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ENHANCING PRAVASTATIN SOLUBILITY THROUGH SOLID DISPERSION AND INCLUSION COMPLEXES WITH 2-HYDROXYPROPYL B-CYCLODEXTRIN: A COMPARATIVE STUDY

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ABSTRACT

Poor solubility in water is a major hurdle for many drugs, causing low oral absorption and bioavailability, leading to the failure of approximately 41% of drugs worldwide. Lipophilic drugs, like Pravastatin, often struggle with low dissolution rates. In this study, two methods were explored to enhance Pravastatin's solubility using 2-hydroxypropyl beta-cyclodextrin as a polymer. Solid dispersion formulations with varying drug-to-polymer ratios were prepared and analyzed, with the 1:3 ratio showing the most significant solubility improvement. Inclusion complexes were created using the kneading method, and again, the 1:3 drug-to-polymer ratio exhibited the highest solubility enhancement. Overall, both techniques proved effective in significantly enhancing Pravastatin's solubility, bringing it within an acceptable range, as assessed in vitro.

Keywords: Solubility, Pravastatin, Solid dispersion, Inclusion complex, Beta-Cyclodextrin.

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INTRODUCTION

Oral drug delivery offers numerous advantages, including stability, precise dosing, ease of production, and reduced risk of side effects [1]. However, achieving optimal oral drug bioavailability, absorption, and release from tablets and capsules remains a significant challenge in the pharmaceutical industry. Many drugs possess a lipophilic nature that hinders their solubility in biological fluids, particularly water, leading to poor dissolution and limited absorption within the gastrointestinal tract. This issue contributes to the failure of approximately 41% of drugs globally [2]. Advancements in medicine necessitate achieving therapeutic effects with lower doses, which is impeded by the low solubility of many compounds in water [3]. The primary reason for diminished clinical effectiveness lies in the premature elimination of poorly soluble drugs from the gastrointestinal tract before they can dissolve and be absorbed [4]. Given that about 70% of the human body comprises water, the successful and effective treatment depends on delivering drugs in low doses with high bioavailability. To enhance

treatment outcomes, concerted efforts are focused on improving the dissolution of poorly water-soluble drugs, thereby enhancing their oral bioavailability [5].

Statins, particularly HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme-A) reductase inhibitors, are widely recognized and frequently prescribed medications for the management of high cholesterol levels and atherosclerosis. These medications function by suppressing the function of the enzyme HMG-CoA reductase, a critical player in the liver's cholesterol metabolism [6, 7]. Pravastatin, a member of the statin family, is a specific inhibitor of HMG-Coenzyme-A reductase. Importantly, at therapeutic doses, pravastatin doesn't completely block the enzyme, allowing for the production of mevalonate, a vital component for normal biological processes. Pravastatin intervenes at early stages, preventing the accumulation of toxic sterols in the body. This safety profile is notable, as pravastatin does not increase the incidence of gallstones or lithogenicity [8].



Pravastatin is widely prescribed for anti hyperlipidemic purposes and is classified as a Class 2 drug in the Biopharmaceutics Classification System (BCS). However, it exhibits very low and non-linear bioavailability primarily due to its poor dissolution properties. Pravastatin possesses a crystalline structure and boasts less than 5% oral bioavailability [9]. It reaches its peak concentration (C_{max}) within 1-3 hours, with a high protein binding rate of 95%. Various techniques, such as micronization, cyclodextrin complex formation, and the use of surfactants and solubilizers, are employed to enhance its dissolution. Moreover, approaches such as incorporating solid dispersions into water-soluble carriers, employing salt formulations, and advancing self-emulsifying microdispersions and nanodispersion systems have been investigated to enhance the solubility, dissolution rate, and overall bioavailability of pharmaceutical compounds with limited solubility [10].

Enhancing the solubility and dissolution of drugs with low water solubility can be achieved through various approaches. These methods include Micronization that involves reducing the particle size of the drug, which increases its surface area. The increased surface area, in turn, leads to improved dissolution [11]. By using surfactants, the solubility of poorly soluble drugs can be improved. Surfactants help in dispersing the drug in the aqueous medium, making it more readily available for dissolution [12, 13]. Water-soluble polymers can be used to form complexes with the drug, increasing its solubility. This method promotes the dissolution of the drug in aqueous solutions [14]. Drug Derivatization by Converting the drug into strong electrolyte salt forms can lead to a higher dissolution rate. These modified forms of the drug are more readily soluble in water [15]. Liquid solid formulations involve converting a drug into a liquid state, which is then incorporated into a solid carrier. This approach enhances drug solubility and dissolution by maintaining the drug in a more dispersible form [16]. Modifying the solid-state of the drug substance is achieved by decreasing the crystallinity of the drug or modifying its crystal lattice. This process results in the formation of solutions and dispersion formulations, ultimately enhancing drug dissolution and solubility [17].

Various carriers have been employed in the previously mentioned approaches to improve solubility and dissolution of highly lipophilic drugs. These carriers encompass a range of polymers such as PEG (polyethylene glycol), PVP (poly-vinyl pyrrolidone), lactose, Chitosan, β -CD (beta-cyclodextrin), and HPMC (hydroxypropyl methylcellulose) [18]. They are widely utilized to augment the water solubility of these lipophilic

drugs. In contemporary pharmaceutical research, a group of non-ionic surfactants known as poloxamers has also emerged as effective agents for increasing water solubility through various techniques [19].

The solubility of drugs is influenced by a multitude of parameters, and by modulating these parameters, we can effectively enhance the solubility of different drugs. Thus, the methods mentioned above are employed to improve solubility by impacting factors such as particle size, surface area, wetting ability, and more [20].

MATERIAL AND METHODOLOGY

Material

Pravastatin was obtained from Global Pharma Rawalpindi, Pakistan as a gift. Hydroxyl propyl beta cyclodextrin, Ethanol, Methanol and chloroform were from Sigma Aldrich (Norway). High pressure liquid chromatography (HPLC) of Milli-Q[®] system by Milford-MA, USA. Membrane filters of size 0.45 μ m were obtained from Sartorius (Germany). All chemicals used in research were of analytical grade.

Methods

Formation of solid dispersion

Solid dispersions, denoted as F1, F2, and F3, were prepared using Pravastatin and hydroxypropyl beta-cyclodextrin in molar ratios of 1:1, 1:2, and 1:3, respectively. The solvent evaporation method was employed for their formulation [21]. The polymer was introduced into hot distilled water, while the drug was added to ethanol at a controlled temperature of $25 \pm 0.50^{\circ}\text{C}$. The polymer solution was carefully added drop by drop into the drug solution with continuous stirring. After an hour of continuous stirring, the resulting formulation was subjected to a vacuum evaporator to remove the solvent. This process yielded a solid mass, which was subsequently ground into a powder and passed through a No.60 sieve. The sieved powder was then stored in an airtight container for further processing [22].

Formation of inclusion complexes

Inclusion complexes were produced using the kneading process [23], where precise measurements of the drug and polymer were employed. Three distinct formulations, namely F4, F5, and F6, were created, each with varying ratios of the polymer. Pravastatin and hydroxypropyl beta-cyclodextrin (HBCD) were combined in molar ratios of 1:1, 1:2, and 1:3 within a mortar.

The procedure commenced with the placement of HBCD in the mortar, followed by the gradual addition of a small quantity of ethanol to form a paste through trituration. Subsequently, the drug was slowly added to the blend, and trituration was maintained for an extra hour. This slurry was then subjected to a 24-hour drying process in an oven to eliminate ethanol. The resultant dried slurry was

subsequently transformed into powder and passed through a No.60 sieve. The resulting powder was stored under specific conditions [24].

Entrapment Efficiency (Product Yield)

The prepared formulations, including solid dispersions and inclusion complexes, were dissolved in a phosphate buffer with a pH of 7.4. This was done to enhance the dissolution of micro particles. Before filtration, the resulting suspensions underwent evaporation to eliminate the solvent.

For the determination of drug content and entrapment efficacy, the residue obtained after filtration was further washed and diluted using phosphate buffer with a pH of 7.4. Subsequently, the absorbance of these samples was measured at 238nm using a UV/VIS spectrophotometer, and this process was carried out in triplicate to ensure accuracy.

The efficacy of the method used was assessed by calculating the product yield. To calculate the entrapment efficiency, the same procedure was followed, but this time with 10mg of the drug.

$$\text{Product Yield} = 100 - \text{Mass loss}$$

$$\text{Mass Loss (\%)} = M_0 - M_1 / M_0 \times 100$$

Where M_0 = Initial weight and

M_1 = final weight

Entrapment efficiency was determined by dividing absorbance of sample containing 10 mg of pravastatin with absorbance of 10 mg of pure pravastatin [25].

Micrometric Properties

Micrometric properties play a crucial role in assessing the flow characteristics of a powdered formulation. Various parameters were employed to evaluate these properties, including bulk density, Hausner's ratio, Carr's index, and the angle of repose.

Bulk Density

(BD) represents the ratio of the mass of the powdered formulation to the volume it occupies. To determine BD, the powdered formulation was placed in a measuring cylinder, and the volume it occupied was visually recorded. The mass of this volume of powder was then measured using an electronic weighing balance [26], and BD was calculated using the formula:

$$BD = \text{Mass of Powder} / \text{Volume Occupied}$$

Tapped Density

It is a measurement of a powder's density after undergoing tapping. The powdered formulation was poured into a measuring cylinder and subjected to repeated tapping. The resulting volume of the powder, with a known mass, was noted, and the tapped density was determined using the following calculation [27]:

$$\text{Tapped Density} = \text{Mass (M)} / \text{Tapped Volume}$$

Hausner's Ratio

This ratio is calculated by dividing the tapped density by the bulk density. A Hausner's ratio below 1.25 signifies favorable flow characteristics of the powder particles [28]. The calculation is executed using the subsequent equation:

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density}$$

The Angle of Repose (θ)

It was measured to assess the powder's flow properties. A value of less than 30 degrees confirms good flow properties of the powder passing through a funnel. The angle of repose for the powdered formulation was determined using a funnel technique and the following equation [29]:

$$\text{Angle of Repose } (\theta) = \tan \theta = \frac{h}{r}$$

Drug Content

Drug Content analysis was conducted on solid dispersions and inclusion complexes formed through solvent evaporation and kneading methods, respectively. This procedure entailed dissolving a precise amount of the formulations in ethanol and subsequently assessing the drug content using a UV-spectrophotometer at 238nm [30].

Solubility Study

Solubility data for both Pravastatin in its pure form and the SV-HPBCD complex were gathered under varying conditions, including pH 1.2 and 7.4 phosphate buffer solutions, as well as in distilled water. The shake flask method was employed for this purpose. The procedure involved adding a predetermined quantity of the sample into test tubes containing 5ml of distilled water, pH 1.2 buffer, and pH 7.4 buffer. These tubes with the samples were vigorously mixed for 5 minutes, followed by placement in a shaking bath for a consistent 48-hour duration at a controlled temperature of $37 \pm 0.5^\circ\text{C}$. To analyze the solubility, a portion of the prepared solution was extracted and then subjected to filtration through $0.45\mu\text{m}$ filters. Subsequently, the filtrate was diluted with the appropriate prepared buffer solution and assessed for Pravastatin concentration using a UV-spectrophotometer at a wavelength of 238nm. This process was conducted to determine the solubility profiles of Pravastatin in different media and conditions [31].

Dissolution Studies

Dissolution testing of pure Pravastatin, inclusion complex, and solid dispersion formulations was carried out using a USP type-2 dissolution apparatus equipped with paddles. In this experiment, 900 ml of Buffer solutions pH 1.2 and pH 7.4 were employed as the dissolution medium. The dissolution process was carried out under consistent conditions at a temperature of $37 \pm 0.5^\circ\text{C}$, with a constant stirring rate of 50.00 rpm as per USP guidelines [32].

At predefined time intervals, 5 ml samples were withdrawn from the dissolution apparatus, and an equivalent volume of buffer was immediately replenished to maintain a consistent volume throughout the experiment. These withdrawn samples were subsequently diluted, filtered, and assessed for Pravastatin content using a spectrophotometer at a wavelength of 238 nm, which measured absorbance. This dissolution study was conducted in triplicate (n=3) to ensure reliability and consistency of the results. From the obtained mean values, cumulative drug release profiles were calculated, and these values were utilized to construct dissolution curves for the purpose of studying release kinetics. The percentage of drug released at various time intervals was assessed and graphed against time, enabling a comprehensive depiction of the drug release patterns from the various formulations [33].

FTIR Spectroscopy

To validate the formation of complexes, FTIR spectra were generated using an IR spectrophotometer (Tensor 27, OPUS software) over a spectral range of 400 to 4000 cm⁻¹. Spectra were recorded for the drug, polymer, physical mixture, and the various formulations. These samples were prepared by grinding the complexes using a mortar and pestle and subsequently subjecting them to infrared radiation. Changes in characteristic peaks in the spectra of the formulations provided evidence of complex formation [34].

Zeta Size and Potential Measurement

An average particle size of the prepared formulations was determined using a Malvern Zetasizer. The microparticles were suspended in filtered (0.24µm) pure water to measure particle size. Additionally, the zeta potential was measured, as it plays a role in the stability of the formulations [35].

Thermal Analysis

To evaluate the stability of microparticles within the prepared formulations, two analytical techniques, namely, differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA), were employed. DSC (Q600TA USA) entailed subjecting the samples to a gradual temperature increase, reaching up to 400°C, in a nitrogen atmosphere, with a heating rate of 10°C/min and a flow rate of 10 ml/min. For the assessment of thermal stability using TGA, complexes were analyzed under an inert atmosphere across a temperature range spanning from 0°C to 800°C. Each sample, weighing 4 mg, was positioned in standard aluminum pans, covered with lids, while an empty aluminum pan served as a reference [36].

SEM Analysis

Scanning electron microscopy (SEM) was employed to examine the shape, morphology, and particle size of Pravastatin-containing formulations. These formulations were affixed to metal substrates using double-sided adhesive tape. The powder was gold-coated with a 10 nm layer and observed under a scanning electron microscope [37].

XRD Studies

For comparison purposes, the physical mixture was analyzed alongside drug samples using powder X-ray diffraction (XRD). XRD analysis was performed to characterize the pure drug and its formulations. XRD diffractograms were obtained in the temperature range of 5.0 to 51°C at an angle of 2θ to analyze the amorphous and crystalline nature of Pravastatin [38].

RESULTS AND DISCUSSION

Aqueous Solubility

The determination of drug solubility involved adding an excessive quantity of the sample was added to 10 ml of distilled water within a sealed test tube. These test tubes were then subjected to sonication for 30 minutes, followed by placement in a uniformly controlled temperature shaking water bath for 24 hours. After this incubation period, a specific quantity of the sample was extracted from the solution, carefully filtered through filter paper, and subsequently diluted with pure ethanol. The drug's concentration was subsequently determined utilizing a UV-spectrophotometer at a wavelength of 238 nm [39]. At the conclusion of the 24-hour period, the solubility of the pure drug was determined to be 154 µg/ml. The solubility of the physical mixture was found to be 358 µg/ml. In the formulations prepared via solid dispersion, solubilities were measured to be 468, 490, and 535 µg/ml, while in the inclusion complexes, the solubility values were 410, 466, and 520 µg/ml (as detailed in Table 1).

These findings align with the research conducted by Shilpi et al. in 2015 [40], who investigated the solubility enhancement of Nelfinavir through its complexation with β-cyclodextrin at various ratios. Our results also demonstrate a significant improvement in the solubility of Pravastatin through complex formation with a polymer at different ratios, further corroborating the potential for enhancing drug solubility via this approach.

Entrapment Efficiency and Product Yield

Different formulations were prepared utilizing both solid dispersion and inclusion complexes, varying the ratios of the polymer, Hydroxypropyl beta cyclodextrin, and the drug. To assess the effectiveness of these methods, the prepared formulations were examined for both entrapment efficiency and product yield. The product yield for

Table 1: Aqueous solubility of drug and prepared formulations.

Sr. No	Formulation	Aqueous Solubility ($\mu\text{g/ml}$)
1	F0	154.0
2	PM	358.0
3	F1	468.0
4	F2	490.0
5	F3	535.0
6	F4	410.0
7	F5	466.0
8	F6	520.0

Table 2: Entrapment efficiency and product yield (%).

Formulations	Entrapment efficiency (%)	Product Yield (%)
F1	81.10 $\pm$ 0.20	85.50 $\pm$ 0.25
F2	84.25 $\pm$ 0.15	89.10 $\pm$ 0.50
F3	89.70 $\pm$ 0.15	92.45 $\pm$ 0.25
F4	78.65 $\pm$ 0.50	81.70 $\pm$ 0.25
F5	82.20 $\pm$ 0.25	86.50 $\pm$ 0.50
F6	85.00 $\pm$ 0.50	89.10 $\pm$ 0.20

Table 3: Micrometrics data of drug and prepared formulations.

Sr. No	Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's ratio	Angle of repose (Θ)
1	Fo	0.626	0.726	1.15	21.20
2	PM	0.656	0.767	1.16	22.40
3	F1	0.646	0.748	1.15	23.60
4	F2	0.639	0.751	1.17	22.80
5	F3	0.635	0.765	1.20	23.40
6	F4	0.642	0.748	1.16	23.81
7	F5	0.636	0.754	1.18	23.10
8	F6	0.647	0.770	1.19	22.80

the different formulations fell within the range of 81.70% to 92.45%, with a precision of $\pm 0.25\%$. Likewise, the entrapment efficiency ranged from 78.65% to 89.70%, with a precision of $\pm 0.50\%$ to $\pm 0.15\%$, as presented in the table. These results collectively indicate that all the formulations achieved entrapment efficiency and product yield percentages that met acceptable standards.

The entrapment of the drug within the micro particles was found to be contingent on the concentration of the polymer employed. Notably, the F3 formulation, which was prepared through the solid dispersion method and had a higher drug-to-polymer ratio of 1:3, exhibited the highest entrapment efficiency at 89.70%. Similarly, the F6 formulation, created with a drug and polymer ratio of 1:3 using the inclusion complexes method, achieved an entrapment efficiency of 85% (Table 2). This observation underscored the correlation between increased polymer concentration and improved entrapment efficiency. The rationale behind this phenomenon lies in the larger number of available cavities within the polymer matrix,

facilitating greater drug incorporation. These findings align with a study by Shashank et al. in 2015 [41], where micro particles were developed using chitosan as the polymer to enhance solubility. Their research also demonstrated that higher concentrations of hydrophilic polymers led to greater entrapment efficiency, further substantiating the relationship observed in our study.

Micrometric Properties

The formulations, which were prepared using both the solid dispersion method (F1, F2, and F3) and the inclusion complexes method (F4, F5, and F6), underwent a thorough examination of their micrometric properties. These properties encompass various flow-related parameters such as tap density, bulk density (BD), angle of repose (Θ), and Hausner's ratio (HR). Hausner's ratio, a key indicator of flow quality, should ideally be less than 1.25 to ensure smooth flow. Notably, the results of these properties fell well within the acceptable limits. Additionally, to qualify as having good flow properties, the angle of repose should be

below 30 degrees. It's worth mentioning that all formulations exhibited an angle of repose measuring less than 25 degrees, a clear indication of excellent flow properties [42]. As depicted in the table 3, all flow parameters were well within the acceptable limits, suggesting an appropriate release of the drug.

FTIR Studies

FTIR spectra were conducted for the drug, physical mixture, and formulations prepared via various methods to ascertain the formation of complexes between pravastatin (the drug) and HBCD (the polymer). Analysis of the FTIR spectra revealed distinct peaks associated with pravastatin (the drug) at 3298.28cm^{-1} , 2947.23cm^{-1} , and 1224.80cm^{-1} . These peaks corresponded to features of cyclic amines, C-H stretching, O-H bending, and C=O stretching. In the FTIR spectra of the HBCD (Hydroxypropyl Beta cyclodextrin) polymer, specific peaks were observed at 1031.92cm^{-1} (C-O stretching vibration), 3296.35cm^{-1} (OH stretching), and 2912.51cm^{-1} (CH stretching vibration). Similar peaks from both the polymer and the drug were evident in the physical mixture. These findings collectively indicate the absence of any significant interaction or complex formation between pravastatin and the HBCD polymer [43, 44].

In contrast, the spectra of the inclusion complexes displayed notable changes. Peaks corresponding to pravastatin, particularly the O-H stretching peak at 3298.28cm^{-1} , disappeared completely, while slight shifts were observed in the peaks at 2947.23cm^{-1} (shifted to 2818.30cm^{-1}) and 1224.80cm^{-1} (shifted to 1244.09cm^{-1}). These spectral alterations strongly suggest the occurrence of bond formation between pravastatin and HBCD (Hydroxypropyl beta-cyclodextrin) within the inclusion complexes. Furthermore, the FTIR analysis of solid dispersion demonstrated that characteristic peaks associated with O-H stretching and C-H stretching at 3298.28cm^{-1} and 2947.23cm^{-1} , respectively, vanished completely. A slight change was observed in the peak at 1224.80cm^{-1} , which shifted to 1261.45cm^{-1} . These findings from the FTIR results of solid dispersion confirm the formation of a complex between the drug and the polymer.

In summary, the FTIR spectra of the drug, polymer, and the various formulations reveal that certain drug peaks either disappeared or shifted to lower values. These changes strongly indicate the formation of complexes between the drug and the hydrophilic polymer, supporting the enhancement of pravastatin's solubility [45]. The results obtained are visually represented in Figures 1.

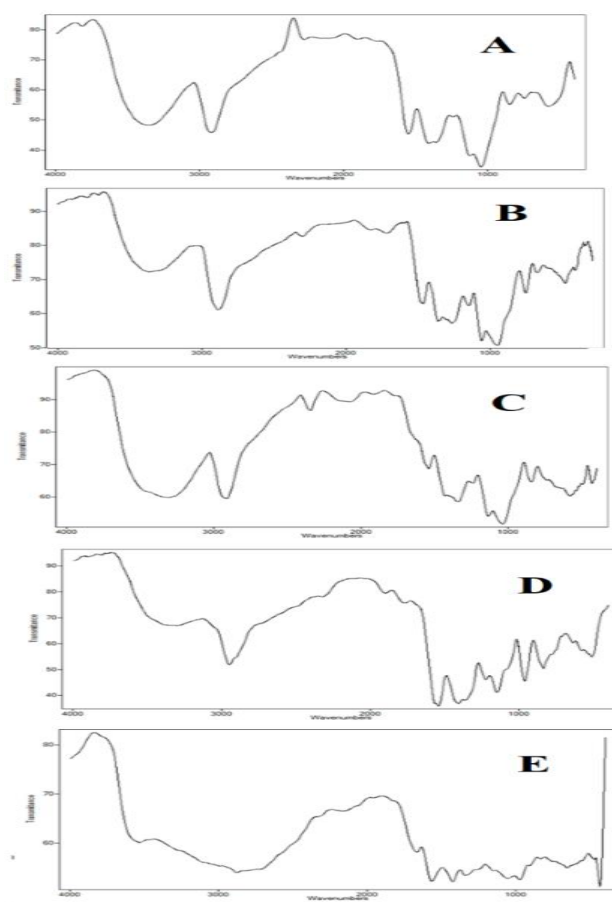


Figure 1: FTIR Spectra of Pravastatin (A), HBCD (B), physical mixture (C), inclusion complex (D), solid dispersion (E).

Scanning-electron Microscopy

The examination of surface structure or morphology, along with the assessment of shape and size distribution of microparticles within the complexes, was performed using SEM (Scanning Electron Microscopy). The drug typically exhibits uniform crystalline particle sizes. Notably, the SEM images of the Inclusion complex and solid dispersion (depicted in Figure 2), which were prepared through kneading and solvent evaporation methods, respectively, displayed an amorphous nature in comparison to the pure drug. These images also provide insights into the loading of the drug onto the polymer and the subsequent release of the drug from the complexes.

Interestingly, these images revealed the presence of small pores on the surface of these complexes. These pores play a crucial role in explaining the mechanism of drug release, which occurs through the penetration of water into the microparticles by entering through these small pores from the surroundings. Our findings are consistent with the research conducted by A.N. et al. in 2007, which emphasized that increased porosity or alterations in the surface morphology of microparticles enhance drug release from formulations prepared through solid dispersion and inclusion complexes [46].

Zeta Sizer and Zeta Potential

The stability and size of the prepared microparticles were assessed using zeta potential

and zeta sizer, respectively. The majority of these microparticles exhibited consistent and uniform sizes, typically falling within the micron range. It's worth noting that the size of particles plays a pivotal role in influencing solubility and drug release from complex or carrier systems. The surface area of particles is directly dependent on their size, with smaller particles resulting in larger surface areas and improved wettability. The average particle size of the prepared formulations was observed to be within the range of 200-500 μm , as depicted in Figures 3. This range signifies that the microparticles were of appropriate size, which is crucial for enhancing solubility and promoting controlled drug release within the complex or carrier system.

Zeta potential serves as a crucial parameter for assessing the stability of formulations, where a neutral zeta potential indicates the stability of the formulation. In our case, the zeta potential of our formulations was found to be neutral, which is a strong indicator of their stability, as visually represented in Figure 3. This stability attribute facilitated the easy dispersion of microparticles and contributed to an increase in their solubility. Our findings align with the results presented by Shashank et al. in 2015. Their study similarly concluded that formulations with a neutral zeta potential exhibit improved solubility and enhanced stability [41].

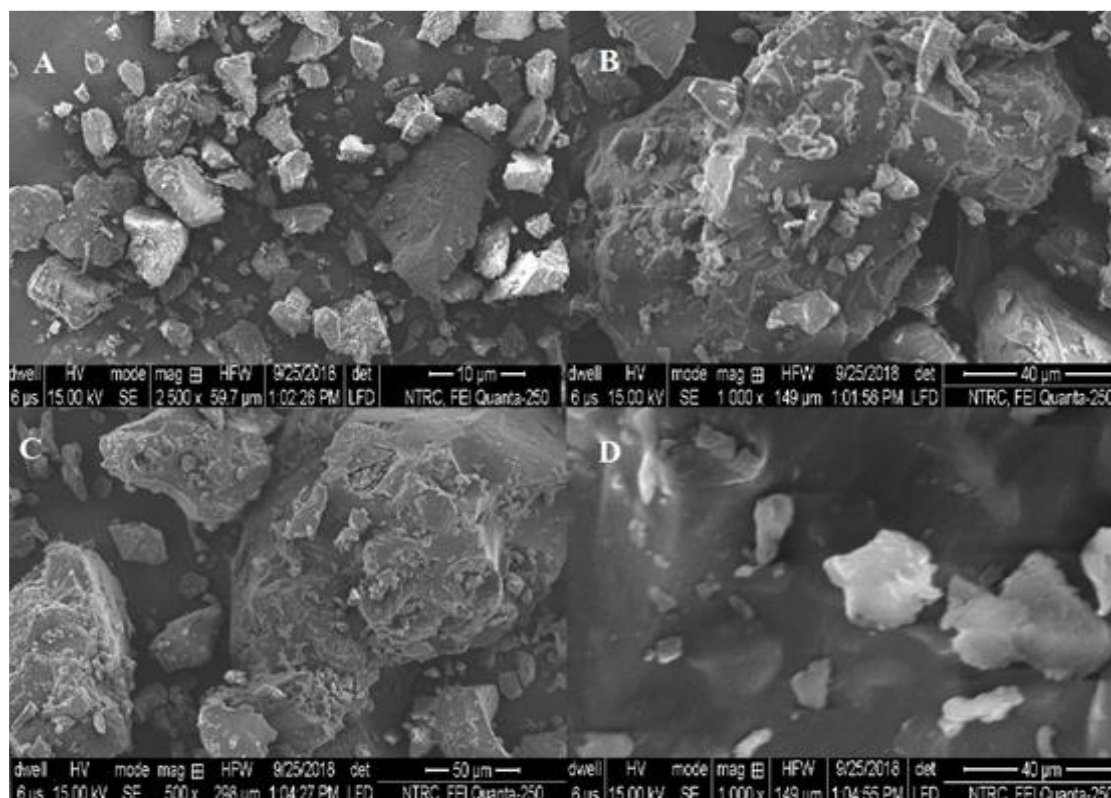


Figure 2: SEM micrograph of solid dispersion (A&B), Inclusion complex (C&D).

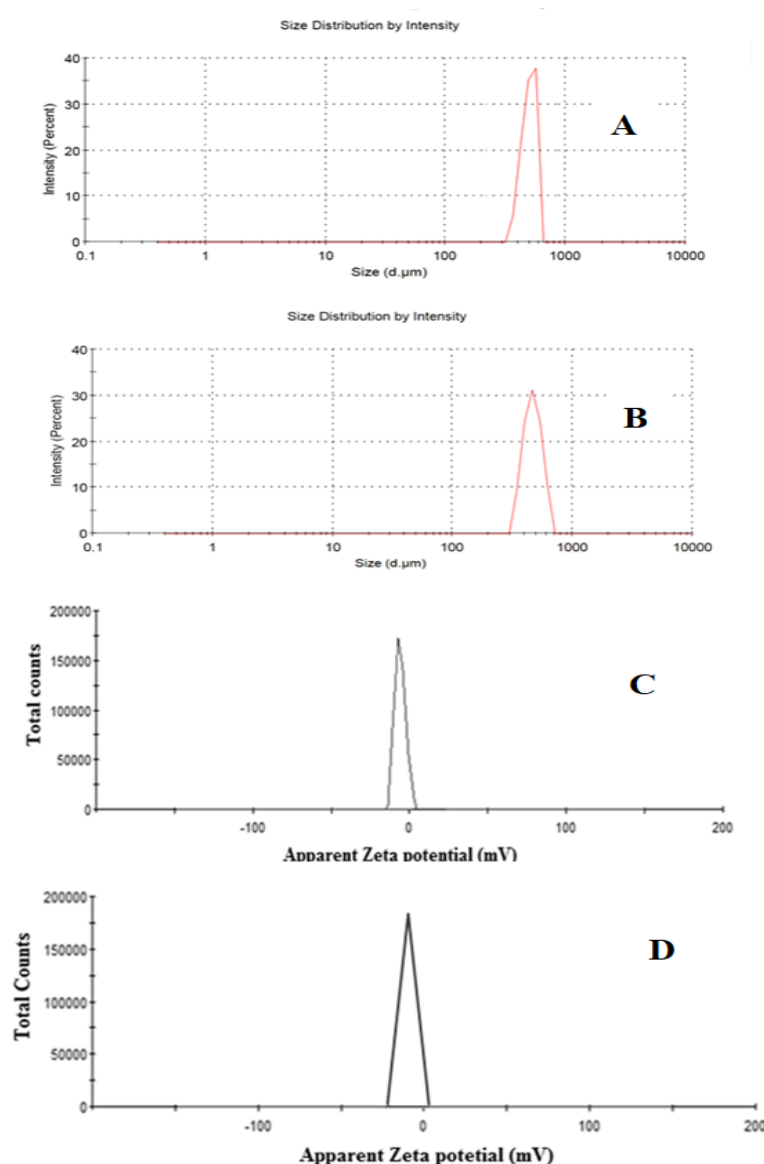


Figure 3: Particles size distribution of microparticles of solid dispersion (A), Particles size distribution of microparticles of inclusion complex (B), Zeta potential of formulation inclusion complex (F6) (C), Zeta potential of formulation solid dispersion (F3) (D).

Thermal Analysis

In order to study the stability of complexation formed between polymer and monomers, prepared formulations by both methods were subjected to thermal analysis. DSC & TGA thermogram of pure drug, HBCD and various formulations of prepared microparticles and results are presented in Figure 4. In the differential scanning calorimetry (DSC) thermogram of the pure drug, pravastatin, a sharp endothermic peak was evident at 215 °C. In contrast, the DSC thermogram of HBCD displayed a peak at 79 °C. In the thermogravimetric analysis (TGA) curve of pure Pravastatin, a gradual mass loss was observed, with a total loss of

approximately 62% in mass recorded up to 366 °C. Conversely, the TGA thermogram of β -CD exhibited a three-step reduction in mass, and at 375 °C, only 23% of HBCD remained. Upon comparing the results of the TGA thermogram of the pure drug with those obtained from the prepared formulation, it became apparent that a slower reduction in mass occurred. Even at 385 °C, the mass loss was only 48%. These findings provide further confirmation of the complexation between the polymer and the drug, indicating enhanced thermal stability. These results align with a study conducted by Chen et al. in 2008, where an improvement in the solubility of a low-water-soluble drug was reported through

complexation with other hydrophilic moieties [47].

X-ray Diffraction Study

The powder characteristics of drug and its formulations were analyzed by XRD. The diffractograms of pure drug, HBCD and formulations are shown in figure 5.

The XRD pattern of pravastatin displayed a series of distinct peaks, indicative of its crystalline nature [48]. In contrast, the XRD pattern of the formulation exhibited fewer peaks, and these peaks had lower intensity. These results strongly suggest

that pravastatin underwent a transformation from its crystalline form to a less crystalline or amorphous form. This transition contributed to an increase in dissolution and solubility, consequently enhancing the release of the drug.

Our findings align with the research conducted by Graeser et al., which also emphasized that the transformation of a drug from its crystalline state to an amorphous form results in improved solubility and enhanced drug release [49].

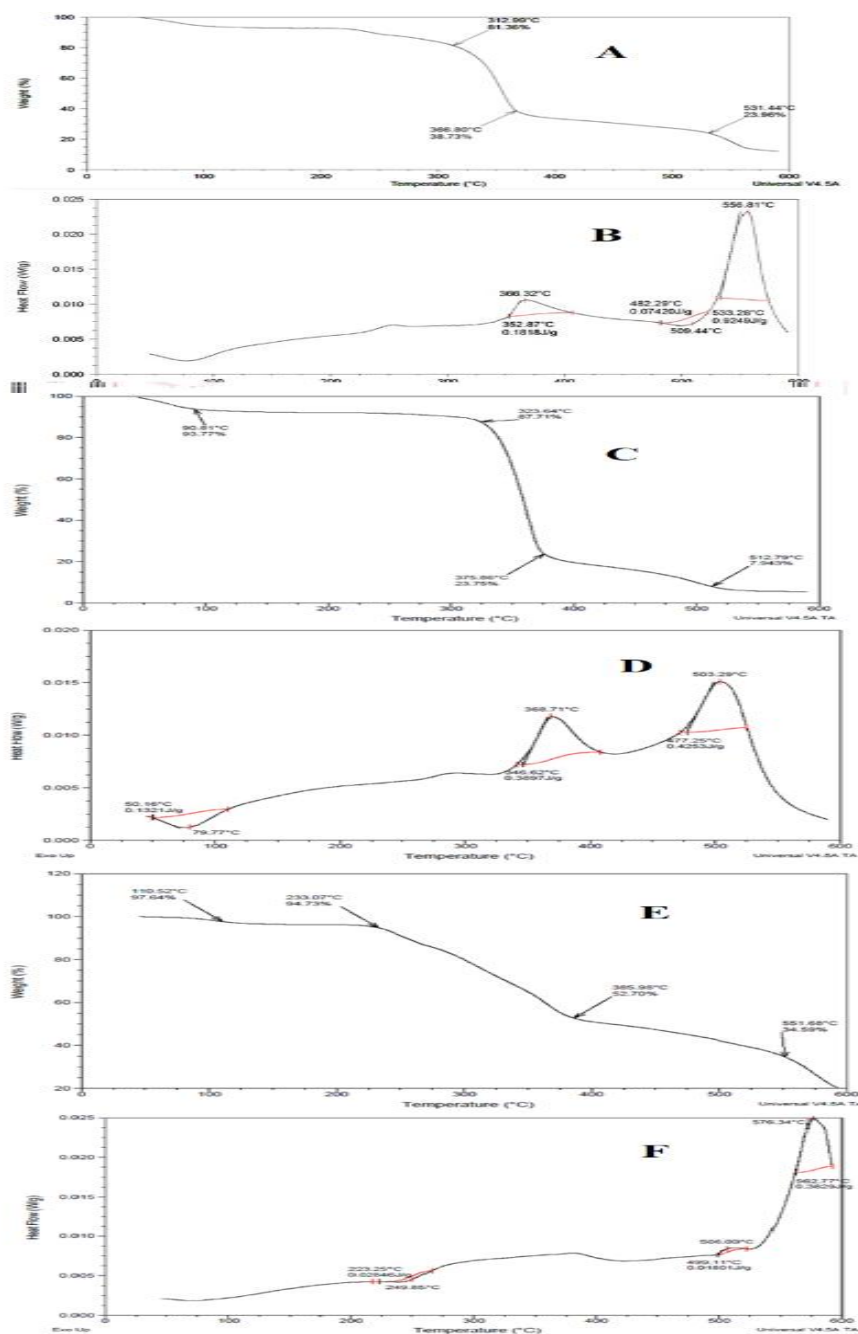


Figure 4: Thermograms, TGA of Pravastatin (A), DSC of Pravastatin (B), TGA of HBCD (C), DSC of HBCD (D), TGA of formulation (E), DSC of formulation (F)

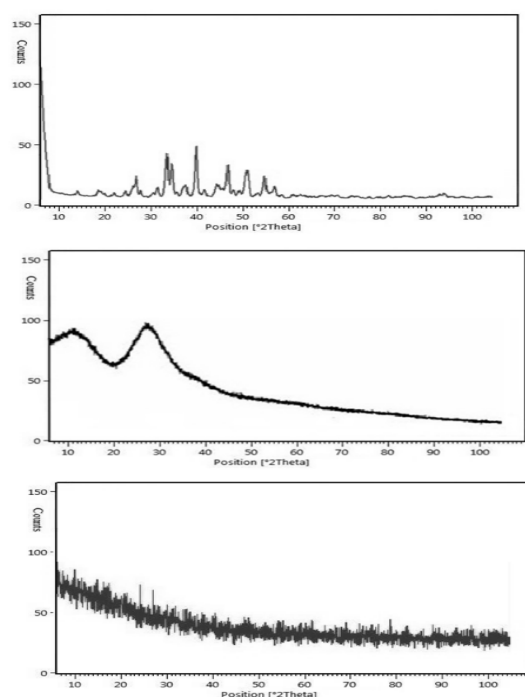


Figure 5: XRD pattern of Pravastatin (A), HBCD (B), Formulation (C).

Dissolution Studies

In our dissolution studies, we employed hydrochloric acid (HCl) buffer with a pH of 1.2 and phosphate buffer with a pH of 7.4 to assess the in-vitro release of the drug. The results of these dissolution studies, including the percent drug release from various formulations, are presented in table 4 and 5, as well as figure 6.

For the pure drug, the release percentage ranged from 10% to 34%. In contrast, the release from different formulations, prepared using solid dispersion and inclusion complexes, at pH 1.2 exhibited a significant improvement, ranging from 38% to 99.91%. Similarly, at a basic pH of 7.4, the release of the pure drug ranged from 11% to 33%, while the release from different formulations ranged from 36% to 99.49%. These results clearly demonstrate that drug release from various formulations was enhanced by using different ratios of the polymer, hydroxyl beta cyclodextrin. This suggests that an increase in the polymer ratio

within the formulations leads to a corresponding increase in drug release. Notably, drug release plays a pivotal role in enhancing the oral bioavailability of lipophilic drugs, as it often represents the rate-determining step [50]. It's worth mentioning that drug release from microparticles prepared by solid dispersion was greater compared to those prepared by inclusion complexes. This phenomenon can be attributed to the decrease in particle size and the modification in the crystal structure of the drug. Oral bioavailability, in essence, depends on the rate of dissolution and the absorption of the drug within the gastrointestinal tract. As particle size decreases, the dissolution rate increases, primarily due to the expanded surface area, our findings align with previous studies, such as Fahmy et al. (2008) [51]. Taken together, the results from our dissolution profile study strongly indicate a significant enhancement in oral bioavailability.

Table 4: *In-vitro* pravastatin release at pH 1.2

Time	F0	PM	F1	F2	F3	F4	F5	F6
30	10.15	36	74.35	76.55	78	67.55	73	75.65
60	15.2	50.35	85.34	87.35	88	78	82	88.45
90	22.4	55.44	94.52	93.96	95.62	81.34	93.65	96.55
120	32.42	71.35	99.31	99.37	99.59	98.9	99.19	99.41

Table 5: *In-vitro* pravastatin release at pH 7.4

Time	F0	PM	F1	F2	F3	F4	F5	F6
30	10.15	38	72.35	74.55	78.67	76.55	78.55	76.65
60	15.20	54.45	86.64	88.15	89.69	82.68	85.88	88.85
90	22.40	60.35	94.62	94.55	95.90	94.68	95.65	96.15
120	32.42	74.45	99.61	99.78	99.85	99.76	99.69	99.91

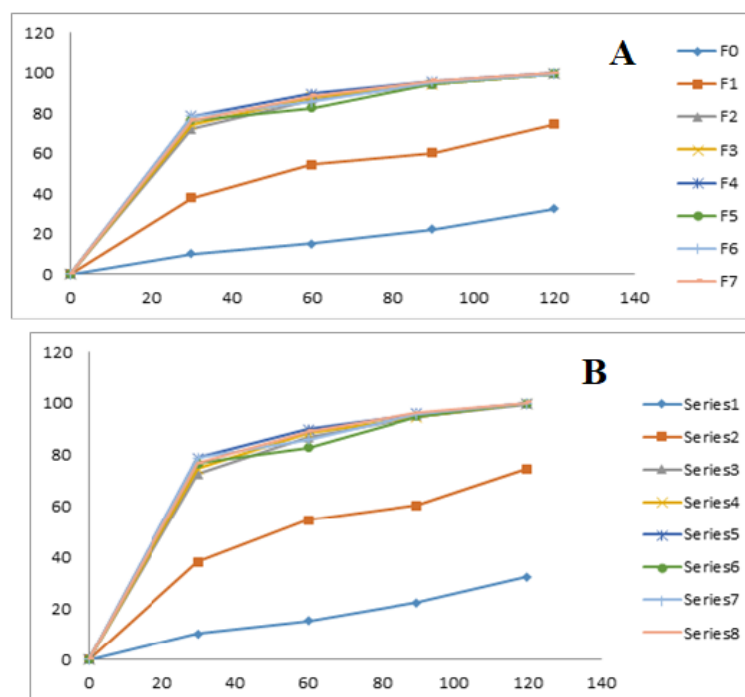


Figure 6: *In-vitro* drug release at pH 1.2 (A) and pH 7.4 (B).

Our dissolution findings underscored the significant enhancement of aqueous solubility and dissolution of pravastatin, the primary drug in this study, achieved through the incorporation of hydroxyl beta-cyclodextrin. Furthermore, it was evident that formulations prepared via the solid dispersion method exhibited a higher release rate when compared to formulations prepared using inclusion complexes. These observations are consistent with the conclusions drawn by Patel et al. in their 2008 study [22], which focused on the solubility enhancement of lovastatin through the utilization of gum derived from locust bean as a polymer. Patel's research similarly found that formulations prepared through solid dispersion exhibited greater solubility and dissolution rates in comparison to formulations formed via inclusion complexes. This alignment in findings further supports the robustness of our results regarding the enhanced dissolution rate achieved with solid dispersion.

CONCLUSION

In our current study, we explored two distinct formulation methods aimed at significantly increasing the solubility of pravastatin. These methods encompassed the utilization of solid dispersion and inclusion complexes, with 2-hydroxypropyl beta-cyclodextrin serving as the key polymer component. Through the application of these techniques, we achieved a substantial enhancement in the solubility of pravastatin. For the solid dispersion of pravastatin, we employed various concentrations of 2-hydroxypropyl β -cyclodextrin as the polymer. Utilizing the solvent

evaporation method, we formulated three distinct preparations and meticulously assessed their solubility enhancement through various parameters. Our findings revealed that the extent of solubility enhancement in pravastatin was directly contingent upon the concentration of the polymer. Consequently, formulations with a drug-to-polymer ratio of 1:3 exhibited the most significant increase in solubility when compared to ratios of 1:1 and 1:2. In the case of inclusion complexes, pravastatin was encapsulated using the kneading method. We observed a direct correlation between polymer concentration and the solubility of pravastatin, with formulations featuring a drug-to-polymer ratio of 1:3 demonstrating the most substantial solubility enhancement. In conclusion, our study demonstrates the efficacy and effectiveness of both solid dispersion and inclusion complex formation via the kneading method as potent tools for enhancing the solubility of poorly soluble drugs, and as a result, we successfully enhanced the solubility of pravastatin to levels deemed acceptable, as assessed in *in vitro* studies.

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