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ENHANCED ORAL BIOAVAILABILITY OF NEBIVOLOL HYDROCHLORIDE THROUGH LIQUISOLID APPROACH: APPLICATION OF NOVEL EXCIPIENTS

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ABSTRACT

Nebivolol hydrochloride is a selective β_1 - antagonist falls under class II biopharmaceutical classification system. In the present investigation liquisolid compaction approach is applied to improve the dissolution and permeability properties thereby enhancing the oral bioavailability of nebivolol hydrochloride. Different formulations were developed by dissolving the drug in mixture of Transcutol HP & Propylene glycol (Non volatile liquid; 1:1 ratio), converting this liquid medication using fujicalin and neusilin as carriers and syloid FP 244 as coating material. *In vitro* drug release profiles of liquisolid compacts shown enhanced drug release when compared to pure drug as well as marketed formulation. The plasma concentration-time profile of healthy wister rats indicated that the oral bioavailability of optimized formulation has been significantly improved when compared to pure drug and marketed formulation. Improved bioavailability might be due to increased wetting properties of drug and improved permeability of the drug due to lipophilic properties of solvent used for wetting. From this study we can conclude that liquisolid technique is one of the promising alternative techniques to improve the bioavailability of class II drugs.

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INTRODUCTION

Recent developments in high throughput screening and combinatorial chemistry used in drug discovery and development resulted in the increased number of drugs with poor aqueous solubility. About 90% of the new chemical entities (NCE's) released in to the market are considered low soluble with high or low permeability (i.e. Class II of Biopharmaceutical Classification System (BCS)). These drugs will be having high absorption number but has low dissolution number. Absorption and bioavailability of these drugs are limited by their dissolution. Hence, these drugs exhibits variable bioavailability and small increment in their dissolution rate results in significant improvement in their oral bioavailability. Due to this fact, it can be said that dissolution is the key factor in successful formulation of BCS class II drugs [1-4].

Over the years, many techniques have been employed to improve the dissolution profile and in turn, bioavailability of water insoluble drugs such as micronization, solid dispersions, salt formation, complexation, miscellar solubilization, hydrotrophy, inclusion complexes, lyophilization, cosolvency etc. Despite the availability, these techniques are suffering from one or two draw backs like reduced micromeritics or altered stability and still needs further development to overcome them [5-8].

One of the novel and most promising techniques for promoting dissolution is the formation of liquisolid compacts among. Liquisolid compacts promotes dissolution rate of water insoluble drugs to a greater extent and also enhances the drug flow property. The liquisolid technology is described by Spireas as liquid medication may be transformed into a free-flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. A liquid lipophilic drug can be converted into liquisolid system without being further modified. On the other hand, if a solid water-insoluble drug is formulated, it should be initially dissolved or suspended in suitable nonvolatile solvent system to produce drug solution or drug suspension of desired concentration [9].

Nebivolol hydrochloride is a class II drug that selectively blocks β_1 receptor with therapeutic applications as antihypertensive and can also used as monotherapy for initial management of uncomplicated hypertension [10]. Nebivolol is having very low oral bioavailability. Hence, the main objective of this current research work is to improve its oral bioavailability by liquisolid compaction. Earlier research was done using a single volatile solvent as a vehicle. In the current research, liquisolid compacts were prepared by using combination of non volatile liquids and novel carriers to improve its oral bioavailability.

MATERIALS AND METHODS

Materials:

Nebivolol Hydrochloride was received as gift sample from Alembic Pharma Ltd., Baroda, India. The following materials were gifted by Abitec Corp., Mumbai, India and were used as received: Capmul MCM (Glyceryl monocaprylate), Capmul C8, Acconon C-80 (Polyoxyethylene 80 coconut glycerides), Captex 200 (Propylene glycol dicaprylocaprate), Captex 355 (Glyceryl tricaprylate), Transcutol HP and Cremophor EL. Plurol Oleique (Polyglyceryl-3 dioleate), Labrafil M 2125CS (Linoleyl macrogol-6 glycerides), and Lauroglycol 90 (Propylene glycol monolaurate) were received as gift sample from Gattefosse, India. PEG 400, Tween 80 and PG were purchased from SD Fine Chemicals, India. Fujicalin (Dibasic calcium phosphate anhydrous) and Neusilin (Magnesium aluminometasilicate) were obtained as gift sample from Fuji Chemical Industry Co. Ltd., Mumbai.

Methods:

1. Saturation solubility studies

Saturation solubility of Nebivolol hydrochloride in different non-volatile solvents and followed by combination of solvents in which drug is shown to have maximum solubility was estimated by conducting saturation solubility studies. Excess amount of drug was added to 10mL of solvent in vial and subjected to continuous shaking using a rotary shaker for 48h at 25°C. Then each solution was centrifuged and clear supernatants were analyzed for drug content and solubility using UV- spectrophotometer at 281nm.

2. Selection of Coating and Carrier Materials:

Two novel carriers fujicalin (dibasic calcium phosphate anhydrous) and neusilin (magnesium aluminometasilicate) were selected as carriers, Syloid FP 244 as coating material and carrier to coating ratio was varied from 5:1 to 10:1.

3. Preparation of liquisolid compacts

From the saturation solubility studies it was observed that the drug is having maximum solubility in Transcutol HP and Propylene glycol when they have used in combination at the ratio of 1:1. Hence the same solvent system has been used as non volatile vehicle. Liquid medication was prepared at 25% W/W and 50% W/W drug concentration by adding the weighed quantity of drug to the required quantity of previously mixed liquid vehicle. Resultant liquid medication was incorporated into carrier and coating material by admixing in a mortar till to get freely flowable non adherent powder. Total quantity of each formulation was adjusted to 100mg to get uniform weight for each formulation with Avicel PH 102. The liquid/powder admixtures were then evaluated for their micromeritics, uniformity of drug content and *in vitro* dissolution.

4. In vitro drug release by dissolution

Dissolution studies of all the prepared formulations were performed using USP Dissolution apparatus II using 500mL of 0.1N HCl. The temperature and speed of rotation maintained were 37±0.5°C and 50rpm respectively. 5mL samples were collected and the equal volume of fresh dissolution medium was replaced at predetermined time points and analyzed using UV-spectrophotometer at 281nm.

5. In vivo evaluation for pharmacokinetic parameters

The in vivo pharmacokinetic study was conducted in white wistar rats. Animals were fed with standard diet throughout the study as there was no impact of diet on drug absorption. Rats weighing 210-260g were divided into 3 groups. Group 1 was administered with pure drug, group 2 was administered with marketed formulation (nebistar 5mg) and the group 3 was administered with optimum formulation at 2mg/kg dose through oral route. Blood samples were collected from retro orbital vein at predetermined time points up to 8h and were centrifuged at 5000 rpm for 5 min. Plasma was collected and stored at - 20°C until analyzed. The plasma samples were analyzed using RP-HPLC and plasma drug concentrations were determined using standard calibration curve. All possible pharmacokinetic parameters (AUC, C_{max}, T_{max}, t_{1/2}) were calculated for each formulation and each subject. Relative bioavailability of optimized formulation was done comparatively with pure drug and marketed formulation.

RESULTS & DISCUSSION:

1. Saturation Solubility Studies:

Saturation solubility studies of nebivolol hydrochloride in different solvents were performed and the results obtained are represented as a bar graph in fig 1. Among all the solvents tested, nebivolol hydrochloride was found to be higher in Transcutol HP (32.5mg/mL), PEG 400 (52.6mg/mL) and Propylene glycol (72.6mg/mL). Saturation solubility of the drug was also estimated in combination of these solvent mixtures at the ratio of 1:1 to check the synergistic effect. It was found that the solubility of drug was increased to 78.9mg/mL within the solvent blend of Transcutol HP: PEG 400 and it was further increased to 87.5mg/mL with the solvent blend of Transcutol HP: PG. Hence the solvent blend consisting of Transcutol HP: PG was selected as non volatile liquid vehicle to improve the dissolution rate of drug.

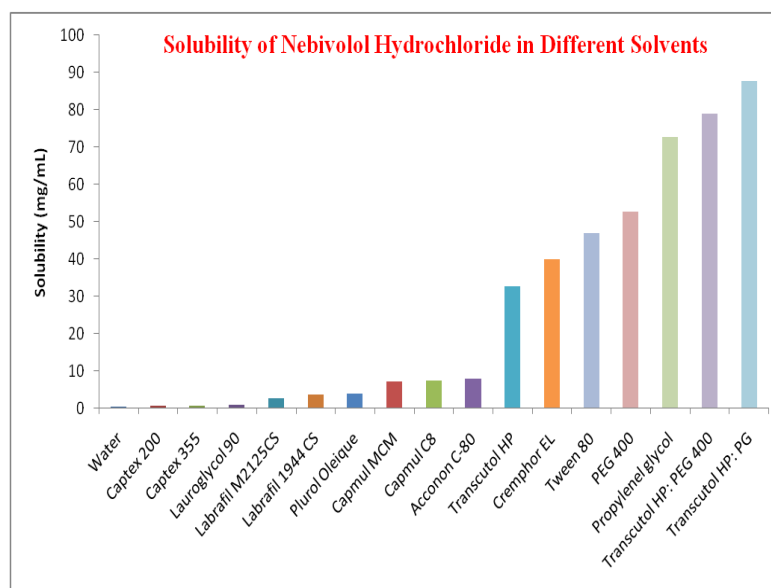


Figure 1: Saturation Solubility of Nebivolol Hydrochloride in Different Solvents.

2. Formulation of Liquisolid Compacts:

Composition of various formulations of liquisolid compacts are represented in table 1.

Table 1: Composition of Liquisolid Compacts of Nebivolol Hydrochloride

Name of the Ingredient	Composition (mg)							
	F1	F2	F3	F4	F5	F6	F7	F8
Nebivolol Hydrochloride	5	5	5	5	5	5	5	5
Transcutol HP	2.5	7.5	2.5	7.5	2.5	7.5	2.5	7.5
Proylene Glycol	2.5	7.5	2.5	7.5	2.5	7.5	2.5	7.5
Fujicalin	25	60	25	60	NA	NA	NA	NA
Neusilin	NA	NA	NA	NA	20	55	20	55
Syloid FP 244	2.5	6	5	12	2	5.5	4	11
Avicel PH 102	62.5	14	60	8	68	19.5	66	14
Total Unit Weight (mg)	100	100	100	100	100	100	100	100
% W/W of Liquid Medication	50	25	50	25	50	25	50	25
Ratio of Carrier to Coating Material (R)	10	10	5	5	10	10	5	5
Loading Factor (Lf)	0.400	0.333	0.400	0.333	0.500	0.364	0.500	0.364

3. Micromeritics and drug content uniformity of liquisolid formulations:

Flow properties of all the formulations were evaluated and the results are shown in table 2. Values of angle of repose (31.5 ± 0.3 - 39.4 ± 0.4), carr's index (13.4 ± 0.2 - 18.3 ± 0.4), and hausner's ratio (<1.24) in all the formulations corresponding to good flow. Flow ability of nebivolol hydrochloride liquisolid formulations was enhanced compared with pure drug.

Table2: Micromeritics and drug content uniformity of liquisolid formulations

Formulation	Angle of Repose	Carr's Index	Hausner's Ratio	Drug Content (%)
F1	34.3 ± 0.3	18.3 ± 0.4	1.20 ± 0.8	99.3 ± 1.2
F2	33.3 ± 0.6	18.7 ± 0.6	1.19 ± 0.7	99.6 ± 1.3
F3	39.4 ± 0.4	16.5 ± 0.5	1.18 ± 0.6	99.7 ± 1.5
F4	32.3 ± 0.7	17.5 ± 0.6	1.17 ± 0.4	99.2 ± 1.2
F5	34.6 ± 0.3	14.2 ± 0.7	1.15 ± 0.8	100.2 ± 1.3
F6	31.8 ± 0.6	13.9 ± 0.5	1.16 ± 0.6	101.2 ± 2.1
F7	31.5 ± 0.3	13.4 ± 0.2	1.14 ± 0.7	102.1 ± 2.2
F8	36.8 ± 0.6	15.9 ± 0.7	1.15 ± 0.6	99.9 ± 1.3

4. In Vitro Drug Release Profile of Liquisolid Formulations

In vitro drug release of liquisolid formulation was estimated using USP Type II apparatus. Dissolution profile of formulations prepared with fujicalin is shown in figure 2 prepared with neusilin is shown in figure 3. Formulations (F6) containing 25% of drug in liquid medication, neusilin as carrier and carrier to coating ratio of 10:1 has shown fastest drug release (100% release in 15 minutes) when compared to other formulations, pure drug (22.5% release in 30 minutes) and marketed formulation (87.8 % release in 30 minutes). Comparative dissolution profile of pure drug, marketed formulation and optimized formulation has shown in figure 4. Improved dissolution rate of optimized formulation might be achieved due to higher amount of liquid vehicle, hydrophilic properties attributed by carrier materials and higher surface area provided by Syloid 244FP. Hence F6 was selected as optimized formulation for evaluating its pharmacokinetic parameters.

Table 3: In Vitro drug release profile of pure drug, liquisolid formulations and marketed formulations.

Time (min)	% Drug Release (Mean \pm SD; n=6)									
	Pure Drug	F1	F2	F3	F4	F5	F6	F7	F8	Marketed
0	0	0	0	0	0	0	0	0	0	0
5	2.5 ± 0.2	44.3 ± 0.3	61.5 ± 0.5	50.8 ± 3.2	64.5 ± 2.2	62.5 ± 3.6	75 ± 3.5	57.8 ± 4.2	71 ± 3.4	15.7 ± 1.5
10	4.9 ± 0.5	57.6 ± 0.5	78.8 ± 2.8	65.4 ± 3.5	75.6 ± 2.6	87.5 ± 3.7	97.8 ± 2.5	77.5 ± 4.5	93.4 ± 2.5	27.6 ± 1.6
15	7.9 ± 0.6	63.5 ± 0.6	87.9 ± 3.2	74.7 ± 4.2	82.4 ± 2.5	92.5 ± 2.5	100.2 ± 3.2	84.3 ± 4.6	96.5 ± 3.7	45.8 ± 2.2
20	12.9 ± 0.5	71.4 ± 2.8	93.4 ± 2.5	81.5 ± 4.5	87.6 ± 3.5	97.4 ± 2.8	100.1 ± 3.6	91.5 ± 2.5	99.8 ± 3.4	65.8 ± 3.4
25	15.7 ± 0.7	82.7 ± 2.2	99.8 ± 3.4	89.8 ± 5.5	92.5 ± 3.6	99.4 ± 3.5	100.2 ± 4.2	97.6 ± 2.6	100.2 ± 3.5	78.9 ± 2.8
30	22.5 ± 0.8	92.5 ± 1.5	100.1 ± 3.6	99.7 ± 4.5	100.1 ± 2.9	100.1 ± 3.9	100.1 ± 4.3	99.8 ± 3.6	100.1 ± 3.9	87.8 ± 3.9

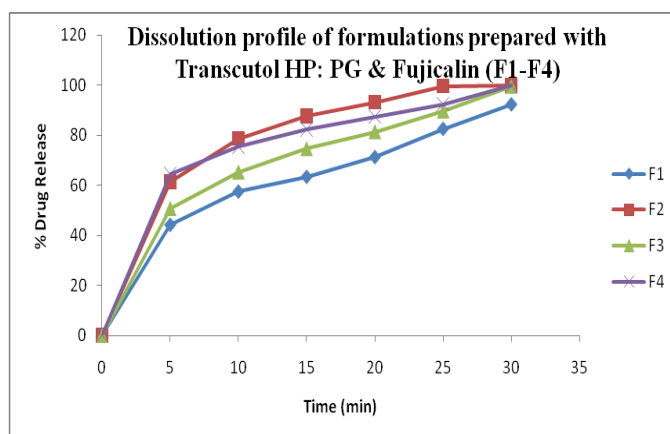


Figure 2: Dissolution profile of liquisolid formulations prepared with fujicalin.

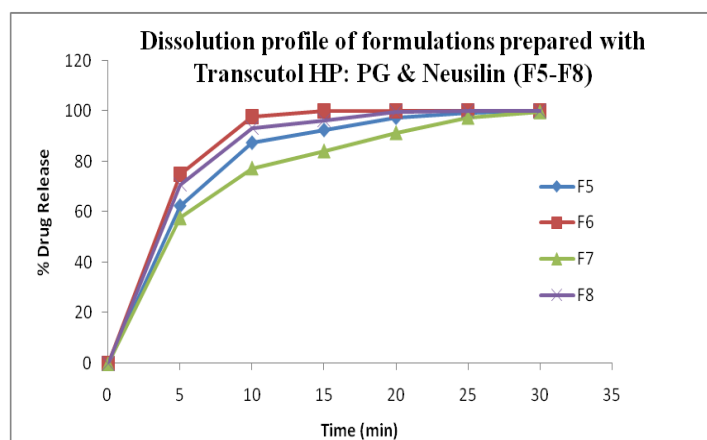


Figure 3: Dissolution profile of liquisolid formulations prepared with neusilin.

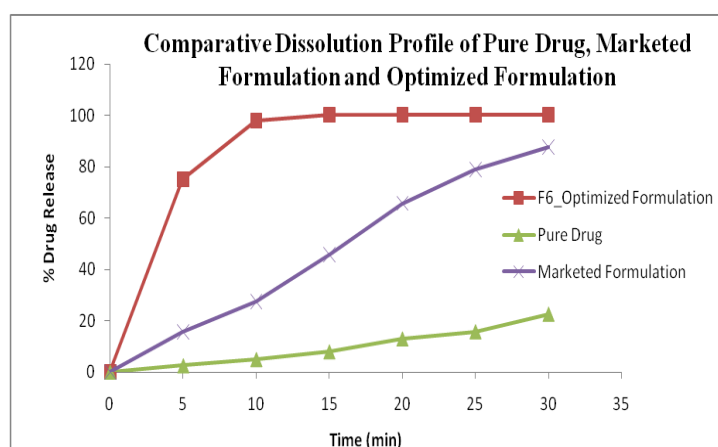


Figure 4: Comparative dissolution profile of pure drug, marketed and optimized formulations.

5. In vivo studies

In vivo studies conducted in wistar rats revealed that the bioavailability of optimized formulation is high compared to pure drug and marketed product. The plasma concentration time profile is given in table 4 and shown in figure 5. The pharmacokinetic parameters are calculated and listed in table 5.

Table 4: Plasma concentration values of pure drug, marketed and optimized formulations.

Time (h)	Plasma Concentration (ng/mL) (n=6; Mean \pm SD)		
	Pure Drug	F6	Marketed
0	0	0	0
0.5	115.6 \pm 23.1	325.6 \pm 18.9	256.5 \pm 23.5
0.75	168.9 \pm 45.6	456.5 \pm 25.6	346.5 \pm 35.6
1	214.6 \pm 56.5	598.7 \pm 37.5	425.6 \pm 56.4
1.5	357.9 \pm 65.4	798.5 \pm 54.6	648.5 \pm 71.4
2	456.4 \pm 78.9	854.6 \pm 65.4	546.5 \pm 64.5
3	335.6 \pm 56.4	654.8 \pm 75.8	425.7 \pm 54.6
4	224.6 \pm 46.5	546.5 \pm 65.4	334.5 \pm 44.5
6	135.4 \pm 33.6	425.6 \pm 54.6	226.5 \pm 37.4
8	102.3 \pm 21.6	322.5 \pm 34.5	171.5 \pm 25.4

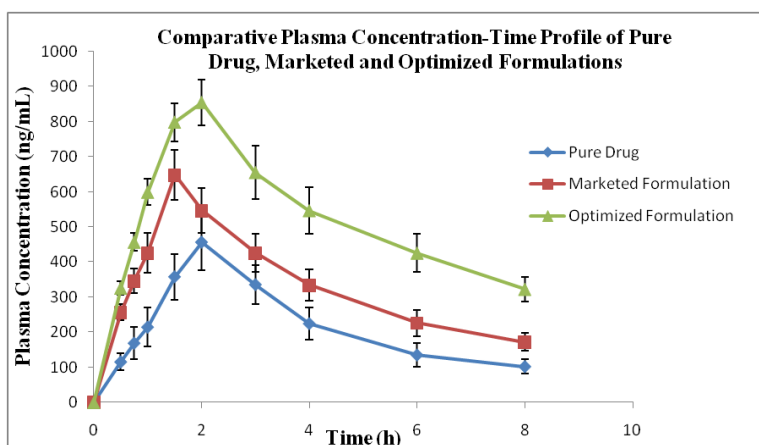


Figure 5: Comparative Pharmacokinetic Profile of Pure Drug, Marketed and Optimized Formulation.

Table 5: Calculated Pharmacokinetic Parameters of Pure Drug, Marketed and Optimized Formulations.

Pharmacokinetic Parameter	Pure Drug	Marketed Formulation	Optimized Formulation
Elimination Rate Constant (K) (h^{-1})	0.14	0.14	0.14
Half-life ($t_{1/2}$) (h)	4.94	4.98	5.00
AUC ($\text{ng}\cdot\text{hr}/\text{mL}$)	2462.64	3861.36	6473.96
C _{max}	464.15	652.5	865.4
T _{max}	1.82	1.85	1.84
Relative Bioavailability of optimized formulation compared with pure drug		2.6	
Relative Bioavailability optimized formulation compared with marketed formulation		1.7	

CONCLUSION

From the results of in vivo pharmacokinetic evaluation conducted in rats, it was observed that the oral bioavailability of optimized formulation was found to be significantly higher than marketed (1.7 times) and pure drug (2.6 times). Hence, it can be concluded that the liquisolid approach using combination of solvents and novel carriers is promising technique to improve the bioavailability of poorly soluble drug such as nebivolol hydrochloride. The recommended future work is to scale up the trails with increased batch size and to optimize the manufacturing process to get the reproducibility of increased bioavailability.

Conflict of Interest:

The authors do not have any conflict of interest.

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Abbreviations:

BCS : Biopharmaceutics Classification System
 NCE : New Chemical Entity
 Ml : Milli Liters
 UV : Ultra Violet
 C : Centigrade
 Ltd : Limited
 W/W : weight by weight
 Mg : Milligrams
 USP : United States Pharmacopoeia
 AUC : Area under the curve
 Min : Minutes
 G : Grams
 $t_{1/2}$: Half-Life
 PEG : Polyethylene glycol
 PG : Propyleneglycol

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