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STABILITY ENHANCEMENT OF LOVASTATIN BY LIQUISOLID COMPACTION TECHNIQUE

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ABSTRACT

The present study is mainly focused on the formulation and solubility enhancement of lovastatin by using liquisolid compaction technique. The lovastatin blend is taken and is dissolved in a non volatile solvent like PEG 400 to produce the drug solution. This is mixed with the carrier material like MCC and the coating materials Aerosil in a rapid mixer granulator. Finally it is mixed with a suitable quantity of superdisintegrant and with the remaining additives like magnesium stearate and lactose in a rapid mixer granulator and then sieved and dried and compacted.

Key words: lovastatin, liquisolid compaction technique, Stability

INTRODUCTION:

Tablets are a solid dosage form containing ingredients with/without suitable diluents and prepared by either by moulding or compression technique. Tablets are most widely used solid dosage forms of medicament. Because of their advantages they are most widely used day by day. Although it is, the formulation of the poorly soluble drugs for the oral delivery presents challenge to the formulation scientists. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved into gastric fluids. For hydrophobic drugs the dissolution acts as a rate controlling step which determines the rate and extent of absorption. Thus one of the major challenges in the drug development today is poor solubility.

It is estimated that 40% of the newly developed drugs show poor solubility or insoluble in water and 50% of the orally administered drugs suffer from the formulation problems related to their low solubility and high lipophilicity. Due to their poor solubility the bioavailability of the drug will also gets decreased. So to prevent this problem and to enhance the solubility the drugs are converted to nano, microparticles by decrease in their particle size. The method of increasing the dissolution rate is adsorption of the drug onto a high surface area carrier. In this technique, the drug is dissolved in an organic solvent followed by soaking of the solution by a high surface area carrier such as silica.

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Here the agglomeration of the drug to the carrier is prevented and due to the presence of residual solvents the usage of toxic solvents is also prevented.

Approaches to enhance the dissolution of the drugs:

The following are the few approaches to enhance the dissolution of the drugs.

Ph adjustment, co solvency, particle size distribution, microemulsions, micelle solubilisation, complexation, superficial fluid process, solid dispersions, hydrotrophy, dried nano suspensions, spherical agglomeration, sono crystallization, cryogenic techniques.

Liquisolid compaction technique:

The solubility is defined as the maximum quantity of solute that can be dissolved in a certain quantity of the solvent or quantity of solution at a specified temperature. The poorly soluble drugs belong to the BCS class II and class IV. The technique of liquisolid preparation is used to formulate the drug solution into the solid dosage forms. Drug solution is generally prepared by dissolving the drug in a non-volatile water miscible solvent. Liquid solid systems refer to the formulations formed by the conversion of liquid drugs, drug suspensions or drug solution in non volatile solvents into dry, non adherent, freely flowing and compressible powder mixture by blending the suspension or solution with the selected carrier and coating materials. The non-volatile solvent with the drug dissolved maybe existing in solution or else suspension is known as “liquid medicament” ‘the liquid medicament is converted into freely flowing, non adhere, dry and readily compressible powder by adding different compressible carriers like: starch, cellulose and lactose etc....and by adding coating materials like: colloidal silicon dioxide, talc etc...

Since the drug is present in the liquid medicament as solubilised or molecular dispersed state the dissolution is enhanced due to the increased surface area as well as wetting area.

Classification of liquid solid systems

The liquid solid systems are classified into two categories:

(a) based on the type of liquid medication contained therein-

(i) powdered drug solutions
(ii) powdered drug suspensions
(iii) powdered liquid drugs

(b) Based on the formulation technique used, the liquisolid systems may be classified into two categories:

(i) liquisolid micro systems
(ii) liquisolid compacts

liquisolid Microsystems: The term liquisolid Microsystems refer to the capsules prepared by combining the drug with a coating material ad with a carrier together with the inclusion f an additive example: PVP in the liquid medication wherein the resulting size may be as much as 5 times that of liquid solid Liquisolid compact systems: the powder can retain only limited amount of liquid while maintaining acceptable flow and compression properties. To calculate the required amount of powder excipients a mathematical approach has been developed by the spireas. This approach is based on the flowable (Φ) and compressible potential (Ψ).

The Ψ number of a powder is defined as the maximum amount of liquid the power can retain inside the bulk while maintaining the acceptable compatibility resulting in compacts of sufficient hardness with no liquid leaking out during compression.

This is also called s "pacticity". The pacticity describes about the maximum crushing strength of a 1gram of a tablet compacted at sufficiently high compression forces. The Φ value represents the maximum amount of given non volatile liquid that can be retained in the bulk while maintaining an acceptable flowability. The weight ratio of the liquid formulation and the carrier material is termed as the "liquid load factor" and is responsible for the flow and compressible properties.

The liquid low factor (Lf) is represented as:

$Lf = W/Q$

The ratio between the weights of the carrier (Q) and the coating material (q) is represented as "R" and is given as:

$R = Q/q$

The liquid load factor with acceptable flowability is determined by

$Lf = \Phi + \Phi (1/R)$ where Φ represents the values of carrier and coating material respectively.

Mechanisms of enhanced drug release from liquisolid systems

The suggested mechanisms include increased surface area of the drug for release, increased aqueous solubility of the drug, improved wettability of the drug particles.

The formation of complex between the drug and excipient changes in the crystallinity of the drug could be found out by using DSC and XRD measurements.

(1) Increased drug surface area: if the drug with in the liquid solid system is completely dissolved in the liquid vehicle, the surface area of the drug available for release is much greater than tht of the drug present in directly compressed tablets.
(2) Increased aqueous solubility of the drug: the solubility of the drug can be increased with the liquisolid systems. The small amount of the vehicle present in the drug is not sufficient to increase the overall solubility of the drug. But however if the liquid vehicle acts as the solvent, then the amount of liquid vehicle diffusing out of the single liquid solid particle together with the drug molecule will enhance the solubility of the drug.
(3) Improved wetting properties: the liquid vehicle acts as a surface active agent and wetting properties are increased. Many poorly soluble drugs have been formulated as liquisolid systems showing enhanced drug release. Different liquid vehicles, carrier and coating materials are used to formulate these drug delivery systems.

MATERIALS AND METHODS:

Materials:

The following materials are used for the preparation of the lovastatin tablets

Lovastatin was gifted from the Fourt's India pharmaceuticals, PEG-400 is gifted from SD Fine chemicals limited, Microcrystalline cellulose was gifted from oxford chemicals limited, Colloidal silicon dioxide, Sodium starch glycollate, Lactose was gifted from ISP technologies Inc., Magnesium stearate was gifted from Nikitha pharmaceuticals.

Methods:

Solubility studies: the solubility of lovastatin was carried out in different solvents like distilled water, PEG 400, Tween 80, glycerine, propylene glycol. Saturated solutions were prepared by adding an excess drug to the vehicles and shaking on the shaker for 5 minutes at 37°C under constant vibration. Filtered samples (1ml) were diluted to 10ml with distilled water an lovastatin was determined spectrophotometrically at 243nm. The average values of the three trials were taken.

Preparation of Lovastatin tablet:

Lovastatin was initially dissolved in the non volatile solvent, PEG 400 as liquid vehicles to produce the drug solution. Microcrystalline cellulose is added to the drug solution by continuous mixing in a rapid mixer granulator. To the above blend the coating material Àerosil is added to get a fine and absorptive particle. Add required amount of disintergrant like Sodium Starch Glycollate and mix will. The remaining materials, like Lubricant, Mg. Stearate and diluents like lactose are added and mixed for a period of 10 to 20 minutes in a rapid mixer granulator. The mixture is passed through sieve # 60 and the granules obtained are dried at 60ºC for one hour. The resultant granules are compressed by tablet press.

Table 1: Formulae of Lovastatin tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug + liquid	240	240	240	240	240	240	240	240	10
MCC	406	406	406	406	513	513	513	513	55
Aerosil	203	203	203	203	171	171	171	171	5
SSG	60	100	40	-	66	-	44	110	15
Magnesium stearate	15	15	15	15	22	22	22	22	5
Lactose	76	36	96	136	88	154	110	44	20
Total Weight	1000	1000	1000	1000	1100	1100	1100	1100	110

PREFORMULATION STUDIES

Standard graph of lovastatin:

The stock solution was freshly prepared by dissolving 10mg Lovastatin in distilled water in a 10 ml volumetric flask (Stock 1) for getting 1 mg/ml strength. 10 ml of the solution was diluted to 100 ml with distilled water (Stock II) to obtain 100µg/ml. From the stock II 10 ml is diluted to 100 ml (stock III) to obtain 10µg/ml. The aliquots of 0.5 to 2.5 ml of stock III were transferred to a series of 10 ml volumetric flask and diluted with distilled water, mix thoroughly and keep aside for 5 minute and measure the absorbance at 243 nm against the blank reagent.

Angle of repose:

The angle of repose of powder mix for direct compression was determined by the funnel method. The powder was taken in a funnel. The height of the funnel was adjusted to 1 cm. The powder was allowed to flow through funnel freely onto the surface until the apex of the pile touches the tip of the funnel. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Angle of repose, **θ = Tan-1h/r**

Where, θ = angle of repose, h = height of the cone

r = radius of the cone base

Angle of repose (in degrees)	Type of flow
< 25	Excellent
25 – 30	Good
30 – 40	Satisfactory
> 40	Very poor

Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 seconds interval. The tapping was continued until no further change in volume was noted.

Bulk density is calculated by using formula

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of the powder}}$$

Tapped density is calculated by using formula

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the powder}}$$

Carr's Index:

The Carr's index of the powder mix was determined by us ing formula:

Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where, LBD = weight of the powder/volume of the packin g

TBD = weight of the powder/tapped volume of the packin g

Carr's index (%)	Type of flow
5 – 12	Excellent
12 – 18	Good
18 – 23	Satisfactory
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

Hausner's Ratio:

From the LBD & TBD data Hausner's ratio was calculated using followingequation.

Hausners ratio =LBD/TBD

Tapped Density:

It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2-second intervals. The tapping was continued until no further change in volume was noted.

TBD =Weight of the powder / volume of the tapped packing.

POST EVALUATION OF TABLETS

All the formulated lovastatin tablets were subjected to the following quality control tests:

Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Hardness:

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10tablets from each formulation was determined by Monsanto hardness tester.

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were de dusted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula

% Friability = [(W1-W2)100]/W1

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

Disintegration test:

The disintegration test was performed using disintegration apparatus. One tablet was placed in each of the six tubes placed in a beaker containing 1000ml of the purified water maintained at 37±2ºC and the apparatus was operated. The time taken for the tablets to disintegrate was noted.

Uniformity of drug content:

Ten tablets were weighed and powdered, 10mg of equivalent of lovastatin was weighed and dissolved in suitable quantity of solvent, the solution was filtered, diluted and the drug cotent was analysed using UV spectrophotometer at 243nm.

Thickness:

Thickness of tablets was important for uniformity of tablet size. Thickness was measured using vernier calipers on three randomly selected samples.

***In vitro* dissolution study of lovastatin tablets:**

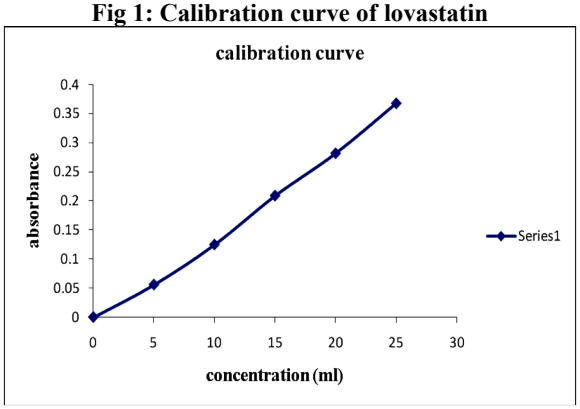
The equipment used is apparatus II, paddle s stirring element. The tablet was allowed to sink up to the bottom of the flask. The temperature maintained was found to be 37±5ºC constantly. The motor was adjusted to a speed constantly about 75rpm and 5ml of the samples were withdrawn at time interval of 5, 10, 15, 20, 25, 30, 40, 50, 60minutes. The volume of the dissolution fluid is adjusted to 900ml by replacing the 5ml of dissolution medium after each sampling. Samples were suitably analysed at 243nm using double beam UV and visible spectrophotometer against blank reagent.

RESULTS AND DISCUSSION

Calibration curve at 243nm

S.No	Quantity (ml)	Absorbance (nm)
1	0	0
2	5	0.048
3	10	0.125
4	15	0.209
5	20	0.282
6	25	0.368

Fig 1: Calibration curve of lovastatin



(1) Pre compression characteristics:

Table 2: Pre formulations studies

Formulation	Angle of repose	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's index	Hausner ratio
F1	25.4	0.44	0.51	15.28	1.18
F2	24.86	0.43	0.5	14.48	1.17
F3	22.9	0.45	0.53	14.04	1.16
F4	22.1	0.42	0.52	14.04	1.16
F5	24.38	0.47	0.54	12.59	1.14
F6	23.14	0.48	0.56	13.3	1.15
F7	20.35	0.46	0.52	12.22	1.14
F8	22.1	0.45	0.51	11.39	1.13
F9	26.1	0.45	0.52	15.4	1.15

The lovastatin melting point is found to be 174.6°C which complies with the I.P standards. The solubility of lovastatin revealed that it is highly soluble in PEG, slightly soluble in propylene glycol, poorly soluble in distilled water. Thus among the solvents used the PEG is selected as the better choice of solvent.

Evaluation of lovastatin compacts:

The lovastatin compacts were evaluated for drug polymer interaction, chemical reaction between the drug and polymer material using **FTIR**. The results obtained indicated no difference between the IR patterns of physical mixtures of lovastatin and polymer.

Flow properties: For the above mentioned formulations the Hauser's ratio is ≤1.18 and angle of repose is ≤25.40. The obtained values indicate fairly good flowability of granules.

(2) Post compression characteristics:

Table 2: Post compression characteristics of Lovastatin tablets

Formulation	Weight (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Disintegration (min)	Friability (gm)
F1	998	4.5	15.5	14	0.35
F2	1003	4.6	15.6	14.3	0.5
F3	1005	4.7	15.6	15	0.6
F4	997	5	15.7	13.55	0.4
F5	1107	5	15.7	15	0.5
F6	1101	4.8	15.6	14	0.5
F7	1097	4.8	15.8	14.1	0.5
F8	1095	4.9	15.4	15.15	0.4
F9	1106	4.5	10.5	16	0.4

For the above mentioned formulations the hardness is between 15.4 – 15.6kg/cm^2 and the friability is between 0.35 – 0.7%. The hardness and friability values indicate for a good mechanical strength.

The disintegration time of the tablets is between 14 – 15min which complies with the specifications as mentioned in the monographs.

***In vitro* dissolution studies:**

Table 4: *In vitro* dissolution studies of Lovastatin tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	14.14	27.15	10.11	9.23	53.64	31.67	40.15	96.56	2.56
10	22.27	31.67	18.43	15.33	76.54	39.59	50.34	101.33	6.68
15	30.83	41.29	27.66	24.77	85.45	28.07	59.95		10.23
20	37.96	58.45	35.45	32.41	98.91	54.3	66.17		15.67
25	44.53	71.56	40.45	39.34	101.24	61.65	74.09		21.34
30	58.89	83.56	51.85	46.35		67.3	78.62		30.89
40	74.89	98.62	67.84	55.56		70.13	85.97		39.78
50	84.56		76.84	64.34		78.53	92.19		51.83
60	97.65		84.44	72.67		86.55	98.98		63.48

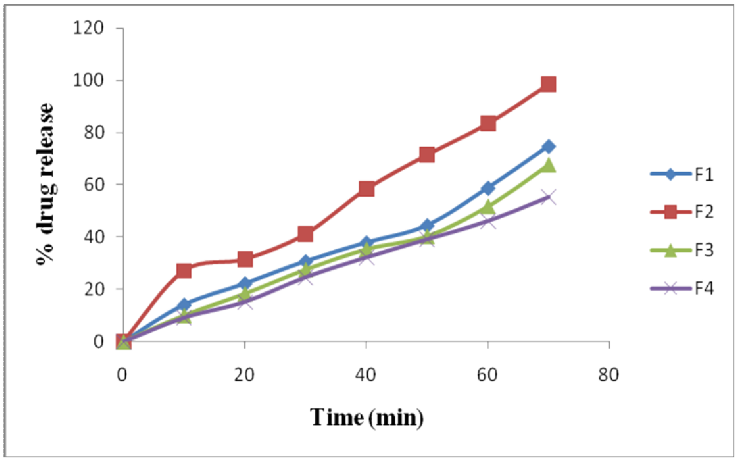


Fig 2: Cumulative drug release from F1, F2, F3, F4

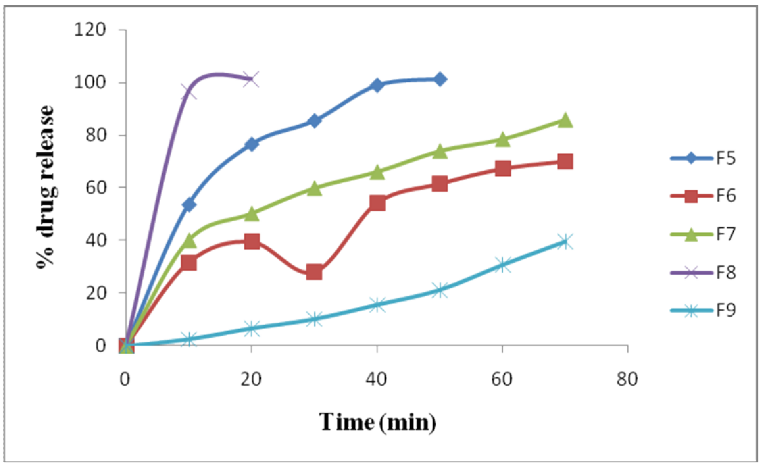


Fig 3: Cumulative drug release from F5, F6, F7, F8, F9

The drug release from the conventional tablet is very poor. Only 15.6% and 39.78% of the drug was released from the dissolution media in 20 minutes respectively. The dissolution of lovastatin by using various dissolution enhancing agents were studied in a different carrier: coating material ratio. Among them F1-F4 formulations contain carrier: coating material ratio as 1: 2. The concentration of superdisintegrant used varied from each formulation accordingly. F2 formulation contains 10% of superdisintegrant and showed 98.62% drug release. F5 – F8 formulations contain carrier: coating material ratio as 1: 3. Among this F8 formulation contain 10% of superdisintegrant and showed 101.33% drug release in 10minutes.

SUMMARY AND CONCLUSION

In the present study lovastatin tablets were prepared with different ratios of carrier and coating material. Microcrystalline cellulose was used as the carrier material and Aerosil is used as the coating material. All the formulations contain sodium starch glycollate as the superdisintegrant except F4 and F6. The carrier: coating material ratios from F1 - F4 formulations are 1:2 and from F5- F8 they were in the ratio of 1:3. The FTIR studies indicated no interaction between the drug and the polymers.

Among all the formulations F2 and F8 are having higher concentration of superdisintegrant and F8 showed maximum drug release of 101.33% in 10minutes with dose dumping and F2 exhibits poor drug release profile . So because of this reason F2 and F8 are not considered as the best formulations.

F5 contains lesser concentration of superdisintegrant (8%) when compared to both F2 and F8 and showed maximum drug release of 101.24 in 25 minutes without any problems. so from the above theory it is concluded that liquisolid compact technique can be used for enhancing the dissolution rate of lovastatin tablets and the method can be used for the manufacturing of tablets.

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