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Formulation and Evaluation of Ganciclovir Novel Buccoadhesive Tablets with Different Polymers

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***Abstract*—** *The main objective of purpose study is to formulate buccal drug delivery system of Ganciclovir by using different types of mucoadhesive polymers which may increase the intimacy and duration of contact between drug- containing polymer and a mucous surface which will increase the residence time of drug in the body and finally increase the bioavailability of this highly water soluble drug. The direct drug absorption and decrease in excretion rate will also increase the bioavailability. 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 form.*

***Keywords*—** *Ganciclovir, Mucoadhesion, HPMC K15M, Ethylcellulose.*

I. INTRODUCTION

The concept of mucoadhesives was introduced in the early 1980s. Mucoadhesion can be defined as the phenomenon of the attachment of natural or synthetic polymers to a mucosal surface[1]

Since from the last 40 years, the concept of mucoadhesion has provided the great application in prolonging the residence time as well as controlled release effect of various bioadhesive dosage forms through different mucosal routes. The formulations based on the mucoadhesive drug delivery system have shown the enhanced bioavailability of many drugs. The use of various mucoadhesive polymers have achieved the significant interest in formulating the sustained release, extended release as well as prolonged release dosage forms. The mucoadhesive drug delivery provides greater absorption and enhanced bioavailability of dosage forms due to the large surface area and higher blood flow in the mucosal cavities[2]

The main advantages of these formulations are: drug targeting, sustained release, increased permanence time in the buccal mucosa, increased bioavailability, and decreased potential adverse effects[3].

Mucoadhesion is known to increase the intimacy and duration of contact between drug- containing polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. Increased residence time and adhesion may lead to lower API concentrations and lower administration frequency to achieve the desired therapeutic outcome[4].

Among all dosage form, oral route is more preferred to patient. Transmucosal routes of drug delivery offer distinct advantages over per oral administration for systemic drug delivery.

The buccoadhesive dosage forms along with sub-lingual tablets, oral gels and ointments, lozenges, rapidly dissolving tablets and chewing gums are the formulations targeting drug delivery in the oral cavity[5].

Bio-adhesion can be defined as a state in which two components, of which one is biological in origin, are held together for extended periods of time by the help of interfacial forces. It is denoted (esp. in pharmacy) as mucoadhesion since the main biomaterial involved is mucus present at various sites in the body[6].

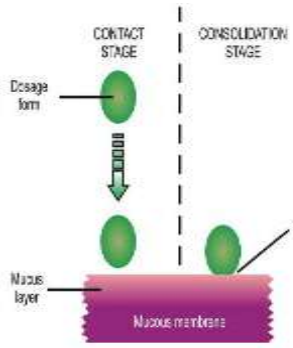

Fig 1: Two steps of mucoadhesion

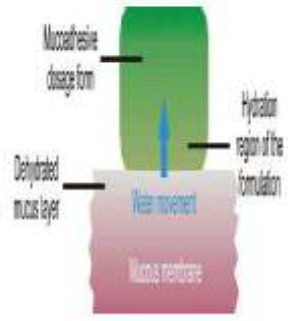

Fig 2: Mucoadhesion theory

Buccoadhesive dosage forms: Over the past few years, different dosage forms intended for buccal drug delivery have been developed. Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry illustrated in the following figure 3.

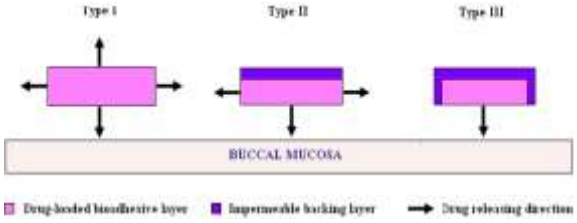

Fig 3: Design of buccal mucoadhesive dosage forms

II. MATERIALS AND METHODS

Ganciclovir was a gift Sample obtained from Natco Pharm ltd., Carbopol was received from Balaji Drugs , HPMC and Guar gum were from Yarrow Chem products Mumbai, Ethyl cellulose,Lactose and Magnesium Stearate from S. d Finechem limited, Mumbai.

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III. Formulation and Development of Ganciclovir Novel Buccoadhesive Tablets

Preparation of buccal tablets containing Ganciclovir:

Direct compression method has been employed to prepare buccal tablets of Ganciclovir using Carbopol 934, HPMC K15, Chitosan and Guar gum as polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table 12). Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min by triturating in a glass mortar & pestle. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. Final lubricated blend equivalent to 290mg was compressed in to tablets using 4 mm round flat punches on 10-station rotary tablet compression machine (Rimek). Upper punch was raised and the backing layer of ethyl cellulose was placed on the above compact. Then 2 layers were compressed into a mucoadhesive bilayer tablet with a total weight of 300 mg/tablet.

TABLE 1. Composition of buccoadhesive tablets containing Ganciclovir

Ingredients (mg)	Formulation code						
	F1	F2	F3	F4	F5	F6	F7
Ganciclovir	250	250	250	250	250	250	250
Carbopol 934	10	20	30	-	-	-	-
HPMC K15M	-	-	-	10	20	30	-
Guar gum	-	-	-	-	-	-	10
Magnesium stearate	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3
Ethyl cellulose	10	10	10	10	10	10	10
Lactose	QS	QS	QS	QS	QS	QS	QS

Evaluation of buccoadhesive tablets containing Ganciclovir [7,8,9,10,11]

A) Precompression parameters:

Determination of angle of repose

A glass funnel is held in place with a clamp and place a graph paper below it. Approximately weighed quantity of powder (mix blend) is poured through the funnel keeping the orifice of the funnel blocked by the thumb. A gap of 6.4 mm is maintained between the bottom of the funnel stem and the top of the powder pile. Again the powder is poured through the funnel keeping the orifice of the funnel blocked by the thumb. The height of the heap is measured. The circumference of the heap is marked by pencil and diameter is determined with the help of scale and finally the radius is determined. Finally the angle of repose is calculated by using formula

$$\theta = \tan^{-1}(h/r)$$

Determination of Bulk Density and Tapped Density

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the Initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals for 100 tapping. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulae.

Bulk density = W / VO

Tapped density = W / VF

Where, W = weight of the initial granules

VO = initial volume of the granules

VF = final volume of the granules.

Hausner's Ratio: It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Compressibility index (Carr's Index): The flow ability of powder can be evaluated by comparing the bulk density and tapped density of powder and the rate at which it packed down.

$$\text{Compressibility index}(\%) = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 100$$

B) Post compression parameters[8,9,10,11]

Weight variation:

The causes for weight variation can be divided into granulation and mechanical problems. If the granule size is large, the dies will not be uniformly filled. Similarly mechanical problems can be traced of lower punches of non-uniform length. All prepared Ganciclovir buccal tablets were evaluated for weight variations as per USP monograph. Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight was calculated, individual tablet weight was then compared with the average value to find out the deviation in weight and percent variation of each tablet was calculated.

Tablet Hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its strength or hardness. The hardness of ten randomly selected buccal tablets was measured by using Monsanto hardness tester which measures the pressure required to break diametrically placed tablets by applying pressure with coiled spring and expressed in Kg/cm2 .The mean and standard deviation values were calculated and reported.

Friability:

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W) and transferred into friabilator. The friabilator was operated at 25rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (Wt). The % friability was then calculated by

$$\%F = (W\text{-}Wt / W) \times 100$$

Tablet thickness[12]*:*

The thickness of each tablet was measured in mm using a digital vernier caliper. The mean and standard deviation values were calculated and reported.

Content Uniformity[13,14]*:*

Two tablets from each formulation were powdered individually and a quantity equivalent to 100 mg of Ganciclovir was accurately weighed and extracted with a suitable volume of 0.1 N HCL. Each extract was suitably diluted and analyzed spectropotometrically at 255 nm.

Swelling study

The swelling behavior of a dosage form was measured by studying its weight gain or water uptake. Buccal tablets were weighed (W0) and placed separately in petri dishes with 5ml of phosphate buffer pH 6.8. At the interval of 1,2,3,4,5,6,7 and

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8 hours, tablets were removed from the petri dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (Wt) and the swelling index (SI) were measured in terms of percent weight gain.

$$SI = \frac{(W_t - W_0)}{W_0} \times 100$$

Where, SI= Swelling index
W0 = Initial weight of dosage form
Wt = Weight of dosage form at time t

Surface pH [15]:

This was determined by allowing the tablet to swell in 10 ml of phosphate buffer (pH 6.8) for 2 hrs. A combined glass pH electrode was brought in contact of the swollen tablet and the pH was measured after 1 min equilibrium.

Ex-vivo mucoadhesion time[16]:

The fresh goat buccal mucosa was tied on the glass side, and a mucoadhesive core side of each tablet was wetted with 2 drops of phosphate buffer pH 6.8 and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 sec. 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°C ± 1°C. After 2 min, a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 h. The time for detach from the goat buccal mucosa was recorded as the mucoadhesion time.

In-vitro drug release study[17]:

The USP type- II rotating paddle method was used to study the drug release from the tablet. The dissolution medium consisted of 900ml of sodium phosphate buffer pH 6.8. The release study was performed at 37± 0.50C, with a rotation speed of 50 rpm. The backing layer of the tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, with appropriate dilutions with phosphate buffer pH 6.8 and were analyzed spectrophotometrically at 255nm.

Release kinetics [19]

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

Zero- order Kinetic model - Cumulative % drug released versus Time

First- order Kinetic model - Log cumulative % drug remaining versus Time

Higuchi ‘s model-Cumulative percentage drug release versus square root of time

Korsmeyer equation / Peppa’s model- Log cumulative percent drug released versus log time

Stability study [20, 21, 22]:

In the present investigation to assess the stability of the Ganciclovir tablet formulations, the optimized batch formulation was packed in aluminium foil in tightly closed container. They were then stored at 40ºC ±2 ºC / 75% RH for two months. The samples were then taken and observed for any physical change and drug content.

IV. Result and Discussion

Preformulation Studies

Solubility Analysis

TABLE 2: Solubility profile of Ganciclovir

Solevent	Solubility
0.1 N HCL	Very soluble
Water	Very soluble
Dimethyl-sulfoxide (DMSO)	Very soluble
Phosphate buffer pH 6.8	Freely soluble

Melting Point determination:

Melting point is within the standard range of 250˚C which shows pure drug Ganciclovir is free from impurities.

TABLE 3: Melting point of Ganciclovir

Sample	Melting point of sample in literature	Melting point of sample experimented determine*
Ganciclovir	250°C	250°C ± 1

Drug and excipients compatibility studies by FT- IR Spectroscopy:

No considerable change in the *FT-IR* peak of Ganciclovir when mixed with excipient compared to pure Ganciclovir

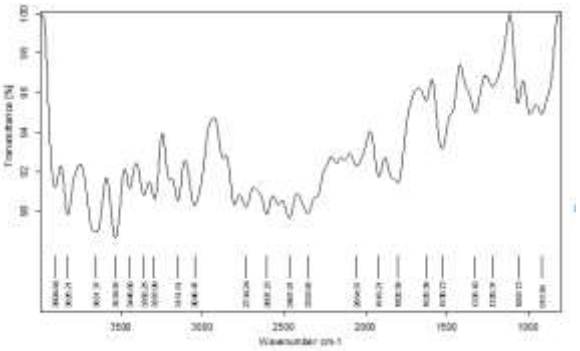

Fig 4: *FT-IR* Spectrum of pure drug Ganciclovir

TABLE 4: *FT-IR* Spectral details of Ganciclovir

SI.NO	Functional group	Frequency (cm-1)
1.	NH2(stretching)	3358.25
2.	N-H(Stretching)	3151.61
3.	C-H(Stretching)	3048.47
4.	C-H(Stretching)	2734.24
5.	C=O(Stretching)	1628.39
6.	C=N(stretching)	1530.73
7.	C=N(bending)	1328.10
8.	C-O-C(stretching)	1220.37

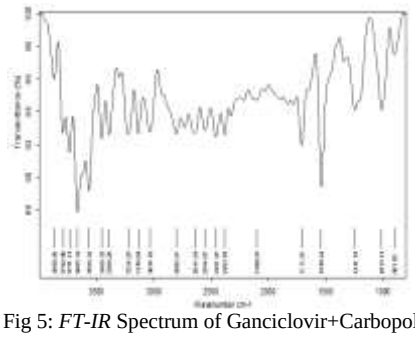

Fig 5: *FT-IR* Spectrum of Ganciclovir+Carbopol

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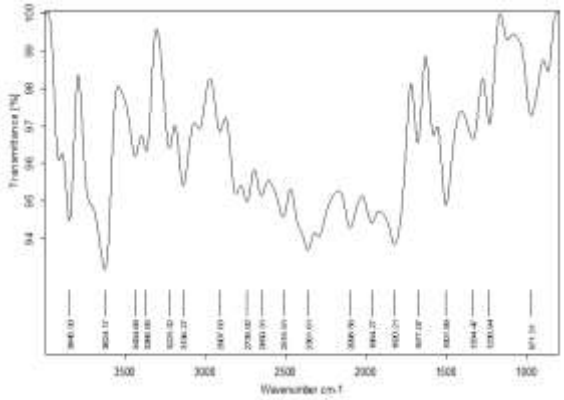

Fig 6: FT-IR Spectrum of Ganciclovir+HPMC

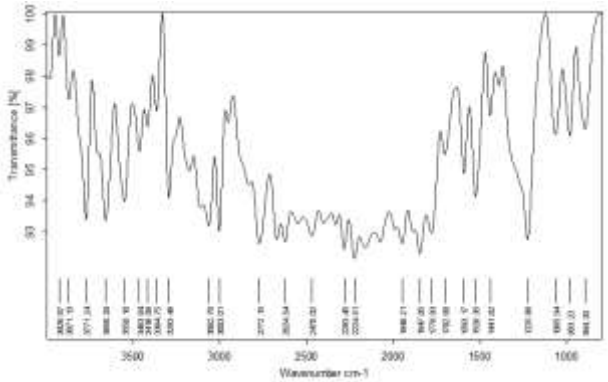

Fig 7: *FT-IR* Spectrum of Ganciclovir+ Guar gum

λmax of Ganciclovir in phosphate buffer pH 6.8

The λmax of Ganciclovir in phosphate buffer pH 6.8 was found to be 252.50 which is shown in below figure.

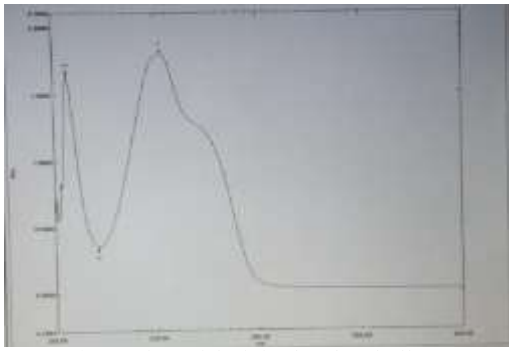

Fig 8: λmax of Ganciclovir in phosphate buffer pH 6.8

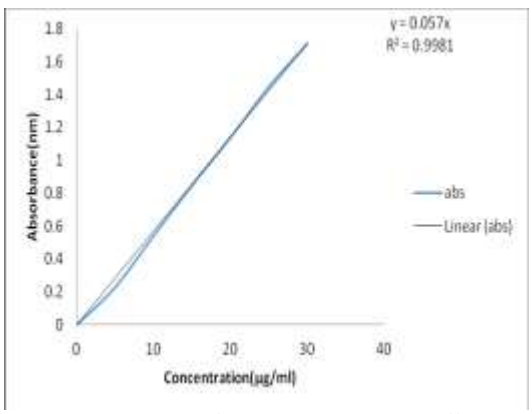

Fig 9: Calibration curve of Ganciclovir phosphate buffer pH 6.8

TABLE 5: Precompression parameters results for formulation F1-F7

Parameters	Formulation code						
	F1	F2	F3	F4	F5	F6	F7
Bulk density (g/cm3)	0.38	0.36	0.37	0.4	0.39	0.39	0.38
Tapped density (g/cm3)	0.456	0.432	0.45	0.45	0.46	0.45	0.47
Angle of repose(˚)	23	24	23	23	23	25	24
Carr's index%	16.66	16.66	17.7	17.7	15.2	13.33	19.1
Hausner's ratio	1.2	1.2	1.2	1.2	1.17	1.15	1.2

TABLE 6: Post- compression parameters results for formulation F1-F7

Parameters	Formulation code						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Thickness(mm)	4.25	4.13	4.16	4.31	4.22	4.25	4.22
Hardness (kg/cm2)	4.8	4.5	5.1	5.0	5.5	5.8	5.1
%Friability	0.69	0.58	0.53	0.65	0.51	0.67	0.52
Weight variation (mg)	310	300	280	290	300	280	300
Drug content (%)	97.87	97.80	97.55	97.46	97.00	97.55	98.0
Surface PH	6.2	7	6.16	6.21	6.57	6.19	6.29

TABLE 7: *In vitro* release study of the formulation F1-F7

Time (hrs)	%CDR			
	F1	**F2**	**F3**	**F7**
0 min	0	0	0	0
30 min	9.59	10.6	23.33	16.86
1hr	19.77	22.68	33.37	17.7
2hr	17.96	37.8	48.05	24.66
3hr	42.99	41.82	49.88	37.32
4hr	44.56	44.58	53.85	53.83
5hr	46.76	48.04	55.17	53.83
6hr	50.66	51.95	56.56	61.47

Formulations F4, F5 & F6 undergone dissolution within 1 minute in the dissolution medium phosphate buffer pH 6.8 and exhibited 100% release. This characteristics behavior is attributed to low viscosity behavior and water soluble property of HPMC K15M. As these formulations could not be able to produce sustained release property, we rejected in-vitro release study of formulation F4, F5 & F6.

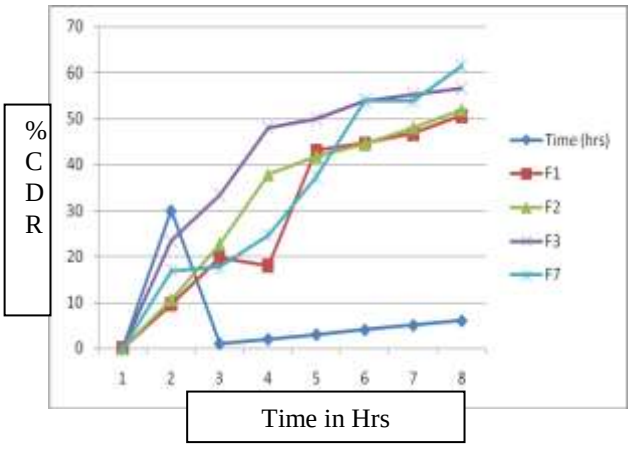

Fig 8: *In vitro* drug release study of all formulations in phosphate buffer pH 6.8

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TABLE 8: Swelling index of the Ganciclovir buccal tablets

Time (hr)	Formulation code			
	F1	F2	F3	F7
1	24.19	24.19	27.66	185.80
2	40.32	53.87	55.33	233.22
3	86.45	113.22	136	222.33
4	120.96	248.38	288	186.66
5	160	299.67	348	-
6	202.25	352.9	411.33	-

TABLE 9: *Ex-vivo* mucoadhesion time (in-vitro residence time) of Ganciclovir tablets

Formulations	*In-vivo* residence time
F1	4 hrs 13 min
F2	4 hrs 55 min
F3	5hrs 35 min
F7	2 hrs 10 min

TABLE 10: Kinetics modeling data

Formulation	Kinetic Drug Release		Mechanism of Release		
	Zero Order	First Order	Higuchi	Korsemeyer Peppas	
	Correlation coefficient (r2)	Correlation coefficient (r2)	Correlation coefficient (r2)	Correlation coefficient	Slope 'n' value
F7	0.9202	-1.608	0.9457	-18.9	0.42

Stability Studies Results

TABLE 11: Stability data of selected F7 formulation stored at 40˚C ± 2˚C and 75 ± 5% RH

No of Days	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	pH	Swelling index	%Drug Content	% CDR
0	4.22	5.1	0.52	6.89±0.068	242.10	98.0	61.47
30	4.22	5.1	0.50	6.66±0.215	242.10	97.5	60.12
60	4.23	5.0	0.50	6.78±0.337	244.0	97.0	60.0

Discussion

Melting point is within the standard range of 250˚C which shows pure drug Ganciclovir is free from impurities. No considerable change in the *FT-IR* peak of Ganciclovir when mixed with excipient compared to pure Ganciclovir. The results of the preformulation studies are represented in table no. 28 & 29. The bulk density and tapped density for core granules were found to be 0.36 to 0.40 g/cc and 0.43to 0.48g/cc respectively. Hausner's ratio values were found in the range of 1.2 to 1.18 indicates good/free flow.

The Carr's index values found in the range of 13.33 to 19.56 % which indicate that powder formulation have fair flow properties and powder bed is compressible. The angle of repose was found in the range of 23˚-25˚ indicating excellent flow property of the powder.

The results of *in-vitro* drug release are represented in the table. From the results given in the table 32,33,34 it was evident that carbopol 934 in the concentration of 30mg (F3), is showing better result 56.56% drug release in 6 hrs when compared with Other two formulations (F1 and F2). *In-vitro* release of Guar gum results given in table 38,39,40 it was evident that guar gum in the concentration of 10mg (F7), is showing better result 61.47% drug release in 6 hrs when compared with other two concentrations

The formulation F1, F2 & F3 containing carbopol showed 40-50% swelling within 2 hrs and was found to be gradually increasing with time this is because carbopol is swellable in water. The formulation F7 containing guar gum showed maximum swelling within two hrs because in cold or hot water guar gum disperses and swells almost immediately to form a highly viscous thixotropic solution.

Guar gum showed less residence time because in cold or hot water it disperses and swells almost immediately to form a viscous thixotropic solution andhence erode and detach faster compared to other formulations. There was no change in color and shape. There were no significant changes indrug content and %CDR. Two months of stability studies revealed that; there was no any significant degradation of the drug.

V. CONCLUSION

The formulations prepared with guar gum in the concentration of 10mg (F10) was showing better result 61.47% drug release compared to other formulation and is thus optimized. It can be concluded that the mucoadhesive buccal tablets of Ganciclovir can be prepared by using different polymers to increase its absorption through buccal mucosa and finally to increase the bioavailability.

REFERENCES

[1] Atul CL, Leena JS, Aniruddha MG, Sima SP, Prabha MR. Formulation and evaluation of buccal tablet of Salbutamol sulphate. Int Res J of Pharm 2011;2(12):238-242.
[2] Shaikh R, Raghurai ST, James GM, David WA, Donnelly R. Mucoadhesive drug delivery systems. J of Pharm and Bioallied Sci 2011;3:89-100.
[3] Laisa Lis Fontinele de sa, Naiane CN et al. Design of buccal mucoadhesive tablets: Understanding and development. J of applied Pharm Sci 2018;8(02):150- 163.
[4] Surendra V, Mahima K, Aruna R, Sapna S. An overview on buccal drug delivery system. Int J of Pharm Sci & Res 2011;2(6):1303-1321.
[5] Joao PF. Site-specific drug delivery systems within the gastro-intestinal tract: From the mouth to the colon. Int J of Pharm 2010;395:44-52.
[6] Peppas NA, Little MD, Huang Y. In: Bioadhesion Controlled release Systems, handbook of Pharmaceutical Controlled Release Technology In Wise DL, editor, Marcel Dekker New York 2005;255-266.
[7] https://en.wikipedia.org/wiki/
[8] Subrahmanyam CVS. In: Micromeritics, textbook of physical pharmaceutics. 2nd edition, Vallabh prakashan, Delhi 2000:222-224.
[9] Aulton ME. The science of dosage form design 2002; 2:205-208
[10] Banker GS, Rhodes CT. Modern pharmaceutics 1990;40:416-417.
[11] Naga KR, Velmurugan S, Deepika B, Vinushitha. Formulation and in-vitro evaluation of buccal tablets of Metoprolol Tartrate. Int J Pharm and Pharm Sci 2011;3(2):239-246.
[12] Arora G, Malik K, Singh I, Arora S. Formulation and evaluation of controlled release Mucoadhesive matrix tablets. Assessment of myrrh oleo gum resin as anatural pharmaceutical excipient. Intern j of pharm sci and drug resh. 2011; 3(2):84-8
[13] Shrisat ST, Alai KS, Jadhav CM, Kacare RV. Formulation and evaluation of buccal bioadhesive tablet of Acyclovir by using spray-

Sujatha Muchalambe, Geetha Lakshmi, Dependra Kumar, Suma, and Mamatha, "Formulation and Evaluation of Ganciclovir Novel Buccoadhesive Tablets with Different Polymers," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 2, Issue 5, pp. 10-15, 2019.

dried Amioca starch/carbopol 940P mixture. Int J of Pharm Res and Dev 2011:3(11):160-167.
[14] Anup KR, Vinod kumar sm, Syed JB, Rabiul H, Roopa K. Formulation and evaluation of Mucoadhesive Buccal tablets of Valsartan. Int. J. Drug Dev & Res 2013;5(4):145-155.
[15] Harikrishnan V, Madhusudhan S, Santhiagu A. Design and evaluation of controlled release buccal tablet of Tizanidine hydrochloride using natural polymer guar gum. Der Pharmacia Lettre 2016; 8(1):73-79.
[16] Dasharath MP, Pratik MS, Chhagan NP. Formulation and evaluation of bioadhesive buccal drug delivery of Repaglinide tablets. Asian J of Pharm 2012;6:171-179.
[17] Babu BR, Saikat D, Ashwin TK, Swathi V. Formulation and *in-vitro* evaluation of Lovastatin buccal tablets. Int Res J of Pharm 2013;4(12):16-19.
[18] Korsemeyer RW, Peppas NA. Macromolecular and modeling aspects of swelling-controlled systems. In: Mansdrofsz, roseman TJ, ad, controlled release delivery systems. New York. Marcel Dekker, 1983:77.
[19] ICH Q1A (R2) Stability testing guidelines: Stability testing of new drug substances and products. [Online]. [Cited 2019-07-17 nov 10];available https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q1ar2-stability-testing-new-drug-substances-and-products
[20] International Conference on Harmonization (ICH), Harmonized Tripartite guidelines for stability testing of new drugs substances and products Q1A(R2) 2003 Feb 6.
[21] Brain RM. Regulatory expects of stability testing in Europe. Drug Dev Ind Pharm 1999;25(7):831-856.

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