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FORMULATION AND EVALUATION OF BUCCOADHESIVE TABLETS OF ACYCLOVIR

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Abstract:

The main aim for the oral delivery of most of the drugs as potential therapeutic agents is their extensive presystolic metabolism, instability in acidic environment resulting into inadequate and erratic oral absorption. Parenteral route of administration is the only established route that overcomes all these drawbacks associated with these orally inefficient drugs. But these formulations are costly, have least patient compliance, require repeated administration, in addition to the other hazardous effects associated with this route. Buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. Buccoadhesive drug delivery is a relatively new drug delivery strategy; these traditional polymers are replaced by novel bio adhesive polymers such as Thiemers and lectins etc. to overcome limitation of traditional polymer. Buccoadhesive characteristics are a factor of both bio adhesive polymer and the medium in which the polymer lives. It is the aim of this article to review buccoadhesive drug delivery by discussing the structure, permeability of buccal mucosa, mechanism of buccoadhesion, novel bio adhesive polymers, buccoadhesive dosage form and their evaluation, recent advances in buccoadhesive drug delivery system. The present work emphasis on the novel techniques used till date and also guides the path for the further studies in which the work is undone. The proposed method can be used for the estimation of these drugs in biological fluids**.** The design, development, standardizing, and quality control of pharmaceutical drugs all depend on rather precise and sensitive analytical procedures.

Keywords: Drug Delivery System, Generic drugs, Acyclovir, UV- Spectrophotometer, FTIR.

Introduction

Over the previous few decades, pharmaceuticals have significantly improved patients' health state. At the same time, spending on medications has accelerated, often outperforming economic growth in many nations. Numerous economists have predicted that if healthcare spending keeps growing at the current rate, the economies of the majority of nations will be negatively impacted. In order to limit the rate of healthcare spending, most governments have started to employ cost-containment measures and have focused more on pharmaceutical spending. Given the escalating expense of healthcare and the fact that generics are frequently marketed at far

lower prices than the original brand-name products, this has made them a desirable alternative for governments and healthcare providers.

Acyclovir

Acyclovir is an agent used to treat infections caused by the herpes simplex virus (HSV). Acyclovir is FDA-approved to treat genital herpes and HSV encephalitis. Non-FDA-approved indications are mucocutaneous HSV, herpes zoster (shingles), and varicella zoster (chickenpox).

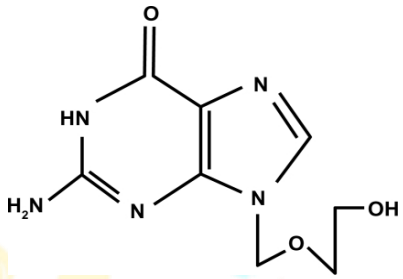

Fig. No. 1 Structure of Acyclovir

Acyclovir differs from previous nucleoside analogues in containing only a partial nucleoside structure: the sugar ring is replaced with an open-chain structure. It is selectively converted into acyclo-guanosine monophosphate (acyclo-GMP) by viral thymidine kinase, which is far more effective (3000 times) in phosphorylation than cellular thymidine kinase. Subsequently, the monophosphate form is further phosphorylated into the active triphosphate form, acyclo-guanosine triphosphate (acyclo-GTP), by cellular kinases. Acyclo-GTP has approximately 100 times greater affinity for viral than cellular polymerase. As a substrate, acyclo-GTP is incorporated into viral DNA, resulting in premature chain termination. Although acyclovir resembles a nucleotide, it has no 3' end. Therefore, after its incorporation into a growing DNA strand, no further nucleotides can be added to this strand. It has also been shown that viral enzymes cannot remove acyclo-GTP from the chain, which results in inhibition of further activity of DNA polymerase. Acyclo-GTP is fairly rapidly metabolized within the cell, possibly by cellular phosphatases.

Material and Method:

The materials and equipment's required in the formulation and evaluation of sustained release tablet of Acyclovir along with the corresponding suppliers is listed in the following tables.

Table 1: List of materials used

Sr.no.	Materials used	suppliers
1	Acyclovir	MSN Lab. Hyderabad
2	Carbopol 940 P	DEF Pharma
3	Hydroxy Propyl methyl cellulose K15	DEF Pharma
4	Microcrystalline cellulose 102	Avantor
5	colloidal silica	Hyqual
6	Disodium hydrogen phosphate	Merck Pvt. Ltd., Mumbai

7	Potassium dihydrogen phosphate	Merck Pvt. Ltd., Mumbai

All other chemicals used were of AR grade procured from Merck Pvt. Ltd. Mumbai.

Table 2: List of equipment's and apparatus used

Sr.no.	Equipment used	Suppliers
1	Weighing balance	Sartorius BT2245
2	UV- Spectrophotometer	U.V. 1900i Shimadzu, Japan.
3	Dissolution apparatus	Electrolab, India.
4	Tablet machine	Chamunda Pharma. ahmedabad(India).
5	Hardness tester	Pfizer type.
6	Roche friabilator	Electrolab, Navi Mumbai, India.
7	Bioadhesion test apparatus	Modified physical balance.
8	Digital pH Meter	Lab India
9	FTIR	Shimadzu, Japan.

Bio adhesion strength and bio adhesion time

Bio adhesive strength of the buccal tablets was measured on the "Modified Physical Balance method". The method used goat buccal membrane as the model mucosal membrane. The fresh goat buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of mucosa was tied to the glass slide which was moistened with phosphate buffer pH 6.8. The tablet was stuck to the lower side of another glass slide with glue. The both pans were balanced by adding an appropriate weight on the left- hand pan. The glass slide with mucosa was placed with appropriate support, so that the tablet touches the mucosa. On the side of balance powder (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The weight required to detach the tablet from the mucosal surface gave the bio adhesive strength. The experiment was performed in triplicate and average value was calculated. Bioadhesive strength was assessed in terms of weight [gm] required to detach from membrane. Bioadhesion strength which was measured as force of adhesion in Newton by using formula.

Force of adhesion (N) = Mucoadhesive strength / 100 X 9.81

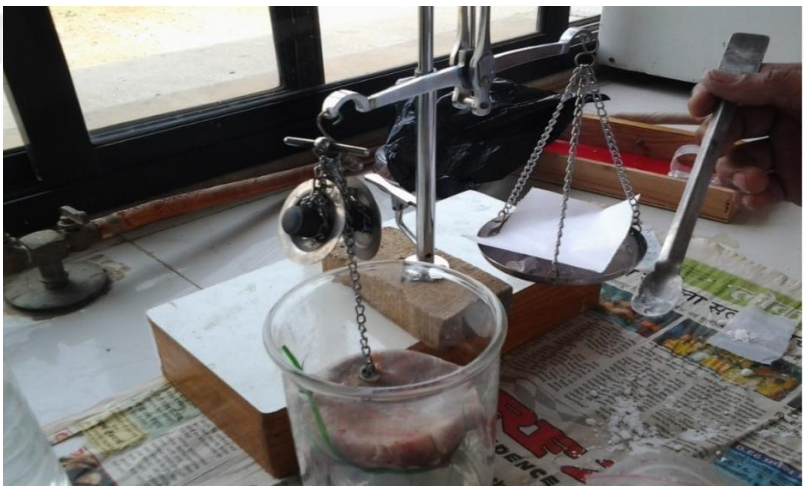

Fig. 2: Modified physical balance for determination of bioadhesive strength

Bioadhesion time determination

The ex-vivo mucoadhesion time was examined after application of the buccal tablet on freshly cut goat buccal mucosa. The fresh goat buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 and kept at 37 ± 1°C. After 2 minutes, stirring was applied slowly to simulate the buccal cavity environment and tablet adhesion was monitored for 8 h. The time for the tablet to detach from the goat buccal mucosa was recorded as the mucoadhesion time.

Results and Discussion

Preformulation Study

Organoleptic properties of drug

The sample of acyclovir received was studied for its organoleptic characteristics such as appearance colour, odour and Melting point. The results are given in Table 3.

Table 3: Physical characteristics of drug

Characters	Inference
Appearance	Crystalline powder
Colour	White to off white
Odour	Odorless
Melting point	257.0 O C

UV spectroscopy (determination of λ max): The Acyclovir Stock solution was prepared in of phosphate buffer of pH 6.8 with a concentration of 700 µg/ml. For the optimum concentration this solution was appropriately diluted with distilled water to obtain a concentration of 70µg/ml. The solution was kept in a fused silica cuvette 10mm. The UV spectrum was recorded into the range of 200-400 nm of shimadzu UV-visible spectrophotometer at 1cm. It showed a λ max at 250 nm showing absorbance 0.4333 A0

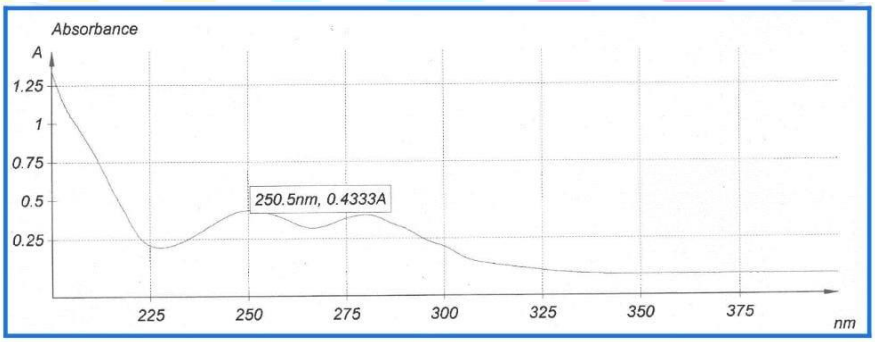

Figure 3: UV spectrum at λ max

Preparation of standard calibration curve of acyclovir

Calibration curve was plotted by taking values of concentration and absorbance.

Table 4: Concentration and absorbance of acyclovir

Sr. No.	Concentration (µg/ml)	absorbance
1	0	0.00
2	7	0.0435
3	17	0.1059
4	35	0.2188
5	70	0.437
6	88	0.541
7	105	0.6551

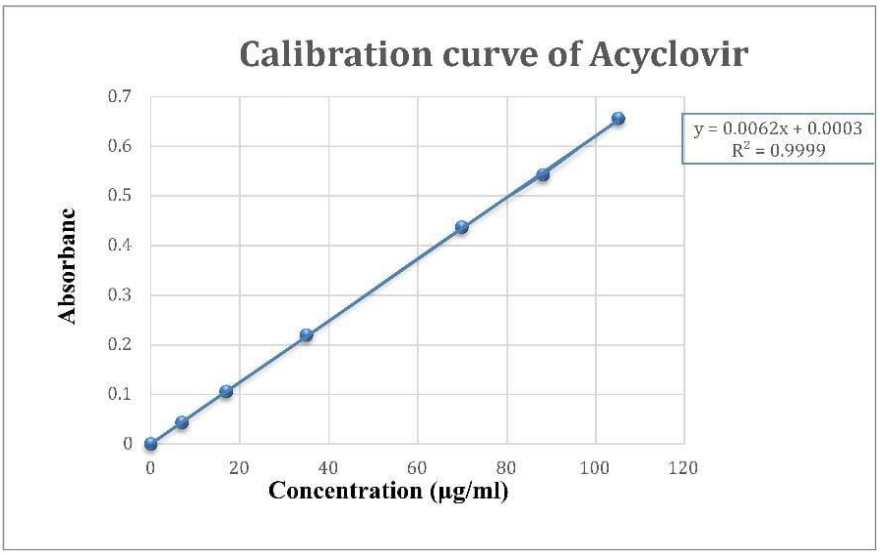

Fig. 4: Calibration curve of acyclovir in phosphate buffer of pH 6.8

The correlation coefficient (R2) = 0.9999

From the graph it is showed that it follows Beer-Lambort's law.

Evaluation Parameter

Precompression parameter

The powder blend of each formulation were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose and result obtained are shown in Table 5.

Table 5: Precompression parameter of formulations

Formulation	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Carr's index	Hausner ratio	Angle of repose (θ)
F1	0.43±0.017	0.51±0.017	12.57	1.15	300.55'±0.74
F2	0.48±0.011	0.37±0.023	13.72	1.14	290.10'±0.34
F3	0.42±0.023	0.53+0.028	13.40	1.14	280.80'±2.58
F4	0.43±0.017	0.51±0.017	13.37	1.15	290.27'±0.27

F5	0.41±0.011	0.47±0.023	12.38	1.14	290.49'±1.16
F6	0.42±0.013	0.50±0.016	13.68	1.14	300.91'±0.71
F7	0.41±0.011	0.53±0.023	12.86	1.15	280.43'±1.39
F8	0.45±0.019	0.52±0.018	13.67	1.14	290.04'±0.48
F9	0.44±0.017	0.51±0.015	13.72	1.15	290.29'±0.66

*Values are expressed in mean ±SD (n=3)

Bulk density

The bulk density values less than 1.2 gm/cm3 indicate good packing and values > 1.5 gm/cm3 are indicates poor packing. The bulk density values for all formulation of powder bulk varied in the range of 0.41±0.011 gm/cm3 to 0.47±0.023 gm/cm3.The values obtained lies within acceptable limits.

Tapped density

The tapped density values for all formulation of powder bulk varied in the range of 0.47±0.023 gm/cm3 to 0.58±0.028 gm/cm3. The values obtained lies within acceptable limits.

Carr's index

The percent compressibility of formulation of powder bulk was determined by Carr's compressibility index. The percent compressibility for all formulation lies within the range of 12.76 % to 13.72 % indicates acceptable flow property

Hausner's ratio

Hausner's ratio was found to be in the range of 1.14 to 1.15 which shows acceptable flow property and good packing ability.

Angle of repose

The of angle of repose for all formulation of powder blend were found to be in the range of 270.90'±2.01 to 300.77'±0.68 indicating good flow property. It can be concluded that the powder blend for all batches possess good flow characteristic.

Post compression parameter

All the formulations evaluated for the post compression parameters, result obtained were shown in Table 6. The average weight from all the formulation were found be in the range 449.31± 4.62 mg to 451.61 +3.93 mg, indicates that the all batches have the average weight as per the official standards. The drug contents in all the batches in the range of 95.06 ± 1.87% to 100.2 ±1.62%. All the batches have good hardness and friability as per standards. Surface pH of the tablets were found in the range of 5.72±0.04 to 6.78±0.05 that indicates no risk of mucosal damage or irritation. The thickness of the tablet was in the range of 3.16 ±0.04 mm to 3.21± 0.02 mm.

Table 6: Post compression parameter of formulation

Formulation	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Weight variation (mg)	Drug content (%)	Surface pH
F1	5.36 ±0.20	3.51 ±0.02	0.34 ±0.04	450.86 ±1.89	97.27 ±1.62	5.84 ± 0.04
F2	5.14 ±0.35	3.37 ±0.05	0.41 ±0.02	451.61 ±3.42	95.06 ±1.63	5.62 ±0.04

F3	5.76 ± 0.30	3.47 ±0.03	0.51 ±0.03	450.66 ±4.07	96.48 ±1.68	6.61 ±0.42
F4	5.41 ±0.20	3.39 ±0.04	0.56 ±0.02	449.31 ±5.72	96.37 ±1.87	6.72 ± 0.05
F5	5.97 ±51	3.17 ±0.07	0.60 ±0.03	450.62 ±4.52	96.86 ± 0.58	6.3 ± 0.03
F6	5.44 ±0.34	3.12 ±0.06	0.62 ±0.01	451.02±2.67	96.47 ±2.14	6.22 ±0.05
F7	5.50 ±0.41	3.20 ± 0.07	0.57 ±0.02	450.58 ±3.41	97.14+3.11	6.64 ±0.04
F8	5.47 ±0.36	3.16 ± 0.03	0.69 ±0.02	450.73 ±2.74	99.8 ±3.29	6.14 ±0.05
F9	5.46 ±0.37	3.17 ± 0.04	0.77 ±0.02	450.41 ±2.61	100.2 ±3.14	6.23 ±0.05

*Values are expressed in mean ±SD (n=3)

Bio adhesive strength and bio adhesive time of formulation

The aim of study is to formulate tablet that can adhere to membrane for about 8 hours and release the drug for 8 hours. It was found that near about all formulation achieve adhesion property and there was no much difference in adhesion time of formulations.

Table 7: Bioadhesive strength and bioadhesion time of different formulations.

Formulation	Bioadhesive strength (gm)	Bioadhesion force (N)	Bioadhesion time (h)
F1	5.14	0.47	5.54
F2	6.98	0.63	6.01
F3	9.56	1.07	7.56
F4	9.05	0.47	7.14
F5	9.63	0.87	7.37
F6	8.57	0.64	6.15
F7	7.68	0.94	6.26
F8	8.67	1.01	7.54
F9	8.17	0.98	6.59

The bioadhesives property of tablets of acyclovir containing varying proportions of polymers was determined with an insight to develop the tablets with adequate bioadhesiveness. For the maximum adhesion of tablet with in buccal cavity the tablet should possess the some bioadhesive strength. All the formulations show optimum level of bioadhesive strength. The bioadhesive strength was found to be in the range of 5.14-9.63 gm. The highest adhesion force and highest strength of the mucoadhesive bond was observed with the formulation F8 and F9. Tablets of formulation F1 and F9 containing showed least adhesion force than tablet of all other formulation.

Bioadhesion time was also found to be optimum which is requiring for the formulation to be remaining within the buccal cavity.

Swelling study of formulations

All the formulations were studied for the percentage swelling index. This is the important parameter to be studied for drug release from polymeric matrix system.

Table 8: Cumulative percent swelling of formulations

Times (h)	Percentage swelling index								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	10	13	16	31	24	21	25	27	28
2	19	20	23	56	50	36	40	49	48
3	27	32	36	72	67	48	52	63	63
4	39	40	45	89	84	60	64	74	75
5	51	56	62	96	95	77	83	89	90
6	64	68	76	99	99	91	92	96	98
7	72	75	80	100	101	96	94	99	100
8	76	82	85	101	102	97	98	100	101

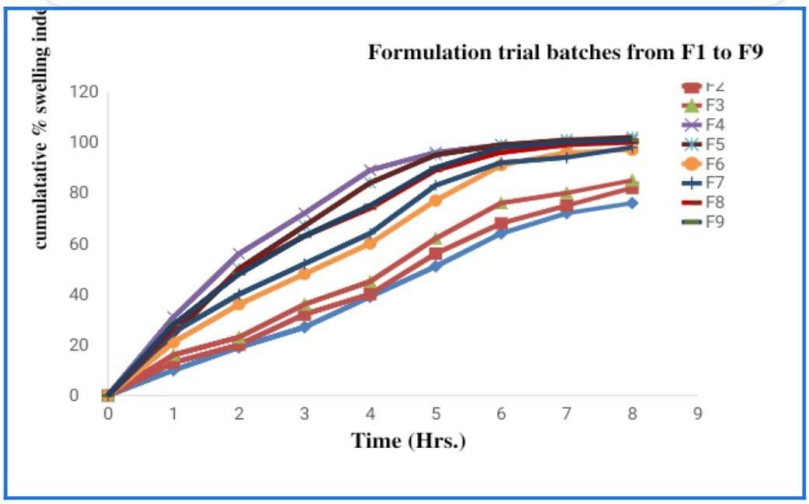

Fig. 5: Percentage swelling index of formulations F1-F6

It should be necessary that polymer to be swell, so by the diffusion it can release the drug. As time increases there was more swelling observed and it also depend upon the ratio of polymer in the formulation, it was clearly observed from result obtained. From the result obtained after swelling study it was concluded that Swelling index increased by increasing concentration of HPMC K15M. In formulation F1 and F2 swelling index is up to 8 h due to initial bursting. In formulation F3, F4, F5, F6, F7, F8 and F9 there is increase in swelling index due to increase concentration of HPMC K15M. So, optimum swelling showed in formulation F8.

Dissolution study

All the formulation evaluated for the percentage drug release. Table 9 showed average cumulative percentage of drug released of formulations.

Table 9: Average cumulative percentage of drug released of formulations

Time	Average percentage of drug release form								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	39	40	32	2	5	13	15	14	15
2	48	45	41	12	14	26	32	36	36
3	65	69	63	24	25	41	44	49	51
4	86	89	78	36	40	58	58	60	61
5	92	98	93	57	60	7	83	89	90
6	99	98	93	57	60	79	83	89	97
7	100	100	98	62	67	87	92	96	97
8	102	101	100	70	74	93	96	99	100

Drug release studies were made to determine whether the release of the drug is slow enough, i.e., which polymer ratio is enough to sustain the release of the drug for 8 h. As we increases the ratio of HPMC K15M in the formulation, there is more swelling were observed which also responsible for the drug release and it also sustained the drug release at the 8 h. The drug release in F1 and F2 formulation is 102% and 101% respectively but there is initial abrupt bursting effect. Drug release in formulation F4, F5, F6 and F7 decreases with increases concentration of HPMC K15M. Drug release in formulation F8 is 99% which sustained at 8 h. Therefore, optimized formulation was F8 having the polymer ratio 1:1.5 [Carbopol 940P:HPMC K15]. From, the comparison study of all formulation it was concluded that the order of drug release among formulations was found to be F9>F8> F7> F6> F5> F4.

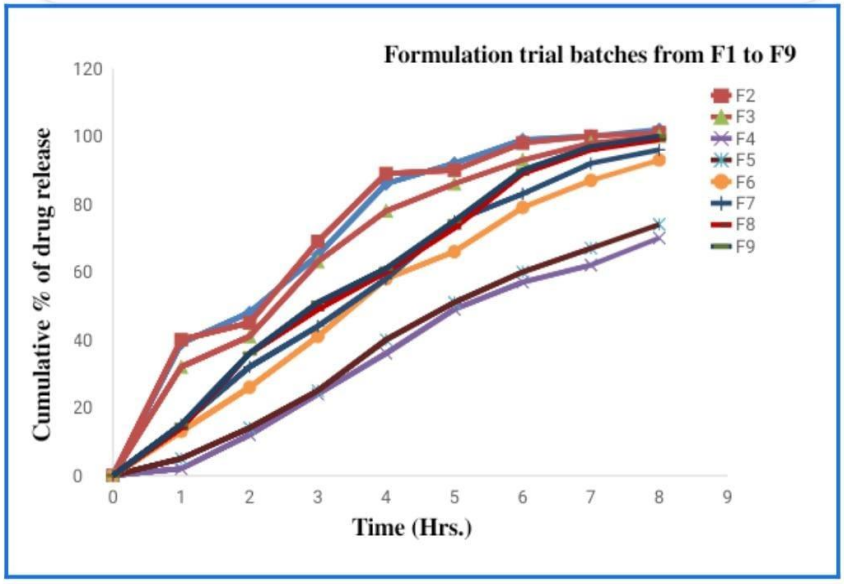

Fig. 6: Cumulative percent drug release profiles of formulations F1-F9

Drug diffusion study

Diffusion study was carried out by using Franz diffusion cell. Table 7.8 showed average cumulative percentage of drug diffusion from formulations.

Table 10: Average cumulative percentage of drug diffusion from F1-F9

Time (h) Average cumulative percentage of drug diffusion from

	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	28	23	10	8	2	12	10	14	15
2	41	39	21	15	8	20	21	24	25
3	58	51	34	18	23	39	34	37	39
4	69	62	48	29	38	61	48	52	53
5	75	71	56	41	51	65	60	67	66
6	78	75	62	52	62	77	81	83	82
7	81	80	71	63	70	89	89	94	92
8	81	83	76	70	82	93	95	99	100

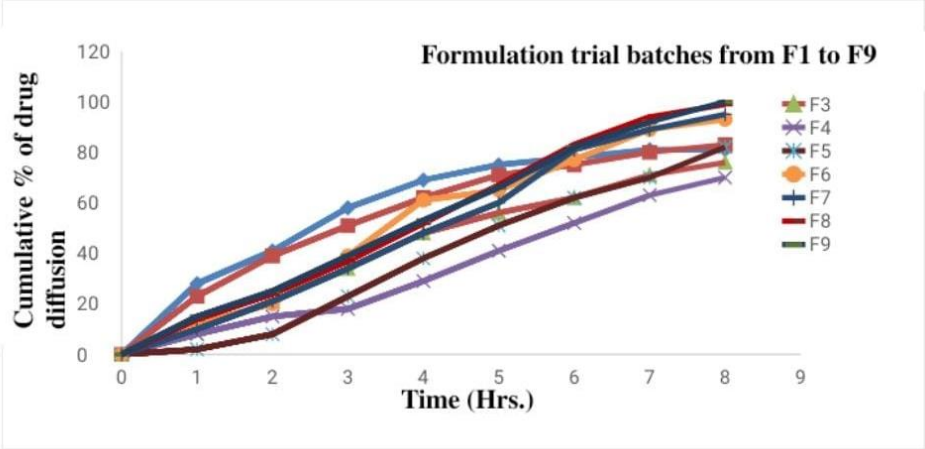

Fig. 7: Cumulative percent of drug diffusion profiles of F1-F9

Drug diffusion studies were made to determine whether the diffusion of the drug is slow enough, i.e., which polymer ratio is enough to sustain the release of the drug for 8 h. As shown in fig 7, that all formulation show the percentage drug diffusion. As we increases the ratio of HPMC K15M in the formulation, there is more swelling were observed which also responsible for the drug diffusion and it also sustained the drug diffusion. The drug diffusion in F1 and F2 formulation was 96.49% and 96.23 % respectively but there is initial abrupt bursting effect. Drug diffusion in formulation F3, F4, F5 and F6 decreases with increases concentration of HPMC K15M. Drug diffusion in formulation F3 is 95.87 % which sustained for 8 h. So, optimized formulation was found to be F3 having the polymer ratio 1:1.5 [Carbopol 940P:HPMC K15M]. Also other formulations show optimum drug diffusion. From, the comparison study of all formulation it was concluded that the order of drug diffusion among formulations was found to be F3> F2> F1> F4> F5> F6.

Drug release kinetics of formulations

The drug release data of the selected formulation (F9) was fitted to various models like zero order, first order, Higuchi's model, Hixon Crowell and Korsmeyer's model. The Kinetic model fitting of drug release data was done with the help of Microsoft excel based software PCP-Disso v2.08. The calculated slope, the intercept and R^2 are shown in Table 7.9. Formulation (F3) was best fitted for Hixon Crowell model with regression value 'R^2' of 0.9534. Slope value suggested that the release of acyclovir from tablets followed Case-II transport mechanism. Formulation (F8) follows zero order release kinetics with regression value 'R2' of 0.9952.

Table 11 : Drug release kinetic of selected formulation (F9)

Model	R2	Slope	Intercept
Zero order	0.9952	14.36	0.0267
First order	0.9908	0.2168	0.0267
Hixon Crowell	0.9937	1.3587	1.1278
Korsmeyer-Peppas model	0.9934	0.9984	0.3427
Higuchi model	0.9836	1.3587	0.1547

Summary and Conclusion

Buccal drug delivery involves systemic or local delivery of drug via the buccal mucus membrane, following administration the drug gets into the systemic circulation thereby avoiding first pass metabolism. Buccal drug delivery of acyclovir would be advantageous as it has very low bioavailability and it under goes extensive first pass metabolism. The present study is aimed to fabricate and develop sustained release buccoadhesive tablets of acyclovir. The scheme of work is divided into five phases. Initially collection of theoretical and technical data was done; this was followed by procurement of materials, fabrication of bioadhesive strength apparatus. Acyclovir obtained from Flamingo Pharmaceuticals Limited, Mumbai. Before, carried out the final batches, the ratio of polymers for final batches were determine by producing the preliminary batches of different ratio, two important parameters were evaluated from it such as drug release and bioadhesion strength. The batch containing polymer ratio in 1:1.5 i.e. Carbopol 940P and HPMC K15M show optimum drug release and bioadhesion time. So, these are selected for the optimized formulation. Finally, buccoadhesive tablets was prepared using various bioadhesive polymers such as carbopol 940 P in combination with HPMC K15 M in different ratio such as 1:0.5, 1:1 and 1:1.5, such 9 different formulations of tablets were prepared. The tablets were prepared by direct compression method using 10 mm flat round punch on multi-station compression machine.

The formulations were evaluated for their physical characteristics like thickness, hardness and friability, weight variation, content uniformity also along with surface pH study, swelling index study were carried out. Bioadhesive strength study was carried out with help of modified physical balance In case of swelling index study it was concluded that swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration. In swelling study, it was found that the amount of HPMC K15M plays an important role in swelling of the matrix and leads to the drug diffusion. In-vitro dissolution study was performed with the help of U.S.P dissolution test apparatus-II with 900 ml of phosphate buffer pH 6.8 at the 100 RPM for 8 h. From the result it was concluded that all formulation shows optimum drug release up to 8 h. It was found that formulation F8 shows maximum drug release because it contains the optimum concentration of polymer. And formulation F9 trial taken as a reproducibility batch. Drug release kinetic was applied to all formulation. Formulation follows zero order and Hixson-Crowell model. From the optimize formulation it was concluded that formulation show case II transport mechanisms. Therefore, the release of drug from the prepared tablets is controlled by swelling of the polymers, followed by drug diffusion through the swelled polymer.

Conclusion

From the present study it was concluded that the buccoadhesive drug delivery system of acyclovir was deliver the drug in sustained release manner for 8 h. Also it successfully avoids the extensive first pass metabolism and improves the bioavailability of Acyclovir. It was also found that Carbopol 940P and HPMC K15M can be promising polymers for buccoadhesive drug delivery systems and also as we increases the ratio of HPMC K15M in the formulation there is decrease in the drug release rate of Acyclovir. The optimized formulation sustained the release up to 8 h, followed Zero order kinetics while the drug release mechanism was found to be case II transport, controlled by diffusion through the swollen matrix. Sustained drug release with adhesion time of about 8 h and good bioadhesive strength was observed in case of optimized formulation. The swollen tablet also maintained its physical integrity during the drug release study.

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