Int J Pharma Res Health Sci. 2019; 7 (6): 3084-89
DOI:10.21276/ijprhs.2019.06.03
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CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Original Article

Formulation and *In Vitro* Evaluation of Oral Disintegrating Films of Lovastatin

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ARTICLE INFO

Received: 20 Sep 2019
Accepted: 12 Dec 2019

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 films of lovastatin were designed with a view to enhance patient compliance. The solid dispersions of lovastatin was prepared by solvent evaporation method in the ratio 1:1, 1:2,1:3,1:4 along with standard deviation three has shown the release of 99.48 % drug in 60 minutes using PVP-K30 and films were prepared by solvent casting method. The prepared solid dispersion are used to mask the bitter taste by a mixture of sucralose and monoammonium glycerrhizinate producing an extended sweetness profile. The prepared formulations of films were evaluated for film thickness measurement, folding endurance study, *in vitro* disintegration time, *in vitro* drug drug release pattern and drug content. FTIR spectroscopy used to study drug-polymers interaction. Among all formulations, F3 show enhanced drug release (99.93%) and . Results from stability studies indicate that the formulated oral disintegrating films are stable for a period of 3 months usnder two different conditions at 25±2°C / 65±5%RH and 40±2°C / 75±5 %RH. Among all formulations, F3 showed drug release with in 15minutes and considered as ideal formulation. The formulation developed is simple, easy to prepare and economical with great applicability, whenever onset of action is required.

Keywords: Lovastatin, Oral disintegrating films, PVPK30, HPMCE5, HPMC E15, Solvent evaporation method, Solvent casting method.

1. INTRODUCTION

Over the past few decades, tendency toward innovative drug delivery systems has majorly increased attempts to ensure efficacy, safety and patient acceptability. As discovery and development of new chemical agents is a complex, expensive and time consuming process, so recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs. Out of those, drug

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delivery system being very eminent among pediatrics and geriatrics is orally disintegrating films (ODFs). These fast disintegrating films have superiority over fast disintegrating tablets as the latter are associated with the risks of choking and friability. This drug delivery system has numerous advantages over conventional fast disintegrating tablets as they can be used for dysphasic and schizophrenic patients and are taken without water due to their ability to disintegrate within a few seconds releasing medication in mouth. 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 esophagus 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 [1-3].

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 reeducates 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 [4].

2. MATERIALS AND METHODS

Lovastatin, Pharmatrain received from hyderabad. HPMC E5, HPMC E15, Propylene glycol, Sorbitol, Aspartame, Tween 80, citric acid purchased from S.D. Fine chemicals, Mumbai.

Drug polymer compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR):

Ten milligrams of drug alone, mixture of drug and polymer were weighed and mixed properly with KBr uniformly. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR-spectrum of the pellet from 450- 4500cm [6].

Preparation of Solid Dispersion of Lovastatin by Solvent Evaporation Method

Solid dispersion of Lovastatin was prepared using solvent evaporation method using PVP-K30 as carrier in drug: polymer ratio of 1:1, 1:2, 1:3, and 1:4 to find out the best ratio based on the improvement of water solubility. Weighed amount of lovastatin and PVP-K30 was dissolved in ethanol to get a clear solution and was further stirred continuously at 40°C until complete solvent gets evaporated to obtain solid mass. Then, solid mass was passed through the sieve no. 44 and stored in a desiccator until used for further studies.

Taste masking of solid dispersion is done by using sucralose and monoammonium glycerrihizante which are prepared in different concentrations 10, 20, 30µg among which 20µg has shown desired results [7].

Formulation of Lovastatin Oral Disintegrating Films: Oral Disintegrating Films of Lovastatin was prepared by solvent casting technique.

Solution 'A' was prepared by dissolving HPMC-E15 (or E 5)polymer in 5 ml of water.

Solution 'B' was prepared by dissolving Lovastatin, Aspartam, Sorbitol & citric acid in 5 ml of ethanol. The solutions 'A' and 'B' were mixed and stirred for 30min. and add Propylene glycol and tween 80 and flavoring agent and taste masking agent and continue stirring for 10mins. The solutions were cast on to glass petri plate of 9 cm diameter and were dried in the oven at 70°C till a peelable film was formed. Then dried films were cut into rectangular shape pieces, with 4.0 cm^2 (2.0 cm × 2.0 cm) total surface area. Desired quantity of Lovastatin was 10 mg (dose of drug) per 4.0 cm^2 films.

Table 1: Formulation of lovastatin film (F1-F9).

Ingredients	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lovastatin + PVPK30	30	40	40	40	40	40	40	40	40	40
Sucralose+monoammonium glycerrhizinate	20	20	20	20	20	20	20	20	20	20
HPMC E5	-	20	30	40	-	-	-	10	20	30
HPMC E15	-	-	-	-	20	30	40	30	20	10
Propylene glycol	10	10	10	10	10	10	10	10	10	10
Sorbitol	32	31	21	11	31	21	11	11	11	11
crossprovidone	3	3	3	3	3	3	3	3	3	3
Aspartame	5	5	5	5	5	5	5	5	5	5
Tween 80	5	5	5	5	5	5	5	5	5	5
citric acid	5	5	5	5	5	5	5	5	5	5
Peppermint oil	5	1	1	1	1	1	1	1	1	1
Total wt. (mg)	110	140	140	140	140	140	140	140	140	140

EVALUATION OF ORAL DISINTEGRATING FILMS

1. Morphological properties

This parameter was checked simply with visual inspection for physical appearance of films and evaluation of texture by feel or touch.

3. Thickness uniformity

All the eight batches were evaluated for thickness by using calibrated Vernier caliper with a least count of 0.01mm. The thickness was measured at three different spots of the films and the average was taken.

3. Weight uniformity of films

Three films of each formulation trial of 2cm x 2cm size were taken and weighed individually in electronic balance and the average weights were calculated.

4. Folding endurance

The folding endurance was measured manually for the prepared films. The flexibility of films can be measured quantitatively in terms of folding endurance. A strip of film

was cut (approximately 2 x 2cm) and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

5. Surface pH

Surface pH was found out by placing the film on the surface of 1ml of distilled water. The surface pH was noted by bringing pH paper near the surface of the films and allowing it to equilibrate for 1min. The change in the colour of pH paper was observed

6. Drug content uniformity test

Drug content uniformity of all nine batches was determined by UV-Spectrophotometric method. For this, each strip at three different places equivalent to 2mg of drug was cut and dissolved in 50ml of 6.8 Ph phosphate buffer solution with continuous stirring. This solution was filtered using Whatt mann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by U.V. Spectrophotometer and the absorbance was recorded at 225nm. Drug content was calculated by using calibration curve of drug.

7. ***In vitro* disintegration test**

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

8. *In vitro* dissolution studies

The in vitro dissolution test was performed in a Paddle dissolution apparatus. The dissolution medium consisted of 900 mL 6.8pH phosphate buffer solution, maintained at 37±0.5°C and stirred at 50 rpm. One film was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and drug release was analyzed spectrophotometrically at 225nm. The volume withdrawn at each interval was replaced with freshly quantity of dissolution medium. Cumulative percent drug release of lovastatin was calculated and plotted against time.

9. *In vitro* Release Kinetics Studies: The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from IR was described by using zero order kinetics or first order kinetics.

10. **Stability studies**

Stability studies were performed at a temperature of 30±2^{0}C/65±5%RH &40±2^{0}C/75±5%RH, over a period of three months (90 days) [8].

3. RESULTS AND DISCUSSION

Drug - Excipients compatibility studies by FT-IR

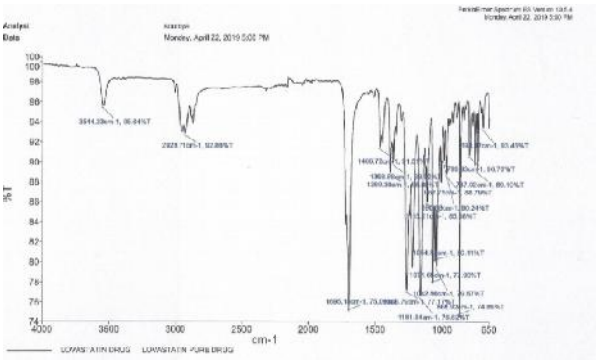

Fig 1: FT-IR spectrum of pure drug Lovastatin

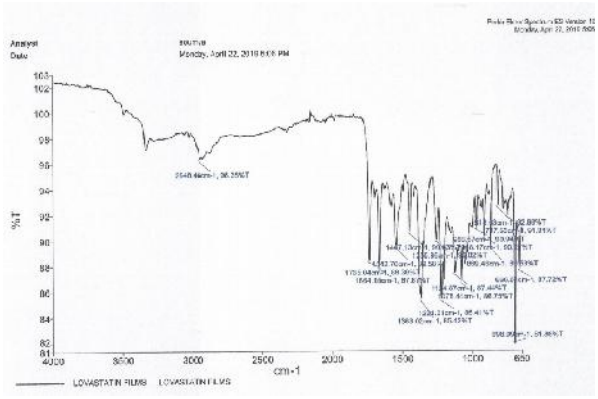

Fig 2: FT-IR spectrum of pure drug Lovastatin with excipients

This proved that drug and excipients were compatible and the study of spectra indicated no chemical reaction.

Table 2: comparative solubility enhancement in solid dispersion

Time (Min)	SD1	SD2	**SD3**	SD4
0	0	0	**0**	0
5	11.85	14.38	**19.63**	20.17
10	17.75	22.53	**36.75**	38.64
15	31.89	36.85	**55.48**	57.27
30	45.64	52.87	**72.63**	72.18
45	62.21	69.53	**85.58**	85.62
60	73.54	85.88	**99.48**	99.52

Discussion: solubility enhancement in solid dispersion is carried out for four formulations among which SD3 has shown better results with 99.48 at 60 minutes.

Table 3: Evaluation parameters of lovastatin oral disintegrating films

Formulation code	**Appearance**	**Thickness (mm)**	**% Weight variation**	**Folding endurance**	**% Assay**	**Disintegration time(sec)**
F0	Smooth and Transparent	**0.234±0.01**	3.5**±0.02**	75±0.76	99.94	102
F1	Smooth and Transparent	**0.234±0.03**	4.2**±0.02**	85±0.74	99.13	19

F2	Smooth and Transparent	**0.271±0.02**	0.9±**0.01**	92±1.2	98.79	24
F3	**Smooth and Transparent**	**0.263±0.01**	2.9±**0.02**	**93**±0.77	**99.93**	**21**
F4	Smooth and Transparent	**0.247±0.02**	3.8±**0.01**	76±1.6	100.17	27
F5	Smooth and Transparent	**0.257±0.02**	4.6±**0.03**	85±0.98	99.48	32
F6	Smooth and Transparent	**0.234±0.03**	5.1±**0.02**	86±1.6	101.07	28
F7	Smooth and Transparent	**0.238±0.02**	2.8±**0.02**	65±1.6	100.29	26
F8	Smooth and Transparent	**0.265±0.01**	3.1±**0.03**	77±1.8	99.37	23
F9	Smooth and Transparent	**0.268±0.01**	3.6±**0.01**	78±1.7	100.53	27

Table 4: *In vitro* drug release data of formulation

Time (Min)	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	**0**	0	0	0	0	0	0
5	3.23±0.01	27.28±0.2	32.31±0.01	**35.11**±0.01	22.48±0.3	25.43±0.01	31.43±0.3	25.13±0.01	23.59±0.2	25.18±0.2
10	5.15±0.02	52.42±0.01	57.83±0.2	**78.41**±0.3	45.39±0.2	48.31±0.3	59.39±0.01	55.82±0.3	52.49±0.3	54.19±0.2
15	7.46±0.02	78.38±0.2	79.41±0.01	**99.52**±0.2	62.59±0.2	71.49±0.01	78.41±0.3	81.39±0.01	80.31±0.2	77.59±0.01
20	8.91±0.01	89.31±0.2	95.38±0.3		79.06±0.01	95.49±0.3	99.54±0.2	99.44±0.2	99.62±0.3	99.19±0.3
25	10.37±0.03	99.4±0.01	99.81±0.01		94.59±0.2	99.93±0.2				
30	13.29±0.01				99.41±0.01					

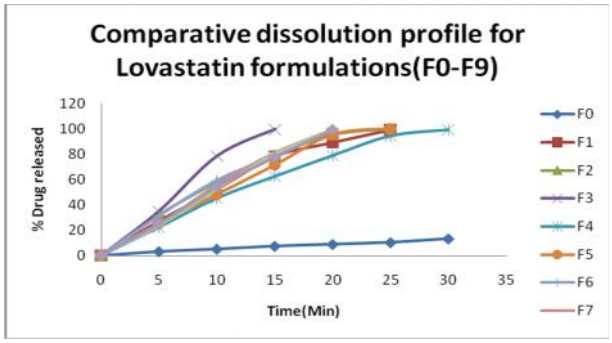

Fig 3: Comparative dissolution profile of lovastatin formulation (F0-F9)

Discussion: Comparative dissolution profile of lovastatin formulation (F0-F9) has been carried out among which F3 formulation has shown drug release 99.52% within 15 minutes.

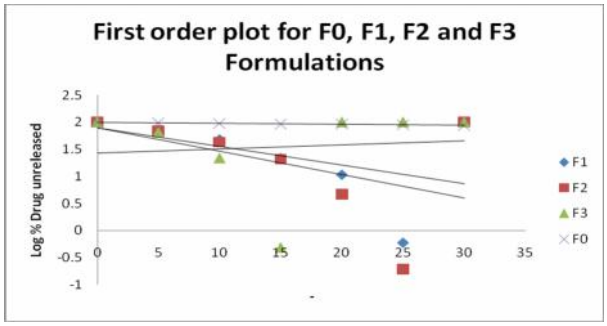

Fig 4: First order plot for F0, F1, F2 and F3 formulations

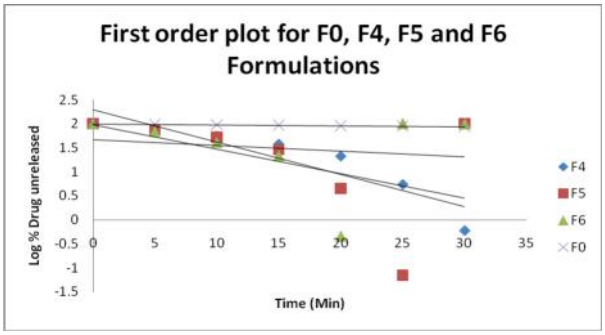

Fig 5: First order plot for F0, F4, F5 and F6 formulations

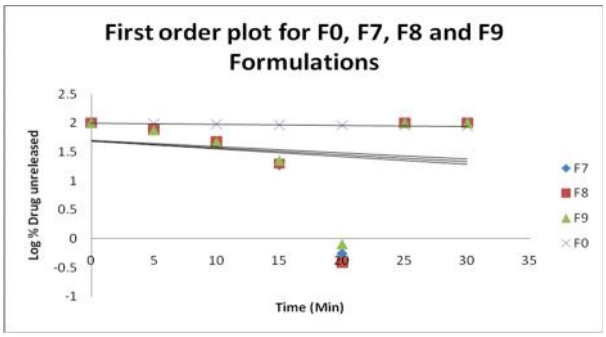

Fig 6: First order plot for F0, F7, F8 and F9 formulations

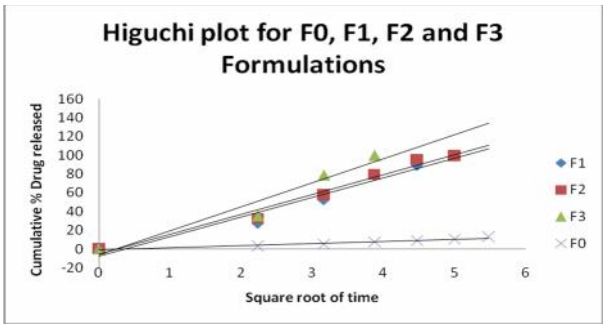

Fig 7: Higuchi plot for F0, F1, F2 and F3 formulations

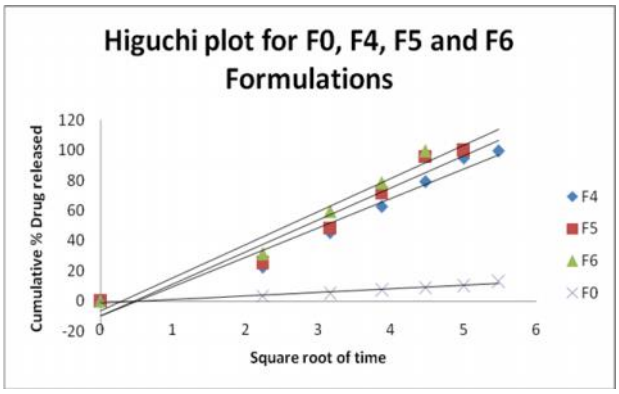

Fig 8: Higuchi plot for F0, F4, F5 and F6 formulations

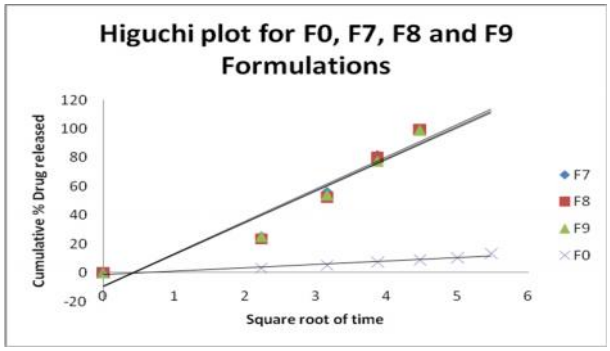

Fig 9: Higuchi plot for F0, F7, F8 and F9 formulations

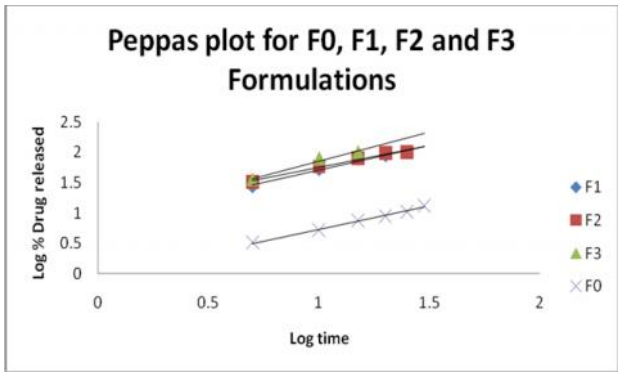

Fig 10: Peppas plot for F0, F1, F2 and F3 formulations

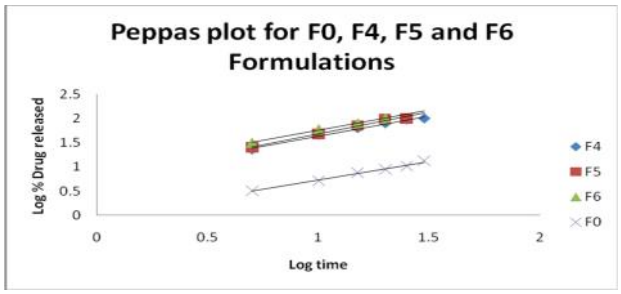

Fig 11: Peppas plot for F0, F4, F5 and F6 formulations

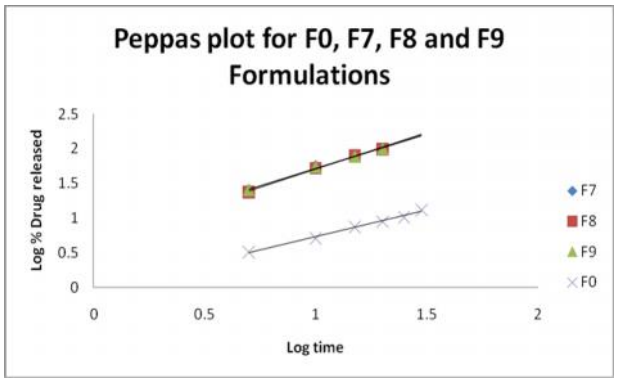

Fig 12: Peppas plot for F0, F7, F8 and F9 formulations

Table 5: R^2 Values for all formulations

Formulation code	Zero order	First order	Higuchi	Peppas
F0	0.993	0.994	0.974	0.996
F1	0.982	0.913	0.981	0.991
F2	0.974	0.916	0.988	0.992
F3	**0.992**	**0.910**	**0.992**	**0.988**
F4	0.988	0.917	0.980	0.995
F5	0.989	0.877	0.971	0.995
F6	0.994	0.868	0.980	0.998
F7	0.997	0.883	0.965	0.996
F8	0.998	0.866	0.958	0.997
F9	0.999	0.878	0.964	0.998

Discussion: The release rate kinetic data for the F3 is shown in table. Drug release data of lovastatin oral disintegrating films follows zero order equation., as the plots showed the linearity r^2 = 0.992 for zero order and r^2 = 0.910 for first order.

Table 6: Results for optimized formulation(F3)

S. No.	Evaluation Parameters	Tablet values
1	Appearance	Smooth and Transparent
2	Thickness (mm)	0.263
3	Weight variation (mg)	3.7
4	Folding endurance	93
5	Disintegration time (Sec)	21
6	Drug content (%)	99.93
7	In-vitro drug release (%) in 15 mins	99.52

Table-7: Comparative dissolution profile for lovastatin 10mg tablet marketed formulation, F3 Formulations

Time(min)	Lovastatin 10mg tablet	F3
0	0	0
5	19.31	35.11
10	31.87	78.41
15	43.12	99.52
20	58.12	-
25	73.29	-
30	85.15	-

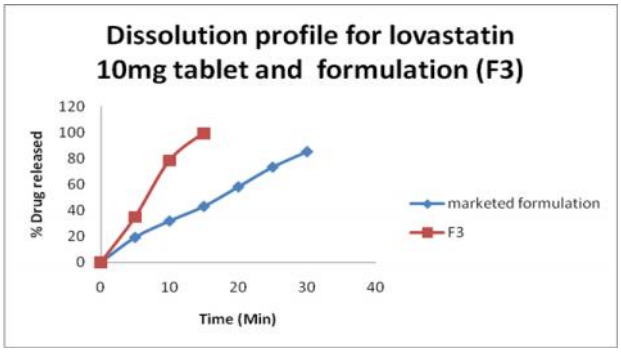

Fig 13: Comparative dissolution profile for Marked formulation and Best formulation F3.

Discussion: Comparative dissolution profile for Marked formulation and Best formulation F3 has been evaluated it has been shown that lovastatin 10 mg tablet drug release was 85.15% in 30 minutes, while F3 formulation shown 99.52% drug release at 15 minutes.

Stability studies best formulation F3:

Selected formulation F3 was packed and stored at 25±2^{0}C / 65±5%RH and 40°C ± 2°C / 75% ± 5% RH or a period of 3 months. Samples were analyzed after storage for 1month, 2month, and 3month and evaluated.

Table 8: Stability studies for optimized formulation F3

Formulation code	Appearance	Thickness (mm)	Weight variation	Folding endurance	% Assay	Disintegration time(sec)	% Drug released	
							25±2^{0}C / 65±5%RH	40±2^{0}C / 75±5% RH
Fisrt day	Smooth and Transparent	0.263	83	93	99.93	21	99.52	99.52
30 days	Smooth and Transparent	0.263	83	93	99.89	22	99.48	99.51

4. CONCLUSION

The developed oral disintegrating films of lovastatin with both improving solubility and taste masking have been achieved by preparing solid dispersions using PVPK30 and a solution of sucralose and ammonium glycerrihizinate. The prepared films has shown desired properties and rapid disintegration time which on administration will result in the rapid therapeutic action and could be used as an alternate to the commercially available tablets resulting in improved patient adherence.

5. ACKNOWLEDGEMENT

The author is thankful to the Deccan School of pharmacy Nampally Aghrapura, Hyderabad, for providing necessary facilities to carry out this work.

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Conflict of Interest: None
Source of Funding: Nil