Studies on Obtaining and Characterization a Pregabalin-cyclodextrin Complex for Taste Masking Purpose

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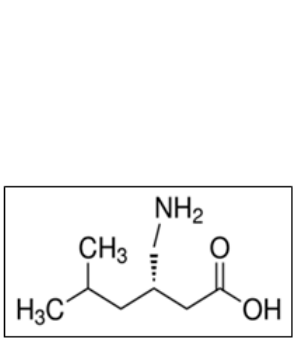
Pregabalin is an anticonvulsant and analgesic drug that stirs more and more the interest of the researchers. Its stability, solubility and taste can be modified by obtaining complexes with cyclodextrins. For this purpose, in the present study betacyclodextrin and hydroxypropyl-betacyclodextrin were included. The obtaining of inclusion complexes was confirmed by ATR-FTIR spectroscopy and UV spectroscopy. The results demonstrated that it is possible to develop inclusion complexes of pregabalin with betacyclodextrin and hydroxypropyl-betacyclodextrin, with moderate efficiency.

Keywords: inclusion complex, pregabalin, betacyclodextrin, hydroxypropyl-betacyclodextrin

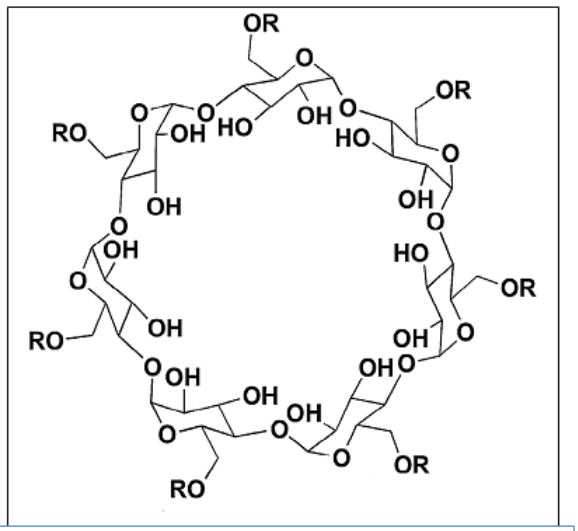
Pregabalin (PGB) is a structural analogue of the neurotransmitter γ-amino-butyric acid (GABA) with the ability to reduce several excitatory releases of neurotransmitters, blocking the development of hyperalgesia and central sensitization [1]. Thus, PGB has antihyperalgesic, anticonvulsant, anxyolitic, analgesic and sleep modulating properties [2]. From the chemical point of view, PGB is (S)-3-(aminomethyl)-5-methylhexanoic acid (fig. 1) [3].

An important strategy to improve the stability and the solubility of drugs is the use of cyclodextrins (CDs), a class of non-toxic cyclic oligosaccharides consisting of α-D-glucopyranose units linked by α-1,4-bonds (fig. 1). Due to their complex structures, CDs exhibit a hydrophilic external part consisting of hydroxyl groups along with a hydrophobic part which contains the hydrocarbon core and glycosidic bonds. The role of the hydrophobic part is to form the host-guest interactions with hydrophobic organic compounds [4].

The present study focuses on obtaining a complex of PGB with cyclodextrins, in order to further formulate it in orally disintegrating tablets (ODTs), with the purpose of taste masking PGB. Orally disintegrating tablets have been developed intensively over the last 15 years, due to their advantages over conventional tablets: rapid disintegration and drug release in the oral cavity; according to the European Pharmacopoeia [5] the time set for disintegration is max. 3 min, but generally, the aim of the ODTs is disintegration in less than 30 s. This characteristics provide increased bioavailability and possibility of administration to certain patient categories (children and elderly). One of the fields in which ODTs find their application is pain management, taking into consideration the fast onset of action of the formulated drugs. However, ODTs present



Pregabalin **(PGB)**



Betacyclodextrin **(BCD: R= H)**
Hydroxypropyl-betacyclodextrin **(HP-BCD: R=CH_3-CH(OH)-CH_2-)**

Fig. 1. Chemical structure of PGB, BCD and HP-BCD

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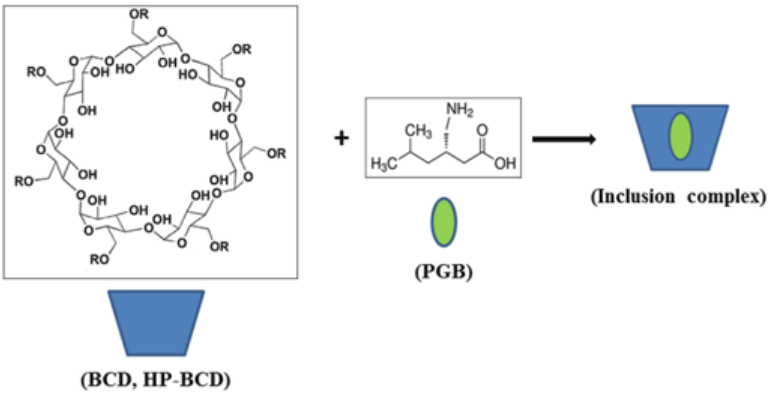

Fig.2. Scheme of the formation of PGB/BCD and PGB/HP-BCD inclusion complexes

certain formulation challenges: providing good palatability and mechanical properties (appropriate hardness and low friability). The former has remained a challenge, especially for the medium and high-dose drugs; the latter problem can be solved by applying compression as a manufacture method, but this generally extends the disintegration time of the ODTs. Within our research, taste masking pregabalin aims at obtaining the active drug in a form that can be easily accepted by the patient when formulated in ODTs by freeze-drying (oral lyophilisates) and compression methods [6-8]. Also, by complexing PGB with CDs, an increase of its stability and dissolution rate can be achieved.

Experimental part

Material and methods

Pregabalin – PGB, (*S*)-3-(aminomethyl)-5-methyl-hexanoic acid, Mesochem Tech., China; betacyclodextrin (BCD) and hydroxypropyl-betacyclodextrin (HP-BCD) both supplied by Fluka, Germany.

Preparation of physical mixture of PG and cyclodextrins: Pregabalin is classified as highly soluble and highly permeable according to the Biopharmaceutical Classification System (BCS). In order to mask its bitter taste we prepared a physical mixture with BCD and HP-BCD as follows: PGB/BCD (1:1 and 1:2) and PGB/HP-BCD (1:1 and 1:2) (fig. 2) [9].

The required molar quantities of the drug and cyclodextrins were weighted accurately and mixed together thoroughly in a mortar, with vigorous trituration, for about three hours. These mixtures were stored in airtight containers until further use.

Optical microscopy was performed on a Zeiss Axiotech optical microscope. All images were obtained at 50 times magnification.

ATR-FTIR spectroscopy: All the combinations of pregabalin with cyclodextrins were characterized by ATR-FTIR measurements using a Biorad FT-IR spectrometer FTS 575 C. The spectra were recorded in the range of 4000–500 cm^{-1} with 32 scans at a resolution of 4 cm^{-1}. Spectral processing was carried out by means of a Horizon MBTM FTIR Software and GRAMS 32 Software (Galactic Industry Corporation, Salem, NH), Version 6.00 [10].

UV spectroscopy analysis, efficiency and loading capacity of inclusion complexes: Complex formation between pregabalin and BCD respectively HP-BCD were studied by spectroscopic method [11]. The UV spectra were obtained on a Perkin Elmer (Lambda 25, USA) UV/Vis Spectrometer. The spectroscopic technique was used to determine the inclusion efficiency (% IE) and loading capacity (% LC) of PGB in the inclusion complex. In this regard, absorbance of various PGB concentrations was recorded in the range 200-700 nm. The maximum peak with minimum interference was detected at 276 nm. Thus, the calibration curve of PGB was obtained. The IE % and LC % were determined as follows [12]:

$$\%\,IE = \frac{\text{Quantity of PGB in the complex}}{\text{Total quantity of PGB}} \times 100 \quad (1)$$

$$\%\,LC = \frac{\text{Quantity of PGB in the complex}}{\text{Total quantity of cyclodextrins}} \times 100 \quad (2)$$

All measurements were performed three times.

Results and discussions

The obtaining of inclusion complexes was confirmed by optical microscopy, ATR-FTIR spectroscopy and UV spectroscopy. In figure 3 are given for exemplification some of the microscopic images of PGB/HP-BCD (1:2) and PGB/BCD (1:2) inclusion complexes.

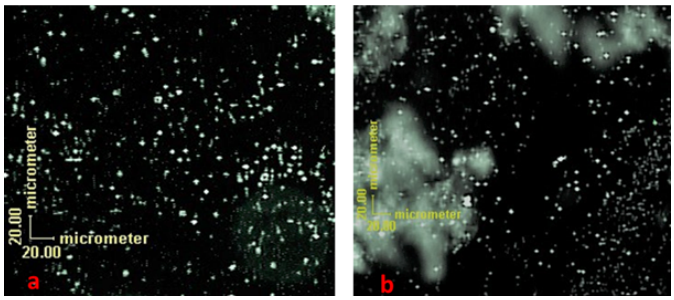

Fig.3. Microscopic images: (a) PGB/HP-BCD (1:2) and (b) PGB/BCD (1:2)

IR Spectra

The following characteristic peaks appear in the IR spectra of pregabalin in combination with BCD and HP-BCD:

HP-BCD: The IR spectra of HP-BCD showed absorption bands at 3420 cm^{-1} for stretching vibrations of OH, 2940 cm^{-1} for CH stretching vibrations and 1153 cm^{-1} and 1100 cm^{-1} for CO stretching vibration. BCD: The IR spectra of BCD sowed absorption bands at 3360 cm^{-1} for stretching vibrations of OH, 2890 cm^{-1} for CH stretching vibrations and 1153 cm-1 and 1076 cm^{-1} for CO stretching vibration.

PGB: The IR spectra of PGB showed absorption bands at 1643 cm^{-1} for N-H; 1543 cm^{-1} for N-O, 1420 cm^{-1} for C-H, 1279 for C-O and 860 for O-H.

In the IR spectra of PGB/BCD (1:1 and 1:2) and PGB/HP-BCD (1:1 and 1:2) we can find all the characteristic peaks of both components: pregabalin and cyclodextrins (table 1, fig. 4 and 5). Typical bands of PGB were still discernable and did not show any shift in IR spectra in any physical mixtures since they correspond to a superposition of their parent components. These results suggest that the hexanoic acid core of PGB has been incorporated into the non-polar cavity of BCD and HP-BCD, respectively. Also, very important is the absence of new absorption bands which demonstrates the lack of formation of new chemical bonds.

Table 1
INTERPRETATIONS OF IR- SPECTRA

Ingredients	Functional groups with wavenumber (cm^{-1})				
	N-H	N-O	C-H	C-O	O-H
PGB	1643	1543	1420	1279	860
BCD	-	-	2890	1153, 1076	3360
HP-BCD	-	-	2940	1153, 1100	3420
PGB/BCD (1:1)	1647	1541	1418, 2911	1280, 1153, 1078	860, 3355
PGB/BCD (1:2)	1647	1541	1420, 2920	1280, 1153, 1079	860, 3366
PGB/HP-BCD (1:1)	1653	1541	1418, 2920	1277, 1153, 1178	860, 3355
PGB/HP-BCD (1:2)	1650	1540	1440, 2922	1275, 1153, 1080	860, 3354

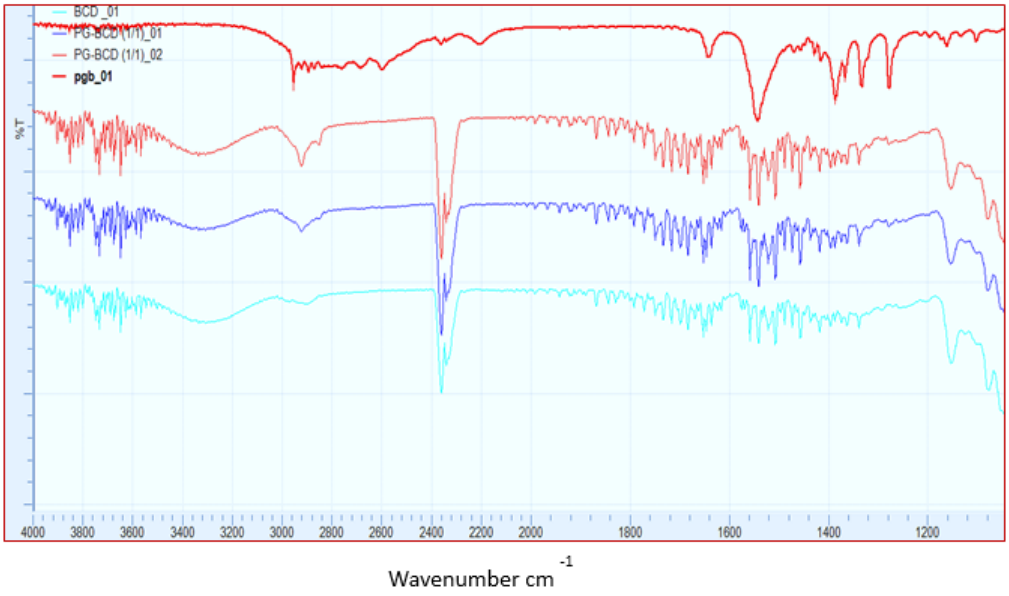

Fig. 4. Inclusion complexes of pregabalin with BCD

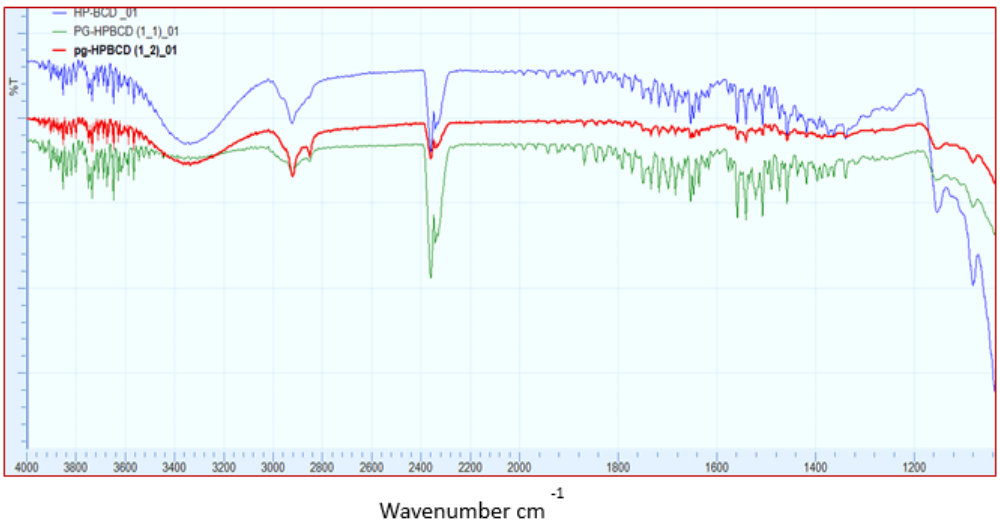

Fig. 5. Inclusion complexes of pregabalin with HP-BCD

UV spectroscopy analysis, efficiency and loading capacity of inclusion complexes:

UV absorption spectroscopy is a helpful method to determine the content of guest molecules in the inclusion complexes [12].

The calibration curve of pure pregabalin (E) was plotted first, depending on the concentration (C): E = f(C) using the Microsoft Excel software (fig. 6). Thus, the linear regression equation was obtained: Y = bx + a, with the interception values a = 0.0799, the slope of the regression equation b = 2.7742 and the correlation coefficient R^2 = 0.9989 (fig. 6).

In this study, UV-VIS spectroscopy is used to determine the inclusion efficiency (IE) and loading capacity (LC) using the content of the guest molecule (PGB) in the complex. IE and LC are quantitative parameters which express the amount of included PGB in the complex with CDs (BCD and HP-BCD). The obtained values suggest that the inclusion efficiency and loading capacity are dependent to the type of CDs used (BCD or HP-BCD) and on the ratio of components (1:1 or 1:2) used during the formation of PGB inclusion complexes (table 2).

Table 2

INCLUSION EFFICIENCY (% IE) AND LOADING CAPACITY (% LC) OF PGB INCLUDED INTO BCD AND HP-BCD

Sample	PGB/BCD (1:1)	PGB/BCD (1:2)	PGB/HP-BCD (1:1)	PGB/HP-BCD (1:2)
% IE	38.11±1.2	44.94±1.9	53.6±2.3	58.5±3.1
% LC	5.34±0.1	5.85±0.3	6.38±0.1	6.79±0.2

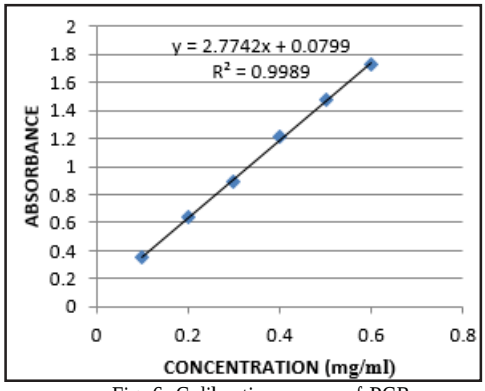

Fig. 6. Calibration curve of PGB

The increase in the % IE and % LC, in the case of HP-BCD, is related to the introduction of hydroxypropyl group in the betacyclodextrin's structure which promotes better interaction with PGB, enhancing the inclusion complex formation. These systems based on cyclodextrins complexation will be able to mask the undesirable properties of pregabalin like bitter taste and help improve the drug efficiency.

Conclusions

In the present research we have prepared some inclusion complexes of pregabalin with cyclodextrines (BCD and HP-BCD) at different molar ratios (1:1 and 1:2) for the final purpose of taste masking PGB, for formulation in orally disintegrating tablets. The results of FT-IR and UV spectroscopy tests have confirmed the formation of inclusion complexes. Also, the results of efficiency and loading capacity determination have demonstrated that it is possible to develop inclusion complexes of PGB with BCD and HP-BCD, with moderate efficiency.

In conclusion, the PGB-BCD and PGB-HP-BCD (1:1 and 1:2) inclusion complexes exhibit improved physico chemical properties for pregabalin. The performed tests provide useful information in the preformulation studies of orally disintegrating tablets used in the treatment of hyperalgesia. Further research will be implemented for formulating the drug into ODTs, including performing palatability studies for demonstrating the benefits of the PGB-CD complexes.

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