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Prepare and Evaluate Mucoadhesive Formulations of Lamivudine with Better Controlled/ Sustained Drug Release Profile

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ABSTRACT

The aim of present study was to formulate & evaluate the mucoadhesive sustained release formulations of lamivudine and to fulfill this aim, two mucoadhesive formulations Gels and Tablets were prepared by using three different polymers: HPMC K15, poloxamer 407 & carbopol 934. Three mucoadhesive gel and nine tablet formulations were prepared and evaluated for various parameters. All three gels were able to give sustained release up to 12 hours. Tablet formulations, F1 to F5 failed to fulfill the aim. Only F6, F7, F8 & F9 formulations were selected, as all gave sustained release up to 12 hours, except F6, which gave sustained release profile only till 7 hours. From the drug release plots, it was concluded that the type of polymer and concentration of polymer have distinct effect on in vitro drug release profile and all the formulations follow first order mechanism with anomalous diffusion or non-fickian diffusion, except carbopol gel and poloxamer tablets. Carbopol gel follows zero order release rate with super case II transport and poloxamer tablets (F6) follow higuchi with non-fickian diffusion. It is concluded that mucoadhesive formulations of lamivudine can be prepared for sustaining its release. And the successful outcome of the present study also encourage for further studies to assess the ability of the mucoadhesive formulations of lamivudine in providing an effective sustained and safe therapy for AIDS.

Keywords: NDDS, ODDS, BDDS, HPMC K 15, Carbopol 934, Poloxamer 407

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INTRODUCTION

The principle of mucoadhesive preparation is simple practical approach and is particularly useful to prolong the retention time of a dosage form in the stomach and improving the oral bioavailability of the drug[1].The aim was to develop drug delivery systems that would increase the absorption of a drug for both local and systemic effects as a result of intimate and prolonged contact at the site of absorption[2-4]. Among the early work on bioadhesive systems is that of Nagai and coworkers, who showed that the treatment was improved for several administration routes when adhesive formulations were used[5]. For example, the treatment of aphthae, an infection in the mouth, and the treatment of uterine cancer were improved with local delivery using mucoadhesive tablets. In addition, mucoadhesive preparations for delivery of insulin through the buccal and the nasal routes of administration were investigated[6,7]. The term mucoadhesion appeared in the literature for the first time in 1977. In a medical research paper describing a clinical trial of a locally delivered anaesthetic. In the mid and late 1980s the concept of mucoadhesion became more commonly recognised[9]. Over the years, mucoadhesive and bioadhesive systems have been used for NDDS, ODDS, BDDS, vaginal, rectal and oral drug delivery[10].

Nowadays, mucoadhesion in the literature, covering a wide variety of applications[11]. In some studies, the term mucoadhesive formulation is used in a routine and noncritical way, e.g. different formulations and polymers have been ranked as more or less mucoadhesive by using randomly chosen methods[12-16]. polymers have been developed and used with the intention of learning more about the kind of interactions that can occur between the formulation and the mucosa[17]. But even now, the understanding of the phenomenon is not yet complete[18]. One of the reasons for this is probably that there are so many different formulations involving a large variety of adhesion mechanisms that no single existing theory can explain them all. In our present work we are preparing two different types of mucoadhesive formulations-mucoadhesive gel and mucoadhesive tablets[19-20].

MATERIALS

Materials used in this study were obtained from the different sources. Lamivudine was a gift sample from Cipla indore Madhya Pradesh, India. Carbopol 974P and Xanthan gum

were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as Aerosil and magnesium stearate were procured from Alfa Laboratories, Mumbai.

METHODS OF PREPARATION OF MUCOADHESIVE GELS:

Preparation of Lamivudine Gel by Using HPMC K15:

2%, 4%, 6%, 8%, 10% & 12%, plane gel formulation of HPMC K15 were prepared in distilled water by simple mixing method[21-23]. 12%, formulation was selected on the bases of consistency of gel. Lamivudine (150mg) was dissolved in small amount of distilled water and then incorporated in 12% HPMC gel with continuous stirring. After that, set aside the formulation for some time at room temperature[24,25].

Preparation of Lamivudine Gel by Using Corbopol 934:

0.5, 1% & 2%, plane gel formulation of Carbopol were prepared in distilled water. Out of these, 1% gel formulation was selected on the bases of gel consistency[26,27]. As on incorporation of lamivudine (150mg), the formulation was precipitated[28,29]. Therefore 0.5% gel was selected to get the desired gel formulation. And gel was prepared by simply adding the lamivudine (already dissolved in small amount of water) into 0.5% carbopol gel, with continuous stirring[30].

Preparation of Lamivudine gel by using POLOXAMER 407:

The Pluronic F127 (Poloxamer 407) were prepared by modification of the "Cold dispersion" method described by Schmolka. The weighed amount of poloxamer (1g) was placed in beaker and left in an oven at 110°C for 15 minutes to obtain a homogeneous liquefied mixture then 150mg lamivudine (which was already dissolved in small amount of water) added with continuous stirring[31]. The solution was cooled to room temperature, & beaker was left in a refrigerator until a clear solution was obtained. The gel was formed when the solution was brought back to room temperature and stored at ambient temperature prior to use.

Formulation of Mucoadhesive Tablets:

Mucoadhesive tablets of Lamivudine were made by direct compression method. Nine formulations (F1-F9) were formulated by using three different mucoadhesive polymers (HPMC K15, Carbopol 934 & Poloxamer 407). Mucoadhesive polymers were used as binder, lactose as diluents and talc as lubricant[32].

The mucoadhesive tablets were prepared by mixing of drug with binder, in a pestle and mortar until homogenized. Then all other excipients were added. Mixture was passed through sieve no. 60. Finally the blend was compressed using the round concave punches (10.3mm in diameter) and dies by rotary tablet punching machine[33]. The tablet weight was adjusted to 500mg and 75 tablets for each batch were prepared. Formula for nine batches is given in table 1.

Table 1: Formula for different tablet formulations.

INGREDENTS (mg)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (Lamivudine)	150	150	150	150	150	150	150	150	150
HPMC K 15	100	150	200	-	-	-	-	-	-
Carbopol 934	-	-	-	-	-	-	20	30	40
Poloxamer 407	-	-	-	75	125	175	-	-	-
Lactose	230	180	130	255	205	155	310	300	290
Talc	20	20	20	20	20	20	20	20	20

EVALUATION PARAMETER FOR MUCOADHESIVE GELS[34-36]:

General Appearance:

A Visual inspection was done to know the general appearance of gels. There should be no sign of grittiness and formulation must be of uniform texture.

Mucoadhesive Force:

Mucoadhesive force of all three gel formulation was determined by method and apparatus reported by Choi et al., 1998 & koffi et al, 2006. (by using goat stomach mucosa).

Drug Release Profile:

Drug release profile of all three gel formulations was carried out in distilled water, by using cellophane membrane and drug release rate kinetics of the formulations was determined by fitting release result in models of data treatment as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model).
2. Cumulative percent drug release versus time (zero order kinetic model).
3. Higuchi release kinetic model.
4. Korsmeyer- peppas model.

EVALUATION PARAMETER FOR MUCOADHESIVE TABLETS[37,38]:

General Appearance:

General appearance was examined by visual inspection. All tablets should be of uniform size, shape, color and surface textures etc.

Weight variation:

Randomly, twenty tablets were selected and individually weighed. The average weight of tablet was calculated. Then individual weight was compared with average weight of tablets. It should be within the range ±5 for tablet more than 324mg.

Thickness:

Six tablets were selected randomly from each batch and thickness was measured by using vernical caliper.

Friability:

Twenty tablets were weighted and placed in Roche friabilator and equipment was rotated at 25 rpm for 4 minute. The tablets were taken out, dusted and reweighed. The percentage friability of tablets should be within range of ±1.

Hardness:

Hardness was determined by using Monsanto Hardness

tester. Six tablets from each batch were tested randomly and the average reading noted.

Swelling index:

Swelling index was determined by method as descried earlier for three tablets of each batch. i.e. tablet was weighed and placed in a beaker containing 200 ml of distilled water. The tablet was gently removed at time intervals such as 1, 10 and 20mins, blotted dry and the weight determined. This was stopped once the tablets start eroding or became too gelatinous and swelling index was calculated.

Mucoadhesive Strength:

Mucoadhesive strength of tablets was measured on the modified physical balance as described earlier by using goat stomach mucosa.

Drug Content:

Take 100mg equivalent weight of crushed powder of tablets and dissolved in 1000ml of distilled water. Solution was filtered and diluted appropriately. Then, solution was analyzed by UV Spectrophotometer at λ max.

In-vitro dissolution studies and release kinetic analysis:

In vitro release rate study of mucoadhesive tablet was carried out by using the Apparatus 2 i.e. Basket apparatus, using distilled water as dissolution media. And absorbance of samples was measured at λ max. To analyze the drug release rate kinetics of the formulations, the results of in-vitro release profiles were fitted to following models.

1. Log cumulative percent drug remaining versus time (first order kinetic model).
2. Cumulative percent drug release versus time (zero order kinetic model).
3. Higuchi release kinetic model.
4. Korsmeyer-peppas model.

RESULT AND DISCUSSSION

Preliminary Investigation of Drug (Lamivudine):

Physical Appearance

Lamivudine was white color powder.

Melting Point

Melting point of lamivudine was found to be 161°C.

Solubility study

Solubility profile of lamivudine in various solvents, are given in table 2.

Table 2: Solubility profile of Lamivudine in various solvents

S. No.	Solvent	Solubility
1	Distilled water	+
2	Ethanol	+
3	Methanol	+
4	Acetone	-
5	Chloroform	-
6	Ethyl acetate	-
7	0.1N HCl	+
8	0.1 N NaOH	+

λ max OF LAMIVUDINE:

λ max of lamivudine was found to be 271.5 nm in distilled water.

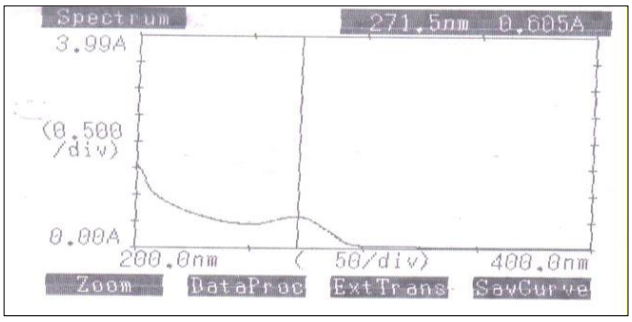

Figure 1: Scanning of Lamivudine in UV range

Standard Curve of Lamivudine

Standard calibration curve of lamivudine was determined by plotting absorbance v/s concentration on double beam U.V. spectrophotometer using λ max = 271.5 nm. Straight line was obtained after plotting concentration on X axis. It follows the beer's law. As beer's law is concentration dependent and on increasing the concentration from 5µg/ml to 30µg/ml, gave liner increase in absorbance[39-40]. The regression equation was y = 0.0247x + 0.0093, which was further used for calculation of concentration of unknown samples. The R^2 value of standard curve was 0.9978, which signify that plot was linear. The results are shown in table 3and figure 1.

Table 3: Absorbance of Lamivudine in distilled water at λ_{max} 271.5 nm

S. No.	Concentration(µg/ml)	Absorbance (nm)±(SD)
1	0	0
2	5	0.116±0.002
3	10	0.238±0.001
4	15	0.334±0.003
5	20	0.493±0.002
6	25	0.613±0.002
7	30	0.738±0.001

EVALUATION PARAMETER FOR MUCOADHESIVE GELS[41]:

General Appearance

All three gel formulations were good texture profile. They were transparent in appearance and no sign of grittiness was observed.

Mucoadhesive Force

Mucoadhesive force of all three gel formulations were determined by using goat stomach mucosa and is given in table 4. Out of all three polymers, Carbopol showed the maximum mucoadhesive force.

Table 4: Mucoadhesive force of polymers used in gel formulations.

S. No.	Polymers	Mucoadhesive force (dyne/cm^2)
1	Poloxamer 407	2.2455
2	HPMC K15	2.6271
3	Carbopol 934	3.3618

Drug Release Study

Drug release study data of all three gels are shown in table 5.

Table 5: Data of Release profile of formulated gels.

Time (hr)	Cumulative % drug release		
	HPMC K15 gel	Poloxamer 407 gel	Carbopol 934 gel
0	0	0	0
1	18.43±1.5	12.92±2.3	4.62±1.9
2	37.45±2.7	27.63±2.8	13.83±3.4
3	46.45±3.8	36.6±3.5	18.8±2.2
4	64.07±2.4	47.43±2.2	25.02±1.5
5	73.56±4.2	59.82±3.1	34.87±1.7
6	83.92±2.8	66.01±4.3	42.09±2.9
7	87.12±2.1	72.32±2.4	61.83±2.6
8	91.32±1.6	79.71±1.8	67.63±1.8
10	94.22±1.2	83.87±1.2	73.98±2.3
12	97.89±0.6	88.95±0.88	78.38±1.4

The above drug release data & plot show that the prepared gel formulations released drug up to 12 hours and more or less, all three gel formulations were giving sustained drug release profile. These gel formulations were further studied to know the drug release kinetics.

Drug release kinetic study:

HPMC K15 gel:

Table 1.6: Data for drug release kinetic study of HPMC K15 gel

Time (hr)	Square root of time	Log time	Cumulative % drug released	Log (Mt/M∞)	Cumulative % drug remaining to release	Log cumulative % drug remaining to release
0	0	-	0	-	100	2
1	1	0	18.43	1.2655	81.57	1.9115
2	1.414	0.301	37.45	1.5734	62.55	1.7962
3	1.732	0.477	46.45	1.6669	53.55	1.7287
4	2	0.602	64.07	1.8066	35.93	1.5554
5	2.236	0.6989	73.56	1.8666	26.44	1.4222
6	2.449	0.778	83.92	1.9238	16.08	1.2062
7	2.645	0.845	87.12	1.9401	12.88	1.1099
8	2.828	0.903	91.32	1.9605	8.68	0.9385
10	3.162	1	94.22	1.9741	5.78	0.7619
12	3.464	1.079	97.89	1.9907	2.11	0.3242

Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer- peppas	
			R^2	n
0.8538	0.9896	0.9598	0.9488	0.6792

On the basis of R^2 values of above release kinetic plots, it was determined that the HPMC gel follows first order drug release kinetic model. As R^2 value of first order, 0.9896 was highest among all. And in Korsmeyer- peppas plot, n= 0.6792 (i.e. 0.45<n<0.89), indicates anomalous diffusion or non-fickian diffusion. That means, release rate of the HPMC gel was controlled by the combination of both, diffusion and erosion release mechanism.

Poloxamer 407 gel

Table 1.7: Data for drug release kinetic study of poloxamer 407 gel

Time (hr)	Square root of time	Log time	Cumulative % drug released	Log (Mt/M∞)	Cumulative % drug remaining to release	Log cumulative % drug remaining to release
0	0	-	0	-	100	2
1	1	0	12.92	1.1112	87.08	1.9399
2	1.414	0.301	27.63	1.4413	72.37	1.8595
3	1.732	0.477	36.6	1.5634	63.4	1.8020
4	2	0.602	47.43	1.6760	52.57	1.7207
5	2.236	0.6989	59.82	1.7768	40.18	1.6040
6	2.449	0.778	66.01	1.8196	33.99	1.5313
7	2.645	0.845	72.32	1.8615	27.68	1.4421
8	2.828	0.903	79.71	1.9015	20.29	1.3072
10	3.162	1	83.87	1.9236	16.13	1.2076
12	3.464	1.079	88.95	1.9491	11.05	1.0433

Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer- peppas	
			R^2	n
0.9211	0.9945	0.9695	0.9725	0.7836

On the basis of R^2 values of above release kinetic plots, it was determined that the poloxamer gel follows first order drug release kinetic model. As R^2 value of first order, 0.9945 was highest among all. And in Korsmeyer- peppas plot, n= 0.7836 (i.e. 0.45<n<0.89), indicates anomalous diffusion or non-fickian diffusion. That means, release rate of the poloxamer gel was controlled by the combination of both, diffusion and erosion release mechanism.

Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer- peppas	
			R^2	n
0.9597	0.9568	0.8883	0.981	1.1678

On the basis of R^2 values of above release kinetic plots, it was determined that the carbopol gel follows zero order drug release kinetic model. As R^2 value of zero order, 0.9597 was highest among all. And in Korsmeyer- peppas plot, n= 1.1678 (i.e. higher than 0.89), indicates super case II transport. As per super Case II transport mechanism, the release mechanism was not significantly influenced by formulation variables swelling dispersed within a glassy polymer. Initially the polymer begin to swell in contact of water, .as the penetrant enters the glassy polymer , the glass transition temperature of the polymer is lowered and become rubbery show diffusion allowing relaxation of macromolecular chains and drug diffuse out from the swollen rubbery area of polymer wall (Bhowmik B.B. et al, 2009).

Evaluation Parameter for Mucoadhesive Tablets[42]:

GENERAL APPEARANCE

General appearance was examined by visual inspection. All tablets were good in appearance; they were white colored oval shaped tablets with smooth surface texture and no pinholes were observed.

WEIGHT VARIATION

All nine tablet batches passed the weight variation test as percentage weight variation was within the pharmacopoeia limits (±5%). Results are shown table 8.

Table 8: weight variation

BATCH CODE	WEIGHT VARIATION (mg) (N=20)	RESULT
F1	498±1.9	PASSED
F2	497±2.6	PASSED
F3	502±1.76	PASSED
F4	499±1.6	PASSED
F5	501±2.8	PASSED
F6	497±2.9	PASSED
F7	496±3.3	PASSED
F8	500±1.88	PASSED
F9	498±2.3	PASSED

1. THICKNESS

Thickness of all tablet batches is given in table 9. The thickness of the tablets was found in the range of 5.6– 6.1 mm.

Table 9: Thickness of tablets

BATCH CODE	THICKNESS (mm) (N=6)
F1	5.8±0.18
F2	5.9±0.177
F3	6.1±0.076
F4	6±0.11
F5	5.8±0.2
F6	5.9±0.16
F7	5.8±0.084
F8	6±0.15
F9	5.9±0.23

2. FRIABILITY

The friability of all nine batches is given in table 1.10. Friability of tablets was observed in acceptable range of 0.34-0.84%. It was within the pharmacopeia limit i.e. less than 1%. That means all tablets had good mechanical strength.

Table 1.10: Friability of tablets.

BATCH CODE	FRIABILITY (%) (N=20)
F1	0.84
F2	0.76
F3	0.72
F4	0.69
F5	0.63
F6	0.56
F7	0.48
F8	0.46
F9	0.34

Hardness

Hardness of all batches is given in table 11. Hardness of the tablets was found in the range of 6.8-9.4 kg/cm2. That was satisfactory for sustained release formulations and also indicates good mechanical strength to withstand physical and mechanical stress conditions while handling.

Table 11: Hardness of tablets.

BATCH CODE	HARDNESS(kg/cm2) (N=6)
F1	6.9±0.15
F2	7.6±0.42
F3	8.4±0.34
F4	7.2±0.22
F5	7.6±0.288
F6	8.2±0.37
F7	7.3±0.15
F8	8.8±0.137
F9	9.3±0.15

Swelling Index

Swelling studies were performed till 20 min because after that carbopol tablets started forming soft gel, which was difficult to handle and HPMC & poloxamer formulations showed erosion (but poloxamer tablets erode slowly then HPMC tablets). Results are given in table 12.

Table 12: Swelling studies of tablets.

BATCH CODE	% swelling index (±SD) (N=3)		
	Time (mins)		
	1	10	20
F1	10.2±2.3	18.6±3.7	32.1±4.2
F2	12.4±1.8	20±3.4	46.3±2.5
F3	15.1±2.4	24.6±2.1	54.2±3.6
F4	13.4±2.2	21.3±4.2	43.5±2.8
F5	17.7±1.5	32.3±5.1	49.6±2.3
F6	22.2±2.5	40.2±3.6	57.2±4.3
F7	27.4±1.2	75±2.6	97.7±3.8
F8	36.7±2.4	84.6±2.1	102±4.1
F9	39.2±1.7	90.3±3.4	116±3.3

Mucoadhesive studies

Mucoadhesive strength of tablets was measured on the modified physical balance as described earlier. The highest adhesion force and highest strength of the mucoadhesive bond was observed with the carbopol formulations. And it was increasing with increase in concentration of polymer.

Table 13: Mucoadhesive strength & force of tablets.

BATCH CODE	MUCOADHESIVE STRENGTH (g) ±SD	MUCOADHESIVE FORCE (N)
F1	17.3±1.4	0.170
F2	21.9±0.95	0.215
F3	24.6±0.74	0.241
F4	20.4±1.2	0.201
F5	23.5±1.5	0.231
F6	27.4±0.99	0.269
F7	33.2±2.2	0.326
F8	37.5±2.3	0.368
F9	42.8±1.8	0.417

CONCLUSION

The aim of present study was to formulate & evaluate the mucoadhesive sustained release formulations of lamivudine. And to fulfill this aim, two mucoadhesive formulations- gels and tablets were prepared by using three different polymers: HPMC K15, poloxamer 407 & carbopol 934. Three mucoadhesive gel and nine tablet formulations were prepared and evaluated for various parameters.

All prepared gel & tablet formulations had good physico-mechanical properties. Among all the formulations, carbopol gel and tablets showed the highest mucoadhesive force, although, each formulation had good adhesive force. All three gels were able to give sustained release up to 12 hours. Tablet formulations, F1 to F5 failed to fulfill the aim. Only F6, F7, F8 & F9 formulations were selected, as all gave sustained release up to 12 hours, except F6, which gave sustained release profile only till 7 hours. From the drug release plots, it was concluded that the type of polymer and concentration of polymer have distinct effect on *in vitro* drug release profile. This can further be justified with *in vivo* studies. And all the formulations follow first order mechanism with anomalous diffusion or non-fickian diffusion, except carbopol gel and poloxamer tablets. Carbopol gel follows zero order release rate with super case II transport and poloxamer tablets (F6) follow higuchi with non-fickian diffusion.

So from this study, it is concluded that mucoadhesive formulations of lamivudine can be prepared for sustaining its release. And the successful outcome of the present study also encourage for further studies to assess the ability of the mucoadhesive formulations of lamivudine in providing an effective sustained and safe therapy for AIDS.

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