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RESEARCH ARTICLE

Dissolution and Stability Enhancement of Poorly Water Soluble Drug – Lovastatin by Preparing Solid Dispersions

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ABSTRACT

Solid Dispersions greatly enhance the surface area and hence the dissolution rate and the bioavailability of poorly water-soluble drugs are raised. Thus solid dispersions of Lovastatin have been formulated to improve its solubility and dissolution characteristics, reduce dosing frequency and to improve its stability. METHODS: Lovastatin solid dispersions were prepared by solvent evaporation method. The prepared solid dispersions were characterized by Fourier transform infrared (FT-IR) spectroscopy and evaluated for various parameters like drug content, solubility and dissolution studies and different physical properties. RESULTS: FTIR of the solid dispersion showed that the peaks of Lovastatin and polymers were distinguishable and hence there was no chemical interaction between drug and polymer after formation of solid dispersions. The data indicated that solubility increased in all cases. Dissolution data of all solid dispersions also indicated increase in dissolution as compared to pure drug and increase was due to wetting phenomenon of superdisintegrants used for preparation of solid dispersions. CONCLUSIONS: The solvent evaporation method was found to be a promising method for formulating uniform and stable lovastatin solid dispersions with enhanced surface area and dissolution rate. The bioavailability also increased due to increased wettability of the solid dispersions.

INTRODUCTION

Greater understanding of dissolution and absorption behavior of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products. Although salt formation, particle size reduction etc. have commonly been used to increase the dissolution rate of drug, there are practical limitations with these techniques. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such approach that shows significantly enhanced absorption of such drugs is to formulate solid dispersion[1]. Such formulations greatly enhance the surface area and hence the dissolution rate and the bioavailability of poorly water-soluble drugs are raised.

DISPERSION OF DRUG WITHIN AN INERT CARRIER IN SOLID STATE IS SOLID DISPERSION SYSTEM:[2]

SOLID DISPERSION TECHNOLOGY:

Solid dispersion technology can be used to improve the *in- vitro* and *in- vivo* dissolution properties of slightly water soluble drugs and to control their dissolution rate[3]. Solid dispersion is a product formed by converting a fluid drug carrier combination into solid state[4]. The mechanism suggested for enhanced solubility and rapid dissolution of dispersion is when the dispersion is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles. For conventional capsules and tablets, the dissolution rate is limited by size of primary particles formed after the disintegration of dosage form. In this case an average particle size of 5µm is usually the lower limit, although higher particle size is preferred for ease of handling, formulation and manufacturing. On the other hand if a solid dispersion is used, a portion of drug dissolves immediately to saturate the gastrointestinal fluid and excess drug precipitates out as colloidal particles or oily globules of submicron size. Because of such early promises in bioavailability enhancement of poorly water soluble drugs, solid dispersion has become one of the most active areas of research in pharmaceutical field[3,5,6].

METHODS OF PREPARATION OF SOLID DISPERSION:[7, 8]

A) MELTING (FUSION) METHOD:

In this method physical mixture of drug and carrier is heated directly until it melts. The molten mixture is then cooled and solidified rapidly in an ice bath. The resulting solid mass is then crushed, pulverized and sieved. The basic reason for increase in solubility is that as the melt is rapidly quenched there is super saturation of the drug where the drug molecules are arrested in solvent matrix by instantaneous solidification, usually rapid solidification is achieved by cooling on stainless-steel plates as it favors rapid heat loss.

B) SOLVENT METHOD:

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In this method both the guest molecule and the carrier are dissolved in common organic solvent followed by total removal of solvent to constant weight. Temperature for solvent evaporation is usually in range of 23-65ºC. The solvent can also be removed by freeze drying or by spray drying.

CHARACTERIZATION OF SOLID DISPERSIONS:[4,8,9,10]

Numbers of methods are available viz. dissolution testing, thermo analytical methods, calorimetric analysis, X-ray diffraction, spectroscopic methods and microscopic methods.

PHARMACEUTICAL APPLICATIONS OF SOLID DISPERSIONS:[11,12,13]

Solid dispersions are used to increase the dissolution and absorption of poorly water soluble drugs, to stabilize unstable drugs, to formulate sustained release dosage forms, to reduce side effects, to convert liquid compounds into formulations such as powders, capsules or tablets.

OBJECTIVES:

Lovastatin is a hypolipedimic agent and is insoluble in water as a result, its oral bioavailability is just less than 5% .This necessitates the administration of unnecessarily larger dose of drug. In addition to this the drug has a half-life of 1.1-1.7 hours which requires frequent administration of drug[14]. Thus attempts have been made to formulate solid dispersions.

1. To improve solubility and dissolution characteristics of Lovastatin, in order to enhance its oral bioavailability by developing solid dispersions using water soluble carriers.

2. To reduce dose, dosing frequency and dose related side effects by developing sustained release tablets in order to improve patient compliance.

3. To improve the stability of lovastatin in stomach by enteric coating of the tablets.

MATERIALS AND METHODS:

MATERIALS:

The chemicals required were Lovastatin (Reddy's Laboratories Ltd. Hyderabad), Hydroxypropyl - methylcellulose (Rexer Pharma Pvt. Ltd. Hyderabad), Crospovidone (Rexer Pharma Pvt. Ltd. Hyderabad), Croscaremellose sodium (Rexer Pharma Pvt. Ltd Hyderabad), Sodium starch glycolate (Rexer Pharma Pvt. Ltd. Hyderabad), Hydroxypropylmethylcellulosepthalate (Rexer Pharma Pvt. Ltd Hyderabad).

The instruments required were FTIR Spectrophotometer (Model - 8400S, Shimadzu Corporation, Koyto, Japan), Differential Scanning Calorimeter (METTLER DSC 30S, Mettler Toledo India Pvt. Ltd., Swizerland), Double Beam UV Spectrophotometer (Model No. UV 2401 PC, Shimadzu Corporation, Koyto, Japan), Digital pH Meter (Model No.335, Systronics, Ahamdabad), Tablet Compression Machine (Type – CMD3 – 16, Cadmach Machinery Pvt. Ltd., Ahamadabad), Tablet Tester (Model No. C – WWTDH 500N, Campbell Electronics, Mumbai), Dissolution test Apparatus (Model No. DA-3, Veego Scientific Devices, Mumbai), Tap Density Tester (Model No. ETD-1020, Electrolab Pvt. Ltd, Goregaon (E), Mumbai), Electronic Weighing balance (Model No. AW-220 and BX - 620S, Shimadzu Corporation, Kyoto, Japan), Heating Humidity chamber (SECOR India, Delhi,India).

METHODS:

1. FT-IR SPECTRUM OF LOVASTATIN:[15] FT-IR spectrum of lovastatin was taken using KBr pellet, between 4000 cm^{-1} to 500 cm^{-1}.

2. STANDARD CALIBRATION CURVE OF LOVASTATIN: In simulated gastric fluid (SGF) (pH 1.2, without pepsin)[16] and, In Simulated Intestinal Fluid (SIF) (pH 6.8 , without pancreatin)[17] and, In Acetonitrile. The absorbances of the various dilutions of Lovastatin were measured at 238 nm using double beam UV visible spectrophotometer. The graph of absorbance versus concentration was plotted.

Sr. No	Composition	Ratio (w/w)
1	Lovastatin : Sodium starch glycolate (SSG) (S1)	1:2
2	Lovastatin : SSG(S2)	1:4
3	Lovastatin : Croscarmelose Sodium (CCS) (S3)	1:2
4	Lovastatin : CCS (S4)	1:4
5	Lovastatin : Crospovidone (CRP) (S5)	1:2
6	Lovastatin : CRP (S6)	1:4
7	Lovastatin : SSG : CCS (S7)	1:2:2
8	Lovastatin : SSG : CRP (S8)	1:2:2
9	Lovastatin : CCS : CRP (S9)	1:2:2

Table No.1: Composition of solid dispersions

3. PREPARATION OF SOLID DISPERSIONS:[7, 8]

Lovastatin and the superdisintegrants were weighed in different ratio as shown in Table I and dissolved in sufficient quantity of acetonitrile, followed by removal of organic solvent by keeping in oven at 40-60^{0}C, till constant weight is achieved. The dried dispersions were passed through sieve no.100. The prepared dispersions were stored in glass vials.

***4.* CHARACTERIZATION OF SOLID DISPERSIONS:**

FT-IR SPECTROSCOPY:[18, 19]

The optimized solid dispersion (S8) were characterized by FT-IR spectra by preparing KBr pellets at scanning range of 4000 – 500cm $^{-1}$.

***5.* EVALUATION OF SOLID DISPERSIONS:**

I) DRUG CONTENT[3]:

The % drug content of each solid dispersion was determined using powder equivalent to 20 mg of Lovastatin and was dissolved in alcohol using the mechanical shaker. To the solution obtained simulated intestinal fluid was added and the solution was then filtered through Whatman filter paper No.42 and required dilutions were made and absorbance was taken at 238 nm.

II) SOLUBILITY:[20]

Solubility was determined in both simulated gastric fluid and simulated intestinal fluid.

III) DISSOLUTION STUDIES:

The dissolution studies on pure drug and solid dispersions were performed. Simulated gastric fluid and simulated intestinal fluid were used as dissolution medium. During dissolution study 10 mL aliquot was withdrawn at different time intervals and same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatman filter paper No.42 and absorbance was measured at 238nm.

6. PHYSICAL PROPERTIES:

Bulk density[21], tapped density[22], compressibility index and hausner ratio were determined for Lovastatin, HPMC, Sodium starch glycolate, Crospovidone, Croscarmilose sodium and optimized solid dispersion (S8).

RESULTS:

1. FT-IR SPECTRUM OF LOVASTATIN:

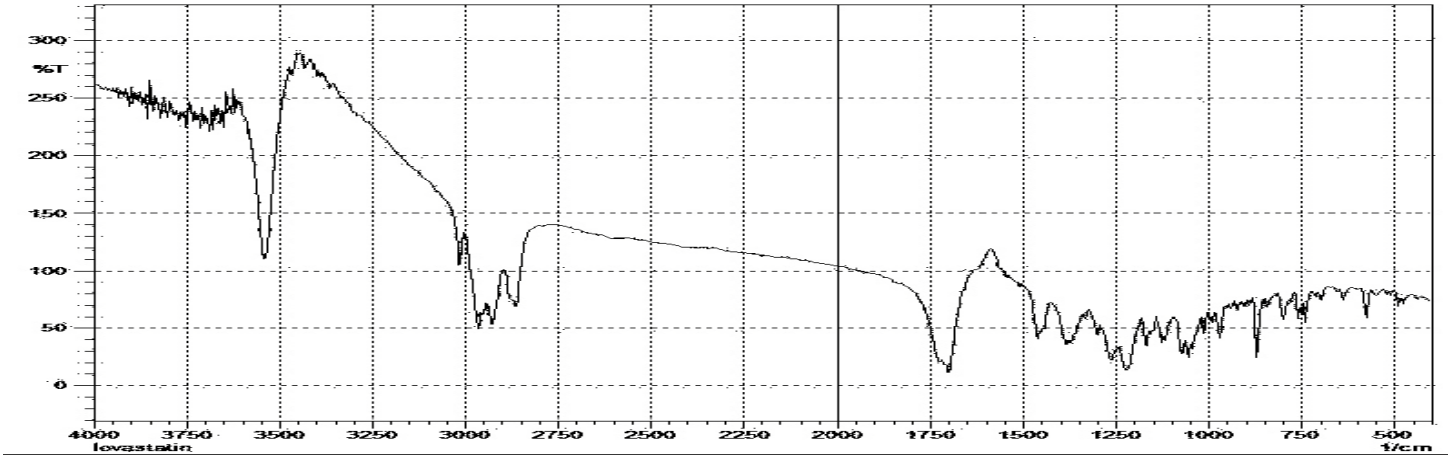

Figure No.1: FT-IR Spectra of Lovastatin

2. CHARACTERIZATION OF SOLID DISPERSIONS:

(A) SOLID DISPERSION WITH SSG AND CRP:

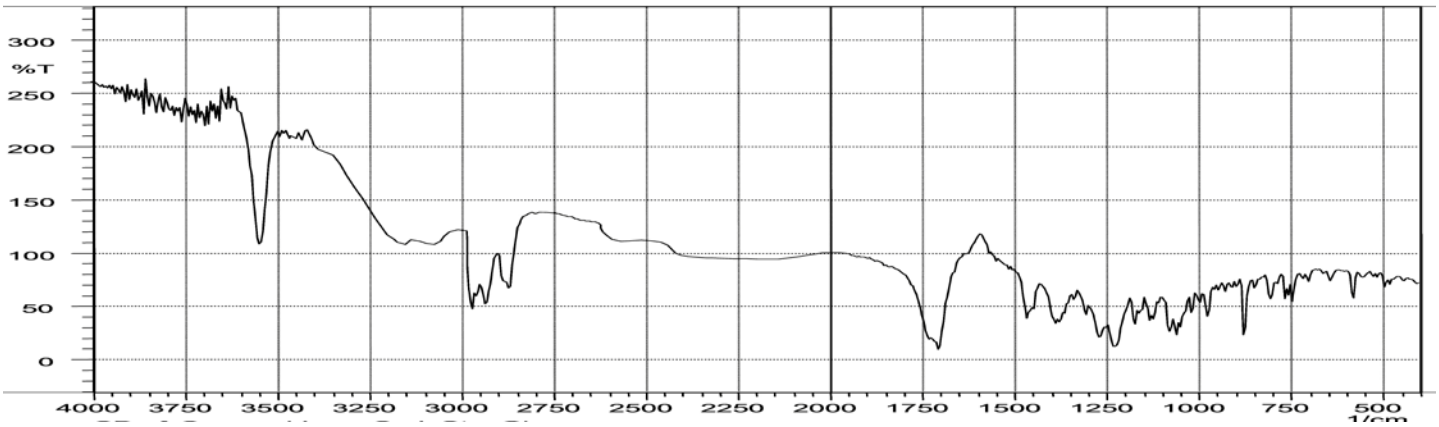

Figure No. 2: FTIR spectra of Solid dispersion with SSG and CRP.

(A) SOLID DISPERSION WITH CCS AND CRP:

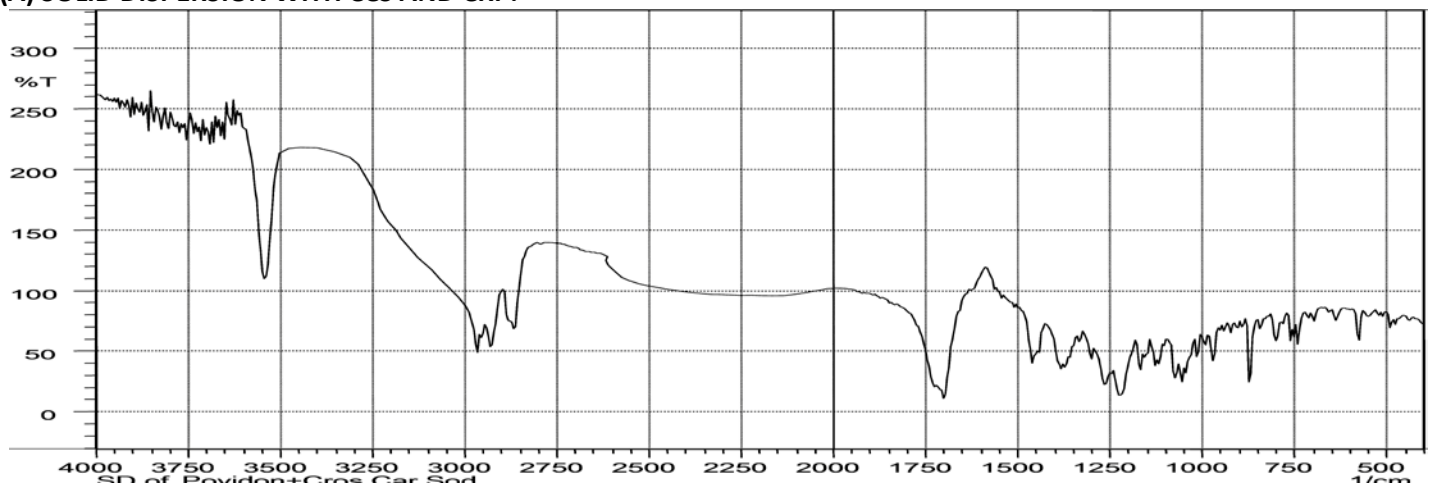

Figure No. 3: FTIR spectra of Solid dispersion with CCS and CRP.

3. EVALUATION OF SOLID DISPERSIONS:

(A) DRUG CONTENT:[3] The drug content of each solid dispersion was as shown in Table No.2

Sr. No.	Composition	Drug content * (%)
1	Lovastatin : SSG (S1)	96.72 ± 0.22
2	Lovastatin : SSG(S2)	95.62 ± 0.23
3	Lovastatin : CCS(S3)	100.05 ± 0.18
4	Lovastatin : CCS (S4)	96.46 ± 0.31
5	Lovastatin : CRP (S5)	96.61 ± 0.27
6	Lovastatin : CRP (S6)	98.97 ± 0.23
7	Lovastatin : SSG : CCS (S7)	96.42 ± 0.07
8	Lovastatin : SSG : CRP (S8)	97.31 ± 0.16
9	Lovastatin : CCS : CRP (S9)	100.00 ± 0.16
(* Represent mean ± S. D.)		**(n= 2)**

Table No.2: Percent drug content in solid dispersions

(B) SOLUBILITY:[20] The solubility of each solid dispersion is as shown in Table No.3

Sr. No.	Solid dispersion	Solubility in SIF (mg/mL)	Solubility in SGF (mg/ML)
1	Pure drug	0.138±0.88	0.189±0.65
2	S1	0.165±0.99	0.224±0.70
3	S2	0.173±0.91	0.232±0.74
4	S3	0.182±0.75	0.240±0.84
5	S4	0.195±0.84	0.250±0.74
6	S5	0.216±0.61	0.253±0.90
7	S6	0.249±0.74	0.255±1.05
8	S7	0.251±0.80	0.257±1.23
9	S8	0.281±0.66	0.291+0.72
10	S9	0.261±0.92	0.273±0.84

Table No.3: Solubility of Lovastatin from various solid dispersions

(C) DISSOLUTION STUDIES:

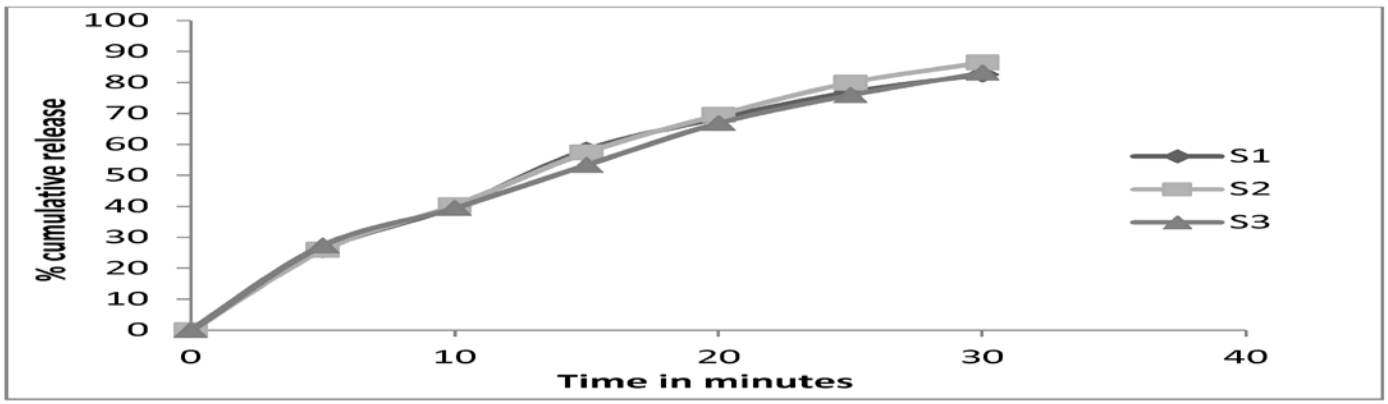

Figure No. 4: *In- vitro* release profile in SGF of lovastatin solid dispersions of batch S1-S3

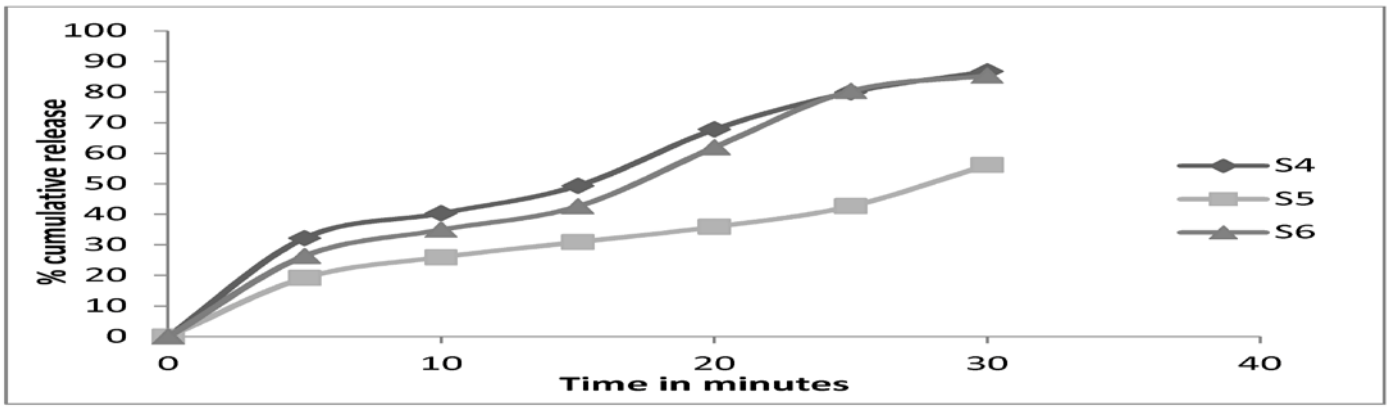

Figure No. 5: *In- vitro* release profile in SGF of lovastatin solid dispersions of batch S4-S6

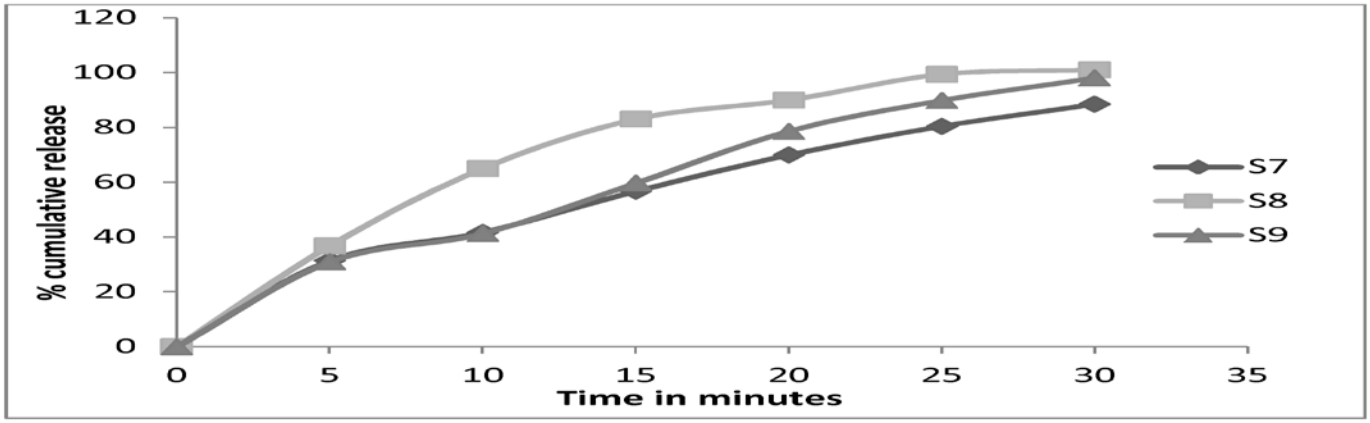

Figure No. 6: *In- vitro* release profile in SGF of Lovastatin solid dispersions of batch S7- S9

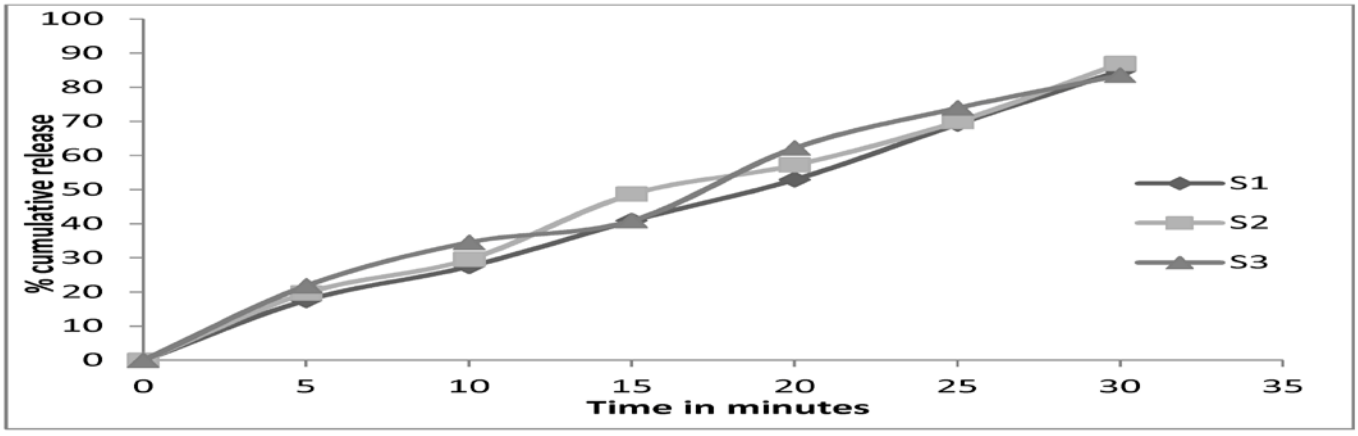

Figure No. 7: *In- vitro* release profile in SIF of Lovastatin solid dispersions of batch S1- S3

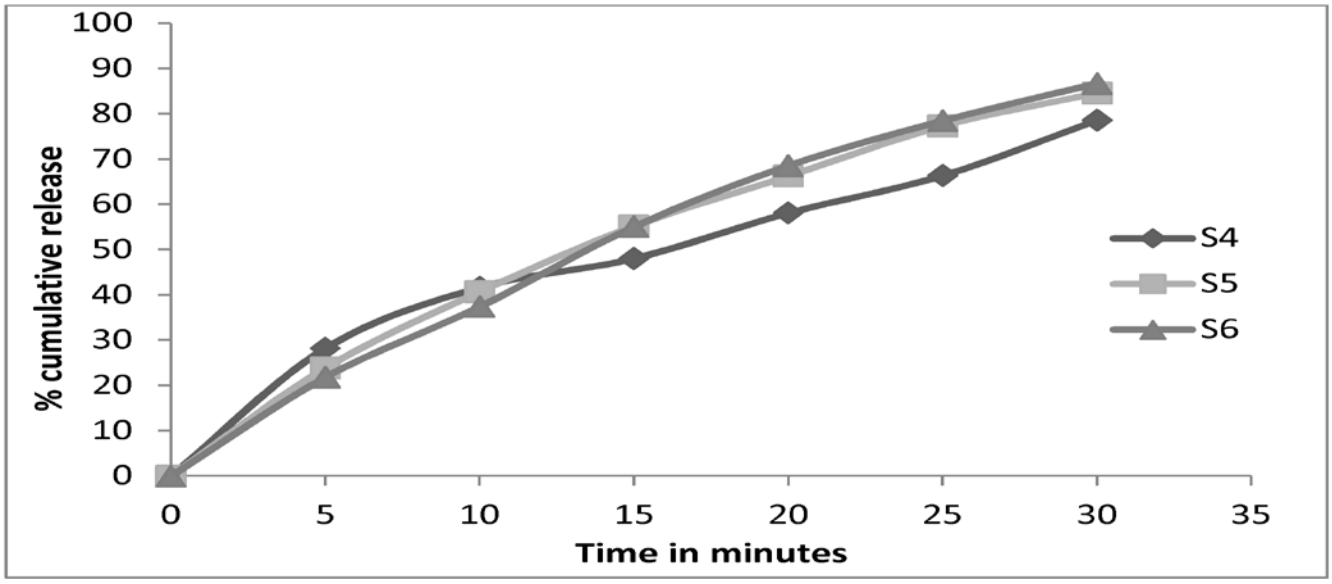

Figure no. 8: *In- vitro* release profile in SIF of Lovastatin solid dispersions of batch S4- S6

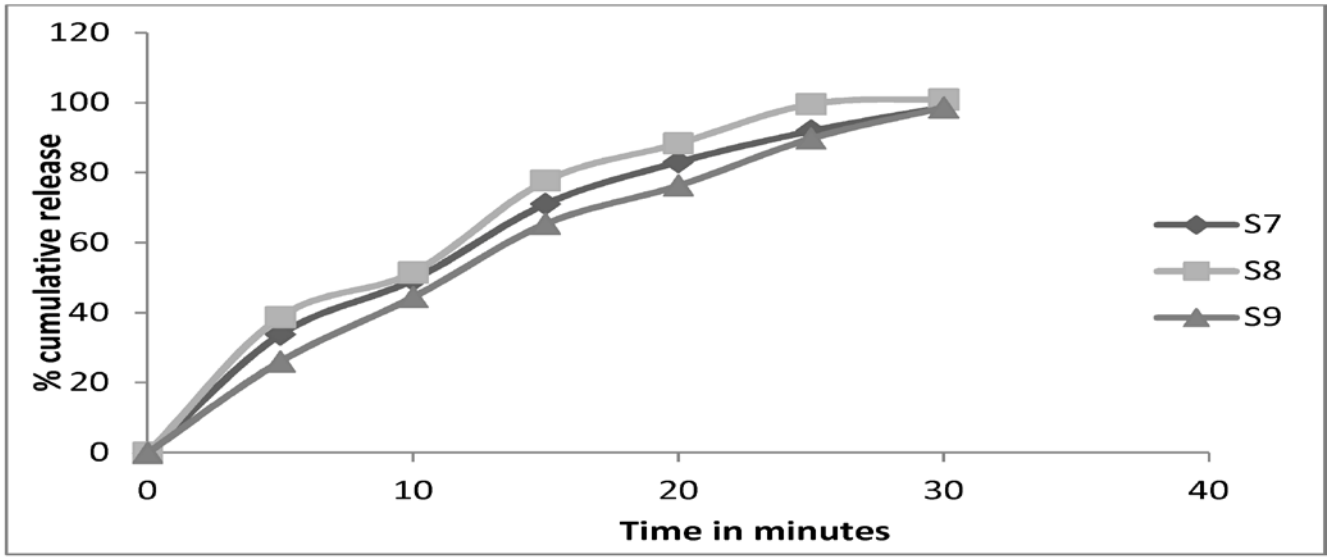

Figure No. 9: *In- vitro* release profile in SIF of Lovastatin solid dispersions of batch S7- S9

(D)Physical properties: The results are summarized in Table No.4

Sr. No.	Parameters	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility index (%)	Hausner ratio
1.	Pure drug	0.261	0.416	36.84	1.58
2.	HPMC	0.338	0.520	35.13	1.54
3.	K100M	0.333	0.510	34.63	1.53
4.	SSG	0.543	0.833	34.78	1.53
5.	CRP	0.430	0.510	15.51	1.18
6.	CCS	0.625	0.710	16.66	1.20

Table No. 4: Physical properties of drug and excipients

DISCUSSION:

The procured sample of Lovastatin was tested for its identification. From the standard calibration curve of drug, it was concluded that drug obeys Beer-Lamberts law in concentration range of 0-50mcg/mL. The linear equation were obtained as

1] Simulated gastric fluid $y = 0.1004x$ $R^2 = 0.9995$

2] Acetonitrile $y = 0.0638x$ $R^2 = 0.9983$

The dissolution data of plain drug in simulated gastric fluid showed that the release of the drug was less in both the medium and thus it was concluded that Lovastatin is poorly soluble drug and erratically absorbed throughout GI and also possess several dissolution related problem and that might be a reason for its poor bioavailability. The solid dispersions were prepared by solvent evaporation method as it is the easiest to perform and most preferred method. Lovastatin and the superdisintegrants were weighed in different ratio and transferred to mortar and kneaded for 45 min. using acetonitrile-water mixture in ratio 1:1, sufficient solvent was added to maintained paste like consistency. The resulting paste was then dried in oven followed by sieving. The solid dispersions prepared by this method had a good flow property. The optimized solid dispersion was characterized by FT-IR spectroscopic method.The FTIR of all physical mixture of drug and polymers shows that all the peaks of drug and polymers were as it is and drug is present in free form. Hence no interaction was observed between them. The FTIR of the solid dispersion also showed no changes in peaks and the peaks of Lovastatin and polymers were distinguishable and showed that there was no chemical interaction between drug and polymer after formation of solid dispersions.

The solubility of all solid dispersions was carried out in both simulated gastric fluid and intestinal fluid. In the solubility of solid dispersion, the data indicated that solubility increased in all cases but highest increase was found in solid dispersion with Crospovidone and sodium starch glycolate prepared in 1:2:2 w/w ratio. The dissolution data of all solid dispersions also indicated increase in dissolution as compared to pure drug and maximum increase was observed in case S8. The batch S8 was considered as optimized batch since it showed statistically significant difference in both solubility and dissolution characteristics. Also the increase in dissolution of Lovastatin in solid dispersions is because of wetting phenomenon of superdisintegrants used for preparation of solid dispersions. More dissolution was observed in case of solid dispersion prepared with crospovidone as compared to that of croscarmellose sodium because wetting efficiency of crospovidone is more in acidic pH as compare to croscarmellose sodium. The fact was supported by Zhao et al 2005[23].

The drug, solid dispersion and polymer were evaluated for the physical parameters. These physical parameters of solid dispersions and excipients concluded that these were considerably good to formulate the tablet using direct compression technique.

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