



Design and Characterization of Buccal Patches of Atomoxetine

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Received: 10-03-2019; Revised: 10-04-2019; Accepted: 05-05-2019.

ABSTRACT

To achieve transbuccal release of Atomoxetine by loading in unidirectional release mucoadhesive buccal patches. Buccal patches of Atomoxetine with unidirectional drug release were prepared using Eudragit-L100, HPMC K15M, and HPMC K4M by solvent casting method. Water impermeable backing layer (Pidilite® Biaxially-oriented polypropylene film) of patches provided unidirectional drug release. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F12, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be within the pharmacopeial limits, invitro drug release studies by using dialysis membrane. Among all the 12 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release within 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

Keywords: Buccal patches, Atomoxetine, Mucoadhesion, transbuccal release non-Fickian diffusion.

INTRODUCTION

Buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligo nucleotides and polysaccharides as well as conventional small drug molecules. The oral cavity can be used for local and systemic therapy. Examples of local therapy would be the treatment of oral infections, dental caries, mouth ulcers and stomatitis. The buccal route is of particular interest with regard to the systemic delivery of small molecules that are subjected to first pass metabolism or for the administration of proteins and peptides. Mucoadhesive drug delivery systems are delivery systems, which utilize the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for an extended period of time. The term 'mucoadhesive' is commonly used for materials that bind to the mucin/mucosal layer of a biological membrane.

In the present work, Buccal penetration of Atomoxetine patch for enhanced penetration through the buccal cavity, thereby reducing dose, minimizing frequency of administration and adverse affects, hence resulting in better patient compliance.

Aim and Objective of the Study

Need for the Study

The increasing need to deliver medication to patients efficiently with fewer side effects and improved

compliance has accelerated the pace of invention of new drug delivery system. Revolutionary drug delivery technology is extended to buccal route apart from oral. The ability to increase the buccal permeation can be a valuable aid when oral administration of drug is associated with problems. Though Atomoxetine is best suitable for the treatment of gastro intestinal disorders through oral administration, it has some limitations such as it requires administration of high dose frequently (20) due to its poor intestinal absorption (30-35%), elimination half life (5 hours) and adverse effects like allergic reactions, Arrhythmia, cardio respiratory arrest, tachycardia, Headache.

Hence there is a need to modify the route of administration for better absorption of the drug. The buccal route of administration may be better suited as it has many advantages over conventional oral route and enhance patient compliance.

Buccal penetration of Atomoxetine cannot be increased by niosomes or liposomes because of its size and rigid character of lipid layer. Hence there is a need for preparation of Atomoxetine patch for enhanced penetration through the buccal cavity, thereby reducing dose, minimizing frequency of administration and adverse affects, hence resulting in better patient compliance.



DRUG PROFILE**Drug: Atomoxetine**

Atomoxetine is the first non-stimulant drug approved for the treatment of attention-deficit hyperactivity disorder (ADHD). It is sold in the form of the hydrochloride salt of atomoxetine.

Bioavailability: 63-94% Half-life: 5 hours Protein binding: At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin, Dose: 10, 18, 25, 40, 60, 80mg or 1.2 mg/kg/day

Materials and Equipment

Atomoxetine, Ethanol, Eudragit L-100, HPMCK15M, HPMCK4M, Methanol. Digital weighing balance (Wensar), Digital pH meter, cyber pH-14LLab India, Franz diffusion cell (Borosil), UV-Spectrophotometer and Lab India.

METHODOLOGY**Determination OF UV Absorption maxima:**

Atomoxetine solution was prepared in 0.1 N HCL and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 270 nm. The procedure was repeated with pH 6.8 phosphate buffer.

Preparation of Standard Calibration Curve of Atomoxetine

100 mg of Atomoxetine was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 0.1 N HCL (pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1 N HCL (pH 1.2) in 100ml to get 100µg/ml (working standard). Then 0.2, 0.4, 0.6, 0.8, and

1 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCL to prepare 2µg, 4µg, 6µg, 8µg, and 10µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 270 nm against 0.1 N HCL (pH 1.2) as blank. The procedure was repeated with pH 6.8 phosphate buffer and absorbances were measured at 271 nm.

Selection of drug and other ingredients:

- Atomoxetine was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for Buccal drug delivery system.
- Eudragit-L100 (mg), HPMCK₄M (mg), HPMCK₁₅M (mg) were selected as matrix forming polymers.
- Propylene glycol and Tween 80 were selected as permeation enhancer and plasticizer.

II. Formulation:**Development of Buccal patches**

Buccal drug delivery patches were prepared by solvent casting method.

Solvent casting method

Eudragit L100, HPMCK₄M and HPMCK15M were weighed in requisite ratios and they were then dissolved in dichloromethane and ethanol as solvent using magnetic stirrer. Atomoxetine (40mg), Propylene glycol and Tween 80 was added to the above dispersion under continuous stirring. The uniform dispersion was poured in the petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches. After 24h, the dried films were taken out and stored in desiccator.

Table 1: Formulations of Atomoxetine Buccal Patch

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Drug(mg)	40	40	40	40	40	40	40	40	40	40	40	40
2	Eudragit-L100(mg)	200	250	300	-	-	-	-	-	-	150	150	-
3	HPMCK4 M(mg)	-	-	-	200	250	300	-	-	-	150	-	150
4	HPMC K15 M(mg)	-	-	-	-	-	-	200	250	300	-	150	150
5	Dichloromethane(ml)	8	8	8	8	8	8	8	8	8	8	8	8
6	Ethanol(ml)	8	8	8	8	8	8	8	8	8	8	8	8
7	Propylene glycol(ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
8	Tween-80(ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Evaluation of Buccal patch by physical methods**Physical appearance**

All the Buccal patches were visually inspected for color, clarity, flexibility & smoothness.

Thickness

This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.



Weight variation

The three disks of 2x2 cm² was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Flatness

Longitudinal strips were cut out from each patch, one the centre and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining present constriction, considering 0% constriction equivalent to 100% flatness.

Folding endurance

The folding endurance was measured manually for the preparation patch. A strip of the films (4x3 cm) was cut evenly and repeatedly folded at the same place till it is broken.

Moisture uptake

The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity inside the desiccators at 84 % RH. After 3 days the films were taken and weighed the percentage moisture absorption of the patch was found.

$$\text{Percentage moisture absorbed} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture content

The patches were weighed individually and kept in a desiccators containing fused calcium chloride at 40°C for 24 h. The patches were reweighed until a constant weight was obtained. Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches.

Swelling study

Completely dried membranes with a specified area (3.83 cm²) were weighed and put in desiccators for 24 h. They were removed and exposed to relative humidity conditions of 75 % (containing saturated solution of sodium chloride) in desiccators. Weight was taken on a single pan balance periodically until a constant weight was obtained. The swelling capacity of the membranes (in weight %) was calculated in terms of percentage increase in weight of membrane over the initial weight of the specimen.

Drug content determination

The patch of area 3.83 cm² was cut and dissolved in PBS pH 7.4. Then solvent ethanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with PBS pH 7.4 to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 270 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Evaluation of Buccal patch by permeation studies**Diffusion cell**

Permeation studies were carried out on Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment. The receptor compartment is 5mm and holds a volume of 15 ml. The receptor compartment is attached to a collecting tube which allows easy collection of hourly sample while the process of diffusion. The donor and the receptor compartment are held together with help of a clap and the diffusion cell was placed on the magnetic stirrer while diffusion studies carried.

The total area of the receptor compartment that is exposed to the Buccal patch for diffusion is 3.83 cm².

In vitro permeation studies using dialysis membrane

In vitro permeation of Atomoxetine from Buccal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and a Buccal patch. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 7.4 and the setup was placed over a magnetic stirrer with temperature maintained at 37°C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12h. They were stored in refrigerated condition till the analysis was performed. The content of Atomoxetine in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined at 270 nm.

Kinetic modeling of drug release**Mechanism of drug release**

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release model

To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$Q = K_0 t$$

Where, Q= amount of drug released at time t



K_0 =zero order release rate constant

The plot of % drug release versus time is linear.

First order release model

The release rate data are fitted to the following equation

$$\ln(100-Q) = \ln 100 - k_1 t$$

Where, Q= percent drug release at time t

K_1 = first order release rate constant

The plot of log % drug release versus time is linear.

C.Higuchi's Release Model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation

$$Q = K_H t^{1/2}$$

Where, Q= percent drug release at time t

K_H = Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear.

Korsmeyer-peppas release model

The release rate data were fitted to the following equation

$$F = (M_t/M) = K_m t^n$$

Where, M_t = drug release at time t

M= total amount of drug in dosage form

F= fraction of drug release at time t

K_m =constant dependent on geometry of dosage form

n=diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if $0.45 < n < 0.89$ then the release is through anomalous diffusion or non-fickian diffusion (Swella &

Cylindrical Matrix). In this model, a plot of log (M_t/M) versus log (time) is linear.

Drug excipients interaction studies

FT-IR spectrum interpretation

IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation were analyzed between wave numbers 4000.0 and 400.0 cm^{-1} .

RESULTS AND DISCUSSION

Standard Calibration curve of Atomoxetine

It was found that the estimation of Atomoxetine by UV spectrophotometric method at λ_{max} 271 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10 $\mu\text{g/ml}$. The regression equation generated was $y = 0.0636x + 0.0751$.

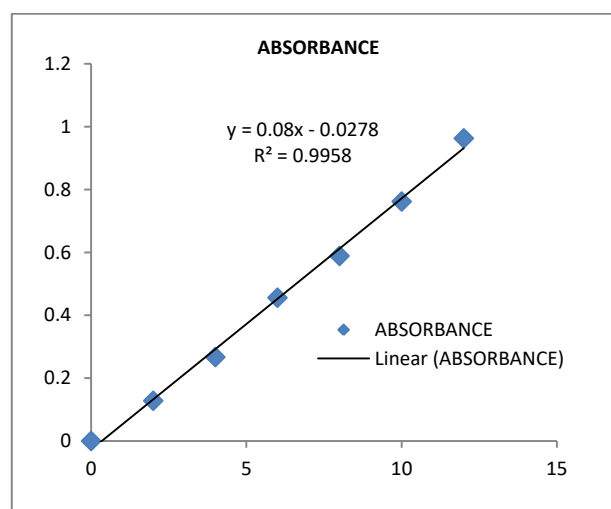


Figure 1: Standard graph of Atomoxetine in pH 6.8 Phosphate buffer

Table 2: Evaluation of Buccal patch by physical methods

Formulation	Thickness (mm)	Folding endurance	Drug content (%)	Moisture uptake (%)	Moisture content (%)
F1	0.3569	20	45	7.98	3.77
F2	0.3520	25	65	25.05	9.2
F3	0.3470	27	57.5	13.09	5.16
F4	0.3496	24	60	15.63	5.66
F5	0.3460	30	67.5	11.73	4.87
F6	0.3517	32	92.5	19.65	12.67
F7	0.3478	40	101.7	9.42	3.43
F8	0.3437	37	85	10.87	4.72
F9	0.3503	34	55	16.44	6.62
F10	0.3532	29	62.5	13.08	6.17
F11	0.3546	26	85	20.63	7.94
F12	0.3503	31	82.5	15.73	6.55

Evaluation of Atomoxetine Buccal patches

Physical appearance

All the Buccal patches were visually inspected for colour, clarity, flexibility.

Flatness

All the Buccal patches were found to be flat without any foams.

The prepared Atomoxetine Buccal patches were evaluated by physical methods such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake and Moisture content and all the results were found to be within the pharmacopeial limits.

Table No 3: Evaluation of Buccal patch by In-vitro permeation studies using dialysis membrane

Time (hrs)	% Drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	9.05	15.1	10.1	9.49	10.9	20.2	17.5	12.0	11.1	12.7	10.0	20.4
2	13.3	19.8	12.8	11.3	19.6	27.8	21.9	17.5	13.0	17.9	12.5	25.4
4	14.6	28.3	21.5	22.6	24.9	42.8	33.5	23.4	23.3	27.4	23.6	33.0
6	21.9	34.1	25.9	32.3	31.2	53.5	40.0	30.9	33.4	32.7	30.9	41.7
8	32.7	41.1	33.4	43.9	38.0	66.3	46.5	48.1	52.7	50.6	36.7	47.9
10	40.4	50.1	44.5	56.3	50.3	82.0	64.2	60.0	66.4	63.0	45.9	63.0
12	54.2	65.8	56.7	69.4	65.9	94.7	91.9	78.7	79.1	74.8	56	80.9

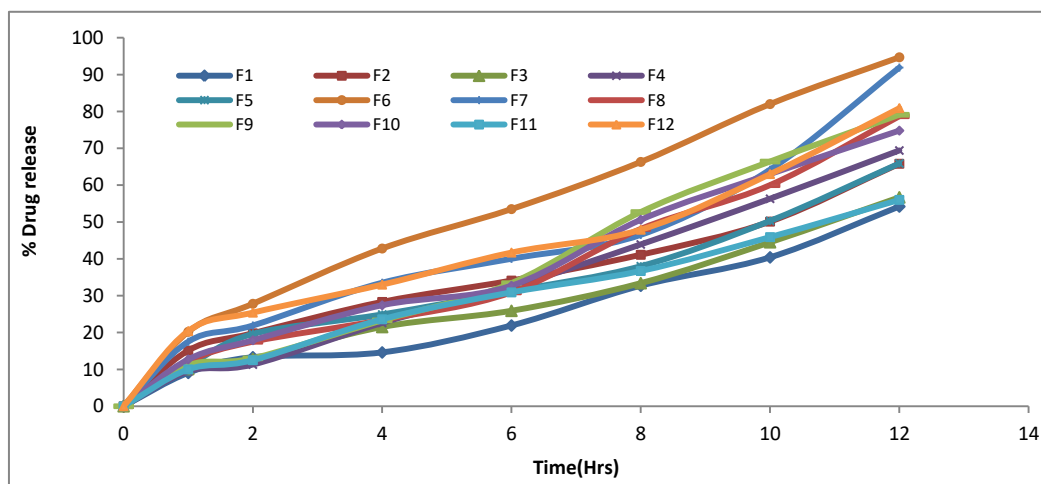


Figure 2: Release profile of In-vitro permeation studies using dialysis membrane

The prepared Atomoxetine Buccal patches were evaluated for In-vitro permeation studies using dialysis membrane, Among all the 12 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release within 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile.

Table 4: kinetics of In-vitro permeation studies using dialysis membrane

Cumulative (%) release Q	Time (T)	Root (T)	Log (%) release	Log (T)	Log (%) remain	Release rate (cumulative % release/t)	1/cum % release	Peppas log Q/100	% drug remain	Q01/3	Qt1/3	Q01/3 -Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
20.2356	1	1.000	1.306	0.000	1.902	20.236	0.0494	-0.694	79.7644	4.642	4.305	0.337
27.80759	2	1.414	1.444	0.301	1.858	13.904	0.0360	-0.556	72.19241	4.642	4.164	0.478
42.87958	4	2.000	1.632	0.602	1.757	10.720	0.0233	-0.368	57.12042	4.642	3.851	0.790
53.59293	6	2.449	1.729	0.778	1.667	8.932	0.0187	-0.271	46.40707	4.462	3.594	1.048
66.38743	8	2.828	1.822	0.903	1.527	8.270	0.0151	-0.178	33.61257	4.642	3.227	1.414
82.0877	10	3.162	1.914	1.000	1.253	8.209	0.0122	-0.086	17.9123	4.642	2.616	2.025
94.7055	12	3.464	1.976	1.079	0.724	7.892	0.0106	-0.024	5.294503	4.642	1.743	2.899



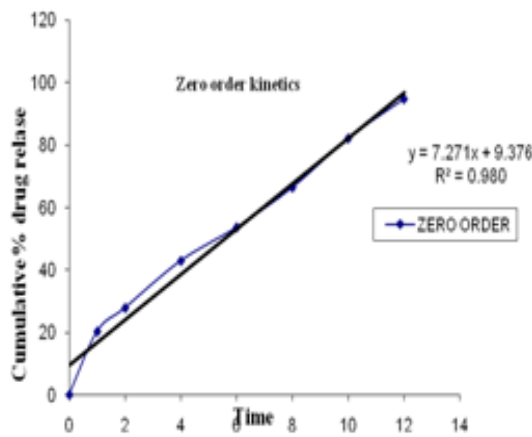


Figure 3: Zero order kinetics

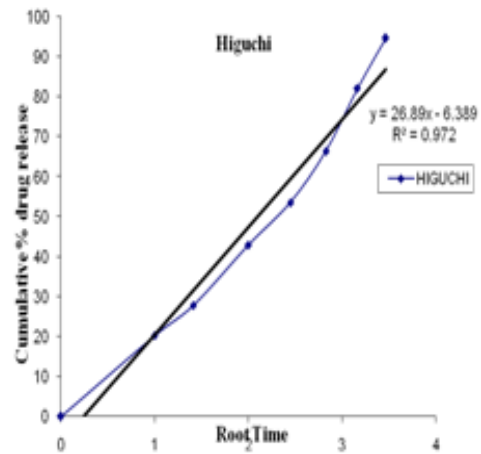


Figure 4: Higuchi plot

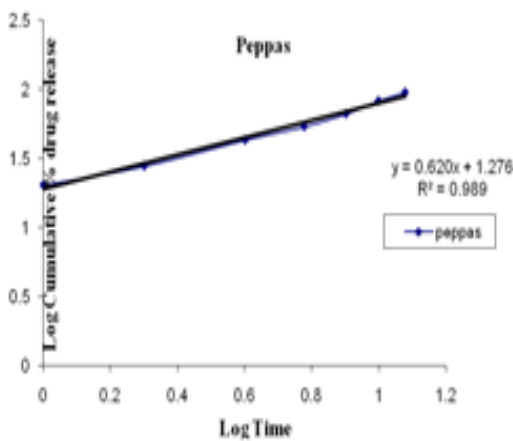


Figure 5: Peppas plot

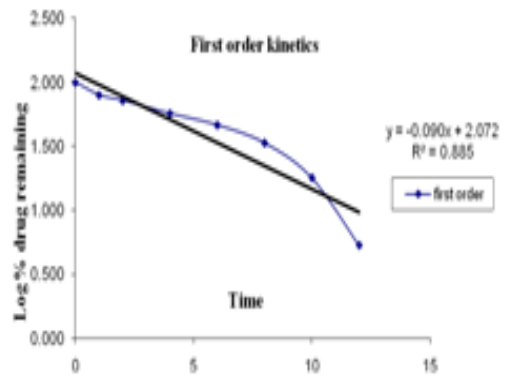
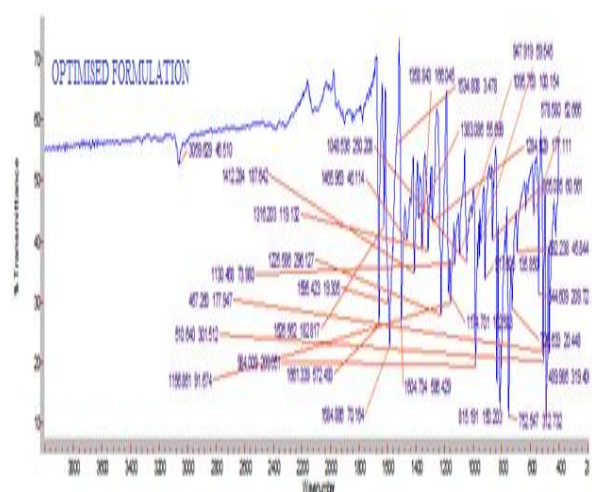
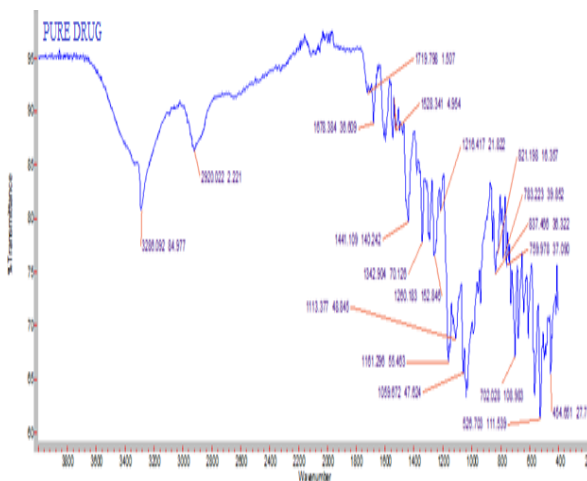


Figure 6: First order kinetics

The kinetics of In-vitro permeation studies using dialysis membrane for F6 formulation was plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. And the n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.



SUMMARY AND CONCLUSION

In present study buccal drug delivery of Atomoxetine was developed to overcome the first pass metabolism and to reduce frequency of dosing compared to oral route. Matrix type of buccal patches was developed by using

polymers Eudragit-L100, HPMCK₄M and HPMCK₁₅M. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween 80 were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions.



Formulations were prepared with the varying concentrations polymers ranging from F1-F12, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content and Swelling study and all the results were found to be were found to be within the pharmacopeial limits, in vitro drug release studies by using dialysis membrane. Among all the 12 formulations F6 formulation which contain HPMC K4M 300mg and Eudragit L-100 60mg had shown 94% cumulative drug release within 12 hours. And compared to HPMC K15M, HPMC K4M showed better drug release profile. For F6 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsmeyer-peppas release model i.e., 0.9892. The n value was found to be 0.6203 which indicates the drug release pattern was found to be non-Fickian diffusion.

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Source of Support: Nil, Conflict of Interest: None.

