentoxyfylline microsphere optimized Formulation.

3.3. Encapsulation efficacy:

Encapsulation efficacy was found to be in the range of 56.24 to 63.45%, which is shown in Table 3. Figure 3. (a) and (b) reveled that, the encapsulation efficacy was dependent on drug loading, concentration of polymer used and cross-linking time. The formulation loaded with high amount of drug showed higher encapsulations. Encapsulation efficacy decreases with an increase in the concentration of $CaCl_2$ and cross linking time [11,12].

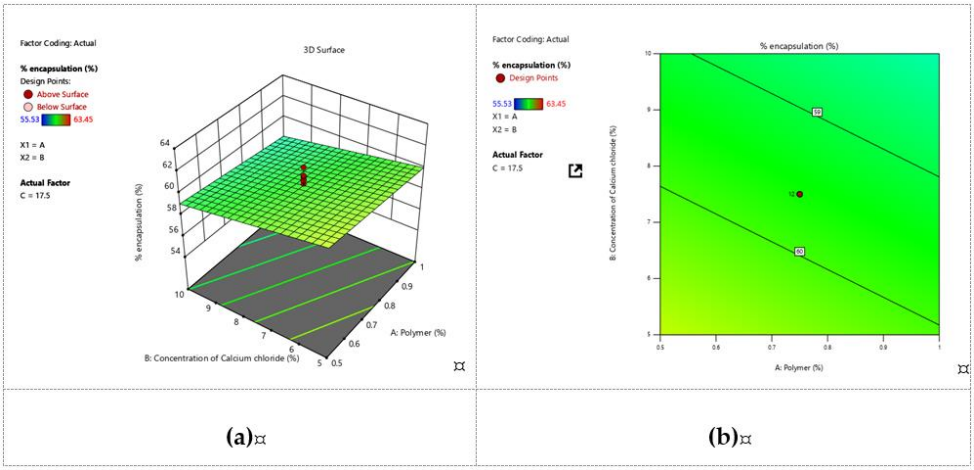


Figure 3. % Drug encapsulation efficacy of Pentoxyfylline microsphere: (a) 3D graph of % encapsulation; (b) Contour graph of % encapsulation.

Table 3. % Drug encapsulation of Pentoxyfylline microsphere.

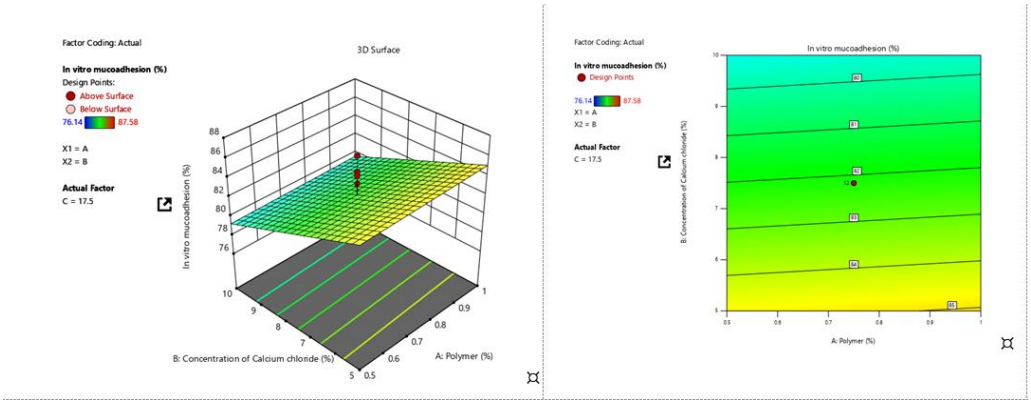
Formulation Code	% Drug encapsulation
PM1	58.63±0.10
PM2	56.24±0.04
PM3	59.75±0.08
PM4	63.45±0.06
PM5	59.27±0.07
PM6	60.45±0.02

3.4. In-vitro mucoadhesion:

In vitro mucoadhesion of all the batches was shown on table 4, and it was found that all the formulation batches were to be in the range of 76.14 to 87.58%. Figure 4 shows that increasing the polymer concentration ratio increases mucoadhesion due to a higher percentage of the polymer interacting with the mucosal surface [13].

Table 4. *In-vitro*mucoadhesion study of Pentoxyfylline microsphere.

Formulation Code	% in-vitro Mucoadhesion
PM1	78.15±0.07
PM2	76.14±0.08
PM3	80.85±0.04
PM4	87.58±0.06
PM5	85.63±0.07
PM6	84.12±0.01



(a) **(b)**

Figure 4. *In-vitro* mucoadhesion study of Pentoxyfylline microsphere: (a) 3D graph of in-vitro mucoadhesion; (b) Coutour graph of in-vitro mucoadhesion.

3.5. In-Vitro Dissolution Study:

A drug release study was conducted using Franz diffusion cells, which have donor and receptor compartments separated by a dialysis membrane. Before dispersing the sample equivalent to 20 mg of drug onto the donor compartment, the dialysis membrane was carefully equilibrated with phosphate buffer at 6.6 pH. The donor compartment is filled with simulated nasal fluid, while the receptor compartment is filled with phosphate buffer at 6.6 pH. pH of nasal cavity is within the pH range, and the solution temperature is kept at 37±0.5°C. To maintain the sink condition, 1 ml of sample was withdrawn and replaced with a fresh sample after a predetermined interval, and samples were spectrophotometrically measured at 274 nm using a UV-spectrophotometer [14,15]. % drug release were shows into table 5.

Table 5. % Drug release study of Pentoxifylline microsphere.

	Drug Release (%)					
Time in Hrs.	**PM1**	**PM2**	**PM3**	**PM4**	**PM5**	**PM6**
0	0	0	0	0	0	0
1	1.89±0.05	0.71±0.04	0.23±0.01	0.23±0.07	1.89±0.05	4.02±0.023
2	13.27±0.09	3.79±0.03	7.1±0.05	2.6±0.05	7.11±0.07	12.81±0.05
3	20.44±0.08	9.49±0.07	15.9±0.04	4.27±0.06	20.4±0.05	30.86±0.09
4	27.11±0.04	18.05±0.05	19.5±0.01	11.39±0.05	35.4±0.07	38.3±0.08
5	31.88±0.03	24.02±0.08	25.21±0.05	20.66±0.03	42.82±0.05	48.53±0.02
6	39.96±0.05	28.55±0.09	30.92±0.05	32.79±0.05	54.23±0.08	61.84±0.07
7	46.16±0.07	34.73±0.05	31.9±0.04	44.23±0.05	66.85±0.07	69.26±0.06
8	53.3±0.08	51.82±0.07	38.07±0.03	54.24±0.04	69.29±0.04	75.69±0.04
9	59.26±0.03	57.36±0.05	43.07±0.02	60.45±0.05	75.93±0.06	79.53±0.03
10	65.22±0.02	60.71±0.04	44.76±0.05	65.7±0.07	78.81±0.04	82.15±0.05
11	67.62±0.07	63.8±0.05	46.66±0.04	72.36±0.06	80.25±0.07	84.05±0.03
12	68.58±0.02	65.01±0.07	47.86±0.07	72.87±0.05	80.96±0.08	84.78±0.01

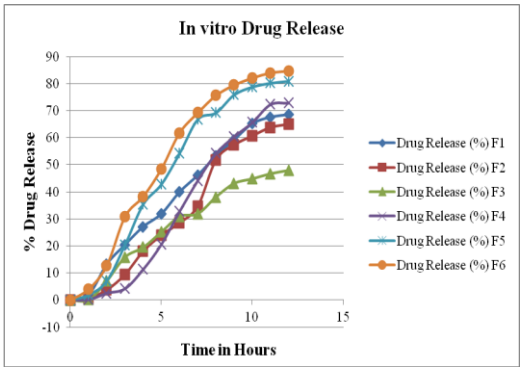


Figure 5. % *In-vitro* Drug Release profile.

3.6. Kinetics of Drug Release:

We investigated the drug release mechanism by applying multiple kinetic modelto study the drug release of the optimized formulations was expressed in figure 6-10. It has been established that the Hixson-Crowell model is suitable for explaining the mechanism by which Sodium Alginate, 2% Carbopol release of Pentoxyfylline.

F6 formulation followed Hixson-Crowell diffusion model of drug release (r^2=0.9697) & it was best fitted to Hixson-Crowell diffusion model. Formulation indicated the Fickian mechanism of drug release when the *n* value was less than 0.5. Details of kinetic study were shown in table 6 [16]).

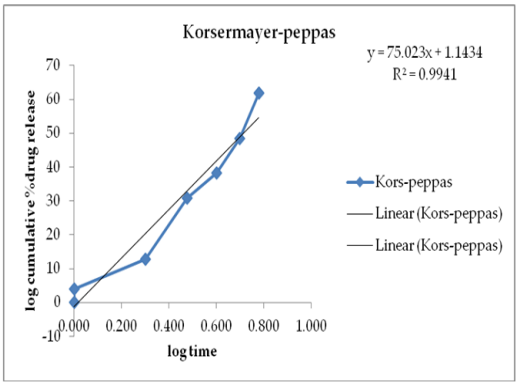


Figure 6. Kinetics of drugs release by Korsemayer-peppas.

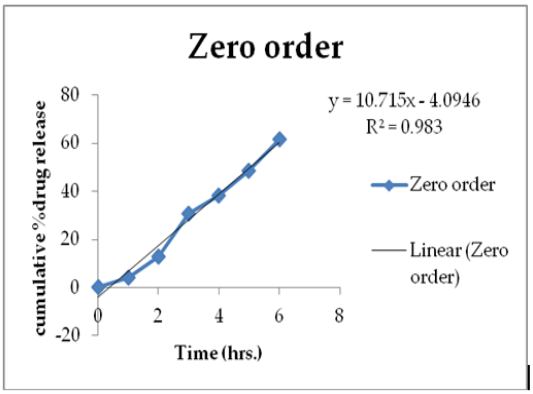


Figure 7. Zero Order Drug Release Kinetics study of Optimized Formulation.

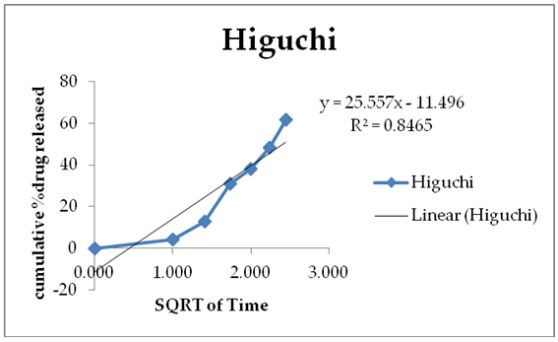


Figure 8. Higuchi Drug Release Kinetics study of Optimized Formulation.

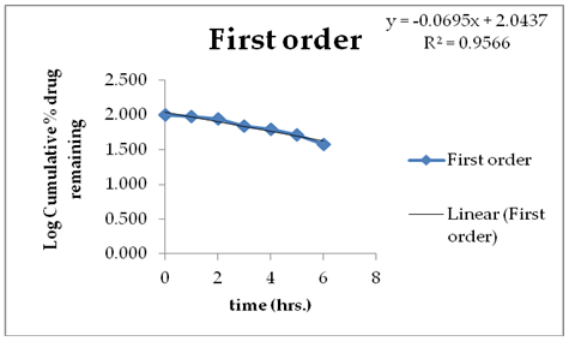


Figure 9. First Order Drug Release Kinetics study of Optimized Formulation.

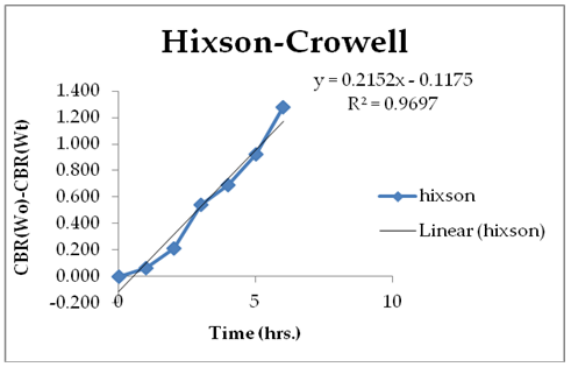


Figure 10. Hixson-Crowell Drug Release Kinetics study of Optimized Formulation.

Table 6. Kinetics model.

	Zero order	First order	Higuchi	Korsermay-er-Peppas	Hixson-Crowell
R^2	0.7925	0.9566	0.8465	0.952	0.9697
K	61.156	2.044	25.55	71.536	-
N	-	-	-	-	0.2152

4. CONCLUSION:

Mucoadhesive Pentoxifylline microsphere by ion induced gelation method was successfully prepared. Carbopol was used as a mucoadhesive polymer.A 2^3 experimental design was employed to identify optimal formulation parameters for a microsphere preparation with the minimum value of particle size and maximum value of in vitro mucoadhesion. From the mathematical models generated, an optimal formulation comprising of drug: polymer ratio (1:2), $CaCl_2$ concentration (5-10 %) and cross-linking time (10-15 min) was identified to provide desired values for particle size 27.01 to 33.78 µm and in vitro mucoadhesion 76.14 to 87.58 %. The surface morphology studied by SEM showed spherical shape and smooth surface of pentoxifylline sodium alginate loaded

microsphere containing 2% w/v of Carbopol. In vitro dissolution tests were performed in pH 6.2 phosphate buffer indicated Fickenian type of transport for the diffusion of drug from the Pentoxyfylline mucoadhesive microsphere.

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Conflicts of Interest: The authors declare no conflict of interest.

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