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LIPID BASED SOLID DISPERSIONS OF NEBIVOLOL HYDROCHLORIDE TO IMPROVE SOLUBILITY AND DISSOLUTION RATE

Veeraganti Alekhya^{1*}, Reddy Sunil², Vijaykumar Nagabandi², Dasari Vijayakalyani²¹Nethaji Institute of Pharmaceutical Sciences, Somidi, Kazipet, Warangal, Telangana, India.²St. Peter's Institute of Pharmaceutical Sciences, Warangal, Telangana, India.

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Abstract

Oral drug delivery remains the most preferred route due to its low cost, convenience, and good patient compliance. However, about 40–70% of new chemical entities show poor oral absorption mainly because of low solubility and slow dissolution, leading to poor bioavailability and formulation challenges. To overcome this limitation, the present study focused on developing lipid-based solid dispersions (LBSDs) of Nebivolol Hydrochloride, a β_1 -adrenergic blocker used for hypertension management, to enhance its solubility, dissolution, and permeability. LBSDs were prepared using different ratios of lipid carriers by the solvent evaporation method, with Fujicalin used as a hydrophilic inert carrier in all formulations. Phase solubility and saturation solubility studies demonstrated a linear increase in drug solubility with increasing carrier concentration. The prepared formulations were evaluated for micromeritic properties, drug content, *in vitro* dissolution, *in vitro* diffusion, and *ex vivo* permeation. Dissolution studies showed that LBSDs significantly improved drug release compared to pure drug and marketed formulation, with Gelucire 50/13 performing better than Gelucire 44/14. The formulation containing Gelucire 50/13 in a 1:5:5 ratio exhibited the highest drug release of $96.9 \pm 1.41\%$ within 1 hour. *Ex vivo* studies using goat intestinal membrane confirmed enhanced permeability of LBSDs. FTIR analysis indicated no drug–excipient interaction, while DSC studies showed peak broadening, suggesting conversion to an amorphous form. XRD results further confirmed partial loss of crystallinity, indicating transformation of the drug into an amorphous state, which contributed to improved solubility and dissolution. Overall, the study concludes that lipid-based solid dispersions of nebivolol hydrochloride effectively enhance dissolution and may improve oral bioavailability.

Keywords: Nebivolol hydrochloride, lipid based solid dispersions, solvent evaporation technique, DSC, XRD, solubility and dissolution.

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*Corresponding Author

Veeraganti Alekhya

Introduction

The oral route is the most preferred method of drug administration due to its convenience, safety, and patient compliance, but many drugs show poor bioavailability because of low solubility and poor membrane permeability. According to the Biopharmaceutics Classification System, Class II drugs possess low solubility and high permeability, making their absorption dissolution-rate limited [1,2]. To overcome this problem, solid dispersion systems are used, where the drug is dispersed in a hydrophilic carrier by methods such as

fusion or solvent evaporation. This technique improves dissolution and bioavailability by reducing particle size, enhancing wettability, preventing aggregation, and converting the drug into an amorphous form with increased surface area for faster dissolution in gastrointestinal fluids [2,3].

Lipid-based drug delivery systems are an effective approach to improve the solubility and bioavailability of poorly water-soluble drugs, especially since nearly 50% of new chemical entities are hydrophobic. These systems use lipids such as triglycerides, fatty acids, phospholipids, and excipients like Gelucire to enhance drug solubilization, dissolution, intestinal permeability, and lymphatic transport, thereby reducing first-pass metabolism and improving therapeutic consistency. They are also useful in transdermal delivery due to their ability to enhance skin

permeation and provide good biocompatibility. However, their limitations include susceptibility to oxidation, thermolability, higher production costs, and specialized storage requirements [4-6]. Nebivolol hydrochloride is chemically α , α' -[Iminobis (methylene)]bis-[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride. It is a selective β_1 -receptor antagonist used in hypertension. Nebivolol blocks this receptor so it reverses the effects of epinephrine, lower blood pressure and heart rate. Nebivolol hydrochloride belongs to BCS Class II drug. Lipid based solid dispersions of nebivolol hydrochloride were prepared by increasing carrier (gelucire 44/14, gelucire 50/13) and inert carrier fujicalin concentrations by solvent evaporation technique which has shown improved solubility, dissolution and permeability [6,7].

MATERIALS AND METHODS

Materials

Nebivolol hydrochloride was a gift sample procured from AET Labs, Hyderabad, Telangana. Gelucire 50/13 and Gelucire 44/14 received from Gattefosc, France. Fujicalin received from Gangwal Chemical Pvt Ltd, Thane. Methanol received from E. Merck, Mumbai, India.

Analytical Method Development

Analytical method to estimate nebivolol hydrochloride in 7.4 pH phosphate buffer: The estimation of nebivolol hydrochloride in 0.1 N HCl was performed using a UV spectrophotometric method. First, a primary stock solution (1 mg/mL) was prepared by dissolving 100 mg of the drug in 100 mL of methanol. This solution was then diluted to obtain a secondary stock of 100 μ g/mL using 0.1 N HCl. Further dilution gave a working solution of 10 μ g/mL. The absorbance of this solution was measured at 281 nm (λ_{max}). Similarly, other concentrations ranging from 20 to 90 μ g/mL were prepared, and their absorbance was recorded at the same wavelength. A calibration curve was plotted using concentration versus absorbance, and the linear regression equation obtained was used to determine the drug concentration in unknown sample [8-10].

Analytical method to estimate nebivolol hydrochloride in 7.4 pH phosphate buffer: For the estimation of nebivolol hydrochloride in pH 7.4 phosphate buffer, a similar procedure was followed. The primary stock solution (1 mg/mL) was prepared in methanol, and then diluted with pH 7.4 buffer to obtain a 100 μ g/mL secondary stock solution. From this, a 10 μ g/mL working solution was prepared and analyzed at 281 nm using a UV spectrophotometer. Additional concentrations (20–90 μ g/mL) were prepared in the same way, and their absorbance values were measured. A calibration curve was constructed, and the regression equation was used to calculate the concentration of the drug in unknown samples [11,12].

Phase solubility studies

In **phase solubility studies**, different concentrations (2%, 4%, 6%, 8%, and 10%) of carriers such as Gelucire 44/14 and Gelucire 50/13 were prepared in distilled water. An excess amount of nebivolol hydrochloride was added to each solution, and the mixtures were shaken continuously for 48 hours to reach equilibrium. After shaking, the solutions were filtered using Whatman filter paper, diluted appropriately, and analyzed at 281 nm using UV spectroscopy. The solubility of the drug was calculated from the absorbance values, and each experiment was performed three times to ensure accuracy and reliability of results [12,13].

Formulation of Solid Dispersions

Lipid-based solid dispersions (LBSD) of nebivolol hydrochloride were prepared to improve its solubility and dissolution. Hydrophilic lipid carriers such as Gelucire 44/14 and Gelucire 50/13 were used in the formulation. Different drug-to-carrier ratios were selected, namely 1:1, 1:3, and 1:5, based on phase solubility study results. Fujicalin was added as an inert carrier in all the formulations to support the dispersion.

The solvent evaporation method was used to prepare the solid dispersions. Initially, 5 mg of nebivolol hydrochloride was dissolved in 5 mL of methanol to form a clear drug solution. The required quantity of lipid carrier and Fujicalin was added to this drug solution and mixed properly. The mixture was transferred into a round bottom flask and placed in a rotary flash evaporator. The solvent was evaporated at 50°C, with a rotation speed of 60 rpm for 15 minutes, leading to formation of solid dispersion. The obtained solid product was collected and dried in a desiccator until completely dry to remove any residual moisture [14-16].

Table 01: Formulation of solid dispersions with Gelucire 44/14 & Gelucire 50/13

Formulation n	Nebivolol HCl (mg)	Gelucire 44/14 (mg)	Gelucire 50/13 (mg)	Fujicalin (mg)	Ratio
SD1	5	5	-	5	1:1:1
SD2	5	15	-	15	1:3:3
SD3	5	25	-	25	1:5:5
SD4	5	-	5	5	1:1:1
SD5	5	-	15	15	1:3:3
SD6	5	-	25	25	1:5:5

The formulated solid dispersions were evaluated for the following micromeritic evaluation & *in vitro* diffusion studies, diffusion studies and *ex vivo* permeation studies as per standard protocol.

Content uniformity of lipid based solid dispersions:

The **content uniformity** of lipid-based solid dispersions of nebivolol hydrochloride was evaluated to ensure that the drug is evenly distributed in each sample. A quantity of the solid dispersion equivalent to 5 mg of the drug was taken in a 50 mL volumetric flask and dissolved in a small amount of methanol. The solution was then sonicated for 30 minutes to achieve complete dissolution. After that, it was filtered using a 0.45 µm membrane filter and diluted to the required concentration. The samples were analyzed using UV spectroscopy to determine the drug content. This process was repeated three times, and the average value along with standard deviation was calculated to check consistency.

In vitro dissolution study:

An ***in vitro* dissolution study** was carried out to see how quickly and how much nebivolol hydrochloride is released from both the pure drug and its solid dispersion form. The test was done using a standard USP Type I (basket) dissolution apparatus at 100 rpm in 900 mL of 0.1N HCl, maintained at body temperature ($37 \pm 0.5^\circ\text{C}$). A sample containing 5 mg of the drug was placed in the medium. At specific time intervals (10, 20, 30, 40, 50, and 60 minutes), small samples (5 mL) were withdrawn and replaced with fresh medium to maintain constant conditions. The collected samples were filtered and then analyzed using UV spectroscopy to measure how much drug had dissolved. Each experiment was repeated three times to ensure accuracy, and the results were used to understand the drug release pattern over time.

Table 2: Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type I (basket)
Medium	0.1N HCl, 7.4 pH phosphate buffer
Volume	900 ml
Speed	100rpm
Temperature	$37 \pm 0.5^\circ\text{C}$
Sample volume withdrawn	5ml
Time points	10, 20, 30, 40, 50, 60, 90, 120 min
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	281 nm

Diffusion study

The **diffusion study** was carried out to compare the drug release from pure drug, marketed formulation, and the best solid dispersion (SD6) of Nebivolol Hydrochloride using a Franz diffusion cell with a gelatin membrane. A

sample equivalent to 5 mg of drug was dissolved in 2 mL buffer and placed in the donor compartment, while the receptor compartment contained 18 mL of phosphate buffer (pH 7.4). At specific time intervals, samples were withdrawn from the receptor side and replaced with fresh buffer to maintain constant conditions. The collected samples were filtered through a 0.45 µm membrane filter and analyzed using UV spectrophotometry at 281 nm to determine the amount of drug diffused over time.

Ex vivo permeation studies

The ***ex vivo* permeation study** was performed to compare the absorption of pure drug, marketed formulation, and the best formulation of nebivolol hydrochloride using goat intestinal tissue. The intestine was collected from a slaughterhouse and cleaned with Krebs–Ringer solution to remove mucus and debris. One end of the intestinal segment was tied and fixed to a tube, and formulations equivalent to 5 mg of drug were introduced into the lumen and sealed. The tissue was then placed in an organ bath maintained at 37°C with continuous aeration. The receptor compartment contained 50 mL of phosphate buffer (pH 7.4). Samples were withdrawn at regular time intervals and replaced with fresh buffer to maintain sink conditions. After filtration through a 0.45 µm membrane filter, the samples were analyzed using UV spectroscopy at 281 nm to measure drug permeation 16-20.

RESULTS AND DISCUSSION

Analytical method to estimate nebivolol hydrochloride

Calibration curve of nebivolol hydrochloride were plotted in different solvents such as 0.1N HCl & 7.4 pH phosphate buffer and are shown in fig. 1 & 2, R^2 and slope values were calculated and are given in table 3.

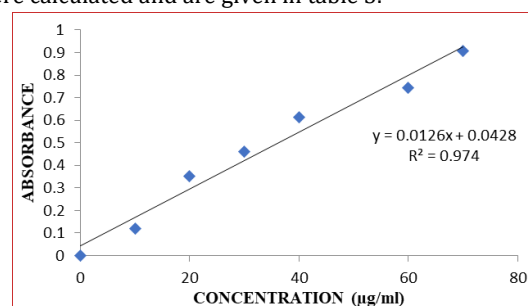


Figure 01: Calibration curve of nebivolol hydrochloride in 0.1N HCl

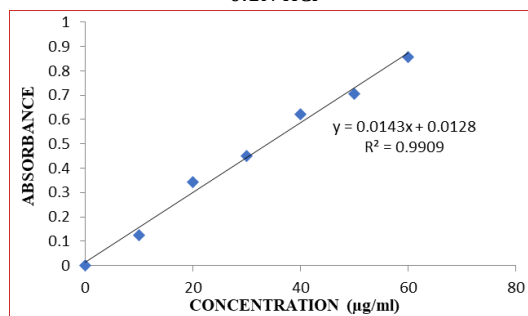


Figure 02: Calibration curve of nebivolol hydrochloride in 7.4 pH phosphate buffer

Table 03: R2 values and slope values of nebivolol hydrochloride in different solvents

Solvent	R2	Slope
0.1N HCl	0.974	0.012
7.4 pH phosphate buffer	0.990	0.014

Phase Solubility Studies

Phase solubility studies of nebivolol hydrochloride in gelucire 44/14

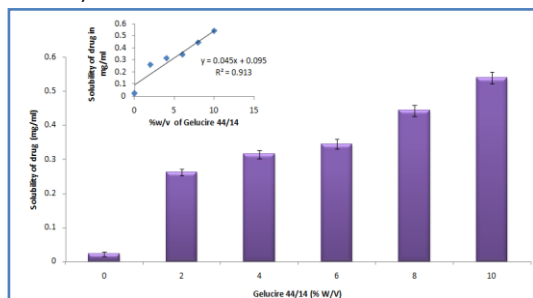


Figure 3: Phase solubility of nebivolol hydrochloride in different concentrations of gelucire 44/1

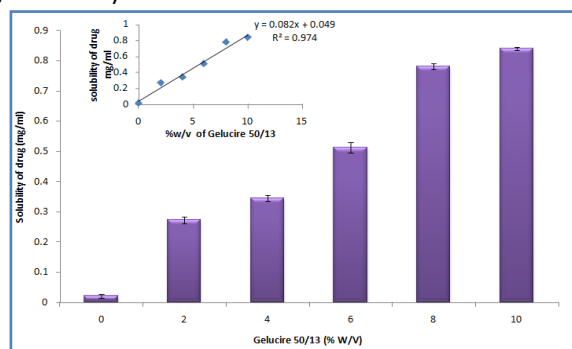
Phase solubility studies of nebivolol hydrochloride in gelucire 50/13

Figure 04: Phase solubility of nebivolol hydrochloride in different concentrations of gelucire 50/13

Table 04: Results of micromeritic properties of all formulations of nebivolol hydrochloride

Code no	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's index	Hausner's ratio	Angle of repose	Drug content (%)
SD 1	352.79 ±2.18	469.53 ±1.63	13.5±0.19	1.1±0.01	31.62±0.7	92.95 ±0.37
SD 2	418.89 ±1.53	727.59 ±2.26	11.9±1.5	1.12 ±0.08	24.85±0.8	97.56 ±0.40
SD 3	348.15 ±1.1	545.67 ±1.45	16.12 ±1.32	0.98 ±0.1	30.35±0.4	95.4±0.17
SD 4	337.40 ±1.25	560.17 ±0.52	13.7±1.25	1.1±0.03	25.56±0.5	93.45 ±0.60
S	248.08	406.08	12.45	1.13	27.7	98.4±

D	±1.62	±1.21	±2.1	±0.0	8±1.	0.30
5				2	3	
S	216.34	313.24	14.15	1.15	26.2	99.43
D	±0.68	±3.2	±1.14	±0.1	3±0.	±0.2
6				1	2	

IN VITRO DISSOLUTION STUDY OF PURE DRUGTable 05: *In vitro* release data of nebivolol hydrochloride in 0.1N HCl & 7.4pH phosphate buffer

Time (min)	% Drug Dissolved	
	7.4 pH phosphate buffer	0.1NHCl
0	0	0
15	8.33±1.33	17.52±1.54
30	10.75±0.78	21.55±1.16
45	14.90±1.55	25.34±0.86
60	21.86±1.54	33.93±1.57
90	25.69±1.57	41.40±1.57
120	32.67±1.74	50.66±1.3

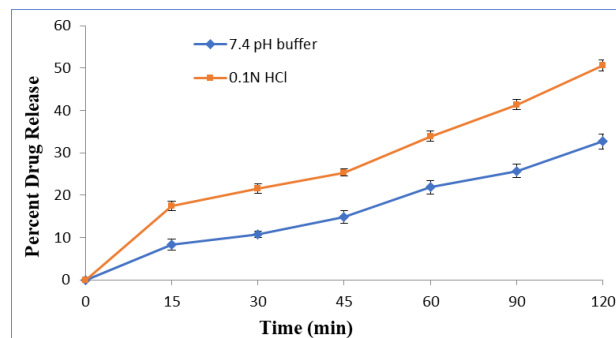
Figure 05: *In vitro* dissolution profile of nebivolol hydrochloride in different media***In vitro* drug release studies of lipid based solid dispersions**

Table 06: Dissolution data of nebivolol hydrochloride, gelucire 44/14 solid dispersions (SD1-SD3 ratios)

Time (min)	% Drug released		
	SD1	SD2	SD3
0	0	0	0
10	22.22±1.39	29.76±1.38	33.67±1.33
20	31.20±1.84	36.25±2.89	45.19±1.54
30	35.15±2.54	42.05±1.79	50.20±2.04
40	38.80±0.86	50.02±1.23	59.48±1.56

50	41.00±1.76	52.63±0.92	65.531±1.42
60	43.54±0.73	54.81±1.71	78.09±1.89

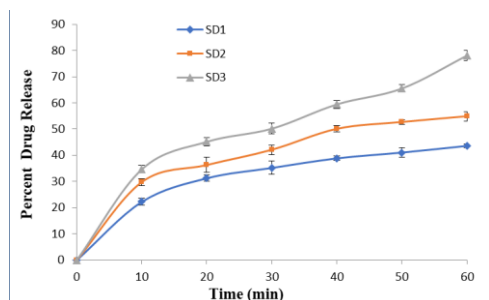


Figure 06: Dissolution profile of nebivolol hydrochloride, gelucire 44/14 solid dispersions (SD1-SD3 ratios)

Table 07: Dissolution data of nebivolol hydrochloride, gelucire 50/13 solid dispersions (SD4-SD6 ratios)

Time (min)	% Drug released		
	SD4	SD5	SD6
0	0	0	0
10	36.33±1	41.55±1.02	44.44±1.38
20	42.71±1.73	52.85±1.53	60.78±1.49
30	51.69±1.38	66.28±0.86	75.53±1.35
40	60.43±1.23	76.65±1.51	82.35±1.52
50	68.06±1.22	83.59±1.19	91.57±0.96
60	76.99±1.05	90.93±0.90	96.9±1.41

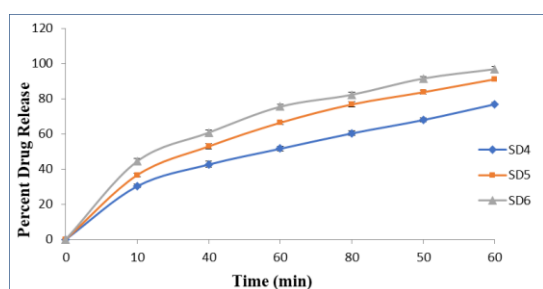


Figure 07: Dissolution profile of nebivolol hydrochloride, gelucire 50/13 solid dispersions (SD4-SD6 ratios)

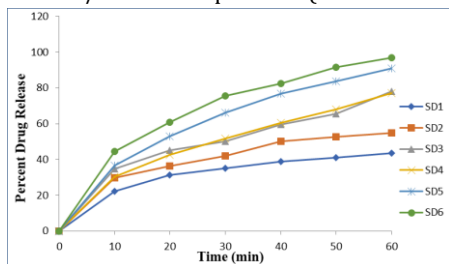


Figure 08: Dissolution profile of all nebivolol hydrochloride solid dispersions (SD1-SD6 ratios)

Table 08: Dissolution parameters of nebivolol hydrochloride, gelucire 44/14, gelucire 50/13 solid dispersions

Parameters	Q10a	Q60a	DE10b	DE60b	MDTc	MDRc	IDRc	t50% ^c (min)
Nebivolol hydrochloride	8.11	22.43	10.32	52	54.16	0.69	0.81	>60
SD1	22.22	43.54	25.63	54.28	35.61	1.77	2.22	>60
SD2	29.76	54.81	31.72	69.4	35.17	2.26	2.98	40
SD3	33.67	78.09	35.29	70.8	30.77	2.68	3.37	30
SD4	36.33	76.99	39.83	60.7	28.69	2.78	3.63	13.8
SD5	41.55	90.93	43.88	70.37	27.22	3.29	4.16	12.1
SD6	44.44	96.9	46.73	75.43	24.74	3.59	4.44	11.3

Table 09: Comparative *in vitro* drug release of pure drug, marketed and best SD6 formulation

Time (min)	% Drug Released		
	Pure drug	Marketed	SD6
0	0	0	0
10	8.11±0.50	29.51±1.44	44.44±1.39
20	11.21±1.02	47.24±1.02	60.78±1.49
30	14.80±1.09	54.93±1.72	75.53±1.35
40	17.97±0.87	63.05±1.89	82.35±1.52
50	20.19±0.87	74.93±1.06	91.57±0.96
60	22.43±0.54	83.06±1.51	96.89±1.4

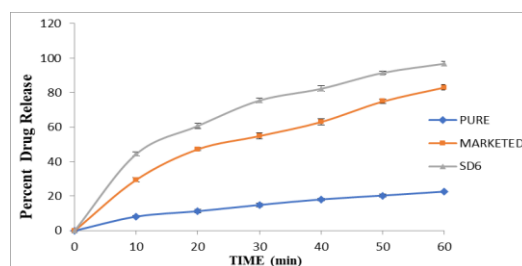


Figure 09: Comparative dissolution profile of pure nebivolol hydrochloride, marketed and best formulation (SD6)

Table 10: Dissolution parameters of pure nebigivol hydrochloride, marketed and best formulation (SD6)

Parameters	Q10a	Q60a	DE10b	DE60b	MDTc	MDRc	IDRc	t50% ^c (min)
Nebivol ol hydroch loride	8.1 1	22. 43	10. 32	52	54. 16	0. 69	0. 81	>60
Markete d	29. 51	83. 05	32. 25	64. 7	15. 35	2. 58	2. 95	17. 2
Best formula tion (SD6)	44. 44	96. 89	46. 37	75. 43	13. 72	3. 59	4. 44	11. 3

a Q: percent drug released at 10 and 60 min.

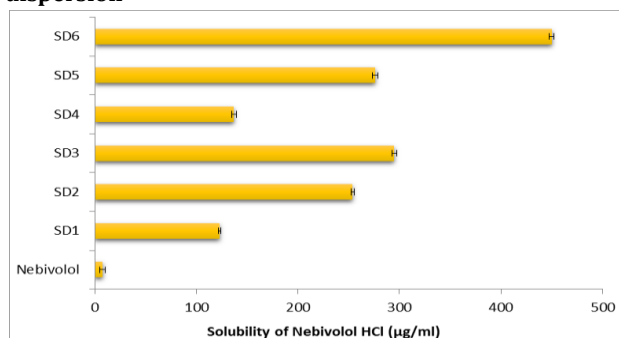
Saturation solubility studies of pure drug and solid dispersion

Figure 10: Saturation solubility studies of all formulations

Comparative diffusion study of pure, marketed and best formulation

Table 11: Comparative diffusion study data of pure nebigivol hydrochloride, marketed & best formulation (SD6)

Time (min)	% Drug Diffused		SD6
	Pure drug	Marketed	
0	0	0	0
15	6.77±0.19	12.99±0.12	15.81±0.25
30	13.05±0.03	21.98±0.39	25.05±0.4
45	16.96±0.53	30.66±0.35	34.24±0.49
60	24.47±2.47	42.08±0.55	46.45±0.63
90	30.43±2.26	51.54±0.70	58.18±1.15
120	42.91±2.89	61.97±0.36	66.19±0.96

150	49.53±1.92	70.83±0.83	75.87±0.90
180	56.55±0.26	80.02±1.74	88.29±0.95

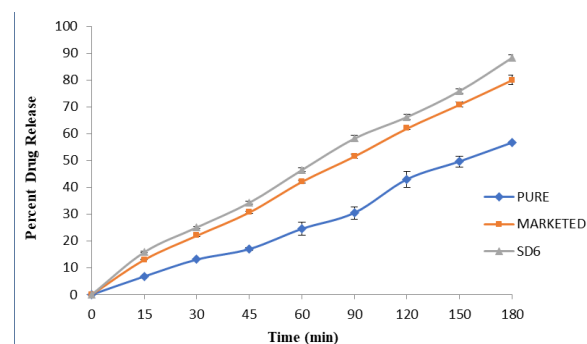


Figure 11: Comparative diffusion profile of pure nebigivol hydrochloride, marketed and best formulation (SD6)

Ex vivo permeation studies:

Table 12: Ex vivo permeability data of pure nebigivol hydrochloride, marketed and best formulation (SD6)

Time (min)	% Drug Permeated		
	Pure drug	Marketed	SD6
0	0	0	0
15	6.09±1.57	8.72±1.66	11.19±1.79
30	12.05±0.78	16.81±1.63	20.26±1.48
45	15.92±1.79	23.39±2.67	30.19±2.33
60	20.50±0.44	39.01±1.68	43.64±2.23
90	28.70±1.84	48.29±1.99	54.17±1.31
120	37.15±0.84	62.22±2.64	69.56±1.61
150	45.98±0.40	70.92±1.17	77.36±2.12
180	50.63±0.82	79.31±0.96	86.34±2.05

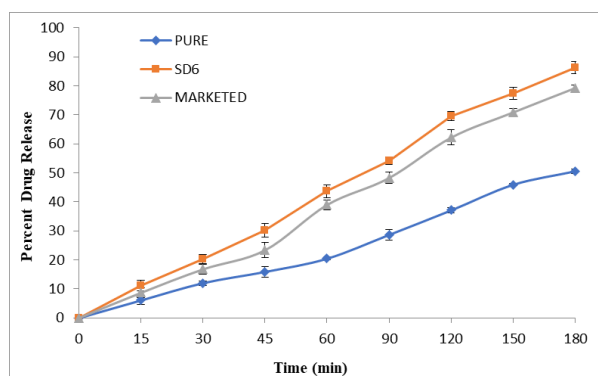


Figure 12: Ex vivo permeability profiles of pure nebigivol hydrochloride, marketed & best formulation (SD6)

Drug and excipient compatibility studies: Fourier Transform Infrared Spectroscopy:

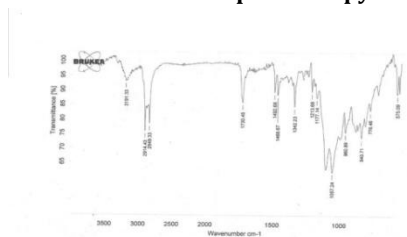


Figure 13: FTIR spectra of best formulation (SD6)

X-RAY Diffraction:

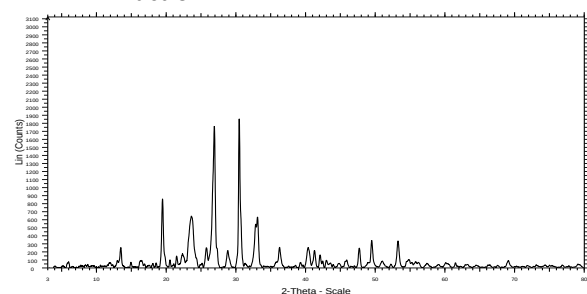


Figure 14: X-ray diffractograms of best formulation (SD6)

Differential scanning calorimetric analysis (DSC):

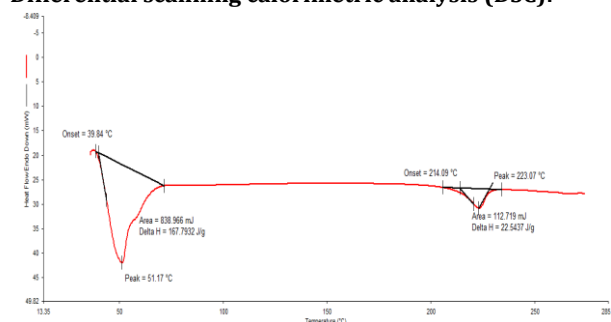


Figure 15: DSC thermogram of best formulation (SD6)

The **best formulation (SD6)** showed good compatibility in Fourier Transform Infrared Spectroscopy(**FTIR**) with no significant peak changes. X-ray Diffraction(**XRD**) revealed a reduction and disappearance of characteristic peaks, indicating conversion of the drug from crystalline to amorphous form. Differential Scanning Calorimetry(**DSC**) showed broad endothermic peaks at 51.17°C and 223.07°C, confirming reduced crystallinity. This amorphization is responsible for the **enhanced solubility and improved dissolution rate** of the formulation.

CONCLUSION

Lipid based solid dispersions of nebivolol hydrochloride were prepared by using different carriers like gelucire 44/14 and gelucire 50/13 has shown improved solubility, dissolution and permeability. However, the dispersion prepared with gelucire 50/13 in 1:5 ratio has shown better results than other formulations. And it was observed that there is no drug-excipient compatibility. It can be concluded that lipid based solid dispersions of nebivolol hydrochloride can be formulated successfully with improved bioavailability.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of this paper.

FUNDING AND ETHICS DECLERATIONS

Not Applicable.

FUNDING

None

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