ORIGINAL ARTICLE

Dissolution improvement of nebivolol hydrochloride using solid dispersion adsorbate technique

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Nebivolol hydrochloride is unique antihypertensive drug, which gets completely absorbed upon oral administration, with t_{max} 1.5-4 h. The poor aqueous solubility leads to slow rate of absorption. An attempt has been made to enhance dissolution of nebivolol (NB) using solid dispersion (SD) and SD adsorbate (SDA) techniques. Various hydrophilic excipients such as polyethylene glycol 6000 (PEG), gelucire 50/13 (GL), and neusilin US2 (NUS) at different ratios were used. The prepared SDA of NB was characterized for % drug yield and other physical characteristics and *in vitro* drug dissolution studies in 0.1N HCl (pH 1.2). The formulation optimized on the basis of *in vitro* drug dissolution and % drug content was also characterized by the Fourier transform infrared (FTIR) spectroscopy; differential scanning calorimetry (DSC), X-ray powder diffractometry analysis (XRD). The FTIR study indicated no interaction between the drug and polymer. DSC thermograms showed the significant change in melting peak of the NB when prepared as SDA suggesting the change in crystallinity of NB. The data from the XRD showed that the drug was still detectable in its solid state in the SDA of PEG and disappeared in case of higher ratio of GL. An increased dissolution rate of NB at pH 1.2 was observed when the drug was dispersed in these carriers in the form of physical mixtures (PMs), SDs by solvent evaporation methods (SMs), SDs by fusion method and SDAs by fusion method. NB released faster from the SDAs than from the pure crystalline drug, the PMs, the SMs, or the SDs. Thus, this study was proved as a promising approach for the improvement of dissolution rate and solubility of NB.

Key words: *Antihypertensive drugs, physical mixture, solid dispersion, solid dispersion adsorbate*

INTRODUCTION

Nebivlol hydrochloride (NBH), chemically α,α'-(iminobis[methylene]) bis (6- fluoro- 3,4-dihydro- 2H-1-benzopyran-2-methanol) is a unique highly effective β-adrenergic blocker. NB selectively blocks the β1-adrenoceptor.[1] Nebivolol (NB) reduces heart rate, rate of myocardial contractility and systemic blood pressure, while increasing diastolic pause. β-blockers are useful prophylactic agents in stable and unstable types of angina. NB is preferable in patients with bronchi spasm, diabetes, peripheral vascular disease, or Raynaud's phenomenon.[2,3] The drug is not official in any pharmacopoeia. However, the low aqueous solubility and poor dissolution of this molecule in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability.[4]

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Various techniques that have been employed to increase dissolution rate include micronization,[5] nanosuspensions,[6] polymorphs,[7,8] complexation,[9,10] solid dispersion (SD),[11-14] prodrugs,[15] buffers[16] and salt formation.[17] SD has become one of the most active areas of research in the pharmaceutical field because it is simple, economic and promising in the bioavailability enhancement of poorly water-soluble drugs. However this conventional SD formulations exhibit problems with the yield, stability upon storage and other micromeritic problems. The literature indicated that the processing, flow properties, compressibility and stability of SD can be improved by the addition of an adsorbent.[18-23]

Thus, the purpose of the current study was to characterize the solid-state properties of the SD

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adsorbate (SDA) system of NB using polyethylene glycol 6000 (PEG) and gelucire 50/13 (GL) as meltable carrier and neusilin US2 (NUS) as adsorbent. The characterization of optimized formulation was done by Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRD). Moreover, solubility and dissolution rate study were performed to qualify the SD comparing with the drug alone or as physical mixture (PM) and solvent evaporation method (SM).[24]

MATERIALS AND METHODS

The active ingredient, NB was received as a gift sample from Torrent Pharmaceuticals Pvt. Ltd., Ahmedabad, India. GL was received from Gattefosse, France. PEG and NUS were used as received from SD Fine-chem Ltd., India and Fuji Chemical Industry Co. Ltd., Japan respectively.

Preparation of solid dispersions and physical mixtures

Physical mixtures

Physical mixtures were prepared by simple mixing the accurately weighed NB and hydrophilic carriers like GL and PEG with the help of spatula for 10 min.

Solid dispersion by solvent evaporation methods

Solid dispersions were prepared by using different ratios of NB and GL 50/13 and PEG. The weighed amount of drug and the carrier was dissolved in solvent (methanol). The mixture was mixed thoroughly and continuously until the solvent used was evaporated and a semisolid mass was obtained. This mixture was dried in vacuum oven (EIE Instrument Pvt. Ltd., Ahmedabad, India) at 45°C. The completely dried mass was pulverized using a mortar and pestle and sifted through mesh number 60 to obtain a uniform particle size and stored in a desiccator at room temperature and evaluated.

Solid dispersion/solid dispersion adsorbate by fusion method.

Solid dispersions were prepared by weighed quantities of NB and GL and PEG. The GL and PEG were molten in a porcelain dish at different processing temperatures. Once homogeneous slurry was obtained, it was cooled rapidly at different cooling temperatures and passed through number 22 sieves to obtain a uniform particle size and stored in a desiccator at room temperature and evaluated. SDAs were prepared similar to that of SD, but only difference was NUS was added after the preparation of homogeneous slurry as that in SD.

Characterization

Drug content

About 10 mg of drug equivalent of PM and SD (theoretical) were weighed accurately and transferred to 50 ml volumetric flask to which 20 ml methnaol was added and sonicated for 15 min and volume was made up with methanol. From this stock solution further dilution were done and assayed using ultraviolet spectrophotometer (UV 1800 Shimandzu).

In vitro dissolution studies

In vitro release of NB was performed using USP dissolution apparatus I (Electrolab TDT - 06 T, Mumbai) in 900 ml of 0.1N HCl at 37°C ± 0.5°C and stirred at 50 rpm. Exactly 10 ml aliquots were withdrawn at predetermined intervals. Sink condition was maintained by replacing the volume equivalent to the quantity removed with fresh dissolution medium. The solutions were diluted with 0.1N HCl and analyzed at 281 nm by UV spectrophotometer (UV 1800 Shimandzu spectrophotometer). The dissolution study was also performed for marketed product (nebicard tablets 10 mg).

Fourier transform infrared spectroscopy

Fourier transform infrared (Jasco FTIR 600 type A, Japan) spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a FTIR spectrophotometer by the conventional potassium bromide pellets. The spectra were scanned over a frequency range 4000-400 cm^{-1}.

Differential scanning calorimetry

The possibility of any interaction between the drug and the carriers during preparation of PM and SD were assessed by carrying out thermal analysis of drug and carrier alone as well as SD using DSC (Perkin Elmer, Pyris-I, Waltham, MA). The weighed amount of the sample was first cooled to −10°C and was held at that temperature for 1 min. The sample was then heated to 250°C at a rate of 10°C/min.

X-ray powder diffractometry

To determine the powder characteristics, XRD studies of drug, carrier alone and optimized formulation of SDA prepared using PEG and GL was performed. XRD patterns were recorded using Philips JPCD software for powder diffractometry. The scanning rate employed was 6° min^{-1} over 10-50° diffraction angle (2 θ) range.

Formulation of the tablet

Solid dispersion adsorbate of NB along with all the excipients were accurately weighed and passed through 22 number sieve. Then the powder was uniformly mixed in polybag. The resulting powder mixture was directly compressed in to tablet using 6 mm punch on rotary tablet machine (Riemek, Karnavati Eng. Pvt. Ltd., Ahmedabad, India).

Characterization of tablet

The prepared tablets were evaluated for hardness, friability, disintegration time, drug content analysis, and *in vitro* dissolution.

RESULTS AND DISCUSSIONS

Nebivolol hydrochloride is a thermostable drug with a melting point 174-176°C and is poorly water soluble. PEG polymers are widely used for their low melting point, low toxicity, wide drug compatibility and hydropholicity.[25,26-30]

GL is a family of vehicles derived from the mixtures of mono-, di-, and tri-glycerides with PEG esters of fatty acids. These are available with a range of properties depending on their hydrophilic-lipophilic balance and melting point range (33-65°C).[31,32] NUS was selected owing to good adsorptive capacity and its good water solubility so as to facilitate rapid desorption of drug. Preliminary studies were carried out to screen best suitable method among PM, SM, and SD, which could improve the dissolution of NB as mentioned in Table 1.

From the evaluation parameters, it was observed that SD showed better results compared to PM and SM. Hence, the drug to polymer ratio was optimized further to prepare SDs and SDAs. The drug, NB, was made to disperse in two different hydrophilic carriers, GL and PEG, to obtain SDs with and without adsorbent NUS as mentioned in Tables 2 and 3.

The *in vitro* dissolution studies of drugs with carrier were evaluated to identify the ratio of drug and carrier. The ratios of 1:2 (batch G4) and 1:3 (batch P4) were selected for further study, owing to the existence of drug at the molecular level as evidenced by the absence of melting endotherms of NB in the thermograms. The co-melt of carrier and the drug was adsorbed separately on to the surface of NUS to prepare free flowing granules of SDA (i.e. batch G7 and batch P7).

The batches G7 and P7 were evaluated further at different processing and cooling temperatures [Table 4] wherein improvement in micrometric properties, yield, drug content, and dissolution was observed.

The batches G12 and P12 were found to be optimum in terms of % yield, drug content and *in vitro* dissolution studies, which could be further processed into a tablet.

Drug release studies were carried out in 0.1N HCl [Figure 1]. Blending of NB with PEG or GL in the form of PMs, SMs, or SDAs could enhance the release of NB. The faster dissolution rate of PMs compared to pure drug was observed for both of carriers and could be attributed to the improvement of wettability of NB particles due to the presence of highly hydrophilic carriers. Dissolution rates for SDAs were greater than those for PMs, SMs, SDs and NB alone. The enhanced dissolution rates of SDAs may be due to many factors such as decreased particle size of

Table 1: Composition and evaluation of batches PPM, PSM, PSD, GPM, GSM and GSD

Batches	PPM	PSM	PSD	GPM	GSM	GSD
Method of preparation	PM	SM	SD	PM	SM	SD
Drug	10	10	10	10	10	10
PEG	10	10	10	-	-	-
GL	-	-	-	10	10	10
% yield[$]	91.8±1.56	92.6±1.82	92.1±1.37	94.3±1.39	90.2±1.67	92.9±1.43
% drug content[$]	96.4±0.58	95.8±0.32	91.7±0.47	93.5±0.42	91.3±0.61	94.6±0.58
% 60[#,$]	48.01±0.44	51.65±0.64	64.92±0.31	60.16±0.43	68.11±0.61	78.08±0.24

[#]Drug release at 60 min; [$]Values represent the mean±SD of 3 experiments. SD: Standard deviation, PPM: PEG600-Drug by Physical mixture method, PSM: PEG600-Drug by Solvent evaporation method, PSD: PEG600-Drug by Solid dispersion method, GPM: Gelucire 50/13-Drug by Physical mixture method, GSM: Gelucire 50/13-Drug Solvent by evaporation method, GSD: Gelucire 50/13-Drug by Solid dispersion method, PEG: Polyethylene glycol, GL: Gelucire 50/13

Table 2: Composition and evaluation of batches P1-P8

Batches	P1	P2	P3	P4	P5	P6	P7	P8
Drug	10	10	10	10	10	10	10	10
PEG	10	20	25	30	35	30	30	30
NUS	-	-	-	-	-	10	20	30
% yield D[$]	92.1±1.37	89.4±1.24	88.6±1.61	93.8±1.06	91.7±1.72	87.2±1.53	90.9±1.24	88.2±1.83
% drug content±SD[$]	91.7±0.47	88.2±0.58	86.7±0.47	92.2±0.32	89.4±0.63	90.3±0.28	93.6±0.39	87.8±0.54
% 60[#]±SD[$]	64.92±0.31	67.52±0.53	77.18±0.47	87.75±0.39	80.01±0.59	88.86±0.44	91.45±0.53	85.14±0.29

*Above all batches were prepared at processing temperature of 70°C and cooling temperature of 25°C, [#]Drug release at 60 min, $Values represent the mean±SD of 3 experiments.
SD: Standard deviation; PEG: Polyethylene glycol 6000; NUS: Neusilin US2

Table 3: Composition and evaluation of batches G1-G8

Batches	G1	G2	G3	G4	G5	G6	G7	G8
Drug	10	10	10	10	10	10	10	10
GL	5	10	15	20	25	20	20	20
NUS	-	-	-	-	-	10	20	30
% yield±SD[$]	92.9±1.43	89±1.82	86±1.67	93±1.48	87±1.59	87±1.74	89±1.34	92±1.64
% drug content±SD[$]	94.6±0.58	92.4±0.49	91.2±0.34	94.7±0.58	90.8±0.47	89.3±0.62	93.3±0.24	87.2±0.37
% 60[#] ±SD[$]	78.08±0.24	78.95±0.59	86.64±0.47	96.01±0.61	91.42±0.38	95.74±0.55	96.63±0.72	93.23±0.54

*Above all batches were prepared at processing temperature of 50°C and cooling temperature of 25°C, [#]Drug release at 60 min, [$]Values represent the mean±SD of 3 experiments.
SD: Standard deviation; GL: Gelucire 50/13; NUS: Neusilin US2

drug, specific form of drug in these SDAs, in addition to the increase in drug wettability and preventing of drug aggregation by each polymer.[33] Furthermore, both PEG and GL affected the crystallinity of the drug could be considered as an important factor in enhancement the dissolution rate. It is known that amorphous drug represents the most ideal case for fast dissolution.[34] The percent of drug dissolved after 90 min (DP) and relative dissolution rate (RDR) after 30 min of NB, PMs, SMs, SMs and its SDAs in PEG or GL prepared at different drug: Polymer ratios were illustrated in Tables 1-3. It is shown that the maximum percent amount of drug dissolved at pH 1.2 was 39.8% and the (RDR30) values were in the range 1.09-1.92 for PM and 1.61-2.05 for SD of the used polymers. Studies of the *in vitro* dissolution rates allow a comparison to be made between NB, PM, SM, G12, P12, G4, P4, and Nebicard (marketed product). The comparative dissolution profiles of all the products are shown in Figures 2-4. The *in vitro* dissolution rates of the both batch G12 and batch P12 were found to be much faster than the pure drug, SDs (G4 and P4), and marketed product.

The infrared spectrum of NB, PEG, NUS, GL, P12, and G12 exhibited significant differences in the intensities of the absorption peaks as observed in Figures 1 and 5. Broadening of various absorption peaks with a slight shift in the position to a lower wavelength was observed; this may be attributed to the intermolecular hydrogen bonding in the SDs which results in improvement of solubility.

Figures 6 and 7 illustrate the thermograms of NB, PEG, NUS, GL, P12, and G12. In G12, the endothermic peak was obtained at 183.02°C. Peaks obtained for NUS are in accordance with those as observed by Passerini *et al*.[35] In thermograms of P12, PEG gave peak at 201.79°C. NUS showed an endothermic peak at around 225.31°C. Lack of melting peak of NB (232.2°C) in the both thermograms of G12 and P12 indicated that the crystallinity of the drug was reduced in SDA. This could be attributed to its composition, whereas, it is composed of a mixture of low melting component rather than a single one.[36] The amorphous state in comparison to crystalline form is a high-energy state and is expected to have a high absorptivity.

To further confirm the state of drug in SDA, XRD was carried out. The XRD pattern of NB, PEG, NUS, GL, P12, and G12 in Figures 8 and 9 revealed high crystallinity of the drug with major diffraction peaks.[37] Diffractrograms of SDs adsorbates (G12 and P12) confirm the presence of the amorphous form of NB.

The decrease in the intensity of the diffractogram in case of the P12 and G12 appeared at 1:3:2 and 1:2:2 ratios, respectively and the peaks of NBH disappeared completely in G12. It could be attributed to the destruction of its crystal lattice, because of melting of drug into carrier. This suggested the formation of an insertion-type solid where drug molecules found the place inside the structure of the carrier without or with a limited deformation of the original crystal lattice. This is common in mixtures of polymeric carriers with small amounts of low molecular weight drugs.[38] From these results, it emerged that the amount of PEG is not sufficient to dissolve the NB completely so oversaturation occurred and pure drug

Table 4: Effect of processing and cooling temperature on evaluation parameters in batches P7 and G7

Batches*	P9	P10	P11	P12	G9	G10	G11	G12
Processing temperature	80	90	70	70	60	70	50	50
Cooling temperature	25	25	5	15	25	25	5	15
% yield±SD$	92.4±1.57	88.6±1.31	91.2±1.68	87.6±1.27	90.1±1.83	88.4±1.24	91.7±1.54	89.5±1.14
% drug content±SD$	92.8±0.52	94.5±0.41	89.6±0.39	93.4±0.28	86.2±0.49	85.7±0.37	88.6±0.51	93.2±0.64
% 60#±SD$	84.85±0.48	85.75±0.39	89.76±0.63	96.27±0.41	93.78±0.71	91.49±0.47	95.18±0.52	98.09±0.36

*The batches P9-P12 comprised of NB; PEG and NUS in ratio of 1:3:2 and G9 to G12 comprised of NB; GL and NUS in ratio of 1:2:2, #Drug release at 60 min, $Values represent the mean±SD of 3 experiments. SD: Standard deviation, NB: Nebivolol, PEG: Polyethylene glycol 6000, NUS: Neusilin US2, GL: Gelucire 50/13

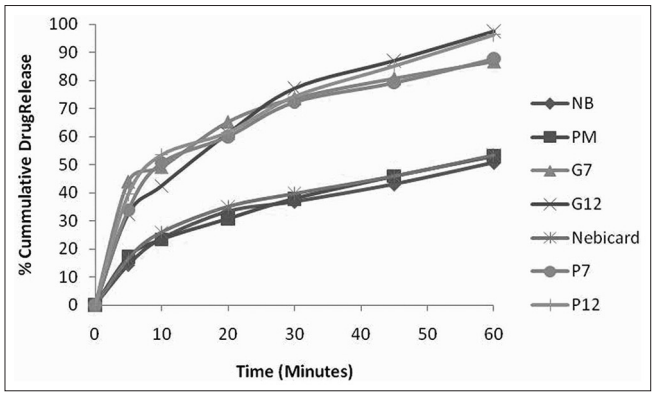

Figure 1: Dissolution profile of optimized formulation of solid dispersion and solid dispersion adsorbate of polyethylene glycol and gelucire, physical mixture, nebivolol, and nebicard

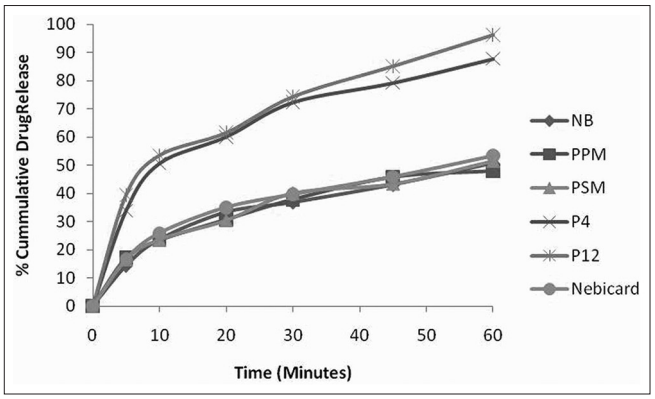

Figure 2: Dissolution profile of optimized formulation of solid dispersion and solid dispersion adsorbate of polyethylene glycol, PPM, NB: Nebivolol and Nebicard

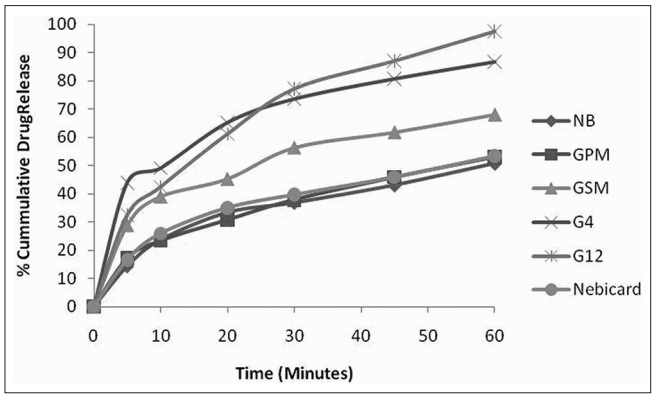

Figure 3: Dissolution profile of optimized formulation of solid dispersion and solid dispersion adsorbate of gelucire, GSM, nebivolol, and nebicard

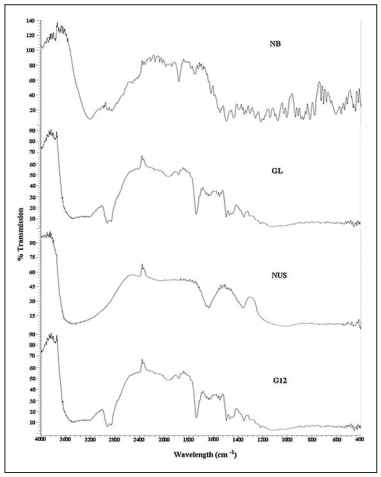

Figure 5: Infrared spectra of nebivolol, gelucire, neusilin US2, and G12

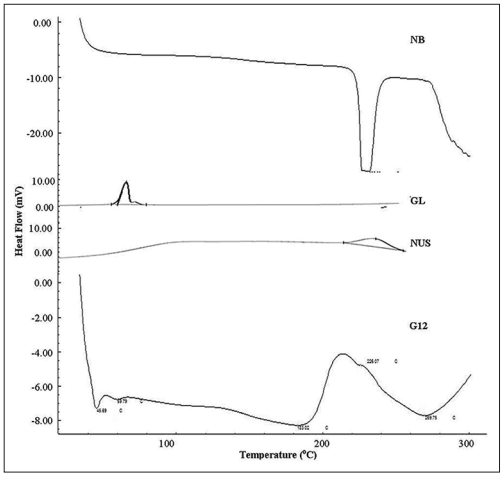

Figure 7: Differential scanning calorimetry spectra of nebivolol, gelucire, neusilin US2, and G12

crystals kept its structure inside the SD and appeared in the diffractogram [Figure 4]. At 1:3:2 ratio the crystallinity of NB was much decreased in case of PEG,[39] while it converted to amorphous state in case of GL at 1:2:2 ratio. No new peaks

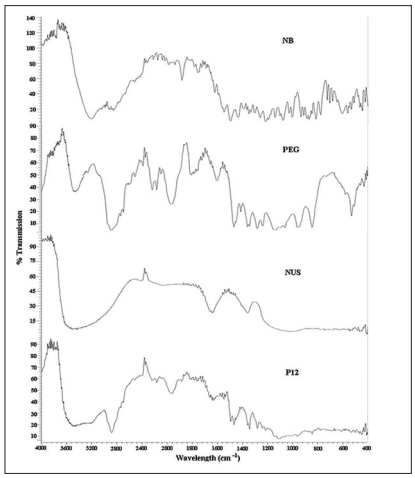

Figure 4: Infrared spectra of nebivolol, polyethylene glycol, neusilin US2, and P12

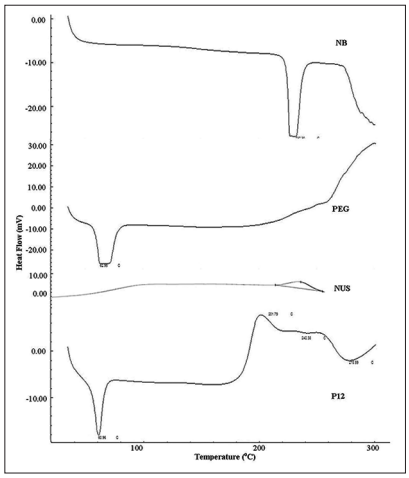

Figure 6: Differential scanning calorimetry spectra of nebivolol, polyethylene glycol, neusilin US2, and P12

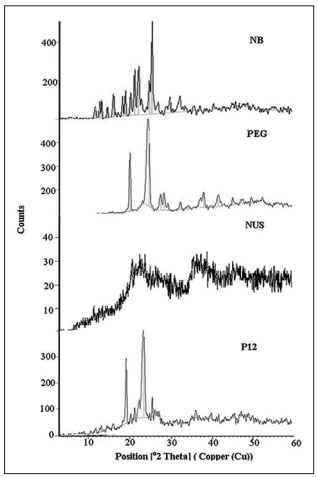

Figure 8: X-ray powder diffractometry spectra of nebivolol, polyethylene glycol, neusilin US2, and P12

could be observed suggesting the absence of the chemical interaction between the drug and the carrier.

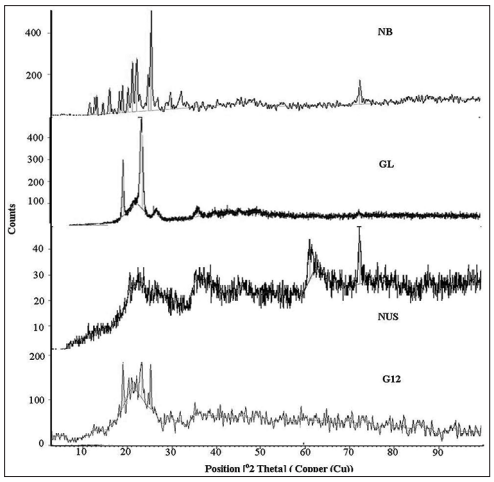

Figure 9: X-ray powder diffractometry spectra of nebivolol, gelucire, neusilin US2, and G12

Table 5: Composition of fast release tablet

Ingredients (mg)	Batch G12
NB	10
GL	20
NUS	20
Pearlitol 25°C	73.75
PVP K30	7.5
Magnesium stearate	1.5
Talc	1.5
Aerosil	0.75
Sodium starch glycolate	15
Total	150

NB: Nebivolol, NUS: Neusilin US2, PVP: Povidone, GL: Gelucire 50/13

Table 6: Evaluation of fast release tablet

Evaluation parameters	Batch G12
Angle of repose (θ)	24.87±1.12
Hardness (kg/cm^2)±SD$^\$$	3±0.42
Friability (%)±SD$^\$$	0.31±0.4
Disintegration time (min±SD$^\$$)	4.42±0.82
% drug content±SD$^\$$	96.3±0.48
%60$^\#$±SD$^\$$	95.46±0.67

$^\#$Drug release at 60 min. $^\$$Values represent the mean±SD of 3 experiments. SD: Standard deviation

The results obtained give an indication of the relative efficiencies of SDA and its potential immediate-release character. G12 resulted in faster dissolution rates compared to P12. This can be attributed to amalgamation of SD and melt adsorption technologies, which has resulted in enhancement in dissolution rate due to the combined effect of SD and increased surface area due to adsorption. Moreover, water solubility of NUS-selected adsorbent allows the drug to be desorbed completely.

It was further decided to formulate a fast release formulation[40,41] of NB using GL as hydrophilic carrier owing to its efficiency to improve its dissolution at a lower ratio when compared to PEG [Tables 5 and 6].

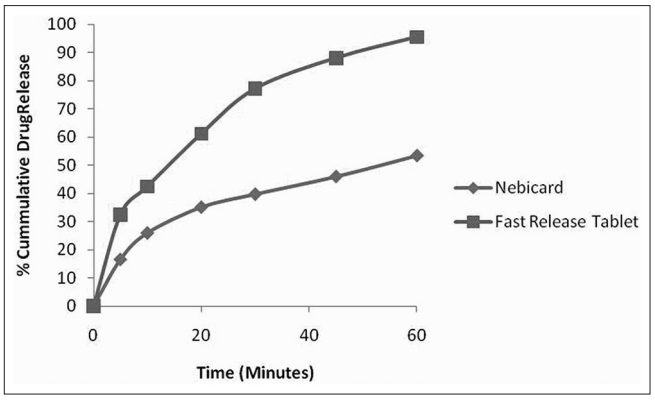

Figure 10: Dissolution profile of Fast release tablet and Nebicard (marketed formulation)

The developed fast release formulation is found to have two-fold improvement in terms of dissolution compared to Nebicard (marketed formulation) [Figure 10].

CONCLUSIONS

An amalgamation of SD and melt adsorption technologies using water-soluble adsorbent has proved to be highly beneficial in the present study for the enhancement of dissolution rate of poorly water-soluble drug due to the combined effect of SD and increased surface area due to adsorption. No decrease in dissolution on storage was observed. Studies with other adsorbents might be performed, which could also impart good flow and compressibility to the formulation. Further studies are needed for obtaining adsorbates in discrete form and for scale-up and validation of the process. It can be concluded from the study that the SDA will be a promising approach in improving the solubility of drugs like NB.

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