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Original Article

UNLOCKING THE POTENTIAL: ENHANCING SOLUBILITY AND BIOAVAILABILITY OF ACYCLOVIR THROUGH SOLID DISPERSION FORMULATIONS

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ABSTRACT

Objective: This study aimed to formulate and evaluate solid dispersions of acyclovir using Polyethylene Glycol (PEG) polymers (PEG 3350, PEG 4000, and PEG 6000) in varying ratios to improve their oral bioavailability.

Methods: Solid dispersions of acyclovir with PEG 3350, PEG 4000, and PEG 6000 were prepared at different weight ratios (1:5, 1:20, and 5:1) using the solvent evaporation method. Physical mixtures were also prepared for comparison purposes. Characterization involved Differential Scanning Calorimetry (DSC) to study thermal behavior, X-ray powder Diffraction (XRPD) to assess the crystalline state, Fourier Transform Infrared Spectroscopy (FTIR) for molecular interactions, and dissolution studies using USP apparatus type 2 to evaluate drug release profiles.

Results: Among the tested formulations, the solid dispersion of acyclovir with PEG 4000 at a 20:1 ratio demonstrated the most favourable dissolution profile, with over 50% drug release within the first 10 min. DSC analysis indicated a significant reduction in the crystallinity of acyclovir within the solid dispersions, particularly with PEG 4000. XRPD confirmed the transformation of acyclovir to an amorphous state, while FTIR spectroscopy revealed molecular interactions between acyclovir and PEG, indicative of enhanced solubility. Dissolution studies further corroborated the superior performance of the 20:1 PEG 4000 formulation, which showed a remarkable increase in solubility compared to other ratios and physical mixtures. Mathematical modeling using the Weibull and Logistic models suggested controlled and predictable release kinetics for the optimized formulation.

Conclusion: Overall, this study underscores the potential of solid dispersion formulations, particularly the 20:1 ratio of PEG 4000 to acyclovir, in enhancing the oral bioavailability of poorly water-soluble drugs, such as acyclovir, offering valuable insights for pharmaceutical formulations and drug delivery systems.

Keywords: Acyclovir, Solid dispersion, Dissolution behavior, PEG polymers, Solubility enhancement, Bioavailability, Drug formulation, Mathematical modelling

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INTRODUCTION

Owing to its simplicity and convenience method of consumption, oral administration of medications is the predominant and preferred means of delivery [1]. Pharmaceutical researchers employ two approaches to improve the oral bioavailability of pharmacologically active compounds: (i) augmenting the solubility and dissolution kinetics of drugs with low water solubility and (ii) enhancing the permeability of drugs with restricted membrane permeability [2].

In pharmaceutical research, numerous methods have been investigated to improve the dissolution characteristics of drugs with poor water solubility in addition to solid dispersions. These methods include salt formation, complexation utilizing cyclodextrins, solubilization of pharmaceuticals incompatible solvents, and particle size reduction [3].

The use of solid dispersion formulations has emerged as a promising and viable strategy for enhancing solubility [4]. As outlined by Chiou and Riegelman [2], solid dispersion systems involve the integration of one or more active compounds into an inert carrier or matrix using techniques such as fusion, solvent evaporation, or melting solvent procedures [5]. In this arrangement, the matrix demonstrates hydrophilic characteristics, whereas the drug itself is hydrophobic [6]. Solid dispersion techniques encompass various categories, including simple eutectic mixtures, solid solutions, glass solutions, glass suspensions, amorphous precipitation within a crystalline carrier, and compound or complex configurations [2].

Although the exact mechanism of improving drug solubility using the solid dispersion technique remains unclear, the underlying principle revolves around the complete elimination of drug crystallinity and achievement of molecular dispersion of poorly soluble compounds within a hydrophilic polymeric carrier [7]. Recently, surfactants have been introduced into formulations to enhance stability, as drug recrystallization and thermodynamic instability can pose challenges, and the use of surfactants mitigates the risk of recrystallization and further amplifies solubility [8].

Acyclovir is a widely utilized antiviral medication designated for treating conditions such as Herpes simplex (type 1) Keratitis, among others [9]. Although acyclovir is the preferred treatment option in many cases, its oral bioavailability remains significantly limited. Conventional treatment routes for Herpes and Keratitis typically involve orally administered tablets, but they suffer from notably low bioavailability, typically falling within the range of 15-30%. Frequent administration of high doses can occasionally result in side effects, such as nausea, diarrhea, rash, and headaches. To address this issue, it is imperative to enhance the solubility and dissolution characteristics of acyclovir, which exhibits low water solubility. The primary aim of this study was to formulate and evaluate solid dispersions of acyclovir using PEG 3350, PEG 4000, and PEG 6000 in varying ratios using the solvent evaporation method [10].

MATERIALS AND METHODS

Chemical reagents

Acyclovir was obtained as a gift from Dar Aldawaa factory (Jordan). All Polyethylene Glycol polymers (PEG 3350, PEG 4000, and PEG 6000) were obtained from Sigma-Aldrich. All solvents used were of HPLC grade and were sourced from Merck Millipore.

Methods of preparation

Solid dispersions of acyclovir with PEG 3350, PEG 4000, or PEG 6000 were prepared in various ratios using the solvent evaporation method. The polymer-drug weight ratios were 1:5, 1:20, and 5:1,

resulting in dispersions containing 5%, 20%, and 80% w/w of acyclovir [11]. The drug/carrier mixture was dissolved in a minimal amount of ethanol and stirred to ensure a uniform dispersion. The solvent was then evaporated at 40 °C for 24 h in an oven. The resulting solid dispersions were pulverized using a mortar and pestle and stored in desiccators at room temperature until use [12].

The selection of PEG and additional polymers for formulating acyclovir solid dispersions was strategically aimed at enhancing drug dissolution and bioavailability. PEG, a well-established hydrophilic polymer known for its biocompatibility and solubilizing properties, was chosen to address the low water solubility of acyclovir [13]. Despite the recent reclassification of acyclovir as a BCS Class III drug with high solubility and low permeability, the inclusion of PEG was hypothesized to significantly impact bioavailability by improving solubility.

Additional polymers and their specific percentages were selected to introduce novelty to the research by exploring potential synergies that have not been previously investigated. The percentages were determined through systematic optimization, balancing the solubility enhancement with the formulation stability. Compatibility assessments confirmed the suitability of PEG and additional polymers to achieve a stable and reproducible solid dispersion.

In summary, the rationale for selecting these polymers and materials was multifaceted, leveraging their solubilizing capabilities, safety profiles, and potential synergistic effects to provide a fresh perspective for acyclovir solid dispersion research.

Preparation of physical mixtures

Mechanical preparation was employed to create physical mixtures of acyclovir and carriers at varying ratios of 20%, 5%, and 80% (w/w). The ingredients were meticulously blended using a mortar and pestle for an approximate duration of five minutes. Subsequently, the resulting powder was carefully stored in a desiccator at room temperature until further utilization [12].

Characterization is required to test the resulting dispersion.

Differential Scanning Calorimetry (DSC), X-ray Powder Diffraction (XRPD), Fourier Transform Infrared Spectroscopy (FTIR), and dissolution studies were used to characterize the solid dispersion.

Hence, the dissolution was most promising for the 1:20 ratio of the drug/carrier; the characterizations using FTIR, DSC, and X-ray analysis were exclusively conducted for this specific ratio.

Differential scanning calorimetry (DSC)

To evaluate drug/carrier interactions within acyclovir solid dispersions and physical mixtures, DSC studies were conducted. In this procedure, 5 mg samples of the solid dispersion and physical mixtures were carefully positioned in sealed aluminum pans equipped with a perforated lid. An empty pan was used as a reference. Before commencing the experiments, the apparatus was calibrated using indium as a reference material. Subsequently, the samples were heated at a rate of 10 °C/min in a nitrogen gas environment ranging from 20 to 400 °C [14].

X-ray powder diffraction (XRPD) studies

The solid-state of acyclovir in the physical mixtures and solid dispersions was evaluated using XRPD. The Analysis was performed K radiation at 2 varying from 5 to 70 °C angular range voltage of 35 kV and current of 20 mA at room temperature at a scan rate of 2 °/min [15].

Fourier transform infrared spectroscopy (FTIR)

Spectroscopic study of the FTIR spectra of the drug, PEG polymer, and solid dispersion of all performed ratios. Ratios were recorded with an FTIR spectrophotometer. The samples were prepared using potassium bromide and scanned for absorbance 4000-800 cm^{-1}.

Dissolution studies

Dissolution studies were conducted using the USP apparatus type 2, commonly referred to as the paddle method. In these experiments, acyclovir solid dispersions and physical mixtures, each equivalent to 25 mg of the drug, were introduced into 900 ml of demineralized water and maintained at 37 °C. The dissolution medium was stirred at 100 rpm using a rotating paddle at 100 rpm [16]. At predetermined intervals, 10 ml aliquots were extracted from the dissolution system, with an equivalent volume of fresh dissolution medium added to maintain a constant volume. The samples were filtered and analyzed for acyclovir content using a UV spectrophotometer at a wavelength of 252 nm [17]. Each measurement was performed in triplicates (n = 3) to ensure consistency and reliability. The samples were analyzed in triplicate (n = 3) to ensure the consistency and reliability of the results [18].

The dissolution study was conducted over a period of 1 h. The concentration of acyclovir in the samples was determined by converting the absorbance values using a standard curve established for pure acyclovir [19].

Preparation of phosphate buffers

To achieve the target pH of the buffer solution, reagents, such as 0.1 N Potassium Dihydrogen Phosphate and 0.2 M Sodium Hydroxide were mixed according to the procedures outlined in the USP. The pH of the resulting buffer solution was measured using a calibrated pH meter to determine the precise pH value. The pH values of the buffers were recorded for future reference.

Preparation of calibration curve

To prepare solutions with concentrations of 2, 4, 6, 8, 10, and 12 µg/ml, precise amounts of solute were dissolved in an appropriate solvent. The prepared solutions were then analyzed using a spectrophotometer over a wavelength range of 200–400 nm. The integrated area under the curve was calculated within the specific range of 241–261 nm. A calibration curve was constructed by plotting the area under the curve against the corresponding concentration [20].

Preparation of stock and working standard solutions

A precise amount of acyclovir (10 mg) was meticulously weighed and transferred into a 100 ml volumetric flask. To this flask, 10 ml of distilled water was added, and the mixture was sonicated for 180 sec. After sonication, the solution was diluted with additional distilled water up to the volumetric mark, resulting in a final drug concentration of 100 µg/ml.

From the prepared solution, 1 ml was withdrawn and further diluted with distilled water to achieve a drug concentration of 10 µg/ml. This resulting solution served as the working standard for subsequent analyses and experiments [20].

Solubility

The solubility of acyclovir, both in pure form and as a solid dispersion, was determined using distilled water as the solvent. In separate procedures, acyclovir and the solid dispersion were each placed in 100 ml stoppered volumetric flasks, to which 10 ml of the respective medium was added. These flasks were then placed in a shaker with a lid and subjected to continuous agitation for 48 h at a temperature of 37 °C, protected from light exposure by careful covering [21].

After the designated period, the samples were filtered using Whatman filter paper no. 45, and appropriate dilutions of the filtrates were prepared for subsequent spectroscopic analysis at a wavelength of 252 nm. The solubility was determined in triplicate, and the average values from these replicates were reported [14].

RESULTS

Preparation of acyclovir calibration curve

Solutions with concentrations ranging from 2 to 12 µg/ml were subjected to spectral scanning from 200 to 400 nm. The Area under the Curve (AUC) values were determined within the range 241-261 nm, as illustrated in fig. 1.

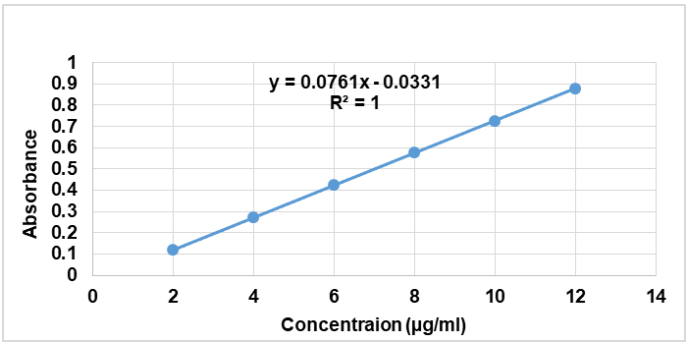

Fig. 1: Calibration curve of pure acyclovir

FTIR

Peak analyses in this study have been previously reported [22, 23]. For pure acyclovir (S1), distinctive peaks were observed, indicating various molecular vibrations, including an O–H bend at 1105.21 cm^{-1}, a C–O stretch at 1047.35 cm^{-1}, and CH_2 wagging at 898.83 cm^{-1}. Additionally, an OH stretch attributed to free moisture at 3737.15 cm^{-1} and a peak at 3190.26 cm^{-1} corresponding to the CH aromatic ring were noted. These findings enhance our understanding of the molecular composition and structural characteristics of acyclovir.

For pure PEG 4000 (S2), distinctive peaks at 842.89, 960.55, 1095.57, 1280.73, 1340.53, 1467.83, 2366.66, and 2883.58 cm^{-1} represented specific molecular vibrations. These vibrations corresponded to the bending of aromatic carbon-hydrogen (C–H) bonds, particularly those associated with two adjacent and unbound hydrogen atoms.

In the context of the solid dispersion (S3), which comprised a blend of pure acyclovir and PEG 4000, discernible peaks associated with acyclovir, such as those attributed to O–H bending and CH_2 wagging, were prominent. Concurrently, distinct peaks related to pure PEG 4000, particularly those linked to C–H bonds, are also readily observable [17].

In the FTIR spectrum of the solid dispersion (S4), the emergence of new peaks at 2000.33 and 1860.20 cm^{-1} signifies the formation of unique chemical bonds or interactions within the solid dispersion. These peaks indicate that novel molecular configurations or associations were not present in the individual components (acyclovir and PEG 4000). Furthermore, the partial disappearance of certain main peaks associated with acyclovir and PEG 4000 suggested alterations or modifications in the original chemical characteristics or structural features of these compounds within the solid dispersion. This phenomenon can be attributed to the interaction and compatibility between acyclovir and PEG 4000, leading to changes in their molecular arrangement.

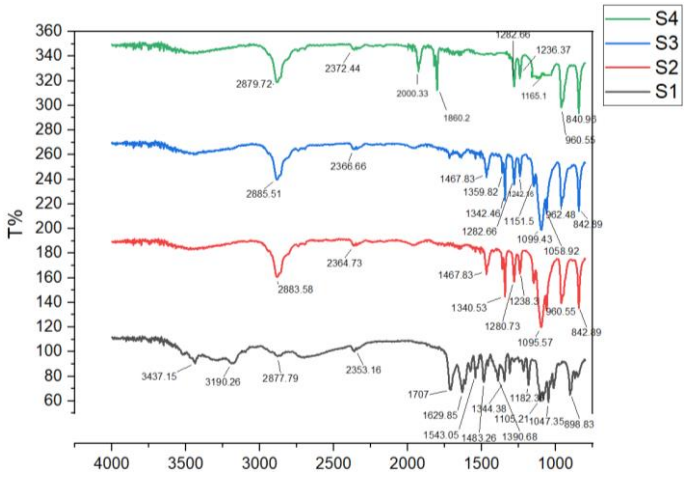

Fig. 2: FT-IR for pure acyclovir (S1), Pure PEG 4000 (S2), Physical dispersion (S3), Solid dispersion (S4)

DSC

DSC thermograms for pure acyclovir, pure PEG 4000, acyclovir, and PEG 4000 physical mixtures and acyclovir solid dispersions with a 10% drug/carrier ratio are shown in fig. 3, providing a comprehensive visualization of the thermal behavior of each component and their respective formulations.

In fig. 3, the DSC thermogram of pure acyclovir shows a significant peak at 252.01 °C, indicative of its characteristic melting point [16]. Notably, the melting point of the solid dispersion, as illustrated in fig. 3, revealed the presence of a new polymorph, suggesting intriguing alterations in its thermal properties. This intriguing observation prompted further investigation into the structural modifications induced by the incorporation of PEG 4000 and their implications for the stability and performance of the formulation.

X-ray

Powder diffraction (XRPD) spectra of the acyclovir solid dispersion revealed a significant amorphous state of the drug within the formulation, in contrast to the crystalline form observed in formulations containing pure acyclovir, PEG 4000, and an acyclovir-PEG 4000 physical mixture. This amorphous state in the solid dispersion was further validated using DSC, as detailed in the previous section.

Furthermore, Masuda *et al.* assessed the co-crystallization of acyclovir with citric acid, wherein X-ray analysis similarly demonstrated the presence of an amorphous structure in their formulation samples. These findings underscore the potential of solid dispersion techniques to enhance the solubility and bioavailability of acyclovir by inducing an amorphous state [24, 25].

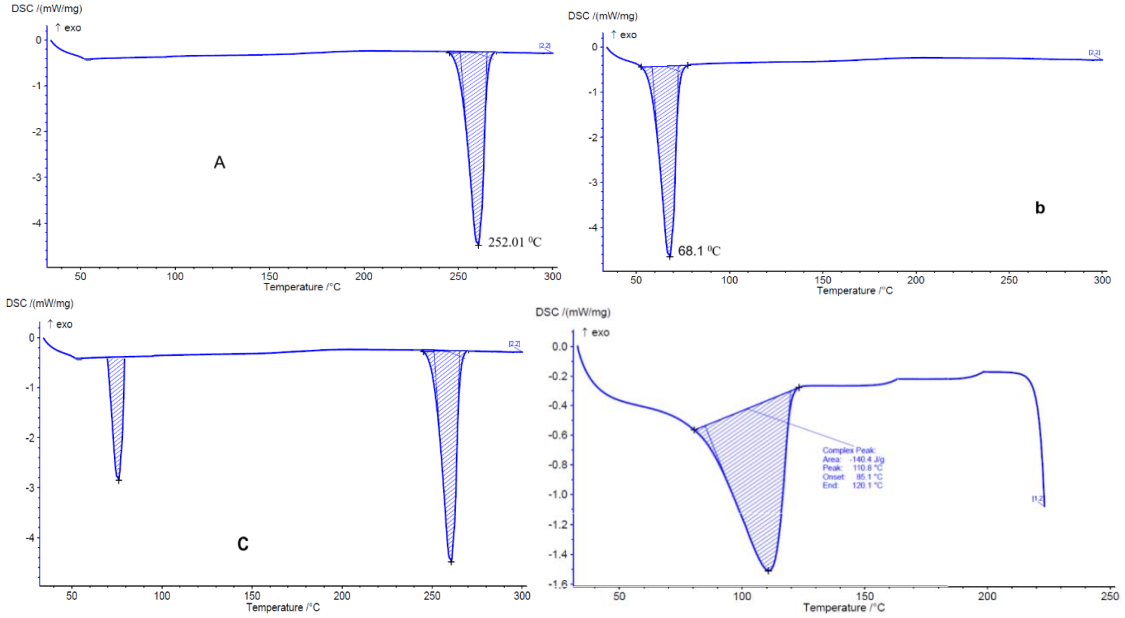

Fig. 3: The DSC spectra for (a) Pure acyclovir, (b) Pure PEG 4000, (c) Physical mixture of acyclovir-PEG 4000 (d) Solid dispersion of acyclovir-PVP (1:20)

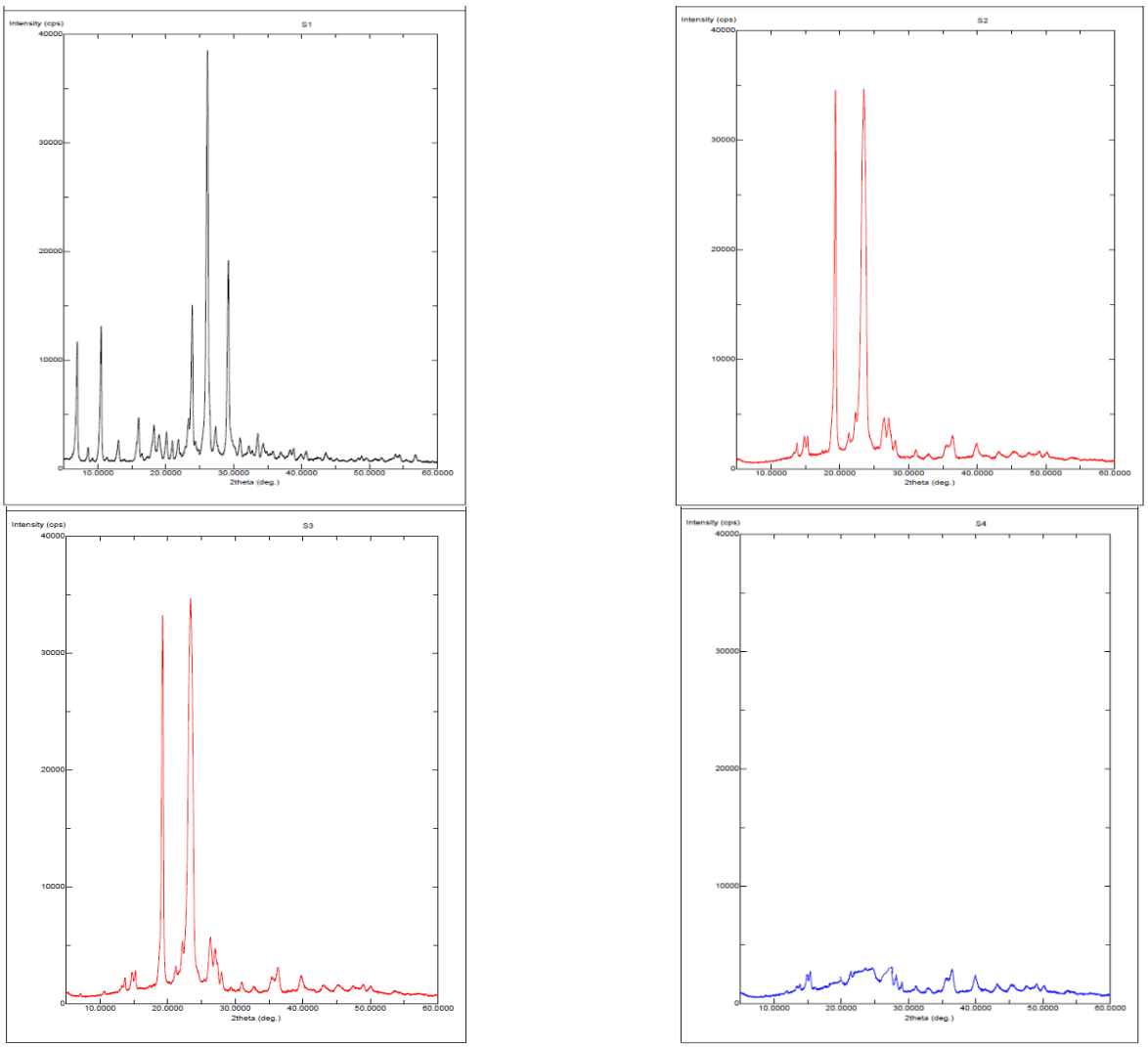

Fig. 4: The XRPD spectra of, (a) pure acyclovir, (b) Pure PEG 4000,(c) Physical mixture of acyclovir-PEG 4000 (d) Solid dispersion of acyclovir-PVP (1:20)

In vitro drug release study

Drug release studies were meticulously conducted on the solid dispersion formulations, with thorough comparisons drawn against both the physical mixture and pure drug release counterparts. The intricate drug release profiles of the acyclovir solid dispersion formulated with three distinct PEG polymers were meticulously scrutinized across a spectrum of polymer percentages [26]. These analytical endeavors are presented in fig. 5, 6, and 7, offering a comprehensive insight into the dissolution behavior of the formulation under varying polymer compositions [27].

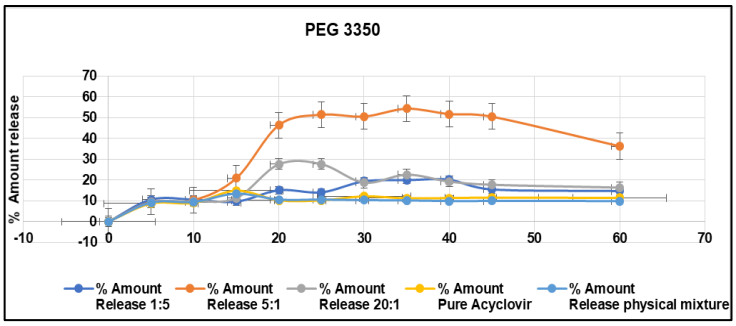

Fig. 5: Drug release profile of acyclovir solid dispersion in PEG 3350, *Data are presented as mean±SD, n=3

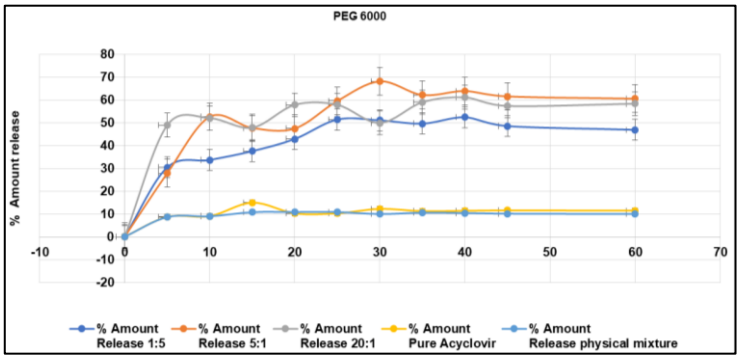

Fig. 6: Drug release profile of acyclovir solid dispersion in PEG 6000, Data are presented as mean±SD, n=3

The experimental results provided compelling insights into the drug release characteristics of acyclovir formulations. Pure acyclovir exhibited constrained release, reaching a maximum of 20%. Remarkably, the release from the physical blend of the three polymers mirrored that from the pure drug. A carrier-to-drug ratio of 1:5 with PEG 4000 and 3350 exhibited no substantial impact on dissolution because of the limited solubility of acyclovir. Conversely, solid dispersions containing PEG 6000 at a 1:5 ratio markedly enhanced dissolution to 58% compared to untreated acyclovir. Intriguingly, increasing the carrier-to-drug ratio to 5:1 significantly augmented drug release across all polymers.

At a 1:20 ratio, PEG 4000 notably improved dissolution compared to that of the pure drug. Among the PEG variants, PEG 4000 exerted a more pronounced influence on dissolution. Its efficiency surpassed that of PEG 3350 at a 20:1 ratio and PEG 6000 at an identical ratio, releasing over 50% of the drug within the first 10 min. Overall, PEG 4000 outperformed PEG 6000, achieving a 74% release after 40 min, a feat unmatched by the other polymers. This superiority might be attributed to the lower viscosity of PEG 4000 compared to that of PEG 6000.

Conversely, the hydrophilicity of PEG 3350 might have hindered drug release owing to its strong affinity for water molecules. Variations in the molecular weight and physicochemical properties of PEG polymers contributed to the divergent release profiles. Higher molecular weight polymers, such as PEG 4000 and 6000, potentially facilitated drug solubilization and diffusion through the solid dispersion matrix, while the viscosity of PEG 6000 led to slower release compared to PEG 4000. These insights underscore the critical role of polymer selection and optimization in enhancing drug release and solubility in solid dispersion systems [14].

In conclusion, optimizing the polymer-to-drug ratio is important for maximizing dissolution rates. Moreover, achieving a balance between polymer hydrophilicity and viscosity is crucial to enhance the solubility of poorly soluble drugs. These findings offer valuable guidance for the formulation of effective solid dispersion systems.

Solubility

The solubility of Acyclovir, both in its pure form and as part of its solid dispersion, was evaluated in distilled water. For this assessment, Acyclovir and the solid dispersion were each placed in separate containers. Subsequently, 10 ml of the respective medium was added to each container, resulting in a total volume of 100 ml within stoppered volumetric flasks. These flasks were then subjected to 48 h of continuous agitation at room temperature on a magnetic stirrer. After 48 h had elapsed, the samples underwent filtration using Whatman filter paper no. 45. Subsequently, aliquots were suitably diluted and analyzed spectroscopically at 252 nm. The aqueous solubilities of various solid dispersions were found to range between 3-30 µg/ml, with a formulation of 20:1 (PEG 4000: acyclovir), which exhibited notably higher aqueous solubility.

Table 1: Solubility of different solid dispersions

Formula	1:5	5:1	20:1	Physical mixture	Pure acyclovir
PEG 4000	30.31±0.003	12.13±0.052	37.94±0.047	10.27± 0.10	5.62±0.011
PEG 6000	7.89±0.020	25.91±0.119	36.69±0.082	9.75±0.101	5.62±0.011
PEG 3300	20.25±0.113	18.39±0.064	22.56±0.098	6.83±0.064	3.75± 0.011

Dissolution best-fitted models

In this comprehensive dissolution study, we investigated the release profiles of acyclovir under different conditions, including various ratios of drug formulations (1:5, 5:1, and 20:1), physical mixtures, and pure acyclovir. Our analysis revealed distinct dissolution behaviors that were successfully captured by mathematical models. For the release of acyclovir at a 1:5 ratio, the Weibull model provided an excellent fit (R^2 = 0.9792), suggesting a unique release mechanism for this formulation. Conversely, for the 5:1 and 20:1 ratio, the Logistic model demonstrated exceptional fitting (R^2>0.9957), indicating a controlled and predictable release pattern. Interestingly, the physical mixture exhibited a linear release model (R^2 = 0.9966), suggesting a simple diffusion process. Finally, pure acyclovir displayed characteristics of the logistic model (R^2 = 0.8392), signifying potential modifications in the dissolution kinetics when administered in its pure form [28]. These findings shed light on the dissolution dynamics of acyclovir under various conditions and provide valuable insights into pharmaceutical formulations and drug delivery strategies.

Table 3 summarizes the dissolution data for the release of 1:5, 5:1, and 20:1, release of the physical mixture, and pure acyclovir, including the best-fitting models and their equations for the purposes of this study.

Table 2: Summarizing the dissolution results for different PEG to drug ratio formulations along with the corresponding best-fitting models, equations, R-squared values (R^2), and root mean square error (RMSE)

PEG: drug percentage	Best fitting model	Equation	R-squared (R^2)	Root mean square error (RMSE)
1:5	Weibull model	$C(t) = A.\exp(-(t/B)^c)$ A=39.6096 B=21.8664 C=1.0196 A, B, and C are the parameters of the Weibull model: A: Scale Parameter-It represents the overall magnitude or scale of the response. B: Shape Parameter-It influences the shape of the Weibull distribution curve. It determines whether the curve is increasing, decreasing, or constant. C: A constant used in the model.	0.9792	1.8509
5:1	Logistic model	$C(t) = A/1+\exp(-B(t-C))$ A=65.2563 B=0.3397 C=11.6687 A, B, and C are parameters of the Logistic model: A: Maximum Value-It represents the upper asymptote or maximum value that the function can reach. B: Growth Rate-It controls how quickly the function changes from 0 to the maximum value. C: Midpoint-It represents the value of t at which the logistic function reaches its midpoint between the minimum and maximum values.	0.9957	1.8193
20:1	Logistic model	$C(t)= A/1+\exp(-B(t-C)$ A=77.7122 B=0.2452 C=12.7003 A: Maximum Value B: Growth Rate C: Midpoint	0.9967	1.4020
Physical mixture	Linear model	$C(t)=A\cdot t+B$ A=0.2830 B=−0.1576 A and B are parameters of the Linear model: A: Slope-It represents the rate of change of the linear relationship between C(t) and t. B: Intercept-It is the value of C(t) when t equals 0.	0.9966	0.6043
Pure acyclovir	Logistic model	$C(t)= A/1+\exp(-B(t-C))$ A=76.3862 B=0.2436 C=12.5843 A, B, and C are parameters of the Logistic model, and their meanings are the same as in the Release 5:1 logistic Model: A: Maximum Value B: Growth Rate C: Midpoint	0.8392	1.2498

In this study, we systematically examined the release profiles of acyclovir under various drug-to-polymer ratios, including 1:5, 5:1, and 20:1, along with a physical mixture and pure acyclovir. The objective of this study was to gain insight into the dissolution behavior of acyclovir under different conditions and formulations. Our findings revealed that among the tested formulations, the 20:1 ratio exhibited the most promising release profile. This formulation demonstrated a controlled and predictable dissolution pattern, as evidenced by its excellent fitting to the Logistic model (R^2 = 0.9967) and a low RMSE of 1.4020. The Logistic model's suitability suggests that the dissolution kinetics for the 20:1 formulation were well-captured, indicating its potential for controlled drug delivery applications. This study underscores the significance of optimizing drug-to-polymer ratios to achieve desired dissolution profiles, with the 20:1 formulation emerging as a noteworthy candidate for further development in pharmaceutical formulations and drug delivery systems.

DISCUSSION

The main focus of this study is to utilize solid dispersion formulations to enhance the solubility of acyclovir, as this approach has proven to be adaptable and successful in addressing the challenges posed by poorly water-soluble drugs. The use of PEG polymers at various ratios is justified by their safe and effective solubilizing properties. This study highlights the importance of optimizing the polymer-to-drug ratio and compares solid dispersion with other methods, highlighting the unique benefits of this specific formulation strategy. Additionally, the integration of dissolution models provides valuable insights into the effectiveness and behavior of the formulation. Solid dispersion technology is a promising approach to address the solubility and bioavailability challenges associated with poorly water-soluble drugs, such as acyclovir [29, 30]. The primary objective of this study was to enhance the solubility and oral bioavailability of acyclovir by formulating solid dispersions using various PEG polymers. Acyclovir's low water solubility and resultant poor bioavailability pose significant challenges in its oral administration, necessitating frequent high doses that often lead to side effects. This study explored the potential of PEG 3350, PEG 4000, and PEG 6000 in improving the dissolution properties of acyclovir. FTIR spectroscopy revealed distinct molecular interactions between acyclovir and PEG

polymers. The emergence of new peaks at 2000.33 and 1860.20 cm^{-1} in the solid dispersions indicated the formation of unique chemical bonds, suggesting interactions that could enhance the drug's solubility. These findings align with previous studies that have demonstrated the efficacy of solid dispersions in modifying the chemical environment of drugs to improve dissolution [31]. DSC thermograms and XRPD patterns provided insight into the thermal and crystalline properties of the formulations. DSC analysis showed the presence of a new polymorph in the solid dispersions, indicating altered thermal properties and suggesting that the drug was in an amorphous state. This was corroborated by the XRPD results, which confirmed the amorphous nature of acyclovir in solid dispersions, which is a critical factor in enhancing solubility and dissolution rates. Similar findings were reported by Serajuddin *et al.* [32], who noted that the amorphous state of drugs in solid dispersions significantly improves their dissolution. Dissolution studies demonstrated a significant improvement in drug release from solid dispersions compared with pure acyclovir and physical mixtures. Notably, the 20:1 ratio of PEG 4000 to acyclovir exhibited the best dissolution profile, releasing over 50% of the drug within the first 10 min, and achieving 74% release after 40 min. This enhanced dissolution can be attributed to the lower viscosity and better solubilizing properties of PEG 4000 compared to PEG 3350 and PEG 6000. These results are consistent with the work of Leuner *et al.* [33], who highlighted the role of PEG in improving the dissolution rate of poorly soluble drugs. Weibull and Logistic models were employed to fit the dissolution data, revealing that the drug release from the 1:5 ratio followed the Weibull model (R^2 = 0.9792), whereas the 5:1 and 20:1 ratios followed the logistic model (R^2>0.9957). These models indicate controlled and predictable release patterns, which are essential for optimizing drug delivery. Similar modeling approaches have been utilized in previous studies to understand drug release kinetics from solid dispersions [34]. Solubility studies further support these dissolution findings. The 20:1 PEG 4000 solid dispersion showed a significantly higher aqueous solubility than pure acyclovir and other formulations. The increase in solubility is likely due to the amorphous nature of the drug in the solid dispersion and the hydrophilic properties of PEG, which enhances the wettability and dissolution rate of acyclovir. These observations are in line with the research by Aravind [16], who discussed the importance of the amorphous state and polymer properties in solubility enhancement.

CONCLUSION

In conclusion, this study underscores the importance of optimizing drug-to-polymer ratios to achieve desirable dissolution profiles for poorly soluble drugs like Acyclovir. The 20:1 formulation exhibited promising dissolution behavior and improved solubility, making it a strong candidate for further pharmaceutical formulation development. These findings contribute to the ongoing efforts to enhance the bioavailability of poorly soluble drugs and improve their therapeutic effectiveness.

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AUTHORS CONTRIBUTIONS

We declare that this work was done by Ruba Malkawi, Jumana Tawalbeh, Suleiman Olimat. The design of the article was created by Ruba Malkawi; the dissolution method and the performance were done by Jumana Tawalbeh; finally, the mathematical models were created by Suleiman Olimat.

CONFLICT OF INTERESTS

There is no conflict of interest

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