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Research Article

Design and Development of Fast Dissolving Sublingual Film of an Aminophylline

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ABSTRACT

The present study was planned to formulate fast dissolving sublingual film of Aminophylline by solvent casting method using a polymer HPMC E_{50} as film forming agent. The *FT-IR* study revealed no interaction between the drug and excipients. Sucrose was added to mask the bitter taste of the drug. FDS Films were prepared by using the drug polymer ratio 1:1 to 1:9. The prepared films were evaluated for physicochemical parameters such as weight variation, thickness, folding endurance, drug content, tensile strength, % elongation, % moisture absorption and *in vitro* dissolution test. Formulations (F2&F3) showed better drug release (99.05%and99.43%) within 210 sec. and also showed less disintegration time (33.33±0.57and37±0.57sec.). The appearance and surface smoothness of formulation (F2) was not good. Therefore, Formulation F3 was selected as the best formulation based on the physicochemical parameter and *in vitro* dissolution studies. Stability study was conducted for the best formulation (F3) as per ICH guidelines and showed no significant changes in physical appearance, weight uniformity, folding endurance, % drug content, % moisture absorption and *in vitro* drug release during study period. Therefore, it can be concluded that the prepared fast dissolving Aminophylline sublingual films might be a potential formulation for the treatment of patient having asthma.

INTRODUCTION

The fast dissolving drug delivery systems came into existence in the early 1970's. Fast dissolving drug delivery systems have a major advantage over conventional dosage forms since the drug rapidly disintegrates and dissolves without the use of water. [1]

Many patients have difficulty in swallowing tablets and capsules especially in cases of dysphagia, coughing, sudden allergic attacks or unavailability of water. Thus, to eliminate the drawbacks of tablets, fast dissolving films can be developed. [2]

The delivery system consists of a very thin oral film, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for GI to be achieved when swallowed. The sublingual route can produce a rapid onset of action within a short period of time due to high permeability and vascularisation of the sublingual mucosa. [3, 4]

Sublingual route can be considered as a novel route of administration because of immediate onset of pharmacological action. Sublingual drug administration means placement of the dosage form under the tongue. From here the drug gets absorbed and reaches directly into the blood stream through the ventral surface of the tongue and the floor of the mouth. [5]

The aim of the study is to prepare fast dissolving sublingual film of Aminophylline to achieve rapid onset of action as required during the asthma. Aminophylline is a compound of the bronchodilator Theophylline with Ethylenediamine in 2:1 ratio. The Ethylenediamine improves solubility, and the Aminophylline is

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usually found as a dihydrate. Aminophylline is less potent and shorter-acting than Theophylline. Its most common use is in the treatment of airway obstruction from asthma or COPD. Aminophylline is both Competitive non-selective phosphodiesterase inhibitor and Non selective adenosine receptor antagonist. [6, 7]

MATERIALS AND METHODS

Aminophylline was purchased from the Indian fine chemical, Mumbai. HPMC E_{50} was obtained from Loba Chemical Pvt. Ltd, Mumbai. PEG400 was obtained from S D Fine-Chem Ltd, Boisar. PG was obtained from Spectrum Reagent and Chemical Pvt. Ltd. Cochin. Citric acid and Peppermint oil was obtained from Nice Chem. Pvt. Ltd, Kerala. Sucrose was obtained from Thermo Fisher Scientific India Pvt. Ltd. Mumbai

Drug Polymer Compatibility Studies

Drug and excipients compatibility study was carried out using FT-IR. Sample and potassium bromide was finely grounded using mortar and pestle at the ratio of 1:100 respectively. A small amount of mixture was placed under a hydraulic press, compressed at 10 kg/cm^2 to form a transparent pellet. The pellet was kept in the sample holder and scanned from 4000 cm^{-1}to 400 cm^{-1} in Shimadzu FT-IR spectrophotometer.

UV Spectrum Analysis of Aminophylline

The standard solution of Aminophylline was prepared by dissolving 10 mg in 50 ml phosphate buffer pH 6.8 (200µg/ml) and further diluted to get different solution having concentration of 10µg/ml solution was scanned between wavelengths of 200-400 nm in UV visible spectrophotometer (Shimadzu-UV-1800 spectrophotometer). The maximum absorption (λmax) of Aminophylline peak was obtained at 271.6nm. **(Fig.1).**

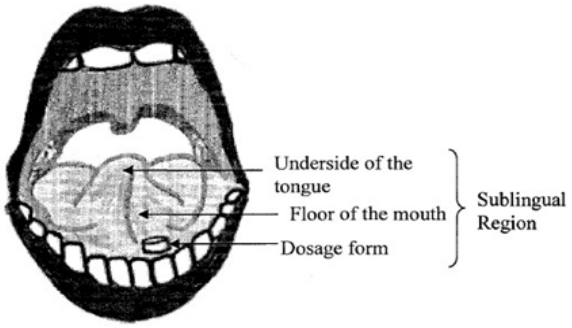

Figure1: Schematic representation of the oral cavity

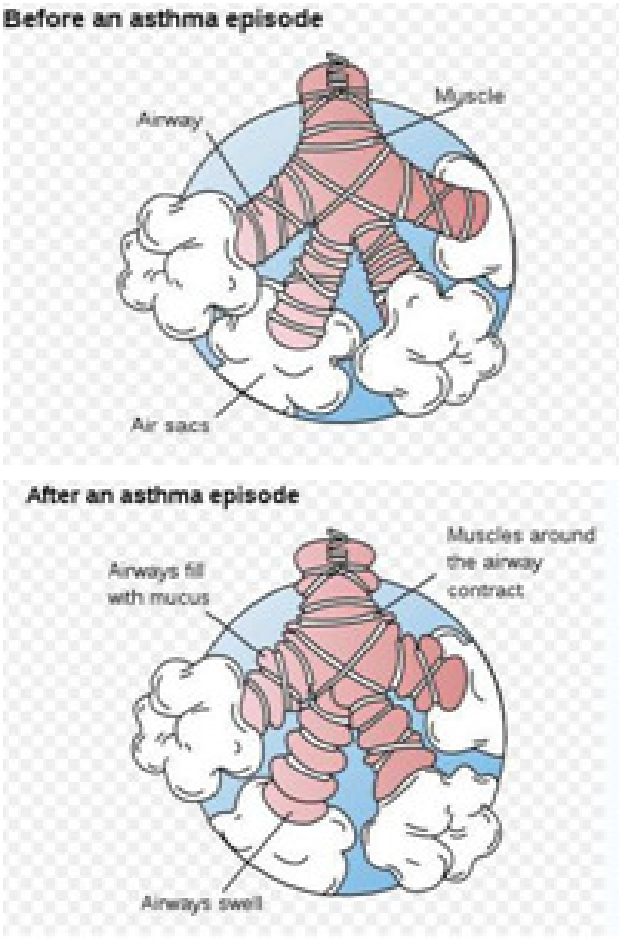

Figure 2: The airways inflammation and bronchoconstriction in asthma

Baseline Curve of Aminophylline

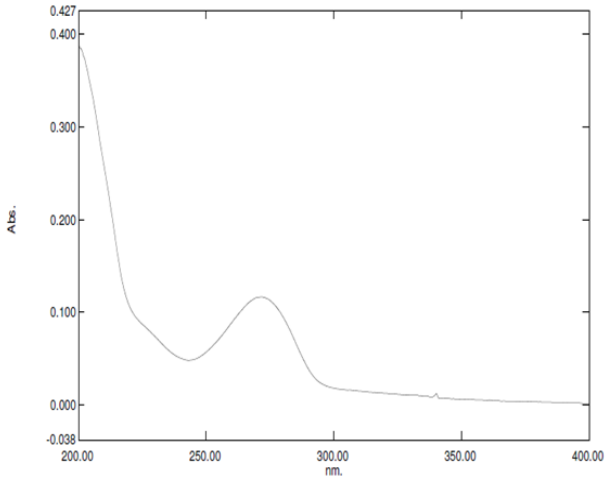

Figure 3: UV Spectrum analysis of Aminophylline Phosphate buffer pH 6.8 λ_{max} 271 nm.

Standard plot of Aminophylline in Phosphate buffer pH 6.8

10 mg of Aminophylline was accurately weighed and transferred in to a 50 ml volumetric flask and dissolved in pH 6.8 phosphate buffer and

volume was made upto 50 ml with pH 6.8 phosphate buffer. The obtained drug solution with concentration of (200µg/ml) was used as the standard stock solution of Aminophylline. The absorbance of all the solution prepared (i.e. concentration of 10, 20, 30, 40 and 50 µg/ml), was measured against phosphate buffer pH 6.8 as a blank at 271nm. Standard curve was plotted **(Fig.2)** between concentration and absorbance and intercept (fixed at 0) and slope (k) values were noted.

Standard Calibration Curve of Aminophylline

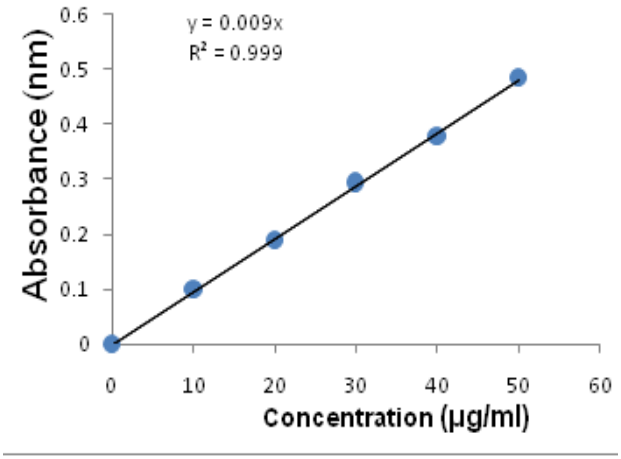

Figure 4: Standard plot of Aminophylline Phosphate buffer pH 6.8

Method of preparation of fast dissolving sublingual film of Aminophylline

Fast dissolving sublingual films were prepared by using solvent casting method. The solution I was prepared by dissolving required quantity of HPMC E50 (ratio1:1 to 1:9) in water and keeping it aside for 4 hours to remove the air bubbles. Accurately weighed drug was added and dissolved in solution I. Solution II was prepared by adding sucrose, peppermint oil, polyethylene glycol 400 and propylene glycol and citric acid and dissolved. Solution II was added to solution I and it was then casted on to petri plates and dried at room temperature for 24 hours. After drying, films were carefully removed from plates and cut it in to required size (2 x 2) cm^2. The samples were then evaluated for various tests **(Table 1)**.

Thickness

The thickness of the film was measured using digital verneir calliper. The thickness of each film was determined at different locations and standard deviation was calculated

Weight Variation

An area of 2 x 2cm^2 of the film was cut at three different places from the casted film. The weight of each film was taken thrice and average weight variation was calculated. [8]

Folding Endurance

The folding endurance is expressed as the number of folds required to break the specimen or to develop visible cracks. This gives an indication of the brittleness of film. Folding endurance was determined manually by repeatedly folding the film at the same place several times till it breaks. [9]

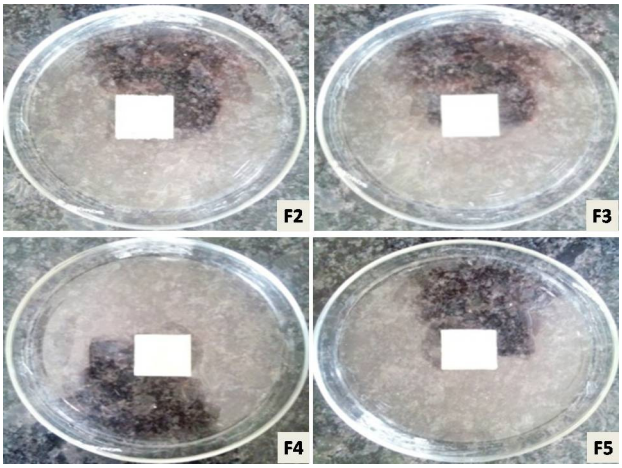

Figure9: Pictures depicting the formulations F2, F3, F4, F5

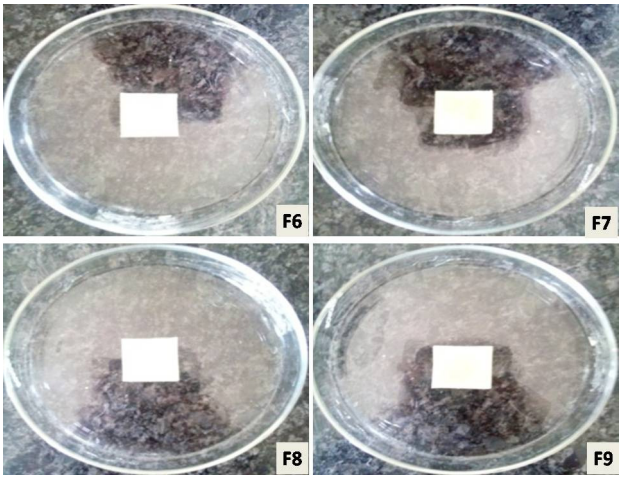

Figure 10: Pictures depicting the formulations F6, F7, F8, F9

Tensile Strength

Tensile strength was measured by using the apparatus fabricated in the laboratory. A film of area 2 x2 cm^2 was cut which did not contain any air bubble. The film was fixed to the assembly and the weight that was required to break the film was noted as well as film elongation was noted using the pointer fixed to the assembly.

Drug and Excipients Compatibility Study By *Ft-Ir*

FT-IR of Aminophylline

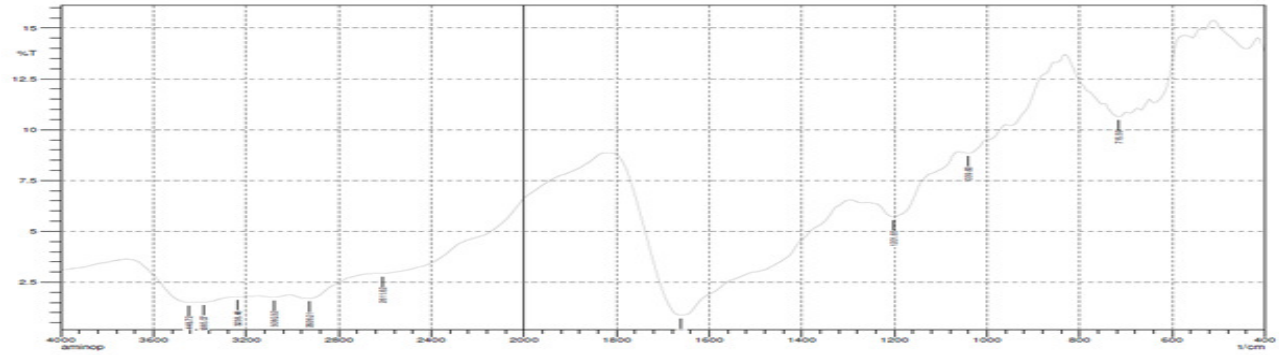

Figure 5: *FT-IR* spectra of Aminophylline

FT-IR of Hydroxy propyl methyl cellulose E_{50}

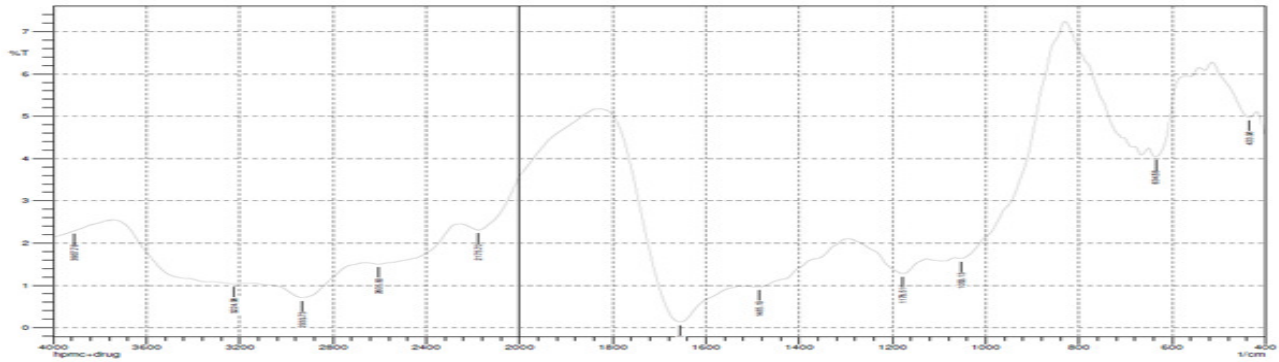

Figure 6: *FT-IR* spectra of Aminophylline and HPMC E_{50}

FT-IR of Aminophylline and HPMC E_{50}

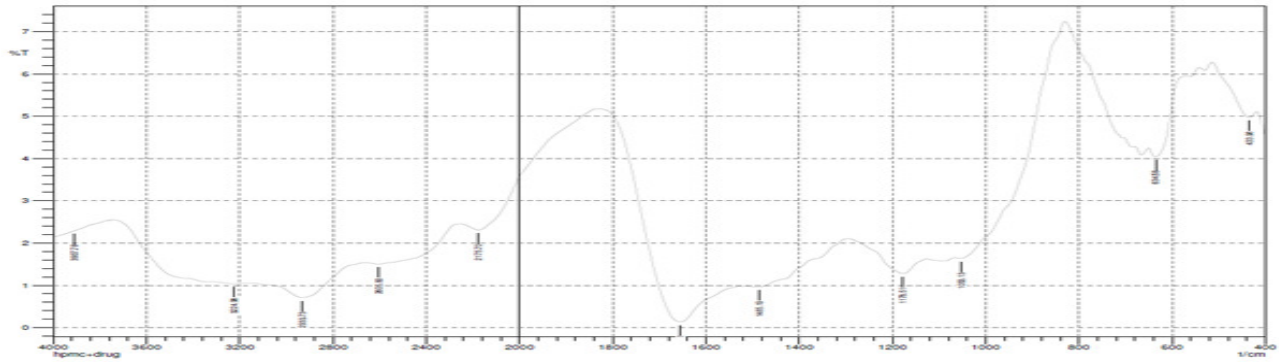

Figure7: *FT-IR* graph of Aminophylline and HPMC E_{50}

FT-IR of Citric acid

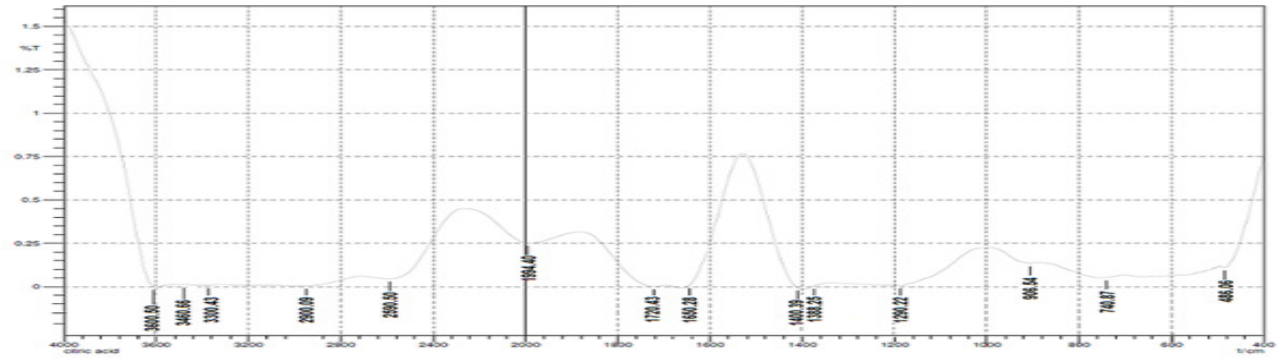

Figure 8: *FT-IR* graph of Citric acid

Table 1: Classification of Asthma

Severity	Symptom Frequency	Nighttimes Symptoms	Peak expiratory flow rate or FEV1 of predicted	Variability of peak expiratory flow rate or FEV1
Intermittent	Less than once a week	Less than twice per month	More than 80% predicted	Less than 20%
Mild Persistent	More than once per week but less than once per day	More than twice per month	More than 80% predicted	20–30%
Moderate Persistent	Daily	More than once per week	60–80% Predicted	More than 30%
Severe Persistent	Daily	Frequent	Less than 60% predicted	More than 30%

Table 2: The composition of different formulations F1 to F9

S. No.	Drug (mg)	HPMC E50 (mg)	PEG 400 (ml)	Propylene glycol (ml)	Citric acid (mg)	Sucrose (mg)	Peppermint oil (ml)
F-1	80	80	1	0.3	70	50	0.3
F-2	80	160	1	0.3	70	50	0.3
F-3	80	240	1	0.3	70	50	0.3
F-4	80	320	1	0.3	70	50	0.3
F-5	80	400	1	0.3	70	50	0.3
F-6	80	480	1	0.3	70	50	0.3
F-7	80	560	1	0.3	70	50	0.3
F-8	80	640	1	0.3	70	50	0.3
F-9	80	720	1	0.3	70	50	0.3

Table 3: Physicochemical parameters of formulation F2-F9

Formulation Code	Weight Variation* (mg)	Thickness* (mm)	Folding endurance*	Tensile Strength* (kg/cm²)
F2	88.07±0.491	0.11±0.01	45.33±1.154	0.859 ±0.008
F3	90.02±0.204	0.113±0.005	61.66±2.081	0.906±0.015
F4	95.41±1.201	0.12±0.01	91.33±1.527	0.973±0.020
F5	99.14±0.338	0.146±0.011	168.33±1.154	1.116±0.15
F6	102.51±1.125	0.16±0.01	221±1.732	1.133±0.015
F7	106.417±0.946	0.186±0.011	274.66±1.527	1.263±0.222
F8	109.76±1.836	0.16±0.01	323±1.732	1.433±0.365
F9	113.59±1.076	0.183±0.009	397.66±1.527	1.58±0.09

Tensile strength was measured using the formula given below:

Tensile strength = Break force / w.t (1+ΔL/L)

Where, W, t and L are width, thickness and length of film respectively; ΔL is increase in length of film. [10]

Percentage Elongation

It was determined by the increase in the length of the film just before the breaking of the film. The formula used for calculating % Elongation is as shown below:

% Elongation = [Final length – Initial length]/ Initial length x 100. [11]

Percentage Moisture Absorption

The prepared films were cut in to 2 x2 cm^2 and weighed and placed in a dessicator containing 100ml of saturated solution of Aluminium chloride at 75 ± 5% RH. After three days the films were taken out and reweighed. The percentage moisture absorption was calculated using the following formula.

%Moisture absorption = Final weight -Initial weight x 100/ Initial weight [12]

Surface pH

The oral film was slightly wetted with the help of water. Then the pH of film was measured by bringing the electrode in contact with the surface of the oral film. This study was performed for each formulations and mean ± S.D were calculated.

Content Uniformity

The film of 2 x 2cm^2 was cut and dissolved in phosphate buffer pH 6.8 and volume was made to 100 ml in a volumetric flask. 1 ml was withdrawn from this solution and made upto 10 ml with phosphate buffer pH 6.8. The absorbance of this solution was measured at 271 nm using UV visible spectrophotometer and the concentration was calculated. By correcting the dilution factor, the drug content was calculated. The test was performed in the triplicates and the standard deviation was calculated. [13]

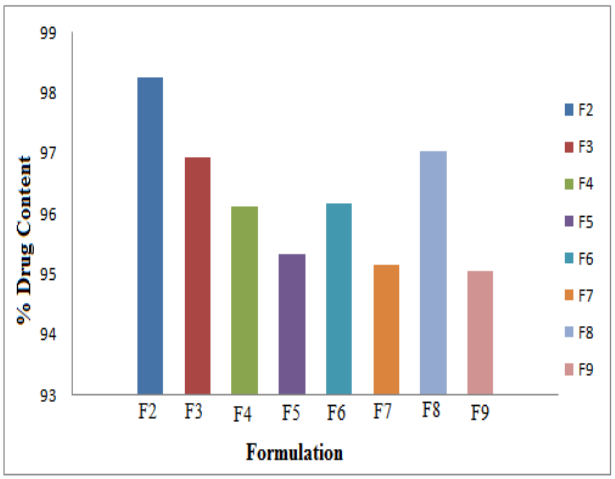

Figure 11: Comparison of % Drug Content of formulations F2-F9

Disintegration time

Disintegration time was performed to ensure the disintegration of film in phosphate buffer pH 6.8. One film from each formulation was introduced in to tube of disintegration apparatus. The apparatus was operated until the film disintegrated and disintegration time was noted. The test was performed triplicate. [14]

***In vitro* dissolution study**

In vitro dissolution study of prepared films was performed in USP dissolution apparatus II (Paddle type) using 300 ml phosphate buffer pH 6.8 as dissolution medium at 50 rpm speed and the temperature maintained at 37 ± 0.5 ^{0}C. The samples were withdrawn at the time intervals of 30 seconds and analyzed spectrophotometrically at 271 nm. [15]

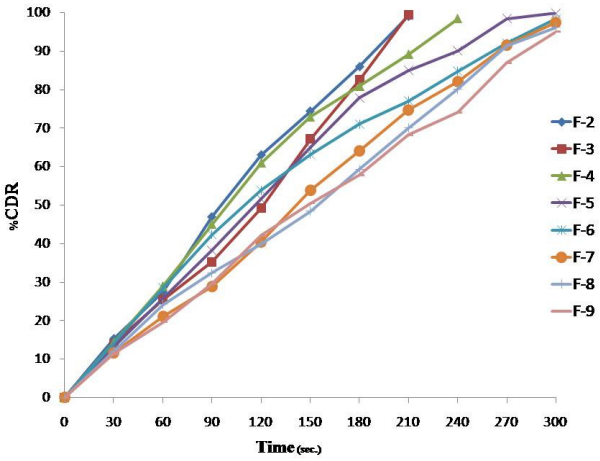

Figure 12: Comparison of *In-vitro* Drug Release profile of formulation F2-F9

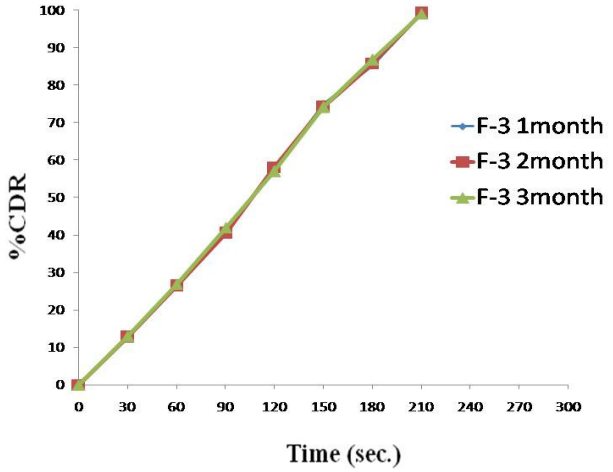

Figure 13: *In vitro* dissolution study for formulation F3 after 1, 2 and 3 months

Stability Studies

The stability study of the formulated film was carried out under different experimental conditions as per ICH guidlines. The film was wrapped in butter paper and then packed in aluminum foil and kept in stability chamber at 40±2^{0}C and 75% RH for the period of 3 months.

Table 4: Physicochemical parameters of formulation F2-F9

%Elongation*	%Moisture absorption	Surface pH*	%Drug Content*	Disintegration time* (sec.)
18.85±0.25	10.1± 0.10	6.72±0.05	98.25±0.633	33.33±0.57
22.75±1.35	12.99± 0.12	6.7±0.17	96.92±0.043	37.33±0.57
19.28±0.43	14.22± 0.89	6.81±0.030	96.11±0.196	92.33±1.15
26.57±0.96	16.70± 0.33	6.88±0.17	95.31±0.284	122.66±1.52
25.72±0.98	19.70± 0.52	6.90±0.015	96.16±0.252	118.33±2.08
30.16±0.566	21.29 ±0.51	6.93±0.02	95.15±0.191	123.66±0.471
34.81±1.216	22.83± 1.0	6.67±0.055	97.03±1.048	120.66±0.577
28.29±0.345	24.83± 0.25	6.74±0.035	95.03±0.170	119.33±1.527

Table 5: *In-vitro* Drug Release profile of formulations F2-F5

Time (sec.)	% Cumulative Drug Release			
	F2	F3	F4	F5
30	15.26±0.93	14.04±0.18	14.35±0.47	13.05±0.10
60	27.48±0.50	25.51±0.52	29±0.86	25.83±0.79
90	46.99±1.44	35.29±0.42	44.98±0.22	38.31±0.41
120	63.04±0.96	49.16±0.72	60.94±0.22	51.55±0.54
150	74.40±1.16	67.14±0.77	72.91±0.25	65±0.12
180	86.04±0.63	82.53±1.45	80.86±0.39	77.83±0.27
210	99.05±0.18	99.43±0.78	89.09±0.33	84.92±0.84
240	-	-	98.88±0.53	90.04±0.23
270	-	-	-	96.41±0.35
300	-	-	-	99.80±0.10

Table 6: *In-vitro* Drug Release profile of formulations F6-F9

Time (sec.)	% Cumulative Drug Release			
	F6	F7	F8	F9
30	14.08±1.01	11.56±0.63	12.05±0.59	11.35±0.37
60	28.57±1.83	21.11±0.49	24.14±0.24	19.61±0.51
90	42.40±1.19	28. ±0.07	32.44±0.72	29.60±0.61
120	53.83±1.87	40.43±0.51	39.89±0.71	42.03±0.52
150	63.20±1.13	53.95±0.23	48.40±0.61	50.53±0.35
180	71.06±0.95	64.16±0.49	59.29±1.15	57.76±0.37
210	77.05±1.57	74.71±0.29	69.99±0.40	68.25±1.23
240	84.74±0.22	82.12±0.21	80.17±1.06	74.08±0.13
270	92.09±0.86	91.60±0.54	91.30±2.05	86.93±0.72
300	98.29±0.69	97.41±0.75	96.18±0.66	95.04±1.00

At each month interval the films were taken and analysed for any changes in weight uniformity, Folding endurance, % Moisture absorption, % Drug content and *In-vitro* dissolution study. [16]

RESULTS AND DISCUSSION

Fast dissolving sublingual films of Aminophylline were evaluated for the various evaluation parameters. The films were prepared by using varying concentrations of film forming polymer

with constant concentration of plasticizers. All the prepared films F2-F9 were flexible and good in appearance except F2.

The slight difference in the thickness of films could be attributed to the uneven surface of the plate. The individual weight of the films was measured and weight variation was calculated. The slight difference in the weight could be proportionately related to the variation in the film thickness. The pH of all the formulations was found in the range of 6.67±0.055 to 6.93±0.02. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity. All the films showed good folding endurance was found to be 45.33±1.154 to 397.66±1.527.

The tensile strength of all the formulations was found in increasing order, it was seen from the results that tensile strength increases with increasing in the concentration of polymer. The percentage elongations of all prepared films were found in the range of 18.85±0.25%to 34.81±1.216%. Formulation F8 had highest percentage elongation.

The disintegration time of the films was found to be in the range of 33.33±0.57 to123.66±0.471seconds. Disintegration time of the films was found to increase with increase in the amount of the polymer. The drug content of formulation F2-F9 was found within the 95.03±0.170 to 98.25±0.633. (**Table.3**)

The % cumulative drug releases of Aminophylline film of formulations F2 to F9 were found to be 95.05±1.00% to 99.43±0.61% between 210 to 300 seconds**.** It shows that the percentage drug release decreases with increasing in polymer concentration. The % drug release of formulations F2 & F3 was 99.05% & 99.43% respectively in quick time (i.e.210 sec.), but the appearance and surface smoothness of formulation F2 was not good. Therefore, formulation F3 was selected as best formulation and used for further studies. (**Table 4, 5**)

The selected formulation F3 was subjected to stability test at 40±2 ^{0}C / 75% RH for 3 months as per ICH guidelines. Every month interval the stored samples were collected and tested to assess their accelerated stability. The films were evaluated for physicochemical parameters such as physical appearance, weight, folding endurance, drug content, percentage moisture absorption and *in vitro* drug release. The results indicate that there were no statistically significant differences between the initial values and the values obtained during the stability studies. **(Table 6, 7) (Fig. 13).**

Table7: Physicochemical evaluation during stability study for formulation F3

Parameters	Condition (40 ±2°C / 75%RH)		
	30 days	**60 days**	**90 days**
Weight uniformity (mg)	90.37±0.96	90.66±1.24	90.75±0.26
Folding endurance	62±1.00	61±1.00	61.33±0.57
% Drug content	96.81±0.63	96.95±0.78	96.22±0.88
% Moisture absorption	13.055±0.07	12.67±0.56	12.96±0.22

Table 8: *In-vitro* drug release study for formulation F3

Time (sec)	% Cumulative Drug Release		
	30 days	**60 days**	**90 days**
30	13.11	12.78	13.02
60	26.45	26.44	26.89
90	41.2	40.43	41.98
120	57.22	58.09	57.01
150	74.9	74.16	74.07
180	85.23	85.88	86.8
210	99.32	99.21	99.13

CONCLUSION

From the present study it can be conclude that fast dissolving sublingual film formulation can be a potential novel drug dosage form for paediatric, geriatric and also for general population. The results of the present study indicated that HPMC E50 could be used as a film forming polymer for formulation of fast dissolving film containing Aminophylline. The selected formulation F3 was found to be stable for a period of three month at 40°C/75%RH. Therefore, it can be concluded that the prepared Aminophylline sublingual films might be a potential formulation for the treatment of patient having asthma.

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