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The Novel Approaches towards Nebivolol by its Solubility Enhancement by Solid Dispersion Technique

Gaurav S. Mude*, Abhilasha Ikhar, Sakshi Mude, Sanjay Nagdev, Mayur Bhurat

Shri. Prakashchand Jain College of Pharmacy and Research, Palakhede, Jamner, Jalgaon

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***For Correspondence**

Gaurav S. Mude, Shri. Prakashchand Jain College of Pharmacy and Research, Palakhede, Jamner, Jalgaon, India

Tel: 08007095656

E-mail: gaurav21pharmamude@gmail.com

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ABSTRACT

The oral drug delivery system is the easiest and simplest way of administering dosage form. It has been estimated that 40% of new chemical entities currently being discovered by poorly water-soluble. Solid dispersion is one of the most successful strategies to improve the dissolution rate of poorly soluble drugs. About 1 gm of drug sample was placed in a watch glass and was observed for appearance, color taste, and odor. Glass capillary method was used to determine the melting point. Nebivolol is a poorly water-soluble drug. Hence various techniques were employed to enhance its solubility in aqueous media and products obtained from each technique were individually characterized and evaluated for solubility enhancement. Evaluation of tablet will go for Angle of Repose, Standard calibration curve, Weight Variation, Hardness, Friability Test, Disintegration Test (U.S.P), Drug Content, Dissolution test, Preliminary studies of Nebivolol, Evaluation of physical mixture method, Evaluation of kneading method, Standardization of calibration curve, Precompression studies, Precompression evaluation of nebivolol hydrochloride solid dispersion formulations, In vitro release data of nebivolol solid dispersion formulation, post-compression evaluation parameter. it was concluded that the dissolution rate of poorly soluble Nebivolol hydrochloride can be effectively enhanced by solid dispersion technique using PEG 6000(1:2). Due to increase solubility and dissolution, this formulation may be helpful to achieve good bioavailability and better therapeutic activity to maintain and control blood pressure levels for ion duration of action.

INTRODUCTION

Oral Drug Delivery

The oral drug delivery system is easiest and simplest way of administering dosage form. It has been estimated that 40% of new chemical entities currently being discovered by poorly water soluble [1]. It is important to realize the solubility problem of these types of drug and method for overcoming the solubility limitation. The solubility has presented challenge for development of suitable oral administration. The formulation of poorly soluble compounds for oral administration .The formulation of poorly water soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientist in pharmaceutical industry.

The oral delivery of drug most widely used for drugs into the systemic circulation, to overcome this solubility problem, in 1961 [2], Sekiguchi and Obi developed a particle method to overcome the limitations with the bioavailability enhancement of poorly water soluble drug. This method was later termed as solid dispersions. Solid dispersion is one of the most successful strategies to improve drug release of poorly water soluble drugs.

Solubility enhancement technique to overcome poor solubility of drug

The techniques that are used to overcome poor drug solubility are discuss as follows

I. Chemical modification

- Salt formation
- Co-crystallization
- Co-solvency
- Hydrotropic
- Nanotechnology

II. Physical modification

- Particle size reduction
- Complexation

III. Solubilisation of surfactants

- Micro emulsion
- Self-micro emulsifying drug delivery system

IV. Solid dispersion

- Physical mixture method
- Kneading method

Solid Dispersion Technique

Solid dispersion is one of the most successful strategies to improve dissolution rate of poorly soluble drug [3]. Solid dispersion can be defined as molecular mixtures of poorly water soluble drug in hydrophilic carriers, which present drug release profile that is driven by polymer properties.

Mechanism for Solubility Enhancement of Solid Dispersion

A number of methodologies can be adapted to improve solubilisation of poorly water soluble drug and further to improve solubility.

- Reduced partial size- When the solid dispersion is exposed to aqueous media, the carrier dissolve and the drug release as fine colloidal particles [4]. The resulting enhanced surface area result in higher dissolution rate of poorly water soluble drug.
- Drug in amorphous state- Poorly water soluble drug in amorphous state tend to have higher solubility. This is because no energy is required to break crystal lattice in amorphous state during dissolution.
- Particle with high porosity- Particle in solid dispersion have been found to have high porosity. The increased porosity of solid dispersion particles hastens the drug release profile [5]. Increase porosity depends on carrier properties i.e. linear polymer result in larger and more porous particles than that of reticular particles.
- Particle with improved wettability- A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement has been verified in solid dispersion.

Pharmaceutical applications of solid dispersion

- To Enhance the absorption of drug
- To obtain a homogenous distribution of a small amount of drug solid state.
- To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.
- To disperse liquid or gaseous compounds.
- To formulate a fast release priming dose in a sustained release dosages form.
- To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier [6].

Advantages of solid dispersion

- To reduce particle size.
- To improve wettability.
- To improve the crystalline structure of drug in amorphous form.
- To mask the taste of drug substance.
- To prepare rapid disintegration oral tablet.
- To stabilize unstable drugs.

- To dispense liquid or gaseous compounds [7].

Disadvantages of Solid Dispersion

- Reproducibility of its physicochemical properties.
- Its formulation into dosages form.
- The scale up manufacturing process

Experimental Work and Result

- Characterization of Drug
- Preliminary Studies
- Organoleptic Properties

About 1 gm. of drug sample was placed in watch glass **(Figure 1)** and was observed for appearance, colour taste and odour **(Table 1)** [8].

Melting Point Determination

Glass capillary method was used to determine the melting point. Drug filled capillary was tied with a thermometer and immersed in liquid paraffin containing Thiele's Tube [9]. It was heated uniformly and the temperatures at which the drug just began to melt and the one at which it melted completely were recorded. Reading were recorded in triplicate and mean value has been reported.

Solubility Study

The solubility study of drug was carried out to select the solvent in which the drug is soluble.

Method: In each selected solvent viz. Tween 20, Acetone, Glycerine, castor oil and water accurately weighted 10mg of drug was placed and solubility observed **(Table 2)** [10].

Enhancement in Solubility of Nebivolol By Various Techniques Of Solubility Enhancement

Nebivolol is a poorly water soluble drug. Hence various techniques were employed to enhance its solubility in aqueous media and products obtained from each technique were individually characterized and evaluated for solubility enhancement [11]. The modified drug sample was prepared by physical modification of solubility enhancement technique.

a. Physical Mixture Method

b. Kneading Method

c. Procedure for preparation of solid dispersion

d. Physical Mixture Method

The required molal ratio quantities of drug and PEG 6000 were weighted accurately and mixed together thoroughly in a molar with vigorous titration for 15-20 min [12]. Their mixture where passed through Sieve No. 44 **(Table 3)**.

Kneading Method

The required quantity of drug and carriers were taken in different ratios, transferred in a beaker and dissolved in sufficient quantity of ethanol and kneaded thoroughly for 30 minutes in a glass mortar [13]. The solid dispersion was stored in desiccators for further solidification for 24 hr. Further it was triturated in a mortar and passed through sieve No.80 [14]. The obtained solid dispersion was stored in tightly closed containers until further use **(Table 4)**.

RESULTS AND DISCUSSION

Direct compression method

Solid dispersion absorbate of Nebivolol along with all the excipients were accurately weighted and passed through 22 number sieves. Then the powder was uniformly mixed in the poly bag. The resulting powder mixture is used for Evaluation.

Evaluation of Tablet

Flow properties

- **Angle of Repose:** The material is poured through a funnel to form a cone. The tip of the funnel should be held close to the growing cone and slowly raised as the pile grows, to minimize the impact of falling particles. Stop pouring the material when the pile reaches a predetermined height or the base a predetermined width. Rather than attempt to measure the angle of the resulting cone directly, divide the height by half the width of base of the cone. The inverse tangent of this ratio is the angle of repose [15].

Standard calibration curve: Standard calibration curve of pure NEBIVOLOL HCL was constructed using UV –Visible

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Figure 1. Sample placed in Watch Glass.

Table 1: Preliminary studies of Nebivolol.

S. No.	Characteristic	Reported	Observed
1	Appearance	Crystalline Powder	Crystalline Powder
2	Taste	Slightly Bitter	Slightly Bitter
3	Odour	Odourless	Odourless
4	Colour	White	White
5	Melting Point	220-222 0C	220-222 0C

Table 2: Solubility studies of Nebivolol.

S. No.	Solubility Study		
a.	Distilled water	Insoluble	Insoluble
b.	Tween 20	Soluble	Soluble
c.	Castor Oil	Soluble	Soluble
d.	PEG 200	Slightly Soluble	Slightly Soluble
e.	PEG 400	Soluble	Soluble
f.	Propylene Glycol	Soluble	Soluble
g.	Acetone	Soluble	Soluble
h.	Glycerin	Soluble	Soluble

Table 3: Composition of Solid Dispersion Prepared by Physical Mixture method.

S. No.	Solid Dispersion System	Ratio
1	Nebivolol: PEG 6000	01:01
2	Nebivolol: PEG 6000	01:02
3	Nebivolol: PEG 6000	01:03
4	Nebivolol: PEG 6000	01:04
5	Nebivolol: PEG 6000	01:05

Table 4: Composition of solid dispersion prepared by Kneading Method.

S. No.	Solid Dispersion System	Ratio
1	Nebivolol: PVP K30	01:01
2	Nebivolol: PVP K30	01:02
3	Nebivolol: PVP K30	01:03

spectrophotometer at 281 nm.

- **Standard drug solution:** 5mg of NCB HCL was accurately weighted and dissolved in 10 ml methanol in 50 ml of volumetric flask. The volume was made up to the distilled water to give 100 microgram/ml.
- **Procedure of standard calibration curve:** A liquate 0.5,0,1.5,,2.0,2.5,& 5.0 ml of 100 microgram/ml NEB HCL standard solution were accurately transferred into a series of 10ml of volumetric flasks and made up to mark with distilled water.

Evaluation of Tablet

Weight Variation

- Take 10 tablets and weighed individually.
- Calculate average weight.

- % Wt. Variation = (Individual Wt/Average Wt) x 100
- The tablet pass the U.S.P test if no more than 2 tablet are out of % limit and if no tablet differs by more than 2 times of % limit.

Hardness

- It is defined as the force required to break a tablet in a diametric compression test.
- Hardness is an unofficial test.
- Hardness is measured by Monsanto tester.

Friability Test

- Friability of tablet can determine in laboratory by Roche friabilator.
- This consist of a plastic chamber that revolves at 25rpm, dropping the tablets through a distance of 6 inches in the friabilator, which is then operate for 100 revolutions.
- The tablets are reweighed. Compress tablet that lose than 0.5% to 10% of the weigh are consider acceptable [16].

% Friability = (W0 – Wf / W0) x 100, where W0- Initial Weight &Wf- Final Weight

Disintegration Test (U.S.P)

- The U.S.P device to test disintegration uses 6 glass tubes that are 3 inch long; open at the top and 10 mesh screens at the bottom end.
- To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid 37 ± 2 ^{0}C.
- Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute.
- Floating of tablets can be prevented by placing perforated plastic discs on each tablet.
- According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screens in the time specified.
- If any residue remains, it must have a soft mass [17].

Drug Content

About 10mg of drug equivalent of PM and SD(theoretical) were weighed accurately and transferred to 52ml volumetric flask to which 20ml methanol was added and sonicated for 15 min and volume was made up with methanol [18]. From this stock solution further dilution were done and assayed using ultraviolet spectrometer (UV 1800 Shimadzu).

Dissolution test

- Dissolution is the process by which a solid solute enters a solution.
- In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

  Dissolution is considered one of the most important control tests performed on pharmaceutical dosage forms.
- Now it developing into a tool for predicting bioavailability, and in some cases, replacing clinical studies to determine bio-equivalence.
- Dissolution behaviour of drugs has a significant effect on their pharmacological activity.
- In fact, a direct relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated [19].

Apparatus-2 (Paddle Type)

- It is same as apparatus-1 **(Figure 2)**, except the basket is replaced by a paddle.
- The dosage form is allowed to sink to the bottom of task before stirring.
- For dissolution test U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, and time limit of the test and assay procedure for the API.
- The test tolerance is expressed as a % of the labelled amount of drug dissolved in the time limit.

Pre compression studies

Flow properties of all the formulation were evaluated and the results are shown in **(Tables 5-11 and Figure 3,4)** solid dispersion technique.

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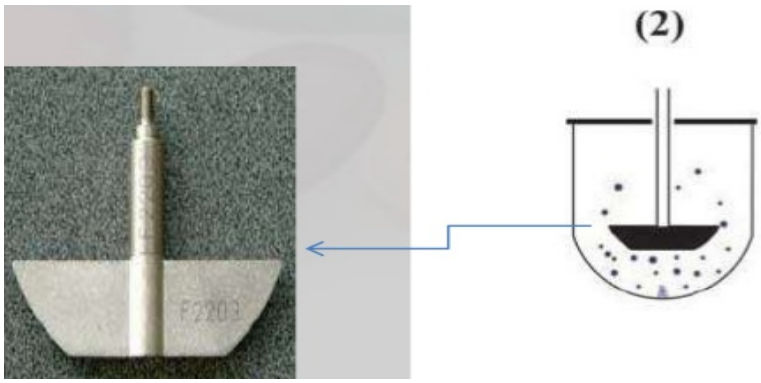

Figure 2. Apparatus used in evaluation of Tablet.

Table 5: Formulation of Tablet.

S. No.	Ingredient	F1	F2	F3	F4	F5
1	Nebivolol	5	5	5	5	5
2	PEG 6000	10	10	10	10	10
3	MCC	228	-	-	113.8	-
4	Lactose	-	228	-	-	113.8
5	Dicalcium Phosphate	-	-	228	115.8	113.8
6	Sodium Starch Glycolate	2.5	2.5	2.5	2.5	2.5
7	Magnesium Stearate	2.5	2.5	2.5	2.5	2.5
8	Talc	2.5	2.5	2.5	2.5	2.5
	Total	250	250	250	250	250

Table 6: Evaluation of physical mixture method.

S. No.	Solid Dispersion System	Ratio	% drug content
1	Nebivolol: PEG 6000	01:01	72
2	Nebivolol: PEG 6000	01:02	99
3	Nebivolol: PEG 6000	01:03	75
4	Nebivolol: PEG 6000	01:04	85
5	Nebivolol: PEG 6000	01:05	90

Table 7: Evaluation of kneading method.

S. No.	Solid dispersion system	Ratio	% drug content
1	Nebivolol PVP K30	01:01	73
2	Nebivolol PVP K30	01:02	98
3	Nebivolol PVP K30	1;3	74

Table 8: Standardization of calibration curve.

S. No	Concentration	Absorbance
1	0.5	0.095
2	1	0.185
3	1.5	0.279
4	2	0.366
5	2.5	0.46

Table 9: Pre compression evaluation of nebivolol hydrochloride solid dispersion formulations..

Formulation	Angle of response (Ø)	Carr's index (%)	Hausner's ratio
F1	24.65	12.16	1.13
F2	25.3	14.11	1.15
F3	28.45	12.21	1.14
F4	24.24	11.15	1.12
F5	25.64	13.13	1.18

Table 10: *In vitro* release data of nebivolol solid dispersion formulation.

Formulation	% drug release (5min)	%drug release (10min)	%drug release (15min)	%drug release (20min)	%drug release (25min)	%drug release (30min)	%drug Release (35 min)	%drug release (40min)
F1	7.04	19.01	33.24	48.3	65.32	80.42	89.9	92.21
F2	8.12	19.32	33.22	41.44	66.28	82.64	91.47	97.01
F3	8.42	19.23	33.48	48.12	66.51	83.82	92.41	97.24
F4	8.68	20.64	38.89	53.86	67.74	84.58	94.47	99.21
F5	7.82	19.48	36.82	52.74	78.24	82.09	93.61	98.34

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Table 11: Result of post compression evaluation parameter.

Formulation	Hardness (kg/cm2)	Weight variation	Friability (%)	Assay (%)	DT(sec)	%DR (30min)
F1	3.5	Pass	0.77	94.23	255	54.76
F2	4	Pass	1.78	92	240	58.43
F3	3,5	Pass	0.78	93.5	130	60.23
F4	4,5	Pass	0.7	95.82	264	100.04
F5	3.5	Pass	1.2	95	131	64.88

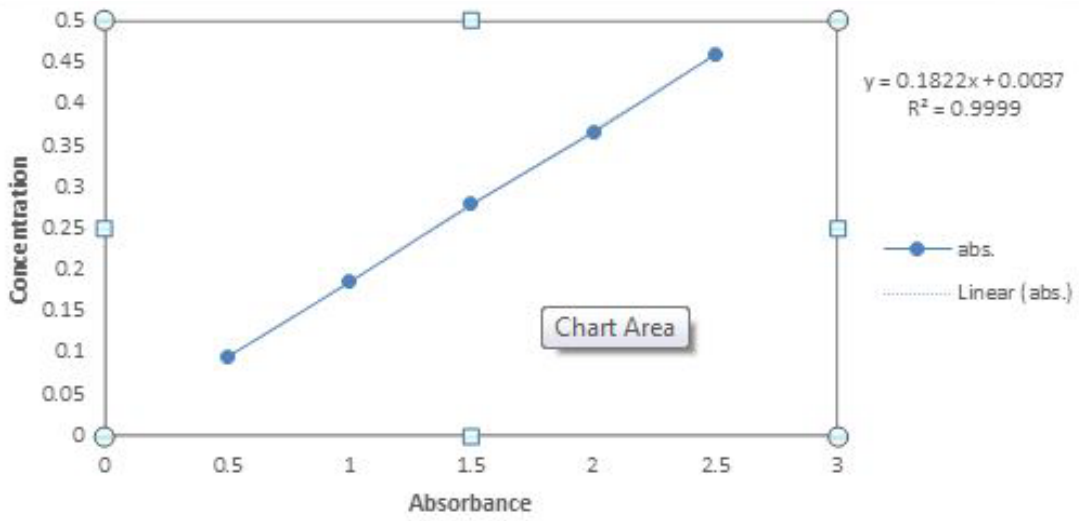

Figure 3. Standardization of calibration curve.

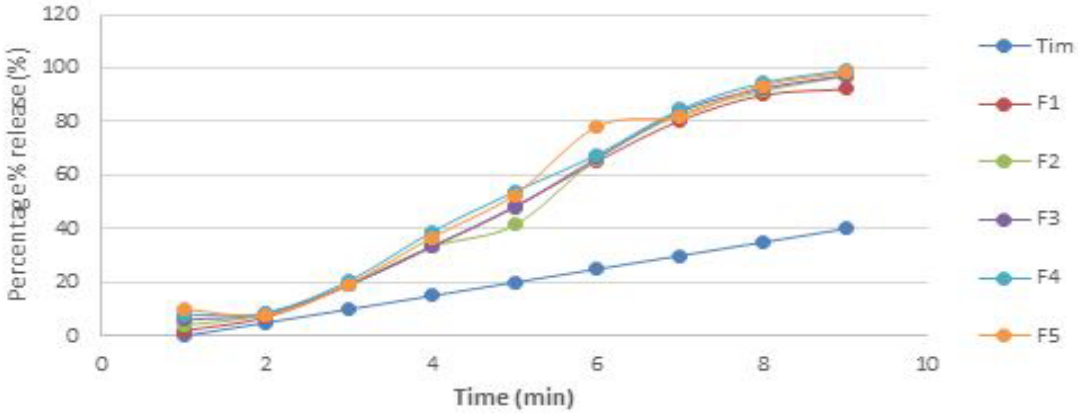

Figure 4. Percentage of drug release.

CONCLUSION

From the result, it was concluded that the dissolution rate of poorly soluble Nebivolol hydrochloride can be effectively enhanced by solid dispersion technique using PEG 6000(1:2). Due to increase solubility and dissolution this formulation may be helpful to achieve good bioavailability and better therapeutic activity to maintain and control blood pressure level for ion duration of action.

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