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FORMULATION AND EVUALATION OF BUCCAL BIOADHESIVE TABLET OF ACYCLOVIR BY USING SPRAY-DRIED AMIOCA STARCH/CARBOPOL 940P MIXTURE

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ABSTRACT

The purpose of this study was to design and optimize an oral controlled release acyclovir mucoadhesive tablet, in term of its drug release and mucoadhesive strength. In the present study, spray-dried Amioca starch/Carbopol 940P mixtures were evaluated as potential buccal bioadhesive tablets. Carbopol (C 940P) concentrations from 5 to 45% were tested. All spray-dried mixtures showed a comparable or better bioadhesive capacity. The bioadhesive capacities of Amioca/Carbopol 940P mixtures were improved by spray-drying. All spray-dried mixtures showed significantly higher work of adhesion values compared to their equivalent physical mixtures. The influence of Carbopol concentration on the in Ex-vivo adhesion time of placebo tablets and in vitro acyclovir release was tested. The ratio Amioca/C 940P 75/25 showed the longest in Ex-vivo adhesion time (16+/-8.5 h). The mixtures containing between 15 and 30% C 974P could all sustain the in vitro acyclovir release over 15 h. The drug loading capacity of a spray-dried mixture containing 25% C 940P was investigated in vitro using acyclovir. The spray-dried mixture could be loaded with 70% drug without loosing its in Ex- vivo bioadhesive and pharmacokinetic properties It can be concluded that by formulating mucoadhesive tablets of acyclovir, its complete release can be ensured prior to absorption window and hence the problem of incomplete drug release and erratic absorption could be solved by increasing the retention of drug in oral cavity for a longer duration.

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Keywords *Drug release, Acyclovir, spray-dried Amioca starch/Carbopol 940P mixtures, Buccoadhesive tablet.*

INTRODUCTION

Nowadays one of the drug delivery system take over the all other drug delivery system because they have more merit in which oral drug delivery are very commone.For systemic delivery, the oral route has been the preferred route of administration for many systemically active drugs due to the ease of administration, patient compliance systems have been developed to act as drug reservoir, from which active substances can predetermined and controlled rate[1]. The progress delivery systems are available. However, it is a the real *in vivo* time of release with solid oral most feasible approaches for achieving a in the oral is to control the oral residence time. Dosage forms with a prolonged oral residence, provide new and important therapeutic options time over which the drug may be released. Thus, they prolong dosing intervals and improve patient compliance[2]. This is especially applicable to delivery of sparingly soluble and insoluble drugs, and preferentially those absorbed in the upper part of small intestine. The placement of the oral cavity offers numerous advantages, especially for drugs exhibiting an absorption window and solubility problems. They can help in optimizing the oral controlled delivery of drugs having 'absorption window' by continuously releasing drug prior to absorption window, over a prolonged period of time, thus ensuring optimal bioavailability[3].

Acyclovir [9-(2-hydroxyethoxylmethyl) guanine], a synthetic purine nucleoside analog derived from guanine, is the most widely used antiviral agent[4]. It is effective in the treatment of herpes simplex virus (HSV), mainly HSV-1 and HSV-2 and varicella zoster virus. According to acyclovir is categorized as a class- III drug i.e. having high solubility and less permeability. The pharmacokinetic parameters of acyclovir, following oral administration, are generally highly variable. It has an average plasma half-life of about 3 hours on average in adults with normal renal function . Its absorption in the GIT is slow, variable and incomplete. The bioavailability of acyclovir after oral administration ranges from 10-30%. Approximately 80% of an oral dose is never absorbed and excreted through feces. Also the frequency of administration of acyclovir is infection[5,6].

In the present work, attempts are made in order to increase the rate and extent of absorption of Acyclovir by retention of drug in oral cavity for a longer duration. The objective of this study is to formulate a mucoadhesive acyclovir tablet and investigate the effect of different polymer concentrations of on the mucoadhesion strength and percent age of drug release. The objective was to investigate the influence of spray-drying compared to physical mixing on the bioadhesive capacities of the mixtures[7].

MATERIALS AND METHOD

Acyclovir was provided exgratis by Biochem Laboratories Ltd; (Mumbai, India). Amioca starch was from National Starch and Chemical Company,USA. Carbopol- 940P (CP) was a gift from Ind-Swift Laboratories (Chandigarh, india).. All other chemicals employed were of analytical grade.

Preparation of the spray-dried Amioca/C940P Mixture:-

First,Amioca starch, an amylopectine corn starch, was pregelatinised in beaker at 140^0C.After melt obtained aqueous starch dispersion was mixed with an aqueous C940P dispersion,a highly cross-linked poly(acrylic acid).Then this aqueous mixture spray-dried using a Labultima spray-dryer model Lu-22 advanced(Sr.no SD-1000/L;Mumbai-68,India)) to obtain a powder[7].

Preparation of the spray-dried Amioca/C940P Physical Mixture:-

The spray-dried Amioca/C940P Physical Mixture were prepared by blending granular Amioca starch with C940P in the ratios 95/5 to 55/45(w/w)[7].

Production of the tablets:-

Bioadhesion measurements were performed on 100mg tablets. For the tablet production the powders were mixed with talc(1%;w/w), as a lubricant and compressed on a JAGUAR,GMD-4-B. equipped with 8mm flat punches[8].

The tablets used in the in-vitro dissolution study contained acyclovir.for the tablet of production the spray-dryed powder was firstly mixed with acyclovir(200mg),next the lubricant(1% talc)was

added and mixed again.the tablet were compressed as described above with tablet weight of 310mg and diameter of 10 mm[8].

Table No.1: Composition of acyclovir buccoadhesive tablet

Ingredients	Amount(mg)
Acyclovir	200
Amioca starch	55-95
Carbopol 940P	5-45
Talc	3
Lactose	q.s

RESULT S AND DISCUSSION

Physical evaluation:-

Five tablets from each formulation were evaluated for uniformity in tablet weight and thickness. Since the tablet weight is 300 mg, 10 tablets from each formulation were examined for friability , using the Roche friabilator[9].

Content uniformity:-

Two tablets from each formulation were powdered individually and a quantity equivalent to 100 mg of acyclovir was accurately weighed and extracted with a suitable volume of 0.1 N HCl. Each extract was suitably diluted and analyzed spectrophotometrically at 254 nm[10].

Table No :2 Physical evaluation of buccal bioadhesive tablet of acyclovir by using spray-dried amioca starch/carbopol 940p mixture

Formulation	Thickness ± SD*	Hardness (kg/cm^2) ± SD*	Friability (%) ± SD*	Weight Uniformity (mg) ± SD*	Uniformity of content ± SD*
F1	5.48±0.14	10.0±0.28	0.85±0.29	Complies	98.56±0.25
F2	5.49±0.83	12.2±0.62	0.63±0.12	Complies	97.35±0.92
F3	5.49±0.67	10.8±0.40	0.53±0.10	Complies	98.73±0.37
F4	5.53±0.32	9.1±0.97	0.69±0.87	Complies	99.46±0.59
F5	5.49±0.14	12.0±0.64	0.67±0.19	Complies	98.57±0.41
F6	5.54±0.38	10.1±0.14	0.54±0.26	Complies	100.74±0.94
F7	5.54±0.21	13.3±0.36	0.51±0.66	Complies	100.25±0.23
F8	5.52±0.73	11.7±0.32	0.53±0.43	Complies	98.22±0.40
F9	5.46±0.20	12.1±0.48	0.72±0.19	Complies	99.38±0.37

Ex-Vivo mucoadhesion studies:-

The working of a double beam physical balance formed the basis of the bio-adhesion test apparatus fabricated . The right pan of a physical balance was removed and replaced with a steel cylinder hanged with a lightweight thread. The height of this total set-up was adjusted to accommodate a glass container below it, leaving a head space of about 0.5 cm in between, A steel block was fabricated with an upward protrusion on one of its face. This was kept inside the glass container, which was then placed below the right hand set-up of the balance. The two sides were then balanced. This test carryout by using goat mucus membrane was excised and washed (at 37°C ± 1°C for 30 min in phosphate buffer saline medium. A constant weight of 10 g was then

placed over the steel block for the total contact period of 5 min[11].

Table No :3 Ex-Vivo mucoadhesion studies of buccal bioadhesive tablet of acyclovir by using spray-dried Amioca starch/carbopol 940P mixture

Formulation	Polymer Conc.(%)	Adhesion Force(N)	Work of Adhesion(ml)
F1	95/5	1.20	0.30
F2	90/10	1.10	0.34
F4	85/15	1.90	0.60
F4	80/20	1.80	0.80
F5	75/25	1.83	0.85
F6	70/30	1.85	0.83
F7	65/35	1.90	0.90
F8	60/40	1.95	1.00
F9	55/45	2.10	1.20

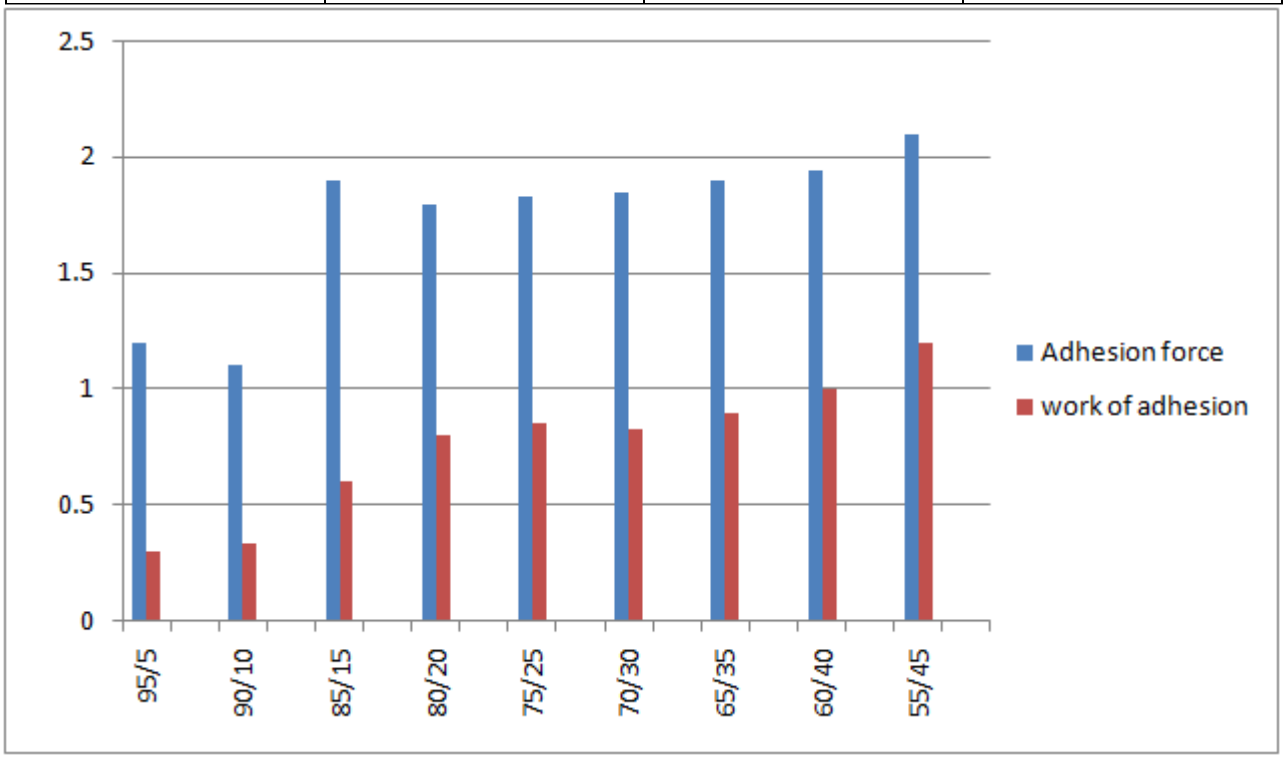

Fig :1 Ex-Vivo mucoadhesion studies

Swelling studies:-

The Swelling studies were carried out by determining the swelling index using USP Type-I Apparatus (Basket). Tablets were initially weighed (W0) and then placed in the basket and revolved at 50 rpm for 12 h. At intervals of 1 h, tablets were removed from basket and weighed(Wt). Then swelling index was calculated by using the formula given in equation[11] :

Swelling index=(Wt - W0 / W0)×100 Eq.

Wt = weight of swollen tablet at each time interval
W0 = initial weight of tablet

Table No 4: % Swelling Index of F1 to F9

Time (hrs)	% Swelling Index								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	32.39 ± 0.92	47.26 ± 0.89	24.69 ± 0.14	42.93 ± 0.47	41.29 ± 0.48	31.34 ± 0.43	67.77 ± 0.5	43.02 ± 0.72	42.94 ± 0.96
2	53.02 ± 0.81	62.83 ± 0.36	38.57 ± 0.88	56.85 ± 0.55	52.47 ± 0.11	45.41 ± 0.54	81.96 ± 0.47	56.85 ± 0.41	58.58 ± 0.44
3	65.44 ± 0.98	75.64 ± 0.61	53.02 ± 0.53	68.79 ± 0.61	72.28 ± 0.34	61.94 ± 0.84	102.03 ± 0.48	72.71 ± 0.84	72.9 ± 0.18
4	82.38 ± 0.41	96.58 ± 0.17	69.23 ± 0.94	91.93 ± 0.84	83.07 ± 0.37	78.69 ± 0.27	116.93 ± 0.25	82.05 ± 0.55	90.82 ± 0.35
5	93.01 ± 0.43	118.38 ± 0.88	82.15 ± 0.59	102.93 ± 0.38	100.74 ± 0.68	93.56 ± 0.68	135.97 ± 0.42	98.19 ± 0.23	106.93 ± 0.52
6	105.15 ± 0.87	133.34 ± 0.63	103.6 ± 0.19	132.16 ± 0.29	121.01 ± 0.65	113.53 ± 0.15	155.47 ± 0.71	119.68 ± 0.54	126.40 ± 0.31
7	122.18 ± 0.61	153.66 ± 0.31	120.41 ± 0.63	147.02 ± 0.43	136.35 ± 0.84	131.85 ± 0.16	166.92 ± 0.44	137.27 ± 0.95	146.27 ± 0.94
8	137.09 ± 0.31	166.37 ± 0.54	137.29 ± 0.82	168.06 ± 0.52	154.61 ± 0.72	147.91 ± 0.81	184.41 ± 0.18	155.21 ± 0.47	157.15 ± 0.47
9	150.39 ± 0.86	182.88 ± 0.55	151.27 ± 0.94	183.67 ± 0.24	171.65 ± 0.53	165.3 ± 0.22	201.85 ± 0.59	167.48 ± 0.58	169.81 ± 0.49
10	175.49 ± 0.32	202.23 ± 0.79	164.15 ± 0.98	202.75 ± 0.45	188.43 ± 0.36	177.83 ± 0.37	222.13 ± 0.53	182.36 ± 0.26	184.03 ± 0.73
11	200.44 ± 0.66	184.57 ± 0.21	182.55 ± 0.51	218.66 ± 0.97	206.41 ± 0.37	197.24 ± 0.25	232.91 ± 0.82	201.57 ± 0.94	207.64 ± 0.92
12	10.27 ± 0.19	171.72 ± 0.10	170.11 ± 0.24	201.23 ± 0.52	195.04 ± 0.58	180.49 ± 0.93	218.18 ± 0.61	211.97 ± 0.85	190.89 ± 0.41

(n=3)

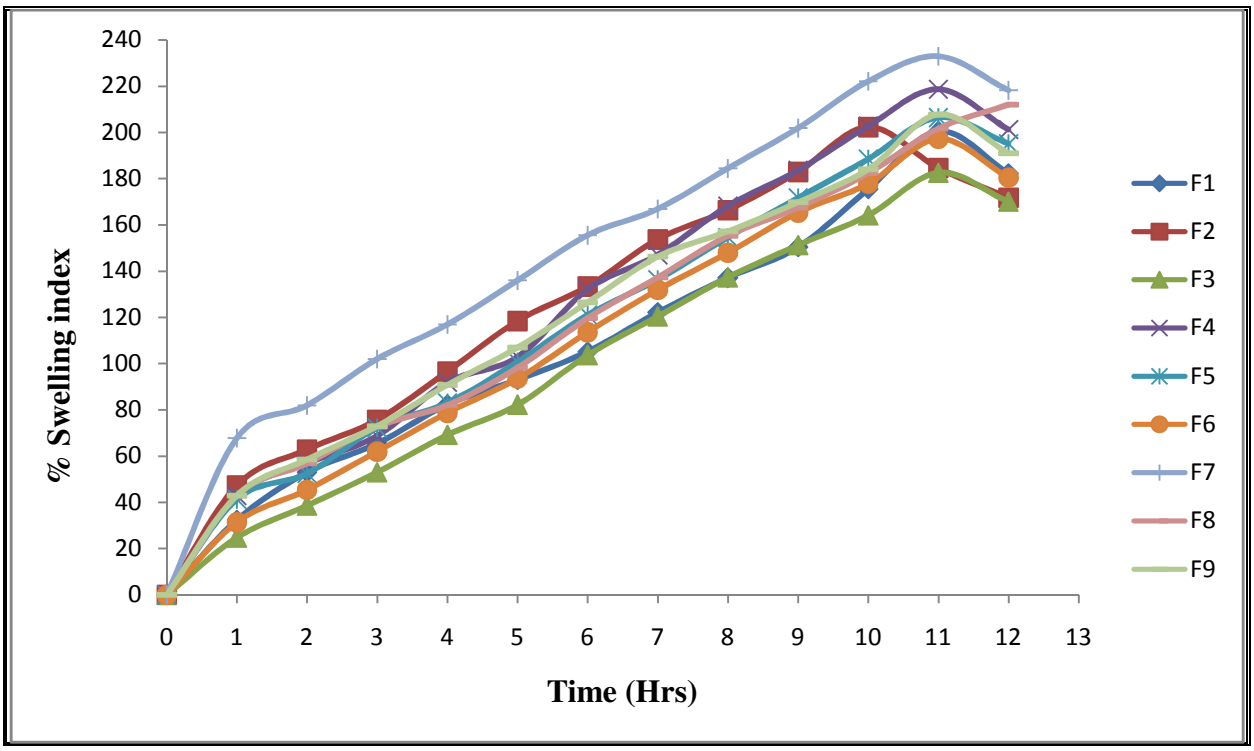

Figure No.2: Plot for % Swelling Index of F1 to F9

In vitro drug release studies:-

Dissolution studies were performed on all the formulations prepared, in triplicate, employing United States Pharmacopoeia (USP)-23 paddle methods (Electrolab, TDT-06P Mumbai) and 0.1 N HCl as the dissolution medium at 50 rpm and 37°C ± 0.5°C and by using same parameter to carry out this test in 6.8 phosphate buffer. A 10mL aliquots of each test sample were withdrawn periodically at suitable time intervals and the volume was replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 254 nm[11,12].

Table No :5 % Drug release of Formulation F1, F2 and F3

Sr. No	Time (hrs)	% Drug release ± SD		
		F1	F2	F3
1	0	0	0	0
2	1	15.21±0.87	13.95±0.49	18.74±0.55
3	2	20.48±0.85	23.27±0.76	27.26±0.27
4	3	25.77±0.62	28.99±0.96	34.78±0.94
5	4	32.10±0.71	36.76±0.93	47.15±0.22
6	5	39.18±0.45	41.45±0.64	58.54±0.63
7	6	45.76±0.44	48.59±0.38	68.61±0.58
8	7	52.60±0.84	55.12±0.52	78.70±0.52
9	8	59.45±0.21	61.45±0.92	89.46±0.72
10	9	66.24±0.42	67.59±0.84	97.07±0.28
11	10	72.43±0.73	77.28±0.25	
12	11	83.77±0.81	86.10±0.72	
13	12	91.53±0.63	95.86±0.71	

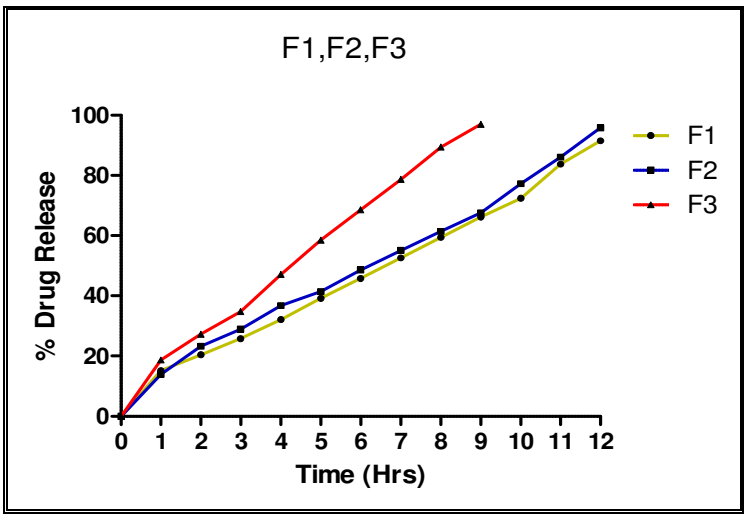

Figure No 3: % Drug Release of Formulation F1, F2, F3

Table No:6 % Drug release of Formulation F4, F5 and F6

Sr. No	Time (hrs)	%Drug release ± SD		
		F4	F5	F6
1	0	0	0	0
2	1	12.92±0.38	21.35±0.88	15.41±0.28
3	2	20.4±0.75	35.69±0.19	21.27±0.69
4	3	29.35±0.54	43.91±0.57	27.12±0.56
5	4	37.53±0.45	49.39±0.84	34.92±0.84
6	5	43.96±0.82	56.85±0.45	41.19±0.27
7	6	52.18±0.61	65.01±0.86	48.31±0.65
8	7	60.14±0.39	72.28±0.11	56.07±0.72
9	8	66.91±0.16	79.60±0.51	67.06±0.71
10	9	72.38±0.41	88.19±0.92	76.33±0.63
11	10	80.34±0.79	93.22±0.49	84.35±0.34
12	11	86.36±0.85	96.19±0.92	91.41±0.15
13	12	92.68±0.56	99.22±0.49	98.69±0.31

Table No:7% Drug release of Formulation F7, F8 and F9

Sr. No	Time (hrs)	% Drug release ± SD		
		F7	F8	F9
1	0	0	0	0
2	1	21.78±0.67	16.26±0.4	26.35±0.77
3	2	29.73±0.48	22.33±0.72	39.56±0.22
4	3	36.94±0.15	30.69±0.84	49.08±0.11
5	4	44.45±0.15	38.02±0.67	53.65±0.94
6	5	51.33±0.92	44.47±0.58	59.64±0.88
7	6	58.53±0.41	52.01±0.89	64.88±0.68
8	7	66.43±0.25	58.85±0.66	72.73±0.35
9	8	73.27±0.74	64.97±0.34	80.27±0.22
10	9	80.35±0.49	71.13±0.81	89.03±0.42
11	10	85.61±0.63	75.95±0.72	97.87±0.33
12	11	90.27±0.46	82.84±0.62	
13	12	94.87±0.84	89.91±0.63	

(n=3)

CONCLUSION:-

This study suggests that the polymers spray-dryer Amioca starch/Carbopol-940P can produce a controlled pattern of drug release in the prepared acyclovir tablets. The high mucoadhesive strength of this formulation. By spray-drying Amioca/Carbopol 940P mixtures a rang of potential bioadhesive carriers was obtained with excellent bioadhesive properties. By ranging the C940P concentration between 5% and 25%, the in Ex-vivo adhesion time of placebo tablets could be varied between 12hr to 16hr. The data from in-vitro release to optimize the F5 to give the better results.

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