ISSN 2582 – 6050

Available Online at www.ijpba.info
International Journal of Pharmaceutical & Biological Archives 2021; 12(3):100-107

RESEARCH ARTICLE

Formulation and *In Vitro* Evaluation of Pitavastatin Oral Thin Films

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Received: 25 May 2021; Revised: 26 June 2021; Accepted: 20 July 2021

ABSTRACT

Introduction: Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of administration, avoidance of pain, versatility, and most importantly patient compliance. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity. Recently, fast-dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better compliance. **Materials and Methods:** Conventionally, these drugs have been administered as parenteral drug delivery systems, which invariably lead to poor patient compliance. This has made the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery. Intraoral fast-dissolving drug delivery system is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releasesthe active agent for local and/or systemic absorption. **Results:** In the present study, an attempt has been made to formulate and evaluate orally disintegrating tablets films of pitavastatin by the solvent cas ting method using povidone and HPMC K4M as superdisintegrants. **Conclusion:** The stability studies were conducted and results suggested that the F8 formulation was stable even after 3 months of time. Based on all the above considerations, these formulas will be subjected to bioavailability studies and if it complies with all the requirement of those studies, the same formula will be commercialized.

Keywords: Pitavastatin, thin films, orally disintegrating tablets films

INTRODUCTION

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of administration, avoidance of pain, versatility, and most importantly patient compliance. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolve on the tongue or buccal cavity. Recently, fast-dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better compliance. These drug delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing.[1] They also impart unique product differentiation, thus enabling the use of line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry that is improved solubility/stability, biological half-life, and bioavailability enhancement of drugs.[2,3] Although oral disintegrating tablets have an advantage of administration without choking and fast disintegration, the disintegrated materials contained in them are insoluble and remain until swallowing. In such cases, formulation of fast-dissolving film will be advantageous.[1-10]

Nearly 35–50% of the general population, especially the elderly and children, suffer from

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dysphagia or difficulty in swallowing, which results in high incidence of non-compliance and ineffective therapy. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, developmentally disabled, non-cooperative, and patients with reduced liquid intake or patients suffering from nausea, as well as patients travelling or who do not have easy access to water. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing, and due to lack of water. Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. In general, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms.[6] Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking.[7] Hence, orally dissolving tablets have come into existence.[11-20]

Even with these differences, most of the exis ting oral dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. Hence, oral film drug delivery is a better alternative in such cases. The oral bioavailability of many drugs is poor because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism. Conventionally, these drugs have been administered as parenteral drug delivery systems, which invariably lead to poor patient compliance. This has made the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery. Intraoral fast-dissolving drug delivery system is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.[21-29]

Drug and Excipient Profile

Drug profile

Drug Name: PITAVASTATIN

Excipient profile

- Croscarmellose sodium
- Hydroxypropyl methylcellulose
- Lactose
- PVA
- Povidone.

MATERIALS AND METHODS

Materials used

Table 1: List of materials

S. No.	Materials	Grade	Company
1.	Pitavas tatin	Pharma	Matrix Pvt. Ltd., Hyderabad
2.	Gelatin	Pharma	S.D. Fine Chemicals, Mumbai
3.	PVA	Pharma	INR Chem., Mumbai
4.	HPMC K4M	Pharma	Hi Media Lab. Pvt. Ltd., Mumbai
5.	Povidone	Pharma	Signet Chemical Corp., Mumbai
6.	PEG 400	--	S.D. Fine Chemicals, Mumbai
7.	Citric acid	--	S.D. Fine Chemicals, Mumbai
8.	Lactose	--	S.D. Fine Chemicals, Mumbai
9.	Trusil mixed flavor R.S.V	--	International Flavors of Fragrance India Ltd., Chennai

Instruments and Equipment Used

Table 2: List of equipment

S. No.	Instruments/equipment	Company
1.	Electronic balance	Citizen CTG – 302
2.	Digital pH Meter	Hanna Ins truments
3.	Hot air oven	Serve well instruments
4.	Tablet dissolution tester (USPXX IV)	Electro Lab
5.	UV spectrophotometer	Shimadzu
6.	FT-IR spectrophotometer	Shimadzu
8.	Humidity chamber	Thermo Lab
9.	Differential scanning calorimetry	METTLER
10.	Scanning electron microscopy	QUANTA-200 FEI

RESULTS AND DISCUSSION

Result

In the present study, an attempt has been made to formulate and evaluate orally disintegrating tablets (ODTs) films of pitavastatin by the solvent casting method using povidone and HPMC K4M as superdisintegrants [Figures 1-6].

Solubility Studies of Pure Drug

Solubility

The solubility of pitavastatin was carried out at 25°C using 0.1 N HCl, 6.8 phosphate buffer, and purified water.

DISCUSSION

From the conducted solubility studies in various buffers, we can say that 0.1 N HCl solutions have more solubility when compared to other buffer solutions.[30-38]

Flow Properties of the Pure Drug

From the above flow properties of the pure drug, it was concluded that all the parameters are within the limits indicating the free flow of drug.

Total 10 formulations were prepared and three different film forming polymers without disintegrants and complete composition of all batches. The films were then characterized by various physicochemical parameters.

UV Spectrum of Pitavastatin

Standard calibration curve of pitavastatin was drawn by plotting absorbance versus concentration. The λmax of pitavastatin in 0.1 N HCl was determined to be 266 nm, as shown. The absorbance values are tabulated in the table below. Standard calibration curve of pitavastatin in the Beer's range between 0 and 50 µg/ml is shown in Figure 7.

Table 3: Flowability based on compressibility index

% compressibility	Flowability
5–12	Excellent
12–16	Good
18–21	Fair passable
23–35	Poor
33–38	Very poor
<40	Very very poor

Compatibility Study

Compatibility studies were performed using Fourier transform infrared (FT-IR) spectrophotometer.

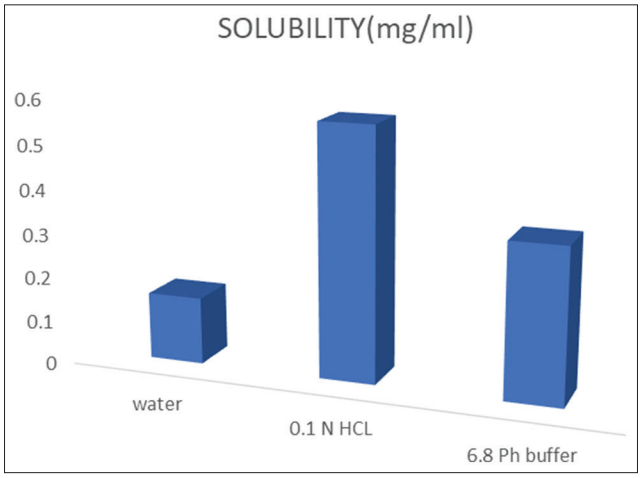

Figure 1: Solubility profile

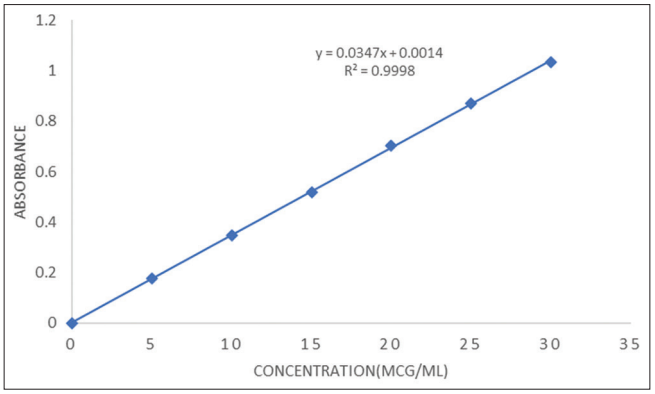

Figure 2: Standard calibration curve for pitavastatin in 0.1 N HCl at λ_{max} 266 nm

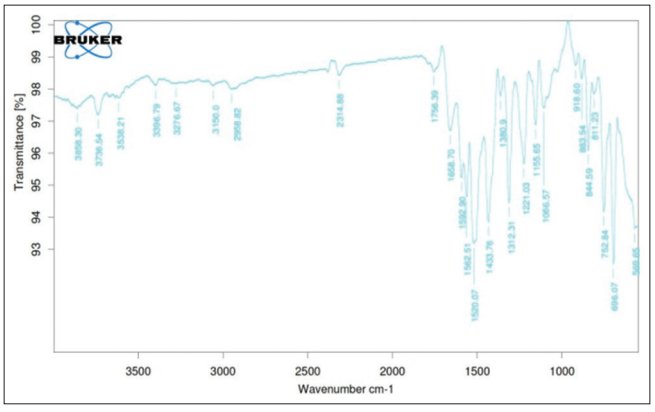

Figure 3: Infrared spectra of pure drug

The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic absorption peaks of pitavastatin were obtained at different wavenumbers in different samples.

The peaks obtained in the spectra of each formulation correlate with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components. The spectra for pure drug and optimized formulation are shown below.

Evaluation of Oral Disintegrating Thin Films Formulations

Physical appearance and surface texture of films

These parameters were checked simply with visual inspection of films and by feel or touch. The observation suggests that the films are having the smooth surface and they are elegant enough to see.

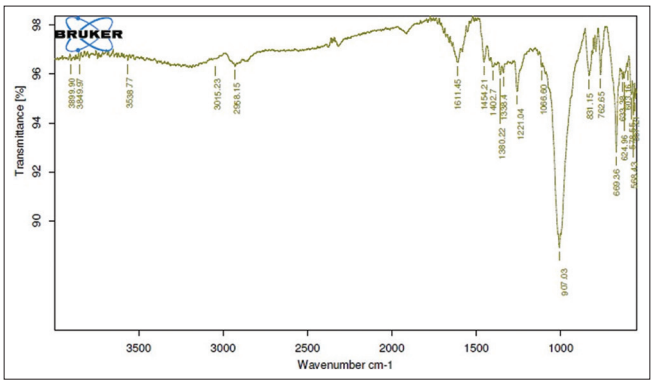

Figure 4: Infrared spectra of optimized formulation

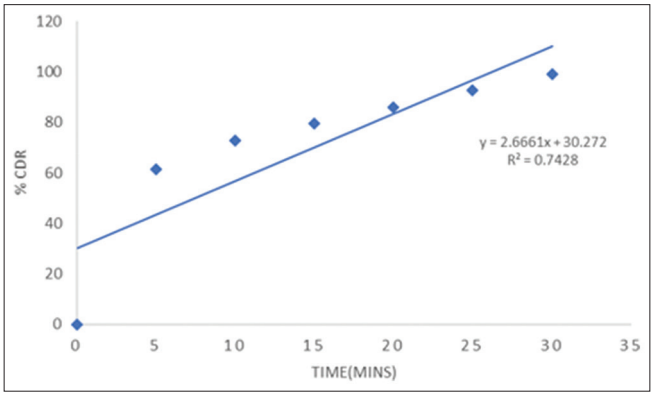

Figure 5: Zero-order release profile of pitavastatin best formulation (F8)

Weight uniformity of films

The weight of prepared films was determined using digital balance and the average weight of all films was given in table. The weight of films measured without the disintegrating agents with 4.5% gelatin and 3.5% PVA was about 63.92, 51.02 mg, respectively. The films prepared from 4% gelatin with different concentrations of povidone as 2%, 4%, and 6% were weighed about 65.90, 67.04, and 66.84 mg, respectively, and with 10% and 15% HPMC K4M were weighed about 65.21 and 68.21 mg respectively. The films prepared from 3.5% PVA with different concentrations of povidone as 2%, 4%, and 6% were weighed about 49.91, 51.22, and 52.18 mg and with 10% and 15% of HPMC K4M were weighed about 72.12 and 51.18 mg, respectively. In all the cases, the calculated standard deviation values are very low which suggest that the prepared films were uniform in weight [Tables 1-10].

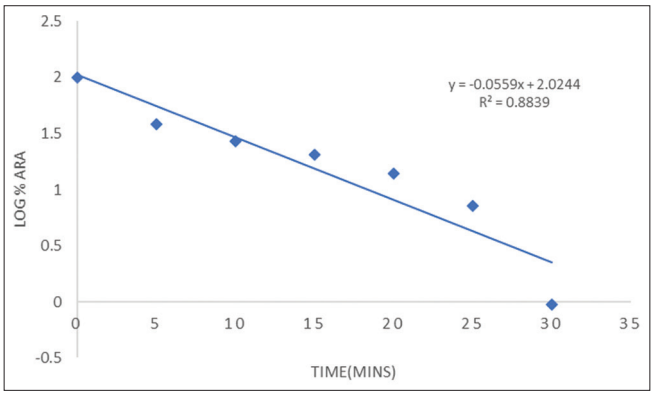

Figure 6: First-order release profile of pitavastatin best formulation (F8)

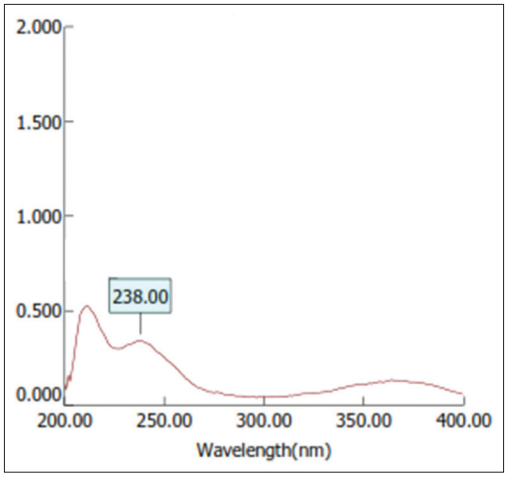

Figure 7: Absorption maxima of pitavastatin in 0.1 N HCl standard calibration curve of pitavastatin in 0.1 N HCl

The thickness of films

The thickness of the films was measured using micrometer screw gauge and the average thickness of all films is given. The thickness of films measured without the disintegrating agents with 4.5% gelatin and 3.5% PVA was about 0.135 and 0.125 mm, respectively. The thickness of films prepared with gelatin having the concentration 4.5% with 2%, 4%, and 6% povidone was about 140, 0.145, and 0.150 mm, respectively, and with 10% and 15% of HPMC K4M were about 0.160 and 0.165 mm, respectively. The thickness of films prepared with PVA having the concentration 3.5% with 2%, 4%, and 6% of povidone was about 0.130, 0.130, and 0.140 mm, respectively, and with 10% and 15% of HPMC K4M were about 0.170 and 0.145 mm, respectively. In all the cases, the calculated standard deviation values are very low which suggest that the prepared films were uniform in thickness.

Folding endurance of films

The folding endurance of the films was determined by repeatedly folding a small strip of the films at the same place till it broke and the average folding endurance of all films is given in Table 11. The folding endurance of films prepared without the disintegrating agents with 4.5% gelatin and 3.5%

Table 4: Solubility

S. No.	Medium	Solubility (mg/ml)
1	Water	0.152
2	0.1 N HCl	0.568
3	6.8 pH buffer	0.347

Table 5: Flow properties of the pure drug

Angle of repose	24.02
Bulk density	0.46
Tapped density	0.54
Carr's index	13.33
Hausner's ratio	1.12

Table 6: Calibration data of pitavastatin in 0.1 N HCl at λ_{max} 266 nm

S. No.	Concentration (μg/ml)	Absorbance*
1	0	0
2	5	0.176
3	10	0.346
4	15	0.518
5	20	0.703
6	25	0.871
7	30	1.035

Table 7: Evaluation of fast-dissolving films of pitavastatin

Formulation code	Avg. weight (mg)	Avg. thickness (mm)	Avg. folding endurance
Fg	63.92	0.135	272
F1	65.21	0.140	287
F2	65.90	0.145	289
F3	67.04	0.150	267
F4	66.84	0.160	271
F5	68.21	0.165	274
F_P	51.02	0.125	265
F6	72.12	0.170	259
F7	49.91	0.130	266
F8	51.22	0.130	277
F9	52.18	0.140	260
F10	51.11	0.145	291

Table 8: Zero-order kinetics data of pitavastatin best formulation (F8)

Time (min)	%CDR
0	0
5	61.37
10	72.93
15	79.57
20	86.07
25	92.85
30	99.05

Table 9: First-order kinetics data of pitavastatin best formulation (F8)

Time (min)	Log %ARA
0	2
5	1.586925
10	1.432488
15	1.310268
20	1.143951
25	0.854306
30	−0.02228

Table 10: Regression coefficients that fit to different drug release kinetics models of pitavastatin best formulation (F8)

Formulation code	Zero order	First order
	r^2	r^2
F8	0.743	0.884

Table 11: Formulation details of pitavastatin oral disintegrating thin films

Formulation	Pitavastatin (mg)	Gelatin (mg)	PVA (mg)	HPMC K4M (mg)	Povidone (mg)	Lactose (mg)	Citric acid (mg)	Trusil flavor (mg)	PEG (mg)
F g	40	4.5	--	--	--	4	4	8	30
F1	40	4.5	--	2	--	4	4	8	30
F2	40	4.5	--	4	--	4	4	8	30
F3	40	4.5	--	6	--	4	4	8	30
F4	40	4.5	--	--	10	4	4	8	30
F5	40	4.5	--	--	15	4	4	8	30
Fp	40	--	3.5	--	--	4	4	8	30
F6	40	--	3.5	--	10	4	4	8	30
F7	40	--	3.5	--	15	4	4	8	30
F8	40		3.5	2	--	4	4	8	30
F9	40	--	3.5	4	--	4	4	8	30
F10	40	--	3.5	6	--	4	4	8	30

PVA was about 272 and 265, respectively. Gelatin, the concentration of 4.5% with 2%, 4%, and 6% of povidone was about 287, 289, and 267, respectively, and with 10% and 15% of HPMC K4M were about 271 and 274, respectively. The folding endurance of films prepared with PVA the concentration 3.5% with 2%, 4%, and 6% povidone were about 266, 277, and 260, respectively, and with 10% and 15% of HPMC K4M were about 259 and 291, respectively.

Surface pH of films

Surface pH was determined by allowing the films to be in contact with 1 ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min and the average surface pH of all films is given.

The surface pH of the films prepared without the disintegrants from 4.5% gelatin and 3.5% PVA was about 6.67 and 6.89, respectively. The films prepared from gelatin in concentration of 4.5% with 2%, 4%, and 6% of povidone were about 6.76, 6.00, and 6.46 and with 10% and 15% of HPMC K4M were about 6.23 and 6.66, respectively. The surface pH of the films PVA in concentration 3.5%, with 2%, 4%, and 6% of cross povidone was about 6.83, 6.06, and 6.33 and with 10% and 15% of HPMC K4M was about 6.06 and 6.76, respectively. Considering the fact that acidic or alkaline pH may cause irritation to the oral mucosa and influence the degree of hydration of polymer, the surface pH of the fast films was determined to optimize drug permeation. Attempts were made to keep the surface pH as close to salivary pH as possible, by the proper selection of the polymer for developing the fast films. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of different films.

The standard deviation values calculated for all the films are very low which conclude that the surface pH of all the films was uniform and within the range.

In vitro disintegration time of films

The disintegration time limit of 30 s or less for ODT described in CDER guidance can be applied to fast-dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for films is 5–30 s. The average disintegration time of different formulation is shown in Table 6.5.

The *in vitro* disintegration time of the films prepared without the disintegrants with 4.5% gelatin and 3.5% PVA were about 72 and 70 s, respectively. The *in vitro* disintegration time of the films prepared with 4.5% gelatin with 2%, 4%, and 6% povidone were about 14, 9, and 12 s, respectively, and with 10% and 15% HPMC K4M were about 19 and 13 s. respectively. The

in vitro disintegration time of the films prepared with PVA in the concentration of 3.5% with 2%, 4%, and 6% povidone were about 12, 7, and 12 s, respectively, and with 10% and 15% of HPMC K4M were about 14 and 15 s, respectively. In all the cases, the calculated standard deviation values are different which suggest that the prepared films show different *in vitro* disintegration time.

Drug Release Kinetics of Pitavastatin

First-order release kinetics data

The *in vitro* dissolution data for best formulation F8 were fitted in different kinetic models, that is, zero order and first order. Optimized formulation F8 follows the first order.

SUMMARY AND CONCULSION

In the present study, oral disintegrating drug delivery sys tems of pitavas tatin were successfully developed in the form of oral disintegrating thin films which offers a suitable and practical approach serving the desired objective of faster disintegration and dissolution characteris tics with increase bioavailability. Oral disintegrating thin films of pitavas tatin were prepared using povidone and CCS as superdisintegrants.

Under the pre-formulation studies, API characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics.

The disintegrants and other excipients were selected based on the satisfying results produced during drug-excipient compatibility studies to develop the final formulation.

The final suitable formulation (F8) was achieved fruitfully by the solvent casting method using polyvinyl alcohol and croscarmellose sodium as disintegrant which exhibited a rapid disintegration time (7.23 s) and *in vitro* drug release (99.05%).

Considering the results of batches containing polyethylene glycol, polyvinyl alcohol, and croscarmellose sodium as disintegrant, it can be concluded that the formulation F8 was meeting the higher *in vitro* correlation limits and in less instance of time when subjected to the comparison with other formulation that includes povidone as the disintegrating agent. It was also observed that solvent casting method was the best suitable method used for immediate drug release.

The s tability studies were conducted and results suggested that the F8 formulation was s table even after 3 months of time.

Based on all the above considerations, these formulas will be subjected to bioavailability studies and if it complies with all the requirement of those studies, the same formula will be commercialized.

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