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DEVELOPMENT AND EVALUATION OF AN AMORPHOUS SOLID DISPERSION-BASED PROBUCOL IMMEDIATE-RELEASE TABLET

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ABSTRACT
Background: In its crystalline form, probucol has an extremely low bioavailability and is a poor water-soluble drug. The main aim of this study was to enhance the solubility and dissolution rate of probucol by using a solvent evaporation method to develop a solid dispersion that contains polyvinyl pyrrolidone K30 (PVP-K30) and polyethylene glycol 6000 (PEG 6000). **Methodology:** The solvent evaporation method is considered superior to other techniques for preparing solid dispersions due to its ability to achieve uniform drug distribution at the molecular level. This method ensures homogeneity by dissolving the drug and carrier in a common solvent, reducing the risk of drug recrystallization and enhancing solubility and bioavailability. **Result:** The drug-to-carrier ratio is the determining factor for dissolution enhancement. The FTIR spectra do not suggest any chemical interaction between PVP-K30 or PEG 6000. The immediate release profiles of both formulations were favourable, with F3 releasing approximately 95.31% of the drug and F6 releasing around 86.77% within 2 hours. This indicates a rapid drug dissolution, which is beneficial for achieving a fast onset of action and enhancing bioavailability. **Conclusion:** The solid dispersion formulations F3 & F6 successfully transformed crystalline probucol to an amorphous state, enhancing solubility & dissolving rates appropriate for immediate-release tablets.

INTRODUCTION

Enhancing the solubility of active pharmaceutical ingredients (APIs) has consistently proven to be a difficult task. APIs that are biopharmaceutical substances (BCS) II and are poorly soluble, resulting in their elimination from the body before their complete dissolution and absorption. One approach to improving the solubility and, consequently, the bioavailability of a drug substance is the development of amorphous solid dispersions (ASDs). ASDs are molecular compounds of the substance in a hydrophilic polymer matrix. The drug's solubility and dissolution rate are increased because of its existence in separate/disordered molecules in the amorphous phase, which prevents the activation energy needed for dissolution in the crystalline state[1]. Converting a crystalline substance to a high-

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energy amorphous state is a widely recognized technique. However, the amorphous form is typically thermodynamically unstable and tends to revert to a more stable crystalline state over time. This suggests that the risk of precipitation is perpetually present during the compound's processing, testing, and storage. This could decrease the dissolution rate and impact the compound's bioavailability following administration[2]. For example, combining hydrophilic polymers with a high glass transition temperature (Tg) has formed a solid dispersion (SD) and has been the subject of extensive research. This has been applied to a variety of drugs[3,4]. An immediate-release tablet with improved solubility and dissolution can enhance probucol's bioavailability and therapeutic efficacy. This formulation could increase the drug's exposure in the body and maintain its release, amplifying its antioxidative and lipid-lowering effects, offering better treatment options for patients with cardiovascular diseases or other conditions benefiting from probucol therapy[5]. The current study uses probucol as an active constituent for a low aqueous soluble drug. It functions as a cholesterol-lowering agent pharmacologically. Various methods have been used to manufacture amorphous SDs with probucol using polyvinyl pyrrolidone (PVP) as a carrier. Combining polyvinyl pyrrolidone (PVP) and polyethylene glycol 6000 (PEG 6000) significantly enhances tablet properties by improving drug solubility, mechanical strength, and dissolution behaviour. PVP, a hydrophilic binder, increases tablet cohesion and hardness, while PEG 6000 acts as a plasticizer and solubility enhancer, promoting faster water penetration and drug release. Together, they form solid dispersions that reduce drug crystallinity, improving solubility and bioavailability, particularly for poorly water-soluble drugs. The hydrophilic nature of PEG 6000 facilitates faster disintegration despite the increased hardness from PVP, resulting in enhanced dissolution rates. Additionally, the combination improves tablet stability by preventing drug recrystallization and maintaining the amorphous state over time. However, excessive concentrations of PEG 6000 may cause tablet softening or stickiness, while too much PVP could increase hardness, potentially slowing disintegration. Overall, the synergistic effect of PVP and PEG 6000 optimizes tablet performance by balancing mechanical strength, disintegration, and drug release. Formulations F3 and F6 are selected based on their superior performance across key evaluation parameters. Both formulations demonstrated enhanced dissolution profiles, achieving faster and more consistent drug release than the other candidates. Additionally, F3 and F6 exhibited improved compatibility with excipients, having favourable particle size distribution and saturation solubility, further supporting their selection. The reproducibility of the results across multiple trials indicated formulation robustness and reliability.

Based on these combined factors, F3 and F6 were identified as the most promising candidates for further development and optimization. No officially marketed solid dispersion (SD)-based probucol immediate-release (IR) tablet exists. Most commercially available probucol formulations are based on crystalline forms rather than solid dispersion technology. Therefore, the primary aim of this research is to develop a pharmaceutical formulation employing different polymer-based ASD technology for the preparation of Immediate-release tablets containing Probucol. The overarching goal is to address the challenges associated with Probucol's limited aqueous solubility, enhance its bioavailability, and ensure an immediate therapeutic effect.

MATERIALS AND METHODS

Materials

Probucol was procured as a gift sample from Yarrow Chem. Pvt Ltd Mumbai, India. PVPK30 and PEG6000 were procured from Loba Chemie, New Delhi. Sodium starch glycolate, microcrystalline cellulose, and talc were from Central Drug House (p) Ltd. New Delhi.

Methods

Pre-formulation Studies

Pre-formulation studies are conducted to identify the physical as well as the chemical properties of the drug alone and in combination with different polymers[6].

Organoleptic Properties

Appropriate procedures are used to determine the different organoleptic qualities of drug samples, such as color, odor, taste, and physical form.

Melting Point

The capillary tube method (MPA 100 melting point apparatus) was used to determine the melting point of the drug sample[7].

Solubility

The drug's solubility was evaluated in triplicate using a magnetic stirrer. An excess quantity of the drug was poured into a beaker containing solvent and stirred for 24 hours using a magnetic

stirrer to make a saturated solution. The saturated solutions were then filtered, diluted as needed, and examined using an ultraviolet-visible spectrophotometer (UV-1900i Shimadzu) [8].

Drug excipients compatibility study

Fourier transform infrared spectroscopy (FTIR) (Model Name: FT/IR-4100 type-A) was used to study drug-excipient compatibility in a non-thermal approach. 2-3 mg of sample was mixed with around 400 mg of dehydrated potassium bromide (KBr) and compacted into clear disks using a hydrostatic press at 6-8 tons of pressure. The scanning range was 500–4000 cm^{-1} with a resolution of 4 cm^{-1}[9].

Method of preparation of drug-loaded solid dispersions

Solid dispersions of Probucol in combination with polymers like PVP K30, PEG 6000, and in combination were formed utilizing different weight ratios by solvent evaporation, as mentioned in Table 1. A predefined amount of the chosen polymers was dissolved in methanol at room temperature, with continuous stirring at 500-600 rpm using a magnetic stirrer [10]. Once a clear solution had been established, the specified quantity of Probucol drug was progressively administered in parts, and the resulting combination was stirred continuously for 1 hr to assure the production of a transparent solution. Following that, the solvent was carefully evaporated at 35°C. The coprecipitate was carefully removed from the beaker, mashed in a mortar pestle, sieved through a 355 µm filter, and kept in a desiccator with $CaCl_2$ for preservation [11,12].

Table 1: Composition of Probucol solid dispersions

Formulations	Polymers	Drug-polymer ratio	Drug / Polymer (mg)
F1	PVP K30	1:2	500/600
F2	PVP K30	1:3	500/1500
F3	PVP K30	1:4	900/1500
F4	PEG 6000	1:2	500/1000
F5	PEG 6000	1:3	500/1500
F6	PEG 6000	1:4	900/1500
F7	PVP K30+PEG6000	1:1:2	300/300/600
F8	PVP K30+PEG6000	1:2:1	300/600/300
F9	PVP K30+PEG6000	3:2:3	600/300/600
F10	PVP K30+PEG6000	3:3:2	600/600/300

EVALUATION OF PROBUCOL SOLID DISPERSION

Determination of Saturation Solubility

The tests were conducted on probucol and solid dispersions to determine the percentage increase in Probucol solubility. Excess samples were transferred into 25 ml volumetric flasks containing 10 ml of 0.1N HCl acidic buffer.

The mixtures were stirred at 100 rpm on a magnetic stirrer for 24 hours at room temperature. The suspensions were then filtered using a 0.45 µm filter. The concentration of Probucol was evaluated using spectrophotometric measurement at 242 nm. Each sample had its solubility assessed in triplicate [10].

Scanning electron microscope (SEM)

The surface topography of the solid dispersion was carried out using a Cambridge Stereoscan S120 SEM operating at an acceleration voltage of 10 kV. After that, they were coated with a thin gold palladium layer using a sputter coater unit[13].

X-ray diffraction (XRD)

The XRD technique (EXPERT-PRO) was used to study the physical properties such as phase composition, crystal structure, and orientation of powder and solid samples. Samples were recorded over the 0.1-100nm[10,13].

Preparation of tablets through direct compression method

Probucol tablets were manufactured using the direct compression process, with the maximum solubility of two optimized formulations (F3 and F6). Table 2 shows the composition of the tablets made from the solid dispersion formulations (F3 and F6).

These formulations were triturated with talc, magnesium stearate, microcrystalline cellulose (MCC), and sodium starch glycolate (SSG) for 15 to 20 minutes. Each combination was then crushed independently into tablets using a single-punch tablet machine by direct compression[14].

Table 2: Composition table of optimised tablets (F3 and F6)

Composition	Qty (mg)
Solid dispersion containing 100 mg drug	250mg
SSG	55mg
MCC pH 101	95mg
Talc	5mg
Magnesium stearate	5mg

EVALUATION OF TABLETS

Content uniformity

20 tablets were randomly selected, and the average weight was determined. Tablets were crushed in a mortar individually, and a precise quantity of tablet triturate was extracted from each blend. The samples were transferred to twenty different volumetric flasks and diluted with purified water until the mark was reached. The mixture was thoroughly dissolved by shaking the contents and allowing it to stand for 30 minutes. The drug content of each tablet was estimated at λmax 242 nm compared to a blank reference and subsequently reported.

Friability (f)

The Roche friabilator was operated for 100 revolutions at 25 rpm for 4 minutes after pre-weighed tablets (n=10) were placed in it. Subsequently, the tablets were powdered and reweighed to determine the extent of their weight loss. The % friability was calculated using the formula [15].

$$\% \, \boldsymbol{Friability} = \frac{\boldsymbol{W1 - W2}}{\boldsymbol{W1}} \times \mathbf{100}$$

Hardness (h)

Hardness (diametral compressive strength) is the force required to break a tablet. Tablets must be capable of enduring mechanical pressure during transportation and handling. The hardness range considered adequate is 4-7 kg/cm2. The granules' firmness was assessed using a Monsanto hardness tester. measured and reported the average hardness of five tablets[6].

Thickness (t) and diameter

Using Vernier callipers, the diameter and thickness of the tablet were assessed. Three tablets were randomly selected and tested from each batch. the average of three readings was taken[8].

In-Vitro Release Studies

The *in vitro* dissolution investigation used the United States Pharmacopeia's (USP) Type-II dissolution apparatus. The dissolving media was 900 ml of pH 1.2 (0.1NHCl) maintained at 37.5±0.5°C for two hours. The paddle speed remained steady at 100 rpm. 5 ml of samples were extracted every 10 minutes. The extracted materials were analysed using UV spectroscopy at a wavelength maximum of 242 nm. To replace the withdrawn amount for the appropriate dissolving medium, the same amount of new pH 1.2 (0.1N HCl) was utilized each time [16].

Kinetic Release Data

The drug release kinetics for the optimized formulations were analysed using the DD solver. The best-fit model was selected by fitting the data obtained from the study into a variety of models, such as the zero-order, first-order, Higuchi, Korsmeyer Peppas, and Hixon-Crowell [8].

Similarity Factor

The in vitro drug release profile of probucol IR tablets was conducted under conditions comparable to those of the test formulation for probucol IR. The similarity factor between the two formulations was assessed using the information obtained from the drug release profile. To evaluate the similarity factor, the DD solver software 26 was used [8].

RESULTS AND DISCUSSION

Pre-formulation Studies

The drug was found to be a white crystalline powder with no odour or taste. Its melting point was between 126 and 128 ºC. The solubility of probucol in 0.1N HCL was 7.18mg/ml.

Drug excipient compatibility study

The drug's FTIR spectrum shows characteristic peaks corresponding to key functional groups, aligning with the IP reference spectrum (2010). This spectral concordance ensures compliance with pharmacopeial standards, verifying the drug's quality, purity, and authenticity. The spectra are illustrated in Figure 1, and the spectrum range is highlighted in Table 3, suggesting compatibility between Probucol and the formulation components. Methanol, a solvent, can significantly influence polymer-drug interactions by altering the drug-polymer matrix's solubility, crystallinity, and miscibility. As a polar organic solvent, methanol enhances the solubilization of hydrophobic drugs, promoting better drug dispersion within the polymer.

EVALUATIONS OF PROBUCOL SOLID DISPERSIONS

Saturation Solubility

The percentage increase in solubility for the different solid dispersion formulations compared to pure Probucol is reported.

Solid dispersion F3 showed an 88.13% increase in solubility, and F6 showed a 79.60% increase in solubility. So, the solid dispersions significantly enhanced the saturation solubility of Probucol, with PVP K30 providing the highest increase of around 88% compared to pure crystalline Probucol.

Table 3: FTIR spectrum of Probucol, PVP K30, PEG 6000, and combination

Wavenumber range (cm^{-1})	Functional group (Observed)
~3500-3200	O-H (Alcohol, Phenol)
~2950-2850	C-H (Alkane)
~1750-1650	C=O (Carbonyl)
~1500-1400	C=C (Aromatic)
~1300-1000	C-O (Ether, Alcohol)

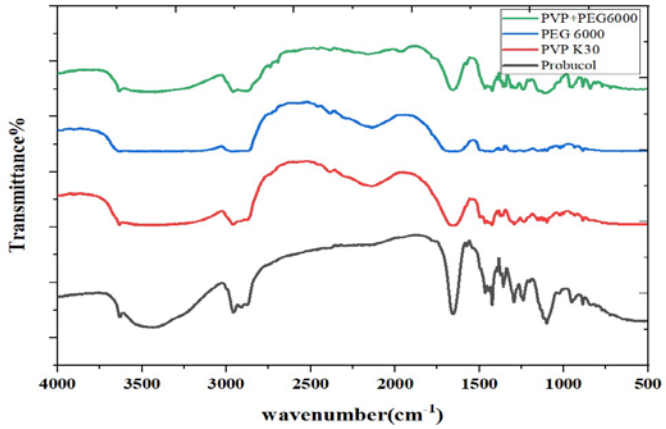

Figure 1: FTIR of Probucol, PEG 6000, PVP K30 and combination

XRD

The XRD pattern of Probucol shows several distinct peaks, as shown in Figure 2. Sharp, well-defined peaks indicate that Probucol has a long-range ordered structure with a periodic arrangement of atoms or molecules in the crystal lattice. The green and blue lines exhibit well-defined, sharp peaks, indicating the presence of crystalline phases. The red and black lines show broader and less intense peaks, suggesting a more amorphous or disordered structure, as shown in Figure 3. The positions and intensities of the peaks differ among the samples, indicating variations in their crystalline structures or compositions. Multiple peaks in some samples suggest the coexistence of different crystalline phases or polymorphs.

SEM

SEM images were obtained for two optimized amorphous solid dispersions, F3 and F6, as shown in Figure 4. The scale bar in the bottom left corner of the images indicates a size range of solid dispersions for formulation F3 and F6 is 20 µm and 50 µm (micrometres). The SEM images show a rough and irregular surface morphology with numerous crevices and porous structures. However, F6 appears to have a more pronounced porous and agglomerated structure compared to F3, which could potentially impact properties such as dissolution rate, bioavailability, and physical stability.

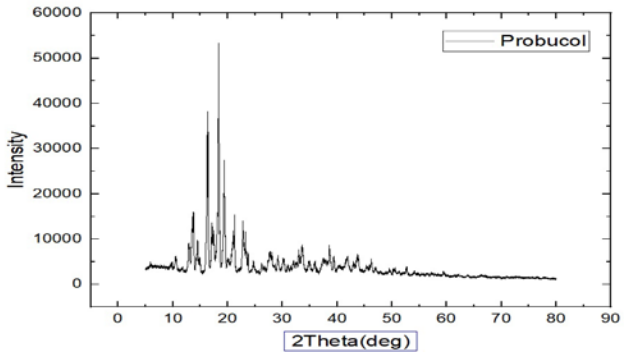

Figure 2: XRD of Pure Drug

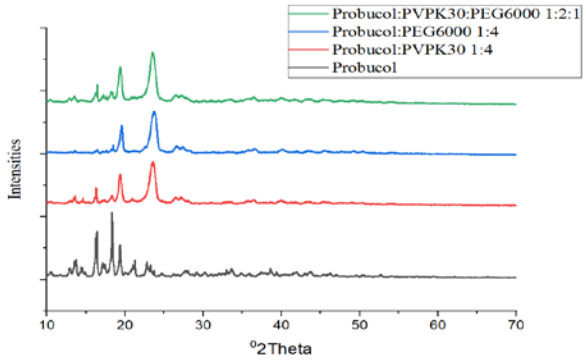

Figure 3: XRD diffractogram of the drug and the mixture of drug polymers in combination

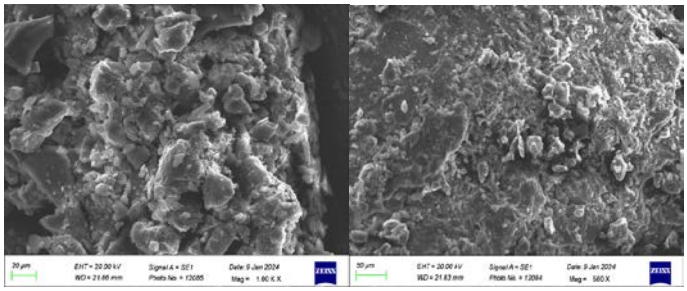

Figure 4: SEM images of amorphous solid dispersions F3 and F6

EVALUATION OF TABLETS

Post Compression Evaluation

All batches of compressed tablets were successfully manufactured via the direct compression technique. The tablets were evaluated for thickness, diameter, weight variation, hardness, content uniformity, and percentage friability as shown in Table 4. The formulations demonstrated acceptable results for

all parameters, remaining within the specified limits and acceptance criteria ranges. The mean diameter and thickness of the tablets were 10.2 ±0.121, 10.6 ±0.127, 3.06 ± 0.117, and 3.11 ± 0.113 mm, respectively. The mean hardness of the tablets was 6.09 ± 1.18 and 6.99 ± 1.14. The tablets successfully passed the friability test, with the percentage of friability for all tablets being below 1%.

In vitro release studies

Table 5 and Figure 5 show optimized formulations' in vitro release data. Formulation F3 exhibits a faster initial drug release rate, with approximately 39.21% of the drug being released within the first 10 minutes. It then shows a faster and more consistent drug release, reaching approximately 95.31% within 120 minutes. F6 shows a slower initial release, with 15.50% in the first 10 minutes, indicating a potential lag phase caused by slower water penetration or stronger drug-polymer interactions. The gradual increase in the release rate over time, reaching 86.77% by 120 minutes, suggests that the formulation might exhibit erosion-controlled or mixed diffusion-erosion behaviour.

Table 4: Post-compression evaluations of tablets F3 and F6

Formulation Code	Content uniformity (mg), n=10 mean ±S.D	Thickness (mm) n=10, mean ±S. D	Diameter (mm) n=10 mean ±S. D	Hardness (Kg/cm^2) n=10 mean ±S. D	Friability (%) n=16 mean ±S. D
F3	9.3 ±1.1	3.06 ± 0.117	10.2 ±0.121	6.09 ± 1.18	0.3 ± 0.06
F6	9.5 ±1.3	3.11 ± 0.113	10.6 ±0.127	6.99 ± 1.14	0.4 ± 0.06

In vitro release studies

The *in vitro* release data of optimised formulations are shown in Table 5 and Figure 5. Formulation F3 exhibits a faster initial drug release rate, with approximately 39.21% of the drug being released within the first 10 minutes, and shows a faster and more consistent drug release, reaching approximately 95.31% within 120 minutes. F6 shows a slower initial release, with 15.50% in the first 10 minutes, indicating a potential lag phase caused by slower water penetration or stronger drug-polymer interactions. The gradual increase in the release rate over time, reaching 86.77% by 120 minutes, suggests that the formulation might exhibit erosion-controlled or mixed diffusion-erosion behaviour.

Table 5: Cumulative percentage drug release of optimised formulations F3 and F6

Time (min)		10	20	30	40	50	60	70	80	90	100	110	120
% Drug Release	**F3**	39.21	48.33	57.50	61.51	68.72	73.42	80.30	85.50	88.64	91.88	93.64	95.31
	F6	15.50	20.10	28.66	35.74	42.85	58.09	65.34	71.21	75.72	79.18	82.24	86.77

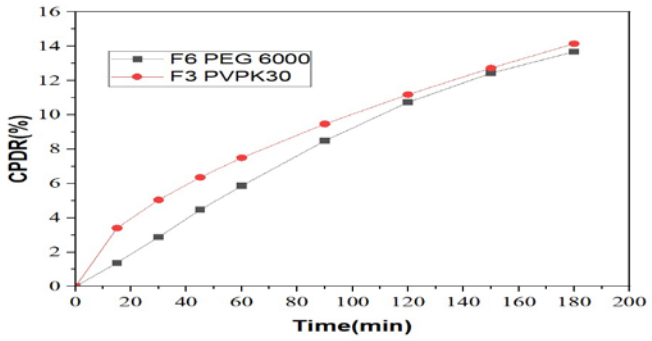

Figure 5: In vitro dissolution profile of optimised formulations F3 and F6

Kinetic Release

The kinetic analysis of the in vitro drug release data for the optimized formulation (F3) was conducted using a DD solver, as depicted in Figure 6. The correlation coefficient (R^2) and the Sum of squares residuals (SSR) for each model were calculated and are presented in Table 6. The findings revealed that the optimized formulation adhered to the Korsmeyer-Peppas model, as it exhibited the lowest SSR value of 24.8521, the highest R^2 of 0.9936, and an adjusted R^2 of 0.9929. Among all the models assessed, the Korsmeyer-Peppas model demonstrated the highest model selection criteria value of 4.7148, indicating that it most effectively characterizes the drug release profile.

Table 6: Kinetic release data

Release Model	R^2	R^2 adjusted SSR	MSC
Zero-order	0.1590	0.1590	0.3142
First-order	0.8927	0.8927	2.0658
Higuchi	0.9308	0.9308	2.5035
Korsmeyer-peppas	0.9936	0.9929	4.7148
Hixon crowell	0.7879	0.7879	1.3839

Similarity Factor

Dissolution studies are performed to ensure product uniformity from batch to batch, to predict bioavailability for formulation and development, and to determine what modifications should

be made to an existing formulation. The dissolution profiles of the formulated tablet (F3) and the marketed tablet of Lorelco by Sanofi were compared using the similarity factor (f2). The similarity factor f2 factor (f2=67.72) was found to be greater than 50, as shown in Table 7, which is within an acceptable range of 50-100; Figure 7 confirms that the release of probucol from prepared formulations was similar to that of the marketed formulations.

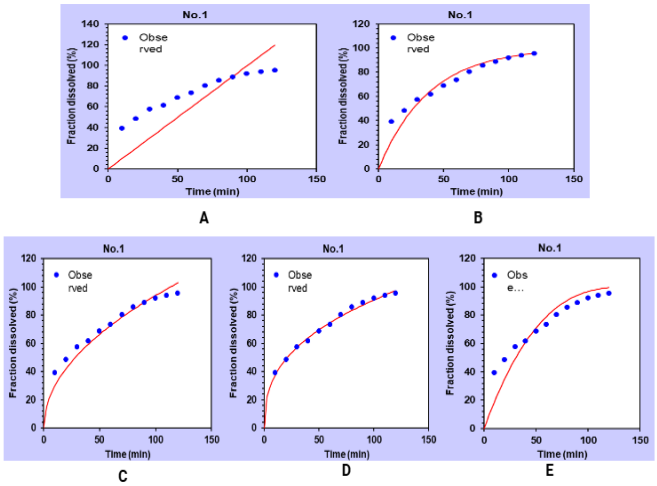

Figure 6: Kinetic Modeling study (A) zero order Kinetic (B) First order Kinetic (C) Higuchi Kinetic (D) Korsmeyer Peppas Kinetic (E) Hixon Crowell Kinetic.

Table 7: Similarity factor data

Time (min)	% Drug release		f2
	Reference	F3	
10	36.32	39.21	75.73
20	45.55	48.33	76.10
30	51.72	57.50	68.93
40	58.88	61.51	70.52
50	64.92	68.72	70.48
60	69.68	73.42	70.50
70	75.42	80.30	69.55
80	78.62	85.50	67.21
90	82.47	88.64	66.17
100	87.03	91.88	66.07
110	93.66	93.64	67.06
120	97.58	95.31	67.72

CONCLUSION

Solid dispersions significantly advance the field of pharmaceutical sciences by addressing one of the most critical challenges in drug development: poor solubility and bioavailability of many active pharmaceutical ingredients (APIs). By dispersing poorly water-soluble drugs in a hydrophilic matrix, SDs enhance drug dissolution rates and solubility, improving absorption and therapeutic efficacy. Solid dispersions of probucol were prepared using three separate polymers: PEG 600, PVP K30, and a combination of the two through solvent evaporation.

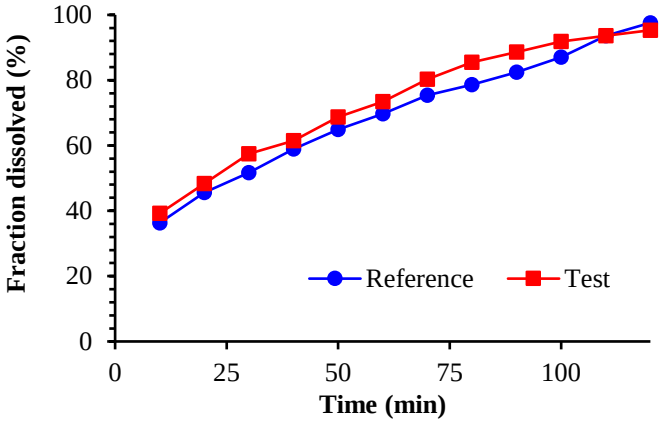

Figure 7: Graph of Similarity factor of test formulation (F3) and reference formulation (Lorelco)

An enhanced product was the outcome of this methodology, as it demonstrated significant improvements in the drug's solubility and dissolution characteristics. The study's results emphasize the significant increase in the dissolution rate of probucol, which was significantly lower in its purified form. Formulation F3 has a more rapid initial drug release rate of about 39.21% within 10 minutes, and achieves approximately 95.31% by 120 minutes, indicating a quicker and more uniform drug release profile. F6 has a more gradual initial release of 15.50% during the first 10 minutes. The progressive increase in the release rate over time, reaching 86.77% at 120 minutes, indicates that the formulation may demonstrate erosion-controlled or mixed diffusion-erosion behaviour. In summary, the solid dispersion formulations F3 and F6 effectively converted crystalline probucol to an amorphous form, resulting in improved solubility and dissolution rates suitable for immediate-release tablets. Some advanced imaging techniques, such as magnetic resonance imaging **(**MRI) and Positron emission tomography (PET), are being explored to visualize the behaviour of SDs in the gastrointestinal tract in real time.

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CONFLICT OF INTEREST
The author(s) do not have any conflict of interest.

AUTHOR CONTRIBUTION
Vaibhav Adhikari and Mansi Butola contributed to writing the original manuscript draft. Vikash Jakhmola wrote and reviewed the manuscript. Abhijeet Ojha edited it. Arvind Negi supervised and conceptualized the whole experimental work.

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