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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES

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ABSTRACT

The buccal route of administration has a number of advantages including bypassing the gastrointestinal tract and the hepatic first pass effect. Buccal Patches are the type of drug formulation that has normally a different course of administration through the buccal mucosa for drug delivery and the now days tablet dosage forms are supplanted by new drug delivery system because of problems like hepatic metabolism, GI toxicity and enzymatic degradation which leads to non-compliance and ineffective therapy. In present work the fast dissolving buccal patches of Amlodipine was prepared by solvent casting method using HPMC K4m, HPMC K100M and PVP and PEG 400 as plasticizer. The prepared patches were evaluated for weight, thickness, folding endurance, surface pH, *in-vitro* drug release and stability studies on optimized formulation. The *in-vitro* drug release was found to be up to 100% within 2 minutes. Thus, the fast dissolving buccal patch of Amlodipine was successfully formulated to achieve a safe, rapid and effective dosage form with enhanced drug dissolution and rapid antihypertensive therapy.

KEYWORDS

Buccal patches, Mucoadhesion, HPMC, PVP and Solvent casting method.

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INTRODUCTION

The various routes of administration can be used in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and fungal infection. For many year mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action. Moreover, the oral cavity is easily accessible for self-medication and can be promptly terminated in

case of toxicity by simply removing the dosage form from the buccal cavity[1].

The Fast dissolving films can be consists of plasticized hydro colloids with which they can be laminated by using techniques such as hot -melt extrusion and solvent casting. They can also provide easy delivery of drug under emetic condition Mouth dissolving film are the new drug delivery system for delivery of drugs through oral cavity and was the developed on the basis of technology of the Trans dermal patch. The buccal drug delivery system containing very thin film to the oral strip and when placed on the patient's tongue oral mucosal tissue gets instantly wet by saliva and rapidly hydrates and adheres to the site of application. Then Film rapidly disintegrates and dissolves to release the medication for absorption through mucosal route or with formula modifications, exist dissolving form will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. Which consist of the liophylisates, the rapid films produced with the formulation that is competitive with the manufacturing costs of conventional tablets[2]. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration.

MATERIAL

Amlodipine were procured by Concept Pharmaceutical Pvt. Ltd, HPMC K4M, HPMC K100M, Polyvinyl Pyrilidone, Propylene Glycol-400, were procured by Themis laboratory, Mumbai. Ethyl Cellulose, NAOH Solution Crosspovidone by Thomas baker Pvt. Ltd, Mumbai.

Definition of FDF

Fast dissolving films most advance form of solid dosage form due to its flexibility. It order to improves efficacy of Active pharmaceutical ingredient (API) dissolving in the short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet.

Although this type of drug administration is commonly termed as oral.

Fast dissolving film should.

Have a pleasant mouth feel.

Be compatible with taste masking.

Buccal drug delivery directectly goes to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Then the Problem such as first pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering drugs via the buccal route[1]. The site for systemic drug delivery has been investigated by many research groups[3,4] and the route has already reached commercial status with several drugs including LHRH and calcitonin[5].

Amlodipine[6,7]

Amlodipine pharmacokinetic ally it is the most distinct Dihydropyridines (DHP). Despite vasodilation, fluid retention is insignificant because of lower Bp. Also inhibit transmembrane influx of calcium ions into vascular smooth muscles and cardiac muscles. It is indicated for the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina.

Chemical Name[8-10]

3-ethyl 5-methyl 2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine-3, 5-dicarboxylate

Molecular formula: [C20H25ClN2O5],

Molecular weight: 567.05g/mol

Melting point: 195-204^{o}C

Functional Categories

Anti- hypertensive agent

Ca channel blocker

Vasodilator agent

Anti anginal agent

Preparation of mucoadhesive buccal patches[11]

Backing layer

For preparing the backing layer EC (1.4g) was dissolved in a mixture of 20ml ethanol and isopropyl alcohol (10ml). 2ml dibutyl phthalate was the added as the plasticizer. The plasticized EC solution was poured into a Petri plate of 7.5cm internal diameter on a level surface and allowed to air dry at controlled rate by covering the Petri plate with a funnel

Mucoadhesive layer containing drug

The layer was prepared by the solvent casting technique, using LP, plasticizer, and other film forming as well as release retarding polymers. The experiment was designed using a 32 full factorial design. Then the quantity of different polymer solutions were mixed in specified ratios. The hydrophilic polymers HPMC K4M, HPMC K100M and PVP□K30 were dissolved separately in ethanol (95%) and then incorporated into one. And then the stirred on a magnetic stirrer (Remi Equipment's Ltd., India) for a period of 1 h to get a homogenous clear solution, followed by sonication for 15 min. Propylene glycol (PG) was the added as a plasticizer and the stirring was continued for another 30 min. To this mixture, the drug solution corresponding to 300mg was the added and mixed thoroughly with continued stirring and kept aside for few hours until all the entrapped air had escaped. This solution was then poured over the preformed backing layer of EC and allowed to dry overnight, undisturbed at room temperature. And Then the Petri plate was covered with an inverted funnel to allow controlled evaporation of the solvent. Then the After careful examination, of the dried patches was removed, and the checked for any imperfections or air bubbles and cut into 25 mm diameter patches. The patches were packed in aluminium foil and stored in a glass container at room temperature till further use

Evaluation of Buccal Patches[12]

Surface pH Determination

To determine surface pH method similar to that used by Botten berg *et al*, A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1ml of distilled water (pH 6.8±0.1) for 2 h at room temperature. The surface pH of the patches was determined in order to investigate the possibility of any side effects, in the oral cavity.

Weight Uniformity and Thickness

Weight variation values (mg) of different Amlodipine patches were found to be in the range of 99-112mg. The average thickness of all the bioadhesive patches ranged from 0.8-0.60mm. there was the proportional gain in weight of patches with that of increase in the thickness of patches. This shows that the patches cast were uniform.

Drug Content Uniformity

The percentage drug content was determined by UV spectrophotometer at 220nm method using the standard calibration curve and the same procedure was repeated for three patches of each formulation. As the drug content values of same formulation did not show a significant difference, it can be concluded that the drug was uniformly dispersed in buccal patches.

Folding Endurance

Three patches of each formulation of bigger size, i.e., 2 x 2cm, were cut using a sharp blade. Folding endurance was determined by repeatedly folding a small strip, of patch at the same place until it ruptured. The number of times the patch could be folded at the same place without breaking resulted in the folding endurance value. The mean value was calculated and recorded

***Ex vivo* Drug Permeation Studies**

Permeation studies: The *in vitro* study of Amlodipine permeation through the cellophane membrane buccal mucosa was performed using a Franz diffusion cell with 8ml capacity. The patch was placed on the mucosa and the compartments clamped together. Then the donor compartment was the filled with 1ml of simulated saliva pH 6.8. And the receptor compartment (8ml capacity) contained isotonic phosphate buffer pH 6.8. The hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100rpm and maintaining the temperature at 37^{o} $\pm 0.5^{o}$C. 1ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 220nm. The graph of % drug permeated v/s time was plotted and flux, permeability coefficient was determined.

Swelling Study[13]

A drug-loaded patch of 1x1 cm2 was weighed. It was kept in a Petri dish and 50ml of phosphate buffer, pH 6.6 was added. After every 5 min it was weighed up to 30 min. The difference in the weighs was calculated.

$$\%S = \frac{Xt}{Xo} \times 100$$

Where,

Xt is the weight or area of the swollen patch

Model Fitting[14]

A good model fit refer to a model that accurately approx the output cumulative release was done using PCP Disso software to find the best fitted kinetic equation for the dissolution profile

Kintetics Drug Release

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* dissolution study of the optimized batch was fitted with various kinetic equations like.

Zero order (% Release =Kt),

First order (log % Unreleased =Kt),

Higuchi's model (% Release =Kt0.5) and

Pappas Korsmeyer equation (% Release=Ktn)

(or) Empirical equation (Power law expression) of

$Mt / M\infty = K\ tn$

Where,

Mt -The Amount of drug release at time t

M∞ - Amount of the drug release at infinite time

K - Constant characteristics, and

n - Diffusional exponent

If n = 0.5 indicates Fickian diffusion mechanism (Higuchi matrix)

n = 0.5 to 1 indicates Anomalous Transport or Non Fickian transport.

n = 1indicates Case II Transport (Zero order release)

n > 1indicates Super case –II transport

Coefficient of correlation (R2) values were calculated for the linear curves obtained by regression analysis of the above plots.

Stability Studies of Amlodipine Buccal Patches[13]

In any rationale design and evaluation of dosage forms, the stability of the active component must be major criteria in determining their acceptance or rejection.

Reasons for Stability-Studies

There might be chemicals degradations of active drug leading to a substantial lowering the quantity of the therapeutic agent in the dosage form.

There may be chemical degradation of the active drug may not be extensive; a toxic product may be formed in decomposition process.

Instability of drugs product can lead to decrease in its bioavaibiltity. This can lead to substantial lowering in the therapeutic efficacy of the dosage form.

During the stability-studies products were exposed at normal condition of heat and moisture. However, the study takes an extended period; thus, it will be suitable to perform accelerates stability-studies where the products are store below excessive condition of heat. In the present work, stability-Study was performed on chosen batch. The patches were stored at temp $40^oC \pm 2^oC$ and RH 75 ± 5% for duration of two month. After an interval of thirty days each Sample was withdrawn and tested for drug diffusion study.

RESULTS AND DISCUSSION

Evaluation of Buccal Patches

Physiochemical evaluation

The Physical appearance of all patches is given in Table No.2. The Flexibility is flexible, Smoothness is smooth, and Transparency is opaque.

Surface pH Determination

The surface pH was determined by using a combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1ml of distilled water (pH 6.8±0.1) for 2 h at room temperature, and pH was noted down, allowing it to equilibrate for 1 minute.

Weight Uniformity and Thickness

The thickness of all the patches is given in Table No.3. The average thickness of all the mucoadhesive patches ranged from 0.42-0.82mm. The weight of patches was measured with digital balance (n=3) and average weight of all the patches is given in Table No.3. Weight variation values (mg) of different amlodipine patches were found to be in the range of 99-113mg. The values were uniform for the patches within the respective group of formulation type. This depicts that the patch cast was uniform.

Drug Content Uniformity

The percentage drug content was determined using the standard calibration curve and the same procedure was repeated for three patches of each formulation. The uniformity was found to be in the range of 90.42% - 98.53%. Results are shown in Table No.3. It can be concluded that the drug was uniformly dispersed in buccal patches.

Folding Endurance

Folding endurance of patches was determined manually by repeatedly folding a film at the same place until it breaks. The prepared Amlodipine patches has sufficient flexibility and good mechanical strength. The folding endurance was found to be increased with increasing concentration and decreasing concentration of polymer. All the patches showed good value of folding endurance (more than 200 was considered to be good) and the formulations F7 - F9 showed folding endurance values more than 300 (Table No.3). This confirms that there will be no breakage of patch till its use.

***Ex-vivo* Permeation study**

This study of Amlodipine can carried out by using the cellophane membrane was performed using a Franz diffusion cell with 8ml capacity. Cellophane membrane was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The receptor compartment (8ml capacity) contained isotonic phosphate buffer pH 6.8. The receptor compartment was the maintained by stirring with a magnetic bead at 100rpm and maintaining the temperature at $37^{o}\pm0.5^{o}C$. One ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 220nm. The graph of % drug permeated v/s time was plotted and flux, permeability coefficient was determined.

Measurement of Mechanical Property

Tensile Strength

The tensile strength was found to be in the range of 10.12 to 15.65kg⁄mm^2. As the concentration of hydrophilic polymer was increased the tensile strength was found to be increased. All film showed 100% flatness.

Swelling Index

The degree of swelling of mucoadhesive polymer is an important factor affecting bioadhesion. All the patches showed maximum increase in swelling after 30min. Figure No.3 below shows the comparative swelling index of different formulations of Amlodipine buccal patches.

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* dissolution study of the optimized batch was fitted with various kinetic mode.

Dissolution profiles were fitted to various model and release data were analyzed on the basis of koresmeyer peppas equation, zero order, first order, higxon, and higuchi kinetics. These different kinetic equations were applied to interpret the release rate from all the formulation.

The best formulation i.e. optimized formulation F3 follow higuchi law kinetics r^2= 0.9996 and slope. So the drug release is of Nonfickian diffusion indicating that release from patches forming system was based on diffusion mechanism for all batches. Hence, the mechanism of drug release from all formulation F1 to F9 was followed diffusion controlled. Then the higuchi model provides information about drug release mechanism.

Accelerated Stability Studies

Stability was carried out on optimized buccal patch formulation for two months. It was found that formulation remained stable at temperature of 40ºC ± 2ºC and relative humidity of 75% ± 5 as per ICH guidelines. The results obtained are shown in Table No.10. The result show that there was no change in physical appearance of buccal patches.

Stability Studies for Drug Diffusion of Batch F3

Batch F3 is selected as optimized batch and further studied for stability study at $40^{o}C$ and 75% RH for 60 days.

Table No.1: Formulation composition mucoadhesive buccal patches

Batches	*Amlodipine* (mg)	HPMC-K4m (mg)	HPMC-K100m (mg)	PVP	Cross Povident	PEG-400	Water	Ethanol
F1	10	9.37	-	15.62	5	0.03	q.s	q.s
F2	10	-	15.62	15.62	5	0.03	q.s	q.s
F3	10	21.87	15.62	15.62	5	0.03	q.s	q.s
F4	10	9.37	9.37	15.62	5	0.03	q.s	q.s
F5	10	-	21.87	15.62	5	0.03	q.s	q.s
F6	10	9.37	15.62	15.62	5	0.03	q.s	q.s
F7	10	21.87	-	15.62	5	0.03	q.s	q.s
F8	10	21.87	21.87	15.62	5	0.03	q.s	q.s
F9	10	21.87	9.37	15.62	5	0.03	q.s	q.s

Table No.2: Physical appearance

Formulation	Flexibility	Smoothness	Transparency
F1	Flexible	Smooth	Opaque
F2	Flexible	Smooth	Opaque
F3	Flexible	Smooth	Opaque
F4	Flexible	Smooth	Opaque
F5	Flexible	Smooth	Opaque
F6	Flexible	Smooth	Opaque
F7	Flexible	Smooth	Opaque
F8	Flexible	Smooth	Opaque
F9	Flexible	Smooth	Opaque

Table No.3: Result of Physiochemical Parameter

Formulation	Surface pH	Weight uniformity	Thickness	Content Uniformity	Folding Endurance
F1	6.33± 0.06	103±2	0.42±0.2	95.40±0.12	256±2.4
F2	6.27± 0.01	105.0±0.5	0.62±0.3	90.42±0.05	250±2.4
F3	6.54 ± 0.06	99±1	0.45±0.2	98.53±0.85	232±2
F4	6.23 ± 0.06	107±0.3	0.50±0.6	94.15±0.18	263±2.5
F5	6.17 ± 0.06	161±2	0.65±0.5	96.42±0.44	282±1.7
F6	6.43 ± 0.06	115±2	0.75±0.6	92.71±0.06	275±3.06
F7	6.47 ± 0.06	117±0.6	0.70±0.6	90.80±0.05	332±2.6
F8	6.23 ± 0.06	108±0.6	0.75±0.8	90.70±0.47	326±4.2
F9	6.63± 0.06	113±2	0.82±0.9	96.46±0.7	330±4.2

All results are shown in mean ± S.D. (n=3)

Table No.4: *Ex-vivo* Permeation Study

S.No	Time (min)	*Ex-vivo* permeation study
1	0	0
2	5	22.55±1.995
3	10	37.22±2.723
4	15	51.08±2.703
5	20	68.23±3.822
6	25	82.48±4.623
7	30	90.04±3.130

All results are shown in mean ± S.D. (n=3)

Table No.5: Tensile Strength and Swelling Index

Formulation	Tensile strength (N/mm^2)	% Swelling Index
F1	10.12	228.95
F2	11.12	238.75
F3	10.16	224.5
F4	13.16	245.98
F5	11.57	220.87
F6	13.16	218.45
F7	11.86	248.15
F8	13.86	245.36
F9	15.65	238.45

***In vitro* Buccal Permeation Study**

Table No.6: Calculation table for permeation study of F1, F2 and F3

S.No	Time (min)	Cumulative percent drug release		
		F1	F2	F3
1	0	0	0	0
2	5	34.73±1.761	36.84±1.885	40.69±1.898
3	10	54.21±2.356	49.05±1.017	55.45±2.010
4	15	65.00±3.543	63.84±2.085	69.00±3.372
5	20	79.00±4.303	76.3±3.571	82.03±4.242
6	25	89.03±4.354	82.81±4.342	90.01±3.354
7	30	95.65±4.17	92.90±4.455	99.48±4.242

All results are shown in mean ± S.D. (n=3)

Table No.7: Calculation table for permeation study of F4, F5 and F6

S.No	Time (min)	Cumulative Percent drug release		
		F4	F5	F6
1	0	0	0	0
2	5	41.02±1.475	37.72±1.640	30.27±1.524
3	10	55.95±2.109	52.37±2.343	37.75±1.540
4	15	65.77±3.614	70.6±3.672	55.13±2.403
5	20	74.79±4.571	80.3±4.415	66.74±3.968
6	25	82.3±4.434	88.19±3.430	81.93±4.750
7	30	94.65±4.858	94.58±4.957	92.72±4.845

All results are shown in mean ± S.D. (n=3)

Table No.8 Calculation table for permeation study of F7, F8 and F9

S.No	Time (min)	Cumulative percent drug release		
		F7	F8	F9
1	0	0	0	0
2	5	37.63±1.269	34.39±1.775	32.27±1.407
3	10	46.35±2.735	52.49±2.887	42.20±2.563
4	15	63.39±3.645	63.28±3.837	55.66±3.959
5	20	72.93±4.750	70.79±4.551	68.79±3.705
6	25	81.83±3.509	82.99±3.661	80.50±4.035
7	30	90.58±4.078	91.52±4.051	88.45±4.173

All results are shown in mean ± S. (n=3)

Table No.9: Analysis of Kinetic Models Fitting

Batch code	Zero order	First order	Hixon Crowell	Korsemeyer and peppas model	Higuchi model
	R^2	R^2	R^2	R^2	R^2
F1	0.9653	0.7590	0.8653	0.9228	0.9982
F2	0.9634	0.7534	0.8591	0.9269	0.9985
F3	0.9583	0.7455	0.8516	0.9556	0.9996
F4	0.9463	0.7344	0.8349	0.9623	0.9981
F5	0.9549	0.7496	0.8530	0.9392	0.9981
F6	0.9883	0.7908	0.9029	0.8303	0.9830
F7	0.9620	0.7515	0.8565	0.9229	0.9974
F8	0.9616	0.7537	0.8575	0.9202	0.9987
F9	0.9788	0.7727	0.8817	0.8698	0.9932

Table No.10: Accelerated stability studies

S.No	Evaluation Parameter	Time period of sampling	
		Initial 30 days	After 60 days
1	Appearance	No change	No change
2	pH	6.54 ± 0.06	6.54 ± 0.08
3	Folding Endurance	232±2	232±4
4	Thickness	0.45±0.2	0.36±0.2
5	Weight Uniformity	99±1	99±1
6	Drug Content (%)	98.53±0.85	98.53±0.85

Table No.11: Stability study of drug permeation batch F3

S.No	Time (min)	Cumulative% drug release at 0 days	Cumulative %drug release after 30 days	Cumulative % drug release after 60 days
1	0	0	0	0
2	5	30.59±1.798	30.59±1.798	30.19±1.119
3	10	50.79±2.544	51.60±2.938	51.33±2.818
4	15	65.15±3.335	64.54±3.994	64.16±3.806
5	20	73.64±3.176	71.77±3.248	70.76±3.554
6	25	84.52±4.244	84.42±3.333	83.34±4.243
7	30	97.54±4.543	96.43±3.421	96.23±4.175

All results are shown in mean ± S.D. (n=3)

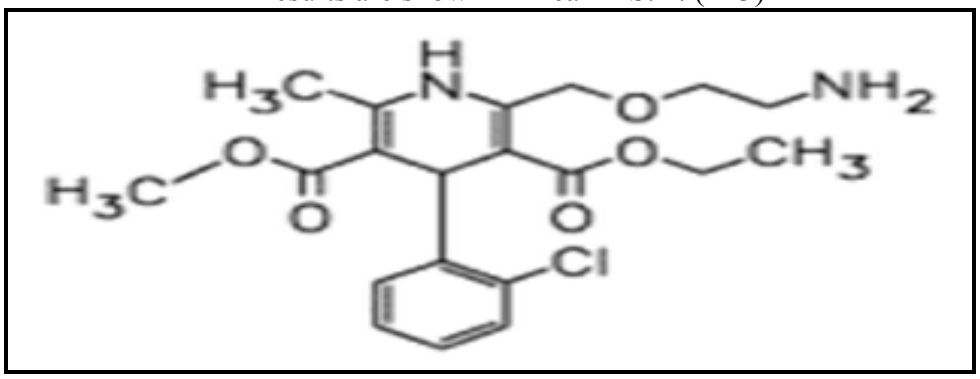

Figure No.1: Chemical structure of Amlodipine

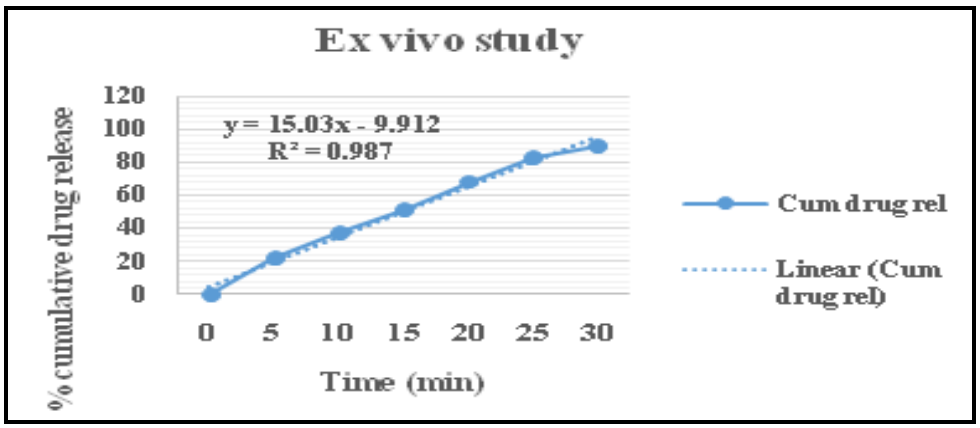

Figure No.2: *Ex –vivo* study

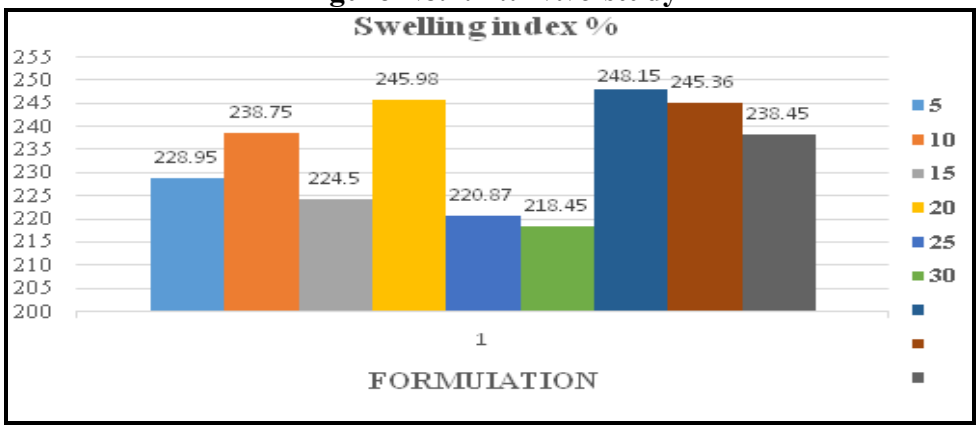

Figure No.3: Bar graph showing % swelling index of Amlodipine buccal patch F3 after 30 min

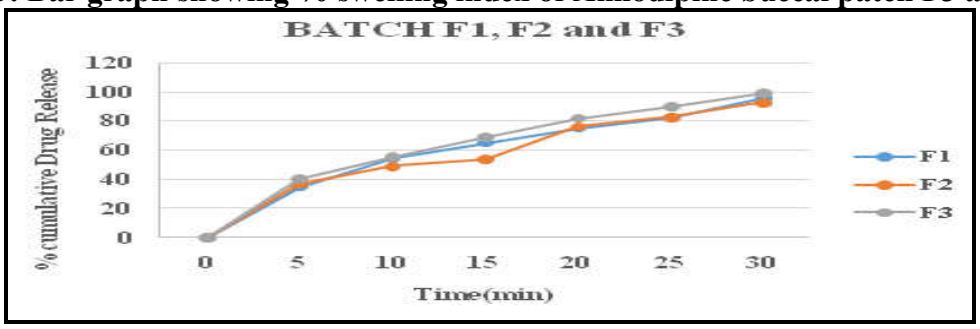

Figure No.4: Permeation study of F1, F2 and F3 batch

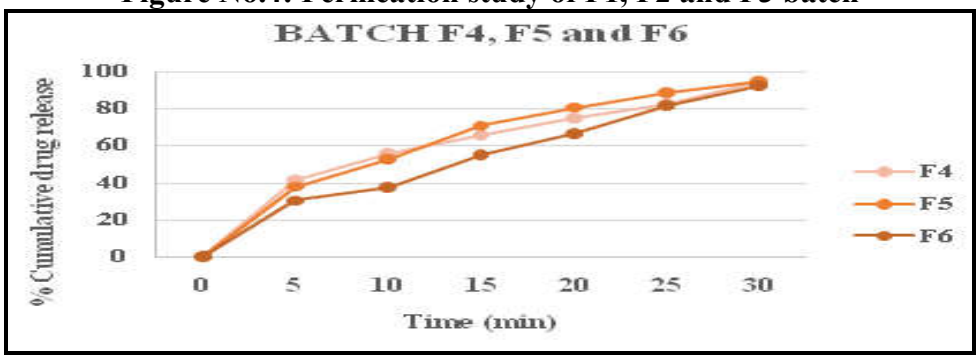

Figure No.5: Permeation study of F4, F5 and F6 batch

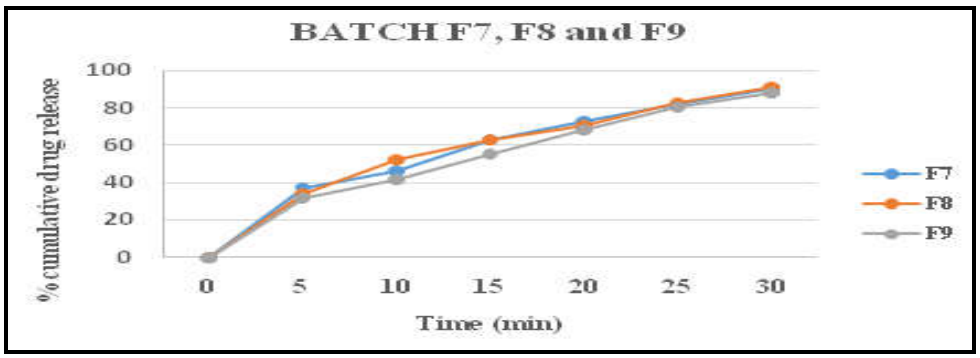

Figure No.6: Permeation study of F7, F8 and F9

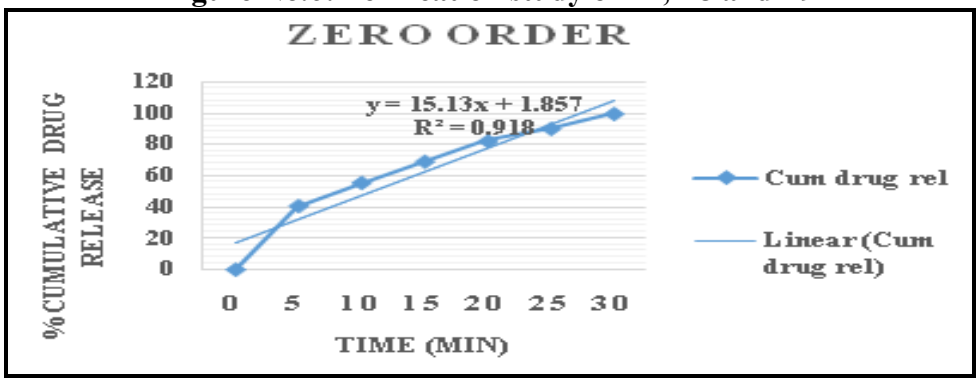

Figure No.7: Zero order Kinetics

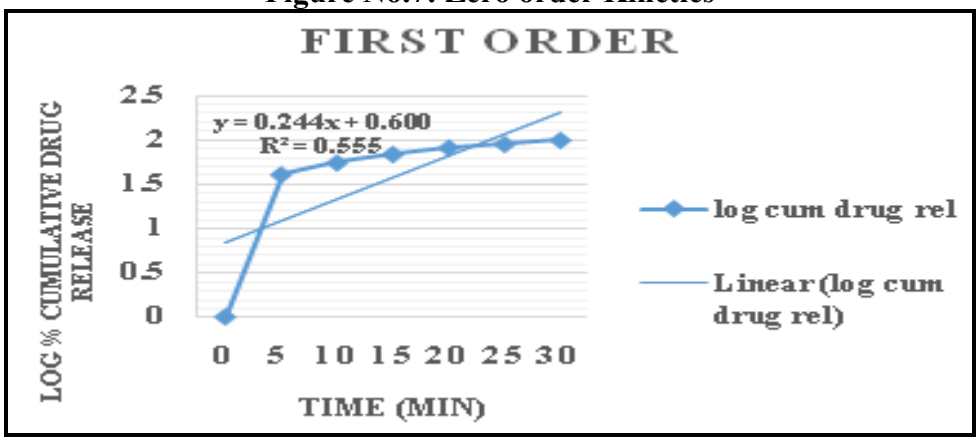

Figure No.8: First Order Kinetics

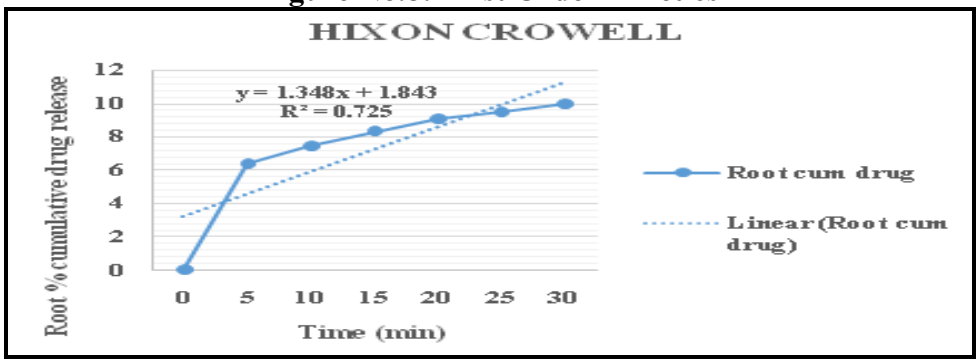

Figure No.9: Hixon Crowell

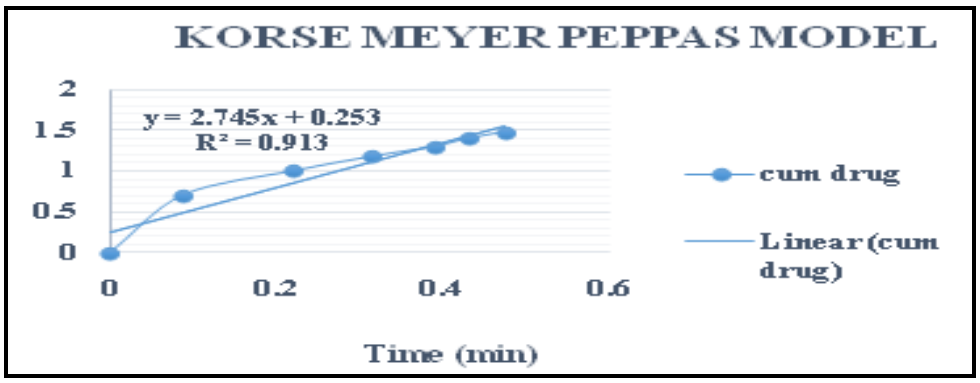

Figure No.10: Korse Meyer Pappas Model

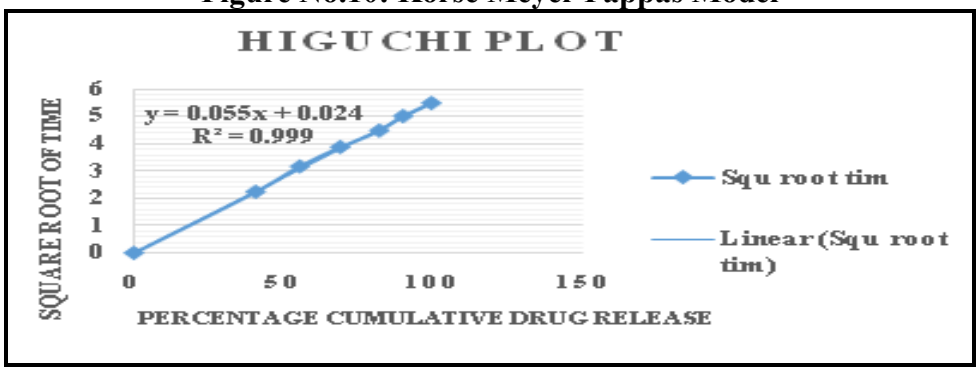

Figure No.11: Higuchi plot

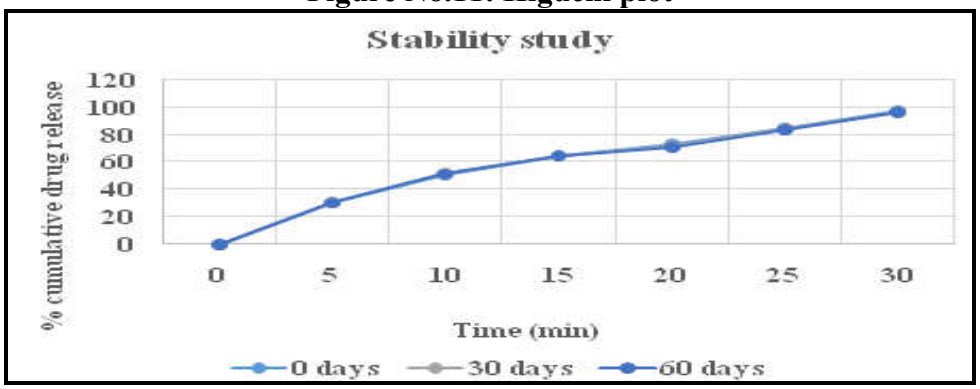

Figure No.12: Comparative stability studies for drug permeation of batch F3

CONCLUSION

Buccal patches of Amlodipine using polymer like HPMC K4m, HPMC k100m, PVP, PEG400 in various proportions and combination showed satisfactory physicomechanical and mucoadhesive characteristics, As the concentrations of polymers were decreased folding endurance and concentration of polymers increased. From drug diffusion studies, it was concluded, concentration of both polymers decreased into primary layer *In-vitro* diffusion rates were increased. Batch F3 was the optimised formulation showing uniform thickness, good % swelling index, % release and good folding endurance.

The formulation F3 showed linear zero order release for 30 min with cumulative % drug diffused of 99.48 from $2cm^2$ patches of batch F3.This present work concludes that the buccal patches shows the promising effect in the pharmaceutical field.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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