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Original Article

Copovidone-Based Stable Nebivolol Hydrochloride Formulation: Dissolution and Characterization Studies

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Abstract

Copovidone Based Stable Nebivolol Hydrochloride Formulation: Dissolution and Characterization Studies. The study aimed to develop a formulation for the poorly water-soluble drug Nebivolol Hydrochloride. The formulation was carried out in two stages. Stage I attempts to enhance the drug's solubility, while stage II deals with the development of a drug-incorporated tablet formulation. Various strategies with different solid dispersion techniques, like solvent evaporation, melt fusion, and kneading, were used to improve the drug's solubility. Drugs and carriers were mixed with the ratios 1:1, 1:2, 1:3, and 1:4. Apart from the solid dispersion method, the hydrophilic carrier was activated with an acidifier and then mixed with the drug. Preformulation studies were conducted, which included API characterization, solubility measurement over a physiological pH range, and drug-excipients compatibility study. FTIR, DSC, and XRD characterized the developed solid dispersion, which shows the drug exists in the amorphous form in the solid dispersion with no molecular interaction. The dissolution profile revealed a significant improvement in drug solubility with solid dispersion compared to pure drugs. Solid dispersion prepared with Drug, Plasdone, and Tartaric Acid exhibits the most improved solubility and formulated immediate release tablet. Stability studies indicate excellent stability of formulation over six months at accelerated and real-time conditions.

Keywords: Acidifier; BCS class; Copovidone; Nebivolol hydrochloride; Solid dispersion; Plasdone.

1. Introduction

The concentration of a drug at the site of action relates to its therapeutic effectiveness. Absorption of the drug into the systemic circulation is the primary requirement to exhibit pharmacological response [1]. Systemic absorption of drugs occurs when drugs get dissolved and pass through a biological membrane [2]. Therefore, dissolution is essential for obtaining a therapeutic amount of drug in the systemic circulation. Biopharmaceutical Classification System (BCS) categorizes drugs into four classes based on two factors, i.e., dissolution of a drug and its permeability through biological membrane.

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Class I (High solubility and High permeability), Class II (Low solubility and High permeability), Class III (High soluble and Low permeability), and Class IV (Low soluble and Low permeability) [3].

Over 40 % of new chemical entities and one-third of official drugs in US Pharmacopeia are under poorly water-soluble drugs [4]. The importance of transit flow has also been described by BCS, which demonstrates the drug absorption process in conjunction with solubility and permeability. A drug can be characterized based on three dimensionless numbers, i.e., dose number (Do), dissolution number (Dn), and absorption number (An) [5]. These are based on physicochemical properties and physiological parameters. So, it becomes challenging for formulation scientists to formulate a poorly soluble drug into a suitable dosage form. Various techniques enhance the solubility of drug-like Micronization, solubilization, and salt formation. Micronization is preferable but cannot be used where the drug is under patent protection. Other techniques cover practical limitations for their application [2]. Solid Dispersion (SD) can be used as an essential tool to improve solubility and dissolution rate—their application suites for a different route of administration in various dosage forms.

Nebivolol Hydrochloride is a beta-adrenergic blocking agent that can be used alone or in combination with other antihypertensive drugs to treat hypertension and heart failure [6]. It is rapidly absorbed after oral administration. It is soluble in (dimethyl sulfoxide, methanol, N, N-dimethylformamide), sparingly soluble in (propylene glycol, ethanol, polyethylene glycol), and very slightly soluble in (dichloromethane, hexane, methylbenzene). The pKa and log P values are 13.52 and 3.21, respectively [6]. It possesses a pH-dependent solubility profile with higher solubility towards acidic pH [7, 8]. The solubility problem is the main obstacle to achieving the desired dissolution [9].

Copovidone has a variety of applications in pharmaceuticals. It is an acetic acid ethenyl ester commercially available with the brand name Plasdone S630 and Kollidon VA 64. It is a white to yellowish-white amorphous powder. Copovidone consists of N-vinyl-2-pyrrolidone and vinyl acetate in a proportion of 60:40 [10]. Both the groups accept hydrogen bonds, which helps in solid dispersion application for solubility enhancement. The vinyl acetate group adds hydrophobicity and reduces hygroscopicity. Vinyl pyrrolidone helps to enhance water solubility, while vinyl acetate reduces glass transition temperature [10-12]. In the present study, efforts were made to develop a formulation to increase the solubility of Nebivolol Hydrochloride. The solid dispersion technique was utilized to improve its solubility. Carriers were selected from hydrophilic and amphiphilic nature. The development of the lead formulation comprised of SD was carried out in two phases. Phase 1 started with solubility enhancement by adopting various methods of SD. In the second phase, the lead SD was incorporated into the dosage form to formulate a tablet by process optimization.

2. Materials and Methods

2.1. Materials

Nebivolol Hydrochloride was obtained from Hetero Drugs, India. BASF, India, provides Poloxamer 407. Klucel LF and Plasdone S630

(Copovidone) were received from Ashland (USA). Analytical-grade chemicals were used for the analysis, and Tartaric Acid was obtained from Sigma-Aldrich (Germany). Gellucire was procured from Gattefosse, India, and the solvents used for analysis were of HPLC Grade. Milli-Q water was utilized for sample preparation.

2.2. HPLC quantification

HPLC system was used to measure the drug content (assay), drug solubility (dissolution profile), and drug degradation profile (related substance). The HPLC method was adopted since the method is described in the draft USP (United States Pharmacopeia) and IP (Indian Pharmacopeia) monograph. Also, the HPLC method is more accurate and precise. Moreover, it also enables the identification of peak interference. The HPLC system using column (C-18, 46 X 150 mm, 5µ), flow rate (1.0 ml/min), 20µl qty as injection volume, run time 5 min, and detection at 281nm was used. The mobile phase used was Buffer pH 3.0: Acetonitrile (55:45).

2.3. Solid dispersion preparation

2.3.1. Solvent evaporation (S.E)

Solid Dispersions were prepared using Nebivolol Hydrochloride and Carriers (Plasdone S630, Poloxamer 40, and Klucel LF) with different weight ratios (1:1, 1:2, 1:3, and 1:4) using the Solvent Evaporation technique. Carriers were dissolved in a sufficient quantity of Methanol. Nebivolol HCl was added under continuous stirring and subjected to evaporation until the solvent was removed and dried in an oven at 50°C. The samples were pulverized using mortar and pestle and passed through #30 sieves.

2.3.2 Melt fusion method

Solid Dispersions by Melt Fusion Method were prepared using carriers like Gellucire 44/14 and Poloxamer 407 in the ratios of 1:1, 1:2, 1:3, and 1:4. Nebivolol Hydrochloride was admixed in molten carriers melted at 50-52 0C and 52-55 0C for Gellucire 44/4 and Poloxamer 407 respectively with constant stirring. The resulting homogenous dispersion was cooled rapidly in an ice bath and kept in a desiccator for 24 Hrs. The prepared solid dispersion was milled and passed through a #30 sieve for uniform particle size.

2.3.3. Kneading technique

The weight amount of Nebivolol Hydrochloride and carriers (Poloxamer 407, Klucel LF) in weight ratios (1:1, 1:2, 1:3, and 1:4) were placed in the mortar, and a small amount of water was poured slowly under continuous stirring. The mixture was kneaded for 30 minutes till a homogenous slurry was obtained, and the samples were dried at 50^0C. The prepared solid dispersion was pulverized and passed through #30 sieved.

2.3.4 Mixing with Plasdone S630 and tartaric acid (PTA) mixture

This method dissolved Tartaric acid in purified water, and Plasdone was incorporated and stirred for 1 hour. Nebivolol Hydrochloride was added to this mixture and mixed for 30 mins. The mixture was dried in an oven at 50±5°C.

The prepared solid dispersion was pulverized and passed through the #30 sieve.

2.3.5. Nebivolol hydrochloride –excipients physical mixtures (PM)

Physical mixtures (PM) of Nebivolol Hydrochloride and various carriers in different weight ratios (1:1, 1:2, 1:3, 1:4) were prepared by mixing the components. Carriers and drugs were accurately weighed, passed through #30 sieves, and mixed well.

2.4. Solid dispersion evaluation

2.4.1. Solubility measurement

The shake-flask method evaluated the solubility of drug carrier solid dispersions (SD). The solid dispersions containing approximately 5mg of Nebivolol Hydrochloride added to distilled water in a screw cap bottle were sonicated for 30 min and then kept in a mechanical shaker for 24 hrs at 25^{o}C. The samples were filtered, diluted, and analyzed by UV spectrophotometer.

2.4.2. Analysis of physical properties of solid dispersion

Various physical characterizations of SD were carried out per the procedure described in the pharmacopeia. These tests include bulk density, tapped density, angle of repose, compressibility index, and Houser ratio. Tests were performed using USP electro lab Tapped and bulk density measurement apparatus. Values were calculated by following equations.

i) Bulk density:

Bulk density (ρo) = M / Vo

Where M = Mass of powder and Vo = Apparent unstirred volume

ii) Tapped density:

Tapped density (ρt) = M / Vt

Where M = Mass of powder and Vt= Tapped volume

iii) Compressibility Index:

Compressibility index =100 (Vo-Vt) / Vo

Where Vo = Bulk volume and Vt = Tapped volume.

iv) Hausner ratio:

Hausner ratio = Vo / Vt

Where Vo = Bulk volume and Vt = Tapped volume.

2.4.3. Analysis of drug content

Drug content in SD was quantified using the HPLC technique. HLPC system was run by using a column (ACE 5 Phenyl 4.6 x 250mm - 5µm or equivalent), 220 nm wavelength, 20 µl injection volume, 1.2 ml/min flow rate, 40 min run time, and water: acetonitrile (1:1) as diluent. Tetrabutylammonium hydrogen sulfate (3.4 g) and diethylamine (0.3 ml) were dissolved in 1 L purified water as a buffer solution. The mobile phase was prepared by transferring acetonitrile (280 ml) into a buffer solution (720 ml) and stirring for 1 minute, followed by filtration. A standard solution was prepared by adding Nebivolol hydrochloride (20 mg) in diluent and diluted to 20 ml. A test sample was prepared by dispersing the test sample (20 mg) in diluent and diluting the volume to 20 ml. Mobile phase (20µl), diluent, standard, and test solution were injected, and the percentage assay was calculated.

2.4.4. In-vitro dissolution

Dissolution behavior was profiled using USP apparatus II (Paddle), dissolution media (0.01N

HCl), speed (50rpm), and volume (900ml) at 37±0.5°C temperature. The required aliquot was withdrawn from each zone between the top of the paddle blade and the surface of the dissolution medium at a predefined time (5, 10, 15, 30, 45, and 60 min). The aliquot was then filtered through a 25 mm nylon syringe filter 0.45µ and quantified by HPLC.

2.4.5. FTIR analysis

The FTIR spectra were obtained using an FTIR spectrophotometer. The samples were previously triturated and mulled with potassium bromide. The disc was prepared by compressing the powder to form a thin pellet and then subjected to FTIR analysis.

2.4.6. Differential scanning calorimetric analysis

The DSC measurement was performed on the Mettler-Toledo DSC 822^e instrument. The samples were heated at a constant rate of 10 °C/min at a 25–300 °C temperature range. Nitrogen gas purging with a 50 ml/min flow rate was maintained.

2.4.7. Powder X-ray diffraction analysis

Powder X-ray diffraction patterns of drug carriers were recorded using a Rigaka, D/may2500 powder X-ray diffractometer, and obtained data containing 2-theta value with intensity was plotted.

2.4.8. Preformulation studies

2.4.8.1. *Drug excipients compatibility studies*

Binary mixtures of drug and excipient in different ratios in the solid state were assessed for compatibility studies. Samples were mixed thoroughly in transparent glass vials and stored at 25°C/60 % RH and 40°C/75% RH in both opened and closed conditions for four weeks. A pure Nebivolol Hydrochloride alone was kept as a reference. Samples were analyzed for physical and chemical interactions.

2.4.9. Prototype formulation development

Based on the SD solubility profile, SD prepared using Nebivolol-Plasdone S630-Tartaric Acid was selected to formulate a tablet dosage form. Excipients were selected based on compatibility study and SD characters. A circular, standard Concave, 6.5 mm punch was selected. The prototype formula was optimized based on trials using different excipients in various concentrations. The prepared tablets were evaluated for in-vitro drug release, drug content, and stability study.

2.4.10. Stability study

Tablets prepared using Nebivolol-Plasdone S630-Tartaric acid were further exposed to stability studies per ICH guidelines. The tablets were stored at 25ºC/60%RH (long term) and 40º C/75%RH (Accelerated) conditions. Samples were withdrawn at pre-defined intervals of 1M, 2M, 3M, and 6M at 40o C/75%RH and 3M and 6M at 25º C/60%RH.

3. Results and Discussion

3.1. Solubility studies

Nebivolol Hydrochloride is poorly soluble in water, with a logP Value of 3.23 [13]. The solubility of SD prepared using different carriers in (Plasdone S630, Poloxamer 407,

Klucel LF, and Gellucire 44/14) was analyzed in various ratios (1:1, 1:2, 1:3, 1:4). The SD was also prepared using Nebivolol hydrochloride with Plasdone-Tartaric acid mixture (1:1:1, 1:2:1,1:3:1, 1:4:1). The solubility was significantly increased with all the Drug-Polymer combinations when compared with pure drug. SD prepared with Klucel LF (1:1) using the kneading method was found to be least soluble compared to other SD, while Nebivolol Hydrochloride with Plasdone-TA mixture (1:3:1) through kneading technique showed significant improvement in solubility and therefore was selected further for formulation development (**Fig. 1-3**).

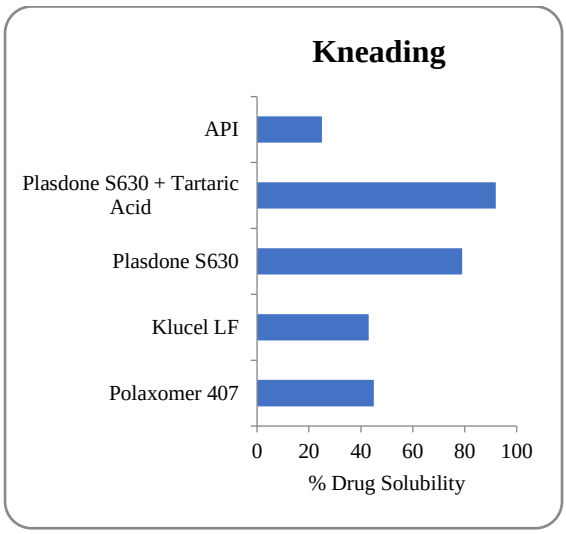

Figure 1. Drug solubility in SD by Kneading.

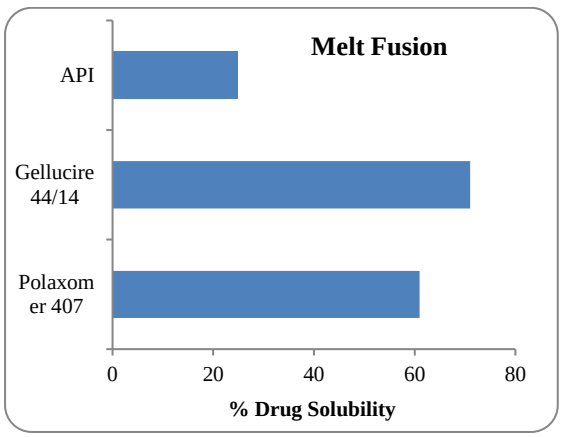

Figure 2. Drug solubility in SD by Melt Fusion.

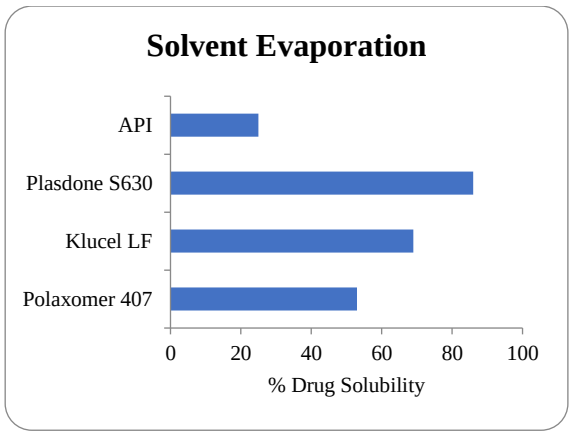

Figure 3. Drug solubility in SD by Solvent Evaporation.

3.2. Physical properties of SD

SD prepared using different techniques was analyzed for physical properties that reflect their flow compaction. Out of all the methods of SD preparation, SD prepared by the kneading technique exhibited better results than others. The results are summarized in **Table 1**.

Table 1: Physical properties of Solid Dispersion.

Formulation batch	Poloxamer 407	Klucel LF	Plasdone S630	Plasdone S630 with Tartaric Acid
Angle of repose	29.02	27.44	28.62	25.32
Bulk density (g/ml)	0.52	0.54	0.57	0.54
Tapped density (g/ml)	0.59	0.71	0.64	0.64
Compressibility Index (%)	11.91	24.32	16.03	16.21
Hauser ratio	1.13	1.32	1.16	1.19

3.3. Analysis of drug content

Drug content analysis was performed on all SDs prepared using various techniques. Drug content was found within the 98.75% to 99.82% range, which complied with the pharmacopeial range of 90% to 110% and showed no significant drug loss during solid dispersion preparation. Results are depicted in **Figure 4-6**.

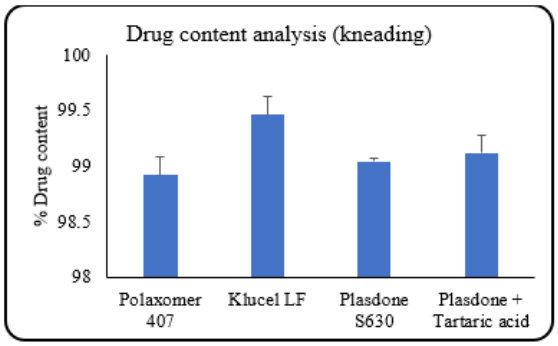

Figure 4. Drug content in SD by kneading.

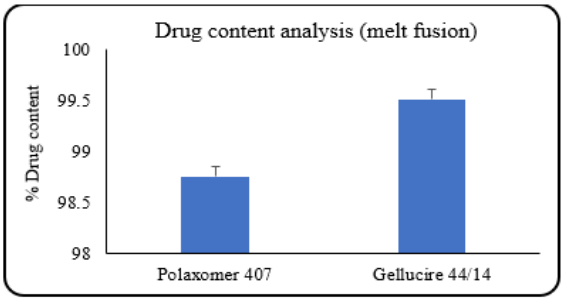

Figure 5. Drug content in SD by Melt Fusion.

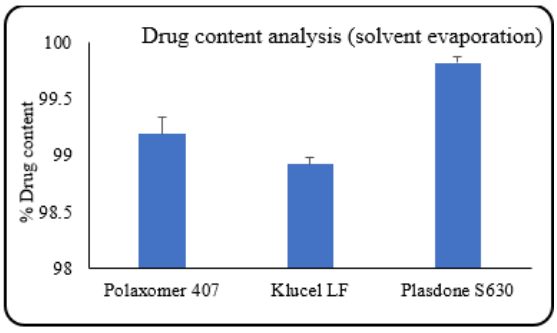

Figure 6. Drug content in SD by Solvent Evaporation.

3.4. In-vitro dissolution

Solubility study data revealed significant solubility improvement in SD compared to pure drug alone. The dissolution profiles were also studied for SD mixtures prepared with different techniques to evaluate the impact on the release profile. Amongst all, drug-treated with a PTA mixture exhibited faster release. Dissolution profiling is shown in **Figure 7-9.** The study also supports this solubility improvement performed [14], which demonstrates dissolution and bioavailability enhancement of poorly water-soluble drugs studied using Plasdone S630.

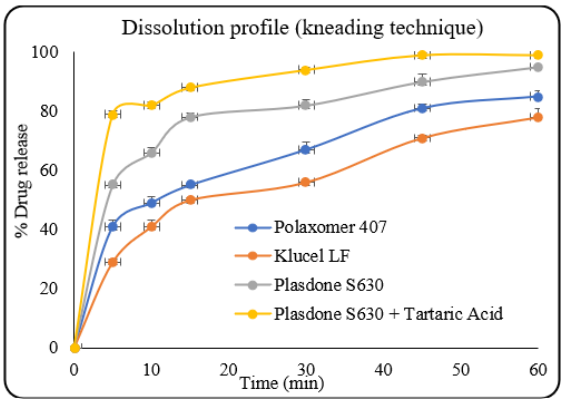

Figure 7. Dissolution profile in SD by kneading technique.

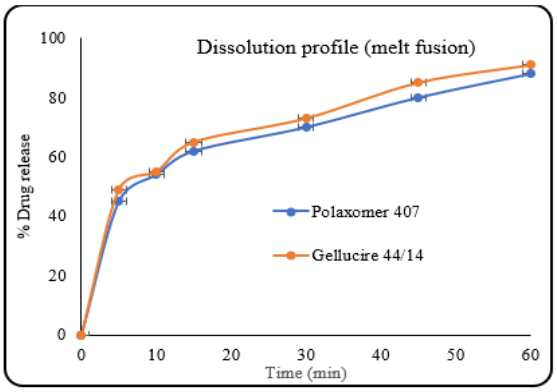

Figure 8. Dissolution profile in SD by melt fusion technique.

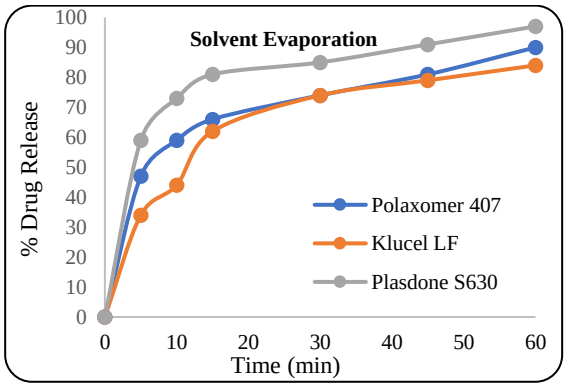

Figure 9. Dissolution profile in SD by solvent evaporation technique.

This solubility improvement and dissolution enhancement may be due to the activation of the ketone group in Plasdone by Tartaric acid. The effect of acidifiers in improving dissolution was reported and demonstrated previously [15]. Plasdone S630 is a copolymer of vinylpyrrolidone and vinyl acetate. Both monomers can accept a hydrogen bond, which helps form a strong bond [10].

The hydrophilic matrix entraps the drug molecule and improves the wettability of drugs in the dissolution medium. The vinyl acetate group imparts hydrophobicity, which helps reduce hygroscopicity and prevent moisture uptake by converting amorphous to crystalline form [10]. The improvement in the dissolution profile may also be due to the pH-dependent solubility of Nebivolol Hydrochloride. The acidifier alters the micro-environmental pH, which is sufficient to allow the drug molecules to be released.

Dissolution behavior through the melt fusion technique using Polaxomer 407 and Gellucire 44/14 improved the dissolution profile. Surrounding a drug with a molten carrier enhances its solubility, accomplished through the melt fusion technique with low melting point carriers. Gellucire with a 1:4 ratio exhibited the most significant solubility enhancement and dissolution profile (Fig. 8). The solubility improvement is also supported by the study performed [16] and demonstrated dissolution improvement of Tiaprofenic acid, a poorly soluble drug with gellucire 44/14. The dissolution enhancement may be due to the emulsifying characteristic of Gellucire 44/14, leading to increased drug wettability in the medium [17]. Gellucire 44/14 is an amphiphilic and pH-independent carrier with an HLB (hydrophilic-lipophilic balance) value of 14, forming an emulsion with a liquid medium and surrounding the drug molecule. The mechanism behind the improved dissolution is explained through the colloidal structure maintained by fractionating gellucire 44/14 into diglycerides, followed by monoglycerides and free fatty acids, improving the drug's solubility [18].

The solubility modification was also compared by using the solvent evaporation technique. Plasdone S630, Poloxamer 407, and Klucel LF were employed as carriers for the solvent evaporation technique. Amongst all, a dispersion with Plasdone through solvent evaporation technique (Fig. 9) demonstrated a remarkable improvement in dissolution profile in a ratio of 1:4. Plasdone S630 is an acetic acid ethenyl ester and is hydrophilic.

The hydrophilic matrix surrounds the drug molecule and permits an increase in drug wettability in the dissolution fluid [12]. It has also been noted that dispersion obtained using the solvent evaporation process allows the drug molecules to be present as finer particles, leading to improved dissolution [19]. Plasdone S630 showed improved efavirenz dissolution by altering a pure drug's surface activity [20].

3.5. FTIR analysis

FTIR spectra of pure drug show the presence of characteristic peak with NH Stretching at 3191 cm^{-1}, C-H stretching at 2848 cm^{-1}, NH & OH bending at 1489 cm^{-1}, C-N stretching at 1303 cm^{-1}, C-O stretching at 1101 cm^{-1}. FTIR spectra were also plotted for SD prepared with different carriers depicted in **Figure 10.** FTIR spectra revealed the presence of characteristic peaks of the drug, indicating no molecular interaction between the drug and the carriers. It is also

supported by a study [8], where Nebivolol solid dispersion was prepared using PEG 6000 and showed solid dispersion spectra were superposition of the drug.

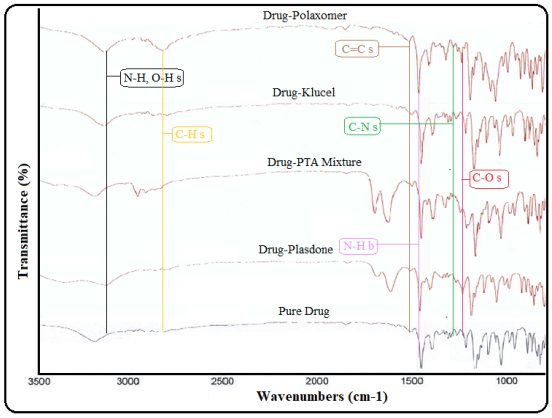

Figure 10. FTIR spectra of (a) Pure drug, (b) Drug-Plasdone, (c) Drug-PTA, (d) Drug-Klucel, (e) Drug-Poloxamers.

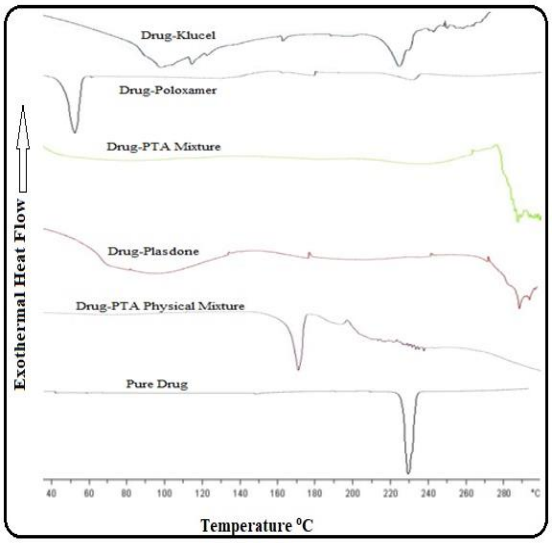

Figure 11. DSC thermogram of (a) Pure Drug, (b) Drug: PTA physical Mixture, (c) Drug: Plasdone, (d) Drug: PTA Mixture, (e) Drug: Poloxamer (f) Drug-Klucel.

3.6. Differential scanning calorimeter (DSC)

The pure drug's DSC thermogram had a distinct, sharp endothermic peak at about 230ºC **(Fig. 11)**, in line with the previous study performed [8, 9]. This sharp endothermic peak showed the drug's crystalline state. This sharp endothermic peak disappeared in drug-PTA solid dispersion. representing the crystalline to amorphous state conversion and contributing to solubility improvement. For other solid dispersions prepared using Klucel LF and Poloxamer 407, a sharp endothermic peak observed with less intensity indicates that the crystallinity of the drug has reduced and exhibits some degree of amorphous nature. It also suggests the inconsistent distribution of the drug throughout the matrix [9]. It also explained the Gellucire impact on tiaprofenic acid solubility enhancement through increasing drug wettability in the dissolution medium [16].

3.7. X-ray powder diffraction

The diffraction spectrum of pure Nebivolol Hydrochloride showed prominent and characteristic peaks expressed as 2-theta values at 13.1, 16.21, 20.12, 22.15, and 25.42, indicating the drug was in the crystalline state. The absence of characteristic peaks and a significant decrease in the intensity of other peaks were observed in SD prepared with a PTA mixture. It may be due to the entrapment of drugs by the PTA (Plasdone Tartaric Acid) complex. This finding is also supported by DSC, indicating the amorphous nature of the drug. SD prepared with Klucel LF also revealed the loss of crystallinity, which may be due to its amorphous nature. The PXRD pattern of the physical mixture indicates the crystalline nature of the drug with sharp and distinct peaks (**Fig. 12**).

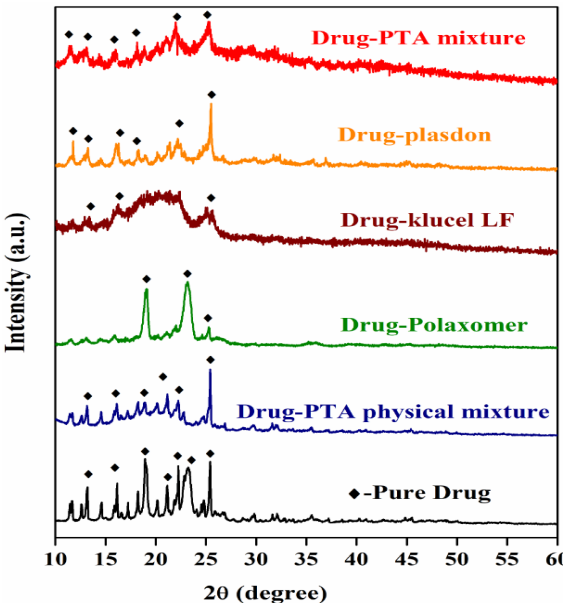

Figure 12. Powder XRD Pattern of (a) Pure Drug, (b) Drug: PTA physical Mixture, (c) Drug: Poloxamer, (d) Drug-Klucel, (e) Drug: Plasdone, (f) Drug: PTA Mixture.

In line with the diffraction spectrum of drug-Plasdone Tartaric acid, drug-Plasdone also shows the characteristic peak with reduced intensity and indicates loss of crystallinity of the drug. The solid dispersion prepared with Klucel LF did not show any intense peaks showing the drug's presence in an amorphous form. *A* hydroxypropyl cellulose-based curcumin solid dispersion was prepared and proved that the curcumin was dispersed within a hydroxypropyl cellulose matrix in the amorphous form [21]. A reduced crystallinity was observed in Poloxamer 407-based solid dispersion since drug-Poloxamer solid dispersion allows Poloxamer to get adsorbed on the drug surface and convert it to an amorphous form [22]. Solid dispersion prepared with Gellucire 44/14 and Poloxamer 407 also shows characteristic peaks with reduced intensity. It may be due to the drug surface being covered by the hydrophilic matrix, which causes a transition from crystalline to amorphous form.

3.8. Drug-excipients compatibility study

The drug Excipient compatibility study was conducted at 1:10 for diluent, 1:5 for disintegrant, and 1:1 ratio for lubricant-based. No significant degradation was observed in all binary mixtures, indicating no physical or chemical reaction between the drug and excipient. No color change was noticed compared to the initial samples. Impurity analysis was carried out to assess chemical interaction. All the impurities levels were found below the quantification limit and considered less significant degradation. A pure solid dispersion sample was kept alone as a reference with a similar exposed condition and found satisfactory. From the compatibility study, it was confirmed that the excipients employed in the study can be used up to a specified concentration that is higher than the usual recommended concentrations. The percent drug content and degradation are summarized in **Table 2**.

Table 2. Drug-Excipients Compatibility study data. % Degradation of 40^0 C/75%RH and 25^0 C/60%RH for all parameters was BQL.

Ingredients	% Drug Content		% Degradation	
	40^0 C/75%RH	25^0 C/60%RH	40^0 C/75%RH	25^0 C/60%RH
SD alone	99.09	99.94	BQL	BQL
SD + Lactose Monohydrate	98.27	98.78	BQL	BQL
SD + Microcrystalline Cellulose PH 102	98.47	98.09	BQL	BQL
SD + Pregelatinized Starch	98.25	97.93	BQL	BQL
SD + HPC LH 11	98.49	98.36	BQL	BQL
SD + Croscarmellose Sodium	98.88	98.71	BQL	BQL
SD + Colloidal Silicon Dioxide	99.17	99.17	BQL	BQL
SD + Magnesium Stearate	98.37	98.88	BQL	BQL

3.9. Formulation development

Among various SD prepared using different carriers and methods, SD made with PTA mixture by kneading technology showed significantly increased solubility and was selected for formulation development. The excipient grade was selected based on the literature, physical characteristics SD, Drug-Excipients Compatibility studies, and the method for tablet manufacturing. Suitable excipients with respective grades were evaluated during initial development trials. For microcrystalline cellulose, PH 102 grade was used, which possesses good flow properties and density, which are primary requisites for the direct compression method. For hydroxypropyl cellulose, low substituted grade LH-11, which exerts binding properties along with disintegrant characteristics, was used.

Various trials were taken to optimize the formulations depicted in **Table 3**. Direct compression was finalized with a final tablet weight of 100 mg. The focus was on disintegration time and hardness optimization, considered important physical parameters.

The trial was initiated with lactose monohydrate and pregelatinized starch blend, which resulted in poor flow. The addition of glidant, i.e., colloidal silicon dioxide, also did not resolve the issue. Subsequently, microcrystalline cellulose was introduced (Table 4.4) along with low-substituted hydroxypropyl cellulose, i.e., LH-11, which acts as a binder and disintegrant.

An increased disintegration time was observed, which needs more disintegration power to break the tablets into fragments. Since Tmax for Nebivolol hydrochloride is less than 2 hours, it requires immediate tablet disintegration to achieve fast dissolution in the gastric fluid. Croscarmellose sodium, a super disintegrant, was introduced along with the microcrystalline cellulose to achieve fast disintegration. Since croscarmellose sodium is a super disintegrant, a low concentration (3%) was used initially, along with 75% microcrystalline cellulose; as a result, the disintegration time was less than 3 minutes. In line with achieving rapid bioavailability through fast dissolution, the concentration of croscarmellose sodium was increased to 4%, and tablet weight was kept constant at 100 mg. The formulation (Trial 7) was analyzed for physicochemical parameters and found satisfactory.

Table 3. Formulation Development Trials.

Ingredients	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Drug: PTA Mixture	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Lactose Monohydrate	73.50	72.50	-	-	-	-	-
Microcrystalline Cellulose PH 102	-	-	71.00	73.00	71.00	75.00	74.00
Pregelatinized Starch	6.00	6.00	7.00	-	-	-	-
HPC LH-11	-	-	-	5.00	7.00	-	-
Croscarmellose Sodium	-	-	-	-	-	3.00	4.00
Colloidal Silicon Dioxide	-	0.75	1.00	1.00	1.00	1.00	1.00
Magnesium Stearate	0.50	0.75	1.00	1.00	1.00	1.00	1.00
Total Wt. (mg)	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**

3.10. Stability study

No significant change was observed in any physicochemical attributes throughout six months. The tablets were subjected to a stability study over six months to assess any deterioration or physical or chemical behavior alteration. The procedures and conditions adopted were per ICH guidelines for the stability study. A focus was given to the impurity profile, an important safety-related factor. Results revealed no significant changes in any physicochemical attributes after six months at accelerated and real-time conditions, which defined drug product quality. The summary study data results are depicted in **Table 4**.

4. Conclusion

Nebivolol Hydrochloride is a beta-adrenergic blocker that is used for the treatment of mild to severe hypertension. Poor aqueous solubility limits its availability in the systemic circulation. The present work reveals an attempt and introduction to implement a new technique for solubility improvement, which is feasible at the industrial scale. Solid Dispersion Methods were selected based on the literature findings, industrial feasibility, and applicability. The physical and chemical properties of excipients were considered to incorporate into the respective method. Preformulation analysis reveals the crystalline nature of the drug. The prepared physical mixture and solid dispersion were analyzed for solubility and physical evaluation. All Solid dispersion techniques employed showed some extent of improvement in solubility and dissolution, but the drug treated with Plasdone S630 and Tartaric Acid exhibited significant improvement in solubility and dissolution. The selected Drug-Carrier Mixture was preceded for further evaluation. The PXRD

Table 4. Stability Study Data Summary.

Conditions	Time Points	Hardness (N)	Disintegration Time (Min)	Assay (%)	Dissolution (%)	Related Substance
Limits	--	30-70 N	NMT 15 min	90-110%	NLT 85% in 30 minutes	SMI: NMT 0.1% SMI: NMT 0.1%
--	Initial	52	78 sec.	99.52	95.62	SMI: BQL SMI: BQL
40^0 C/75%RH	1 M	50	83 sec.	98.13	93.34	SMI: BQL Total: 0.04%
	2 M	48	72 sec.	96.77	92.56	SMI: BQL Total: 0.1%
	3 M	51	71 sec.	95.18	91.86	SMI: 0.02% Total: 0.16%
	6 M	48	86 sec.	94.87	89.63	SMI: 0.04% Total: 0.22%
25^0 C/60%RH	3 M	54	80 sec.	97.25	92.73	SMI: BQL Total: 0.1%
	6 M	49	76 sec.	96.42	90.46	SMI: 0.02% Total: 0.13%

data revealed a loss in crystallinity in SD, which was prominent in the physical mixture. This change in crystalline to the amorphous state may be due to changes in the micro-environment. Preformulation studies were performed to evaluate the compatibility of the Drug-Carrier Mixture with the selected excipients, and no significant change was observed. The Drug-Carrier Mixture was formulated into Tablets, and physical and chemical parameters were evaluated. Stability Testing was performed per ICH Guidelines for pharmaceutical Stability Testing at different Temperature and Humidity conditions. No significant change was observed in any physical and chemical parameters when subjected to accelerated and real-time conditions.

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Conflict of interest

The authors declare to have no conflict of interest.

References

[1] Sanklecha M. A systematic review on solid dispersion: Enhancing the solubility of poorly soluble drug. *Austin J Nanomed Nanotechnol*. *(*2020*)* 8(1): 1059.

[2] Dhirendra K, Lewis S, Udupa N, Atin K. Solid Dispersions: a review. *Pak J Pharm Sci* (2009) 22(2): 234- 236.

[3] ICH Harmonised guideline, Biopharmaceutics classification system-based biowaivers M9 (2019) 1-9.

[4] Lipinski C. Avoiding investment in doomed drugs, is poor solubility an industry wide problem. *Current Drug Discovery* (2001) 4: 17-19.

[5] Niazi S. *Handbook of Bioequivalence Testing. CRC Press.* (2014) 162.

[6] Drug Bank. *http:// www.drugbank.ca*.

[7] Khalaf Z, Ardelean S, Draganescu D, Ardelean M, Lupuleasa D. Delivery of Nebivolol Hydrochloride from immediate release tablets. *Studia Universitatis "Vasile Goldis", Seria stiintele Vietii (2015)* 25 (1):47-50.

[8] Shah I, Bhatt S, Yadav A. Enhancement of solubility and dissolution of Nebivolol by solid dispersion technique. *Int. j. pharm. pharm. sci. (2014)* 6(7): 566-571.

[9] Avachat A, Raut V. Solubility and dissolution enhancement of Nebivolol hydrochloride using hydrophilic carriers. *Asian J. Pharm. Sci.* (2012) 7 (5): 337-345.

[10] Ashland.com. https://www.ashland.com/industries/pharmaceutical/oral-solid-dose/plasdone-s-630-and-s630-ultra.

[11] Raymond. C, Paul. S. Handbook of Pharmaceutical Excipients. *Pharmaceutical Press* (2009) 6.

[12] Rahman, M., Lester J., Keshtmand, M., El-saleh, F., Farzana, V. and Durig, T. Comparison of amorphous solid dispersion of piroxicam in plasdone S-630 copovidone prepared by spary drying and hot melt extrusion. *Ashland Pharmaceutical Technical Report* (2013) 93.

[13] Bystolic.2008 Jun. USFDA. https://www.accessdata.fda.gov.

[14] Sun, Y., Rui, Y., Wenliang, Z. and Xing, T. Nimodipine semi-solid capsules containing solid dispersion for improving dissolution. *International Journal of Pharmaceutics* (2008) 359: 144–149.

[15] Trana T, Trana P, Choib H. Hanc H, Leea B. The roles of acidifiers in solid dispersions and physical mixtures. *Int. J. Pharm.* (2010) 384: 60–66.

[16] Saygh M. S. Enhanced dissolution rate of tiaprofenic acid using Gelucire44/1. *Scientia Pharmaceutica* (2002) 70 (3): 295-307.

[17] Roussin, P. and Laforet, J. Investigating semi-solid formulations: Physical characterization and stability study of Gelucire 44/14. *Farmacevtski Vestnik* (1997) 8 :260-261.

[18] Fernandez, S., Chevrier, S., Ritter, N., Mahler, B., Demarne, F., Carrière, F. and Jannin, V. In Vitro Gastrointestinal Lipolysis of Four Formulations of Piroxicam and Cinnarizine with the Self Emulsifying Excipients Labrasol and Gelucire 44/14. *Pharmaceutical Research* (2009) 26 (8): 1901–1910.

[19] El-Badry M, Fetih G, Fathy M. Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gellucire 50/13 and PEG4000. *Saudi Pharm J* (2009) 17: 217–225.

[20] Sathigari, S. K., Radhakrishnan, V. K., Davis, V. A., Parsons, D. L., and Babu, R. J. Amorphous-state characterization of efavirenz—Polymer hot-melt extrusion systems for dissolution enhancement', *Journal of Pharmaceutical Sciences* (2012) 101 (9): 3456–3464.

[21] Mai, N. N. S., Otsuka, Y., Kawano, Y., and Hanawa, T. Preparation and characterization of solid dispersions composed of curcumin, hydroxypropyl cellulose and/or sodium dodecyl sulfate by grinding with vibrational ball milling. *Pharmaceuticals* (2020) 13 (11): 383.

[22] Munir, R., Hadi, A., Khan, S. D., Asghar, S., Irfan, M., Khan, I. U., Hameed, M., Inam, S., Islam, N., Hassan, S. F., Ishtiaq, M., Akhtar Shah, P., Iqbal, M. S., Khalid Syed, H., Khames, A., and A. S. Abourehab, M. Solubility and Dissolution Enhancement of Dexibuprofen with Hydroxypropylbetacyclodextrin (HPβCD) and Poloxamers (188/407) Inclusion Complexes: Preparation and In Vitro Characterization. *Polymers* (2022) 14 (3): 579.