Original Article

PREPARATION AND EVALUATION OF MUCOADHESIVE MICROCAPSULES OF ACYCLOVIR FOR ORAL CONTROLLED RELEASE

Ishwar Chandra Giri[1]*, Santosh Kumar Singh [1]

[1] Department of Pharmacy, Suresh Gyan Vihar University, Jaipur – 302017, Rajasthan, India.
Corresponding Author: Ishwar chandra Giri, Department of Pharmaceutics, Suresh Gyan Vihar University, Jaipur, Rajasthan.
Email: icgiripharma@gmail.com

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Abstract

Mucoadhesive microcapsules become adhesive on hydration and hence used for localizing the drugs to a particular target site of gastrointestinal tract (GIT) for prolonged period of time. Acyclovir [9-(2-hydroxyethoxymethyl) guanine] (ACV), is a synthetic purine nucleoside analog derived from guanine which is considered as the first agent to be licensed for the treatment of herpes simplex virus (HSV-1, HSV-2) infections and is the most widely used drug for infections such as cutaneous herpes, genital herpes, chicken pox,varicella zoster infections through interfering with DNA synthesis and inhibiting viral replication. Acyclovir has low bioavailability of 20%. It undergoes hepatic metabolism and its elimination half-life is 2-3hrs.Therefore the possible way by which this can be overcome is by formulating a sustained release mucoadhesive formulation.The mucoadhesive microcapsules of Acyclovir (F1-F16) were successfully prepared by Emulsion Solvent Evaporation method using polymers Sodium Alginate, Sod CMC, HPMC K4M and Carbopol 940. FTIR studies did not reveal any significant drug interactions.The prepared microcapsules had good spherical geometry with smooth surface as evidenced by scanning electron microscopy. The average particle size of mucoadhesive microcapsules of Acyclovir was found to be in the range of 289±2.28µm to 399±3.12µm.The formulation F16 was selected as the best formulation as it showed Percentage yield (97.6%), Entrapment efficiency (87.5±0.32%), Mucoadhesion test (70±3.32%) and Swelling index (74.6±2.24%). The *In-vitro* drug release (F16) was found to be (98.12±0.24 %) at the end of 12 hours. The formulation F16 followed Zero order kinetics with Higuchi mechanism. The optimized formulation F16 stored at elevated temperature such as 25^0C/60% RH and 40^0C/75% RH for 3 months. The results of accelerated stability studies revealed no significant changes were observed in drug entrapment efficiency, swelling index and *invitro* of drug release studies. Based on all the above evaluation parameters it was concluded that the formulation F16 acyclovir microcapsules was found to be the best formulation among all the formulations and can be used in the treatment of herpes simplex virus (HSV-1, HSV-2) infections.

Keywords: Emulsion Solvent evaporation, Drug entrapment efficiency, Swelling index, *In-vitro* drug release.

Introduction

Mucoadhesive Microcapsules become adhesive on hydration and hence used for localizing the drugs to a particular target site of gastrointestinal tract (GIT) for prolonged period of time. Moreover, it is easy for administration, no patient compliances and flexibility in the formulation. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in gastrointestinal tract (GIT) is to control gastro retentive drug delivery system which will provide important therapeutic options. Mucoadhesive Microcapsules delivery system is an attractive due to ability of adherence to the mucosal surface and releases the entrapped drug in a sustained release [1]. Bioadhesion phenomenon is associated with biological surface and mucoadhesion associated with mucin layer

of a mucosal tissue. Mucoadhesive Microcapsules have advantages like efficient absorption, enhanced bioavailability of the drugs, maximum utilization of drugs and much more intimate contact with intestinal cells, better patience compliance and targeting to specific absorption site [2-4].

Acyclovir [9-(2-hydroxyethoxymethyl) guanine] (ACV), is a synthetic purine nucleoside analog derived from guanine[3,4] which is considered as the first agent to be licensed for the treatment of herpes simplex virus (HSV-1, HSV-2) infections and is the most widely used drug for infections such as cutaneous herpes, genital herpes, chicken pox, varicella zoster infections through interfering with DNA synthesis and inhibiting viral replication [5]. According to the Biopharmaceutical Classification System (BCS), ACV falls under the BCS Class III drug i.e. soluble with low intestinal permeability and needs to be administered in large doses orally or intravenously to obtain the desired therapeutic effect. ACV is almost completely unionized, has maximum solubility 2.5 mg/ml at pH 7.0, soluble in acidic pH and is predominantly absorbed from the upper gastrointestinal tract (GIT). Acyclovir has low bioavailability of 20%. It undergoes hepatic metabolism and its elimination half-life is 2-3hrs. Therefore, it is selected as a suitable drug for the design of mucoadhesive Microcapsules with a view to improve its oral bioavailability and increase its drug release in sustain manner.

Materials and Methods:

Acyclovir was a gift sample from Alpha drug laboratory, Indore. Sodium Alginate was obtained from Finar chemicals limited, Ahmadabad. Carbopol 934P was purchased from S.D. Fine chem. Ltd, Mumbai. HPMCK100M was purchased from Yarrow chemicals ltd, Mumbai. All other reagents used were of analytical grade.

Formulation of Mucoadhesive Microcapsules of Acyclovir

Trial And Error Method:

(Preliminary experiments) previously many trials were run for the preparation of mucoadhesive Microcapsules of Acyclovir by emulsion solvent evaporation technique using different polymers. Trials were made by changing the temperature, stirring speeds, concentration of polymer, Span-80. After so many trials, it was concluded that temperature play a very critical role in the formation of Microcapsules, it is a continuous process of stirring. Every step in the process was optimized by performing experiments through trial-and-error method.

Preparation of Mucoadhesive Microcapsules of Acyclovir :

Table no : 01, Formulation of Mucoadhesive Microcapsules of Acyclovir

Ingredient	**Formulation code**															
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
Acyclovir (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
Sodium Alginate (mg)	200	400	600	800												
Sodium Carboxy Methyl Cellulose (NACMC) (mg)	--	--	--	--	200	400	600	800	200	--	--	--	--	--	--	--

Hydroxy Propyl Methyl Cellulose(HPMC K4M) (mg)	--	--	--	--	--	--	--	--	200	400	600	800	--	--	--	--
Carbopol 940 (mg)	--	--	--	--	--	--	--	--	--	--	--	--	200	400	600	800
Ethanol (ml)	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Liquid paraffin (ml)	49	49	49	49	49	49	49	49	49	49	49	49	49	49	49	49
Span-80 (ml)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Acyclovir mucoadhesive Microcapsules are prepared by Emulsion Solvent Evaporation technique using four polymers i.e., Sodium Alginate, Sod.CMC, HPMC K4M and Carbopol 940. The following are the steps for the preparation of Microcapsules. In this method first the accurately weighed polymer is added to 50ml of ethanol and homogenised by continuous stirring at 500-600 rpm. To this accurately weighed amount of drug was added and stirring is continued until a homogenous dispersion is formed. Separately, 50ml of liquid paraffin containing 1ml Span80 was placed on a mechanical stirrer and homogenised. The above formed polymer-drug dispersion (aqueous phase) was added slowly to liquid paraffin in a thin-stream over 2-3 minutes. This emulsion was stirred at 2000 rpm and heated to 80 °C for 3-4 hrs. After that the microspheres were separated by filtration, the excess of paraffin oil was eliminated by repeated washing (3 times) with n-hexane (50 ml) and finally dried overnight at room temperature to yield free flowing spherical products

Evaluation and Characterization of Mucoadhesive Microcapsules of Acyclovir

Particle Size Determination:

Determination of average particle size of mucoadhesive Microcapsules of Acyclovir was carried out by optical microscopy in which the stage micrometer was employed. According to microscopic method of analysis, minute quantity of Microcapsules was suspended in liquid paraffin and spread on a glass slide and placed on mechanical stage of microscope. Size of 100 Microcapsules was determined in each batch for calculating average particle size [6,7]

Percentage Yield

The total amount of mucoadhesive Microcapsules obtained were weighed and evaluated for percentage yield [7].

Percentage yield = Actual yield/ Theoretical yield x100

Drug Entrapment Efficiency:

The mucoadhesive Microcapsules were powdered using mortar and pestle. Accurately weighed 20mg drug equivalent of Microcapsules were suspended in 30ml of pH 1.2 HCL buffer and sonicated for 30minutes. The

resulting solution was filtered, and made upto 100ml with pH 1.2 HCL buffer. The solution was filtered after suitable dilution, Acyclovir content in filtrate was analyzed at 254nm using UV-Visible spectrophotometer. The obtained absorbance was plotted on standard curve to get exact concentration of entrapped drug. Calculating this concentration with dilution factor and volume we get the percentage of actual drug encapsulated in Microcapsules [8]. The drug entrapment efficiency was determined using following relationship.

% Drug entrapment efficiency = Actual drug content/Theoretical drug content x 100

Loose Surface Crystal Study (LSC)

This study was conducted to estimate the amount of drug present on the surface of the Microcapsules. 20mg of mucoadhesive Microcapsules were suspended in 20ml of pH 1.2 HCL buffer. The samples were shaken vigorously for 15min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 254nm. Percentage of drug release with respect to entrapped drug in the sample was recorded [8].

Swelling Index (SI):

The dynamic swelling behaviour of Acyclovir mucoadhesive Microcapsules was studied by mass measurement. The Microcapsules were incubated with 25ml pH 1.2 HCL buffer in petri dishes at 37 °C. The Microcapsules were taken out at different time intervals and blotted carefully without pressing hard to remove the excess surface liquid. The swollen Microcapsules were weighed using the electronic microbalance (Model BL-220H, Shimadzu, Japan) [9,10]. The studies were performed in triplicate and average values were taken in data analysis.

SI= (Weight of wet Microcapsules − Weight of dry Microcapsules)/ Weight of dry Microcapsules x 100

Mucoadhesive Testing by *In vitro* Wash-Off Test:

The mucoadhesive property of the Acyclovir mucoadhesive Microcapsules was evaluated by an *in vitro* adhesion testing method known as the wash-off method. Freshly excised pieces of stomach mucosa (4×5 cm) from sheep were mounted onto glass slides (3×1 inch) with poly cyanoacrylate glue. Two glass slides were connected with a suitable each wet rinsed tissue specimen and immediately thereafter the support were hung onto the arm of a USP tablet disintegrating test machine. When disintegrating test machine was operated, the tissue specimen was given a slow, regular up and down movement in the test fluid (900ml) at 37 °C contained in 1000ml vessel of the machine. At the end of 1 hour and at hourly interval up to 12 hours, the machine was stopped and the number of Microcapsules still adhering to the tissue was counted [11,12]. The test was performed in stomach (pH 1.2). Mucoadhesion was calculated using formula:

% Mucoadhesion = Number of Microcapsules applied/ Number of Microcapsules adhered x100

Scanning Electron Microscopy (SEM):

The mucoadhesive Microcapsules were observed under a Scanning Electron Microscopy. The Microcapsules were mounted directly onto SEM sample stub using double-sided sticking tape and coated with gold film with ion splitter with gold target with resolution 3nm, 10nm, 40nm and a vacuum system is fitted to it [13].

***In vitro* Drug Release Studies:**

In vitro drug release study was carried out in USP dissolution test apparatus. A quantity of mucoadhesive Microcapsules equivalent to 200mg of Acyclovir Microcapsules was kept in basket type apparatus and immersed

in 900ml of Phosphate buffer, pH 1.2 in 900ml dissolution flask and temperature was maintained at 37±0.5^{0}C throughout the study. At predetermined time intervals 5ml of samples was withdrawn, for 12 hrs, by means of a syringe fitted with prefilter and same was replaced into the dissolution flask containing buffer. The absorbance of sample was measured at 254nm after required dilution with the fresh medium (pH 1.2). All the studies were conducted in triplicate [14,15].

Kinetics of *In vitro* Drug Release:

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. The exact mechanism of Acyclovir release from the microsphere was further studied by kinetic models. The drug release data was analyzed by zero order, first order, Higuchi, Korsmeyer Peppa's and Hixon Crowell models. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test [16].

Accelerated Stability Studies:

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product, which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The optimized formulation, F16 were subjected to accelerated stability studies as per ICH guidelines i.e. 25^{0}C/60% RH and 40^{0}C/75% RH in air tight high density ethylene bottles for 3 months in stability chamber. The samples were taken out at 0, 30, 60 and 90 days. Mucoadhesive Microcapsules were evaluated for the different physicochemical parameters i.e., Drug entrapment efficiency, swelling index and *invitro* of drug release [17].

Results and discussion

Percentage Yield:

Percentage yield of different formulations, F1-F16, were calculated and the yield was found to be in the range of 87.5% to 97.6% respectively. This higher percentage yields indicates that this Emulsion Solvent Evaporation method was very useful for adoption in the formulation of Acyclovir mucoadhesive Microcapsules. The formulation F16 showed higher percentage yield 97.6%. The results were tabulated in the Table No: 02

Particle Size Analysis:

Particle size distribution of mucoadhesive Microcapsules of Acyclovir was determined by optical microscope fitted with an ocular micrometer and stage micrometer. All the formulations of mucoadhesive Microcapsules F1-F16 show uniform size distribution. The average particle size of mucoadhesive Microcapsules of Acyclovir was found to be in the range of 289±2.28µm to 399±3.12µm.

Drug Entrapment Efficiency:

The Entrapment efficiency was found to be in the range of 68.4±1.33 % to 87.5±0.32%. The percentage of entrapment was found to be higher, 83.7±2.17 % for F4, 85.7±2.22 % for F8, 86±3.12% for F12, 87.5±0.32% for F16, formulation. The formulation, F16 was found to be highest percentage of drug entrapment efficiency i.e., 87.5% by using drug and carbopol 940 in the ratio of 1:4. This improved entrapment efficiency is due to the greater proportion of polymers with respect to the amount of drug. The results are shown in Table No: 02.

Loose Surface Crystallography: (LSC)

Loose surface crystallography studies were conducted for all the drug loaded formulations F1-F16. Surface associated drug content of mucoadhesive Microcapsules decreased with increase in concentration of the polymer. As the concentration of polymer increased from F1-F4, F5-F8, F9-F12, F13-F16, it showed increase in entrapment efficiencies and hence decreased surface drug contents. But in the formulations with low polymer concentration the surface associated drug content was more in F1 (31.6±0.22%), F5 (28.7±0.17%), F9 (29.3±0.15%), F13 (23.4±0.32%), formulations due to lower entrapment efficiency. Hence, the results were shown in Table No: 02

Table no:02. Evaluation parameters of Mucoadhesive Microcapsules of Acyclovir Formulations F1-F16

Formulation Code	**Percentage Yield (%)**	**Drug Entrapment Efficiency (%)**	**LSC (%)**
F1	89.0	68.4±1.33	31.6±0.22
F2	93.3	75.8±1.91	24.2±0.36
F3	95.2	76.8±2.4	23.2±0.18
F4	96.2	83.7±2.17	16.3±0.10
F5	87.5	71.3±0.21	28.7±0.17
F6	94.3	72.6±0.17	27.4±0.21
F7	96.2	82±3.32	18±0.45
F8	97.1	85.7±2.22	14.3±0.32
F9	90.0	70.7±1.03	29.3±0.15
F10	95.0	76.2±2.5	23.8±0.16
F11	96.1	79±1.24	21±0.26
F12	97.3	86±3.12	13.5±0.18
F13	94.5	76.6±0.28	23.4±0.32
F14	95.6	80.3±1.38	19.7±0.16
F15	96.7	85.3±0.17	14.7±0.34
F16	97.6	87.5±0.32	12±0.24

All values are represented as mean ± standard deviation (n=3)

Swelling Index: (SI)

Swelling property was mostly affected by the concentration of polymers. As the concentration of polymers increases the swelling capacity increased. The swelling index for all the formulations i.e., F1-F16 was determined in pH 1.2 Hcl buffer. The swelling index increased from F1 (40.2±1.30%) to F4 (60.2±1.46%), F5 (44.8±1.04%) to F8 (64±3.98%), F9 (50.2±8.54%) to F12 (68.2±4.60%), F13 (43±6.1%) to F16 (74.6±2.24%), in pH 1.2 Hcl buffer at the end of 12 hrs. The increase in Swelling Index is due to the increase in polymer concentration. The optimized formulation, F16 was found to have high swelling index i.e., 74.67±2.24% at the end of 24 hrs by using drug and carbopol 940 in the ratio of 1:4. The results are shown in Table No: 03

***In-vitro* Mucoadhesion Test:**

The result of *in vitro* Mucoadhesion test after 12 hrs is shown in Table No: 03. The percent Mucoadhesion increased with increase in concentration of mucoadhesive polymer. The percentage mucoadhesion were increased in formulation F4(67±0.92%), F8(68±1.13%), F12(63±2.07%) and F16(70±3.32%). The optimized formulation F16, was found to have higher mucoadhesion i.e., 70±3.32% at the end of 12hrs, by using drug and carbopol 940 in the ratio of 1:4.

Figure 01: *In vitro* Mucoadhesion Test

Table 03: Swelling Index Percentage and Percentage of Mucoadhesion of Formulations F1 to F16

Formulation Code	**Swelling Index (%)** **(In 12hrs)**	**Mucoadhesion (%)** **(In 12 hrs)**
F1	40.2±1.30	50±2.08
F2	44.6±0.52	59±1.0
F3	56.4±0.62	60±1.23
F4	60.2±1.46	67±0.92
F5	44.8±1.04	57±1.02
F6	52.2±1.20	62±0.98
F7	60.4±2.48	64±1.11
F8	64±3.98	68±1.13
F9	50.2±8.54	55±1.27
F10	62±7.64	57±1.13
F11	64.6±2.84	60±1.33
F12	68.2±4.60	63±2.07
F13	43.0±6.1	57±1.07
F14	56.2±0.86	62±0.56

F15	68.2±5.18	67±0.89
F16	74.6±2.24	70±3.32

All values are represented as mean ± standard deviation (n=3)

***In-Vitro* Drug Release Studies:**

The *in-vitro* drug release studies of Acyclovir mucoadhesive Microcapsules was carried out in pH 1.2 HCL buffer as dissolution medium and the results are given in Table No: 04 to 07 and Figure No: 02 to 05. As the concentration of mucoadhesive polymer increased, the drug release also increased proportionally. The percentage of drug release for formulations F1-F4 was found to be in the range of 70.37±0.11% to 90.89±0.28%, F5-F8 was found to be in the range of 70.7±0.82% to 89.8±0.56%, F9-F12 was found to be in the range of 72.5±0.62% to 90.2±0.50%, F13-F16 was found to be in the range of 75±0.71% to 98.12±0.24 %, at the end of 12hrs. The optimized formulation F16, was found to be controlled and higher percentage of drug release i.e., 98.12±0.24 % at the end of 12 hrs. This is obtained by using drug and carbopol polymer in the ratio of 1:4. From this data we can find that the polymers which are used in the formulations have controlled the drug release to great extent which would be helpful in reducing the number of administrations and thereby improving the patient compliance.

Table no. 04: *In vitro* drug release for formulations F1-F4

Time (hours)	**F1**	**F2**	**F3**	**F4**
1	5.81±0.1	5.6±0.32	9.5±0.11	10.82±0.4
2	7.5±0.16	9.86±0.24	14.11±0.19	16.79±0.13
3	10.22±0.10	17.9±0.11	21.35±0.44	21.62±0.19
4	20.45±0.17	25.1±2.1	28.1±0.16	29.9±0.11
5	26.33±0.22	38.6±0.19	33.48±0.21	38.49±0.7
6	31.49±0.13	42.94±0.31	38.64±0.35	49.27±0.19
7	35.92±0.32	49.38±0.10	49.91±0.41	56.6±2.5
8	45.27±0.18	57.64±0.44	57.06±0.10	69.3±0.52
9	55.43±0.22	66.1±0.25	62.2±0.45	72.4±0.27
10	61.31±0.43	72.5±0.33	67.6±0.34	79±0.19
11	67.29±0.19	78.3±0.28	75.6±0.22	86.18±0.43
12	70.37±0.11	82.5±0.30	88.41±0.51	90.89±0.28

All values are represented as mean ± standard deviation (n=3)

Figure 02: Comparison of In-vitro drug release for formulations F1-F4

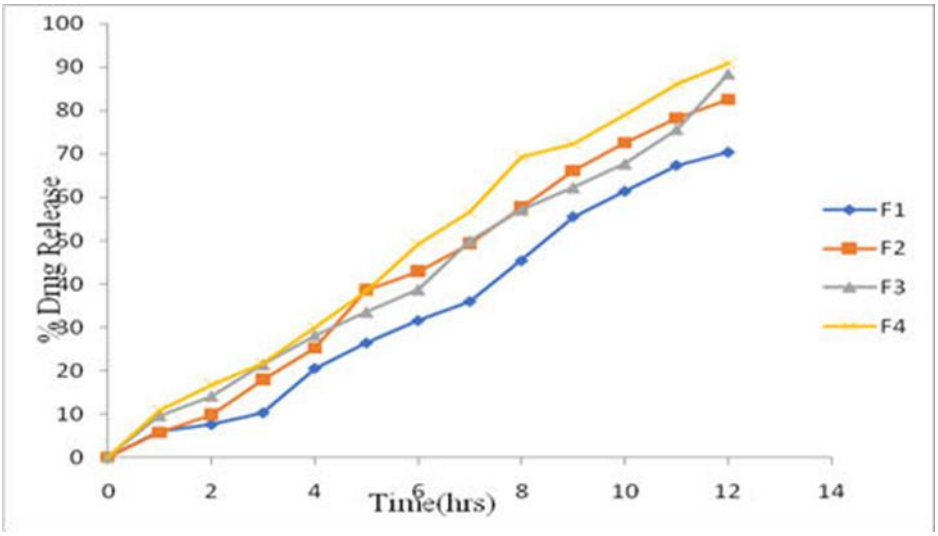


Table 05: In vitro drug release for formulations F5-F8

Time(hours)	**F5**	**F6**	**F7**	**F8**
1	4.97±0.14	7.39±0.08	9.96±0.21	11.41±0.18
2	9.14±0.07	10.22±0.13	12.67±0.32	22.22±0.37
3	17.95±0.08	19.39±0.04	20.45±0.24	38.63±0.44
4	21.82±0.12	24.64±0.18	26.6±0.64	46.51±0.53
5	27.53±0.50	29.72±0.31	31.95±0.55	53.75±0.25
6	32.6±0.43	35.6±0.67	38.84±0.25	58.34±0.35
7	38.48±0.23	40.02±0.50	47.91±0.48	64.59±0.22
8	49.82±0.49	49.09±0.08	55.72±0.72	69.22±0.53
9	55.88±0.46	54.79±0.30	61.96±0.61	73.84±0.28
10	61.31±0.89	60.94±0.43	68.08±0.45	76.47±0.12
11	66.11±0.39	67.64±0.26	74.05±0.52	82.71±0.38
12	70.7±0.82	75.52±0.56	80.95±0.74	89.8±0.56

All values are represented as mean ± standard deviation (n=3)

Figure 03: Comparison of In vitro drug release for formulations F5-F8

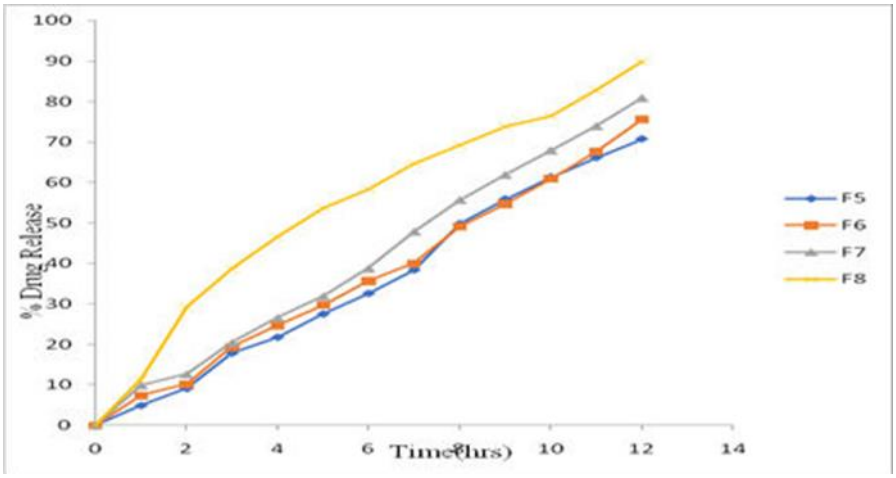


Table 06: In vitro drug release for formulations F9-F12

Time (hours)	**F9**	**F10**	**F11**	**F12**
1	4.16±0.5	8.5±0.11	8.32±0.4	9.3±0.15
2	8.68±0.10	10.95±0.19	17.94±0.17	18.76±0.28
3	17.95±0.15	19.27±0.12	27.17±0.22	25.17±0.33
4	23.99±0.23	25.79±0.32	33.6±0.10	30.15±0.11
5	29.43±0.18	32.31±0.16	38.66±0.17	39.86±0.26
6	35.76±0.33	38.57±0.19	45.55±0.22	49.28±0.19
7	40.84±0.48	43.09±0.53	59.43±0.55	58.88±0.35
8	45.82±0.28	50.07±0.65	63.67±0.37	65.39±0.50
9	51.25±0.19	58.39±0.27	69.38±0.25	71.18±0.44
10	59.41±0.56	65.46±0.16	73.9±0.65	79.03±0.32
11	66.57±0.32	71.97±0.42	80.88±0.29	85.45±0.74
12	72.55±0.62	78.23±0.39	86.22±0.43	90.2±0.50

All values are represented as mean ± standard deviation (n=3)

Figure 04: Comparison of *In vitro* drug release for formulations F9-F12

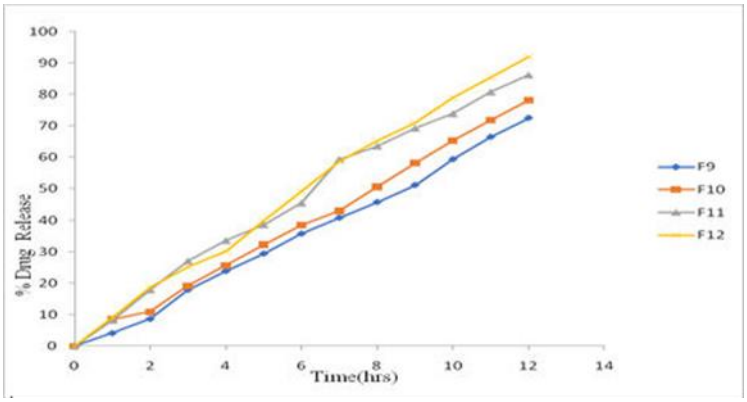
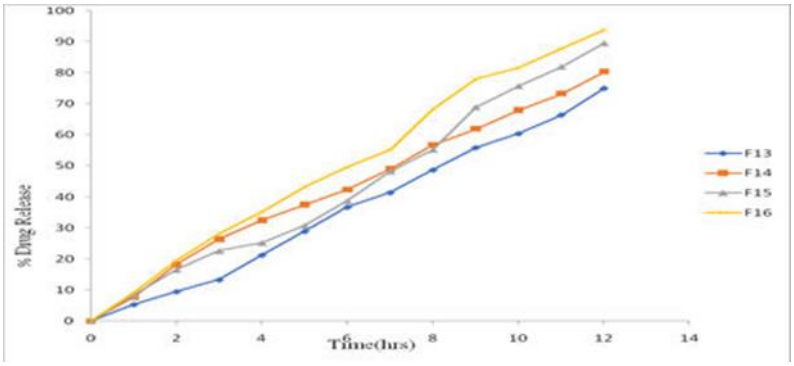


Table 07: In vitro drug release for formulations F13-F16

Time (hours)	**F13**	**F14**	**F15**	**F16**
1	5.33±0.9	7.71±0.21	8.24±0.12	9.04±0.18
2	9.5±0.15	18.31±0.32	16.58±0.33	19.59±0.74
3	13.39±0.20	26.45±0.53	22.65±0.45	28.17±0.32
4	21.26±0.18	32.51±0.68	25.17±0.67	35.15±0.53
5	28.96±0.33	37.59±0.55	30.77±0.51	43.12±0.54
6	36.75±0.29	42.39±0.33	38.67±0.62	49.54±0.22
7	41.46±0.19	49.1±0.61	48.16±0.58	55.15±0.45
8	48.72±0.44	56.72±0.53	55.25±0.87	68.23±0.55
9	55.97±0.31	61.94±0.72	68.96±0.66	77.92±0.38
10	60.47±0.54	67.92±0.84	75.74±0.71	81.5±0.26
11	66.57±0.32	73.25±0.77	81.97±0.55	87.7±0.54
12	75.05±0.71	80.32±0.65	89.50±0.36	98.12±0.24

All values are represented as mean ± standard deviation (n=3)

Figure 5: Comparison of In vitro drug release for formulations F13-F16



In-vitro Drug Release Kinetics of Formulations F1-F16

The kinetics of In vitro drug release was determined by applying the drug released data to various kinetic models such as zero order, first order, Higuchi, Korsmeyer Peppas and Hixon Crowell. Drug release kinetic data for Acyclovir mucoadhesive Microcapsules were shown in Table No: 08. The formulation F16 followed Zero order kinetics with Higuchi mechanism.

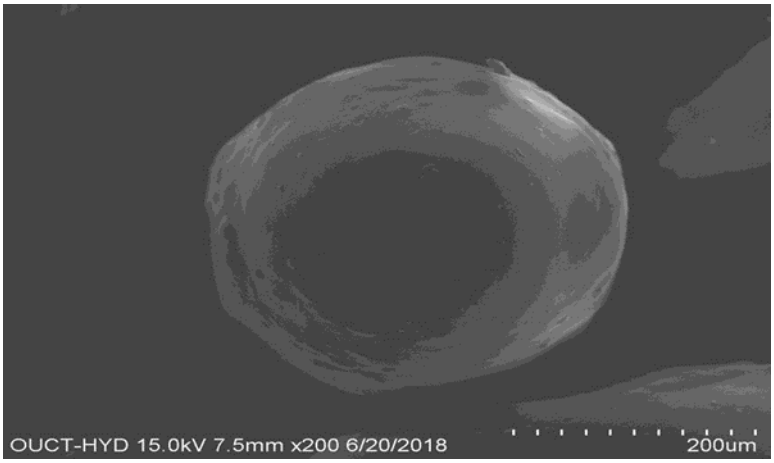
Table 08: In-vitro Drug Release Kinetics data of Formulations F1-F16

Formulation Code	Zero order (R2)	First order (R2)	Higuchi (R2)	Korsmeyer Peppas (R2)	n	Hixon Crowell (R2)
F1	0.993	0.981	0.994	0.991	0.835	0.991
F2	0.985	0.980	0.993	0.993	0.952	0.982
F3	0.994	0.969	0.983	0.985	0.924	0.985
F4	0.992	0.985	0.978	0.982	0.388	0.990
F5	0.995	0.964	0.985	0.965	0.569	0.979
F6	0.983	0.958	0.976	0.973	0.668	0.973
F7	0.990	0.945	0.981	0.994	0.870	0.985
F8	0.989	0.973	0.968	0.990	0.468	0.980
F9	0.994	0.979	0.973	0.992	0.358	0.989
F10	0.995	0.968	0.980	0.975	1.066	0.972
F11	0.992	0.973	0.958	0.960	1.239	0.965
F12	0.990	0.961	0.963	0.955	0.456	0.977
F13	0.997	0.971	0.978	0.994	1.017	0.980
F14	0.993	0.954	0.962	0.993	0.727	0.968
F15	0.989	0.975	0.986	0.978	0.796	0.988
F16	0.998	0.987	0.997	0.996	0.467	0.993

Scanning Electron Microscopy (SEM):

Surface morphology and internal cross-sectional structure of the mucoadhesive Microcapsules were investigated with scanning electron microscope. SEM photomicrographs of the optimized formulation were shown in the Figure No:12. The Microcapsules were smooth and spherical. Very less particulate matter of the drug was seen on the surface of Microcapsules indicating uniform distribution of the drug in the polymer network.

Figure 06: Scanning Electron Micrograph of F16 Formulation



Accelerated Stability Studies:

The optimized formulation F16 stored at elevated temperature such as 250C/60% RH and 400C/75% RH for 3 months. The results of stability studies revealed no significant changes were observed in Drug entrapment efficiency, swelling index and invitro of drug release studies. The results were shown in Table no: 09

Table 09: Stability studies

Characteristics	**Initials**	**30 days**	**60 days**	**90 days**
	25˚±2˚C 60±5 % RH	**25˚±2˚C 60±5 %RH**	**25˚±2˚C 60±5% RH**	**40˚±2˚C 75±5 % RH**
Drug Entrapment Efficiency (%)	87.5±0.32	86.5±0.2	85.2±0.12	85.1±0.32
Swelling Index (%)	74.6±2.24	73.6±2.20	72.8±1.14	72.6±0.22
In vitro drug release (%)	98.12±0.24	97.20±0.21	96.75±0.19	96.2±0.55

Conflicts of interest:

NIL

Conclusion

The mucoadhesive Microcapsules of Acyclovir were successfully prepared by Emulsion Solvent Evaporation method technique using polymers Sodium Alginate, Sod.CMC, HPMC K4M and Carbopol 940 individually and confirmed that it is a best method for preparing mucoadhesive Microcapsules of Acyclovir from its higher

percentage yield. FTIR studies did not reveal any significant drug interactions. The prepared Microcapsules had good spherical geometry with smooth surface as evidenced by scanning electron microscopy. On comparing the major criteria in evaluation such as percentage yield, entrapment efficiency, swelling index and in- vitro drug release. The formulation F16 was selected as the best formulation as it showed Percentage yield (97.6%), Entrapment efficiency (87.5±0.32%), Swelling index (74.6±2.24%), and In vitro drug release (98.12±0.24 %). Based on all the above evaluation parameters it was concluded that the formulation F16 was found to be the best formulation among all the formulations and can be used in the treatment of herpes simplex virus (HSV-1, HSV-2) infections.

References

1. Bhatt DA and Pethe AM. Mucoadhesive drug delivery systems: An Overview. Journal of Pharmacy Research, 2010; 3(8): 1743-1747.
2. Khan AB and Mohammana R. Review on Mucoadhesive drug delivery system: novel approaches in modern era. Journal of pharmaceutical science, 2014:4(2): 128-40.
3. James RK and Ikramul H**.**Development and Optimization of Acyclovir Loaded Mucoadhesive Microspheres by Box–Behnken Design, Journal Pharmaceutical Science. 2019;18(1): 1-12.
4. Tao Y., Lu Y.,SunY., Gu B., Lu W. Development of mucoadhesive microspheres of acyclovir with enhanced bioavailability. International Journal Pharmacy. 2009; 378, 30-36.
5. Jalón EG., Blanco P, Ygartua P. and Santoyo, S. Increased efficacy of acyclovir-loaded microparticles against herpes simplex virus type 1 in cell culture. Europian Journal Pharm. Biopharm. 2003;56: 183-187.
6. Deshmukh MT and Mohite SK. Preparation and evaluation of mucoadhesive Microcapsules of Fluoxetine Hcl. International Journal of Pharmaceutical Sciences and Research, 2017; 8(9): 3776-3785.
7. Sriram N and Katkam P. Formulation and evaluation of mucoadhesive Microcapsules of pioglitazone Hydrochloride. Journal of Encapsulation and Adsorption sciences, 2016:6: 22-34.
8. Brahmaiah B. Formulation and evaluation of extended release mucoadhesive Microcapsules of simvastatin. International Journal of Pharmaceutical and Biomedical research, 2013;4(1): 57-64.
9. Talasila S and Sultana M. Formulation and evaluation of mucoadhesive Microcapsules of chitosan loaded with ramipril. *American journal of advanced drug delivery*, 2017;2: 32-58.
10. Deshmukh MT and Mohite SK. Formulation and evaluation of mucoadhesive Microcapsules of Fluoxetine Hydrochloride. International journal of pharmaceutical research, 2016; 8(9): 3776-3785.
11. Amin ML and Ahmed T. Development of floating mucoadhesive Microcapsules for site specific release of Metronidazole. International journal of pharmacy and pharmaceutical sciences, 2016; 7(5): 208-214.
12. Velmurugan S and Ali MA. Preparation and evaluation of maraviroc mucoadhesive Microcapsules for gastro retentive drug delivery. International journal of pharmaceutical sciences, 2016; 6(7): 218-224.
13. Guntiboyina KV and Umachigi SP . Formulation and evaluation of Propranolol Hydrochloride Microcapsules. Journal of pharmaceutics and Nanotechnology, 2016; 2(2): 2347-7857.
14. Khan AB and Thakur RS. Formulation and evaluation of mucoadhesive Microcapsules of Tenofovir disoproxil fumarate. International Journal of Pharmacy and Pharmaceutical Sciences, 2016;11(1): 112-122.
15. Comoglue T. Preparation and in-vitro evaluation of Pantoprazole loaded Microcapsules. United States pharmacopeial convention, 2016; 5(15): 295-302.
16. Parmar H, Bakhliwal S and Gujhrati N. Different methods of formulation and evaluation of Mucoadhesive Microcapsules. International Journal of Applied Biology and Pharmaceutical Technology, 2010; 1: 1160-1163.
17. Jain NK. Progress in controlled and novel drug delivery system. CBS publisher and distributers, 2017; 353-376.