Trop J Nat Prod Res, June 2021; 5(6):1138-1141

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Effects of Prosochit® Binder on the Dissolution and Permeation of a BCS Class IV Drug

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ARTICLE INFO

Article history:
Received 03 May 2021
Revised 06 June 2021
Accepted 24 June 2021
Published online 01 July 2021

ABSTRACT

Prosochit® (PC) is a novel excipient available in variants: Prosochit® 201, 101 and 102 having varying binding and performance-modifying properties. This study investigates the effects of the different types of Prosochit® on the dissolution and permeation of hydrochlorothiazide, a BCS class IV drug. Compatibility of Prosochit® with hydrochlorothiazide was investigated using Fourier Transform Infrared Spectroscopy (FTIR). Six batches of hydrochlorothiazide tablets were formulated by wet granulation; batches F1 to F3 containing 3% PC201, PC101 and PC102 respectively and batches F4 to F6 containing 6% PC201, PC101 and PC102 respectively. The release properties of the tablets and the intestinal permeability of the drug were studied in comparison with a marketed product. The FTIR spectra revealed no adverse interaction between Prosochit® and hydrochlorothiazide. The cumulative amount of drug released in 1 h was in the order: marketed product > F1 > F2 > F6 > F3 > F5 > F4. Even though the test tablets exhibited low dissolution rates, substantial amounts of the drug were eventually released after 1 h to enable adequate permeation of the drug. The test tablets were characterized by better permeation profiles compared to the marketed product; and batch F1 which contains 3% PC201 was characterized by a markedly high amount of drug permeated in 5 h. Of the Prosochit® types and concentrations investigated, 3% PC201 is the most suitable binder for optimizing the dissolution and permeation of hydrochlorothiazide.

Keywords: BCS class IV, Dissolution, Hydrochlorothiazide, Permeation, Prosochit®.

Introduction

A new excipient to be used as a binder may be designed to provide opportunities to address poor bioavailability obstacles of certain drugs when used for their formulation.[1] Prosochit® is a co-processed excipient of two biopolymers (prosopis gum and crab shell chitosan) developed by co-precipitation. Prosopis gum is a hemicellulose with xylose and galactose being the major sugar units while fructose and glucose are present in smaller quantities.[2] Chitosan has a heterogeneous chemical structure made up of 1-4 linked 2-acetamido-2-deoxy-*β*-D-glucopyranose and 2-amino-2-deoxy-*β*-D-glucopyranose.[3] Prosopis gum is a mucoadhesive polymer while chitosan at moderate concentration enhances dissolution and permeation.[4]

Prosochit® is presently available in three forms as Prosochit® 201 (PC201), Prosochit® 101 (PC101) and Prosochit® 102 (PC102). They are developed by utilizing prosopis gum and crab shell chitosan in the ratios 2:1, 1:1 and 1:2 respectively. The Fourier transform infrared spectra of the three types of Prosochit® are not significantly different because they are of the same components, the only difference being the proportions used.[4] A previous work involved the use of these excipients at concentrations equivalent to 2% w/w prosopis gum in tablet formulation of artemether which is a BCS class II drug having low solubility as the only biopharmaceutical challenge. The work showed that the three types of this new excipient, Prosochit® (compared with prosopis gum) offered better release of artemether, and PC102 gave the best result.[5]

Hydrochlorothiazide (HCTZ) is indicated for the treatment of hypertension and for oedema associated with congestive heart failure or hepatic cirrhosis.[6] It is also useful in the treatment of renal tubular acidosis, hypercalciuria and for preventing osteopenia and osteoporosis.[7] An oral dose of 12.5-100 mg of this drug is characterized by t_{max} of 1-5 h and bioavailability of 65-75%.[8] The drug has been categorized as BCS (Biopharmaceutics Classification System) class IV,[9] the category that is known for the worst biopharmaceutical challenge of low solubility - low permeability.[10] With hydrochlorothiazide having more biopharmaceutical challenges (of low solubility and low permeability) compared with artemether, more varied concentrations of these new excipients will be experimented. This present work is aimed at investigating the effects of Prosochit® binder on the dissolution and permeation of a BCS Class IV drug so as to determine the appropriate Prosochit® type and concentration that will deliver the drug most effectively.

Materials and Methods

Materials

The materials used include Prosochit® 201, 101 and 102 developed by co-processing as described in NG Patent 2016/00355.[4] Other materials used are: a marketed hydrochlorothiazide tablet formulation registered by the Nigeria's FDA (National Agency for Food and Drug Administration and Control), hydrochlorothiazide powder (Hopkins & Williams, England), lactose (BDH Chemicals, Poole, England), corn starch (BDH Chemicals, Poole, England), magnesium stearate (BDH Chemicals, Poole, England), talc (BDH Chemicals, Poole, England), hydrochloric acid (FSA Laboratories Supplies, England) and phosphate buffered saline (FSA Laboratories Supplies, England).

Fourier transform infrared (FTIR) spectroscopy

Samples (2 mg each) of Prosochit® 101, pure hydrochlorothiazide powder and a physical mixture of the two materials in ratio 1:1 were

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Citation: Olorunsola EO, Adedokun MO, Samuel OU, Joseph MG. Effects of Prosochit® Binder on the Dissolution and Permeation of A BCS Class IV Drug. Trop J Nat Prod Res. 2021; 5(6):1138-1141. doi.org/10.26538/tjnpr/v5i6.26

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

taken for FTIR spectroscopy. Each sample was prepared in a potassium bromide disk in a hydrostatic press at 6-8 tons pressure; and the FTIR spectrum was recorded at scanning range of 500-4000 cm^{-1} using a spectrophotometer (Cary 630 Model, Agilent Technologies Inc., United States).[11]

Preparation of granules by wet granulation

Six batches of hydrochlorothiazide granules were prepared using wet granulation method based on the formula in Table 1. The different types of Prosochit®: PC201, PC101 and PC102 were used separately at two binder concentrations of 3 and 6% w/w for the formulation of the hydrochlorothiazide granules. A 2.5 g quantity of hydrochlorothiazide powder, 2.5 g of corn starch, and the required amount of lactose were carefully weighed and transferred into a ceramic mortar. The powders were triturated to form a homogeneous mixture. The required amount of the binder was weighed and transferred into a 25 mL beaker containing 4 mL of distilled water. The binder was left for few minutes for hydration in order to form mucilage which was added to the powder mixture in the mortar, and then mixed together to form a damp mass. The mass was screened through a 2.0 mm mesh and dried in a hot air oven (Gallenkamp, Germany) at 60°C for 45 min. The dried granules were further screened through a 1.0 mm mesh.[5]

Preparation of tablets

The required amounts of magnesium stearate and talc were weighed and gently blended with the granules; and the mixture was compressed into tablets using a single punch tableting press fitted with 8.00 mm flat-faced punches (Cadmach Ahmedabad, India) at a constant compression force of 15 kN.[5]

Table 1: Formula of hydrochlorothiazide tablets

	Batches					
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Hydrochlorothiazide (%)	10	10	10	10	10	10
Corn starch (%)	10	10	10	10	10	10
Lactose (%)	75	75	75	72	72	72
PC201 (%)	3	-	-	6	-	-
PC101 (%)	-	3	-	-	6	-
PC102 (%)	-	-	3	-	-	6
Talc (%)	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate (%)	0.5	0.5	0.5	0.5	0.5	0.5

In vitro drug release study

Drug release study was carried out using the USP basket method. The dissolution was done at 100 rpm (revolutions per minute) using the RCZ-6C3 dissolution apparatus containing 900 mL of 0.1 N HCl at 37± 0.5°C. Aliquots (5 mL) were withdrawn at 10 minutes' intervals over a period of 1 h, and replaced with equivalent volume of the fresh dissolution medium maintained at the same temperature. The samples were filtered through a Whatman filter paper No. 2, and then assayed using a UV-spectrophotometer (UNICO-spectrophotometer, UV-2100 PC, Shanghai instrument Co., China) at a wavelength of 273 nm.[12] The cumulative percent drug released was calculated and then plotted against time for each formulation.

Ex vivo permeation study

Drug permeation study was done using the method described by Sharma *et al*.[13] A portion of *Sus domesticus* (pig) intestine purchased from a local slaughterhouse within 1 h of sacrificing the animal was cut into segments and used as donor compartment chamber.

One end of the intestine was tied and then filled with 5 mL of phosphate buffer (pH 6.8).

A tablet was introduced into the compartment and the intestine tied at the other end. The donor compartment was immersed into a dissolution apparatus containing 900 mL of the receptor medium of the phosphate buffer. Aliquots of 5 mL were withdrawn at 30 minutes' intervals from the dissolution medium with replacements using fresh medium. Sample withdrawal was done over a period of 5 h, and the samples were filtered using Whatman filter paper No. 2. The resulting solutions were analyzed using a UV-spectrophotometer (UNICO-spectrophotometer, UV-2100 PC, Shanghai instrument Co., China) at a wavelength of 273 nm. A graph of cumulative percent drug permeated was plotted against time for all the formulations.

Statistical analysis

Data were presented as mean ± standard deviation; and analyzed by applying one-way analysis of variance (ANOVA) followed by Turkey–Kramer multiple comparison test using GraphPad Instat-3 software. Significance of differences was set at *p-values* less than 0.05.

Results and Discussion

Compatibility of Prosochit® with hydrochlorothiazide

The FTIR spectra of hydrochlorothiazide powder and PC101 as well as the physical mixture of the two ingredients are shown in Figure 1a-c. Prosochit® 101 was used as a representative of the three types of Prosochit® for the compatibility studies being that their FTIR spectra are not significantly different. The three types of Prosochit® have the same chemical composition, the only difference being the proportion of the constituents.[4]

The FTIR spectrum of HCTZ (Figure 1a) showed unique peaks between 670.9 and 3,522.3 cm^{-1}. Strong signals were found at the fingerprint region of 650-1,400 cm^{-1}. The absorption peaks at about 670-900 cm^{-1} are indicative of C-H bending of aromatic ring. In the double bond region (1,500-2000 cm^{-1}), several peaks were also detected indicating the carbon-carbon double bond of the aromatic ring and the presence of sulfur-oxy compounds. The peaks detected about 1,700 cm^{-1} region indicated the presence of carbonyl double bond. In the triple bond region (2,100-2,500 cm^{-1}), no peak was detected informing no carbon-carbon triple bond. Also in the single bond area (2,500-4,000 cm^{-1}), several peaks were detected; the peaks between 3000 and 3500 cm^{-1} indicated the presence of aromatic bonds (C-H stretching) and primary amine stretching.[14] These observations are reflective of hydrochlorothiazide.

The FTIR spectrum of PC101 (Figure 1b) showed unique peaks between 704.5 and 3213.0 cm^{-1}. Strong signals were detected in the fingerprint region (650–1400 cm^{-1}) indicating C-H bending of aromatic ring. The peaks at 1,488 and 1,636 cm^{-1} are indicative of carbon-carbon double bond. No peak was detected in the triple bond region (2,000- 2500 cm^{-1}) indicating the absence of carbon-carbon triple bond. Some peaks were also observed at single bond region (2,500-3,400 cm^{-1}) indicating the presence of aromatic ring.[14]

The spectrum of the physical mixture had about 18 peaks. All the major peaks found in the spectrum of the physical mixture were detected in the individual components; the only difference was in the location and intensity of the peaks. There was no sign of formation of a new compound. Hence, Prosochit® is compatible with hydrochlorothiazide.

In vitro dissolution

The dissolution profiles of the tablets are illustrated in Figure 2. The drug release from the marketed product was very rapid, releasing about 44% of the drug in only 10 minutes; and 60% in 1 h, eclipsing all the formulated batches. The amount of drug released in 1 h is in the order marketed > F1 > F2 > F6 > F3 > F5 > F4. The dissolution study was carried out using 0.1N hydrochloric acid because drug dissolution is expected to take place in the gastric region. The low values of percent drug release obtained from this study are not unexpected because hydrochlorothiazide is a BCS class IV drug with characteristic low solubility.[10] Lower concentration of the novel excipient is better than the higher concentration in terms of drug release enhancement because the component polymers are also binding agents. Prosopis gum is characterized by high binding property;[15] hence, higher concentration will hinder drug release.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Chitosan, at low concentration, that is, below 10% is known to enable immediate drug release while higher concentrations brings about sustained release.[16] These two factors justify the trend of the release profile with 3% PC201 (F1) producing the best release followed by 3% PC101 (F2). In the descending order of dissolution rate, batches F1 and F2 are followed by batch F6 which contains 6% PC102. The amount of chitosan in that batch (F6) is well below 10% within which chitosan promotes immediate drug release. The variation of F3 in the trend of dissolution rate correlates with the insufficient amounts of the polymers to produce adequate drug release. Batch F4 which contains the highest amount of prosopis gum, a strong binder, had the slowest dissolution rate. The different release profiles observed with the different batches is as a result of the ability of different polymers used as binders to influence drug release at different extents.[1]

Ex vivo permeation

The permeation profiles of the tablets are shown in Figure 3. The cumulative percent drug permeated at time 5 h is in the order F1 > F3 > F2 > F4 > F5 > F6 > marketed product. All the test formulations exhibited higher amount of drug permeated compared with the marketed product; and formulations containing 3% Prosochit® exhibited higher amount of drug permeated compared to those containing 6% Prosochit®. Phosphate buffer (pH 6.8) was used for the permeation study because the drug absorption is expected to take place majorly in the intestine. The study was done to cover a period of 5 h because hydrochlorothiazide is characterized by t_{max} of 1-5 h.[8] Since the cumulative percent drug permeated at time 5 h was in the order F1 > F3 > F2 > F4 > F5 > F6 > marketed product, the ability of the excipients to increase drug permeation is 3% PC201 > 3% PC102 > 3% PC101 > 6% PC201 > 6% PC101 > 6% PC102. The batch containing 3% PC201 exhibited a markedly high amount of drug permeated in 5 h compared to every other batch. Even though the two components of Prosochit® are known to be useful as binders, both of them also promote drug permeation. Prosopis gum is a mucoadhesive polymer while chitosan is a permeation enhancer.[5,15] Prosochit® 201 at a concentration of 3% provided the best permeation enhancement as the binding effect of the two components at that concentration is minimal while they are still able to enhance drug permeation. The cumulative percents drug permeated for the batches at 5 h are generally higher than the cumulative percents drug released at 1 h. The implication of this statement is that even though the tablets exhibited low dissolution rates, substantial amounts of the drug are eventually released after 1 h to enable adequate permeation of the drug.

In contrast to the previous work of Olorunsola *et al*. which showed that PC102 (containing higher proportion of chitosan) brought forth the best release of artemether,[5] this work has shown that PC201 (containing higher proportion of prosopis gum) brought forth the best enhancement of dissolution and permeation of hydrochlorothiazide. This can be ascribed to the fact that artemether, a BCS class II drug only has solubility challenge while hydrochlorothiazide a BCS class IV drug is characterized by low solubility and low permeability. The good delivery properties of Prosochit® is the combined bioadhesive effect of prosopis gum and the dissolution-enhancing and permeation-enhancing effects of chitosan. Co-processing provides a synergy of functionalities and masking the undesirable properties of individual excipients. These phenomena have been illustrated in many instances such as improved tablet performance,[17] development of directly compressible excipients,[18] development of directly compressible excipient for sustained-release formulation,[19] development of directly compressible excipient for formulation of dispersible tablets,[20] and formulation of oral fast dissolving tablets.[21] Co-processing has been so effective in optimizing drug delivery in some instances that it has been described as an alternative to development of novel chemical entities.[22]

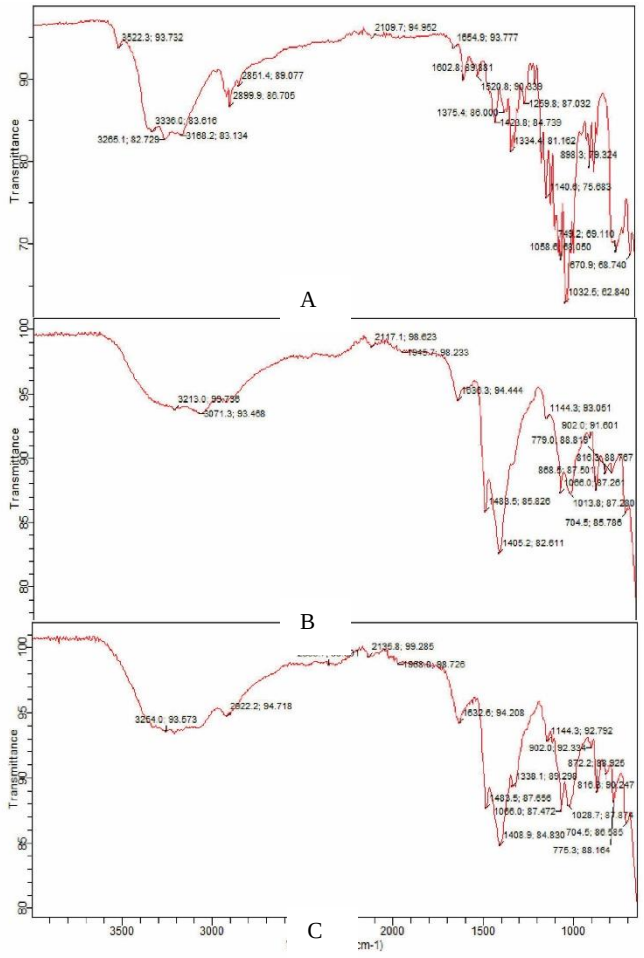

Figure 1: FTIR spectra of (a) hydrochlorothiazide powder, (b) PC101, (c) hydrochlorothiazide + PC101

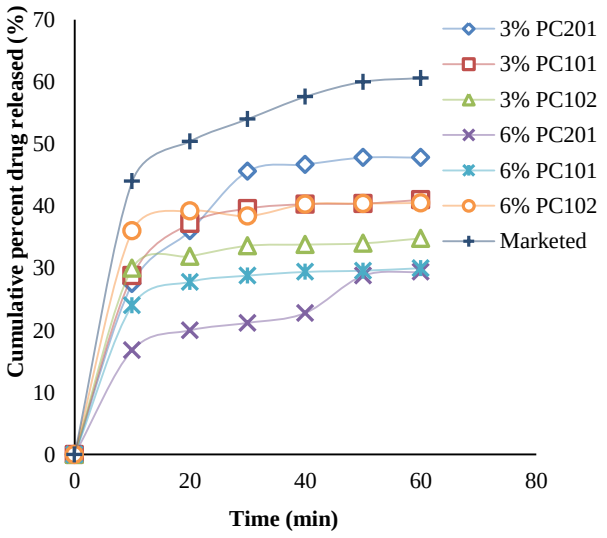

Figure 2: Dissolution profile of the formulations

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

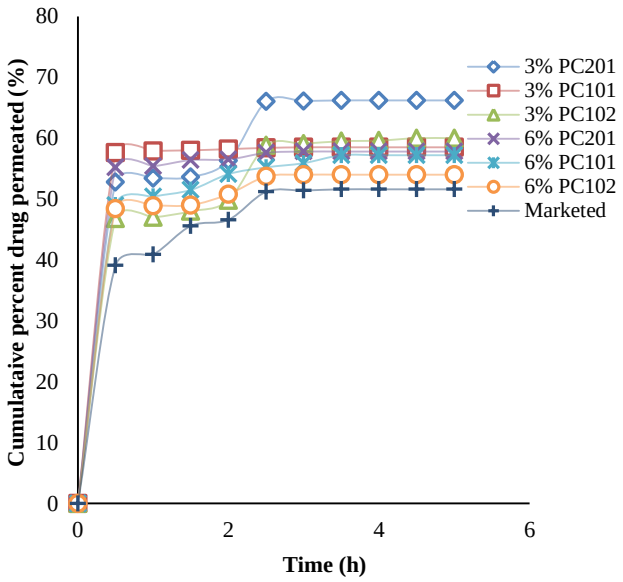

Figure 3: Permeation profile of the formulations

Conclusion

Prosochit® is compatible with hydrochlorothiazide and may be used as a binder in its tablet formulation without adverse interactions. Its effect on the delivery of hydrochlorothiazide is more pronounced on permeation than dissolution. Of the Prosochit® type/concentration investigated, 3% PC201 has the most pronounced effect on improving the dissolution and permeation of hydrochlorothiazide, a BCS class IV drug.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

This work was supported by the Nigerian Tertiary Education Trust Fund through the 2019 National Research Grant (Reference number TETFund/DR&D/CE/NRF/STI/37/VOL1).

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