Formulation Development and Evaluation of Fast Dissolving Films of Anti-asthmatic drug

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ABSTRACT

Asthma is a chronic disease that affects the airways of your lungs. Doxofylline Bioavailability is 63% due to hepatic first pass metabolism. Fast dissolving films have become a novel approach to oral drug delivery system because it provides convenience and ease of use over other solid dosage forms. The principle of doxofylline FDFs preparation offers a simple and practical approach to achieve quick onset of action for the dosage form and bypass the hepatic first pass effect of drug leads to reduction of dose which can lead to reduction in side effect associated with the drug. The films were prepared by solvent casting method. The prepared films were evaluated for thickness, disintegration time, folding endurance, drug release, and drug content.

Keyword: - *Asthma, Doxofylline, fast dissolving films, solvent casting method*

1. INTRODUCTION

Among the various routes, oral route is the most agreeable route for the delivery of the drug till date due to ease of ingestion, pain avoidance and versatility. However oral drug delivery system still want some advancements to be created due to their some drawbacks associated to particular class of patients which includes geriatric, pediatric and dysphasic patients as they have dysphagia (i.e. difficulty in swallowing or chewing) and due to fear of choking solid dosage form. The long onset time, low bioavailability and dysphagia, patients turned the manufacture to the liquid orals and parental. But the liquid orals have the issue of accurate dosing mainly and parental are most painful drug delivery, thus most patients' incompliance.

To overcome the issues related with solid, liquid and parenteral dosage form a novel oral dosage form is developed know as fast dissolving films (FDFs). FDFs are the most advanced form of oral solid dosage form due to additional flexibility and comfort. It improve the effectiveness of Active Pharmaceutical Ingredients (APIs) by dissolving within minute in oral cavity once the contact with saliva without chewing and no need of water for administration.

1.1 SPECIAL FEATURE OF FILMS

- Thin elegant film
- Dosage accuracy
- Self administration is feasible
- Fast disintegration and rapid drug release
- Available in various sizes and shapes
- Excellent mucoadhesion
- Requires no water
- Most acceptable dosage form for dysphasic patients

1.2 FORMULATIONS INGREDIENTS

1. Drug (API) 5-30%
2. Film forming agent 45%
3. Plasticizers 20%

4. Flavoring agent Q.S
5. Sweetening agent 3-6%
6. Surfactant Q.S
7. Saliva stimulating agent 2-6%

1.3 ADVANTAGES OF BUCCAL FILM

1. All tablet dosage forms and liquid preparations primarily enter the blood stream via the GIT, which subjects the drug to first-pass effects. As a result, such formulations typically need higher doses and usually have a delayed onset of action. Vice-versa, Buccal and sublingual film drug delivery can avoid these issues and gives quicker onsets of action at lower doses.
2. Buccal film has larger surface area that promotes fast disintegration and dissolution in oral cavity.
3. Thin film is additional stable, durable and fast dissolving than other conventional dosage forms.
4. Thin film enables to improve dosage accuracy relative to liquid formulations, since every film is manufactured in such a way that it contains a precise amount of the drug.
5. Bypass the variation in the absorption and metabolism association with the oral administration.
6. Most of the time lower dose is adequate.
7. Permits a fast termination of the medication, if needed, by simply removing the buccal film from the mouth.
8. ODTs are fragile and brittle, which requires special package for protection during storage and transportation. Since the films are flexible they're not as fragile as most of the ODTs. Hence, there is a simple transportation, storage and consumer handling.

1.4 DISADVANTAGES OF BUCCAL FILM

1. The main disadvantage is that only a small percentage of the drugs can be delivered via Buccal delivery system.

2. Eating and drinking may become restricted.

2. METHODOLOGY

Material: Doxofylline was gifted from Ami Life sciences Pvt.ltd. HPMC E15 was from Rankem, Mumbai. Citric acid, PEG 400 and tween 80 from Vishal chem. Mumbai. All the chemicals used are of analytical grade.

2.1 METHOD

Solvent Casting Method

Step 1: Aqueous solutions 1: polymer +distilled water, allowed to stir for 2h. (The polymeric solution was kept aside for 1hr removes the air bubbles)

Step 2: Aqueous solutions 2: drug with other excipients dissolved in specific proportion in distilled water.

Step 3: Aqueous solution I and II were mixed and stirred for 1hr. And it was then casted on petriplate and dried at room temperature for 24hrs.

Step 4: After drying, film were Carefully Removed from plate and cut into required size (4×4 cm^2), packed in aluminum foils and kept for further use.

Table-1: Formulation of fast dissolving films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Doxofylline(mg)	100	100	100	100	100	100	100	100	100
HPMC E-15(mg)	250	250	250	300	300	300	350	350	350

PEG400(%w/w)	10	15	20	10	15	20	10	15	20
Tween 80(%w/v)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Citric acid(mg)	20	20	20	20	20	20	20	20	20
Aspartame(mg)	10	10	10	10	10	10	10	10	10
Menthol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

2.2 Determination of λmax

Preparation of Standard Stock Solution

A stock solution of Doxofylline (1000 µg/ml) was prepared by dissolving 100 mg Doxofylline in 100 ml volumetric flask with distilled water and PBS 6.8 separately. From the solution (1000µg/ml), accurately measured 10 ml of solution was transferred in to 100 ml of volumetric flask and diluted with water and PBS 6.8 separately to obtain the concentration of 100µg/ml (standard stock solution).

Preparation of Working Sample Solutions

From the stock solution (100µg/ml), accurately measured standard working sample solutions of Doxofylline (0.5,1.0,1.5,2.0 and 2.5ml & 1.0,2.0,3.0,4.0,5.0,6.0ml) were transferred to a series of 10 ml of volumetric flasks and diluted to the mark with water and PBS 6.8 to obtain the concentration of 5-25µg/ml and 10-60µg/ml respectively. The absorbance of prepared solutions of Doxofylline in water and PBS 6.8 were measured at 274 and 273 nm using UV-visible spectrophotometer against water and PBS 6.8 as blanks.

2.3 Evaluation of Fast Dissolving Films

2.3.1 Thickness

The thickness of the film was measured by using screw gauge at different position of the film and the average thickness was calculated.

2.3.2 Weight variation

4×4 cm^2 film was cut at three different places in the cast film. The weight of each film was taken & then weight variation observed.

2.3.3 Folding Endurance:

This test was performed by cutting the fast dissolving film of size 4× 4 cm^2. The films were folded at same place until it broke. The no. of times a film could be folded without breaking gave the value of folding endurance.

2.3.4 In-vitro disintegration time

Disintegration time was determined visually in a Petridis containing 30 ml of pH 6.8 phosphate buffer. The solution were stirred gently every 10 s. The disintegration time is the time when the film starts to breaking or disintegrate.

2.3.5 Surface pH

A digital pH meter (AE MAX) was employed for this purpose. The film kept in a Petri dish was moistened with 10 ml of distilled water and kept for 1-2 minutes. The pH was measured by bringing the electrode with the surface of the film.

2.3.6 Drug content

Drug content of all the batches was determined by UV spectrophotometric method. For this randomly selected film from each batch was dissolve in 50ml of phosphate buffer pH 6.8. After complete solubilization, the solution was diluted appropriately, filtered and analyzed at 273 nm using UV-Visible Spectrophotometer.

2.3.7 Percentage moisture loss

Individually, the prepared films were weighed and kept in desiccators containing fused anhydrous calcium chloride for 72 h. After 3 days (72 h) the films were removed and reweighed, and the average percentage moisture loss of the films was measured by using the formula, below

% Moisture Loss = [Initial weight- Final weight/ Final weight] ×100

2.3.8 In-vitro dissolution studies

- Apparatus - USP Type–II (paddle type) Dissolution Apparatus
- Dissolution media quantity - 300ml
- Medium - Phosphate buffer (pH 6.8)
- Temperature - 37± 0.5 ºC
- RPM - 50rpm
- Sampling intervals time - 0,1,2,3,4,5,6,7,10 (min)
- λmax – 273 nm

3. RESULT

3.1 Calibration Curve of Doxofylline in Water

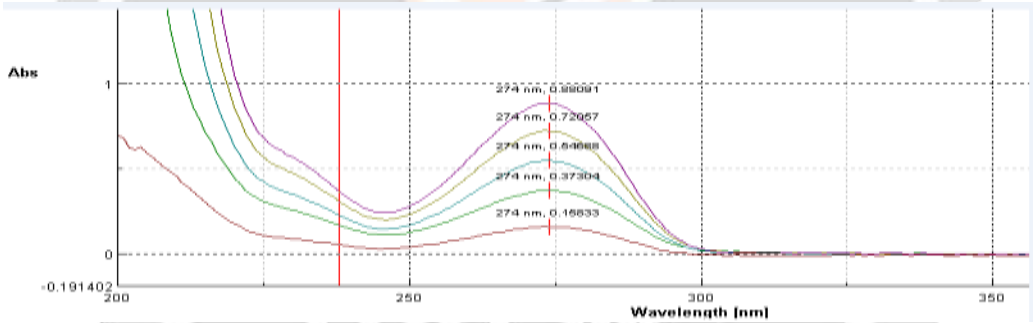

Fig 1- Overlay Spectra of Doxofylline in Water

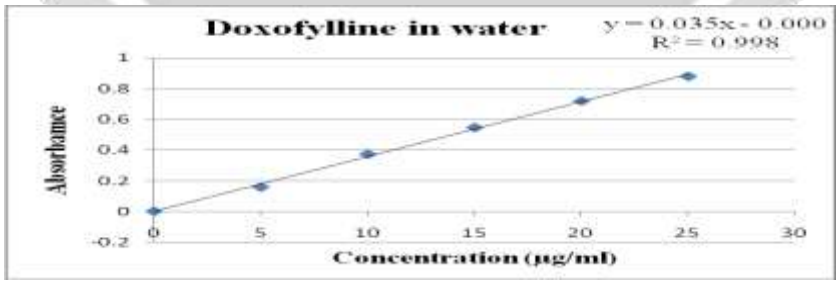

Fig 2 - Calibration Curve of Doxofylline in Water

Table 2: Concentration and Absorbance of Doxofylline in Water

Concentration(µg/ml)	Absorbance (mean ± SD) (n=3)
5	0.1583±0.0030
10	0.373±0.0018

15	0.546±0.0043
20	0.720±0.0035
25	0.880±0.0025

3.1 FT-IR studies:

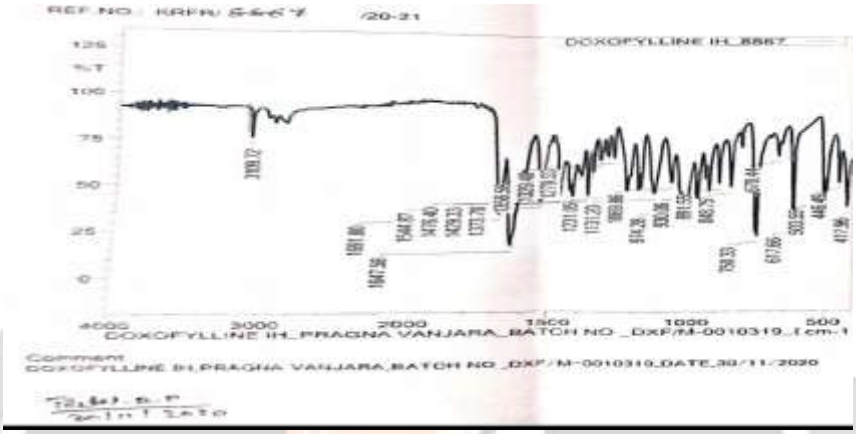

Fig 3- FTIR Spectrum of Doxofylline

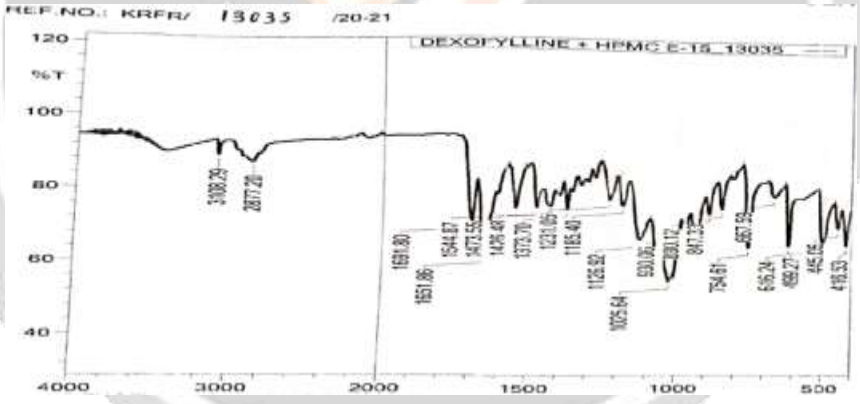

Fig 4- FTIR Spectrum of Doxofylline + HPMC E15

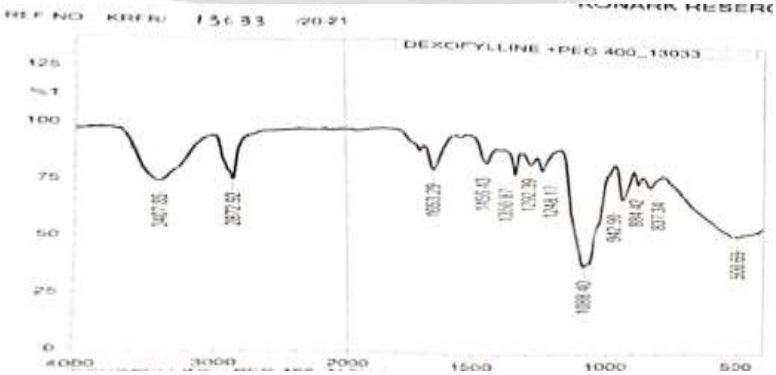

Fig 5- FTIR Spectrum of Doxofylline + PEG400

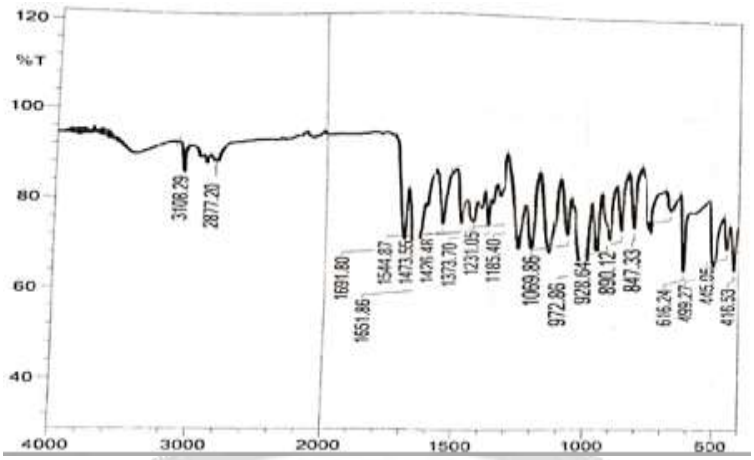

Fig 6- FTIR Spectrum of Final formulation

3.2 Thickness

Thickness of the film was in the range of 0.52±0.01 to 0.70±0.04. It was observed that thickness of films increased with increasing polymer concentration.

3.3 Weight variation

Weight of the film was in the range of 114±2.8 to 274±1.9. It was observed that Weight of the film increased with increasing polymer concentration.

3.4 Disintegration time

F3 film shows less disintegration time within 29 sec.

3.5 Folding endurance

Increase the value of HPMC and PEG increase the value of folding endurance of the film. Folding endurance was found to be 114 to 237.

3.6 Surface PH

Surface PH was in the range of 5.31±0.12 to 5.94±0.05

3.4 Moisture loss (%)

Moisture loss of the film was in the range of 1.66±0.08 to 3.08±0.07. For the films optimum Moisture loss is required as more Moisture loss film lose its flexibility.

3.5 %Drug content

It was observed that drug was distributed uniformly. The % drug content was found to be in the range of 95.56% to 99.48%.

Table-3: evaluation data of batches

Batch	Thickness (mm)	Weight variation (mg)	Disintegration time (sec.)	Folding endurance	Surface PH	Moisture loss (%)	%Drug content
F1	0.52±0.01	114±2.8	36	114	5.31±0.12	1.71±0.11	97.71± 0.22
F2	0.59±0.05	127±1.7	33	125	5.82±0.20	1.66±0.08	98.89±0.14
F3	0.56±0.02	119±3.2	29	139	5.56±0.11	1.79±0.03	99.21±0.35
F4	0.59± 0.01	194±2.4	44	152	5.63±0.16	1.98±0.05	99.31±0.54
F5	0.61±0.04	204±1.4	37	163	5.67±0.02	1.74±0.12	99.48±0.17
F6	0.62±0.02	212±2.7	34	179	5.86±0.07	1.69±0.05	99.85±0.25
F7	0.68±0.01	257±1.8	62	198	5.71±0.08	2.08±0.04	95.56±0.20
F8	0.70±0.04	268±3.6	55	219	5.91±0.16	2.71±0.04	97.04±0.51
F9	0.69± 0.03	274±1.9	47	237	5.94±0.05	3.08±0.07	99.08±0.52

Table 4: In-vitro Dissolution of Batches

% Drug Release									
Time (min)	F1	F2	**F3**	F4	F5	F6	F7	F8	F9
0	0	0	**0**	0	0	0	0	0	0
1	31.12± 0.14	32.28± 0.10	**35.49± 0.22**	26.05± 0.12	28.18± 0.07	29.63± 0.19	21.14± 0.18	23.10± 0.02	26.57± 0.14
2	41.22± 0.14	43.29± 0.10	**42.19± 0.22**	36.15± 0.12	38.48± 0.07	40.28± 0.19	32.02± 0.18	34.18± 0.02	35.47± 0.14
3	55.05± 0.19	58.67± 0.18	**60.34± 0.36**	48.85± 0.21	51.64± 0.11	53.14± 0.20	41.31± 0.15	43.81± 0.17	45.65± 0.18
4	68.39± 0.21	71.36± 0.45	**76.12± 0.24**	59.68± 0.25	62.65± 0.18	64.48± 0.14	52.56± 0.29	53.28± 0.14	56.10± 0.22
5	81.75± 0.32	83.71± 0.63	**92.15± 0.15**	73.08± 0.08	75.46± 0.26	79.59± 0.54	61.45± 0.16	62.34± 0.20	64.15± 0.27
6	94.12± 0.38	97.02± 0.28	**99.68± 0.14**	84.79± 0.09	86.11± 0.07	90.28± 0.18	71.98± 0.41	74.27± 0.18	79.41± 0.31
7	97.84± 0.27	98.91± 0.20		92.21± 0.02	93.81± 0.31	96.42± 0.18	82.52± 0.47	85.18± 0.28	88.01± 0.11
8				96.11± 0.08	97.09± 0.20	99.48± 0.02	90.47± 0.31	92.08± 0.11	94.31± 0.23
10				98.67± 0.21	99.76± 0.01		96.52± 0.11	97.69± 0.13	99.48± 0.18

4. CONCLUSIONS

Fast dissolving films of doxofylline was successfully formulated by using Solvent Casting method and was developed to a satisfactory level, in terms of Disintegration time, Folding endurance, % Drug Release, and drug content. Formulation F3 with 250mg HPMC E15 and 20% PEG 400 shows quick disintegration. Formulation F3 also shows the highest drug release of 99.68% within 6min.

5. REFERENCES

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