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FORMULATION AND EVALUATION OF ZIDOVUDINE MUCOADHESIVE BUCCAL PATCHES

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ABSTRACT

Objective: The purpose of this study was to develop and evaluate mucoadhesive buccal patches of Zidovudine by solvent casting technique. Zidovudine has very short half-life and undergoes first pass metabolism by liver making it possible candidate for buccal delivery. Methods: Polymers such as Gelatin, HPMC, and sodium alginate were incorporated into the patches in different proportion as to determine the most suitable selection of polymeric blend ratio in enhancing optimum drug release. PEG-400 used as plasticizer. The buccal patches were evaluated for physicochemical properties such as thickness, weight and drug content uniformity, folding endurance, percentage moisture intake, percentage moisture loss, surface pH, swelling index and *in vitro* drug release studies. Drug-polymer compatibility studies were done by Fourier transform infrared (FTIR). There were no interaction between the drugs and polymers. The formulated Zidovudine buccal patch was found to be smooth in appearance, uniform in thickness, weight, and good folding endurance. Result: Among the 6 formulation, only P1 and P4 formulation were subjected to *in vitro* drug release studies which chose based on satisfactory physicochemical parameters. Based on the *in vitro* drug release studies result, the P1 buccal patch which contain high amount of sodium alginate showed good results but it has initial rapid release which can lead to a toxic effect to the patient. Formulation P4 exhibit slow drug release pattern in steady state with no fluctuation or burst effect with cumulative percentage drug release of 74.53% in 6 hours. Therefore, it can be concluded that, P4 buccal patch with combination of gelatin (100mg) and HPMC (150mg) were chosen as the best formulation among the other formulations for the buccal drug delivery. Conclusion: The release of Zidovudine from formulated patches followed zero order kinetics, as the correlation coefficient (R^2 value) was higher for zero order release, so the drug release mechanism is controlled release. Zidovudine buccal patch can be one of the alternative dosage form available for the administration of Zidovudine.

KEY WORDS: Buccal patches, gelatin, Zidovudine, mucoadhesive, HPMC, PEG

INTRODUCTION

There are various routes for administering drug to achieve therapeutic effects. Oral route drug delivery considered the most common as well as the most convenient route for most of the patients [1]. Among the several route of delivering medicine, transmucosal drug delivery is considered having advantage over the peroral drug delivary[2]. Transmucosal routes of drug delivery includes the oral cavity, mucosal linings of the nasal, rectal, ocular and vaginal [3]. One of the transmucosal route of drug delivery which having promising advantage for local and systemic effect is buccal mucosa route other than sublingual route. The buccal route of drug delivery offers several advantages for controlled drug delivery for extended periods of time. Buccal drug delivery is a highly effective way to improve bioavailability by offering a close contact between the buccal mucosa which is rich in vascularization. This eventually enhances direct entry of drug molecules into the systemic circulation and bypasses the first pass metabolism by liver. It's also avoids the enzymatic activity along the gastrointestinal pathway which be made up of different pH environment. Its directly target the specific site of interest. Buccal drug delivery is well accepted as the buccal cavity is easily accessible for self-medication. There is no pain associated with administration as seen in injection, thus provide an alternative dosage form. It also can be given for patient who is unconscious patient as well. In addition dose related side effects may be able

to be reduced in case of toxicity. In addition it offers an alternative way when enteral route causes difficulty in swallowing, nausea or vomiting or intestinal failure. Zidovudine is an antiretroviral drug which is widely used in the treatment of HIV infection causing AIDS. It is a nucleoside analogue reverse transcriptase inhibitor, and was the first anti-HIV drug to be introduced. It is indicated for HIV infection in combination with other antiretroviral drugs; prevention of maternal-fetal HIV transmission. Zidovudine has poor bioavailability of 60-70% and half-life is 1 hour which is very short. Zidovudine is required to be administered in multiple times per day, in higher doses in order to maintain therapeutic levels, for example 300mg two times per day or 200mg thrice daily and women pregnant women for the prevention of maternal to foetus transmission of HIV infection have to administer it 100mg for 4-5 times in a day[4]. Therefore, multiple dosing with bitter tasting drug reduces the patient compliance especially in case of pediatrics. These make Zidovudine as an appropriate candidate for being incorporated into buccal patch as this dosage form having better advantage than oral tablet form. In the presented study, an attempted was to formulate mucoadhesive buccal patch of Zidovudine using HPMC E 15, sodium alginate and gelatin by solvent casting method.

MATERIALS AND METHODS

MATERIALS

Zidovudine was purchased from YSP Sdn.Bhd. HPMC E15, Sodium alginate, gelatin, ethanol and PEG 400 were purchased from R&M Chemicals, Malaysia. All chemicals used were of analytical grade. Weighing balance (PBL, Mettler Toledo (M) Sdn.Bhd), UV Spectrophotometer (Jasco, Japan and V-630), magnetic stirrer, Vernier caliper, test tubes, rectangular mould, glass rods, beakers, measuring cylinders, desiccator, pH meter, self-fabricated Franz Diffusion cell were used in this study.

METHODS

Preparation of standard curve in phosphate buffer pH 6.8[5]

Standard Zidovudine 100mg was weighed and dissolved in pH 6.8 phosphate buffer in a 100mL volumetric flask. The flask was shaken and volume was made up to the mark with pH 6.8 phosphate buffer to give a solution containing 1000µg/ mL (stock solution I). From the stock solution I, pipette out 10mL and placed into 100mL volumetric flask. The volume was made up to mark with pH 6.8 phosphate buffer to give a stock solution containing 100µg/mL (stock solution II). The steps were continued for other aliquots in different volumetric flasks which made up to same 10ml phosphate buffer pH 6.8.solution to get drug concentration of 100µg/ml -1000µg/ml. Wavelength of 266nm was used to estimate the absorbance of these drug solutions. This procedure has done repeatedly three times to validate the calibration curve.

Drug-excipient Compatibility studies

The stability of a formulation depends on the compatibility of the pharmacologically active ingredients with the excipients. To determine the drug-excipient compatibility among the selected ingredients, interactive studies have been performed by using Fourier Transform Infra-Red spectroscopy (FTIR).

Preparation of Zidovudine-Containing Buccal Patches [6]

Zidovudine buccal mucoadhesive patches were prepared using 3.5cm^2 rectangular moulds by solvent casting technique [7] which composed of different proportion of polymers. Table 1 shows the composition of buccal patches of Zidovudine in which Patch code P1-P3 consist the same amount of Gelatin (100mg) and varying sodium alginate (150 -50mg) and P4-P6 of HPMC (150mg-50mg) respectively. Polyethylene glycol 400 was used as plasticizer at a concentration of 30% of dry weight of polymers. Phosphate Buffer saline pH 6.8 and ethanol was used as solvent in the casting method. HPMC, gelatin and sodium alginate was dissolved appropriately according to as stated at Table 1 using combination of phosphate buffer saline pH 6.8 and ethanol as solvent system. The polymeric solutions were stirred on magnetic stirrer for 1 hour. To this, 30% w/w of PEG-400 was added as plasticizer. Fifty milligrams of Zidovudine accurately weighed and dissolved in sufficient quantity of ethanol then was incorporated in to the different proportion containing polymeric mixtures. These mixtures were allowed to stir on magnetic stirrer for 30 minutes to ensure uniform distribution is achieved. 5ml of drug containing polymeric solution poured into rectangular moulds of diameter of 2.2cm with an area of 3.5cm^2 by placing on a leveled surface. Aluminium foil was used as backing membrane. Inverted glass funnel were placed on top of the moulds to avoid sudden evaporation and allowed to dry overnight at

room temperature 25°C to form flexible film. Dried patches were carefully removed, checked for any imperfections or air bubbles. The patches have been packed in aluminium foil and stored in desiccators to maintain the integrity and elasticity of the patches until further use.

Table 1: Composition of Buccal patches of Zidovudine

Patch code	Zidovudine (mg)	Total amount of polymer (mg)	Gelatin (mg)	Sodium alginate (mg)	HPMC (mg)	PEG 400 (%)	Solvents (mL)	
							PBS pH 6.8	Ethanol
P1	50	250	100	150	-	30	3	2
P2	50	200	100	100	-	30	3	2
P3	50	150	100	50	-	30	3	2
P4	50	250	100	-	150	30	3	2
P5	50	200	100	-	100	30	3	2
P6	50	150	100	-	50	30	3	2

*HPMC: Hydoxypropylmethylcellulose *PEG: Polyethylene glycol

Evaluation methods of buccal patches of Zidovudine

Weight Uniformity Test

Three samples of buccal patches form each batch were randomly taken and weighed individually on digital weighing balance. The average reading and standard deviation of the patches were calculated [6].

Thickness uniformity

The thickness of the patches was measured at different sites on three patches of each batch using Vernier caliper and the mean and standard deviation were calculated [6].

Folding Endurance

Folding endurance was determined by repeatedly folding the film at the same place till it broke. This test was repeated for three samples from each batch. The average reading and standard deviation of the patches were calculated [6].

Surface pH

The surface pH of the patches were determined to investigate the possibility of any irritation side, in-vivo, because an acidic or alkaline pH may cause irritation to the buccal mucosa. Therefore, the idea behind the test is to keep the surface pH as close to neutral as possible. For the determination of surface pH, three patches from each formulation were kept in contact with 1ml of distilled water for 1h, in a test tube. The pH was noted by bringing the electrode of pH meter near to the surface of the film and allowing it to equilibrate for one minute. The average reading and standard deviation of the patches were calculated [6].

Swelling Index

Swelling index were determined by placing the pre-weighed patches on glass slide from each formulation allowed to swell on the surface of an agar plate kept in an incubator maintained at 37°C. Increased in the weight of the patch were determined after 1 hour.

The swelling index were computed by using the formula: Swelling Index (%S) = W2-W1/ W1 x100 where,

W1 is the dry weight of buccal patch before placing on agar plate and W2 is the weight of swollen buccal patch after 1 hour [6].

Determination of Percentage Moisture Absorption

The percentage moisture absorption test was carried out to ensure physical stability or integrity of buccal films. The buccal patches were weighed accurately and placed in the desiccators containing 100ml of saturated solution of aluminum chloride, which maintains 75% ± 5% relative humidity. After 3 days, the films were reweighed and the percentage moisture absorption were calculated using the formula [8]:

$$\text{Percentage Moisture Absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Determination of Percentage Moisture Loss

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were reweighed. The percentage moisture loss were obtained using the below formula [8].

Percentage Moisture Loss (%) = Initial weight – Final weight x100

Final weight

Determination of Drug Content

The drug contents in the buccal patches were determined by dissolving each patch from each batch separately in 100ml phosphate buffer saline [pH = 6.8) and shaken vigorously for 6-8hr at room temperature. The resulting solutions were quantitatively transferred to volumetric flasks and appropriate dilutions were made with phosphate buffer pH 6.8. The resulting solution then were filtered through a filter paper and analyzed for Zidovudine content at 266nm in UV spectrophotometer against a blank. The average readings from three different patches were taken as final reading. The drug content was estimated from the calibration curve [9].

In vitro drug release studies

Franz diffusion cell was used for In vitro drug release studies of buccal patches. It consists of two compartments, one is donor compartment and another is receptor compartment. A freshly prepared egg membrane was used as semi permeable membrane. The egg membrane was mounted between the donor and receptor compartment. The formulation buccal patches were placed on egg membrane and the compartment was clamped together. The donor compartment was filled with 1ml of phosphate buffer pH 6.8. The receptor compartment (10ml capacity) was filled with phosphate buffer pH 6.8, which maintained at 37oC ± 0.2oC and a tiny metal bead was placed in the receptor compartment. The whole assembly was placed on the magnetic stirrer. 2ml of aliquots were withdrawn at every 30min for 6 hours from the receptor compartment while equal volume of fresh medium was replaced after each sampling. The drug release from patch determined by measuring the absorbance using UV spectrophotometer at 266nm against a blank [10].

Statistical analysis

All experimental data were expressed as the mean ± standard deviation. The data obtained from different formulations were analyzed by one-way analysis of variance (ANOVA) procedure using the Microsoft Excel 2013. A statistically significant difference was considered at $P < 0.05$.

Kinetics of drug release

The result of in vitro drug release studies data of Zidovudine buccal patches were fitted by linear regression analysis according to zero order, first order kinetics and according to Higuchi's model and Korsemeyer-Peppas to determine mechanism of drug release[11].

RESULT AND DISCUSSION

The calibration curve for Zidovudine was developed by using phosphate buffer pH 6.8. The curve was plotted with the drug concentration ranging from 100-1000mcg/ml which was observed the absorbance under UV spectrophotometer at wavelength of 266nm. The absorbance against the concentration of Zidovudine in standard solution was shown in Figure 1. The standard calibration curve found to be linear at concentrations ranging from 100 to 1000µg/mL (Y = 0.001x + 0.0438) with correlation coefficient of 0.9896.

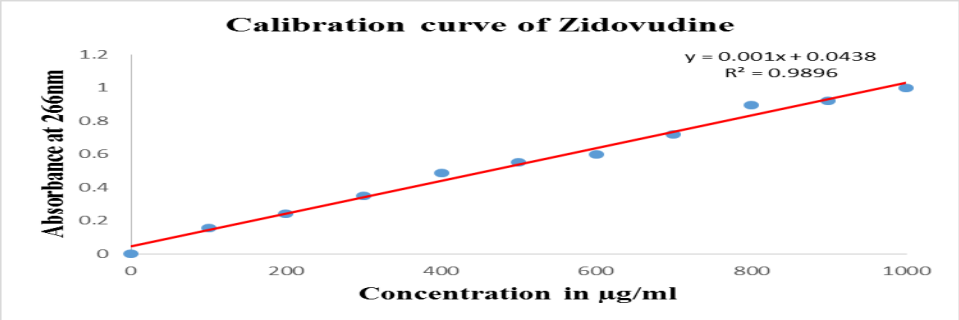

Figure 1: Standard Calibration Curve of Zidovudine in Phosphate buffer pH6.8

The drug-excipient studies were confirmed by Fourier Transform Infrared Spectrophotometer (FTIR) using KBr disc method. The IR spectra obtained for the pure drug, polymers and combination of drug and polymers was elucidated for important functional groups and interpretation are presented in Figure 2-4. A close look into the FTIR spectral data, following are the characteristic vibrational frequency bands have been observed. A sharp 'v' shaped stretching vibrational frequency band at 3459.11 cm^{-1} indicating the presence of –N-H stretching frequency cm^{-1} of secondary amine. The vibrational stretching frequency displayed at 2081.85cm-1 suggesting the presence of Azide moiety in its basic structure. An intense vibrational frequency bond appeared at 1668.05cm^{-1} exhibited the presence of C=O carbonyl stretching frequency band. With respect to the developed formulations, which have been developed in the present study we could establish the non-covalent interaction formed between Zidovudine and other selected excipients. In summary, the characteristic vibrational frequency band (FTIR peaks) of Zidovudine has been clearly identified in the FTIR spectra of the formulations developed. However this observation would be the remarkable contribution indicating the existence of zidovudine in its original form. Hence the formulations were investigated further for the stability studies.

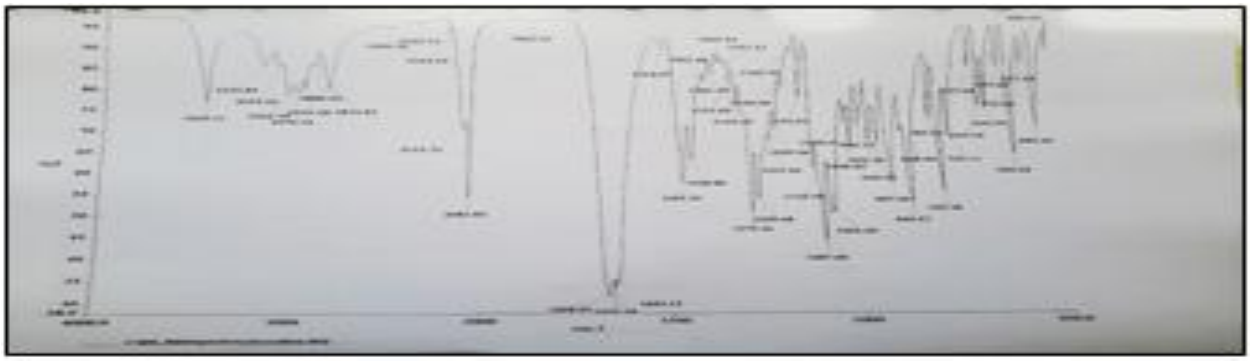

Figure 2: FTIR spectra of Zidovudine pure drug

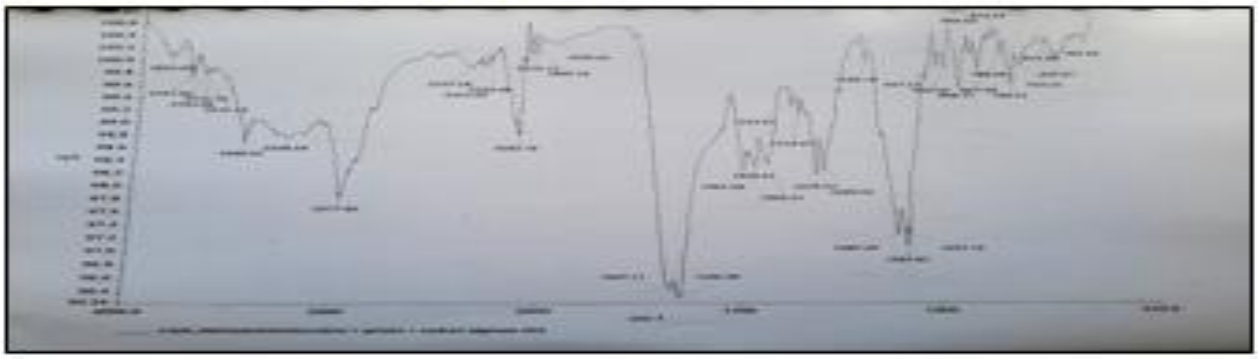

Figure 3: FTIR of Spectra of Zidovudine + Gelatin + Sodium Alginate

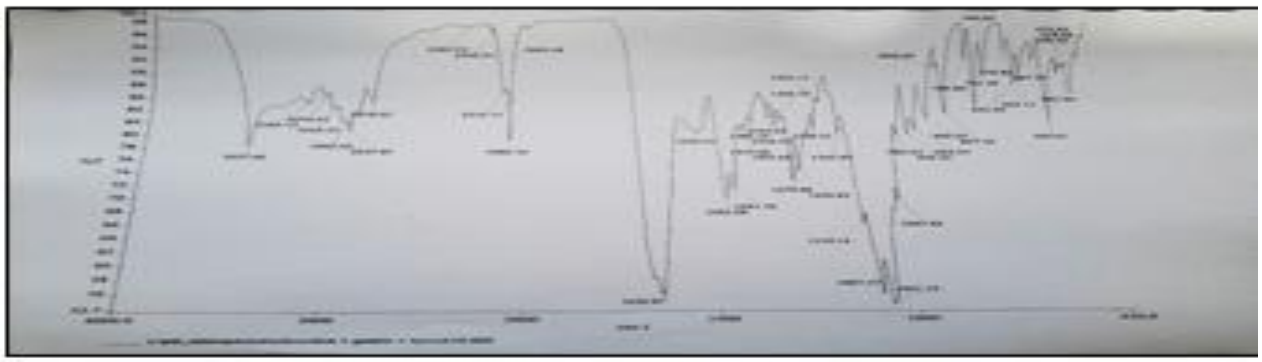

Figure 4: FTIR of Spectra of Zidovudine + Gelatin + HPMC E 15

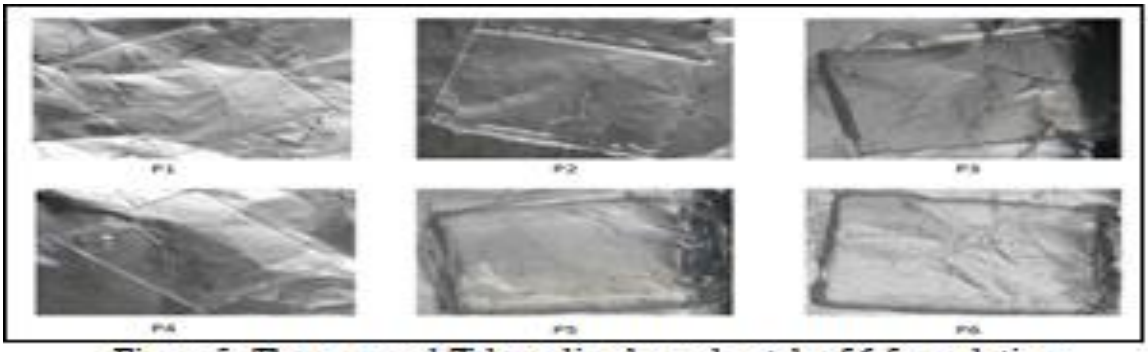

Figure 5: The prepared Zidovudine buccal patch of 6 formulations

Table 2: Physicochemical parameters of various formulations of buccal patches

	Thickness uniformity		Weight uniformity		Folding endurance	
Patch Code	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
P1	0.22	0.0058	221.82	0.0436	358.00	2.6458
P2	0.20	0.0075	221.08	0.0208	261.00	3.0000
P3	0.19	0.0058	220.46	0.1474	160.00	2.0000
P4	0.21	0.0058	222.02	0.0265	334.00	1.0000
P5	0.21	0.0058	221.33	0.0208	256.00	2.6458
P6	0.18	0.0058	221.15	0.0153	137.67	3.2146

*Mean: n=3, *SD: Standard Deviation

Table 3: Physicochemical parameters of various formulations of buccal patches

Patch Code	**Surface pH**		**Moisture absorption %**		**Moisture loss %**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
P1	6.46	0.0058	2.95	0.0058	2.76	0.0153
P2	6.37	0.0100	2.60	0.0153	2.28	0.0153
P3	6.39	0.0153	2.50	0.0153	2.42	0.0200
P4	6.44	0.0058	2.52	0.0058	2.33	0.0252
P5	6.57	0.0208	2.42	0.0058	1.97	0.0208
P6	6.59	0.0100	2.33	0.0208	1.79	0.0153

*Mean: n=3, *SD: Standard Deviation

Table 4: Physicochemical parameters of various formulations of buccal patches

Patch Code	**Swelling index**		**Drug content uniformity**	
	Mean	**± SD**	**Mean**	**± SD**
P1	17.58	0.080	49.65	0.120
P2	16.39	0.060	48.03	0.844
P3	14.93	0.010	48.78	0.248
P4	17.07	0.040	49.05	0.482
P5	15.34	0.032	48.52	0.478
P5	12.58	0.031	48.23	0.382

*Mean: n=3, *SD: Standard Deviation

Preparation of Zidovudine buccal patches

Zidovudine buccal mucoadhesive patches were prepared by solvent casting technique which composed of different proportion of polymers and combination of Gelatin, HPMC E15, and Sodium alginate. Polyethylene glycol 400 was used as plasticizer and mixture of Phosphate Buffer saline, pH 6.8 and ethanol was used as solvent. During the formulation of patches many trial and error have done with placebo to find out which polymer proportion will give the satisfactory buccal patch formation. Among various hydrophilic polymers tried, gelatin were selected as a base polymer while sodium alginate and HPMC E15 were used in combination with different concentration. PEG 400 were used as plasticizer in order to form flexible as well as to avoid brittleness of the prepared patches. 6 type of formulation were prepared where P1-P3 consist of sodium alginate and P4-P6 consist of HPMC E15 in various concentration along with gelatin as base polymer. The prepared buccal patches shown in Figure 5 were packed

in aluminium foil and kept in desiccator, until it was used for further evaluation. The prepared buccal patches were subjected to various physicochemical evaluation. The drug was loaded in the films using various proportion of polymers. Among the 6 formulation P1 and P4 formed very well defined patch with uniform smoothness. The thickness of buccal patch were measured with the help of Vernier caliper as shown in the Table 2. All the patches were found to be in the uniform thickness. The thickness of the patches were varied from 0.18 ± 0.0058 to 0.22 ± 0.0058. P1 has the highest thickness, whereas P6 has the lowest thickness. The low standard deviation and $P<0.05$ indicate there were no significant differences in the thickness of the patches. These shows that there were good pouring technique during casting the solution into the mould which resulted in uniform thickness formation as well as uniform drying of the patches.

Table 2 shows the results of the weight uniformity test of all the formulated patches of each batch. The weight variation ranged between 220.46 ± 0.1474 to 222.02 ± 0.00265, which indicate that all the formulation exhibited uniform weight with $p<0.05$ indicating the uniformity of the patches. The patch with highest exhibited weight was P4 with 220.46 ± 0.1474 and the most light was P3 222.02 ± 0.00265. The order of the weight of the film is P3 < P2 < P6 < P5 < P1 < P4. Weight and thickness uniformity is essential to ensure a uniform release of drug during release studies. The weight is differ among the 6 formulation based on total polymer content.

The folding endurance values shows the number of times a patch can be folded at the same place without breaking. This test was carried out to assess the flexibility as well as the integrity of the patch. The folding endurance of the patch was revealed in Table 2. The folding endurance ranges from 353 ± 2.6458 to 137.67 ± 3.2146. The mean difference was found to be significant at $p<0.05$. P1 and P4 formulation shows better folding endurance of more than 300 exhibits the formed patches are flexible as well as reveal a good filming properties. Higher folding endurance was observed in formulation P1.

An acidic or alkaline pH may cause irritation to the buccal mucosa. Therefore, determination of the surface pH of the patches is essential to investigate the possibility of any irritation on the mucosal membrane. Surface pH of formulation P1 to P6 varied from 6.37 ± 0.0100 to 6.59 ± 0.0100 has shown in Table 3. The mean difference was found to be significant at $p<0.05$. The surface pH of all formulation were within the limits of salivary pH hence expect no mucosal irritation will present and eventually achieves patient compliance.

The moisture uptake studies indicate the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture [12]. The moisture absorption percentage study of various film were done for period of 3 days. The results of the percentage moisture absorption were shown in Table 3. The mean difference was found to be significant at $p<0.05$. It was found that the percentage of moisture uptake increases with increasing amount of natural hydrophilic polymers such as Sodium alginate and gelatin than the HPMC containing formulation. The highest percentage moisture absorption can be seen in formulation P1, 2.95 ± 0.0058 and the least can be seen in P6 2.33 ± 0.0208. The order of the percentage moisture absorption is P6 < P5 < P3 < P4 < P2 < P1. The percentage moisture loss study of various film were done for period of 3 days. The results of the percentage moisture loss were shown in Table 3. The mean difference was found to be significant at $p<0.05$. The highest percentage moisture loss can be seen in formulation P1, 2.76 ± 0.0153 and the least can be seen in P6 1.79 ± 0.0153. The order of the percentage moisture loss is P6< P5< P2< P4< P3< P1. The low moisture content in the formulation is favorable in order to protect from microbial contamination due to its hygroscopic nature.

Table 4 indicates the results of percentage swelling of Zidovudine mucoadhesive buccal patches. The polymer with good swelling property is expected to be a better choice for mucoadhesive application. The mean difference was found to be significant at $p<0.05$. From the table it was found that P1 is having highest swelling index, 17.58 ± 0.080 and the lowest was P6 12.58 ± 0.031. Swelling is more pronounced in the P1 and P4 where there is higher concentration of sodium alginate (150mg) and HPMC (150mg) respectively compared to the others. It is clearly stated that higher the concentration of the hydrophilic polymer, higher the swelling rate be due to quick hydration of polymers[13]. When the mucoadhesive polymers come in contact with aqueous media, it become swell. The rate and extend of water uptake of a polymer will be able to determine the mucoadhesive strength of buccal patches[14]. Appropriate swelling behavior of a buccal adhesive system is essential for uniform and prolonged release of

the drug and effective mucoadhesion. Drug content uniformity for each formulation done and were analysed by using UV spectrophotometer. Table 4 showed that the uniform values of drug in each patch. Good uniformity of drug content among the batches was observed with all formulation and ranged between 48.03 ± 0.844 to 49.65 ± 0.120 mg that is 96.07% to 99.30%. The mean difference was found to be significant at $p<0.05$. The result in this study was capable of producing patches with uniform drug content and minimal patch variability. P1 and P4 show the highest Zidovudine content among the others that is 99.30% and 98.07% respectively. These studies are important tool that predict that how actually the drug will behave inside the body or *in vivo*. The release of the drug from the formulation is depending on the physicochemical properties as well as physiological characteristic of the buccal cavity. The diffusion rate of drug from the formulation is determined by the nature of the polymers where it controls the release of the drug across the patches.

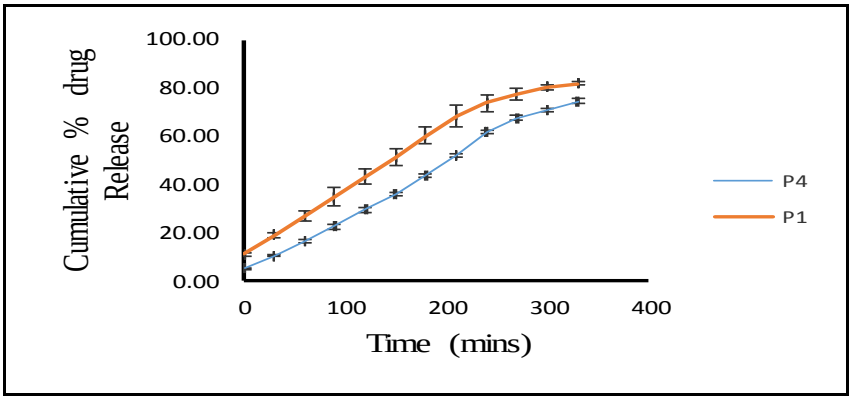

Figure 6: Percentage cumulative release of drug for buccal patches of P1 and P4

Table 5: Compilation of *In vitro* release of Zidovudine at 6 hrs of P1 and P4

Time (mins)	Mean ± SD (%) Cumulative drug release	
	P1	**P4**
0	0	0
30	10.70 ± 0.819	4.77 ± 0.252
90	18.67 ± 1.026	10.23 ± 0.651
60	26.57 ± 2.214	16.33 ± 0.503
90	34.60 ± 3.650	22.30 ± 1.058
120	43.30 ± 3.300	29.30 ± 0.917
180	51.13 ± 3.592	35.93 ± 0.702
210	60.13 ± 3.556	43.37 ± 0.603
240	68.47 ± 4.537	51.97 ± 0.802
270	73.60 ± 3.704	61.50 ± 0.600
300	77.53 ± 2.268	67.53 ± 0.961
330	80.33 ± 1.201	71.07 ± 0.709
360	81.67 ± 0.751	74.53 ± 0.802

*Mean: n=3, *SD: Standard deviation

Table 6: Kinetic parameters of the release data of Zidovudine from buccal patches

Formulation	Zero order		First order		Higuchi		Korsemeyer-Peppas	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n
P1	0.9765	0.238	$7.00E^{-6}$	$1.00E^{-5}$	0.9543	4.978	0.9951	0.7732
P4	0.9953	0.223	0.0112	0.0005	0.8984	4.485	0.9444	0.7769

R^2: Regression coefficient, K_0: Zero order release rate constant, K_1: first order release rate constant, K_H: Higuchi rate constant, n: release/slope exponent

Among the 6 formulation P1 and P4 were selected to further investigate for in vitro drug release study based on physical appearance, folding endurance, swelling index, percentage moisture absorption, moisture loss and drug content uniformity. The test were carried out in triplicate for each formulation using Franz diffusion cell. The results in Table 5 exhibit the in vitro drug

release profile of the selected Zidovudine buccal patches of formulation of P1 and P4 with the cumulative percentage of drug release for each. Both the formulation consist same quantity of gelatin with different concentration of HPMC and Sodium alginate. P1 have 150mg sodium alginate and 100mg of gelatin while P4 have 150mg HPMC and 100mg of gelatin. In vitro drug release study were carried out using Franz diffusion cell, egg membrane as the semipermeable membrane and phosphate buffer pH 6.8 as the diffusion medium. The cumulative percentage of drug release was acquired for a period of 6 hours. The cumulative percentage of drug release at 6th hour varied for both the formulation where P1 shows is 81.67 ± 0.751, and P4 is 74.53 ± 0.802. The data was plotted as percentage cumulative drug release versus time shown in Figure 6. According to figure 6 the cumulative percentage of drug release at 6th hour was highest in P1 with 81.67%, the initial drug release within ½ hour is 10.70% and during the 3rd hour 51.13% of drug released. Whereas P4 have cumulative percentage drug release of 74.53% at the 6th hour and the initial drug release with ½ hour is 4.77% and during the 3rd hour it shows 35.93%. The rate of drug release of P1 is very fast compared to P4. P1 also shows the initial burst effect which can be toxic effect. Slow and steady drug release can be observed in P4 which provide sustained drug release. Higher concentration of hydrophilic polymer, sodium alginate in P1 may cause the initial burst effect within the 3hours. According to the literature increase in drug release from buccal patch found to be increasing with the concentration of hydrophilic polymers. Based on this study, P4 found to be the best formulation in order to release the drug in sustained manner. For a buccal drug delivery, the preferable drug release pattern is slow and steady release as exhibited by P4. Even though sustained effect was achieved to a greater extent but it lacks complete drug release at 24 hrs. So it needs further study to release the complete drug from the prepared formulations. For a better drug release penetration enhancer should be incorporated in to the formulation to improve the drug release from the formulation. The *in-vitro* drug release profiles for P1 and P4 were fitted into various models like zero order (% cumulative drug release vs time), first order (log % cumulative drug remain vs time), Higuchi equation (% cumulative drug release vs square root of time) and Korsemeyer-Peppas equation (log % cumulative drug release vs log time). The values for each model were plotted in a graph as shown in Figure 6.1, 6.2, 6.3, and 6.4 respectively. The r^2 values for zero order, first order, Higuchi and Korsemeyer-Peppas kinetic models were calculated and compared shown in Table 6. The regression value for zero order in range between 0.9765 and 0.9953, whereas, the regression value for first order equation was found between $7.00E^{-6}$ and 0.0112. The regression value for Higuchi model ranged between 0.8984 and 0.9543 whereas for Korsemeyer Peppas, the regression value found to be between 0.9444 and 0.9951. Correlation coefficients of formulation P4 showed higher correlation with zero order plots (R^2:0.9953) than Korsemeyer (R^2:0.9444), Higuchi (R^2:0.8984) and first order (R^2:0.0112) whereas Formulation P1 showed higher correlation coefficient with Korsemeyer-Peppas plots (R^2:0.9951), than Zero order (R^2:0.9765), Higuchi (R^2:0.9543) and first order (R^2: $7.00E^{-6}$). So, predominant drug release mechanism is controlled release which the drug release is independent of the concentration. According to Korsmeyer where 'n' is the release exponent, indicative of mechanism of drug release. When 'n' value is <0.5, the release mechanism is said to be Fickian, which controlled by the diffusion of the drug, and when 'n' is between 0.5-1, release was said to be non-Fickian. From the Korsemeyer Peppas equation the slope values ('n') of both P1 and P4 was found to be 0.7732 and 0.7769 respectively. Here, the value of 'n' for both formulations was found to be between 0.5 and 1, suggesting that the drug follows non-Fickian release which indicates the formulation adapted erosion and diffusion mechanism for drug release.

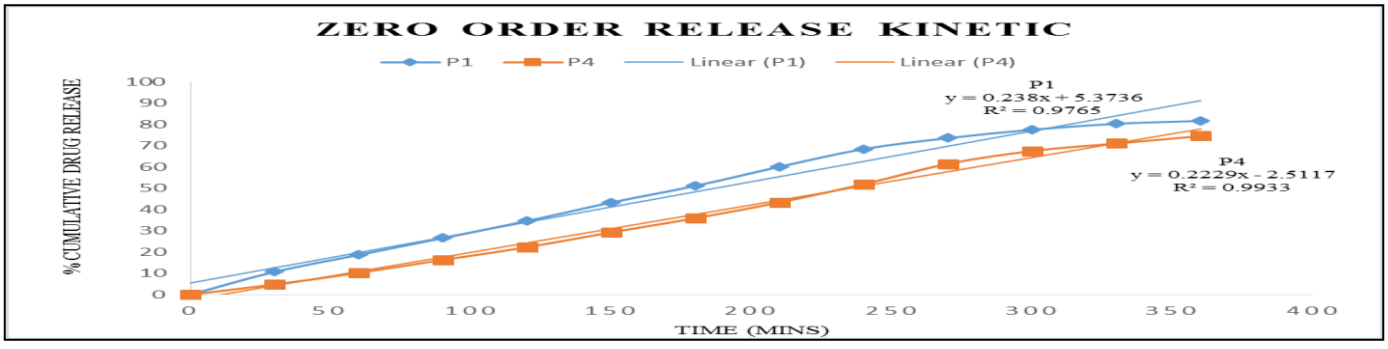

Figure 6.1: Zero order release kinetic profile of formulation P1 and P4

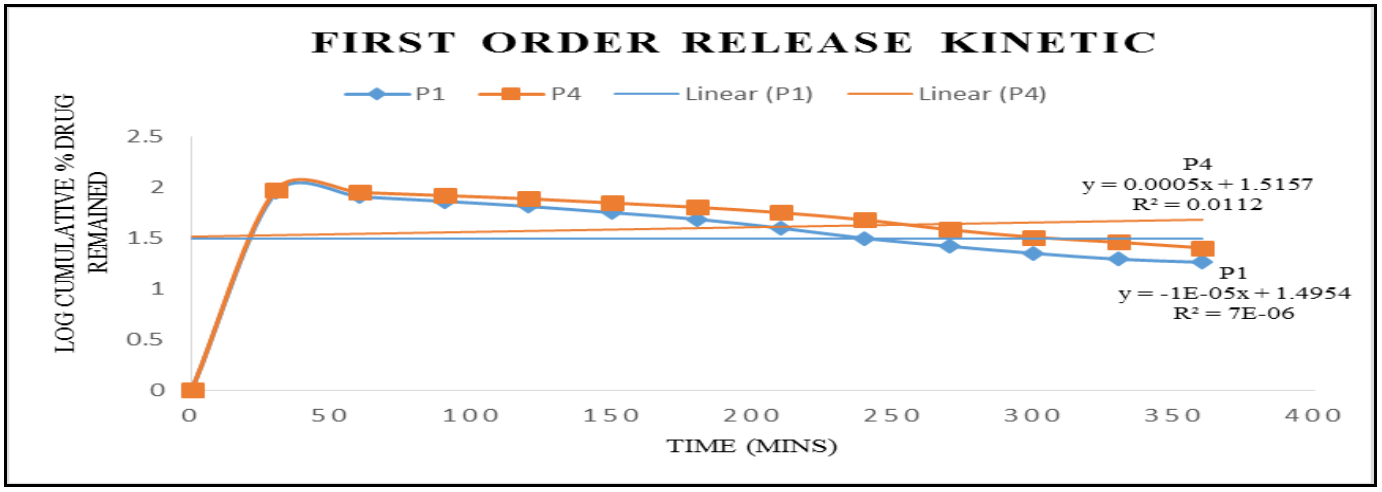

Figure 6.2: First order release kinetic profile of formulation P1 and P4

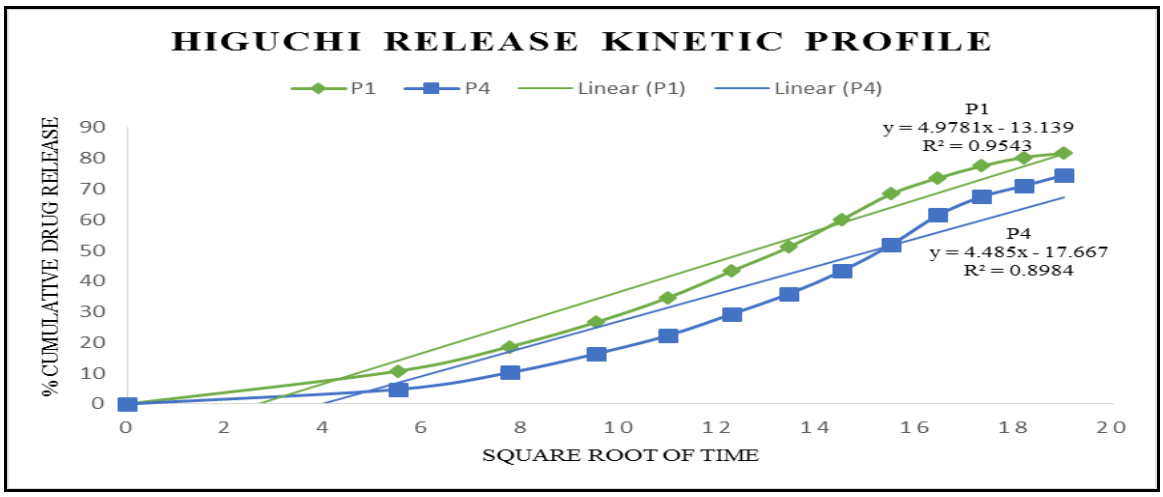

Figure 6.3: Higuchi release kinetic profile of formulation P1 and P4

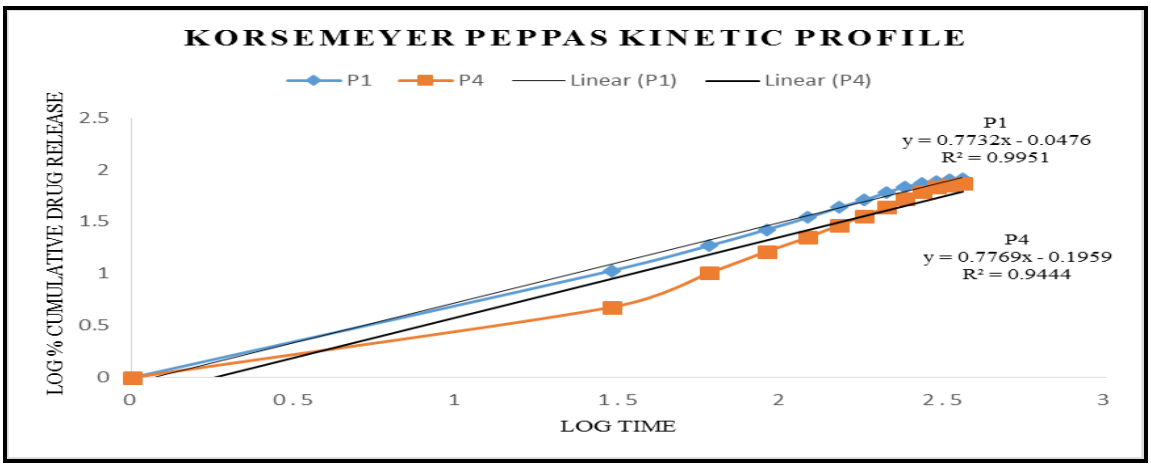

Figure 6.4: Korsemeyer - Peppas kinetic profile of formulation P1 and P4

CONCLUSION

In the present study, an attempt was made to formulate Zidovudine buccal patches by solvent casting method employing polymers such as HPMC and sodium alginate along with gelatin in different proportion and combination. The main concern in such dosage form was to design buccal patches of Zidovudine in the sense of increase in bioavailability by bypassing the first pass metabolism and to achieve control drug release in therapeutic range for an extended period as well as reduce the dosing frequency in the treatment of HIV infection. Among the 6 formulation, only P1 and P4 formulation were subjected to in vitro drug release studies

which was chosen based on satisfactory physicochemical parameters. Both the formulation P1 and P4 follows zero order and Korsemeyer-Peppas kinetic drug release mechanism. P4 buccal patch with combination of gelatin (100mg) and HPMC (150mg) were chosen as the best formulation among the other formulations for the sustained drug release of buccal drug delivery. As a conclusion the formulated buccal patches of zidovudine using Gelatin, HPMC E15 and Sodium alginate in various proportions showed satisfactory physicochemical and mucoadhesive characteristics. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release from these formulated Zidovudine buccal patches. Hence further investigation in respect to mucoadhesive strength, and in vivo and ex-vivo drug release and permeation is required to support it optimum drug release and therapeutic effectiveness from the buccal patch.

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