Formulation Development , Optimization and Evaluation of Fast Dissolving Sublingual Film Containing Aminophylline (Respiratory Stimulant)

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ABSTRACT

Mouth dissolving sublingual films is very useful in patient such as bedridden geriatric, pediatric, or Developmentally disabled who face difficulty is swallowing conventional capsule or tablets and syrups or liquid orals leading to ineffective therapy. Mouth dissolving sublingual films are play important role in current pharmaceutical research. They are easy and convenience over other formulations such as immediate release tablets and orally disintegrating tablets. Oral sublingual films is oral solid dosage form that dissolves and disintegrates within in a minute when placed in mouth under the tongue without chewing or without taking water. In recent time it is observed that during covid -19 pandemic , covid -19 virus attack on the respiratory track it show the symptoms like cough, difficulty in breathing or shortness of breath, chest pain ,etc. The respiratory failure is main cause of death, to overcome this situation many respiratory stimulants are used during these pandemic, which is available in market, which is widely used for critical condition patients which are admitted in ICU. The need of respiratory stimulant during these disaster in communicable disease has much been faced by entire world. Aminophylline is used in the parenteral form, but the parenteral route is not much preferred by the most of the patients .Number of patients refer the oral route than any other route of administration. Fast dissolving sublingual route is the best option for such cases to provide instant effect of drug and overcome the condition.

Key words:- Aminophylline1, mouth dissolving sublingual films2, HPMC k153, Propylene glycol4, polyethylene glycol5.

Introduction:

The oral route of administration has always been preferred over other routes of administration namely, parenteral, topical,

rectal and vaginal by the medical practitioners, manufactures due to patient acceptance[1, 2]. Ease of administration, convenience and cost effectiveness has been the rezone behind the popularity of this route among the patient population [1, 3].The oral cavity has unique environment that offers its potential as a site for drug delivery [2]. In modern days there has been a lot of advancement in the oral solid drug delivery system, from conventional dosage form such as tablets and capsules to modified release dosage forms and recently fast dissolving dosage forms. The limitation has been the reason of mouth dissolving drug delivery system. Fast dissolving sublingual films are solid dosage forms that disintegrate and dissolve when placed in the mouth without taking water [2]. Fast dissolving sublingual films are gaining popularity and acceptance among pediatric, geriatric and dysphasia patients who fear chocking. Fast dissolving sublingual films provides convenience, ease of administration and faster onset of action, as the drug absorbed through oral mucosa and enters the systemic circulation, bypassing the first pass metabolism.

Most of the drug is swallowed orally with the saliva and the absorption of drug takes place in the gastro-intestinal tract. The dosage forms were firstly introduced in 1970's as an alternative to the conventional immediate release tablet and capsule which require swallowing the dosage form. Fast disintegrating dosage forms are available in the market for variety of drugs [4, 5]. Orally dissolving films were introduced in the market breath fresheners and personal care product such as dental care strips and soaps strips. It is also useful whether local action desired such as local anaesthetic for toothache, oral ulcers, cold sores or teething. However these dosage forms are introduced in United States and European pharmaceutical markets for better therapeutic benefits [6]. The oral dissolving films are prepared using water soluble or water swellable film forming polymers due to which the film dissolves rapidly when placed on the tongue in the oral cavity. Hydroxy propyl methyl cellulose is the water soluble polymer which was used as a film forming agent at low viscosity. The most preferred grades of HPMC film formers are k15, E15, etc.

Aminophylline is methylxanthine bronchodilator composed of theophylline and ethylenediamine. Theophylline relaxes the smooth muscles of the bronchial airways and pulmonary blood vessels as well as reducing airway responsiveness to histamine, methacholine, adenosine and other chemical mediators.

Aminophylline is used together with other medicines to treats the acute systems of asthma, bronchitis, emphysema, and other lung disease in a hospital setting. Aminophylline belongs to a group of medicine known as bronchodilators. Bronchodilators are medicines that relax the muscles in the bronchial tubes (air passages) of the lungs. They relive cough, wheezing, short ness of breath, and troubled breathing by increasing the flow of air through the bronchial tubes[7].

MATERIALSANDMETHODS

Chemicals :- Aminophylline, HPMC, Aspartame, Polyethylene glycol , Ascorbic acid, Citric acid, Propylene glycol.
Apparatus: Glass petriplates, magnetic stirrer, Dissolution Apparatus, UV Spectrophotometer, Weighing Balance.

Experimental Design/Preparation of Fast Dissolving Sublingual Film

An formulation design consisting of six formulations was setup using two factors at three levels to optimize fast dissolving Sublingual film of Aminophylline. Solvent Casting Techniques was used in the preparation of films. The independent variables used included to numeric factors X1-Concentration of polyethylene glycol, X2-Concentration of PG.

HPMC K-15 used as film forming agent was dripped in water mixture. The polymer solution was agitated on a magnetic stirrer until homogeneous. PG and PEG plasticizer used as film modifier was added to the polymer solution and agitated till homogeneous. Citric acid used as saliva stimulating agent, ascorbic acid as Anti-Oxidant and flavoring agent Aspartame as Sweetening Agent and Drug Was Dissolve in the remaining amount of water an added to polymer solution. The prepared formulation was expelled on glass petriplate and dried at room temperature. The dried films were carefully strip and cut in 2cm x 2cm film raped in Aluminum foil and stored. The prepared films were evaluated for weight, thickness, Surface PH, folding Endurance, tensile strength, Dissolution, % drug elongation and drug release.

CODE	F1	F2	F3	F4	F5	F6
Aminophylline	980 mg	980 mg	980 mg	980 mg	980 mg	980 mg
HPMCK15	(200mg)	(250mg)	(300mg)	(200mg)	(250mg)	(300mg)
PEG400	10%(1ml)	10%(1ml)	10%(1ml)	-	-	-

PG	-	-	-	10%(1ml)	10%(1ml)	10%(1ml)
Citric Acid	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Aspertame	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
SSG	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Waterqs	15ml	15ml	15ml	15ml	15ml	15ml

Table-1: Formulation table For Fast Dissolving Sublingual Film

Drug Excipients Compatibility:

The formulation in the dry state was evaluated for drug excipients compatibility. The study was complete out using deferential scanning colorimetry. The thermograms of drug and drug with polymer were recorded at a scanning rate of 1^{o} C/ mint in temperature ranges of 100^{o}C to 400^{o}C in Nitrogen atmosphere. The recorded thermograms were observed for any change in appearance or shift in the peaks.

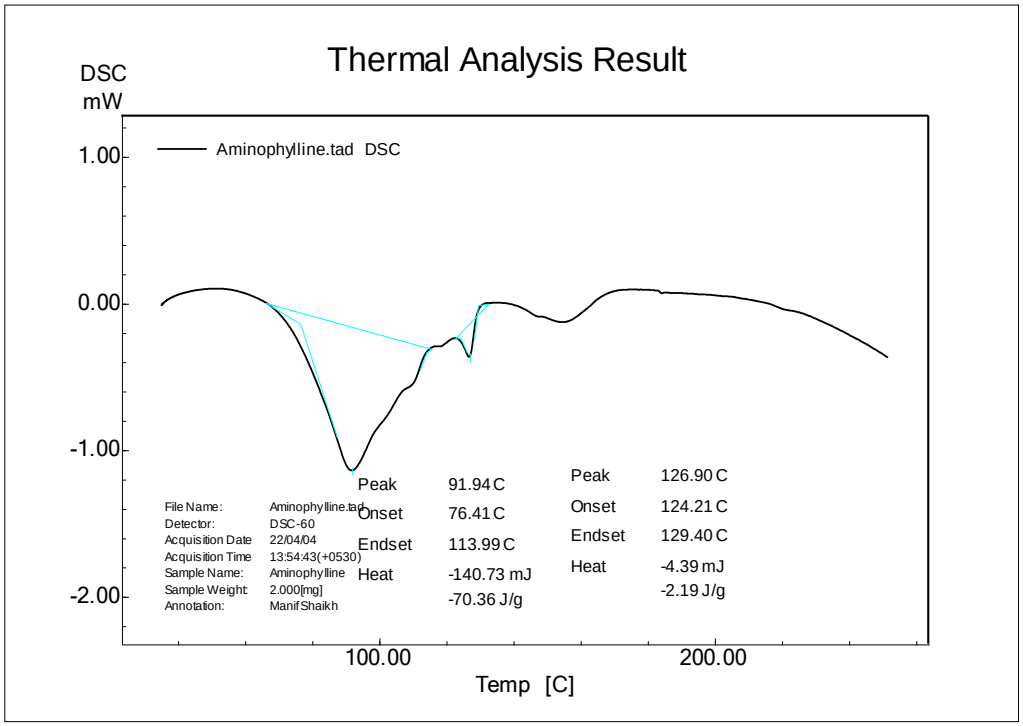

Fig-1:**DSC Of Aminophylline**

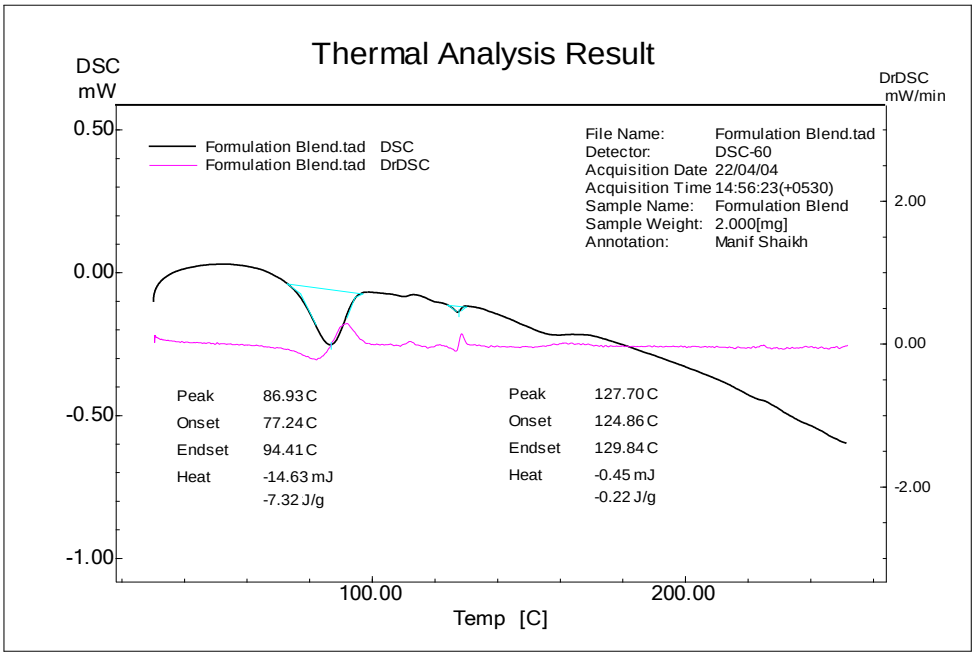

Fig- 2: **DSC of Aminophylline with Excipients**

Evaluation of Mouth Dissolving Films

Physical Appearance: The films obtained were observed visually for uniformity, clarity and thickness.

Microscopy: The topology and morphology of the formulated films were observed by placing a 2cmx 2cm cut film under the scanning electron microscope.

Weight: The formulated films are cut at 2cm x 2cm were weight on Sartorius electronic balance. An average of the readings of four films was recorded.

Thickness: The film thickness was measured at three places per film using micrometer. Average of the readings of three films was recorded.

Folding Endurance: The films were separately folded in a plane with the hand till it produced visible crack and number of times it was folded to produce visible crack was noted as the folding endurance and averages of three films were recorded [8, 9].

Tensile Strength:

Tensile strength is strength where the maximum stress applied on the film till it breaks. Tensile strength was calculated using the formula given below[10].

$$\textbf{Tensile strength} = \frac{load\ at\ Failure}{Film\ thickness\ x\ film\ width} x\ 100$$

An average and standard mean of three readings of film were recorded.

Disintegration Time: For the evaluation of Disintegration time disintegration apparatus IP was used . Average of the readings of three films was recorded and standard deviation found.

Batch NO	Thickness (mm)	Weight variation (mg)	Folding endurance	Disintegration Time (Sec)	Surface PH	Tensile Strength (gm/cm^2)
F1	0.256 ±0.011	133.66± 3.055	**250<**	25.66±2.081	**6.8**	50.04±1.09

F2	0.326 ±0.005	128.0 ±2.0	**250<**	27.0±3.065	**6.8**	44.12±1.84
F3	0.251 ±0.01	125.0 ±3.0	**250<**	29.33±2.081	**6.8**	48.07±2.06
F4	0.271 ±0.005	137.66± 1.527	**250<**	30.00±2.00	**6.8**	49.90±1.76
F5	0.291 ±0.01	128.03± 1.732	**250<**	33.66±1.527	**6.8**	52.32±1.74
F6	0.304 ±0.011	129.33± 2.309	**250<**	36.00±2.00	**6.8**	46.53±1.07

Table-2: Evaluation table For Fast Dissolving Sublingual Film

Batch No / **Time in Min**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
5	12.13	8.37	12.25	22.17	18.62	23.28
10	25.49	24.59	28.52	55.98	40.87	53.18
15	39.5	47.87	50.9	63.25	69.49	62
20	60.48	73.45	76.37	79.52	82.65	70.85
25	89.37	84.96	84.21	84.65	89.25	81.46
30	96.25	97.2	97.31	97.61	97.87	91.65

Drug Release: Modified dissolution apparatus is used for determine the drug release by Ding et al. 20 ml of phosphate buffer PH 6.8 was used as dissolution medium. The films was placed in 50 ml beaker containing 20 ml of dissolution medium and adjoin in dissolution apparatus-IP and run at speed of 100 rpm. The sample was drawn at 5, 10, 15, 20, 25 and 30 mint and content was measured spectrophotometric ally at 272 nm, using UV Shimadzu[11].

Table-3: Percentage Drug Release of Fast Dissolving Sublingual Film

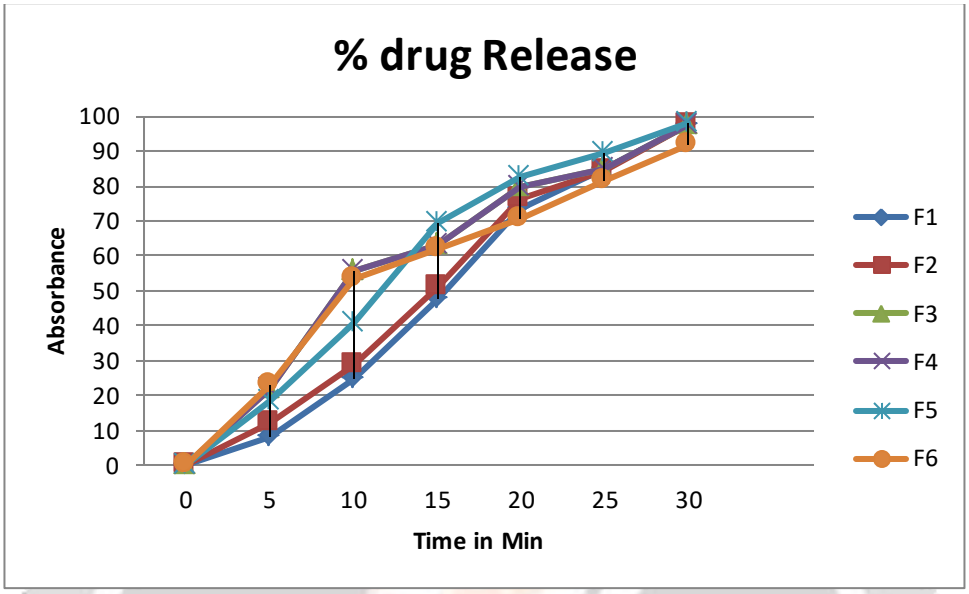

Chart -1: Percentage Drug Release

Stability Study:
The best formulation was separated and tested for stability at room temperature and ambient Humidity for 90 days [8].

RESULTSAND DISCUSSION

Preliminary Trials: The drug Aminophylline is water soluble so film forming polymers that should be formed transparent films would be ideal. Hence placebo films should be prepared using polymer, such as HPMC K15, E15, sodium alginate. HPMC k15 was found to be produce good result with non-tacky, transparent film. Among the plasticizers' used PEG and PG were screened.

Experimental Design: The preliminary trials for the formulation of fast dissolving sublingual film helped to select the factors for the study and concentration to be used. With the help of solvent casting method oral fast dissolving sublingual films were prepared and evaluated.

Drug Excipients Compatibility: On differentiation of the thermograms of pure drug Aminophylline and drug with excipients it was observed that the endothermic pick of the pure drug was found to be at 129.90^{o} C (Fig. No. 1) while in with the excipients it was found to be at 127^{o}C. (Fig No. 2)The slight shift may be due to presence of polymers. Since there were no major changes in thermograms it ruled out any possibility of incompatibility.

Evaluations of films: All the formulated film were found to have good uniformity, clearity, were easily peelable and non-sticky. The films were found to weight between 125mg to 137mg having thickness between 0.251mm to 0.326 mm. the folding endurance was found to be more than 250 folds. Increasing concentration of HPMC K15 increases the folding Endurance of fast dissolving sublingual film. The PH of all the films was found to be 6.8 which is close to neutral PH and rules out any chances of irritation of oral mucosa. The % drug release profile of the film is in chart No 01.

Stability Study: The stability studies was carried out on the optimize batch were found to be within the specification. The films were clear, non-tacky having folding Endurance more than 250, disintegration time 30 sec and releasing 97% drug completely at the end of 30 min.

Conclusion:- The fast dissolving sublingual film of Aminophylline that would provide ease of administration to Asthmatic Patient of any age group was successfully developed. Design of formulation was found to be useful tool in understanding the influence of excipients on the performance of film. The formulation batches was successfully evaluated. The formulation F4 were found to be the best optimized batch with disintegration time of 30 sec and Drug release of 97% at the end of 30 mints.

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