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# Pulmonary Arterial Hypertension - A Concept Change in Drug Delivery

**Jisha James[1], John Thomas[2], Vivek[3]**

[1]Department of Pharmacy, Shri Jagadish Prasad, Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajastahan 333001 India
Email: *jishajohn201[at]gmail.com*

[2]Department of Pharmacy, Shri Jagadish Prasad, Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajastahan 333001 India
Email: *thomasjohnthomas1[at]gmail.com*

[3]Department of Pharmacy, Shri Jagadish Prasad, Jhabarmal Tibrewala University, Vidyanagari, Jhunjhunu, Rajastahan 333001 India
Email: *pharmvivek16[at]gmail.com*

**Abstract:** ***In urgent medical situations such as Pulmonary Arterial Hypertension (PAH), immediate medication is crucial. The oral route remains the primary method for administering drugs. This study utilized a combination of film-forming polymers, including Hydroxy propyl methyl cellulose (HPMC E15LV) and 2-Hydroxy propyl Beta cyclodextrin (HPBCD), along with Xanthan gum and propylene glycol 400 in varying concentrations. Ten formulations were developed and assessed for their fast-dissolving oral film (FDOF) characteristics, such as film colour, thickness, brittleness, peeling ability, transparency, surface smoothness, tackiness, and film-forming capacity, as well as content uniformity, dispersion time (DT), and dissolution rate. The optimized FDOF (F2) demonstrated excellent properties, with content uniformity of (98.3±0.3), a DT of (13±3) seconds, and a dissolution rate of (99.2±2.0) within 10 minutes. Infrared (IR) spectroscopy was conducted to detect any physicochemical interactions between the drug and polymer, revealing no interaction. Differential scanning calorimetry (DSC) was used to examine any changes in the melting points of the active pharmaceutical ingredients (API) and excipients in F2. The DSC thermograms indicated no significant change in the melting endotherm of the pure drug and the drug in the optimized formulation F2. A comparative analysis with the marketed formulation of Macitentan fast-dissolving oral tablet (OPSUMIT 10) showed that F2 possess a promising dissolution property comparable to the marketed formulation***.

**Keywords:** Macitentan, Fast dissolving oral film, dispersion time, and dissolution rate, physicochemical interaction

## 1. Introduction

The most preferable route of drug administration is still the oral route mainly due to patient compliance. Swallowing of the oral tablet formulation is still remaining as a major problem in the case of paediatric and geriatric patients and patients who may not have ready access to water especially in travelling [1]. Fast dissolving formulations have been developed as need of time for the fas t delivery of drugs for certain type of ailments which need fast medication. [2, 3] Oral fast Disintegrating dosage form have started gaining popularity & acceptance as new drug delivery system due to better patient compliance. [8] Out of the various fast dissolving formulation tablets are the most preferred dosage form for geriatric, paediatrics and patient experiences strain or dysphagia. in swallowing so that lead to noncompliance. [1, 2]. Development of newer fast disintegrating formulations were started in 1970's and got wide acceptance in the treatment of special conditions of patients with fast medication. Mouth dissolving oral tablets have the drawback of feeling grittiness in mouth and may cause choking, difficulty in swallowing tablets in some patients. To beat the issues of mouth dissolving tablets, a new drug delivery system for the oral delivery of the drugs, was investigated which is known as Fast dissolving films/oral dispersible film/ mouth dissolving films / oral disintegrating film/ oral dissolving film.[4] Pulmonary hypertension (PH) is a progressive, life-limiting condition impacting the patient´s exercise capacity and quality of life, especially in the advanced disease stages. With pulmonary hypertension, the rise in blood pressure is caused by changes in the cells that line your pulmonary arteries. These changes can cause the walls of the arteries to become stiff and thick, and extra tissue may form. The blood vessels may also become inflamed and tight.[5]. At the most recent World Symposium on Pulmonary Hypertension (WSPH 2018, Nice), PH in adults and children was redefined as an increase in mean pulmonary artery pressure (mPAP) >20 mmHg at rest, as assessed by cardiac catheterization [6,7]. Pulmonary arterial hypertension (PAH) is characterized hemodynamically by pre-capillary PH, defined by a pulmonary artery wedge pressure ≤15 mmHg and a pulmonary vascular resistance index (PVRi) >3 Wood units in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thromboembolic PH or other rare diseases (8). Pediatric PAH is a rare condition that affects 2–16 per million children [9-10]. Endothelin (ET), a peptide produced primarily by vascular endothelial cells, has been characterized as a powerful vasoconstrictor and mitogen for smooth muscle [11,12]. Activation of the ET system has been shown in both plasma and lung tissue [13] of PAH patients, as well as in animal models of PAH, supporting a prominent role of ET in the pathogenesis of this condition [14]. The purpose of this study was to examine the efficacy of ten FDOF formulations of macitentan, an oral endothelin type A receptor-selective antagonist, in pulmonary arterial hypertension (PAH).

## 2. Materials and Methods

Macitentan was purchased from MSN labs, Hyderabad. Film forming polymers, HPMC E6LV, was purchased from colourcon Asia Pvt Ltd. The solubilizer, HPBCD was obtained from Cyclolab. The stabilizing agent, Xanthan gum

was purchased from CP Kelco and the sweetening agent, sodium saccharin was purchased from Nutra Sweet Company. The Vanillin flavour from Firmenich. All other ingredients were of analytical grade. Pre-formulation study covers all physical and chemical parameters of active Pharmaceutical ingredient (API) andinactive ingredients. And Pre-formulation data covers like solubility in various pH buffers, flow rate, and inactive ingredients compatibility studies with API.

### 2.1 Calibration curve of Macitentan

Solutions of Macitentan was (1 ppm, 2 ppm, 4 ppm, 6 ppm, 8 ppm, 10 ppm, 12 ppm, 14 ppm, 16 ppm, 18 ppm, 20 ppm, 30 ppm) was prepared using pH 7.5 pH phosphate buffer with 0.1 % CTABand the absorbance was measured using UV Visible spectrophotometer Shimadzu UV-1800 spectrophotometer at 262 nm as in Figure 1.

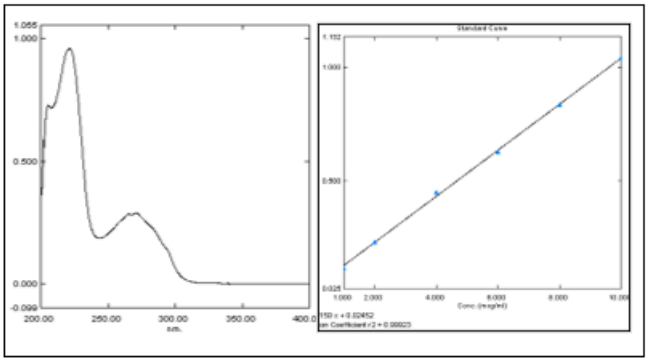

**Figure 1:** Absorption spectra and calibration curve of macitentan

### 2.2 Preparation of Macitentan FDOF

The objective of this study was to develop fast-dissolving oral films (FDOF) of Macitentan, with a dosage of 10 mg per 4 $cm^2$ film. The procedure was conducted using a digital magnetic stirrer equipped with a medium-sized magnetic bead. The film-forming polymer, Hypromellose, was precisely measured and added to a small quantity of purified water in a beaker, which was then sealed with aluminum foil and allowed to hydrate for 24 hours to ensure complete hydration. On the following day, xanthan gum was incrementally incorporated, and the solution was stirred at 75 rpm for the initial 30 minutes, followed by 50 rpm for an additional 1.5 hours. Subsequently, propylene glycol was introduced, and stirring continued for 30 minutes at 50 rpm. Ethanol, Macitentan, HPBCD, sodium saccharin, vanilla, and FD&C Red were dissolved in an adequate amount of purified water and added to the polymer mixture. This film-forming solution was thoroughly mixed to achieve uniformity. A clean and dry petri dish was selected, and the solution was poured into it. The drying process was carried out at 45°C in a hot air oven for 6 hours. The petri dish was then removed and allowed to cool to room temperature. The FDOF was carefully peeled using a surgical scalpel by making a small incision on one side of the petri dish. Smaller FDOFs of 4 $cm^2$ were cut from the larger FDOF and primarily packaged in aluminum foil, followed by secondary packaging in a self-sealing polyethylene bag to minimize moisture penetration. The prototype formulation was developed using the polymer Hypromellose E15LV, and the resulting FDOFs (Figure 2 & Table 1) were evaluated for various parameters.

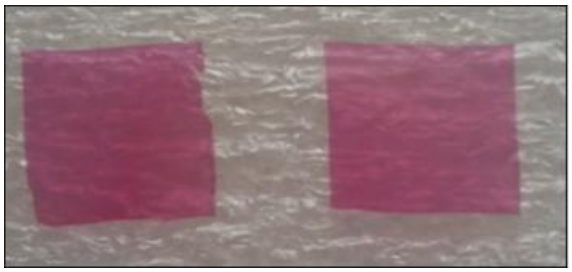

**Figure 2:** Macitentan FDOF of 4$cm^2$

**Table 1:** Formulation of Macitentan FDOF

| S. No | Code & Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Macitentan | 159. | 159. | 159. | 159. | 159. | 159. | 159. | 159. | 159. | 159. |
| 2 | HPMC E15LV | 500. | 500. | 400. | 400. | 400. | 350 | 280. | 280. | 240. | 200. |
| 3 | HPBCD | 50.0 | 100. | 150. | 175. | 200. | 200. | 180. | 180. | 250. | 250. |
| 4 | Propylene glycol | 120. | 140. | 160. | 140. | 140. | 140. | 140. | 140. | 140. | 140. |
| 5 | Xanthan gum | 10 | 10 | 10. | 10. | 8. | 8. | 8. | 5. | 5. | 5. |
| 6 | Sodium Saccharin | 20 | 20. | 20. | 20. | 20 | 20. | 20 | 20. | 20. | 20. |
| 7 | Tween 80 | 10 | 10 | 10 | 10. | 10 | 10 | 10 | 10 | 10. | 10. |
| 8 | Water sufficient | qs | qs | qs | qs | qs | qs | qs | qs | qs | qs |
| 9 | Vanilla flavor | qs | qs | qs | qs | qs | qs | qs | qs | qs | qs |
| 10 | Amaranth | qs | qs | qs | qs | qs | qs | qs | qs | qs | qs |
| 11 | Ethanol | qs | qs | qs | qs | qs | qs | qs | qs | qs | qs |

## 3. Evaluation of Macitentan FDOF

### 3.1 Preliminary Evaluation of FDOF'S

Primary physical evaluation of FDOF'S by visual inspection for characteristics such as color of film, thickness of film, brittleness of film, peeling ability of film, transparency of film, surface smoothness of film a in table 2.

**Table 2:** Primary physical evaluation of FDOF

| Code and properties | Film property | Track property | Ease of handling | Taste |
|---|---|---|---|---|
| F1 | Good | Non-tacky | Easy to peel | ++++ |
| F2 | Excellent | Non-tacky | Thin, flexible and easy to peel | +++++ |
| F 3 | Good | Tacky | Soft, easy to peel | ++++ |
| F 4 | Average | Non-tacky | Slightly thick | +++ |
| F 5 | Good | Non-tacky | Soft, Thick, easy to peel | ++++ |
| F 6 | Good | Non-tacky | Soft, thick& easy to peel | ++++ |
| F 7 | Good | Non-tacky | Thin, tough& flexible | ++++ |

| | | | | |
|---|---|---|---|---|
| F 8 | Average | Non-tacky | Thick | ++++ |
| F 9 | Poor | Non-tacky | Very thin soft& difficult to peel | +++ |
| F 10 | Average | Non-tacky | Thick | ++++ |

### 3.1.1 *In vitro* quality control tests

The large film of 63.64 $cm^2$ was cut into even squares pieces of 4 $cm^2$ (2 cm x 2 cm) each and assess to verify the following parameters.

### 3.1.2 Uniformity of weight

Uniformity of weight test determines the uniformity of weight among the FDOFs in one batch of a formulation was done as described in Dinge A *et. al*., (2008), Devi V K *et. al*., (2003) [16,17] The weight of FDOFs was assessed by an digital balance with a precision of 1 mg. For uniformity of weight test, 10 FDOFs are randomly selected and weighed individually to determine the average weight.

### 3.1.3 Thickness

The thickness of FDOF is the least measure related directly to the DT. Thickness of FDOFs was assess using digital Vernier caliper with a precision of 0.010 mm i.e. 10 µm. Ideally FDOFs can have thickness up to 100 µm as discussed in Raju S *et. al*., (2011); R Choudary D R *et. al*. (2011).[18,19]

### 3.1.4 Folding endurance study

Folding endurance was assessed by repeated folding of the FDOF at the same place till the FDOF breaks. The number of times the FDOF is folded without breaking is computed as the folding endurance as per the method discussed in Shinde A J *et. al*. (2008) [20].

### 3.1.5 Surface pH Study

Surface pH is the measure of pH on the surface of the FDOF. This test was executed by placing a large enough water drop on the surface of the FDOF and then the bulb of pH electrode was touched with the surface of water drop. It was performed using a well calibrated pH meter as described in Raju S *et. al*., (2011); Choudary D R *et. al*. (2011) [18,19].

### 3.1.6 Content Uniformity

The assay or Active Pharmaceutical Ingredient (API) content denotes the amount of API found in a unit of Fast Dissolving Oral Film (FDOF) from a batch. Measuring the API content is crucial for assessing how the API is distributed within each small FDOF, as outlined by Raju S et al. (2011) and Choudary D R et al. (2011) [18,19]. This procedure enables the evaluation of content uniformity. The assay is performed using any standard assay method specified for the specific API in recognized pharmacopoeias. API content uniformity is assessed by examining the API content in individual strips. It was measured in percentage.

### 3.1.7 *In Vitro* Disintegration test studies

The invitro disintegration study was carried out as per the method discussed inNehal Siddiqui MD *et. al*., (2011) [21] Typical DT for strips is 5 sec to 30 secs. The medium of study was phosphate buffer pH 6.8.

### 3.1.8 Dissolution profile studies

Dissolution profile was implemented using the standard rotating basket apparatus as (Apparatus 1) described in the USP as per the procedure described in Hiroyoshi Shimoda *et. al.,* (2009) [22]. The selection of dissolution medium will be as per the sink conditions and the highest dose of the API.Paddle speed was maintained at 75 rpm and 900 mL freshly prepared 0.05 M Acetate Buffer, pH 5.0 was used as a dissolution medium. The samples solution of 5 mL was withdrawn at programmed time intervals of 1 min, 2 min, 4 min, 6 min, 8 min, 10 min and 12 minutes and replaced with fresh medium. The sample solutions were filtered through what man filter paper and concentrations were measured at $\lambda$ = 215 nm.

### 3.1.9 Fourier transform infrared spectroscopy (FTIR)

A compatibility study of Macitentan and excipients in the final formulation following the procedure described in Kai Bin Liew *et. al.,* (2011) [23]. The analysis was executed in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectra of the samples were obtained using KBr pellet, prepared with hydraulic press with small amount of each sample after careful grinding of each sample with KBr. The spectral width was 400-4000$cm^{-1.}$

### 3.1.10 Differential scanning colorimetry

Differential scanning colorimetry (DSC)study was performed to know any changes in the melting points of the API and excipients and comparing the same in the formulations as per the procedure discussed in Doaa Ahmed EI-Setouhy*et. al*., (2010) [24]. DSC studies were executed using DSC 60, having TA60 software, Shimadzu, Japan. The equipment is very accomplished as far interaction and compatibility studies at pre-formulation stage was concerned and used to evaluate melting point and any other phase transitions of API with excipients and polymers. DSC was performed on pure API, excipients and optimized formulation. DSC measurements were taken on a shimadzu DSC-60 and samples were heated at the rate of 10°C min in an aluminium cup.

### 3.1.11 Stability studies

Stability of a formulation means, the quality and efficacy of a formulation to remain unchanged of its physical parameters, chemical parameters, organoleptic characteristics and toxic levels as per the method mentioned in Yellanki SK *et. al*., (2011). The purpose of stability testing is to provide evidence of how the quality and safety of a API or a formulation varies with time under the influence of a various of environmental factors such as heat, relative humidity and light. Stability studies were executed for 6 months period at two different conditions.

1) 40°C/75%RH- Accelerated conditions as per regulatory guidelines.
2) 25°C/60%RH- Long term conditions as per regulatory guidelines.

Optimized formulation (F2) was preferred for stability studies on the basis of satisfactory drug release pattern. Samples were wrapped in butter paper and packed in Alu – Alu pouches. Then loaded in Stability chamber in accelerated conditions for 6 months according to regulatory ICH guidelines.

**3.1.12 Comparison of final optimized formulation with innovator product**

A comparative study of F2 of the formulation of Macitentan FDOFs was done with a market formulation of opsumit 10 mg manufactured by Actelion Pharmaceuticals Inc. to compare the release pattern of the Macetentan form FDOF as Pulmonary arterial hypertension (PAH) need a fast medication

## 4. Results and Discussion

Ten distinct formulations were developed and evaluated by systematically varying the polymer concentrations. Initial trial batches were conducted to optimize the polymer levels, with the Macitentan dose maintained at 10 mg per 4 cm² film. Each formulation was prepared by incrementally increasing the amount of HPMC E6LV by 10 mg, while adjusting the concentrations of HPBCD, propylene glycol 400, and xanthan gum to achieve the desired film characteristics. The properties of the fast-dissolving oral films (FDOFs), as presented in Tables 2 and 3, were meticulously assessed. Based on the evaluation data, formulations F2, F8, and F10 exhibited satisfactory physical characteristics. Among these, formulation F2 was identified as the optimized formulation, as it demonstrated superior FDOF properties, enhanced taste, and a non-tacky surface. The physical performance of the FDOFs was further examined through visual and tactile inspection, and the observations obtained from this evaluation are discussed below.

1) The FDOF were evenly colored and elegance was satisfactory.
2) The increased thickness of FDOF is attributed to the maximizes in the amount of HPMC.
3) The brittle in nature of F4, F8, F9 and F10 formulations are due to insufficient amount of plasticizer added to the formulation.
4) F5, F6, F8 and F10 were observed to be thick.

The FDOF F1, F2, F3, F5, F6 formed from all the formulations had smooth surface on either side. A

### 4.1 *In Vitro* Drug Release Studies

Most of the times the dissolution profile study is very difficult due to nature of the FDOF to float onto the dissolution medium when the paddle apparatus is employed. Hence, basket apparatus is used. *In vitro* DT considering wetting time, *in vitro* DT and cumulative % drug released, formulation F9 wasconsidered to be better than other formulations as shown in table 4 and Figure 4.Based on the experimental data, formulations F1**,** F2**,** andF4 established a substantially good result on drug release when compared to the others. Among these**,** formulation F**2**exhibited the most satisfactory drug release performanc**e** and showedan overall better formulation profile**.** Therefore**,** F2 was selected for further studies and in-depth evaluation.

**Table 3:** Evaluation studies of Macitentan FDOF

| CODE | Thickness (µm) | Weight Variation (% w/w) | Folding Endurance (count) | Surface pH | Content Uniformity/ assay (%) | *In Vitro* DT (sec) |
|---|---|---|---|---|---|---|
| F1 | 82±2 | 54.25± 2 | 93±4 | 6.28±0.03 | 96.5±0.8 | 17±3 |
| F2 | 86±2 | 60.84± 3 | 96±4 | 6.25±0.03 | 98.3±0.3 | 13±3 |
| F3 | 89±2 | 56.94± 2 | 97±4 | 6.69±0.03 | 91.8±0.6 | 29±4 |
| F4 | 76±2 | 57.36± 3 | 117±3 | 6.58±0.02 | 89.1±0.5 | 28±3 |
| F5 | 85±1 | 59.47± 2 | 104±3 | 6.67±0.03 | 90.1±1.0 | 21±2 |
| F6 | 85±1 | 55.34± 2 | 96±3 | 6.59±0.04 | 96.3±0.3 | 22±3 |
| F7 | 86±1 | 50.85± 2 | 103±3 | 6.36±0.03 | 92.8±0.3 | 19±3 |
| F8 | 86±2 | 49.36± 4 | 102±3 | 6.37±0.04 | 91.9±0.4 | 16±4 |
| F9 | 83±2 | 52.35± 2 | 118±2 | 6.03±0.02 | 96.5±0.3 | 18±2 |
| F10 | 82±2 | 51.34± 2 | 112±2 | 6.10±0.04 | 97.0±0.3 | 16±3 |

**4.1.1Drug interaction studies by FTIR**

The bioactive compound Macitentan shows a band at 1643 $cm^{-1}$, associated with the heterocyclic C=C bond, a band at 1453 cm-1 due to C-H bending, and a band at 1333 $cm^{-1}$ linked to S=O. Additionally, the spectra reveal bands at 1586 $cm^{-1}$ attributed to N-H bending. Xanthan gum shows distinct bands at 2898 $cm^{-1}$ for C-H stretching, at 1645 cm-1 for heterocyclic C=C, and at 1452 $cm^{-1}$ for C-H bending. The FTIR spectrum of the film containing Macitentan exhibits bands that align with Macitentan's molecular structure, including bands at 2921 $cm^{-1}$ for C-H stretching, at 1773 $cm^{-1}$ for C=O stretching, at 3427 cm-1 for N-CH3, at 1389 $cm^{-1}$ for S=O, and at 1588 cm-1 for C-H bending. The Macitentan film formulation shows peaks at 2901 cm-1 for C-H stretching and at 3429 $cm^{-1}$ for N-CH3. Therefore, the presence of these characteristic absorption bands in both Macitentan and the film containing it indicates that there are no changes happen the physical or chemical reactions between the drug and the inactive components in the formulation.

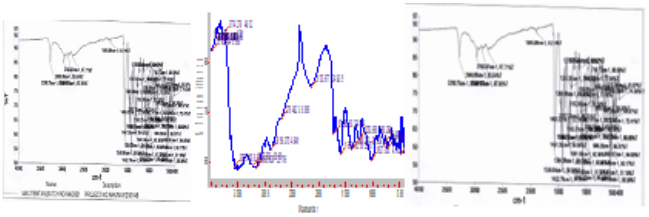

**Figure 3:** Comparative study of IR spectroscopy of pure Macitentan, Xanthan gum and Macitentan loaded FDOF (F2)

**4.1.2 Drug and inactive ingredient suitability studies by DSC**

Differential Scanning Calorimetry (DSC) thermograms showed no significant change in the melting endotherm of the macitentan compared to the formulated form present in the optimized formulation (170°C). The minimal variation

indicates that there was no noteworthy interaction between the drug and the inactive ingredient in the formulation. According to the drug-excipient compatibility studies, formulation F2 showed no notable changes in melting point, confirming that the drug and excipients are compatible and chemically stable when combined

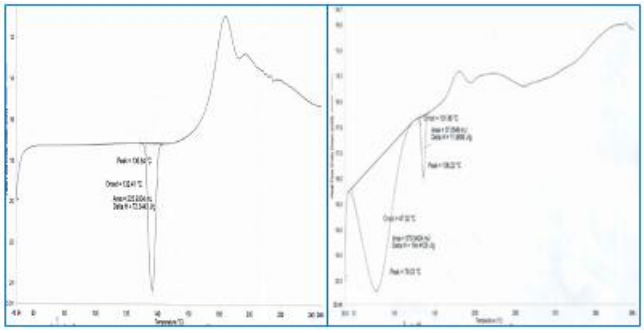

**Figure 4:** Comparative interactive Study of pure Macitentan and Macitentan loaded FDOF (F2)

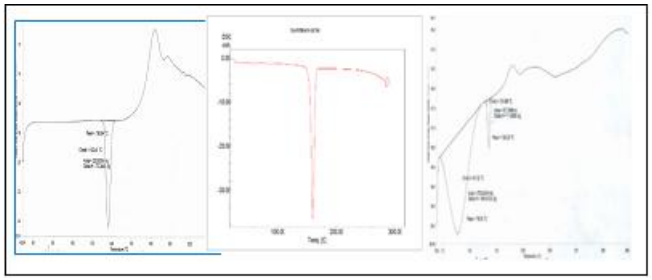

**Table 4:** Comparison of DSC thermograms

| Name of the ingredient | Melting point |
|---|---|
| Macitentan | 132.4 |
| Xanthan gum | 130 |
| HPMC E15 LV | 172 |
| Optimized formulation (F2) | 131.8 |

### 4.1.3 Stability Studies of FDOF formulation(F2)

The selected formulation(F2) which shows better profile was chosen for a 6-month stability study due to its high cumulative percentage of drug release. These stability studies were carried out over a 6-month period in compliance with regulatory ICH guidelines. The selected optimized formulation was designated for these studies based on its satisfactory drug release pattern. The stability studies adhered to the regulatory ICH guidelines for a duration of 6 months. Throughout the 6-month stability period, no significant changes were observed in key parameters such as physical appearance, disintegration time (DT), assay values, and drug release behavior. Built on the data obtained and in accordance with ICH Q1(A) stability guidelines, the stability of the product can be estimated at 24 months under recommended storage conditions

**Table 5:** Stability studies of Macitentan FDOF- F2 under conditions of 40 ±2ºC /75 ±5% RH.

| Test time against the selected F2 | DT (sec) | The drug loaded by assay in % | Drug release by In-vitro method in % | Clarity |
|---|---|---|---|---|
| 0 days | 13 ± 3 | 98.3 ± 0.3 | 99.1 ± 1.5 | Clear |
| 1 month | 12 ± 4 | 98.0 ± 0.2 | 98.4 ± 3.61 | Translucent |
| 3 months | 12 ± 5 | 97.6 ± 0.4 | 97.2 ± 2.71 | Transparent |
| 6 months | 13 ± 3 | 97.5 ± 0.3 | 97.5 ± 6.72 | Translucent |

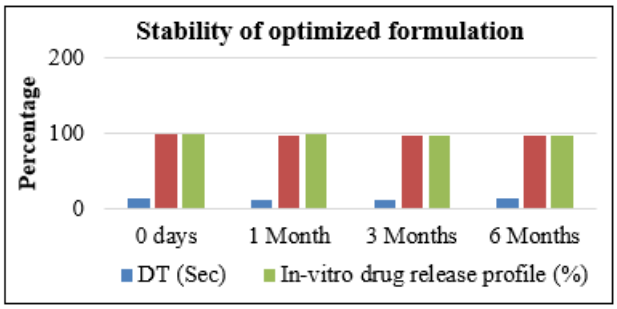


**Figure 5:** Stability of optimized FDOF formulation F2

### 4.1.4 Comparative evaluation study of selected preparation with commercial marketed preparation

Based on the aforementioned studies, formulation F2 was identified as the optimal choice for the development of Macitentan Fast Dissolving Oral Films (FDOFs). To evaluate its efficacy, the drug release profile of F2 was compared with that of the innovator product, OPSUMIT® 10 mg tablets. The findings indicated that F2 exhibited a significantly accelerated drug release in comparison to the marketed product. Specifically, F2 achieved nearly 100% drug release within 10 minutes, underscoring its rapid dissolution characteristics, whereas the OPSUMIT tablet displayed a slower release profile. This rapid release behaviour positions F2 as a promising alternative to conventional tablet formulations.

**Table 6:** Comparison of drug release with the marketed medication OPSUMIT-10mg tablets

| Duration of release in minutes | start | 1 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|---|
| F2 | 0 | 41.5+ 1.2 | 62.6+ 1.4 | 78.7+ 1.5 | 81.7+ 2.0 | 90.7+ 2.3 | 99.1+ 2.0 |
| OPSUMIT-tablets (10mg) | 0 | 28.0 ± 1.4 | 41.4± 0.6 | 64.6± 2.3 | 71.3 ± 2.3 | 82.0 ± 2.3 | 90.2 ± 1.8 |

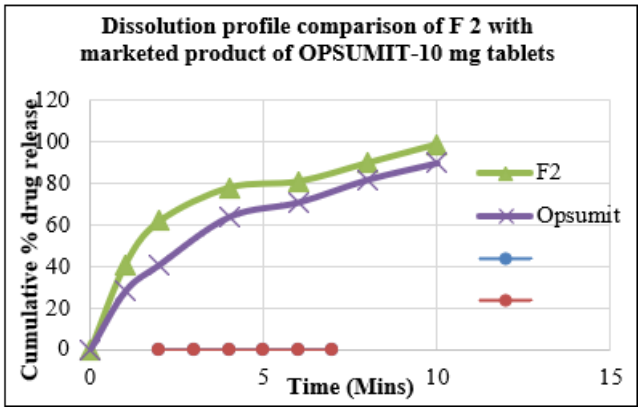


**Figure 6:** Dissolution profile comparison of F2 with innovator product of OPSUMIT -10 mg tablets

## 5. Conclusion

Extensive research in oral fast dissolving formulation for the rapid release is much preferred for the technology for the special condition such as PAH. The novel delivery systems cover vast group of patients especially geriatric and paediatrics. Out of the 10-formulation developed Formulation 2 (F2) was found optimal in FDOF properties

and the drug releasing patterns. So, it can be concluded that the oral films with so many advantages and high patient compliance have glowing futuristic opportunities

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**Conflict of interest**
There is no conflict of interest

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## Author Profile

**Mrs Jisha James** is working as a faculty in the Department of Pharmaceutics at MGM College of Pharmacy, Kannur. She is currently pursuing her PhD in Pharmacy from Shri Jagdish Prasad Jhabarmal Tibrewala University (JJTU). She obtained her Bachelor of Pharmacy (B.Pharm) degree from St. John's College of Pharmacy, Bangalore, in 1997 and her Master of Pharmacy (M.Pharm) degree from KM College of Pharmacy, Madurai in 1999. With over 20 years of teaching experience, she has been actively involved in undergraduate and postgraduate

pharmacy education, contributing significantly to academic excellence and student mentoring.

**Dr. John Thomas** was born in Anikkad, Kerala, on 19 February 1973. He completed his PhD in Pharmaceutical Sciences from the Research Development and Innovation Centre (RDIC), C.U. Shah University, Gujarat, India, in 2020. He obtained his Master of Pharmacy (M.Pharm) degree in Pharmaceutical Chemistry from JSS College of Pharmacy, Ooty, under The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India, in 1999.

**Dr. Vivek Chauhan** is a Professor in the Department of Pharmaceutics at Metro College of Health Sciences and Research (MCHSR), Greater Noida, India. He is actively involved in teaching and research in the field of Pharmaceutics and is currently guiding PhD students.