GSC Biological and Pharmaceutical Sciences, 2018, 03(02), 035–042

Available online at GSC Online Press Directory

GSC Biological and Pharmaceutical Sciences

e-ISSN: 2581-3250, CODEN (USA): GBPSC2

Journal homepage: https://www.gsconlinepress.com/journals/gscbps

(RESEARCH ARTICLE)

Formulation and evaluation of lovastatin oral disintegration thin films

Pagilla Pragathi *, Vishnu P, Konde Abbulu

Department of Pharmaceutics, CMR College of Pharmacy, Kandlakoya (V), Medchal Road, Hyderabad, India.

Publication history: Received on 12 October 2017; revised on 02 May 2018; accepted on 05 May 2018

https://doi.org/10.30574/gscbps.2018.3.2.0061

Abstract

Lovastatin is a statin drug used to prevent and treat coronary heart disease and to treat high cholesterol. In the present study, oral disintegrating thin films (ODTs) of lovastatin were designed with a view to enhance patient compliance by solvent casting method. In the solvent casting method, Croscarmellose sodium (CCS) (2, 4 and 6 % w/w), Crospovidone (10 and 15% w/w) as superdisintegrants were used in different concentrations with Gelatin, Poly vinyl alcohol (PVA) as a film forming base for the formulation of oral disintegrating thin films of lovastatin. The prepared formulations of films were evaluated for film thickness measurement, folding endurance study, *in-vitro* disintegration time, *in-vitro* drug release pattern and drug content. FTIR spectroscopy used to study drug-polymers interaction. Among all formulations, the formulation (F8) prepared by 4% crospovidone show enhanced drug release (99.27%) and it showed good stability for period of three months. Conclusively, the present study documents the development of a commercially viable formula lovastatin ODTs with rapidity in reducing heart problems.

Keywords: Croscarmellose sodium; Crospovidone; Lovastatin; Oral disintegrating thin films

1. Introduction

Among the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and most importantly patient compliance [1]. Many patients especially geriatric and paediatric have difficulty to swallow the tablets and hard gelatin capsules. Fast dissolving drug delivery systems (FDDDS) were developed as an alternative to tablet, capsule and syrups [2]. Oral fast dissolving film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers, which rapidly disintegrate or dissolves on tongue or in the buccal cavity [3].

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance [1]. But the most evident drawback of oral dosage forms like tablets and capsules are difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatric, bedridden, nauseous patients [4]. Fast dissolving drug delivery systems (FDDDS) were developed as an alternative to tablet, capsule and syrups. These systems consist of the solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Rapid-dissolving oral thin film is a solid dosage form, which disintegrate or dissolve within 1 min when placed in the mouth without drinking of water or chewing [5]. After disintegrating in mouth, enhanced the clinical effect of drug through pre-gastric absorption from mouth pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [1].

Lovastatin, a specific and potent competitive inhibitor of 3-hydroxy3-methyl glutaryl coenzyme A (HMG-CoA) is a powerful serum cholesterol-lowering drug in humans and other species. It inhibits HMG-CoA reductase (E.C 1.1.1.34),

*Corresponding author
E-mail address: pragathireddypagilla@ gmail.com

the first committed enzyme of cholesterol biosynthesis [6-7]. *Lovastatin* is a statin drug used to prevent and treat coronary heart disease, and to treat high cholesterol [8]. Therefore, the objective of present work was to develop oral disintegration thin films of lovastatin and evaluate for its different physical properties and drug release study.

2. Material and methods

2.1. Chemicals

Lovastatin (Matrix Pvt. Ltd. Hyderabad), Gelatin, PEG 400, Citric acid, Sucrose (S. D. Fine Chemical Limited, Mumbai), HPMC (Himedia Lab. Pvt. Ltd., Mumbai), Crospovidone, Croscarmellose sodium (Signet Chemical Corporation Pvt. Ltd., Mumbai), Trusil mixed flavor RSV (International flavors of fragrance, India Ltd).

2.2. Instruments used

Electronic balance obtained from (Citizen CTG – 302), Digital pH meter (Hanna Instruments, Italy), Hot air oven (Servewell Instruments, Bangalore), Tablet dissolution tester (USPXXIV) (Electro Lab), UV spectrophotometer (Shimadzu), FTIR spectrophotometer (Shimadzu), Humidity chamber (Thermo Lab.), Differential scanning calorimetry (METTLER), Scanning electron microscopy (QUANTA-200 FEI, Netherland).

2.3. Drug-excipient compatibility study

FTIR spectra of pure drugs, polymers used, and blends were recorded on KBR disk method using FTIR-8400S Spectrophotometer with IR solution software (Shimadzu, Japan) to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm^{-1} using 20 scans with 4 cm^{-1} resolution.

2.4. Formulation of oral disintegrating thin films (ODT) of lovastatin

The oral disintegrating thin films of lovastatin were prepared by solvent casting method [9-10] employing mercury as substrate. The ODT films were prepared using polymers like gelatin, PVA. Propylene glycol (PEG) is used as plasticizer. The calculated amount of polymer was dispersed in three forth volume of with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. The calculated amount of lovastatin was incorporated in the polymeric solutions after levigation with required volume of PEG. The solution was casted on to mercury substrate then kept in hot air oven at 40 ˚C. The films were punched in to size 2 cm diameter containing 4 mg of lovastatin. For the trial and error method different concentrations of film forming polymers were used like gelatin and PVA. It has been found that 4.5% of gelatin, 3.5% of PVA shows better films. Therefore this concentration of gelatin and PVA used for preparation of ODT film of lovastatin. In addition to this CCS and crospovidone are also added in the thin film in different concentration which gives different type of formulation of lovastatin as shown in table 1. With the same procedure the films of 4.5% gelatin, 3.5% PVA were prepared without the super disintegrating agents named as Fg and Fp respectively.

Table 1 Formulation details of lovastatin oral disintegrating thin films

Formulation	Lovastatin (mg)	Gelatin (mg)	PVA (mg)	CCS (mg)	Crospovidone (mg)	Sucrose (mg)	Citric acid (mg)	Trusil flavor (mg)	PEG (mg)
F g	50	4.5	--	--	--	4	4	8	30
F1	50	4.5	--	2	--	4	4	8	30
F2	50	4.5	--	4	--	4	4	8	30
F3	50	4.5	--	6	--	4	4	8	30
F4	50	4.5	--	--	10	4	4	8	30
F5	50	4.5	--	--	15	4	4	8	30
Fp	50	--	3.5	--	--	4	4	8	30
F6	50	--	3.5	--	10	4	4	8	30
F7	50	--	3.5	2	--	4	4	8	30
F8	50		3.5	4	--	4	4	8	30
F9	50	--	3.5	6	--	4	4	8	30
F10	50	--	3.5	--	15	4	4	8	30

2.5. Evaluation of lovastatin ODT

Lovastatin ODTs were evaluated for weight uniformity, thickness uniformity, folding endurance, surface pH, *in vitro* disintegration time, and drug content uniformity [9-10].

2.5.1 *Weight uniformity*

Three films of the size 2 cm diameter were weighed individually using digital balance and the average weights were calculated.

2.5.2 *Thickness*

Thickness of the films was measured using screw gauge with a least count of 0.01 mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

2.5.3 *Folding endurance*

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 2x2 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance [11].

2.5.4 *Surface pH*

Surface pH was determined by the films were allowed 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.

2.5.5 *In vitro disintegration time*

Disintegration test was performed in the USP disintegration time testing apparatus. The 0.1 N HCl solution used as medium. The films were places in the tubes of the container and disintegration time was recorded.

2.5.6 *Drug content uniformity*

The films were tested for drug content uniformity by UV spectrophotometric method. Films of 2 cm diameter were cut from three different places from the casted films. Each patch was placed in 100 ml volumetric flask and dissolved in 0.1N HCl solution and 0.2 ml is taken and diluted with water up to 10 ml. The absorbance of the solution was measured at 238 nm using UV/visible spectrophotometer (Shimadzu UV-1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

2.6. In-vitro dissolution Study [12]

In vitro dissolution of lovastatin oral disintegrating thin films was studied in USP XXIV dissolution test apparatus 900 ml 0.1 N HCl solution was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37 ± 0.5 ºC throughout the experiment. One film was used in each test. Samples of dissolution medium (5 ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 238 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent lovastatin released was calculated and plotted against time.

2.7. Stability studies

Stability studies were carried out at 40 ˚C / 75 ± 0.005 % RH for the selected formulation for the period of 3 months for their physical appearance, drug content and *in-vitro* dispersion time.

3. Results and discussion

3.1. Drug-excipient compatibility study

Compatibility studies were performed using FT-IR spectrophotometer. 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 Lovastatin were obtained at different wave numbers in different samples.

The spectra for pure drug and optimized formulation are shown below. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components [13].

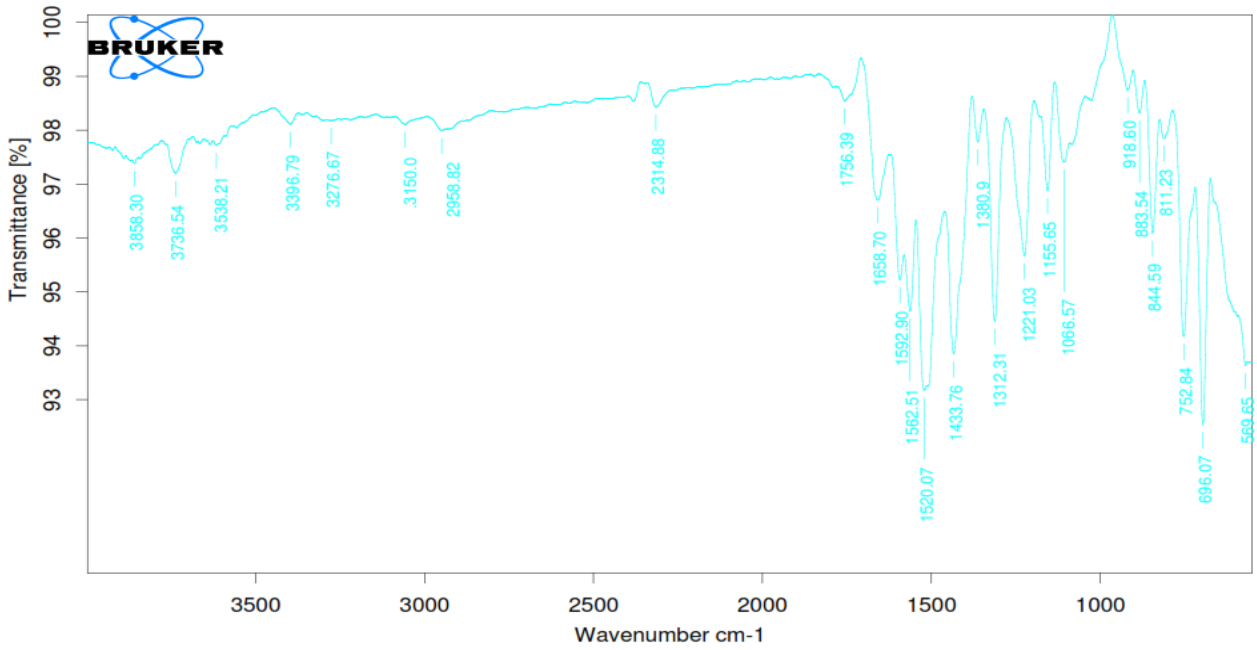

Figure 1 FTIR spectrum of pure drug lovastatin

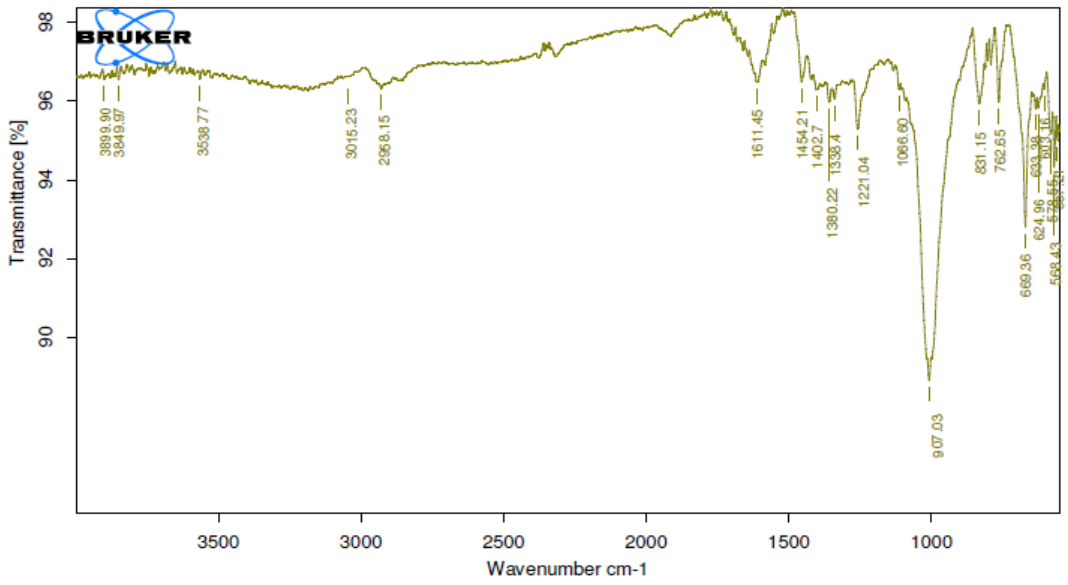

Figure 2 FTIR spectrum of optimized formulation

3.2. Preparation of lovastatin ODTs

The oral disintegrating thin films (ODTs) of lovastatin were designed by solvent casting method using Croscarmellose sodium (CCS) (2, 4 and 6 % w/w), crospovidone (10 and 15% w/w) as superdisintegrants, gelatin and polyvinyl alcohol (PVA) as a film forming base. Ten different formulation of lovastatin ODTs were prepared.

Table 2 Evaluation of fast dissolving films of lovastatin

Formulation Code	Weight (mg)	Thickness (mm)	Folding Endurance
Fg	63.92 ± 0.12	0.135 + 0.010	272 + 1.674
F_1	65.21±0.28	0.140±0.005	287±2.340
F_2	65.90±0.31	0.145±0.010	289±2.640
F_3	67.04±0.21	0.150±0.010	267±1.000
F_4	66.84±0.38	0.160±0.015	271±1.730
F_5	68.21±0.41	0.165±0.005	274±1.000
Fp	51.02 ± 0.24	0.125 + 0.005	265 + 1.253
F_6	72.12±0.11	0.170±0.010	259±3.310
F_7	49.91±0.32	0.130±0.020	266±2.000
F_8	51.22±0.23	0.130±0.015	277±3.460
F_9	52.18±0.41	0.140±0.015	260 ±1.000
F_{10}	51.11±0.22	0.145±0.015	291±2.000

Results are expressed as mean±SD where, n=3.

The prepared films were homogenous, colorless, smooth, and rough surface. The weight variation was found to be minimum as indicated by a small standard deviation of ± 0.33 mg. This observation also shows the uniform distribution of the ingredients in ODTs. The folding endurance of all batches observed between 259 to 291. The thickness shows a narrow range of 0.125 to 0.170 mm further substantiating the above inference. The results showed uniformity in thickness.

Table 3 Evaluation of lovastatin ODTs

Formulation Code	Drug content uniformity (%)	*In vitro* disintegration time (Sec)	Surface pH
F_g	95.54± 0.253	72.21± 0.253	6.67±0.154
F_p	96.52± 1.443	70.43± 0.165	6.89± 0.122
F_1	96.66± 0.925	14.33± 0.171	6.76± 0.153
F_2	98.04± 1.539	9.10± 0.435	6.00± 0.100
F_3	97.33± 0.369	11.50± 0.591	6.46± 0.115
F_4	95.00± 1.056	18.76± 0.151	6.23± 0.152
F_5	97.66± 1.396	12.86± 0.151	6.66± 0.152
F_6	96.66± 1.396	14.10± 0.479	6.06± 0.153
F_7	97.66± 1.545	12.00± 0.100	6.83± 0.057
F_8	98.86± 1.175	7.23± 0.151	6.06± 0.152
F_9	97.24± 1.001	11.93± 0.057	6.33± 0.152
F_{10}	96.76± 0.350	15.41± 0.076	6.76± 0.152

Surface pH of the film was measured in the range of 6-6.89 for all formulations (Table 3). Results show that surface pH of films are in the range of healthy human saliva, which is 6.3–7.3 [14]. Thus, the films are safe to be used in buccal cavity

without any problem of irritation and thus patient acceptance will not be affected. Drug content of lovastatin ODTs was in the range of 96–98.86% implying uniform distribution of drug in the films. FDA recommends that, orally disintegrating tablets should be considered as solid oral preparations that disintegrate fast in mouth, with an *in-vitro* disintegration time of approximately less than or equal to 30 seconds, when the disintegration test conducted to the United States Pharmacopeia (USP) disintegration test method [15-17]. Lovastatin ODTs showed disintegration time of 9-18 sec and passes the limit for disintegration time.

Table 4 *In vitro* dissolution of lovastatin ODTs

	% Cumulative drug release (% CDR)											
Time (min)	**Fg**	**F1**	**F2**	**F3**	**F4**	**F5**	**FP**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0	0	0	0	0	0	0	0
5	40.82	58.45	68.65	60.3	56.59	65.87	45.46	58.45	61.23	72.37	62.16	58.45
10	43.6	64.94	74.22	64.94	62.16	73.29	48.24	63.09	69.58	77.93	71.44	64.94
15	51.03	70.51	78.86	75.15	67.73	76.08	53.81	72.37	74.22	82.57	78.86	70.51
20	56.59	77.01	84.43	82.57	74.22	81.64	59.38	80.72	78.86	89.07	84.43	77.93
25	58.45	84.43	88.14	87.21	81.64	86.28	62.16	85.36	87.21	91.85	89.07	83.5
30	61.23	91.85	98.35	94.63	89.07	95.56	64.02	92.78	94.63	99.27	96.49	91.85

The results obtained in the *in vitro* drug release for the formulations were tabulated in table. *In vitro* dissolution study of all the batches showed >90 % drug dissolution in 30 min. The formulations F2, F5, F8 and F9 show drug release up to >71% at the end of 10 min. Rapid drug dissolutions were observed in F87 which release 77.93 and 99.27 at the end of 10 and 30 min respectively as shown in Table 4.

3.3. Drug release kinetics of lovastatin

The experimental results of formulation F8 with zero order and the first order kinetics model, correlation coefficient are 0.226 and 0.838. *In–vitro* drug release data of formulation (F8) obtained was fitted to kinetic models Zero order, first order, to know the pattern of drug release and mechanism of drug release from the ODTs. Formulation F8 followed first order with a good correlation coefficient (r2=0.838).

3.4. Stability studies

The selected formulation was evaluated for stability studies which was stored at 40 °C at 75% RH tested for 3 month and was analyzed for their physical parameters, *in vitro* dispersion time and drug content at 1 month interval. The residual drug contents of formulations were found to be within the permissible limits which were estimated by measuring drug content uniformity. Lovastatin ODTs were found to be physically and chemically stable as they showed no significant change in terms of physical characteristics and drug content at a room temperature.

Table 5 Stability of F8 formulation of lovastatin ODTs

Stability period in months	**Physical appearance**	***In-vitro* dispersion time (sec)**	**Drug content (%)**
1	+++(Excellent)	7.33	98.40
2	+++(Excellent)	7.95	98.10
3	++(good)	8.35	97.75

Formulation F8 was stored at 40 °C and 75% relative humidity for stability study

4. Conclusion

In the present study oral disintegrating drug delivery system of lovastatin was successfully developed in the form of oral disintegrating thin films. The optimized formulation of lovastatin ODTS (F8) was stable over a period of three months. These lovastatin ODTS offers a suitable and practical approach for faster disintegration and dissolution characteristics with increase bio-availability. For commercialization of optimized formulation of lovastatin ODTS (F8), bio availability studies should be performed in future.

Compliance with ethical standards

Acknowledgments

All authors are thankful to Department of Pharmaceutics, CMR College of Pharmacy, Kandlakoya (V), for providing library and laboratory facility for carrying out present research work.

Disclosure of conflict of interest

The authors have declared that no conflict of interest exists among them.

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How to cite this article

Pagilla P, Vishnu P and Konde A. (2018). Formulation and evaluation of lovastatin oral disintegration thin films. GSC Biological and Pharmaceutical Sciences, 3(2), 35-42.