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PREPARATION AND EVALUATION OF ZIDOVUDINE MUCOADHESIVE MICROSPHERES

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ABSTRACT

Zidovudine mucoadhesive microspheres were studied using carbopol, sodium alginate and mucilage obtained from drumstick as mucoadhesive polymers. Microspheres were prepared at 1:2 and 1:3 core coat ratios by conventional orifice-ionic gelation method and are evaluated for drug content, encapsulation efficiency, *in vitro* wash off test and *in vitro* drug dissolution. Microspheres were found to be discrete, spherical and free flowing with uniform drug distribution. The encapsulation efficiency increases as the concentration of sodium alginate increases. Microspheres prepared using drumstick mucilage shows maximum drug release over the period of 12hr when compared to microspheres prepared using chitosan and carbopol. The dissolution data were subjected for model fitting using dissolution software PCP DISSO V.3, in each case best fit model was found to be Korsemeyer's peppas and exponential 'n' value was greater than 0.45, indicate the drug release from microspheres was non fickian i.e., swelling followed by erosion mechanism.

KEYWORDS: Zidovudine; Sodium alginate; Carbopol; Drumstick; Chitosan; in *vitro* dissolution.

INTRODUCTION

The main goal of drug delivery systems is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for a prolonged period. The pointing of the goal is towards the two main aspects regarding drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement means targeting a drug to a specific organ or a tissue while temporal delivery refers to controlling the rate of drug delivery to that specific organ or a tissue.[1] The conventional dosage systems can give rise to alternative periods of inefficacy or toxicity. These difficulties have been called for the development of new administration techniques for bioactive compounds, directed towards attaining the steady state plasma concentration.[2] Primary objectives of controlled drug delivery system are to ensure the safety and to improve efficiency of drug as well as patient compliance. This is achieved by better control over plasma drug level and less frequent dosing. Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner.[3] Microspheres in general, have the potential to be used for targeted and controlled release drug delivery, but coupling of mucoadhesive properties to microspheres has additional advantages, e.g. efficient absorption and enhanced bioavailability of drug due to a high surface to volume ratio and much more intimate contact with the mucus layer.[4] Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.[5,6]

Acquired immunodeficiency syndrome (AIDS), caused by human immune deficiency virus (HIV) and is an immune suppressive disease results in life threatening opportunistic infections and malignancies.[7,8] Zidovudine originally synthesized in 1964 as a potential anticancer agent, was approved as first antiretroviral agent ever in 1987 for the treatment of AIDS.[9,10] However along with its therapeutic effectiveness, zidovudine is also associated with certain limitations like poor bioavailability, dose dependent hematological toxicity, short biological half-life, low therapeutic index etc. Administration of antiviral agents like zidovudine is required chronically or possibly for the life time of the patient. In case of oral route the dose of zidovudine ranges from 3mg/kg to 10mg/kg body weight at every four hours interval to maintain the constant therapeutic blood levels. These frequent dosing intervals are undesirable in terms of patient compliance and

generating toxicity (associated with excessive plasma levels) immediately after oral or intravenous administrations. In order to succeed in an effective therapy for AIDS, it is crucial to maintain the systemic drug concentration consistently above their target antiretroviral concentration throughout the course of their treatment without much oscillation in its plasma levels, which can be done by formulating controlled or sustained release dosage forms of zidovudine. Therefore, zidovudine is an ideal candidate for sustained release microsphere formulation, resulting in more reproducible drug absorption and reducing the dosing frequency, thereby improving patient compliance as compared to immediate release dosage forms. Literature survey suggests different natural biodegradable polymers used in sustained release microcapsules of zidovudine.[11,17]

Thus, in present study an attempt was made to prepare and evaluate mucoadhesive microspheres of zidovudine using synthetic polymer carbopol, natural mucoadhesive polymer chitosan and experimental natural mucilage prepared from drumstick.

MATERIALS AND METHODS

Materials: Zidovudine obtained from Hetero Drugs Private Ltd, sodium alginate, carbopol, chitosan and calcium chloride were purchased from LNR chemicals, Yarrow chemicals, central house and SD fine chemicals Mumbai respectively. Drumstick was obtained from local market.

Methods

Preparation of drumstick mucilage: The 50g of dried drumstick powder was soaked in 150ml distilled water for 24 h in a round bottom flask. Further, it was boiled for 1 h under reflux with occasional stirring and kept aside for 2 h for the release of mucilage into water. The material was filtered through a muslin bag and hot distilled water (25 ml) was added through the sides of the marc and squeezed well in order to remove the mucilage completely. Concentrate the aqueous filtrate to 1/3rd of its volume then to this add equal volume of ethanol to precipitate the mucilage. The obtained precipitate is kept in a refrigerator for overnight for effective settling. After complete settling of the precipitate it was filtered and dried the residue at 37º C. The obtained dried powder was subjected for identification test to confirm its identity. The prepared drumstick mucilage powder was stored in well closed container for further study.

Preparation of mucoadhesive microspheres

Orifice ionic gelation method:[18-19] Orifice ionic gelation is a method to prepare microspheres using combination of Ca^{2+}as cationic components and alginate as anion.[20] Sodium alginate and mucoadhesive polymer chitosan were dissolved in purified water (10ml) separately. Then both the solutions were mixed to form homogeneous polymer solution. The drug was added to the polymer solution and mixed thoroughly with help of pestle and mortar to form viscous dispersion. The resulting dispersion was added drop wise into 10% w/v calcium chloride solution (100ml) through a syringe with needle (size no 21) with continuous stirring at 500 rpm. The added droplets were retained in the calcium chloride solution for 15 minutes to produce spherical rigid microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45^{0}C for 12 hours and stored in desiccators. Similarly sodium alginate/drumstick mucilage microspheres and sodium alginate/carbopol microspheres were prepared. The different formulae of mucoadhesive microspheres are given in table 1.

Table 1: Formulae of zidovudine mucoadhesive microspheres.

Batches	Core: Coat	Zidovudine	Sodium alginate	Chitosan	Carbopol	Drumstick
B-1	1:2(3:1)	500	750	250	----	----
B-2	1:3(3:1)	500	1125	375	----	----
B-3	1:2(3:1)	500	750	----	250	----
B-4	1:3(3:1)	500	1125	----	375	----
B-5	1:2(3:1)	500	750	----	----	250
B-6	1:3(3:1)	500	1125	----	----	375

Evaluation

Production yield: The dried microspheres of each batch are weighed separately and percentage yield is calculated by using following equation,

$$\text{Production yeild} = \frac{\text{Practical weight}}{\text{Theoretical weight(polymer + drug)}} \times 100$$

Drug content: Mucoadhesive microspheres equivalent to 50 mg zidovudine were weighed and powdered. This was dissolved or extracted in methanol in 100 ml volumetric flask and made up to volume. The solution was shaken occasionally for 1h and filtered. From this 1ml of solution was diluted up to 100 ml with phosphate buffer pH 7.4 in 100 ml volumetric flask. The drug content was analyzed by measuring absorbance at 266nm in a UV spectrophotometer using phosphate buffer pH 7.4 as blank. The studies were carried out in triplicate.

Encapsulation efficiency: 100 mg of mucoadhesive microspheres were accurately weighed. They were powdered and extracted with 100 ml of methanol. Further it was serially diluted with phosphate buffer pH 7.4. The resulting solution was analysed for zidovudine drug content by measuring absorbance in a UV-

spectrophotometer at 266 nm using phosphate buffer pH 7.4 as blank. The studies were carried out in triplicate. Encapsulation efficiency (%) was calculated using the formula.

$$\text{Encapsulation effeciency} = \frac{\text{Actual amount of drug encapsulated}}{\text{Theoretical drug content}} \times 100$$

FTIR spectral studies: The compatibility between pure drug and polymers were detected by IR spectra obtained on Perkin Elmer 1600 series, (USA). The pellets were prepared on KBr–press. To prepare the pellets, a few mg of the mucoadhesive microspheres were ground together in a mortar with about 100 times quantity of KBr. The finely ground powder was introduced into a stainless steel die. The powder was then pressed in the die between polished stainless steel anvils at a pressure of about 10t/in2. The spectras were recorded over the wave number range of 4000 to 500 cm-1.

Scanning electron microscopy: The particle size, shape and surface morphology of microspheres were examined by scanning electron microscopy (SEM). Microspheres were fixed on aluminum studs and coated with gold using a sputter coater SC 502, under Vacuum [0.1 mm Hg]. The microspheres were then analyzed by scanning electron microscopy (SEM) [Model JSM-840 A, Joel. Japan].

Particle size: Particle size and size distribution of zidovudine mucoadhesive microspheres were measured by sieve analysis method. Different sizes in a batch are separated by sieving using a range of standard sieves 10/22, 22/44 and the amounts retained on different sieves were weighed. Studies were carried out in triplicate. The average sizes of the microspheres were calculated by using the equation.

$$D_{Avg} = \frac{\sum Xifi}{fi}$$

Where, X_i- Mean size range;
F_i -Percentage material retained on the smaller sieve size range.

Swelling index: Microspheres equivalent to 50mg were placed in glass vial containing 10ml of phosphate buffer pH 7.4 at 37°C±0.5°C in the incubator with occasional shaking. The microspheres were removed periodically, blotted with filter paper and observed for weight changes. The swelling index was calculated by,

$$\text{Swelling index} = \frac{We - Wo}{Wo} \times 100$$

Where, We - Weight of swollen microspheres;
Wo- Weight of dried microspheres.

***In vitro* wash-off test:** The everted rat intestinal mucosa of 1cm^2 area was tied to a glass slide (3X1 inch) with thread. Microspheres were spread (~50) onto wet and rinsed tissue specimen. The slide was then hung onto grooves of the USP tablet disintegrating test apparatus. The tissue specimen was given a slow, regular up-and-down movement in a beaker containing phosphate buffer pH 7.4 (500ml) at 37°C. The number of microspheres still adhering to tissue was calculated at the end of 30min, 1h and at the hourly interval up to 8h.

***In vitro* dissolution study:** The amount zidovudine release from mucoadhesive microspheres was investigated by using USP type I basket apparatus and 900ml of phosphate buffer pH 7.4 used as dissolution medium. Mucoadhesive microspheres equivalent to 50 mg of zidovudine filled in hard gelatin capsules were used for the study. A speed of 50 rpm and temperature of 37 ± 0.5^{o}C was maintained throughout the experiment. At fixed intervals viz., 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h, aliquots (5 ml) was withdrawn and replaced with fresh dissolution media to maintain the sink condition. The concentration of drug released at different time intervals was then determined by measuring the absorbance at 266 nm against blank. The studies were carried out in triplicate. The *in vitro* dissolution data of mucoadhesive microspheres were tabulated and calculated by using dissolution software viz., PCP DISSO V3.0.

RESULTS AND DISCUSSION

The mucoadhesive microspheres of zidovudine were prepared by orifice-ionic gelation method using sodium alginate: mucoadhesive polymers. The percentage production yield was found to be in the range of 65.45±1.43 to 82.01±0.49 and is manageable with little loss of drug during the formulation stage. The drug content was found to be in the range of 97.23±1.83 to 99.08±0.49, low SD and CV value indicates uniform distribution of drug within the various batches of microspheres prepared. The drug encapsulation efficiency was found to be in the range of 68.40±0.58 to 80.01±0.65 and it is increases with increase in the concentration of sodium alginate, the mucoadhesive microspheres prepared with carbopol shows higher drug encapsulation efficiency than the mucoadhesive microspheres prepared with chitosan and drumstick mucilage. This could be attributed due to formation of larger microspheres with increasing concentration of sodium alginate, thus entrapping more amount of drug table 2.

Table 2: Evaluation data of zidovudine mucoadhesive microspheres.

Batches	% Yield ±SD	% Drug content ±SD	% Encapsulation efficiency ±SD
B-1	74.34 ±1.12	98.01 ±1.02	68.40 ±0.58
B-2	75.21 ±0.46	98.49 ±0.82	72.58 ±0.69
B-3	79.53 ±0.85	98.68 ±0.67	76.23 ±1.25
B-4	82.01 ±0.49	99.08 ±1.23	80.01 ±0.65
B-5	65.45 ±1.43	97.23 ±1.83	60.44 ±1.42
B-6	71.25 ±1.23	98.56 ±0.95	66.21 ±1.26

The study of FTIR spectra of zidovudine loaded mucoadhesive microspheres as per shown in figure 1, demonstrated that the characteristic peaks for C–Br stretch alkyl halides, C–N stretch aliphatic amines, C–N stretch aromatic amines, C=O stretch carbonyls, O–H stretch, H–bonded alcohols, phenols were appeared at 563 cm^{-1}, 1101 cm^{-1}, 1269 cm^{-1}, 1672 cm^{-1} and 3419 cm^{-1} respectively. The absorption peaks were almost similar to those obtained from the pure drug and fabricated mucoadhesive microspheres. Hence FTIR study confirms that drug was compatible with the polymer and there is no drug polymer interaction.

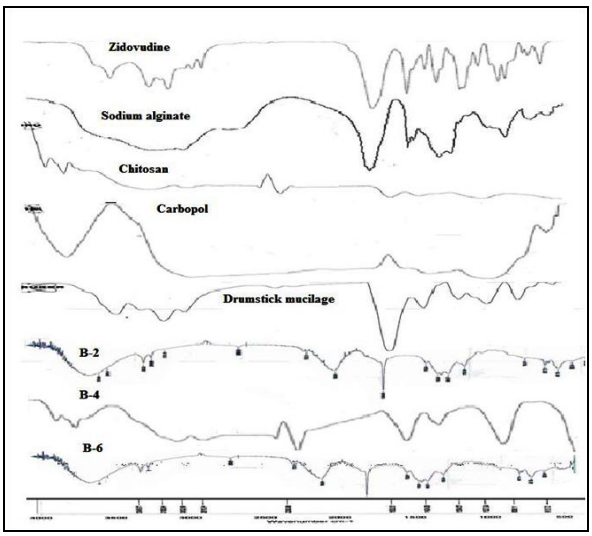

Figure 1: Comparative FTIR spectra of zidovudine, sodium alginate, chitosan, carbopol, drumstick mucilage B-2, B-4 and B-6 mucoadhesive microspheres.

The microspheres were distributed in the range of 639.36µm to 714.18 µm and the size of microspheres is depending upon concentration of sodium alginate used in the formulation. The increase in size of microspheres was observed with increase in concentration of sodium alginate. This could be due to increase in viscosity of the polymeric dispersion, which eventually lead to formation of bigger particle during ionic gelation. The average sizes of different batches are given in table 3 with its histogram in figure 2.

Table 3: Size analysis of zidovudine mucoadhesive microspheres

Batches	B-1	B-2	B-3	B-4	B-5	B-6
Size Range (D Avg)µ	662.4	674.4	639.6	659.5	688.2	700

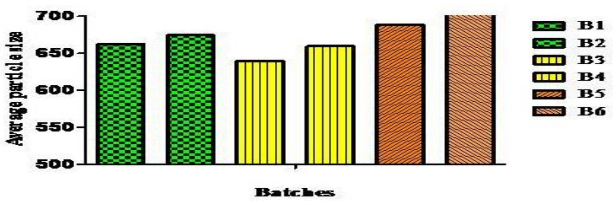

Figure 2: Histogram of particle size analysis of zidovudine mucoadhesive microspheres.

The SEM photographs of the optimized zidovudine mucoadhesive microspheres formulation (B-2, B-4 and B-6) are taken at different magnification are depicted in the figure 4 and digital photographs in figure 3. The SEM photographs revealed that the zidovudine microspheres were discrete and spherical in shape and the outer surface of microspheres was coarse rough texture, with few pores, mild cracks and completely covered with coat materials which could be due to the surface association of zidovudine with sodium alginate.

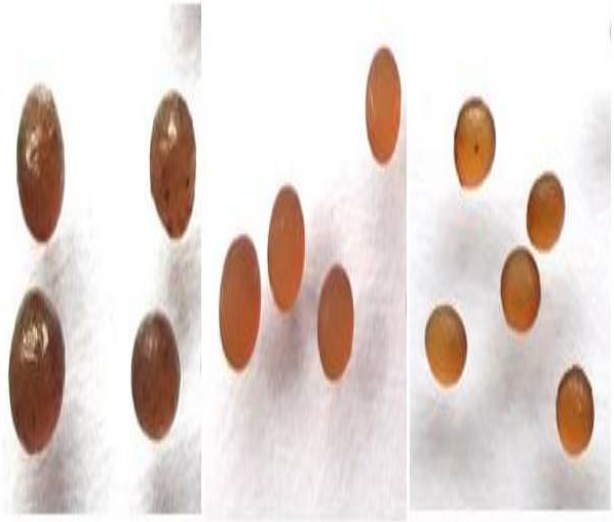

Figure 3: Digital photographs of B-2, B-4 and B-6 optimized mucoadhesive microspheres.

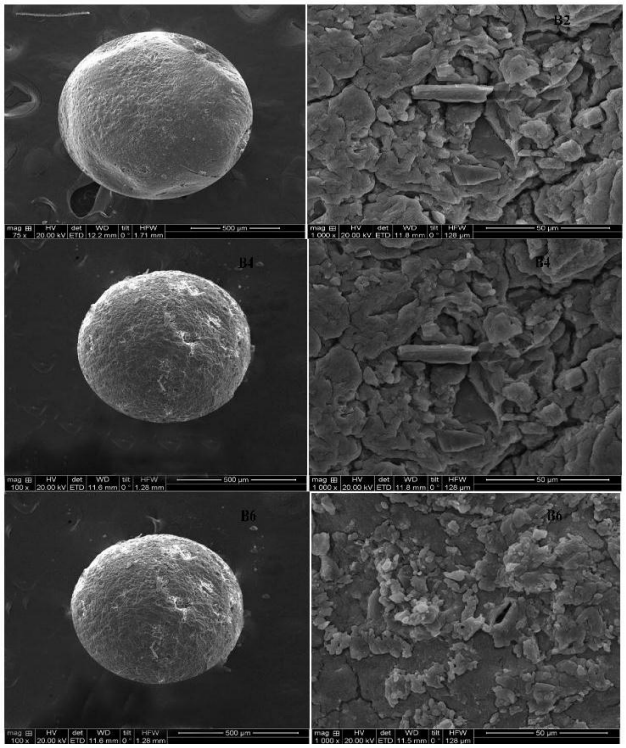

Figure 4: SEM photographs optimized mucoadhesive microspheres.

The swelling ratio depends upon concentration of polymer and type of mucoadhesive polymer used in the formulation. Swelling ratio shows direct relationship with sodium alginate concentration and it is increased with increasing in the concentration of sodium alginate. The relative swelling index data are given in table 4.

Table 4: Relative swelling index data of mucoadhesive microspheres.

Time (in hr)	B-1		B-2		B-3		B-4		B-5		B-6	
	Wt. (mg)	R.S	Wt. (mg)	R.S	Wt. (mg)	R.S	Wt. (mg)	R.S	Wt. (mg)	R.S	Wt. (mg)	R.S
0	100	0	100	0	100	0	100	0	100	0	100	0
0.5	123	0.23	130	0.3	142	0.42	154	0.54	135	0.35	146	0.46
1.0	130	0.3	144	0.44	159	0.59	190	0.90	173	0.73	181	0.81
1.3	178	0.78	183	0.83	199	0.99	246	1.46	214	1.14	222	1.22
2.0	210	1.1	226	1.26	246	1.46	309	2.09	291	1.91	306	2.06
3.0	250	1.5	269	1.69	301	2.01	328	2.28	346	2.46	359	2.59
4.0	289	1.86	321	2.21	383	2.83	386	2.86	414	3.14	430	3.30
5.0	300	2.0	368	2.68	406	3.06	419	3.19	463	3.63	494	3.94
6.0	314	2.14	425	3.25	450	3.50	461	3.61	510	4.10	527	4.27

The mucoadhesion is a phenomenon in which two materials, at least one of which is biological are held together by means of interfacial force. The *in vitro* mucoadhesion data of mucoadhesive microspheres carried out with everted rat intestinal mucosa in presence of phosphate buffer pH 7.4. The percentage of microspheres retained on everted intestinal mucosa after 6 h was found in the range of 40 to 56%. The *in vitro* wash-off test results indicates that concentration and type of mucoadhesive polymer show little difference in the mucoadhesive property. Chitosan retained more number of microspheres than carbopol and drumstick mucilage table 5.

Table 5*: In Vitro* wash off test of zidovudine mucoadhesive microspheres.

Time(in hr)	B-1		B-2		B-3		B-4		B-5		B-6	
	No.	%	No	%	No	%	No	%	No	%	No	%
0	50	0	50	0	50	0	50	0	50	0	50	0
0.5	48	96	49	98	48	96	48	96	47	94	49	98
1.0	46	92	46	82	45	90	46	92	44	88	45	90
2.0	42	84	44	88	41	82	43	86	40	80	41	82
3.0	39	78	41	82	36	72	40	80	37	74	36	72
4.0	35	70	37	74	31	62	34	68	33	66	30	60
5.0	29	58	32	64	26	52	28	56	26	52	25	50
6.0	24	48	26	56	20	40	21	42	20	40	20	40
7.0	20	40	21	42	16	32	14	28	14	28	15	30
8.0	17	34	18	36	10	20	12	24	09	18	11	22

***In vitro* dissolution studies:** The cumulative drug release from the mucoadhesive microspheres were polymer dependent. Microspheres prepared with sod alginate: carbopol at both ratios shows lesser drug release than the sod alginate: chitosan which intern less than the sod alginate: drumstick mucilage. The *in vitro* dissolution data and profiles were given in table 6, 7 and profile in figure 5. The drug release decreases with increasing amount of mucoadhesive polymer the reason may be the higher proportion of polymer and mucilage which provide more gel strength and longer diffusion path length compared to smaller proportion of polymer and mucilage. In mucoadhesive microspheres prepared with mucilage isolated from natural sources the release rate was maximum at low concentration of coating material and as the concentration increased the release rate was decreased. It is mainly attributed to the influence of swelling property on the release of the drug from the microspheres. Mucoadhesive microspheres prepared with drumstick mucilage shows greater drug release when compared to microspheres prepared by chitosan while lesser than microspheres prepared by using carbopol. The dissolution data were subjected for model fitting using dissolution software PCP DISSO V.3. In all the cases the best fit model was found to be Korsemeyer's peppas with exponential 'n' value was greater than 0.45 indicating the release was non-fickian i.e., swelling and erosion mechanism.

Table 6: *In vitro* dissolution data of zidovudine mucoadhesive microspheres.

	Cumulative percentage drug released ± SD					
Time (hr)	**B-1**	**B-2**	**B-3**	**B-4**	**B-5**	**B-6**
0.25	5.38 ± 0.45	4.86 ± 0.48	4.21 ± 0.22	4.12 ± 0.59	5.60 ± 1.23	4.34 ± 0.22
0.5	9.43 ± 0.60	8.78 ± 0.58	8.78 ± 0.78	7.22 ± 0.78	9.91 ± 0.58	7.61 ± 1.03
0.75	12.99 ± 0.81	12.34 ± 1.01	12.36 ± 0.39	9.73 ± 0.82	14.68 ± 0.65	13.49 ± 0.78
1	17.73 ± 0.99	17.47 ±1.59	15.26 ± 0.59	12.38 ± 0.99	18.66 ± 0.98	16.81 ± 0.60
1.5	22.50 ± 0.61	23.01 ± 0.81	18.84 ± 0.45	19.32 ± 0.46	24.21 ± 0.36	21.32 ± 0.6
2	26.52 ± 1.48	29.76 ± 0.41	22.84 ± 0.81	24.75 ± 0.61	29.79 ± 0.45	25.85 ± 0.38
2.5	30.82 ± 1.0	34.59 ± 0.60	28.81 ± 0.59	28.78 ± 0.58	34.63 ± 0.98	32.48 ± 0.81
3	35.01 ± 0.25	39.06 ± 0.61	32.86 ± 0.59	35.04 ± 1.05	39.10 ± 0.67	36.64 ± 0.39
4	44.94 ± 0.81	45.51 ± 1.08	41.60 ± 0.81	42.11 ± 0.84	45.54 ± 0.96	43.76 ± 0.61
5	54.14 ± 1.28	52.76 ± 1.11	48.97 ± 0.82	48.31 ± 0.38	54.8 ± 0.78	50.74 ± 1.04
6	63.90 ± 1.59	58.89 ± 0.99	57.15 ± 0.40	55.19 ± 1.01	61.26 ± 1.26	60.88 ± 0.80
8	69.70 ± 1.20	67.00 ± 0.84	65.25 ± 0.79	64.18 ± 0.79	72.50 ± 1.9	68.61 ± 0.23
10	80.20 ± 1.08	80.60 ± 0.31	77.02 ± 0.59	73.49 ± 0.79	82.23 ± 0.48	78.85 ± 0.97
12	91.15 ± 1.12	90.38 ± 1.01	87.25 ± 0.97	85.43 ± 0.79	98.25 ± 0.32	93.29 ± 0.82

Table 7: Model fitting data of zidovudine mucoadhesive microspheres.

Models	B-1	B-2	B-3	B-4	B-5	B-6
Zero order	0.9670	0.9612	0.9533	0.9596	0.9516	0.9427
1st order	0.9857	0.9905	0.9007	0.9632	0.9833	0.9840
Matrix	0.9709	0.9720	0.9797	0.9746	0.9767	0.9821
Hix. Crow	0.9964	0.9955	0.9732	0.99000	0.9947	0.9931
Peppas	0.9970	0.9967	0.9974	0.9943	0.9976	0.9947
n	0.7578	0.7922	0.7115	0.7967	0.7266	0.7413

k	14.085	13.095	17.157	14.7942	16.0183	15.7910
Best fit	Peppas	Peppas	Peppas	Peppas	Peppas	Peppas

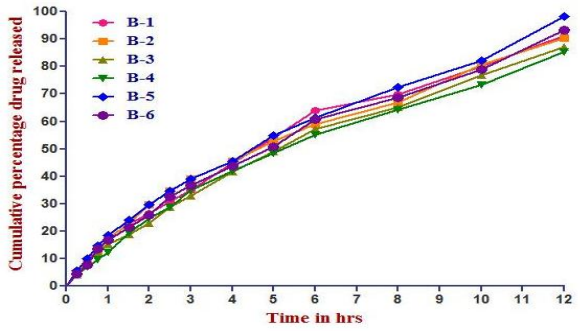

Figure 5: *In vitro* dissolution profiles of zidovudine mucoadhesive microspheres.

CONCLUSION

Zidovudine mucoadhesive microspheres were conveniently prepared by orifice-ionic gelation method using sodium alginate in combination with drumstick mucilage, chitosan and carbopol for the controlled release of zidovudine over the period of 12 hrs. The swelling of microsphere and drug release depends upon the polymer concentration. The best fit model was found to be Korsemeyer's peppas in all the batches prepared with exponential 'n' was greater than 0.45, indicating non fickian i.e., swelling and erosion mechanism. Thus, it can be concluded that orifice-ionic gelation technique could be used to prepare zidovudine mucoadhesive microspheres for oral controlled drug delivery.

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