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PREPARATION AND CHARACTERISATION OF β-CYCLODEXTRIN NEBIVOLOL INCLUSION COMPLEX

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ABSTRACT: Nebivolol HCl (NEB) is antihypertensive drug having β-adrenergic blocking properties. Although NEB is rapidly absorbed after oral administration, it has low bioavailability (12%), due to its low water solubility. The purpose of present work was to enhance the solubility and dissolution rate of NEB by inclusion complexation technology. Complexation is the association between two or more molecules to form a noncovalent based complex that has higher solubility than the drug itself. From solubility standpoint, complex can be put in to two categories, stacking complexes and inclusion complexes. The aim of this work was to study the influence of β-cyclodextrin (β-CD) on the biopharmaceutical properties of Nebivolol HCl. To this purpose the physicochemical characterization of NEB-β-cyclodextrin binary systems was performed both in solution and solid state. Present study includes deals with the preparation of inclusion complex of NEB ß-cyclodextrin as carrier and to evaluate NEB ß-cyclodextrin inclusion complex for various parameters viz., % practical yield, drug content, *in vitro* release study, drug-excipients interaction study, etc

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INTRODUCTION: Nebivolol hydrochloride is a class II drug that selectively blocks β1 receptor with therapeutic applications as antihypertensive and can also used as monotherapy for initial management of uncomplicated hypertension. The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of NEB by preparing inclusion complexation with β-cyclodextrin by five different methods viz. physical mixture, kneading, microwave irradiation, co-evaporation and freeze drying method. The prepared inclusion complex were evaluated for % practical yield, drug content, *invitro* dissolution rate studies and interactions between drug and carriers using DSC, XRD, FTIR and SEM studies [1, 2].

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Cyclodextrin are cyclic (α-1, 4)-linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrin are not perfectly cylindrical molecules but the toroidal or cone shaped. Based on this architecture, the primary hydroxyl groups are located on the narrow side of the cone shape, while the secondary hydroxyl groups are located on the wider edge.

During the past two decades, cyclodextrin and their derivatives have been of considerable interest in the pharmaceutical field because of their potential to form complexes with a variety of drug molecules. Cyclodextrin are used to increase the solubility of water insoluble drug through inclusion complexes formulation. The hydrophobic cavity of cyclodextrin is capable of trapping a variety of molecules within to produce inclusion complexes. Many advantages of drugs complex with cyclodextrin have been reported in scientific literature which includes-increased solubility,

enhanced bioavailability, improved stability, masking of bad test or odor, reduced volatility, transformation of liquid or gas into solid form reduced side effect, and the possibility of a drug release system, etc. The solid state characteristics of the drug after preparation and during storage will depends on the processing variables as well as the characteristics of the system.

When the objective of the formulation is to attain faster dissolution rates, presence of amorphous of the drug and improved dissolution rate would therefore be a result of presence of amorphous high energy forms of the drug as well as the ability of the cyclodextrin to form a soluble complexes with the drug, the performance of the product over the shelf life would depend on the ability of the cyclodextrin to prevent crystallization of the amorphous drug to its stable crystalline forms. However the use of cyclodextrin in the solid oral dosage forms is limited to low dose drugs with large stability constant due to mass limitations of oral dosage.

In this study, an attempt was made to improve the solubility and dissolution rate of Nebivolol by complexing with β-Cyclodextrin, thereby increasing its bioavailability and therapeutics efficiency. The complex of β- cyclodextrin with Nebivolol was prepared by using physical mixture method, kneading method, microwave irradiation method, co-evaporation method and freeze drying method at 1:1, 1:2, 1:3 stoichiometric ratio.

The characterization of drug with β-Cyclodextrin using differential scanning calorimetry (DSC), powder X-ray diffractometry (PXRD), FTIR, *In vitro* aqueous solubility and dissolution rate profile of complexes were performed. Complexation is a unique technique used to increase solubility, dissolution and bioavailability of poorly water-soluble drugs [3, 4, 5, 6].

MATERIALS:

The Nebivolol supplied by Watson Pharma limited (Mumbai, India), β-Cyclodextin obtained from Loba Chemie Pvt. Ltd. (Mumbai, India)

METHODS:

Phase solubility studies:

Phase solubility studies were performed according to the method reported by Higuchi and Connors.An excess amount of Nebivolol was added to 20 ml of solution i.e distilled water, 0.1N HCl and phosphate buffer pH7.4 containing various concentrations of β-Cyclodextin (0, 2, 4, 6, 8 and 10 mM) into the glass vials. The contents were shaken for 48 hours at room temperature on rotary flask shaker.

After equilibrium, the samples were withdrawn, filtered through a Whattman paper and appropriately diluted. A portion of samples were analyzed by UV spectrophotometer at 281 nm. The apparent stability constant was calculated from the initial straight portion of the phase solubility diagram using the following equation:

$$Kc = \frac{\text{Slope}}{\text{Intercept } (1 - \text{slope})}$$

Preparation of Inclusion complexes:

After determining the optimum proportions of drug with the complexing agent the inclusion complexes were prepared using following methods:

1) Physical mixture method:

The required molar (1:1, 1:2, 1:5) ratio quantities of drug and β-CD were weighed and mixed separately in mortar by vigorous trituration for 1 hrs. The mixtures were then passed through sieve no. 40 and were stored in airtight container until further use[7].

2) Kneading Method:

In this method, a solution of distilled water and methanol (1:1) was used as moistening agent and was added to accurately weighed molar quantities of each of β-CD. To this molar quantities of drug were added with constant grinding. This grinding was continued for 1hour and the consistency of pastes was maintained using the appropriate quantities of moistening agent. These pastes were finally dried in a hot air oven at 40ºC for 24 hours. The dried pastes were then passed through sieve number 40 and the resulting mass was collected and stored in airtight containers until further use[7].

3) Microwave irradiation method:

The required molar quantities of drug and each of β-CD were triturated in a glass mortar using minimum quantity of solvent mixture (Methanol: Water = 1:1 v/v). This mass was then kept in microwave oven, which was set at power level 2,

and the reaction was allowed to take place for 90 seconds. After this more amount of solvent mixture was added to reaction mixture and then precipitated mass was filtered out. These precipitates were dried in hot air oven at 60ºC for 24 hours to finally get a white powder mass of inclusion complexes of drug with cyclodextrins. These inclusion complexes were collected and stored in airtight containers until further use[7].

4) Co-evaporation method:

This method involves dissolving of the drug and β-CD separately in to two mutually miscible solvents such as methanol and water respectively, mixing of both the solutions to get molecular dispersions of drug and complexing agents and finally evaporating the solvent under vaccum to obtain solid powdered inclusion complex. The resulting mixture is stirred for 24hours and evaporated under vaccum at 45^0 C. the dried mass was pulverized and passed through a sieve number40 [7].

5) Freeze drying method:

In order to get a porous, amorphous powder with high degree of interaction between drug and cyclodextrine, freeze drying technique is considered as a suaitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and cyclodextrine at reduced pressure. The required molar quantities of drug was added in aqueous solution of β-CD. The resulting solution were frozen at -20^0 C overnight and lyophilized in freeze dryer maintained at freezing temperature of (-70 to-75^0C), vaccum applied in dried chamber 0.1mbar at ambient temp.(16 to 20^0C). The lyophilized powder was passed through a sieve no. 40 and stored in sealed glass vials [7].

TABLE 1: FORMULATION INGREDIENTS, PREPARATION METHOD OF NEBIVOLOL ß-CYCLODEXTRIN INCLUSION COMPLEX

Batch Code	Composition	Method	Ratio
F1	ß-cyclodextrin + Nebivolol	Physical mixture	1:1
F2	β-cyclodextrin + Nebivolol	Physical mixture	1:2
F3	ß-cyclodextrin + Nebivolol	Physical mixture	1:5
F4	ß-cyclodextrin + Nebivolol	Kneading method	1:1
F5	ß-cyclodextrin + Nebivolol	Kneading method	1:2
F6	ß-cyclodextrin + Nebivolol	Kneading method	1:5
F7	ß-cyclodextrin + Nebivolol	Microwave irradiation method	1:1
F8	ß-cyclodextrin + Nebivolol	Microwave irradiation method	1:2
F9	ß-cyclodextrin + Nebivolol	Microwave irradiation method	1:5
F10	ß-cyclodextrin + Nebivolol	Co-evaporation method	1:1
F11	ß-cyclodextrin + Nebivolol	Co-evaporation method	1:2
F12	ß-cyclodextrin + Nebivolol	Co-evaporation method	1:5
F13	ß-cyclodextrin + Nebivolol	Freeze drying method	1:1
F14	ß-cyclodextrin + Nebivolol	Freeze drying method	1:2
F15	ß-cyclodextrin + Nebivolol	Freeze drying method	1:5

Evaluation of Nebivolol- β cyclodextrin inclusion complex:

1) Physical Appearance:

All the batches of Nebivolol - ß-cyclodextrin inclusion complex were evaluated for colour and appearance.

2) Percent Practical Yield (PY):

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Inclusion complex were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = Practical Mass (SD) / Theoretical Mass (Drug + Carrier)] ×100

3) Assay or Drug content estimation:

Accurately weighed complexes equivalent to 5mg of Nebivolol were transferred in 25ml volumetric flask. 10ml methanol was added and sonicated for 5min.volume was made up to 25ml with distilled water. This solution was filtered using whattman filter paper in 25ml volumetric flask, again make upto the volume with distilled water up to 25ml. 1ml solution was withdrawn and diluted upto 10ml distilled water and determined spectro photometrically at 281nm

4) Solubility Studies:

To the glass vials containing 5 ml of distilled water, excess quantity of drug and each Inclusion complex type were added separately. These vials were shaken on laboratory shaker for 24 hours. The resulting solutions were filtered, appropriate dilutions were made using distilled water and the absorbances were recorded at 281nm.

5) Thin Layer Chromatography:

The solvent system for running TLC of Nebivolol was Toluene: Methanol: Triethylamine (3.8:1.2:0.2). Each Inclusion complex was subjected to TLC using pure Nebivolol as reference sample. Rf values for each were calculated.

6) Spectral Analysis:

1. UV-Visible Spectrum recording:

UV spectra of pure Nebivolol powder and its Inclusion complex were recorded in methanol.
Also a blank was run using methanol.

2. IR Spectrum Analysis:

Fourier transform infrared (FTIR) spectroscopy was employed to characterize any possible interaction between drug and carrier in the solid state on a FTIR spectrophotometer by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000–400cm^{-1} with a resolution of 4 cm^{-1}.

7) Differential Scanning Calorimetric Analysis:

The possibility of any interaction between the drugs and the carriers during different approaches was assessed by carrying out thermal analysis of drug as well as the optimized formulation, using DSC. DSC analysis was performed using Perkin Elmer Analyzer Jade DSC on 4 to 5 mg samples. Samples were heated in an open aluminium pan at a rate of 10°C/min conducted over a temperature range of 50 to 300°C under a nitrogen flow of 20 ml/min.

8) X – Ray Diffraction Studies:

To determine the powder characteristics, X-ray powder diffraction studies of drugs alone as well as that of the optimized formulation was performed. X-ray powder diffraction patterns were recorded on Bruner AXS, DH advancd model. The scanning rate employed was 6° min-1 over 10 to 50°C diffraction angle (2θ) range.

9) Scanning Electron Microscopy:

Morphology of prepared solid dispersion was examined by scanning electron microscope (Jeol model) operating at 10.0 kV accelerating voltage. For conventional imaging in the SEM, specimens must be electrically conductive, at least at the surface, and electrically grounded to prevent the accumulation of electrostatic charge at the surface. Therefore the optimized solid dispersions were carbon coated before being subject to electron scanning. The energy of electron beam was set at 10 kV.

10) Dissolution Studies:

Each type of Inclusion complex sample equivalent to 5 mg of Nebivolol was subjected to dissolution test using Dissolution Test Apparatus USP XXII (Type–II). Pure Nebivolol was used as control and was subjected to similar dissolution test using 5 mg of pure drug.

Test Parameters used for Dissolution Test

Speed of Paddle: 50 rpm.
Temperature of Dissolution Medium: 37°C ± 0.5°C
Apparatus Type: USP XXII (paddle)

Procedure:

Inclusion complex equivalent to 5 mg of Nebivolol were placed in various dissolution medium (0.1N HCl and phosphate buffer pH7.4)and apparatus was run. 5 ml aliquots were withdrawn at time intervals of 5min., 10min., 15min., 20min., 25min., 30min., 35min., 40min., and 50min.55min. 60min. and 5ml of fresh dissolution medium was added after each with drawl. Each sample was filtered through Whatman filter paper (No 41) and absorbances were measured at 281 nm using UV visible double beam Spectrophotometer (Shimadzu, UV-1800).

RESULT AND CONCLUSION:

In the present investigation, an attempt was made to improve the solubility and dissolution rate of a drug Nebivolol by complexation method using ß-cyclodextrin as carrier. Inclusion complex was prepared by Physical mixture,Kneading method, co-evaporation method, Microwave irradiation method and freeze drying method. The prepared

inclusion complex were evaluated for number of parameters like DSC, FTIR, XRD, percent practical yield, drug content uniformity studies, and *In- vitro* drug release studies etc.

TABLE 2: STANDARDIZATION OF ASPIRIN

Characteristics test (performed)	Standard as per the manufacturer sheet (Aspirin)	Observation
Description	White crystalline powder	Complies
Melting range	220^0C-223^0C	220^0C
Solubility	Water	Insoluble
	Methanol	Freely soluble
	0.1N HCl	Soluble
	Phosphate buffer 7.4pH	Soluble
Identificat ion	As per Indian Pharmacopoeia	Positive

TABLE 3: STANDARD CALIBRATION DATA OF NEBIVOLOL IN 0.1N HCL

Concentration (µg/ml)	Absorbance at 281nm
5	0.094
10	0.201
15	0.284
20	0.395
25	0.484
30	0.589
35	0.664
40	0.782

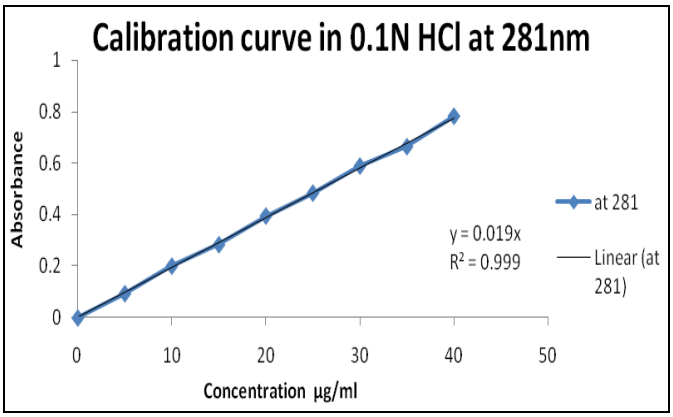

FIGURE 1: STANDARD CALIBRATION CURVE OF NEBIVOLOL IN 0.1N HCL

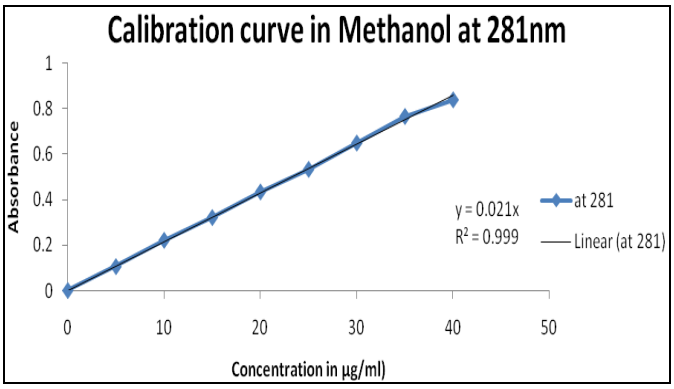

FIGURE 2: STANDARD CALIBRATION CURVE OF NEBIVOLOL IN METHANOL

TABLE 5: DRUG CONTENT UNIFORMITY STUDIES, PERCENTAGE PRACTICAL YIELD AND SATURATION SOLUBILITY STUDIES OF NEBIVOLOL ß-CYCLODEXTRIN INCLUSION COMPLEX

Sr.no.	Method of preparation	Ratios	Drug content/Assay	Percent yield	Saturation solubility µg/ml
1	Pure drug	-	-	-	19.97
2	Physical mixture	1:1	78.85	92.63	42.7
		1:2	83.95	98.57	46.15
		1:5	88.19	99.01	50.35
3	Kneading	1:1	85.76	83.40	42.9
		1:2	89.90	94.02	47.35
		1:5	91.28	97.91	63.25
4	Microwave irradiation	1:1	89.46	91.25	41.9
		1:2	90.95	93.21	48.05
		1:5	93.57	97.53	65.35
5	Co-evaporation	1:1	87.33	94.94	42.1
		1:2	91.04	95.37	48.7
		1:5	92.57	98.73	72.65
6	Freeze drying	1:1	96.04	84.62	43.3
		1:2	97.93	85.56	59.3
		1:5	100.04	90.22	76.6

Inclusion complex of Nebivolol were prepared by different method using carrier as ß-cyclodextrin. In the present work, total 15 formulations were prepared and their complete composition is shown in Table. The entire Inclusion complexes prepared were found to be fine and free flowing powders.

The results of percent practical yield studies are shown in **Table 5**. The % Practical yield of the prepared Inclusion complex was found to be in the range of 83.40 – 99.01 %. The actual drug content of all the 15 formulations is shown in **Table 6**. The drug content of the prepared Inclusion complex

was found to be in the range of 78.85 – 100.04 % indicating the application of the present methods for the preparation of inclusion complex with high content uniformity. The maximum % drug content was found to be 100.04% in F15

TABLE 6: DISSOLUTION PROFILE OF PURE DRUG, OPTIMIZED BATCH F15 AND MARKETED PREPARATION IN 0.1N HCL

Time (min.)	% Cumulative drug release ± S.D		
	Pure drug	Marketed product	F15 (1:5) Lyophilized inclusion complex)
5	4.95±0.96	27.9±0.20	52.2±0.99
10	5.85±0.89	31.05±0.85	54±0.85
15	9.67±1.04	32.85±1.41	57.15±0.63
20	13.5±0.90	36.9±0.63	60.3±0.95
25	16.67±0.97	40.95±0.88	62.1±0.22
30	18.22±0.88	42.25±0.89	64.8±1.07
35	21.82±0.96	44.95±0.98	66.15±0.94
40	23.17±1.21	47.75±0.96	67.27±0.25
45	25.87±0.91	49.45±0.87	68.62±0.38
50	26.32±0.90	51.15±0.88	69.97±0.99
55	27±1.12	53.95±0.86	71.1±0.87
60	27.45±1.01	54.3±0.79	72.67±0.88

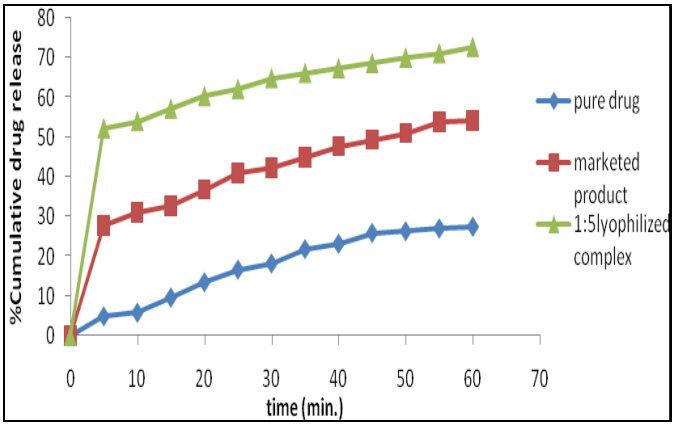

FIGURE 3: COMPARISION OF OPTIMIZED BATCH WITH PURE DRUG AND MARKETED FORMULATION OF NEBIVOLOL IN 0.1N HCL

TABLE 4: STANDARD CALIBRATION DATA OF NEBIVOLOL IN METHANOL

Concentration (µg/ml)	Absorbance at 281nm
5	0.105
10	0.221
15	0.321
20	0.434
25	0.533
30	0.649
35	0.766
40	0.839

Drug release from Inclusion complex was faster than pure drug. Cumulative percent drug released after 60 minutes was 72.67 for F15, while it was 27.45% in 60 minutes for pure drug Nebivolol. *In vitro* release study revealed that there was a marked increase in the dissolution rate of Nebivolol from all inclusion complexes when compared to pure Nebivolol itself. From the in-vitro drug release profile, it can be seen that formulation F-15 containing ß-cyclodextrin (1:5 ratio of drug: ß-cyclodextrin) show higher dissolution rate i.e. 72.67% compared with other formulations. In all above formulations, the drug Nebivolol is in the free state and available for absorption.

Fig. 4A shows the FTIR spectrum of NEB and its optimized solid dispersions. Characteristic peaks of NEB at 3190.36 cm-1 (N-H stretching), 3215 cm-1 (O-H stretching), and 1101.78 cm-1 (cyclic ether C-O stretch), 1621 cm-1(aryl substituted C=C), 1303.71 cm-1 (C-N stretch) and 2942.72 (C-H stretch) were observed.

The polymer taken in this study is ß-cyclodextrin which contains number of secondary hydroxyl group and primary ─OH group. These two functionalities present in the molecules have shown a broad peak around 3400cm-1 corresponding to primary and secondary ─OH groups. C─H absorption is notice at 2921.63 and 2379.73 cm-1. Strong absorption peak is also notice at 1027.87 cm-1. These data are in conformity with structure of the ß-cyclodextrin. When these two constituents, Drug and polymer ß-cyclodextrin used for the required formulation. The IR spectrum of which has shown the presence of all the functionalities present in the drug as well as ß-cyclodextrin suggests these during the preparation of formulation chemical reaction between two has not taken place.

The formulated product is just take physical mixture none of the functional groups absorption is not affected. The formulation done by taking drug and the polymer in 1:2 ratio. Hence this formulated is a physical mixture of all the two constituents but not the reaction product of any constituents.

Comparing the FTIR data of formed optimized complex with Nebivolol. It was found that the peak observed for complexes (**Figure4C**) is identical with each other at near about same characteristics

peaks. Therefore from IR data it was confirmed that there was absence of undesired interaction or chemical interaction with excipient (i.e no changein chemical nature of drug molecule). The drug remained stable in complex formed. There was H-H bond formation take place due to interaction between Nebivolol and β-cyclodextrin $1^0$and 2^0 alcoholic group in tern resulted in to complex formation leading to solubility enhancement.

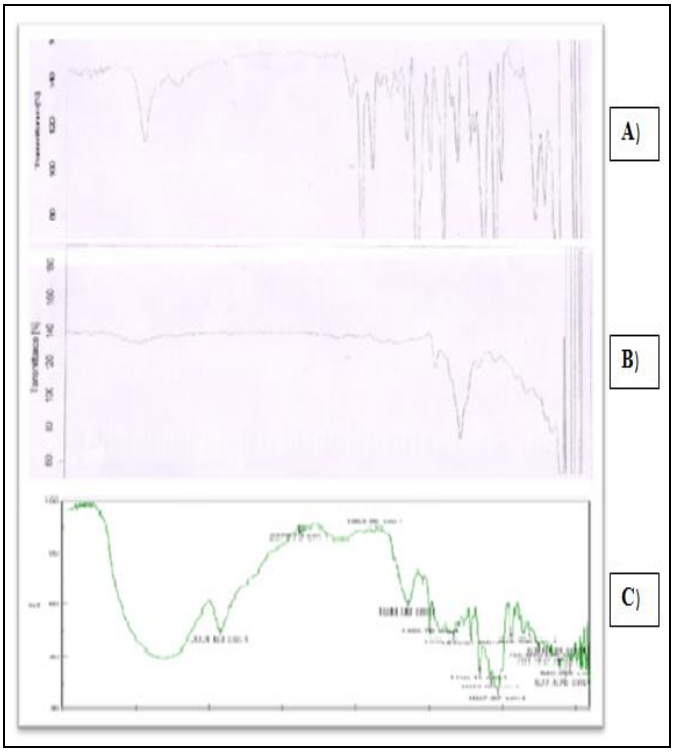

FIG. 4: FTIR SPECTRA OF A=NEBIVOLOL, B= ß-CYCLODEXTRIN, C=FORMULATION F15

The drug Nebivolol subjected for DSC study, it started melting at 224.4˚C and completed at 233.88˚C, suggesting that these narrow range of melting is due to the present of single compound in the pure form. The carbohydrate polymer ß-cyclodextrin is taken for DSC measurement this polymer has given rang to wide range to melting process started at 110˚C to 160˚C.

This is the characteristics behavior of the carbohydrates. When the formulation obtained by the drug and ß-cyclodextrin for DSC study two melting ranges are obtained in one peak, melting process started at 90.4˚C and reach the peak at 130.93˚C in an another peak process started at 210˚C reach the peak at 226.02˚C, suggesting that, when these two molecules (Drug and ß-cyclodextrin) used for the formulation product obtained is nothing but a physical mixture of the two. In all above formulations, the drug Nebivolol is in the free state and available for absorption.

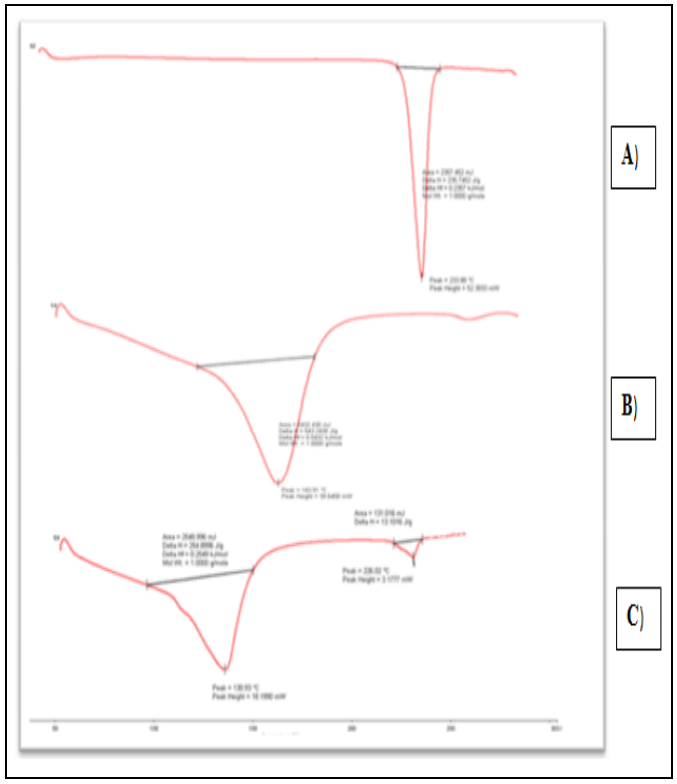

FIG. 5: DIFFERENTIAL SCANNING OF CALORIMETRIC THERMOGRAM OF A =NEBIVOLOL, B = ß-CYCLODEXTRIN AND C = FORMULATION F15

For conventional imaging in the SEM, specimens must be electrically conductive, at least at the surface, and electrically grounded to prevent the accumulation of electrostatic charge at the surface. Therefore the optimized inclusion complex were carbon coated before being subject to electron scanning. The energy of electron beam was set at 10 kV. Nebivolol existed as needle shape crystals (**Figure 6a**), whereas β-Cyclodextrin seen as clusters present in compact form consist of irregular size crystals (**Figure 6b**).

The complex appeared in the form of irregular shape reduced size particles in which the original morphology of both component disappeared and tiny particles of irregular size were present (**Figure 6d**). Therefore, the reduced particle size increased the surface area and close contact between the hydrophilic carriers and Nebivolol might be responsible for solubility enhancement.

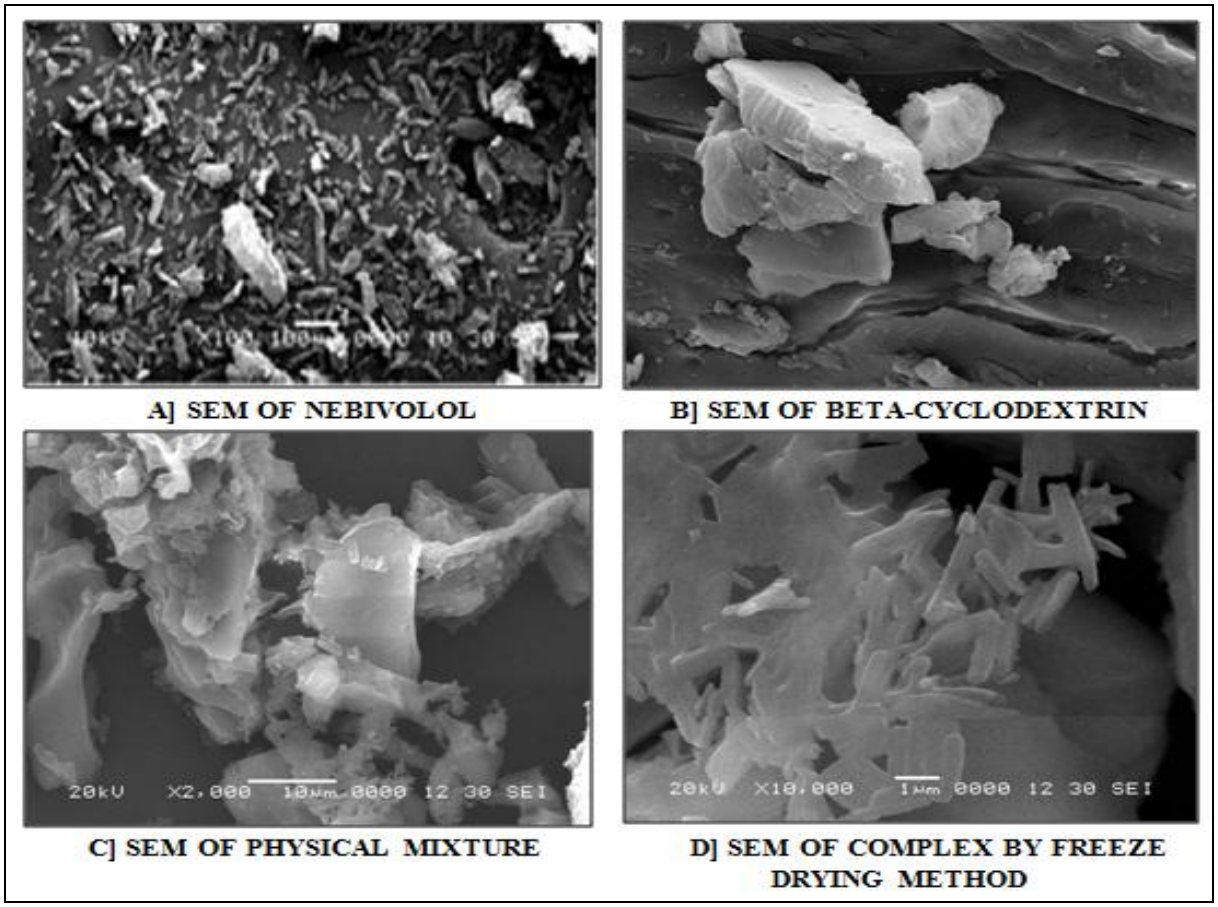

FIGURE 6 : SEM IMAGES OF A) PURE DRUG NEBIVOLOL B) BETA- CYCLODEXTRIN C) PHYSICAL MIXTURE AND D) INCLUSION COMPLEX BY FREEZE DRYING METHOD

CONCLUSION: The data obtain from the study of Nebivolol ß-cyclodextrin inclusion complex in which the ß-cyclodextrins used as a complexing agent. The following points can be concluded: The dissolution rate of Aspirin from inclusion complex i.e., F1-F15 was significantly higher than that of pure drug, inclusion complex prepared by Freeze drying method showed faster drug release than the other method, IR studies indicated that no chemical interaction between drug and polymer took place during preparation of inclusion complex of Nebivolol and ß-cyclodextrin, DSC studies indicated that Nebivolol was homogeneously distributed within the carrier in an amorphous state and no drug crystallized out of the dispersion suggesting that drug and polymer exist in the form of a mixture rather than the reaction product.

In-vitro drug release of Nebivolol ß-cyclodextrin inclusion complex of 1:5 (F15) showed higher drug release, the IR study showed that there was no chemical interaction between Nebivolol and polymer ß-cyclodextrin. From overall formulation, F-15 is the best formulation containing 1:5 ratio of ß-cyclodextrin and Nebivolol.

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REFERENCES:

1. Olga Hilas, Danielle Ezzo**,** Nebivolol (Bystolic), a Novel Beta Blocker for Hypertension, Drug Forecast,2009;34: 4
2. Amelia Avachat, Vijay Raut, Solubility and dissolution enhancement of Nebivolol hydrochloride using hydrophilic carriers, Asian Journal of Pharmaceutical Sciences,2012; 7 (5): 337-345
3. Brewster M. E., Loftsson T., Cyclodextrin as pharmaceutical solubilizers, Advanced drug delivery review,2007; 59: 645-666
4. Szejtli Jozsef, Past present and future of cyclodextrin research, Pure applied chemistry,2004; 76, 1829-1833
5. Martin E. M., Cyclodextrin and their uses: A Review , process biochemistry,2003; 30:5-7
6. A. Magnúsdóttir, M. Másson and T. Loftsson: Cyclodextrins, J. Incl. Phenom. Macroc.Chem.2002; 44: 213-218.
7. Patil J.S., Kadam D.V., Inclusion complex system a novel technique to improve the solubility and bioavailability of

poorly soluble drugs: A Review, Int. J. of Pharm sci. review and research,2010; 2:30-32
8. Loftsson T., Marcus E., Role of cyclodextrins in improving drug delivery, Journal of drug delivery,2004;4:2-8
9. Vemula V. R., Lagishett, Solubility enhancement techniques, Int. J. of Pharm sci. review and research,2010;5:41-51
10. Patric J.S., Martins physical pharmacy and pharmaceutical sciences, V edition, Lippincott Williams and Wilkins Philadelphia,2006;231-266,595-597
11. Brahmnkar D., Jaiswal S., Biopharmaceutics and pharmacokinetics: A Treatise, II edition, Vallabh prakashan,2009; 27:343-357
12. Aulton M.E, The science of dosage form design, IIedition, Churchill Livingstone, 2002; 16: 23, 234.
13. Strickley R.B., Solubilizing excipients in oral and injectable formulations, Pharm. Res. 2004; 21(2): 201 – 230.
14. Saharan A.V, Kukkar V, Dissolution enhancement of drug, Part I: Technologies and effect of carriers,2009; 2:107-124
15. Anil J Shinde, Solubilization of Poorly Soluble Drugs: A Review, Pharmainfo.net,2007; 5 (6):1-25
16. Shabnam Ain, Betty Philip, Kamala Pathak, Preformulative Assessment of Preformed Complexes of Gemfibrozil, with Cyclodextrins, PDA Journal of Pharmaceutical Science and Technology, 2008; 62(4), 300-308.
17. J. A. Castillo, J Palomo-Canales, J.J Garcia, J.L. Lastres, F. Bolas, J.J. Toraddo, Preparation and Characterization of Albendazole b-Cyclodextrin Complexes, Drug Development and Industrial Pharmacy,1999; 25(12):1241–1248.
18. M. Chavanpatil, F.D. Daware, D.S. Shakleya, P.R. Vavia, Enhancement of Oral Bioavailability of Rofecoxib Using β-Cyclodextrin, Journal of Inclusion Phenomena and Macrocyclic Chemistry,2002; 44: 145–149.
19. K. P. R. Chowdary, Buchi N. Nalluri, Nimesulide and b-Cyclodextrin Inclusion Complexes: Physicochemical Characterization and Dissolution Rate Studies, Drug Development and Industrial Pharmacy, 2000;26(11):1217–1220
20. Sunita Dahiya and Kamla Pathak, Physicochemical Characterization and Dissolution Enhancement of Aceclofenac -Hydroxypropyl b-cyclodextrin Binary Systems, PDA J Pharm Sci and Tech, 2006; 60: 378-388.
21. Kale Rajendrakumar, Saraf Madhusudan, Tayade Pralhad, Cyclodextrin complexes of valdecoxib: properties and anti-inflammatory activity in rat, European Journal of Pharmaceutics and Biopharmaceutics, 2005; 60: 39–46.
22. Mihaly Kata, Rita Ambru, Zoltan Aigner, Preparation and Investigation of Inclusion Complexes Containing Nifluminic Acid and Cyclodextrins, Journal of Inclusion Phenomena and Macrocyclic Chemistry,2002; 44: 123–126
23. M.K. Manolikar, M.R. Swant, Study of solubility of isoproturon by its complexation with b-cyclodextrin, Chemosphere, 2003; 51: 811–816.
24. Stratos Maragos,Helen Archontaki,Panos Machora, Georgia Valsami, Effect of Cyclodextrin Complexation on the Aqueous Solubility and Solubility/Dose Ratio of Praziquantel, AAPS PharmSciTech,2009;10:4.
25. Norased Nasongkla, Enhancement of Solubility and Bioavailability of β-Lapachone Using Cyclodextrin Inclusion Complexes, Pharmaceutical Research, 2003; 20(10):1626-1633.
26. Yalcon Ozkan, Tamer Atar, Necati Dikmen, Improvement of water solubility and in vitro dissolution rate of gliclazide by complexation with β-cyclodextrin, Pharmaceutica Acta Helvetiae, 2000; 74:365–370.
27. Chinna Reddy Palem, Shewta Patel, Varsha B. Pokhapkar, Solubility and Stability Enhancement of Atorvastatin by Cyclodextrin Complexation, PDA J Pharm Sci and Tech, 2009;63: 217-225.
28. Swati Rawat, Sanjay K. Jain, Solubility enhancement of celecoxib using β-cyclodextrin inclusion complexes, European Journal of Pharmaceutics and Biopharmaceutics 2004; 57: 263–267.
29. Pradeep R. Vavia, Inclusion Complexation of Nimesulide with b-Cyclodextrins, Drug Development and Industrial Pharmacy, 1999; 25(4):543–545.
30. Shengfeng Wang, Inclusion complexes of fluorofenidone with b-cyclodextrin and hydroxypropyl-b-cyclodextrin, Drug Development and Industrial Pharmacy, 2009; 35(7): 808–813.
31. Preeti V. Bankar,Improved Dissolution Rate of Leflunomide using Hydroxypropyl-β-Cyclodextrin Inclusion Complexation by Freeze-Drying Method, International Journal of Drug Delivery,2012; 4:498-506.
32. Bystolic™ Prescribing Information, Forest Pharmaceuticals Inc., 12/2007.
33. Angie Veverka, Nebivolol in the treatment of chronic heart failure, vascular health and risk management, 2007; 3(5): 647-654.
34. Indian Pharmacopoeia Government of India, Ministry of Health and Family Welfare. Delhi: Published by the controller of Publications, Volume II, 2010; 1758.
35. D. Murali, Spectrophotometric Determination of Nebivolol Hydrochloride in Bulk and Pharmaceutical Formulations, Asian Journal of Chemistry; 2013; 25(6): 2981-2984.
36. Sirisha N, Haripriya A, Simultaneous quantification of nebivolol hydrochloride and hydrochlorothiazide by first derivative UV- Spectroscopy, Der Pharmacia Lettre,2013; 5 (2):78-84.
37. Tripti Sharma, Development And Validation Of UV Spectrophotometric Method For Determination Of Nebivolol Hydrochloride Following ICH Guidlines And Study Of Its Degradation Profile, Asian Journal of Pharmaceutical and Clinical Research,2012;5(4)

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