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IMPROVEMENT OF AQUEOUS SOLUBILITY AND DISSOLUTION RATE OF SIMVASTATIN THROUGH VARIOUS SOLID DISPERSION TECHNIQUES

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ABSTRACT
The present work dealt with Improvement of Aqueous Solubility of Poorly Soluble drug -Simvastatin (SIM) through various Solid dispersion techniques such as Solvent evaporation method, Fusion or melting method and Solvent melt method at different drug: carrier ratios. Simvastatin, a BCS Class II drug, exhibits low solubility and high permeability. Consequently, its dissolution rate becomes the rate-limiting step for drug absorption. This study aimed to improve the solubility and dissolution rate of Simvastatin by increasing its solubility and dissolution characteristics through solid dispersion technique using polyethylene glycol (PEG 4000) as hydrophilic carrier. The prepared solid dispersions were characterized by FTIR-Spectroscopy, differential scanning calorimetry, X-ray powder diffraction, and dissolution studies. The solid dispersion prepared by solvent melt method in 1:6 (Drug: Carrier) ratio –SM4SD3 shown better dissolution. The optimized solid dispersion (SM4SD3) was formulated into Fast disintegrating tablets (F1-F10) by direct compression method using various superdisintegrants such as sodium starch glycolate, crospovidone and Croscarmellose sodium. The prepared FDTs were evaluated for its pre and post compression parameters. The drug excipient compatibility studies carried out by FTIR revealed no interaction between the components in the solid dispersion, while the XRD and DSC studies revealed a reduction in the crystallinity of the solid dispersions. In vitro dissolution studies showed Improve dissolution of Fast disintegrating tablets incorporated with high concentration of Croscarmellose sodium (F10) as it rapidly promotes disintegration and dissolution.

KEYWORDS: Simvastatin, Solubility, Solid dispersions (SD), Polyethylene glycol, Binary systems, Bioavailability, Superdisintegrants.

1. INTRODUCTION
Solubility is vital for drug bioavailability, especially for poorly soluble drugs. Solid dispersions, combining a hydrophilic matrix with a hydrophobic drug, enhance solubility by dispersing the drug at a molecular level in a water-soluble carrier. This method improves bioavailability and addresses solubility issues affecting around 40% of drugs. Poor solubility often results from high lipophilicity and strong intermolecular forces, with techniques like micronization, pH adjustment, and solid dispersion used to improve it (Payal. D et al., 2021). Poor aqueous solubility in drugs is often due to high lipophilicity and strong intermolecular forces. Methods like micronization, chemical modification, pH adjustment, and solid dispersion are used to improve solubility. The Biopharmaceutical Classification System (BCS) guides formulation strategies based on solubility and permeability. For example, simvastatin requires effective solubility enhancement to ensure bioavailability (Brahmankar D.M & Sunil B.jaiswal, 2009) Solid dispersions significantly enhance simvastatin's solubility by dispersing it in water-soluble carriers, increasing dissolution rates in gastrointestinal fluids. This technique, introduced by Sekiguchi and Obi, improves dissolution and bioavailability by dispersing hydrophobic drugs in carriers like eutectic mixtures or amorphous precipitations (Sekiguchi et al., 1961). Various methods for preparing solid dispersions include solvent evaporation, fusion/melting, and melt extrusion. These methods aim to enhance solubility and bioavailability while addressing challenges like thermal decomposition (solvent evaporation) or addressing drug-matrix compatibility issues (fusion method) (A Kumar et al., 2011). For instance, solid dispersion techniques represent versatile approaches to improving the solubility and bioavailability of poorly soluble drugs like simvastatin, crucial for overcoming formulation challenges in pharmaceutical development (Pawar.SR. et al., 2019). Solid dispersions improve patient acceptance and bioavailability but face challenges like instability,

handling issues, and formulation complexities. Techniques such as differential scanning calorimetry, FT-IR spectroscopy, and scanning electron microscopy are essential for analyzing the physical structure and drug-carrier interactions (Heike Bley et al., 2010). Fast disintegrating tablets (FDTs) and superdisintegrants are innovative approaches to improve drug delivery for patients with swallowing difficulties. FDTs disintegrate in the mouth within seconds, facilitating rapid drug absorption. Superdisintegrants like croscarmellose and sodium starch glycolate enhance disintegration by promoting water absorption and swelling, improving the wettability and dispersibility of the tablet. Despite their benefits, superdisintegrants can be expensive, sensitive, and hygroscopic, posing some limitations in their use (Ved Parkash et al., 2011).

2. MATERIALS AND METHODS

Materials

In this research, Simvastatin was provided as a gift sample by Krebs Biochemicals & Industries Limited. Sodium starch glycolate (SSG), Croscarmellose sodium (CCS), Crospovidone (CP), Mannitol, Microcrystalline cellulose (MCC), Magnesium stearate, and Talc were sourced from S.D. Fine Chemicals Ltd, Mumbai, India. All additional chemicals employed were of analytical grade.

Solubility Studies

Solubility is a vital pre-formulation parameter as it directly affects the dissolution rate and bioavailability of a drug.

Method: A precise amount of the drug was weighed and added to 10 ml of the solvent (distilled water, 0.1N hydrochloric acid, phosphate buffer at pH 6.8, and phosphate buffer at pH 7.2). The mixture was continuously stirred for 24 hours. After stirring, the solution was filtered using Whatman filter paper. The filtrate was then appropriately diluted, and the concentration of simvastatin was measured using a UV spectrophotometer at the drug's λmax of 240 nm, using the respective solvent as the blank (Payal D. et al., 2021).

Identification of λmax of Simvastatin

A stock solution of Simvastatin (1000 µg/ml) was prepared by dissolving 100 mg of the drug in methanol and diluting the mixture to a final volume of 100 ml. From this stock solution, 1 ml was further diluted to 10 mL with methanol to obtain a 100 µg/mL solution, which was subsequently diluted to achieve a concentration of 10 µg/ml. This final solution was scanned in the UV-visible range (200-400 nm), and the spectrum displayed a peak at 240 nm (λmax).

Preparation of calibration curve

The calibration curve for the drug was prepared spectrophotometrically, based on its UV absorption at λmax 240 nm in methanol for quantitative estimation. Solutions with concentrations ranging from 5 to 30 µg/ml were prepared from the stock solution. Specifically, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 ml of the stock solution were pipetted into a series of 10 ml volumetric flasks, and the volume was adjusted to the mark with methanol to achieve final concentrations of 5, 10, 15, 20, 25, and 30 µg/ml. The absorbance of these samples was measured at the drug's λmax of 240 nm, using methanol as a blank. The absorbance values were then plotted against the corresponding drug concentrations to generate a calibration curve (Table 5; Fig. 6).

Drug and Excipient Compatibility Studies

Excipients are crucial in pharmaceuticals, aiding drug administration and protection. This study ensures no harmful interactions, maintaining the drug's stability, efficacy, and safety.

- **Fourier transform infrared spectroscopy (FTIR)**

FTIR was employed to analyze drug-excipient interactions in Simvastatin and its solid dispersion with Polyethylene glycol 4000. Compatibility studies were performed using a Bruker Alpha ATR FT-IR Spectrophotometer. Samples were prepared via the potassium bromide (KBr) pellet method and scanned from 4000 to 400 cm^{-1} at a resolution of 1 cm^{-1}. This analysis helped identify potential interactions between the drug and excipients.

- **X-Ray Diffraction (XRD)**

XRD was utilized to examine the crystalline structure of Simvastatin and its solid dispersions, assessing their form and interactions with excipients. The analysis was conducted using a Shimadzu XRD-7000 Maxima, with CuKα radiation at 40 kV and 50 mA. The samples were scanned from 5° to 90° 2θ in 0.02° steps (Hou, P. et al., 2013).

- **Differential Scanning Calorimetry (DSC)**

DSC was used to analyze 5 mg samples of Simvastatin and its solid dispersions in sealed aluminum pans. The analysis was conducted using a Shimadzu DSC-60, with scans performed from 0°C to 200°C at a rate of 10°C/min under a nitrogen flow of 30 ml/min, with an empty pan as the reference.

Formulation and Preparation of Solid Dispersions

Table 1: Formulation of Solid dispersion by solvent evaporation method.

Formulation code	Ratio	Drug (mg)	PEG 4000 (mg)	Total weight (mg)
S4SD1	1:2	200	400	600mg
S4SD2	1:4	200	800	1000mg
S4SD3	1:6	200	1200	1400mg

Table 2: Formulation of Solid dispersion by Fusion/ Melting method.

Formulation code	Ratio	Drug (mg)	PEG 4000 (mg)	Total weight (mg)
M4SD1	1:2	200	400	600mg
M4SD2	1:4	200	800	1000mg
M4SD3	1:6	200	1200	1400mg

Table 3: Formulation of Solid dispersion by Solvent melt method.

Formulation code	Ratio	Drug (mg)	PEG 4000 (mg)	Total weight (mg)
SM4SD1	1:2	200	400	600mg
SM4SD2	1:4	200	800	1000mg
SM4SD3	1:6	200	1200	1400mg

Preparation of Solid Dispersions of Simvastatin

- **Solvent Evaporation Method**

Solid dispersions of Simvastatin in PEG 4000 were prepared using the solvent evaporation method at ratios of 1:2, 1:4, and 1:6, designated as S4SD1, S4SD2, and S4SD3, respectively. PEG 4000 was dissolved in isopropyl alcohol in a china dish, and Simvastatin was gradually added with continuous stirring until a homogeneous solution was achieved. Stirring continued until the solvent had evaporated. The resulting powder was dried, sieved through a #120 sieve, and weighed. The solid dispersions were stored in a desiccator for further evaluation. Advantages of this method are its low temperature requirements and its ability to prevent the thermal decomposition of drugs and carriers. Disadvantages include increased production costs, the risk of incomplete solvent removal, potential negative effects of solvents on drug stability, and the challenge of choosing a suitable solvent (Manohar Chouhan et al., 2021).

- **Fusion /melting method**

In this procedure, Polyethylene glycol (PEG-4000), the hydrophilic carrier, was melted by heating. Simvastatin was then incorporated into the molten PEG-4000. The mixture was quickly solidified by placing it in an ice bath while stirring. Once solidified, the mass was dried, crushed, sieved, and stored in a desiccator for further analysis (Jatinder Kaur et al., 2012). Solid dispersions were prepared with ratios of 1:2, 1:4, and 1:6, and were labeled as M4SD1, M4SD2, and M4SD3, respectively.

- **Solvent melt method**

In this method, PEG 4000, the hydrophilic carrier, was melted in a china dish, while Simvastatin was dissolved in isopropyl alcohol. The drug solution was then added to the melted PEG 4000, and the mixture was stirred continuously to get a homogeneous solution. This solution was rapidly solidified in an ice bath while stirring. The resulting solid mass was dried, crushed, sieved, and stored. Solid dispersions were prepared in ratios of 1:2, 1:4, and 1:6, and were labeled as SM4SD1, SM4SD2, and SM4SD3, respectively.

Evaluation of Solid Dispersions

- **Estimation of drug content**

A precise amount of solid dispersion containing Simvastatin (equivalent to 20 mg of the drug) was accurately weighed and dissolved in 100 mL of methanol. The solution was sonicated to ensure complete dissolution and then filtered through a 0.45 µm membrane filter. The filtered solution was appropriately diluted and analyzed for drug content by measuring its absorbance at 240 nm using a UV spectrophotometer. The actual Simvastatin content in the sample was determined based on the absorbance value, and the drug content was calculated using the following equation.

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in SD}}{\text{Theoretical amount of drug in SD}} \text{ X } 100$$

- **Determination of percentage yield**

The percentage yield of the prepared solid dispersion formulations was calculated using the following equation. The determination was performed in triplicate.

$$\% \text{ Yield} = \frac{\text{Actual weight of solid dispersion}}{\text{Total weight of drug and carrier}} \times 100$$

- **Aqueous Solubility Studies**

Prepare an excess amount of pure Simvastatin and solid dispersions in 10 mL of distilled water separately. Constantly shake the mixtures for 24 hours to allow them to reach equilibrium. After equilibration, filter each solution through a membrane filter. Dilute the filtered solutions as necessary and measure their absorbance at 240 nm.

- **In vitro dissolution Studies of Solid dispersion**

In vitro dissolution studies were performed using a USP Type II (paddle) dissolution apparatus at 100 rpm, with 900 mL of phosphate buffer (pH 6.8) maintained at 37±0.5 °C. A 20 mg sample was introduced into the dissolution medium. At 10-minute intervals, 10 mL samples were withdrawn and replaced with fresh media.

These samples were filtered, diluted, and analyzed using a UV spectrophotometer at 240 nm, with a suitable blank. Each sample was analyzed in triplicate, and the average (±SD) readings were recorded.

Evaluation of the blend for FDTs incorporating Simvastatin solid dispersions

The powder blend composed of SM4SD3, along with super disintegrants, mannitol, MCC, and other additional excipients, underwent an evaluation focusing on pre-compression parameters. The assessment covered flow properties, determined through the angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio. These parameters are vital for confirming that the blend exhibits appropriate flow behavior, ensures accurate dosing, maintains uniformity across tablets, and upholds the quality of the final product (Table.8).

Formulation of Fast disintegrating tablets with Optimized Solid dispersion (SM4SD3)

Table 4: Formulation of Fast disintegrating Tablets.

Ingredients (mg)	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Solid dispersion (equivalent to 20mg of SIM)	140	140	140	140	140	140	140	140	140	140
Sodium starch glycolate	–	15	20	25	–	–	–	–	–	–
Crospovidone	–	–	–	–	15	20	25	–	–	–
Croscarmellose	–	–	–	–	–	–	–	15	20	25
Mannitol	100	85	80	75	85	80	75	85	80	75
Micro crystalline cellulose	30	30	30	30	30	30	30	30	30	30
Aspartame	5	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2
Total wt. of tablet (mg)	280	280	280	280	280	280	280	280	280	280

Formulation Procedure for Fast Disintegrating Tablets using SM4SD3 via Direct Compression

Each ingredient was carefully weighed according to the specified formulation and passed through a #60 sieve to achieve a uniform particle size. The solid dispersion (SD) containing the equivalent of 20 mg of Simvastatin was then combined with disintegrants, mannitol, microcrystalline cellulose, and aspartame, and the mixture was blended for 10-15 minutes to ensure uniform distribution. Afterward, sieved talc and magnesium stearate were added and mixed for an additional 3-5 minutes.

The resulting blend was compressed into tablets using an 8 mm round flat-faced punch machine, with the compression force adjusted to achieve optimal tablet hardness, size, and friability. The finished tablets underwent evaluation for weight variation, hardness, friability, disintegration time, and dissolution rate. Upon successfully passing all quality control tests, the tablets were packed in appropriate containers to shield them from moisture and light. This method produced fast-disintegrating tablets with rapid release, enhanced solubility, and improved dissolution rates (Akshada Gavhane et al., 2022).

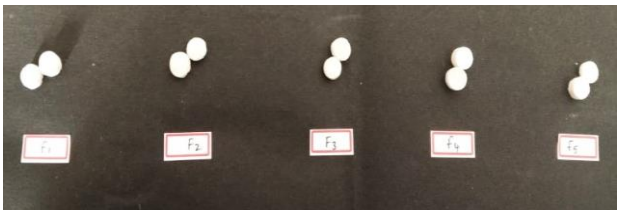

Fig. 1: Formulation of fast disintegrating tablets (F1-F5).

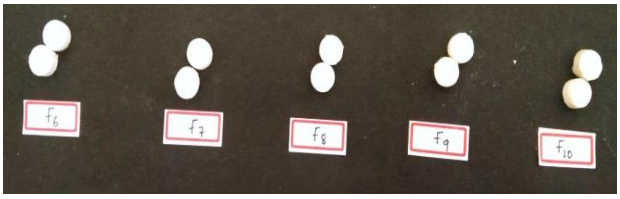

Fig. 2: Formulation of fast disintegrating tablets (F6-F10).

Evaluation of Fast Disintegrating Tablets

The formulated FDTs, prepared with the SM4SD3 powder blend and other tablet excipients, were checked for post-compression parameters. These assessments included tests for hardness, friability and weight variation, drug content, dissolution, and disintegration time, all conducted according to standard procedures. The results of these evaluations are depicted in Table 8.

Drug content of Fast disintegrating tablets

Dissolve a 20 mg simvastatin tablet in a (100 ml) volumetric flask containing phosphate buffer solution at pH 6.8. Filter the solution to eliminate any insoluble particles. Collect 1 ml of the filtrate and transfer it to a new 100 ml volumetric flask. Dilute this solution to the mark with the same phosphate buffer (pH 6.8) and mix thoroughly. Measure the absorbance of the diluted solution at 240 nm using a spectrophotometer. Determine the concentration of simvastatin in mg/ml from the absorbance reading, then multiply by the dilution factor to calculate the drug content in the original tablet. Repeat this procedure in triplicate for accuracy.

$$\% \text{ Drug content} = \frac{\text{Actual amount of drug in SD}}{\text{Theoretical amount of drug in SD}} \text{ X } 100$$

In-vitro Disintegration Test

To determine the in-vitro disintegration time of a tablet, a disintegration test was conducted using an apparatus compliant with I.P. specifications. Each of the six tubes in the basket was loaded with a single tablet and a disc. The apparatus was filled with a pH 6.8 solution, kept at 37±2°C. The basket was then subjected to a cyclic motion, rising and falling at a rate of 30 cycles per minute in the pH 6.8 solution at the maintained temperature. The disintegration time was recorded as the duration required for the tablet to completely break down, leaving no residual fragments in the apparatus.

Dissolution studies of fast disintegrating tablets

In-vitro drug release studies were conducted using a USP dissolution test apparatus II (paddle type). The FDTs were subjected to dissolution in 900 mL of phosphate buffer at pH 6.8, with the apparatus operating at 50 rpm and maintained at 37 ± 0.5°C. At specified time intervals, 10 mL aliquots were withdrawn and replaced with fresh dissolution medium. The drug concentration in each aliquot was measured using a UV spectrophotometer (Analytical Technologies Limited) at 240 nm, with a suitable blank used for calibration. All measurements were performed in triplicate, and the average values (± SD) were recorded.

Comparative study with marketed sample

A comparative in-vitro drug release study was carried out using the marketed tablet (Z0COR*20 mg). The study utilized a USP Type II dissolution apparatus, with phosphate buffer at pH 6.8 as the dissolution medium, maintained at 50 rpm and 37 ± 0.5°C. Samples of 10 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The drug content of each sample was quantified using a UV spectrophotometer at 240 nm. The study was conducted in triplicate, and the average results were analyzed and compared with those of the pure drug and the optimized F10 tablet.

Stability studies of Fast disintegrating tablets:

Stability testing for tablets from batch F10 was performed following ICH guidelines under accelerated conditions of 40ºC and 75% relative humidity for a period of 3 months. The tablets were stored in capped vials and aluminum strips within a stability chamber. Analytical evaluations of the tablets were conducted at 0, 30, 60, and 90 days, focusing on in-vitro drug release and drug content. Additionally, a visual inspection was carried out at the end of the testing period to identify any physical changes in the solid dispersions (Shamsuddin et al., 2016).

3. RESULTS AND DISCUSSIONS

Solubility studies

The drug demonstrated varied solubility across different solvents. It was nearly insoluble in water, with a solubility of 0.493 mg/ml. In phosphate buffer solutions, solubility increased slightly, reaching 0.754 mg/ml at pH 6.8 and 0.637 mg/ml at pH 7.4. In 0.1N HCl, the solubility was measured at 0.653 mg/ml. Conversely, the drug was readily soluble in organic solvents, with solubility values of 0.726 mg/ml in chloroform and 1.094 mg/ml in methanol.

Calibration curve of Simvastatin:

Table 5: Calibration curve data for Simvastatin.

Concentration (µg/ml)	Absorbance
0	0
5	0.141
10	0.291
15	0.421
20	0.562
25	0.741
30	0.912

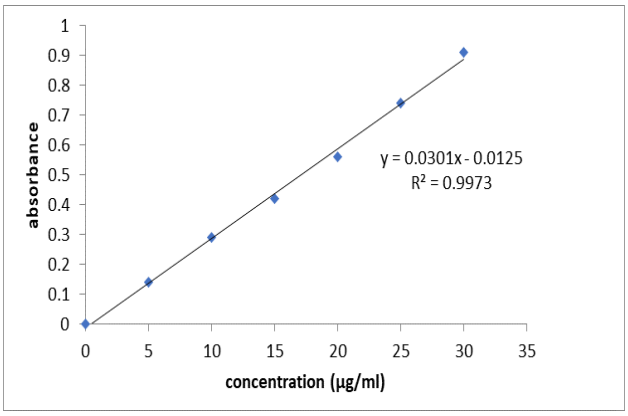

Fig. 3: Standard Calibration Curve for Simvastatin.

Drug and Excipient Compatibility Studies

Fourier transform infrared spectroscopy (FTIR)

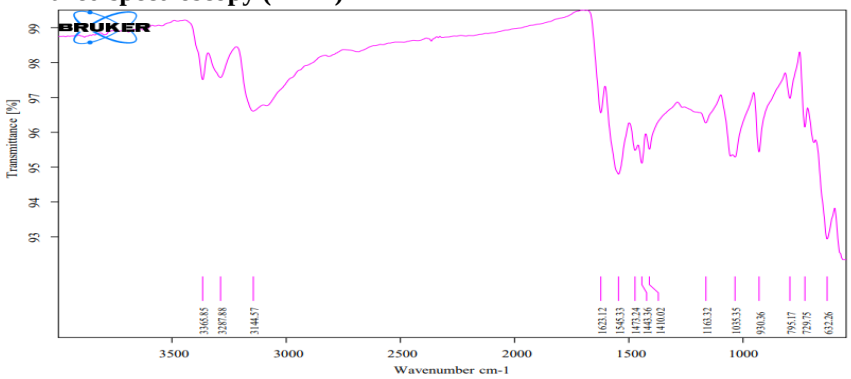

Fig. 4: FTIR Spectra of Pure Simvastatin.

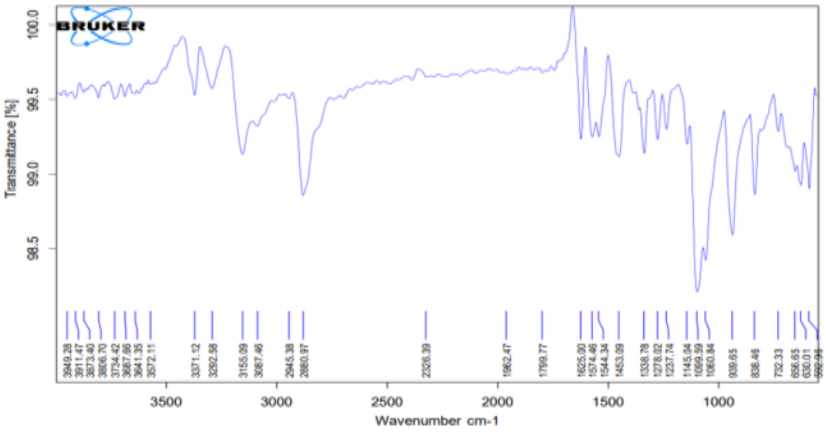

Fig. 5: FTIR spectra of Solid dispersion (SIM+PEG 4000).

The FTIR spectra reveal a broad peak in the range of 3267-3144 cm^{-1}, which corresponds to O-H groups present in both Simvastatin and PEG 4000. A peak at 1623.12 cm^{-1} is associated with C=O stretching in Simvastatin. Peaks in the 1442-1400 cm^{-1} range are linked to C=C stretching vibrations in Simvastatin. Additionally, peaks between 1242-1170 cm^{-1} suggest C-O stretching, typical of esters in Simvastatin and ethers in PEG 4000. The FTIR spectra for Simvastatin and the solid dispersion (Simvastatin + PEG 4000) do not show significant shifts or changes in key peaks, indicating that there are no major interactions between Simvastatin and PEG 4000.

X-ray Diffraction (XRD)

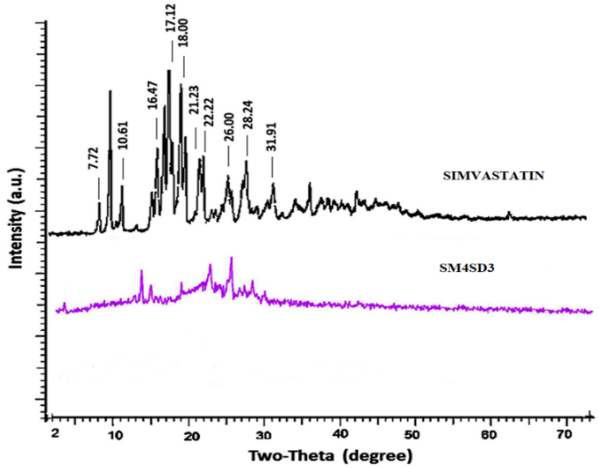

Fig. 6: XRD Patterns of Simvastatin and Optimized-SD (SM4SD3).

The XRD pattern of pure Simvastatin exhibits sharp, well-defined peaks, confirming its highly crystalline structure. In contrast, the XRD pattern of SM4SD3 shows broader and less intense peaks, indicating a

transition towards a more amorphous state. This reduction in crystallinity, as evidenced by the decreased intensity of characteristic peaks, As a result, Simvastatin in SM4SD3 has become less crystalline or more amorphous. This shift is expected to improve the drug's solubility and dissolution rate, potentially making SM4SD3 a more effective formulation.

Differential Scanning Calorimetry (DSC)

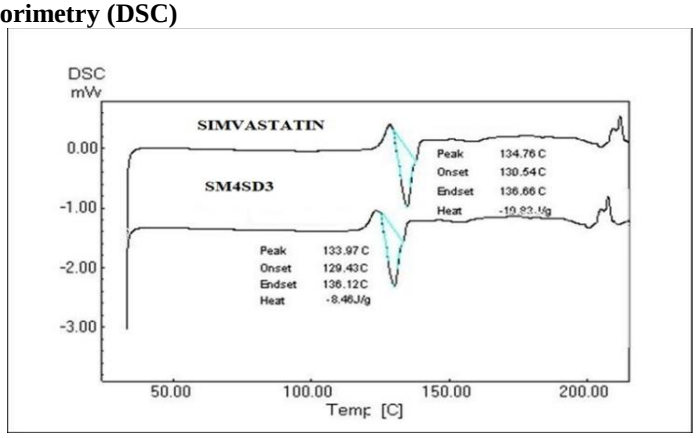

Fig. 7: DSC thermograms of Pure Simvastatin and Optimized SD (SM4SD3).

The DSC thermogram reveals similar thermal behavior for Simvastatin and SM4SD3, with melting points at 134.76°C and 133.97°C, respectively. The onset and set temperatures are also close, with heat of fusion values of -10.82 J/g for Simvastatin and -8.46 J/g for SM4SD3. The endothermic peaks indicate melting, with no exothermic peaks observed, suggesting no crystallization or decomposition. These similarities imply that SM4SD3 is closely related to Simvastatin, likely as a solid dispersion with minor differences in thermal properties.

Evaluation of Solid Dispersions

Table 6: Percentage yield and % Drug content of solid dispersions.

Formulation	Percentage Yield	%Drug content
S4SD1	82.11±0.961	79.22±0.003
S4SD2	82.87±1.023	78.75±0.017
S4SD3	81.23±1.104	87.26±0.012
M4SD1	79.08±0.025	80.73±0.007
M4SD2	82.01±1.621	81.61±0.013
M4SD3	80.27±1.621	82.48±0.003
SM4SD1	83.18±1.321	84.89±0.002
SM4SD2	88.09±0.984	88.13±0.006
SM4SD3	87.06±0.369	92.14±0.006

The percentage yield and drug content of the solid dispersions were determined using a specific formula, with the results summarized in Table 12. It was noted that as the carrier ratio increased, the percentage yield tended to decrease, likely due to challenges encountered during the sieving process. The drug content values varied between 78.75±0.017 and 92.14±0.006, while the percentage yield ranged from 79.08% to 87.06%.

Aqueous Solubility Studies

Table 7: Aqueous solubility of Solid Dispersions.

S. No.	Formulation	Aqueous Solubility (mg/ml)
1	S4SD1	0.038±0.001
2	S4SD2	0.035±0.003
3	S4SD3	0.037±0.002
4	M4SD1	0.043±0.002
5	M4SD2	0.045±0.006
6	M4SD3	0.046±0.001
7	SM4SD1	0.042±0.003
8	SM4SD2	0.044±0.004
9	SM4SD3	0.047±0.001
10	Pure drug	0.024±0.002

Aqueous solubility studies were conducted following the procedure outlined in the experimental procedure. The Formulation SM4SD3 achieved the highest solubility at 0.047±0.001 mg/ml, significantly surpassing the pure drug's solubility of 0.024±0.002 mg/ml. The solid dispersions overall exhibited improved aqueous solubility when compared to the pure drug. These findings are summarized in Table 7.

In-vitro dissolution Studies of drug and solid dispersion

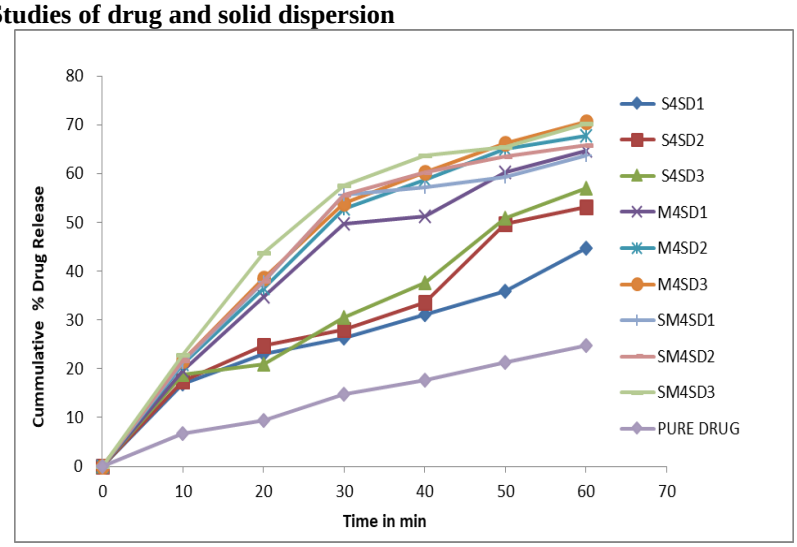

Fig. 8: In-vitro dissolution study of Solid-dispersions.

In this research, the in vitro dissolution characteristics of Simvastatin and its solid-dispersions, including S4SD1-S4SD3, M4SD1-M4SD3, and SM4SD1-SM4SD3, were conducted. At 10 minutes, the pure drug showed 6.65% release, while solid dispersions ranged from 16.97% (S4SD1) to 22.80% (SM4SD3). By 30 minutes, the pure drug release was 14.73%, with S4SD3 at 30.57%, M4SD3 at 53.90%, and SM4SD3 at 57.48%. At 60 minutes, the pure drug released 24.73%, while S4SD3 reached 57.03%, M4SD3 69.34%, and SM4SD3 70.39%. The solvent melt method (Chen.Y et al.., 2011), particularly SM4SD3, demonstrated superior drug release due to the higher proportion of PEG 4000(Velaz.I et al., 1998), enhancing solubility and dissolution, and was selected for formulating Fast Disintegrating Tablets (FDTs) using direct compression.

Evaluation of the blend of FDTs containing Solid dispersions of Simvastatin

Table 8: Pre compression evaluation of SM4SD3 with tablet blend.

Batch	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner Ratio	Carr's Index (%)	Angle of repose (°)
F_1	0.478±0.49	0.542±0.03	1.13±0.02	10.5±0.13	24.5±0.4
F_2	0.496±.0.32	0.554±0.09	1.11±0.06	13.8±0.08	23.2±0.6
F_3	0.462±0.44	0.493±0.07	1.06±0.01	22.3±0.12	24.9±0.4
F_4	0.451±0.89	0.523±0.04	1.15±0.03	15.2±0.09	21.5±0.3
F_5	0.461±0.68	0.498±0.10	1.08±0.02	20.5±0.12	22.8±0.6
F_6	0.485±0.78	0.513±0.58	1.05±0.04	16.5±0.08	24.7±0.4
F_7	0.439±0.62	0.501±0.12	1.14±0.06	21.2±0.16	23.1±0.8
F_8	0.476±0.52	0.495±0.96	1.03±0.02	19.1±0.09	22.2±0.6
F_9	0.431±0.84	0.472±0.78	1.09±0.01	17.0±0.14	21.6±0.3
F_{10}	0.438±0.44	0.503±0.07	1.14±0.01	11.4±0.12	24.4±0.8

Results averaged from three determinations

The precompression parameters for all formulations demonstrated favorable flow properties. The angle of repose varied between 21.5±0.3° and 24.9±0.8°, bulk density ranged from 0.431±0.84 to 0.496±0.32 gm/cm^3, and tapped density spanned from 0.472±0.78 to 0.554±0.09 gm/cm^3. The compressibility index was observed to be between 10.5±0.13% and 22.3±0.12%, and the Hausner's ratio ranged from 1.03±0.02 to 1.15±0.03. All these values fell within the acceptable pharmacopoeial limits.

Evaluation of Fast Disintegrating Tablets

Evaluation of post-compression parameters

Table 9: Post compression evaluation of FDTS of SM4SD3.

Formulation Code	Thickness (mm)	Hardness (kg/cm²)	Weight Variation (mg)	Friability (%w/v)	Disintegration Time (sec)	Drug Content (%)
F1	4.24±0.03	3.4±0.3	276.2±1.8	0.87±0.08	40±0.24	89.2±0.16
F2	4.10±0.05	3.1±0.4	278.4±1.6	0.84±0.10	36±0.21	84.3±0.12
F3	4.14±0.01	2.8±0.6	274.8±1.8	0.79±0.11	31±0.18	87.2±0.08
F4	4.12±0.03	3.4±0.5	276.4±1.5	0.93±0.01	27±0.22	88.9±0.04
F5	4.20±0.03	3.5±0.5	275.3±1.3	0.88±0.12	32±0.24	91.5±0.07
F6	4.18±0.05	3.2±0.4	274.6±1.9	0.81±0.09	29±0.16	93.2±0.01
F7	4.21±0.03	2.8±0.4	275.6±1.8	0.94±0.03	26±0.21	92.6±0.06
F8	4.20±0.02	3.0±0.5	273.2±0.8	0.86±0.16	30±0.12	93.8±0.03
F9	4.26±0.06	2.8±0.6	275.3±1.2	0.82±0.10	28±0.18	92.0±0.12
F10	4.24±0.2	2.6±0.4	276.5±1.6	0.92±0.04	21±0.14	93.8±0.18

Post-compression evaluation of all formulations showed consistent results. Thickness fell within the range of 4.10±0.05 mm to 4.26±0.06 mm, and hardness was between 2.6±0.4 and 3.5±0.5 kg/cm². Friability was below 1%, indicating good tablet integrity. Weight variation was between 273.2±0.8 and 278.4±1.6 mg, within pharmacopoeial limits. Drug content ranged from 84.3±0.12% to 93.8±0.18% indicating good content uniformity.

In-vitro dissolution Studies of Fast disintegrating tablets

Table 10: In-vitro dissolution study of FDTs.

Time (min)	Cumulative % Drug Release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
10	40.37	56.85	63.12	65.02	64.16	65.12	66.37	63.86	64.28	67.21
20	43.52	58.24	65.03	67.87	64.64	67.23	68.03	65.72	67.04	70.34
30	50.94	59.48	65.68	68.03	66.32	69.89	70.17	67.81	69.16	73.45
40	56.37	62.73	66.82	69.04	67.02	72.13	71.28	68.62	71.12	75.24
50	57.62	65.38	69.12	70.65	68.54	73.97	73.94	70.12	73.41	77.12
60	61.04	67.32	72.52	74.32	71.22	74.24	77.20	73.18	75.32	**81.03**

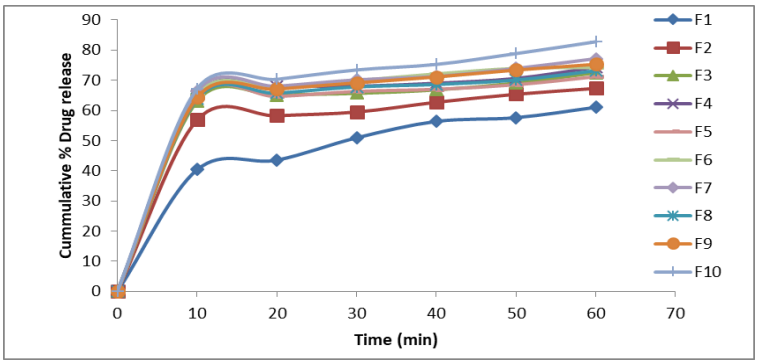

Fig. 9: In-vitro dissolution study of FDTs.

Fast disintegrating tablets (FDTs) of Simvastatin (F1-F10) were formulated using direct compression, incorporating different proportions of super disintegrants: Sodium Starch Glycolate (SSG), Cross Povidone (CP), and Croscarmellose Sodium (CCS). Dissolution testing revealed that formulation F1, which did not contain any super disintegrants, achieved a drug release of 61.04% after 60 minutes.F2, F3, and F4, containing SSG, had releases of 67.32%, 72.52%, and 74.32%, respectively, with F4 being the highest. F5, F6, and F7, with CP, showed 71.22%, 74.24%, and 77.20% releases, with F7 being the highest. F8, F9, and F10, containing CCS, had releases of 73.18%, 75.32%, and 81.03%, respectively, with F10 being the highest. Among formulations F4, F7, and F10, which had higher proportions of super disintegrants at a 1:6 ratio, F10, with a high concentration of croscarmellose sodium, showed the highest drug release performance at 81.03% in 60 minutes (Satheesh Jogala et al., 2016, Battu SK.et al., 2007). Therefore, F10 is concluded to be the optimal formulation for fast disintegrating tablets due to its superior drug release performance.

Comparative study with marketed sample

Table 11: Comparative study of % Drug release.

Time (min)	Cumulative % drug release		
	Pure drug	F10	Marketed product
0	0	0	0
10	6.65	67.21	75.43
20	9.43	70.34	83.16
30	14.73	73.45	95.82

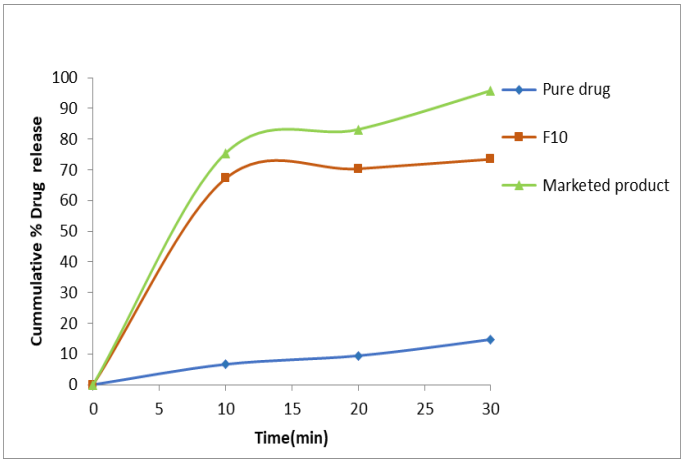

Fig. 10: Comparative study of % Drug release.

The comparative in vitro dissolution study showed that the marketed product (Z0COR*20mg) had the highest drug release of 95.82% at 30 minutes. In contrast, the pure drug and the optimized formulation (F10) released 14.73% and 73.45% of the drug, respectively. The marketed formulation demonstrated a significantly higher drug release compared to both the pure drug-Simvastatin and the optimized formulation (F10).

Stability studies of Fast disintegrating tablets

Table 11: Data of stability studies for Optimized batch- F10.

S.no.	Characteristics	Initial	At the end of 1month	At the end of 2month	At the end of 3month
1	Physical appearance	Almost white	No change	No change	No change
2	Drug content (%)	97.54%	97.23%	96.83%	95.65%
3	In vitro drug release	88.78%	86.95%	83.98%	81.85%

4. CONCLUSION

In this study, Simvastatin's aqueous solubility was enhanced using solid dispersions with PEG-4000 through three methods: Solvent Evaporation, Melting, and Solvent-Melt, each with varying drug-to-carrier ratios. Nine formulations were prepared: S4SD1, S4SD2, S4SD3 (Solvent Evaporation), M4SD1, M4SD2, M4SD3 (Melting), and SM4SD1, SM4SD2, SM4SD3 (Solvent-Melt). Among these, the Solvent-Melt method at a 1:6 ratio (SM4SD3) exhibited the best drug release. SM4SD3 was then formulated into fast-disintegrating tablets (FDTs) using super disintegrating agents SSG, CP, and CCS. The optimized formula, F10, containing high CCS concentration, showed the best release. FT-IR studies confirmed that there were no interactions between the drug and the excipients. XRD and DSC analyses indicated a decrease in the crystallinity of the solid dispersions, with all parameters adhering to official standards. The Fast Disintegrating Tablets (FDTs) achieved a drug release of 81.03% within 60 minutes and disintegrated in 21 seconds. When comparing the optimized formulation (F10) and the pure drug to the marketed product, the pure drug exhibited a release of 14.73%.formulation F10 shown 73.45% and Marketed product shown 95.82% in 30 min. The study concludes that solid dispersion methods, especially the Solvent-Melt method, significantly improve Simvastatin's solubility and dissolution rate. FDTs with CCS exhibited the best release, demonstrating the efficacy of these techniques for poorly soluble drugs.

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