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Formulation and evaluation of lovastatin porous tablets

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ABSTRACT

This dissertation work was done with an aim to design porous tablets of Lovastatin and evaluation of the tablets for various parameters including in vitro drug release studies. Lovastatin tablets were formulated by using microcrystalline cellulose as filler, camphor and menthol as subliming agents, crospovidone and CCS and sodium starch glycolate as super disintegrant and magnesium stearate as lubricant. The powdered blend were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, friability, thickness, weight variation, hardness, and drug content. The formulation F6 is formulated by using subliming agent and super disintegrant where it can ensure burst release of the drug so that the release cannot be interlinked. The formulation F6 containing 10% of menthol showed disintegration time of less than 1min after drying. Menthol as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release. All other parameters viz: Hardness, Thickness, Weight variation and drug content were also found to be within limits. The disintegration time and drug content of the tablets were found to be satisfactory even after subjecting the tablets to stability studies at 40^{o}C and 75%RH for 1 month and 3 months respectively.

Keywords: Camphor, Menthol, Crospovidone and CCS.

INTRODUCTION

Dosage forms are also referred to as “Drug Delivery Systems” or “Finished Drug Products”. A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms[4]. The tablet is one of the most preferred dosage forms, because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms[5].

Sublimation

Sublimation is the process of transformation directly from the solid phase to the gaseous phase without passing through an intermediate liquid phase. Sublimation is an endothermic phase transition that occurs at temperatures and pressures below a substance's triple point in its phase diagram[9].

At normal pressures, most chemical compounds and elements possess three different states at different temperatures. In these cases, the transition from the solid to the gaseous state requires an intermediate liquid state. Note, however, that the pressure referred to here is the partial pressure of the substance, not the total (e.g., atmospheric) pressure of the entire system. So, all solids that possess an appreciable vapor pressure at a certain temperature usually can sublime in air (e.g., water ice just below 0°C). For some substances, such as carbon and arsenical, sublimation is much easier than evaporation from the melt, because the pressure of their triple point is very high, and it is difficult to obtain them as liquids.

Sublimation requires additional energy and is an endothermic change. The enthalpy of sublimation (also called heat of sublimation) can be calculated as the enthalpy of fusion plus the enthalpy of vaporization. The reverse process of sublimation is deposition. The formation of frostis an example of meteorological deposition.

The key to rapid disintegration for mouth dissolving tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix. Hence to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation[7]. In studies conducted by Heinemann and Rothe, Knitsch et al., and Roser and Blair, inert solid ingredients that displayed high volatility (e.g., ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane were compressed along with other excipients into a tablet. The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.

AIM AND OBJECTIVE

- The rationale of this investigation was to develop immediate release monolithic tablets of Lovastatin using sublimation technique[6]. Immediate release tablets of Lovastatin were prepared by the direct compression using subliming agents like camphor and cross povidone and cross caramellose sodium as super disintegrant. The sublimation technique is mainly used to ensure burst release by forming porous tablet matrix so that it does swell and entrap Lovastatin which results in poor absorption of Lovastatin. Subliming agents are sublimed from the tablets by drying in hot air oven at 60^{o}C for 12 hrs. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, and *in vitro* dissolution.
- To produce a quality tablet, in a validated and GMP-way, it is important that the selected press is capable of :
  - Providing sufficient tablet hardness
  - Preventing cross-contamination
  - High yield
  - Accurate and individual weight control.
- These requirements seem obvious but are not so easily accomplished. So as to avoid the above risks, the present study is undertaken by compressing it into a monolithic tablet using subliming agents and superdisintegrants.
- Subliming agents increases the porosity of the tablets and ensures burst release of the drug[8].

METHODOLOGY

Preparation of calibration curve for lovastatin

Preparation of calibration curve in 0.1n hcl

10 mg lovastatin pure drug was taken into a 10ml standard flask and dissolved in 0.1N HCL. The volume of stock solution was made up to 10 ml with 0.1N HCL. From the above stock solution, 1 ml was transferred into a 10 ml volumetric flask and volume was adjusted to 10 ml that corresponded to 100 µg/ml lovastatin in solution. From that solution different aliquots of 1.0,2,3,4,5 ml were transferred to 10ml volumetric flask, volume was adjusted with 0.1N HCL , which gave a concentration of 10,20,30,40,50 µg/ml of final standard. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 238 nm.

Formulation and development of lovastatin immediate release tablets

Formulation of Lovastatin porous tablets by direct compression method

Porous tablets of Lovastatin were prepared by direct compression method employing camphor and menthol as sublimating agents[2]. The concentrations of the above ingredients were optimized as shown in below table on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release rate enhancing disintegrants and other excipients, except magnesium stearate, in ascending order of their weight. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate was added and mixed for not more than 1 min (to ensure good lubrication.) About 200 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 8 mm flat-surface punches. The hardness of the tablets was adjusted at 4-6 kg/cm^2 using a Monsanto hardness tester.

Compression

The lubricated blend was compressed using following parameters:

Compression parameters

Tooling: 8mm round punch.

Average weight: 200mg.

Table-:1 Composition of Formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Lovastatin	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Camphor	10	--	20	--	20	--	--	--
MCC	127	127	113	113	105	105	105	105
LM	42	42	42	42	42	42	42	42
Menthol	--	10	--	20	--	20	20	20
CCS	8mg	8mg	12mg	12mg	20mg	20mg	--	--
CP	--	--	--	--	--	--	12mg	20mg
Mg.stearate	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Total weight	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg

.

MCC- Micro crystalline cellulose, CCS- Cross caramellose sodium, CP- Cross Povidone , LM- Lactose monohydrate

RESULTS AND DISCUSSIONS

Pre-formulation studies

Description

These tests were performed and the results were illustrated in the following table:

Table no: 2 Table showing the description of Lovastatin (API)

Test	Description
Colour	White Crystalline powder

Result

The results were found as per specifications.

Solubility

These tests were performed and the results are illustrated in the table.

Table no: 3 Table showing the Solubility of Lovastatin (API) in various solvents.

Solvents	Solubility

Water	In soluble
pH6.8 Phosphate buffer	Soluble
Methanol	Soluble
Chloroform	Soluble

Melting Point

This test is performed and the result was illustrated in the following table.

Table no: 4 Table showing the melting point of API's

Material	Melting Point
Lovastatin	**174** ^{0}

Result

The Result was found to be within limit.

Standard graphs for lovastatin

Table No: 5 Standard graphs for Lovastatin

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
10	0.091
20	0.201
30	0.296
40	0.399
50	0.493
60	0.633

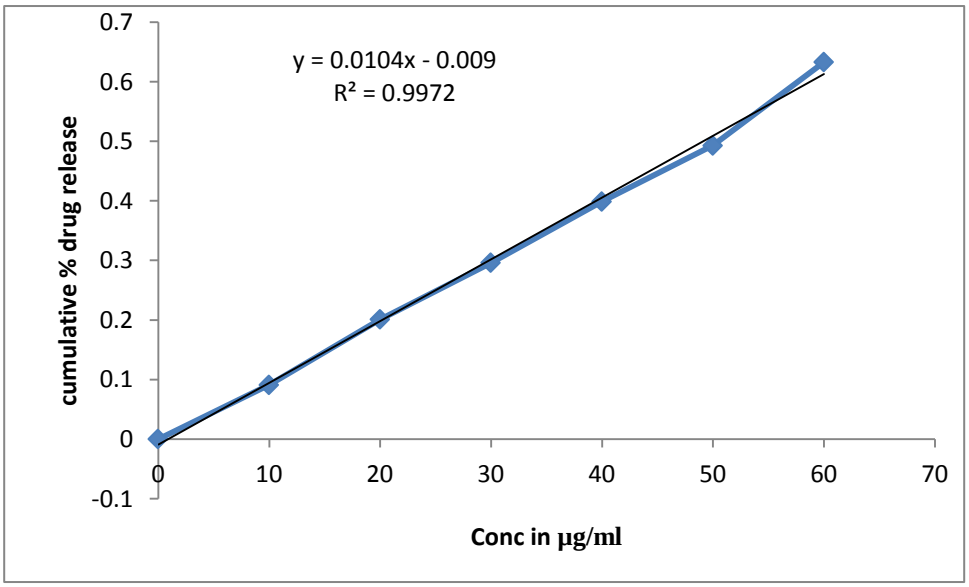

Figure No: 1 Standard graph of Lovastatin

Drug excipient compatibility studies

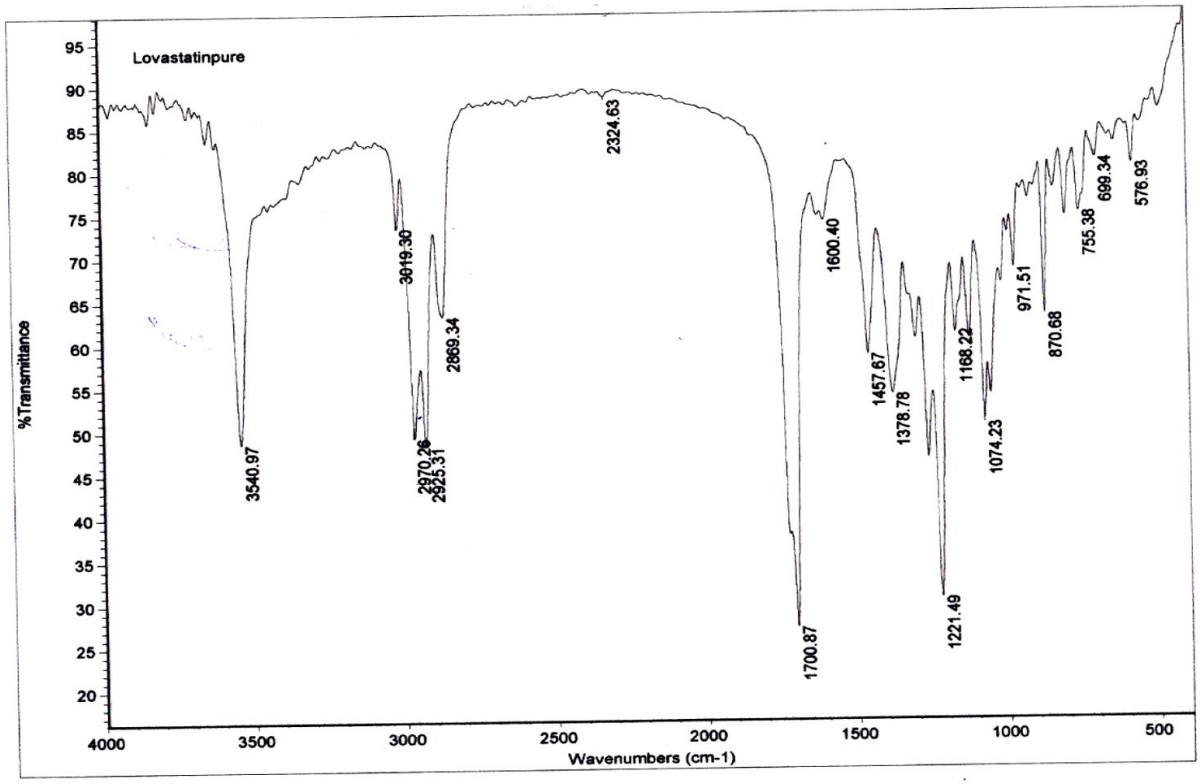

Fig no: 2 FTIR Spectra of Lovastatin pure drug

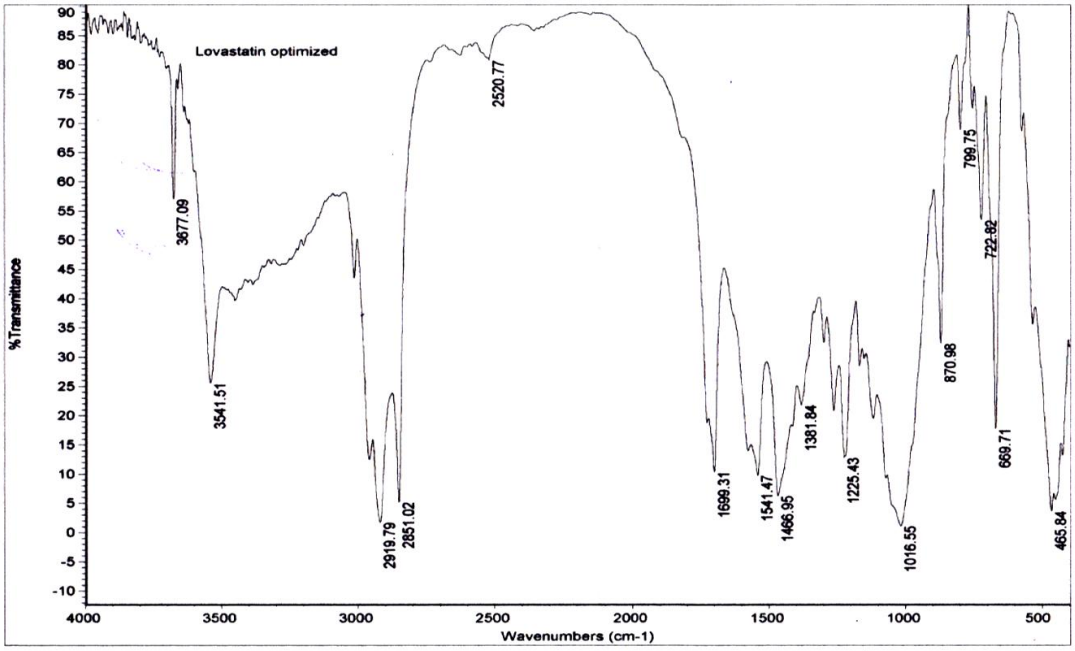

Fig no: 3 FTIR Spectra of Lovastatin optimized formulation

Preformulation studies

Table no-6 Pre-compression parameters for formulation batches

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Compressibility index (%)	Hausner's ratio	Angle of repose
F1	0.721±0.045	0.87± 0.01	17.126±0.6	1.206±0.06	26.62±0.21
F2	0.710±0.043	0.873±0.04	19.714±0.7	1.251±0.04	27.46±0.11
F3	0.41±0.045	0.483±0.5	15.113±0.8	1.178±0.08	28.32±0.31
F4	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06±0.31
F5	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58±0.15
F6	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44±0.11
F7	0.41±0.048	0.483±0.49	15.113±0.9	1.178±0.07	28.32±0.33
F8	0.710±0.032	0.873±0.036	19.714±0.6	1.26±0.05	27.46±0.15

Result

All the formulations were evaluated for bulk density, tapped density, % compressibility, hausner's ratio and angle of repose. The results of % compressibility, hausner's ratio and angle of repose were found to be between 12- 19, 1.11-1.26 and below 30 respectively. These results show that the formulations have very good flow properties.

Evaluation parameters of tablets

The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content[3]. The evaluated parameters were within acceptable range for all the formulations.

Table no: 7 Evaluation parameters of formulations of porous tablets before drying

Formulation code	Thickness (mm)	Hardness (KP)	Friability (%)	Average weight variation (mg)	Drug content (%)	Disintegration Time ± S.D. (min)
F1	3.29	5.0	0.54	202.1	99.13±0.53	4.2
F2	3.05	3.5	0.45	205.6	96.27±0.64	3.3
F3	3.38	3.5	0.35	201.8	97.63±0.55	4.5
F4	3.50	3.5	0.41	201.9	98.36±0.58	3.4
F5	3.43	4.0	0.42	205.4	98.33±0.62	4.3
F6	3.27	3.5	0.31	203.6	98.64±0.84	2.9
F7	3.38	4.1	0.26	2016	99.2	7 mins 10 secs
F8	3.36	4.1	0.23	202.0	98.6	7 mins 5 secs

Observations

From the above Table, it is observed that the thickness, hardness, friability, weight variation and content uniformity of the porous tablets before drying were in the passable range. The F1, F3, F5 formulations containing camphor as the subliming agent didn't show much effect on the disintegration time. The disintegration of F6 formulation was found to be of 2'.9"mins which is satisfactory. The disintegration of F7 & F8 was found to be more than 7 mins.

Table no.8 Evaluation parameters for formulations of porous tablets after drying

Formulation code	Thickness ± S.D. (mm)	Hardness ± S.D. (Kp)	Average weight variation (mg)	Drug content (%)	Disintegration Time ± S.D.
F1	3.29	3.7	201.3	99.26	1min 10sec
F2	3.05	3.8	203.2	96.38	43sec
F3	3.38	4.1	200.9	97.03	1min
F4	3.50	4.1	200.00	98.26	36sec
F5	3.43	4.2	203.4	98.29	57sec
F6	3.27	4.8	201.8	98.60	20sec
F7	3.38	4.3	200.9	99.36	5 mins
F8	3.36	4.3	200.3	99.56	5 mins 34 secs

Observations

From the above Table, it is observed that the thickness, hardness, weight variation and drug content of the porous tablets were in the passable range. The F1, F3, F5 formulations containing camphor as the subliming agent didn't show much effect on the Disintegration time where as the optimized formulation F6 10% camphor and CCS 10 % showed better results The Disintegration time of F6 formulation after drying was found to be of 20" sec (20sec) which is satisfactory[10].F7 and F8 trails were with crospovidone as disintegrant but the disintegration time was more than 5 mins.

RESULTS OF IN-VITRO RELEASE PROFILE

Table.9 In-Vitro Release Profile of Lovastatin from formulations F1-F8

Time	F1	F2	F3	F4	F5	F6	F7	F8
10 mins	32.56	38.26	42.52	48.96	50.38	58.92	12.56	18.26
15 mins	46.28	48.03	50.36	56.48	61.94	69.52	26.28	28.03
20 mins	55.23	60.58	62.85	68.92	70.56	77.89	35.23	40.58
30 mins	60.65	65.92	70.59	74.56	77.89	82.56	40.65	50.92
45 mins	72.36	74.82	75.62	80.82	83.56	98.45	52.36	54.82
60 mins	80.56	80.49	82.51	85.45	88.95	100.59	60.56	60.49

Observations

The in-vitro drug release profiles of Lovastatin from all the formulations F1 to F8 are shown in the above Tables. From the results, it is observed that the dissolution profiles of the formulated products (F1, F2, F3, F4 & F5) didn't meet the proper dissolution profile of Lovastatin i.e 85% of drug release in 45mins. The formulations F6 showed 98.45% of drug release within 45mins[1].The formulationsF7, F8 showed 60% in 60 mins after change in disintegrant i.e Crospovidone even with increase in concentration of the crospovidone.

STABILITY STUDIES

Lovastatin tablets of F6 formulation were packed in HDPE (High density polyethylene) container with child resistant caps (CRC) and induction sealed. These bottles were charged for stability study at 40^0C &75% RH.

After one month

Tableno-:10 Physical evaluations of Tablets for stability studies of Optimized formulation:

Parameter	Initial	40^0C / 75%RH

Colour	White	White
Surface	Smooth	Smooth
Disintegration	20sec	22sec
Assay	98.60	98.0

Observation

The Lovastatin porous tablets were subjected to stability studies at 40°C and 75% RH for 1 month and from the above results, it was found that there is no significant effect on the tablets.

After Three months

Table no-:11 Physical evaluations of Tablets for stability studies of optimized formulations:

Parameter	Initial	40°C / 75%RH
Colour	White	White
Surface	Smooth	Smooth
Disintegration	20sec	25sec
Assay	98.60	96.70

Observation

The Lovastatin porous tablets were subjected to stability studies at 40°C and 75% RH for 3 months and from the above results, it was found that there is no effect on the tablets and was found to be within the limits according to ICH guidelines.

CONCLUSION

Preformulation studies of powder blend had shown that the blends had passable parameters like Angle of Repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. it is observed that based on compressibility index and it was concluded that the blend showed passable flow characteristics. The formulation F6 is formulated by using subliming agent and super disintegrant where it can ensure burst release of the drug so that the release cannot be interlinked. The formulation F6 containing 10% of menthol showed disintegration time of less than 1min after drying. Menthol as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release.

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