ijlpr 2024; doi 10.22376/ijlpr.2024.14.1.P1-P11

International Journal of Life science and Pharma Research

ISSN 2250-0480

Research Article

Carvedilol Solid Dispersion Capsules

Advancing Carvedilol's Therapeutic Impact: A Study On Solid Dispersion Capsules for Improved Efficacy

Pavan Kumar, Subhash PG, Hindustan Abdul Ahad*, Pawan Dhamala and Suprith D

Department of Pharmaceutics, RR College of Pharmacy, Chikkabanavara, Bangalore-90, Karnataka, India

Abstract: This study aimed primarily to improve and evaluate the dissolution rate of Carvedilol by employing a solid dispersion technique with β-Cyclodextrin as the carrier. Three distinct methods were utilized to create Carvedilol-containing solid dispersions: The Kneading method, Physical mixture, and Solvent evaporation method. These methods incorporated β-Cyclodextrin at varying drug-carrier ratios (1:1, 1:2, and 1:3). The initial phase encompassed pre-formulation assessments, including the establishment of a calibration curve, determination of lambda maximum, melting point determination, investigation of solubility in different solvents, and evaluation of Carvedilol-polymer compatibility through FTIR analysis. Subsequent post-formulation analyses included tests for weight variation, Carvedilol content, lock length, moisture permeation, disintegration time, in-vitro dissolution, and stability. The results of the pre-formulation tests were consistent with established references. FTIR analysis revealed no interactions between the Carvedilol and the carrier. Carvedilol content, weight variation, and disintegration time tests met the permissible limits outlined in IP standards. Both lock length and moisture permeation tests conformed to the criteria. However, due to Carvedilol's limited solubility, dissolution was inadequate. Among the in-vitro dissolution profiles, the "KN3" formulation, prepared using the Kneading method with a 1:3 ratio of Carvedilol to Carrier, employing β-Cyclodextrin as the carrier, exhibited superior discharge at 94.671%, outperforming other preparation methods.

Keywords: Carrier, Carvedilol, Cyclodextrin, Dissolution, Solubility.

***Corresponding Author**

Hindustan Abdul Ahad , Department of Pharmaceutics, RR College of Pharmacy, Chikkabanavara, Bangalore-90, Karnataka, India

Received On 12 September 2023
Revised On 24 November 2023
Accepted On 14 December 2023
Published On 2 January 2024

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Pavan Kumar, Subhash PG, Hindustan Abdul Ahad, Pawan Dhamala and Suprith D , Advancing Carvedilol's Therapeutic Impact: A Study On Solid Dispersion Capsules for Improved Efficacy.(2024).Int. J. Life Sci. Pharma Res.14(1), P1-P11 http://dx.doi.org/10.22376/ijlpr.2024.14.1.P1-P11

1. INTRODUCTION

Improving the oral absorption of drugs with low water solubility is a formidable and enduring obstacle in pharmaceutical advancement[1]. This challenge is of paramount importance, given that the efficacy of many drugs hinges on their ability to dissolve in gastrointestinal fluids and be efficiently assimilated into the bloodstream. When dealing with drugs exhibiting poor water solubility, the risk of reduced bioavailability and diminished therapeutic effectiveness looms large[2]. Researchers in the pharmaceutical industry continually engage in pioneering approaches to surmount this hurdle, employing techniques such as solid dispersions, nanotechnology, lipid-based formulations, prodrugs, amorphous formulations, complexation, Nano suspensions, and salt formation[3-5]. By tailoring these strategies to the unique characteristics of each drug, pharmaceutical scientists strive to ensure that patients receive the full therapeutic benefits of medications, even when their inherent low water solubility poses a formidable challenge[6]. The active compound's dissolution rate and extent from solid medication forms critically influence the speed and extent of drug absorption. This pivotal role becomes especially prominent when managing drugs characterized by poor water solubility, as the dissolution process emerges as a key limiting factor within the gastrointestinal tract's absorption mechanism. Essentially, for these drugs, the challenge lies in their ability to efficiently dissolve and transition from their solid state into a form that can be readily absorbed into the bloodstream. When this dissolution process is hindered due to low water solubility, it significantly impedes the drug's absorption, potentially affecting its therapeutic effectiveness and bioavailability. Pharmaceutical research continually seeks innovative solutions to address this fundamental issue, aiming to enhance these drugs' solubility and dissolution rate for improved patient outcomes[7,8]. Bioavailability challenges frequently arise when dealing with highly hydrophobic drugs, primarily because their complete absorption within the digestive system is obstructed. These drugs, characterized by a pronounced aversion to water, encounter difficulties dissolving in the gastrointestinal fluids necessary for absorption[9]. Consequently, their journey from ingestion to effective absorption becomes a complex process marked by reduced dissolution rates and incomplete uptake into the bloodstream. This inherent hydrophobicity poses a substantial hurdle to achieving optimal bioavailability, necessitating innovative pharmaceutical strategies and formulations to enhance the solubility and absorption of such drugs, ultimately ensuring their therapeutic efficacy in clinical settings[10]. The solid dispersion technique is a highly successful strategy for surmounting this challenge. This widely recognized approach efficiently tackles the issues of limited solubility, slow dissolution rates, and, consequently, concerns about bioavailability often encountered with poorly water-soluble drugs[11]. This method centers on the dispersion of the drug within an inert carrier that easily dissolves in water while preserving a solid state. Dispersing the drug can significantly improve its solubility and dissolution rate, ensuring it readily transforms into a form efficiently absorbed within the gastrointestinal tract. The solid dispersion technique has proven to be a valuable tool in enhancing the bioavailability of hydrophobic drugs, ultimately contributing to their improved therapeutic effectiveness in clinical applications[12]. Solid dispersion incorporates one or more active substances into a solid carrier or matrix, with the carrier usually being inert. This dispersion is achieved through various techniques, including fusion (melting)[13], solvent-based methods, or combining both. In essence, it involves mixing the active drug compound with the inert carrier to produce a uniform and solid state dispersion[14]. Solid dispersion techniques are particularly valuable for improving poorly water-soluble drugs' solubility and dissolution characteristics, thereby enhancing their bioavailability and overall therapeutic efficacy. The choice of a specific method, whether fusion, solvent-based, or a hybrid approach, depends on the drug's properties and the desired characteristics of the final solid dispersion formulation[15,16]. A wide array of methodologies is at the disposal of pharmaceutical scientists to create solid dispersions, catering to the diverse characteristics of drug compounds and formulation requirements. These methods include the fusion Technique (In this method, the drug and carrier are heated until they melt and form a homogeneous mixture. The mixture is then cooled to solidify the dispersion), solvent Evaporation (the drug is dissolved in a suitable solvent, and the carrier is dissolved or suspended in the same or a different solvent)[17]. The drug and carrier solutions are then mixed, and the solvent is evaporated, leaving behind a solid dispersion); fusion-solvent hybrid approach (This approach combines elements of both fusion and solvent-based methods)[18]. The drug is partially dissolved in a solvent, and this solution is mixed with the carrier. The mixture is then heated to evaporate the solvent, leading to the formation of a solid dispersion); Melt Adsorption (In melt adsorption, the drug is mixed with a molten carrier, and the drug molecules adhere to the surface or intermingle with the carrier as it cools and solidifies), Physical Blending (This method involves mechanically mixing the drug and carrier in their solid states. While it's a simpler approach, achieving uniform distribution may require specific equipment and optimization), and Kneading (this involves mixing the drug and carrier while adding a solvent. The resulting wet mass is then dried to create a solid dispersion). These methodologies and other similar techniques provide flexibility in addressing the specific challenges posed by different drug compounds and formulation requirements. The choice of the appropriate method depends on factors such as the drug's physicochemical properties, desired release characteristics, and the intended dosage form. Solid dispersions are crucial in improving the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs, making them a valuable tool in pharmaceutical development[19].

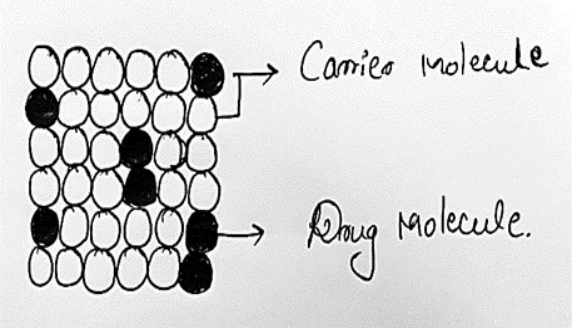

Fig 1: Schematic structure of the solid solution

Carvedilol operates as a dual-action agent, antagonizing α and β adrenoreceptors, and is employed to treat various cardiovascular conditions such as angina, congestive heart failure, cardiac arrhythmias, and hypertension. This compound consists of a racemic mixture where the S (-) enantiomer exhibits nonselective β-blockade, and both the R (+) and S (-) enantiomers display comparable potency in alpha-blockade. Classified as a BCS Class II drug due to its low solubility and high permeability, carvedilol's efficacy as an oral antihypertensive is impeded by its limited water solubility[20]. This limitation leads to challenges related to inconsistent bioavailability and bioequivalence[21]. Given its chemical stability and a half-life of 7 to 10 h, carvedilol is a suitable candidate for developing solid dispersion capsule formulations. Because of its substantial first-pass effect and relatively short duration in the bloodstream, carvedilol is particularly well-suited for the solid dispersion capsule approach. Among various dosage forms, capsules are favored for their ease of use and straightforward manufacturing. In oral drug delivery systems, capsules remain the preferred choice due to their compactness, uniform dosing, and painless administration. The primary objective of this research is to create a solid dispersion of the water-insoluble Carvedilol drug, enhancing its water solubility. The goal is to formulate it into capsule form using a manual capsule-filling machine for conventional applications.

2. MATERIALS AND METHODS

Carvedilol was sourced from Yarrow Chemicals, located in Mumbai, India. β-Cyclodextrin, PEG-4000, and PVP K 30 were procured from Balaji Chemicals in Kolkata, India. All other chemicals employed in this research, including those previously mentioned, were of analytical reagent (A.R) grade.

2.1. Identification and characterization of Carvidolol

Initial inquiries were carried out on the active pharmaceutical ingredient (API), which involved (Carvidolol) evaluating solubility, determining the melting point, and conducting compatibility studies.

2.1.1. Solubility

Carvedilol, a medication commonly used for hypertension and heart failure treatment, exhibits varying solubility characteristics in different solvents. It demonstrates moderate solubility in water, allowing for preparing aqueous formulations for oral administration. In contrast, its solubility is higher in methanol, a polar solvent, making it useful for specific pharmaceutical applications and analytical procedures. Additionally, carvedilol is even more soluble in chloroform, a nonpolar solvent often employed in laboratory settings for organic compound extraction. The choice of solvent for carvedilol depends on its intended use, with water-based formulations being the preferred option for oral administration due to their safety and compatibility with the human body. However, researchers and analysts may utilize methanol or chloroform in laboratory environments for specific purposes, considering factors such as temperature and pH that can influence solubility. Pharmaceutical manufacturers may also employ various excipients and techniques to enhance carvedilol's solubility and bioavailability.

2.1.2. *Melting Point Determination*

The precise determination of Carvedilol's melting point was accomplished using Thiel's tube methodology. This technique involves carefully placing a small quantity of Carvedilol inside a slender glass tube and then gradually applying heat. Observers monitor the substance's transition from a solid to a liquid state, and the temperature at which this transformation takes place is meticulously recorded as the melting point. Thiel's tube methodology is widely recognized for its accuracy and effectiveness in minimizing contamination risks, rendering it the method of choice for assessing the purity of received Carvedilol samples.

2.1.3. FTIR Spectroscopy

In this study, Fourier-transform infrared (FTIR) spectral analysis was conducted on the isolated Carvedilol and the polymer, individually and in physical mixtures. The primary aim was to discern any alterations in the Carvedilol's chemical composition that might arise from interactions with the polymer. It involved a thorough examination of absorption peaks present in the spectra and comparing them to a reference spectrum to identify any shifts or changes, thereby shedding light on potential molecular interactions or modifications between the Carvedilol and the polymer.

2.1.4. Determination of λ_{max}

In this experiment, a 1 mg/ml stock solution of Carvedilol was prepared by dissolving 100 mg of the Carvedilol in a small volume of phosphate buffer at pH 7.4. This concentrated stock solution was then diluted further to a final volume of 100 ml within a 100 ml volumetric flask, using additional phosphate buffer at pH 7.4. This dilution aimed to create a set of solutions with varying concentrations, spanning the range of 10 µg/ml. After preparing the dilutions, the next step involved determining the λ_{max} of the Carvedilol solution. It was accomplished by scanning the solution across a spectrum ranging from 400 to 200 nm. By monitoring the absorption or

absorbance of light at different wavelengths, the λ_{max} could be identified. The λ_{max} represents the wavelength at which the Carvedilol solution absorbs light most strongly, which is a crucial parameter for various analytical and spectroscopic applications, particularly in pharmaceutical and chemical analysis.

2.1.5. Standard Calibration Curve of Carvedilol

A 1 mg/ml Carvedilol stock solution was prepared by dissolving 100 mg of the Carvedilol in a 100 ml volumetric flask containing Phosphate buffer at pH 7.4 (Stock Solution-I). Taking from the Stock Solution-I, 10 ml of solution was pipetted out and further diluted to a total volume of 100 ml in a 100 ml volumetric flask using Phosphate buffer at pH 7.4. From stock solution II, incremental volumes of 0.5, 1, 1.5, 2, and 2.5 ml were withdrawn and mixed with a Phosphate buffer solution at pH 7.4 to reach a final volume of 10 ml in individual 10 ml volumetric flasks. This series of dilutions led to the creation of solutions with concentrations of 5, 10, 15, 20, and 25 µg/ml from the Stock Solution II. The UV-visible spectrophotometer was employed to measure the absorbance of these appropriately diluted solutions at a wavelength of 243 nm. A calibration curve was meticulously plotted using the collected data, positioning concentration along the X-axis and absorbance along the Y-axis. The correlation coefficient, denoted as 'R^2,' was computed to assess the curve's reliability and accuracy.

2.2. Preparation of solid dispersion

2.2.1. Kneading Method

For the preparation of Carvedilol solid dispersion, the kneading method was employed. It involved the combination of Carvedilol, β-Cyclodextrin, PEG-4000, PVP K 30, and Ethanol. The procedure commenced by mixing the solvent and the polymer in a glass mortar, creating a consistent paste. The Carvedilol was then gradually incorporated into the paste, followed by trituration for an hour. Adjustments to the water content were made empirically to maintain the paste's texture. The resulting paste underwent 24 hours of drying in a hot air oven. The dried powder was sieved to achieve specific particle sizes and stored within a desiccator until further analysis.

2.2.2. Physical Mixing Method

In this experimental procedure, a physical mixture was prepared by combining Carvedilol with the carrier substances β-Cyclodextrin, PEG-4000, and PVP K 30 in different ratios, specifically 1:1, 1:2, and 1:3. The mixing process was carried out manually using a mortar and pestle. After blending these components, the resulting mixture was passed through a mesh with a size of no. 40, likely to ensure uniformity and particle size consistency in the mixture. Subsequently, the mixture was stored in a desiccator for 48 hours. This methodology is commonly used in pharmaceutical and material science research to create homogeneous mixtures of Carvedilol with excipients or carriers (β-Cyclodextrin, PEG-4000, and PVP K 30) in different proportions. The sieving step helps achieve a consistent particle size distribution, which is crucial for Carvedilol formulation and dosage uniformity. Storing the mixture in a desiccator ensures that it remains in a controlled, dry environment, which can be important for maintaining the stability and quality of the mixture during further analysis or experimentation[22].

2.2.3. Solvent Evaporation Method

In this experimental procedure, various ratios of Carvedilol and PVP at 1:1, 1:2, and 1:3 were combined using solvent evaporation. The polymer PVP was initially dissolved in ethanol, serving as the solvent. Gentle heating up to approximately 50°C and continuous stirring was applied to facilitate the gradual evaporation of the ethanol solvent, forming a homogeneous solid mass. This mass was subsequently crushed to ensure uniformity, followed by vacuum desiccation for 24 hours to remove any remaining moisture or solvent. After this drying step, the material was further pulverized, subjected to another round of vacuum desiccation for an additional day, and then divided into different sieve fractions, likely for precise particle size control. Finally, these fractions were stored within desiccators, creating a dry environment to maintain the stability and quality of the material for subsequent use. This method is frequently employed in pharmaceutical and material science research to create controlled-discharge formulations and composite materials, incorporating drugs like Carvedilol into polymer matrices like PVP with specific ratios and particle size distributions[23].

2.3. Polymer Selection

A series of different combinations of solid dispersions were prepared to identify the optimal polymer for producing solid dispersions. These formulations typically included a range of polymer options, such as β-Cyclodextrin, PEG-4000, and PVP K30, in combination with ethanol. The purpose of these experiments was likely to assess how well each polymer interacted with the active ingredient or compound, possibly Carvedilol, and to evaluate their potential as carriers for solid dispersion formulation. Solid dispersions are a crucial approach in pharmaceutical development to enhance the solubility and bioavailability of poorly water-soluble drugs. By testing various combinations of polymers and solvents, researchers can determine which formulation yields the most desirable results regarding Carvedilol solubility and stability, aiding in selecting the most suitable polymer for the intended pharmaceutical application (Table 1).

Table 1: List of Formulations from KN1 to SE3

Ingredients (mg)	KN1	KN2	KN3	PM1	PM2	PM3	SE1	SE2	SE3
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
β-Cyclodextrin	10	20	30	10	20	30	10	20	30
PEG-4000	10	20	30	10	20	30	10	20	30
PVP K30	10	20	30	10	20	30	10	20	30
Ethanol (95%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

2.4. Formulation development

The prepared solid dispersions were intended to be filled into hard gelatin capsules primarily because this method is convenient and easy to handle. Filling solid dispersions into hard gelatin capsules offers several advantages, including precise dosing, ease of administration, and formulation protection from external factors such as moisture and light. This approach is commonly employed in pharmaceutical formulation to ensure accurate and controlled delivery of the active ingredients to patients while also providing a user-friendly method for healthcare professionals and patients to take the medication.

2.5. Filling of hard gelatin capsule

The procedure commenced by placing empty gelatin capsules on a removable surface, ensuring that their bodies were facing downward, a step known as rectification. The cap portions of the capsules were then separated from their bodies. Using a plastic spatula, the desired formulation was carefully introduced into the capsule bodies, with precise dosing of utmost importance and any excess powder removed. Subsequently, the capsule caps were reunited with the capsule bodies, effectively sealing the capsule shells. Once the capsules were successfully filled and closed, they were extracted from the apparatus, a step referred to as the ejection of filled capsules. This method ensures accurate and controlled formulation dosing into individual capsules, making it suitable for pharmaceutical and medicinal applications.

2.6. Evaluation of formulated solid dispersed carvedilol capsules

2.6.1. Weight variation test

The formula to calculate the percentage deviation from the average weight is typically given by eq.1:

$$\%\ deviation \frac{(individual)-W(average)}{W(average)} X100 \text{--- (1)}$$

Weighed each capsule and recorded its weight. Calculated the average weight of all the capsules by summing up the individual weights and dividing by the number of capsules. For each capsule, subtract the weight of the shell from the gross weight to get the net weight of the contents. Use the formula above to calculate the % deviation for each capsule by plugging in the individual weight and the calculated average weight [24, 25].

2.6.2. Drug Content

The process for Carvedilol content analysis involves the preparation of a solution from various solid dispersions. Approximately 12.5 mg of Carvedilol (or its equivalent) is initially accurately weighed and added to a 100 ml volumetric flask. This flask is then filled up to the mark with pH 7.4 phosphate buffer, creating a Stock I solution. Next, a 1 ml aliquot of the Stock I solution is carefully transferred to a 10 ml volumetric flask, and the volume is adjusted to 10 ml using pH 7.4 phosphate buffer. This step creates a more diluted solution for analysis. The quantification of Carvedilol content in the prepared solutions is carried out using a spectrophotometer set at a specific wavelength, in this case, 243 nm. The spectrophotometer measures the absorbance of light by the Carvedilol molecules in the solution at this particular wavelength. The concentration of Carvedilol in the solid dispersion samples can be determined by comparing the measured absorbance to a calibration curve or standard. Spectrophotometry at a specific wavelength is a widely used and reliable method for quantitative analysis in pharmaceutical and chemical research, allowing for the accurate determination of the concentration of a substance in a solution based on its light-absorbing properties at a known wavelength. In this case, it is applied to assess the Carvedilol content in the solid dispersion samples[26].

2.6.3. Lock Length

The evaluation process involved using Vernier calipers, a precise measuring tool, to assess certain aspects of the capsules. This assessment aimed to verify whether the capsules had been adequately compressed and whether their locking mechanism was functioning correctly and remained intact. Vernier calipers were likely employed to measure the dimensions or characteristics of the capsules, ensuring their quality and proper functioning[27].

2.6.4. Disintegration Time

The assessment of solid gelatin capsule disintegration confirms the Carvedilol substance's full accessibility for dissolution and absorption in the gastrointestinal tract. The established disintegration test for these capsules follows the exact protocol and equipment detailed in the document titled 'Quality Control Tests for Tablets.' In this process, the capsules are placed in a basket-rack setup that is rhythmically immersed in a temperature-controlled fluid bath, set at 37 ± 2°C, with a frequency of 30 cycles per minute. The capsules' performance is observed over the duration specified in the relevant monograph to ensure compliance with disintegration standards[28]. This procedure ensures the capsules disintegrate properly, facilitating effective Carvedilol discharge and absorption[29].

2.6.5. Moisture permeation test

In order to perform this test, capsules are placed together with desiccated pellets that have the ability to change color upon exposure to moisture. These capsules, along with the pellets, are enclosed within a single container. The container is then placed in an environment with a predetermined humidity level for a specified period. If the environment is sufficiently humid, the pellets will absorb moisture and undergo a color change. This color change in the originally dry pellets indicates moisture absorption within the container. After the designated exposure time, the weight of the capsule that underwent the test is compared to the weight of the original capsule before the test was conducted. The difference in weight between these two measurements indicates the

extent of water that the capsule and the desiccated pellets have absorbed. This process evaluates how well the capsule packaging protects its contents from moisture and humidity, which can be important for maintaining the stability and effectiveness of the enclosed substances (e.q.2)[30].

$$\%\ moisture\ permeation\ = \frac{W(Final)-W(Initial)}{W(Initial)} X100 \text{--- (2)}$$

2.6.6. In-Vitro Dissolution studies

The dissolution testing was conducted according to the USP standards using the rotating paddle method. The samples under evaluation were enclosed within hard gelatin capsules. The test was carried out using a dissolution apparatus as specified by USP. A volume of 900 ml of phosphate buffer with a pH of 7.4 was chosen as the dissolution medium, and the temperature was maintained at 37 ± 0.5°C throughout the test. The stirring speed of the apparatus was set to 50 rpm. Samples were drawn from the dissolution medium at specific time intervals. To maintain "sink conditions" and ensure consistent results, the withdrawn volume was replenished with a fresh phosphate buffer at pH 7.4. The withdrawn samples were then subjected to analysis to determine the percentage of Carvedilol that had been discharged into the dissolution medium. This analysis was performed using a spectrophotometer, measuring the absorbance of the samples at a wavelength of 243 nm[26]. This procedure is designed to assess the rate and extent of Carvedilol discharge from the capsules under the specified conditions, providing insights into their dissolution characteristics and potential bioavailability[31].

2.6.7. Statistical analysis

The data in the study were analyzed using Microsoft Excel 2016, with statistical summaries presented as mean values accompanied by their respective standard deviations (SD). Excel's functionality was leveraged to compute these descriptive statistics, clearly representing the central tendency and data variability, which are vital components of data analysis and interpretation.

3. RESULTS

3.1. Solubility and melting point constraints

The results of these studies significantly shape our choice of solvents/vehicles for formulation and related investigations. By evaluating dissolution behaviors under various conditions, we gain insights into how different solvents impact Carvedilol discharge, aiding in optimal formulation design. This knowledge is pivotal in predicting bioavailability, ensuring regulatory compliance, and refining dosage forms for improved Carvedilol delivery and performance. Carvedilol exhibited high solubility in chloroform and methanol, limited solubility in 0.1N HCl, good solubility in PBS (pH 7.4), and minimal solubility in distilled water. This study is of significant importance as the melting point is an intrinsic characteristic of a Carvedilol and plays a vital role in evaluating its purity. The melting of Carvedilol demonstrated a melting point of 113.2±3.1°C. This analysis helps confirm the Carvedilol's identity and ensures its quality assessment.

3.2. FTIR results

The FTIR spectra analysis indicated that the distinctive peaks and stretches unique to the Carvedilol remained unchanged and detectable even in the combined spectrum of the Carvedilol and excipient. This suggests that the chemical and structural properties of the Carvedilol were not significantly altered or affected by the presence of the excipient, demonstrating compatibility between the two components in the formulation. This information is valuable in pharmaceutical development and formulation, ensuring that the Carvedilol's integrity and efficacy are maintained when combined with other substances (Figure 2).

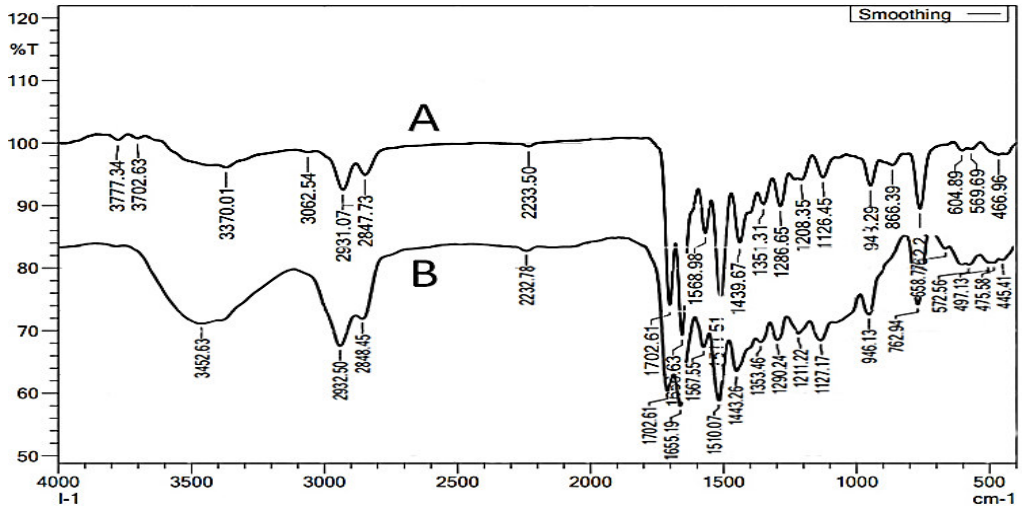

Fig 2: FTIR spectra of A) Carvedilol; B) Carvedilol with excipients

3.3. Calibration Curve results

The λ_{max} of Carvedilol, has been determined to be 243nm. This value signifies the specific wavelength at which Carvedilol molecules exhibit their maximum absorbance, absorbing light most effectively at this point. This information is crucial in pharmaceutical research and quality control, enabling scientists to develop analytical methods for identifying and

quantifying Carvedilol in various applications using UV-visible spectroscopy.

3.4. Characteristics of formulated capsules

Consistent weight was observed in all capsules, with minimal variation detected among different formulations. This uniform weight profile indicates the effective dispersion of the Carvedilol within the capsules across various batches tested. Detailed results of the percentage weight variation were within the limits (Table 4). This data underscores the quality and uniformity of the product, which is crucial in pharmaceutical quality control and ensures reliable dosing (Table 2). The estimation of Carvedilol content was carried out, and absorbance readings were recorded using a UV spectrophotometer. The Carvedilol content for the formulated products, labeled from KN1 to SE3, consistently falls within 95.04±2.87 to 99.21±3.14%, as specified in Table 2. Notably, the KN1 formulation exhibited a notably higher Carvedilol content than the other formulations, indicating its potency and consistent dosage within the product range. The length of the lock mechanism on the Carvedilol capsule was accurately measured using the vernier caliper technique, and the recorded measurements fell within a range of 17.60±0.05 to 17.66±0.09mm. Remarkably, it's worth noting that the lock length of the KN2 formulation exceeded that of the other formulations, indicating a potential variation in the capsule design or production process for this specific formulation (Table 2). The results for all formulations consistently showed a range of moisture permeation values from 2.038% to 4.773%, as detailed in the table. These findings underscore the significance of the formulation's composition and structure in controlling moisture ingress, which is crucial for maintaining pharmaceutical products' stability and shelf life (Table 2).

Table 2: Evaluation Tests of Formulated Capsules

Formulation	Weight Variation (%)	Carvedilol Content (%)	Lock length (mm)	Moisture permeation (%)	Disintegration Time (sec)
KN1	305±3.15	99.21±3.14	17.65±0.01	3.20±0.03	32.26±2.16
KN2	305±0.22	97.57±2.85	17.60±0.05	3.24±0.21	31.58±1.55
KN3	305±0.01	96.68±3.08	17.62±0.02	2.03±0.18	30.29±1.08
PM1	305±1.17	97.70±4.19	17.61±0.08	3.18±0.15	34.28±1.41
PM2	305±1.35	97.57±2.12	17.62±0.05	2.22±0.05	33.80±1.03
PM3	305±1.34	96.20±3.45	17.63±0.03	2.42±0.07	33.28±0.89
SE1	305±1.33	95.52±1.66	17.61±0.05	3.92±0.16	32.03±1.41
SE2	305±4.37	95.04±2.87	17.63±0.06	4.77±0.11	32.61±1.37
SE3	305±1.34	95.58±2.56	17.66±0.09	2.24±0.07	32.24±1.32

KN: kneading method solid dispersions; PM: physical mixture method solid dispersions; SE: solvent evaporation method solid dispersions; All the readings are in mean ± SD (n=3)

3.5. Kinetics of Carvedilol Discharge

The *in-vitro* discharge data were analyzed using various kinetic models, including zero-order, first-order, Higuchi, and Korsemeyer-Peppas equations, to understand the Carvedilol discharge patterns. Among these models, formulations PM1, PM2, PM3, SE2, and SE3 exhibited conformity to zero-order kinetics, with respective R^2 values of 0.9904, 0.9854, 0.9816, 0.995, and 0.9946. It suggests a consistent and uniform discharge rate regardless of concentration, indicating a controlled mechanism. In contrast, formulations KN1 and SE1, with R^2 values of 0.9966 and 0.9926, displayed discharge mechanisms involving a combination of diffusion and erosion control. Notably, a solute diffusion exponent (n) exceeding 0.89 characterized the Carvedilol discharge from these formulations as super case II transport, suggesting a more complex discharge behavior. On the other hand, formulations KN2 and KN3 adhered to the Higuchi model, with matching R^2 values of 0.9817 (Table 3 and Figure 3). It indicates that diffusion was the primary governing factor for the Carvedilol discharge mechanisms in these formulations. These insights into the kinetics of Carvedilol discharge are valuable in pharmaceutical formulation development and can help tailor Carvedilol delivery systems to meet specific therapeutic requirements.

Table 3: Kinetic modeling plot of Carvedilol Capsule formulations (KN1-SE3)

Formulation	Zero-order	First order	Higuchi model	Korsmeyer- Peppas	
				R^2	n
KN1	0.9818	0.9435	0.9815	0.9966	0.686
KN2	0.9808	0.9430	0.9817	0.9753	0.696
KN3	0.9772	0.9457	0.9784	0.9743	0.668
PM1	0.9904	0.9739	0.9713	0.9751	0.718
PM2	0.9854	0.9746	0.9825	0.9751	0.675
PM3	0.9816	0.9768	0.9745	0.9727	0.646
SE1	0.9948	0.9479	0.9594	0.9926	0.977
SE2	0.9950	0.9548	0.9744	0.9896	0.915
SE3	0.9946	0.9603	0.9627	0.9867	0.862

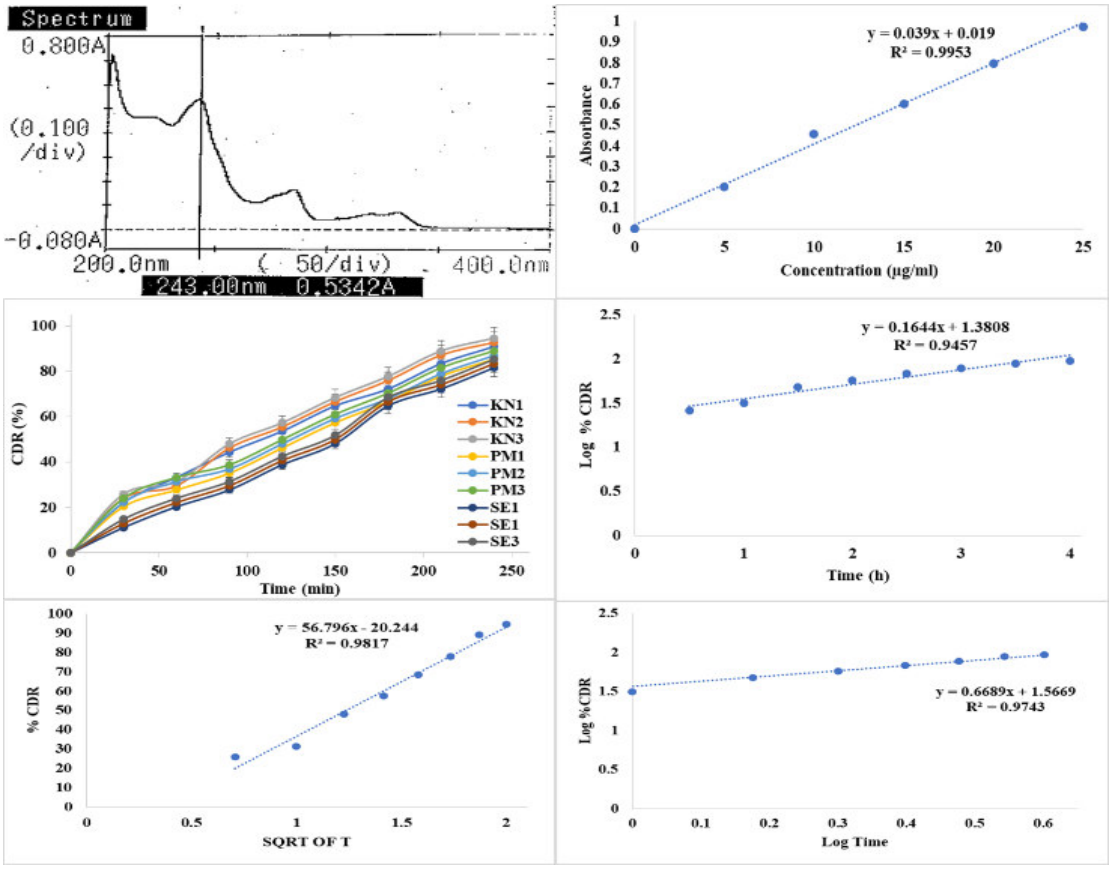

Fig 3: A) λ_{max} of Carvedilol; B) Calibration Curve of Carvedilol; C) *In-vitro* drug discharge profile of formulations; D) First order plot of KN3; E) Higuchi's plot for KN3 F) Korsmeyer's plot for KN3

4. DISCUSSION

4.1. Advantages and Limitations of Solid Dispersion

The size of primary particles generated following dose breakdown limits the dissolution rate of capsules and tablets. The average particle size is 5 m. However, larger particles are recommended for handling, formulation, and production convenience. A fraction of the medicine is used to saturate the gastrointestinal fluid, with excess precipitating as tiny colloidal particles or greasy globules. Because of its anticipated bioavailability increase, solid dispersion is an important topic of study in the pharmaceutical profession [32]. Preclinical safety and early clinical research on novel chemical entities with minimal water solubility can be aided by solid dispersions. They produce a combination of poorly water-soluble drugs and highly soluble carriers, resulting in faster dissolution and higher bioavailability. In solid dispersions, particles with increased wettability and porosity are also employed. Because no energy is required to break up the crystal lattice during the dissolution process, drugs in an amorphous form can improve drug release. Because of the necessity for a high carrier volume, solid dispersion technology confronts hurdles in pharmaceutical product development, needing more than 50% to 80% w/w. Because of the high energy metastable form's decreased solubility and dissolution rate, oral bioavailability is varied. Instability, variations in crystallinity, and possible destabilization by physical treatment such as pulverization and aging are all disadvantages of solid dispersions.[33]. Selecting the appropriate solvent or vehicle for formulating a pharmaceutical compound like Carvedilol is a fundamental step in drug development. Different solvents have varying solubility for a given drug, which can significantly influence its bioavailability. In the study, it's noted that Carvedilol exhibited high solubility in chloroform and methanol, limited solubility in 0.1N HCl, good solubility in PBS (pH 7.4), and minimal solubility in distilled water[34] Dewan et al., 2012 also observed similar solubility of Carvedilol. Understanding these solubility profiles helps in formulating the drug effectively. Solvents with higher solubility may be preferred for drug delivery systems requiring rapid dissolution, while those with lower solubility might be suitable for sustained-release formulations[35]. The melting point of a pharmaceutical compound is a critical parameter. It confirms the identity and purity of the substance. A consistent melting point within a narrow range indicates high purity, whereas deviations may suggest impurities or altered chemical properties. This analysis is pivotal for ensuring the quality and efficacy of Carvedilol-containing products [36]. Such identification was also practiced by Shamma et al., 2013. Even slight variations in the melting point could significantly impact the drug's performance. FTIR is a powerful technique used to investigate a drug's chemical structure and compatibility with excipients. In this study, the fact that the distinctive peaks of Carvedilol remained unchanged in the presence of excipients indicates that the drug's chemical and structural properties were not significantly altered. This compatibility is crucial because it ensures that the drug remains effective and stable when formulated with other substances, essential for developing safe and efficient pharmaceutical products Yamsani et al., 2007 [37] did a compatibility study by the same method. Determining the specific wavelength at which Carvedilol exhibits maximum absorbance (λ_{max}) is essential for analytical purposes. It allows pharmaceutical scientists to develop analytical methods using UV-visible spectroscopy for accurately identifying and quantifying Carvedilol in various applications [38] Beattie et al., 2013 found absorption maxima of carvedilol at the same wavelength. This wavelength represents the point at which the drug absorbs light most effectively,

providing a reliable basis for quantification. Uniform weight across different formulations and accurate estimation of Carvedilol content are crucial for pharmaceutical quality control. Consistent weight ensures that each capsule or dosage unit contains the intended amount of the drug, providing reliable dosing to patients. Arun Raj et al., 2017 [39] also found uniform weight across different formulations of Carvedilol. Accurate content estimation, falling within the specified range, is essential to meet regulatory requirements and ensure that the formulated products meet desired Carvedilol content specifications. Precise measurements of the lock mechanism length on Carvedilol capsules help assess the consistency in capsule design and production processes. Variations in lock length could indicate potential issues in manufacturing, which could affect the capsule's integrity or ability to release the drug properly. Consistency in capsule design ensures that patients receive the intended dose consistently across different batches. Kajale et al., 2020[40] observed consistencies in lock length across all formulations. Moisture permeation in pharmaceutical formulations can significantly impact product stability and shelf life. The study attributes variations in moisture permeation to the concentration of hydrophilic polymers and differences in the resistance of the matrix network structure. Understanding these factors is critical for maintaining the quality and efficacy of pharmaceutical products over time Arregui et al., 2019[41]. Controlling moisture ingress is essential to prevent drug degradation and ensure product safety. Analyzing *in-vitro* discharge kinetics involves studying how Carvedilol is released from various formulations over time. Different formulations exhibit distinct discharge patterns, which can be mathematically modeled. For example, zero-order kinetics suggest a consistent and uniform discharge rate regardless of concentration, indicating a controlled mechanism Halder et al., 2020[42]. In contrast, formulations displaying super case II transport or diffusion-controlled mechanisms have more complex discharge behavior. Understanding these kinetics helps pharmaceutical scientists tailor Carvedilol delivery systems to meet specific therapeutic requirements, such as sustained or immediate release, optimizing drug performance and patient outcomes Thomas et al., 1982[43]. The observation that solid dispersions exhibit zero-order release in vitro drug release studies is an intriguing and valuable finding in pharmaceutical research. Zero-order release kinetics means the drug release rate remains constant over time, resulting in a linear cumulative drug release profile[44]. It contrasts first-order or other kinetics, where the release rate decreases with time[45].

4.2. Potential Clinical Applications and Future Directions

Solid dispersions of carvedilol can be used in clinical applications to improve the drug's solubility, bioavailability, and therapeutic efficacy. Solid dispersions can increase the solubility of carvedilol, leading to improved bioavailability. The body can absorb and utilize more of the drug, potentially reducing the required dosage and minimizing side effects. Solid dispersions make the drug less dependent on food intake. It can improve patient compliance and dosing flexibility. Carvedilol is often used in combination with other medications to manage cardiovascular conditions. Solid dispersions can facilitate the development of combination therapies, where multiple drugs are co-formulated into a single dosage form, enhancing patient convenience and treatment adherence. The current investigation yields a good outcome; it can be stated that the solid dispersion approach is superior to other solubility enhancement strategies for increasing carvedilol solubility and drug discharge. The scope for pharmacodynamic and pharmacokinetic assessments, as well as long-term stability studies, as per current ICH standards, for the improved formulation is suggested.

5. CONCLUSION

In conclusion, this research addresses the challenge of improving the oral bioavailability of poorly water-soluble drugs, focusing on Carvedilol using solid dispersion techniques. The study successfully created solid dispersed Carvedilol capsules through kneading, physical mixing, and solvent evaporation, enhancing solubility and dissolution. Careful polymer selection influenced Carvedilol discharge profiles, validated by critical parameter evaluations. In-vitro dissolution studies revealed diverse discharge mechanisms. Formulation KN3, achieving 94.67% Carvedilol discharge, highlights the approach's potential. This research enhances understanding solid dispersion's impact on Carvedilol, laying a foundation for further formulation refinement and optimization. The findings contribute to improving Carvedilol delivery systems, especially for challenging compounds, promising advancements in pharmaceutical therapeutic efficacy.

6. ACKNOWLEDGEMENTS

The authors are thankful to the college management for their encouragement and support.

7. ABBREVIATIONS

FTIR: Fourier transform Infra-red; IP: Indian Pharmacopoeia; PEG: polyethylene glycol; PVP: Poly Vinyl Pyrrolidone; AR: Analytical Reagent; λ_{max}: Absorption maxima; nm: Nanometers; mg: milligrams; ml: Milliliters; µg: microgram; USP: the United States Pharmacopoeia; rpm: rotations per minute; SD: standard deviations; PBS: Phosphate buffer solution; HCl: Hydrochloric acid; Q.S: Quantity sufficient.

8. AUTHORS CONTRIBUTION STATEMENT

Pavan Kumar conceived of the presented idea. Subhash P G: developed the theory and performed the computations. Pawan Dhamala and Suprith D: verified the analytical methods. Hindustan Abdul Ahad: investigated and supervised the findings. All authors discussed the results and contributed to the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

10. REFERENCES

1. El Hoffy NM, Abdel Azim EAA, Hathout RM, Fouly MA, Elkheshen SA. Glaucoma: management and future perspectives for nanotechnology-based treatment modalities. Eur J Pharm Sci. 2021;158:105648. doi: 10.1016/j.ejps.2020.105648, PMID 33227347.
2. Ouyang J, Zhang Z, Deng B, Liu J, Wang L, Liu H, et al. Oral drug delivery platforms for biomedical applications. Mater Today. 2023;62:296-326. doi: 10.1016/j.mattod.2023.01.002.
3. Nambiar AG, Singh M, Mali AR, Serrano DR, Kumar R, Healy AM, et al. Continuous manufacturing and molecular modeling of pharmaceutical amorphous solid dispersions. AAPS PharmSciTech. 2022;23(7):249. doi: 10.1208/s12249-022-02408-4, PMID 36056225:249. Nambiar AG, Singh M, Mali AR, Serrano DR, Kumar R, Healy AM, et al. Continuous manufacturing and molecular modeling of pharmaceutical amorphous solid dispersions. AAPS PharmSciTech. 2022;23(7):249. doi: 10.1208/s12249-022-02408-4, PMID 36056225.
4. Tambe S, Jain D, Agarwal Y, Amin P. Hot-melt extrusion: highlighting recent advances in pharmaceutical applications. J Drug Deliv Sci Technol. 2021;63:102452. doi: 10.1016/j.jddst.2021.102452.
5. Sayed N, Khurana A, Godugu C. Pharmaceutical perspective on the translational hurdles of phytoconstituents and strategies to overcome. J Drug Deliv Sci Technol. 2019;53:101201. doi: 10.1016/j.jddst.2019.101201.
6. Rostamabadi H, Falsafi SR, Rostamabadi MM, Assadpour E, Jafari SM. Electrospraying is a novel process for synthesizing particles/nanoparticles loaded with poorly water-soluble bioactive molecules. Adv Colloid Interface Sci. 2021;290:102384. doi: 10.1016/j.cis.2021.102384, PMID 33706198.
7. Han J, Wei Y, Lu Y, Wang R, Zhang J, Gao Y, et al. Co-amorphous systems for the delivery of poorly water-soluble drugs: recent advances and an update. Expert Opin Drug Deliv. 2020;17(10):1411-35. doi: 10.1080/17425247.2020.1796631, PMID 32683996.
8. Aiassa V, Garnero C, Longhi MR, Zoppi A. Cyclodextrin multicomponent complexes: pharmaceutical applications. Pharmaceutics. 2021;13(7):1099. doi: 10.3390/pharmaceutics13071099, PMID 34371790.
9. Abdul AH, Bala AG, Chintaginjala H, Manchikanti SP, Kamsali AK, Dasari RRD. Equator assessment of nanoparticles using the design-expert software. Int J Pharm Sci Nanotechnol (IJPSN). 2020;13(1):4766-72.
10. Toutain PL, Bousquet-mélou A. Bioavailability and its assessment. J Vet Pharmacol Ther. 2004;27(6):455-66. doi: 10.1111/j.1365-2885.2004.00604.x, PMID 15601440.
11. Haranath C, Reddy JL, Ahad HA, Reshma T, Shubha BN. Aquasomes: A novel approach for the delivery of bioactive molecules. J Pharm. 2022;11:5325-30.
12. Kousar S, Abdul Ahad HA, Chinthaginjala H, Babafakruddin P, Lakunde J, Tarun K. Gas generating floating tablets: A quick literature review for the scholars. Asian J Res Chem. 2022;15(2):171-5. doi: 10.52711/0974-4150.2022.00029.
13. Ahad HA, Chinthaginjala H, Meharajunnisa B, Vandana N, Gudisipalli R, Nikhila P. Past work done on the matrix tablets: A quick reference for the research beginner in sustained-release dosage forms. Int J Pharm Investigation. 2023;13(3):367-72. doi: 10.5530/ijpi.13.3.047.
14. Ahad H, Kumar G, Chinthaginjala H, Tarun K, Reddy G. A competent Review of computer imitations of pharmacokinetic and pharmacodynamic arrangements. S Afr Pharm J. 2023;90(1):29-34.
15. Annepogu H, Ahad HA, Nayakanti D. Determining the best poloxamer carrier for thiocolchicoside solid dispersions. Turk J Pharm Sci. 2020;17(4):372-80. doi: 10.4274/tjps.galenos.2019.78800, PMID 32939132.
16. Jwalapuram R, Ahad HA, Haranath C, Thadipatri R, Varshitha C, Kumar YB. A desktop reference to the solubility enhancement of drugs with the aid of surfactants. Int J Life Sci Pharm Res. 2020;11(5):11-6.
17. Ahad HA, Chinthaginjala H, Tarun K, Reddy G, Adam AO, Ali A, et al. Hylocereus undatus fruit extraction on percent yield using Design-Expert software: a revelation for the enormousness of temperature and contact time. Egypt Pharm J. 2023;22(1):49. doi: 10.4103/epj.epj_97_22.
18. Newman A, Zografi G. Considerations in the development of physically stable high drug load API-polymer amorphous solid dispersions in the glassy state. J Pharm Sci. 2023;112(1):8-18. doi: 10.1016/j.xphs.2022.08.007, PMID 35948156.
19. Ahad HA, Chinthaginjala H, Rahamtulla S, Pallavi BP, Shashanka C, Prathyusha J. A comprehensive report on solid dispersions by factorial design; 2021.
20. Villanueva C, Torres F, Sarin SK, Shah HA, Tripathi D, Brujats A, et al. Carvedilol reduces the risk of decompensation and mortality in patients with compensated cirrhosis in a competing-risk meta-analysis. J Hepatol. 2022;77(4):1014-25. doi: 10.1016/j.jhep.2022.05.021, PMID 35661713.
21. Benkel T, Zimmermann M, Zeiner J, Bravo S, Merten N, Lim VJY, et al. How carvedilol activates β2-adrenoceptors. Nat Commun. 2022;13(1):7109. doi: 10.1038/s41467-022-34765-w, PMID 36402762.
22. Annepogu H, Ahad HA. Unique solid dispersions by microwave fusion technique with etoricoxib and thiocolchicoside: in vivo evaluation and comparison with marketed formulation. app. 2022;10(2):104-13. doi: 10.13189/app.2022.100204.
23. Ahad HA. Appraising best polyethylene glycol carrier for thiocolchicoside solid dispersions. J Pharm Chem Biol Sci. 2018:355-64.
24. Annepogu H, Ahad HA, Nayakanti D. Journal of Pharmaceutical and Scientific Innovation. Determining the Best Poloxamer Carrier for Thiocolchicoside Solid Dispersions. Turk J Pharm Sci. 2020 Aug;17(4):372-80. doi: 10.4274/tjps.galenos.2019.78800, PMID 32939132.
25. Harsha SS, Ahad HA, Haranath C, Dasari RR, Gowthami M, Varam NJ, et al. Exfoliation technique of composing and depictions of clopidogrel bisulphate afloat microspheres. J Evol Med Dent Sci. 2020;9(14):1156-60. doi: 10.14260/jemds/2020/251.
26. Krstić M, Manić L, Martić N, Vasiljević D, Mračević SĐ, Vukmirović S, et al. Binary polymeric amorphous carvedilol solid dispersions: in vitro and in vivo characterization. Eur J Pharm Sci. 2020;150:105343. doi: 10.1016/j.ejps.2020.105343, PMID 32376386.
27. Paudel A, Geppi M, Van den Mooter GVD. Structural and dynamic properties of amorphous solid dispersions: the role of solid-state nuclear magnetic

resonance spectroscopy and relaxometry. J Pharm Sci. 2014;103(9):2635-62. doi: 10.1002/jps.23966, PMID 24715618.
28. Tanaka N, Imai K, Okimoto K, Ueda S, Tokunaga Y, Ibuki R, et al. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): in vivo evaluation. J Control Release. 2006;112(1):51-6. doi: 10.1016/j.jconrel.2006.01.020, PMID 16545477.
29. Annepogu H, Ahad HA, Nayakanti D, Ahad HA. Valuing the best poloxamer carrier for thiocolchicoside solid dispersions. Turk J Pharm Sci. 2020 Aug;17(4):372-80. doi: 10.4274/tjps.galenos.2019.78800.
30. Newman A, Knipp G, Zografi G. Assessing the performance of amorphous solid dispersions. J Pharm Sci. 2012;101(4):1355-77. doi: 10.1002/jps.23031, PMID 22213468.
31. Shravani Y, Ahad HA, Haranath C, gari Poojitha B, Rahamathulla S, Rupasree A. Past decade work done on cubosomes using factorial design: A fast track information for researchers. Int J Life Sci Pharm Res. 2021;11(1):124-35.
32. Serajuddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999 Oct;88(10):1058-66. doi: 10.1021/js980403l, PMID 10514356.
33. Kalia A, Poddar M. Solid dispersions: an approach towards enhancing dissolution rate. Int J Pharm Pharm Sci. 2011;3(4):9-19.
34. Dewan I, Hossain MA, Islam SA. Formulation and evaluation of solid dispersions of carvedilol, a poorly water soluble drug by using different polymers. Int J Res Pharm Chem. 2012;2:585-93.
35. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727. doi: 10.5402/2012/195727, PMID 22830056.
36. Shamma RN, Basha M. Soluplus®: a novel polymeric solubilizer for optimization of carvedilol solid dispersions: formulation design and effect of method of preparation. Powder Technol. 2013;237:406-14. doi: 10.1016/j.powtec.2012.12.038.
37. Yamsani VV, Gannu R, Kolli C, Rao ME, Yamsani MR. Development and in vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharm. 2007 Jun 1;57(2):185-97. doi: 10.2478/v10007-007-0015-7, PMID 17507315.
38. Beattie K, Phadke G, Novakovic J. Carvedilol. Profiles Drug Subst Excipients Relat Methodol. 2013;38:113-57. doi: 10.1016/B978-0-12-407691-4.00004-6.
39. Arun Raj R, Harindran J. Formulation and evaluation of carvedilol solid dispersion tablets for solubility enhancement. Eur J Biomed PharmSci. 2017;4(2):337-48.
40. Kajale AD, Gadewar CK, Kothari PP. Formulation and evaluation of floating microencapsules of diltiazem hydrochloride by hot melt granulation method. Res J Pharm Technol. 2020;13(1):227-32. doi: 10.5958/0974-360X.2020.00046.3.
41. Arregui JR, Kovvasu SP, Kunamaneni P, Betageri GV. Carvedilol solid dispersion for enhanced oral bioavailability using rat model. J app pharm sci. 2019;9(12):42-50. doi: 10.7324/JAPS.2019.91207.
42. Halder S, Ahmed F, Shuma ML, Azad MAK, Kabir ER. Impact of drying on dissolution behavior of carvedilol-loaded sustained release solid dispersion: development and characterization. Heliyon. 2020;6(9):e05026. doi: 10.1016/j.heliyon.2020.e05026, PMID 33005811.
43. Thomas NL, Windle AH. A theory of case II diffusion. Polymer. 1982 Apr 1;23(4):529-42. doi: 10.1016/0032-3861(82)90093-3.
44. Naser YA, Tekko IA, Vora LK, Peng K, Anjani QK, Greer B et al. Hydrogel-forming microarray patches with solid dispersion reservoirs for transdermal long-acting microdepot delivery of a hydrophobic drug. J Control Release. 2023 Apr 1;356:416-33. doi: 10.1016/j.jconrel.2023.03.003, PMID 36878320.
45. Yang R, Zhang GGZ, Zemlyanov DY, Purohit HS, Taylor LS. Release mechanisms of amorphous solid dispersions: role of drug-polymer phase separation and morphology. J Pharm Sci. 2023 Jan 1;112(1):304-17. doi: 10.1016/j.xphs.2022.10.021, PMID 36306863.