

# POLYELECTROLYTE COMPLEXES OF CHITOSAN FOR PRODUCTION OF SUSTAINED RELEASE TABLETS OF BUPROPION HCL

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## Abstract

Chitosan (C) has the ability to form hydrogel by polyelectrolyte complexation. Electrostatic attraction among amine group of chitosan and anion groups of other polyelectrolytes leads to formation of polyelectrolyte complex. The objective of this study was preparation of Bupropion sustained release tablets by chitosan polyelectrolyte complexes with natural and synthetic polymers such as Eudragite L100 (E), xanthan (X) and carbopol 934 (CP).

The formation of polyelectrolyte complex between chitosan and aforementioned polymers was confirmed by FT-IR. Then 100 mg bupropion sustained release tablets were prepared by direct compression method at different ratios of each chitosan/polyelectrolyte complex. The ratio of (C) to (X) in polyelectrolyte complex was 1:1, 1:2, 1:4, 3:4. The ratio of (C) to (CP) 934 was 1:1, 1:2 and the ratio of (C) to (E) was 3:4, 1:2, 1:4. Physical properties of tablets like: content uniformity, weight variation, hardness, friability, and dissolution test in 3 mediums (water, HCl 0.1 N and saline buffer phosphate solution pH 7.4) were evaluated. Drug release from physical mixture with the same ratio of polymers in the complexes was compared with the polyelectrolyte complexes. Mean dissolution time (MDT) of  $P C_1 X_1$  was significantly greater than other formulations of C:X series. Among C:CP and their pure polymers,  $P C_1 CP_1$  showed the greatest MDT in water and acidic medium and among the complexes of C:E, and these pure polymers,  $P C_1 E_4$  in acidic medium showed slower drug release compared with other formulations in this series. These formulations released bupropion by a Higuchi kinetic model and showed greater MDT compared to their pure polymers or their physical mixtures in the same ratios.

## Rezumat

Chitosanul (C) are capacitatea de a forma un hidrogel prin complexare polielectrolitică. Atracția electrostatică între gruparea amino a chitosanului și grupările anionice ale altor polielectroliti conduce la formarea de complecși polielectrolitici. Obiectivul acestui studiu a fost prepararea de comprimate cu eliberare prelungită cu Bupropion folosind complecși polielectrolitici ai chitosanului cu polimeri naturali și sintetici, cum ar fi Eudragite L100 (E), xantan (X) și carbopol 934 (CP).

Formarea de complecși polielectrolitici între chitosan și polimerii menționați mai sus a fost confirmată prin spectroscopie FT-IR. Au fost preparate comprimate cu eliberare susținută de 100 mg bupropion prin metoda comprimării directe de complex chitosan / polielectrolit în diferite rapoarte. Rapoartele dintre (C) și (X) în complexul polielectrolitic au fost de: 1:1, 1:2, 1:4, 3:4. Raportul dintre (C) și (CP) 934 a fost de: 1:1, 1:2, iar rapoartele dintre (C) și (E) au fost de: 3:4, 1:2, 1:4. Au fost evaluate proprietățile fizice ale comprimatelor precum: uniformitatea conținutului, variația de greutate, duritatea, friabilitatea și testul de dizolvare în 3 medii (apă, HCl 0,1N și soluție salină tampon fosfat de pH 7,4). Eliberarea substanței active din amestecurile fizice cu același raport de polimeri în complecși a fost comparată cu cea eliberată din complecși polielectrolitici. Timpul mediu de dizolvare (MDT) din  $P C_1 X_1$  a fost semnificativ mai mare decât din alte formulări din seria C:X. Între C:CP și polimerii lor puri,  $P C_1 CP_1$  a prezentat cea mai mare MDT în apă și în mediu acid iar între complecșii de tipul C:E, și polimerii puri,  $P C_1 E_4$  a prezentat o eliberare mai lentă de substanță activă în mediu acid, comparativ cu alte formulări din această serie. Eliberarea bupropionei din aceste formulări a urmat o cinetică de tip Higuchi și a arătat o mai mare MDT a compușilor complexați polielectrolitic comparativ cu polimerii puri sau amestecurile lor fizice în aceleași raporturi.

**Keywords:** Chitosan, polyelectrolyte complex, bupropion HCl, Eudragite L100, xanthan, Carbopol 934

## Introduction

Chitosan is the deacetylated derivative of chitin, with different degrees of deacetylation (70-95 %) and molecular weights (10-1000 kDa). It is composed of  $\beta$ -1,4-linked glucosamine (deacetylated units) and *N*-acetyl-d-glucosamine (acetylated units) [1, 2]. Chitosan has been used in pharmaceutical formulations as a release-controlling agent with limited capacity due to its

fast dissolution in the stomach. Therefore, its chemical modifications such as co-polymerization or derivatization have been applied. Physical modification of this polymer including complex formation by non-covalent strategies like electrostatic, hydrophobic and/or hydrogen bonding forces between the polymeric chains are approaches with less toxicological profiles [3-5].

Amino groups on the C2 position of glucopyranose units of chitosan can interact electrostatically with the anionic groups and produce polyelectrolyte complexes. Polyelectrolyte complexes of chitosan reported so far by using the natural polyanions include pectin, alginate, carrageenan, xanthan gum, carboxymethyl cellulose, chondroitin sulphate, dextran sulphate, hyaluronic acid. Synthetic polyanions investigated for complex formation with chitosan are poly (acrylic acid), polyphosphoric acid, poly (L-lactide) [6]. Polygalacturonic acid [7], sodium dextran sulfate [8], carboxymethyl cashew gum [9], fibroin [10], sodium carboxymethyl cellulose [11], "angico" gum [12], gum kondagogu, gelatine, poly- $\gamma$ -glutamic acid and maleic starch half-ester are also reported among the polyelectrolyte complex forming agents with chitosan.

Chitosan-alginate or chitosan-carrageenan have been reported as prolonging drug release systems for diltiazem chlorhydrate [13]. Controlled release matrix tablets of diltiazem and ibuprofen have been prepared by a three-dimensional network inter polyelectrolyte complex between chitosan and polycarbophil [14]. Chitosan/pectin complexes with pH-sensitive swelling ability have been used for colon-specific localization of vancomycin [15]. Cross-linked chitosan complexed with chondroitin sulphate is another polyelectrolyte complex reported for preparing colonic matrix tablets [16]. Bupropion hydrochloride is an antidepressant of the aminoketone class, chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitors, or other known antidepressant agents. Its structure is designated as  $(\pm)$ -1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. Its molecular weight is 276.2 with the molecular formula  $C_{13}H_{18}ClNO$  HCl. It is a white, crystalline powder, highly soluble in water [17-19].

Wellbutrin<sup>®</sup> SR is supplied for oral administration as 100, 150 and 200 mg, film-coated, sustained-release tablets. Each tablet contains the labelled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

The mean elimination half-life of bupropion hydrochloride after chronic administration is  $21 \pm 9$  hours, and its steady-state plasma concentration is reached within 8 days. Following oral administration of Wellbutrin<sup>®</sup> SR to healthy volunteers, peak plasma concentrations are achieved within 3 hours [20]. Bupropion is 84 % bound to human plasma proteins at concentrations up to 200  $\mu\text{g/mL}$ . It is extensively metabolized in humans and has three active metabolites. The

fraction of the oral dose of bupropion excreted unchanged in the urine is only 0.5 % [21].

The Food and Drug Administration (FDA) mandated the dissolution specifications for Wellbutrin<sup>®</sup> SR to be 25–45 % released at the first hour, 60–85 % released at 4 h and not less than 80 % after 8 h [22].

In general, bupropion hydrochloride is very unstable when diluted with excipients. Cysteine hydrochloride stabilizes bupropion hydrochloride in the sustained release (SR) tablet formulations by providing an acidic environment, stabilizing the protonated amine. Therefore, any reformulation must not create instability in bupropion hydrochloride. Hypromellose is another excipient that is reported to cause some instability in Wellbutrin<sup>®</sup> SR tablets [22]. The aim of the present study was the obtaining of bupropion hydrochloride SR tablets using polyelectrolyte complexes as natural, abundant and novel excipients for retarding drug release and studies the drug stability in the new SR tablet formulation of bupropion HCl. In this regards polyelectrolyte complexes of chitosan with xanthan, carbomer and Eudragit L100 were used for obtaining the SR matrix tablets of this drug. As far as our information allows this technique has not been used for production of bupropion SR tablets yet.

## Materials and Methods

### Materials

Bupropion HCl (Dipharma, Italy), chitosan (Fluka, Switzerland), Eudragit L100 (RhomPharma, Germany), Carbapol P934 (BFGoodrich, US), xanthan gum (Arthur Bran well, England), Avicel PH 101 (FMC, US), magnesium stearate,  $\text{KH}_2\text{PO}_4$ ,  $\text{Na}_2\text{HPO}_4$  and acetone were all from Merck, Chemical Company (Germany).

### *Production of polyelectrolyte complex of chitosan and xanthan*

All complexes of chitosan with xanthan, carbomer and Eudragit were prepared in different ratios chosen by the preliminary studies. 100 mL of 0.4 % aqueous solution of xanthan gum was mixed with 100, 75, 50, and 25 mL of 0.4 % solution of chitosan in 0.1 M HCl to give different complexes of C:X with ratios of 1:1, 3:4, 1:2 and 1:4. The mixtures were incubated at 37°C for 24 h and then centrifuged for 15 min at 15000 rpm. After drying for 24 h at room temperature they were triturated in a mortar.

### *Production of polyelectrolyte complex of chitosan and carbomer*

100 mL of 0.4 % aqueous solution of carbomer was mixed with 100 and 50 mL of 0.4 % solution of chitosan in 0.1 M HCl to give different complexes of C:CP with ratios of 1:1 and 1:2. The mixtures

were incubated at 37°C for 24 h and then centrifuged for 15 min at 15000 rpm. After drying for 24 h at room temperature they were triturated in a mortar.

*Production of polyelectrolyte complex of chitosan and Eudragit L100*

100 mL of solution of 1 % Eudragit L100 in acetone was mixed with 75, 50 and 25 mL of 1 % solution of chitosan in 0.1 M HCl to give different complexes of C:E with ratios of 3:4, 1:2 and 1:4. The mixtures were incubated at 37°C for 24 h and then centrifuged for 15 min at 15000 rpm. After drying for 24 h at room temperature they were triturated in a mortar.

*FTIR studies on pure polymers and polyelectrolyte complexes*

Transparent films of KBr disks were prepared with 1:100 ratio of each polymer and the polyelectrolyte complexes to confirm the obtaining of complexes by FTIR (WQF-SLOFTIR, China).

*Production of sustained release tablets of bupropion HCl tablets*

100 mg of each polyelectrolyte complex (including: chitosan, carbopol, xanthan gum or Eudragit and their mixtures) were mixed with 100 mg of bupropion HCl, 2 mg of magnesium stearate and 48 mg of Avicel PH101. The mixture was compressed in a rotary tabletting machine (Kilian Co, GMBH, Koln-Neihs, Type: KS43373-202, Germany). For comparison other tablets with physical mixtures of chitosan with each of the polymers with the same composition were prepared to study the effect of polyelectrolyte complexes on the drug release. Table I shows the formulation of the tablets. The 2 alphabetic digits in formulation codes indicate the type of polymers and the 2 numbers are the ratio of polymers in the polyelectrolyte complex (*P*) or physical mixtures (*M*). The tablets were evaluated for content uniformity, weight variation, hardness, friability, and disintegration time according to the USP 29 requirements [23].

**Table I**

Composition of different tablets of Bupropion HCl prepared by polyelectrolyte complexes (*P*) of chitosan (*C*) with xanthan (*X*), Carbopol (*CP*) and Eudragit L100 (*E*) or their physical mixtures (*M*)

| Formulation code                 | Bupropion HCl | Chitosan | Xanthan gum | Carbopol P934 | Eudragit L100 | Magnesium stearate | Avicel PH101 |
|----------------------------------|---------------|----------|-------------|---------------|---------------|--------------------|--------------|
| C                                | 100           | 100      |             |               |               | 2                  | 48           |
| P C <sub>1</sub> X <sub>1</sub>  | 100           | 50       | 50          |               |               | 2                  | 48           |
| P C <sub>3</sub> X <sub>4</sub>  | 100           | 42.9     | 57.1        |               |               | 2                  | 48           |
| P C <sub>1</sub> X <sub>2</sub>  | 100           | 33.3     | 66.7        |               |               | 2                  | 48           |
| P C <sub>1</sub> X <sub>4</sub>  | 100           | 20       | 80          |               |               | 2                  | 48           |
| X                                | 100           |          | 100         |               |               | 2                  | 48           |
| P C <sub>1</sub> CP <sub>1</sub> | 100           | 50       |             | 50            |               | 2                  | 48           |
| P C <sub>1</sub> CP <sub>2</sub> | 100           | 33.3     |             | 66.7          |               | 2                  | 48           |
| CP                               | 100           |          |             | 100           |               | 2                  | 48           |
| P C <sub>3</sub> E <sub>4</sub>  | 100           | 42.9     |             |               | 57.1          | 2                  | 48           |
| P C <sub>1</sub> E <sub>2</sub>  | 100           | 33.3     |             |               | 66.7          | 2                  | 48           |
| P C <sub>1</sub> E <sub>4</sub>  | 100           | 20       |             |               | 80            | 2                  | 48           |
| E                                | 100           |          |             |               | 100           | 2                  | 48           |
| M C <sub>1</sub> X <sub>1</sub>  | 100           | 50       | 50          |               |               | 2                  | 48           |
| M C <sub>1</sub> CP <sub>1</sub> | 100           | 50       |             | 50            |               | 2                  | 48           |
| M C <sub>1</sub> E <sub>4</sub>  | 100           | 20       |             |               | 80            | 2                  | 48           |

*Content uniformity test of the tablets*

Each tablet was added to an appropriate amount of water to prepare the concentration of 0.33 mg/mL. The obtained mixture was promptly homogenized (Silverson, L9R, England) at 5000, 10000 and 15000 rpm each time for 30 sec. Then the homogenization step was repeated for another two times with 2000 rpm and 5000 rpm for 30 seconds. The homogenate was filtered through a 0.45 µm filter and 4 mL of the solution was diluted 10 times with water. The absorbance of the solution was measured spectrophotometrically (Shimadzu, UV-mini1240, Japan) at  $\lambda_{\text{max}}=255$  nm. According to US Pharmacopoeia from the 10 tested tablets none of them should have the expected drug out of the range of 90-110 % [23].

*Dissolution test of tablets*

Tablet dissolution behaviour was studied using paddle method according to USP 29 [23] in 900 mL of phosphate buffer saline (pH 7.4), water or HCl 0.1 N (pH 1.2) at 37±0.5°C with 50 rpm in a dissolution tester (Pharmatest PTWS3, Germany). Sampling was carried out at 0.5, 1, 1.5, 3, 4, 5, 6, 7 and 8 hr. Each time 2 mL of the medium was withdrawn and replaced with 2 mL of fresh medium. The samples were measured spectrophotometrically at 252.5 nm (for phosphate buffer saline), 255 nm (for water) and 253.7 nm (for HCl 0.1 N), respectively. According to the USP 29 sustained release tablets of bupropion should release 25-45 % of the drug after 1 h, 60-85 % after 5 h and not less than 80 % after 8 h in water medium.

**Dissolution efficacy (DE %)**

Dissolution efficacy is defined as the area under the dissolution curve at the specific time divided by the total area under the curve (which represents the total dissolution at that time) [24]. For a tablet dosage form, this parameter is calculated by the following equation:

$$DE_t \% = \frac{\int_0^t y dt}{y_{100} t} \times 100 \quad (1),$$

where  $y$  is the percent of drug released as a function of time,  $t$  is the total time of drug release and  $y_{100}$  is 100 % of drug release.

**Mean dissolution time (MDT)**

MDT [25] is calculated from the amount of drug released to the total cumulative drug, measure of the release process. The lower the MDT is, the faster the release rate:

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \quad (2),$$

where  $i$  is the release sample number,  $n$  is the number of release sample time,  $t_{mid}$  is the time of the midpoint between  $i$  and  $i-1$  and  $\Delta M$  is the additional amount of drug released between  $i$  and  $i-1$ .

**Drug release mechanism studies**

Peppas equation  $M_t / M_\infty = Kt^n$  was also used to determine drug release mechanism from tablets. In this equation  $M_t / M_\infty$  is the fraction of drug released in a certain time,  $K$  is the drug release rate constant and  $n$  is the diffusion exponent. The diffusion mechanism was determined according to Table II [26].

**Table II**  
Determination of the diffusion mechanism according to diffusion exponent ( $n$ ) in Peppas equation  $M_t / M_\infty = Kt^n$

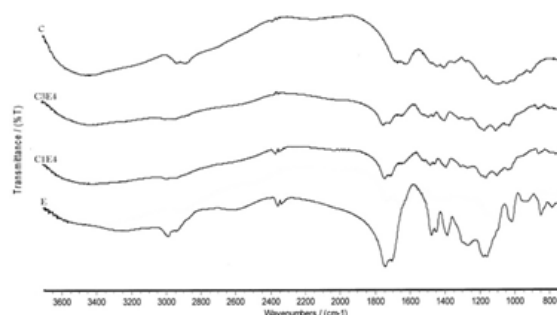
| $n$               | Diffusion mechanism     |
|-------------------|-------------------------|
| $< 0.45$          | Fickian                 |
| $0.45 < n < 0.85$ | Anomalous               |
| $n = 0.89$        | Case II transport       |
| $n > 0.89$        | Super Case II transport |

**Stability studies**

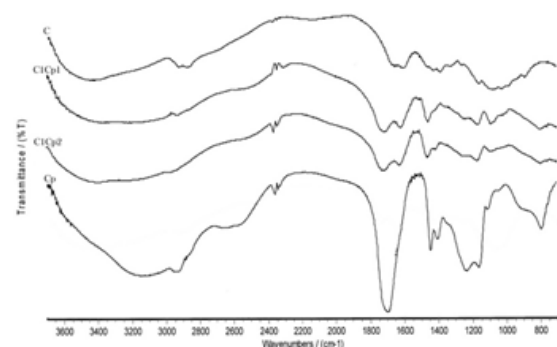
Optimized formulations of bupropion tablets were subjected to accelerated stability studies to assess their stability with respect to physical appearance, drug content and drug release characteristics after storing them under stress conditions of 40°C / 75 % RH for 3 months in sealed glass vials.

**Results and Discussion****FT-IR spectrum of polyelectrolyte complexes**

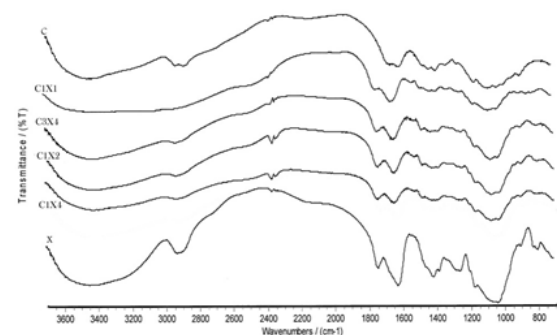
To evaluate the accuracy and confirm the production of polyelectrolyte complexes, FT-IR spectra were studied for pure polymers and polyelectrolyte complexes (Figures 1, 2 and 3).

**Figure 1.**

FT-IR spectra for pure chitosan (C), pure Eudragit L100 (E) and the complexes of  $C_1E_4$  and  $C_3E_4$

**Figure 2.**

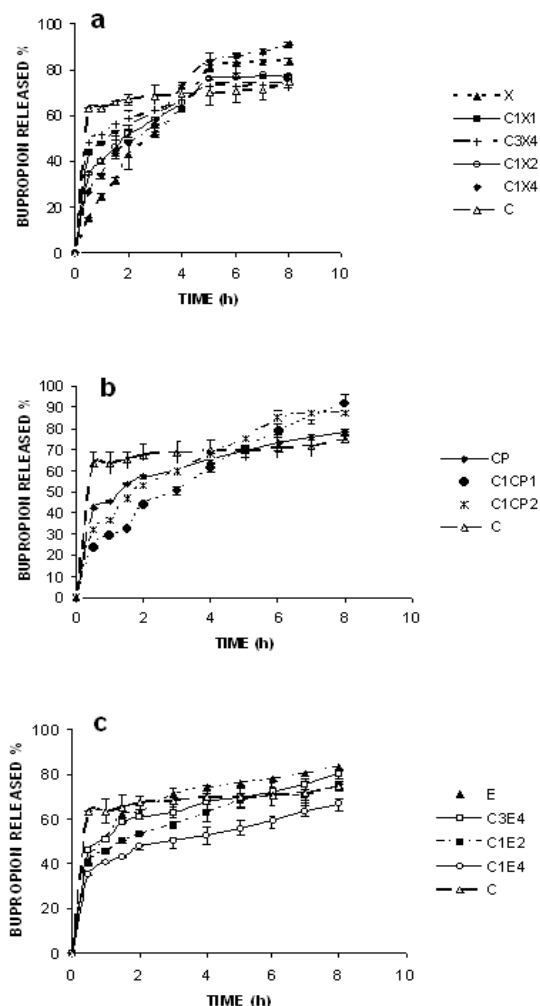
FT-IR spectra of pure chitosan (C), pure carbomer (CP) and the complexes of  $C_1CP_1$  and  $C_1CP_2$

**Figure 3.**

FT-IR spectra of pure chitosan (C), pure xanthan (X) and the complexes of  $C_1X_2$  and  $C_3X_4$

Chitosan is a linear amino polysaccharide composed of  $\beta$ -D-glucosamine units which are linked through  $\beta$ -glycoside connections [24]. In media containing water and acid, chitosan will gain positive charge due to the protonation of its amino group. Therefore, addition of a negatively charged molecule would lead to precipitation [27] that shows the formation of polyelectrolyte complex.

According to Figures 1-3, comparison of the FTIR spectra of Eudragit L100 carbomer and xanthan gum with the spectra of pure chitosan and their complex demonstrates ionic interaction between carboxylic groups at  $1700\text{ cm}^{-1}$  for Eudragit L100 and carbomer and at  $1620\text{ cm}^{-1}$  the anionic carboxylate of xanthan gum with primary amine groups of chitosan which its N-H bending vibration is observed in the region of  $1650\text{--}1580\text{ cm}^{-1}$  in the pure chitosan. In the complexes these functional peaks are attenuated. Absorption bands at  $1650\text{ cm}^{-1}$  (for chitosan) and  $1700\text{ cm}^{-1}$  (for polyanions) may be used to monitor the complex formation, on taking into account that they are characteristic for these polymers. The FT-IR spectrum of the complex evidenced that the band at  $1650\text{ cm}^{-1}$  shifted to  $1700\text{ cm}^{-1}$ , while the characteristic band for polyanions remained unchanged, which clearly indicates the presence of both polymers in the composition of the final polyelectrolyte [28].



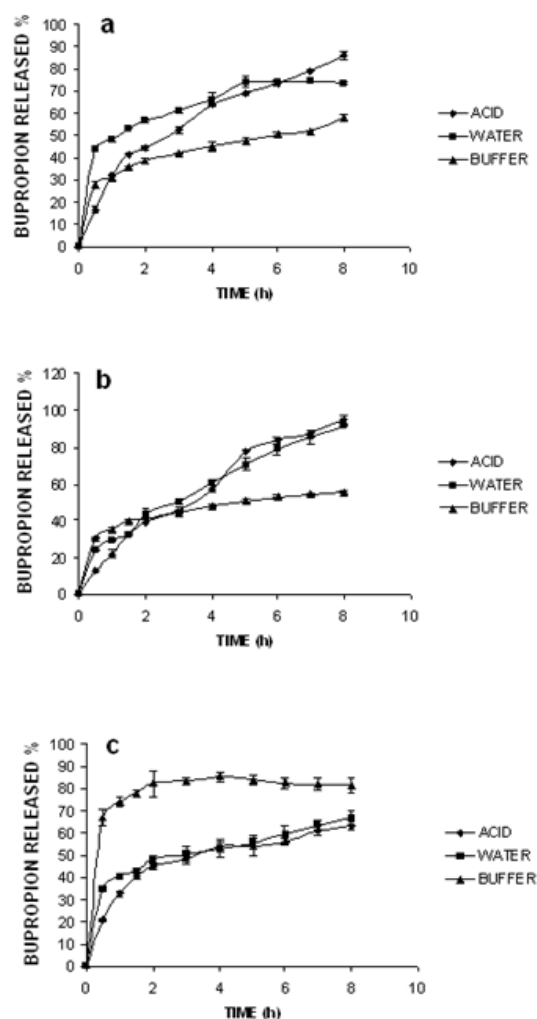
**Figure 4.**

The percentage of bupropion hydrochloride released from sustained release tablets containing a) chitosan/xanthan, b) chitosan/carbomer, c) chitosan/Eudragit L100 polyelectrolyte complexes in water (n=3)

#### *Physicochemical properties of tablets*

All the tablets were acceptable in the content uniformity and none of the ten tested tablets were out of the 90-110 % limitation. According to USP standards the weight variation of  $\pm 7.5\%$  is acceptable and none of the tablets were out of this limitation. The hardness of all tablets was in the acceptable range of 40-80 N and their friability was less than 1 % which demonstrates adequate hardness and compressibility.

Based on the aforementioned results the formulations of polyelectrolyte complexes and drug had acceptable flow and compressibility and therefore, direct compression is a suitable method of preparation for these tablets.

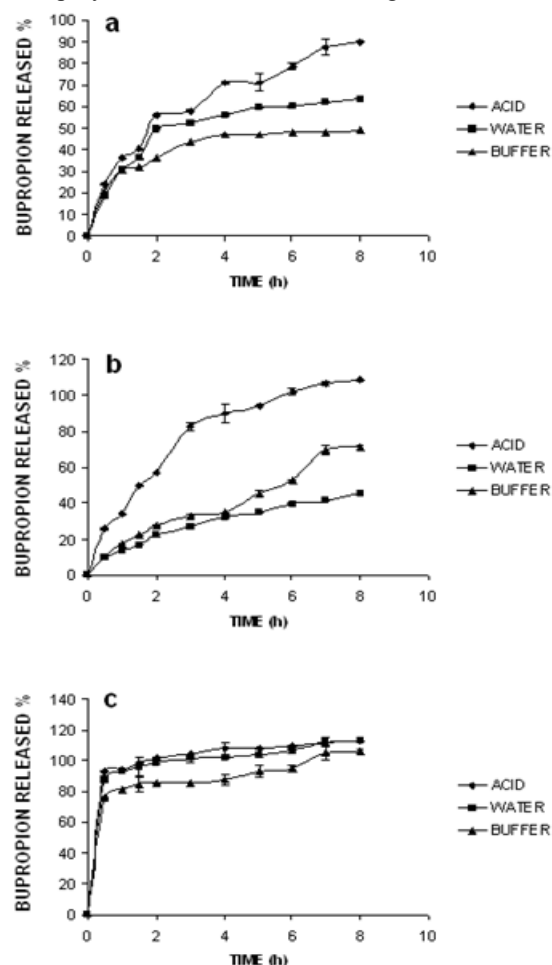


**Figure 5.**

Comparison between the percentage of bupropion hydrochloride released from sustained release tablets containing polyelectrolyte complex of a) chitosan: xanthan (1:1), b) chitosan: carbomer (1:1), c) chitosan: Eudragit L100 (1:4) in three mediums, water, HCl 0.1 N and phosphate buffer saline (pH=7.4) (n=3)

### Bupropion hydrochloride release profiles from different tablets

The release tests performed according to USP29 [23] for tablets with different ratios of different chitosan polyelectrolyte complexes are shown in Figure 4. While Figure 5 compares drug release from sustained release tablets of different complexes in three different media, water, HCl 0.1 N and phosphate buffer saline (pH 7.4) to see if the drug release is pH dependent or not. The obtained results presented in Figure 5 are compared with the drug release profile from physical mixtures of the same polymers and same ratios in Figure 6.



**Figure 6.**

Comparison between the percentage of bupropion hydrochloride released from sustained release tablets containing physical mixture of a) chitosan: xanthan (1:1), b) chitosan: carbomer (1:1) and c) chitosan: Eudragit L100 (1:4) in three mediums, water, HCl 0.1 N and phosphate buffer saline (pH 7.4) (n=3)

To compare the dissolution data, dissolution efficiency (DE) until 8 hr of dissolution test and MDT were used as independent parameters to drug release kinetic model. The results are shown in Table III.

**Table III**

The values of dissolution efficiency (DE<sub>8</sub> %) and mean dissolution time (MDT) of bupropion HCl release in water from different tablet formulations (n=3)

| Formulation code                 | DE <sub>8</sub> % ± SD | MDT (h) ± SD |
|----------------------------------|------------------------|--------------|
| C                                | 66.8 ± 3.8             | 0.83 ± 0.61  |
| P C <sub>1</sub> X <sub>1</sub>  | 62.6 ± 1.3             | 1.26 ± 0.31  |
| P C <sub>3</sub> X <sub>4</sub>  | 63.2 ± 2.0             | 1.12 ± 0.06  |
| P C <sub>1</sub> X <sub>2</sub>  | 61.4 ± 0.8             | 1.63 ± 0.09  |
| P C <sub>1</sub> X <sub>4</sub>  | 54.8 ± 0.7             | 2.63 ± 0.02  |
| X                                | 43.6 ± 0.8             | 2.64 ± 0.17  |
| P C <sub>1</sub> CP <sub>1</sub> | 58.5 ± 0.2             | 2.83 ± 0.01  |
| P C <sub>1</sub> CP <sub>2</sub> | 64.6 ± 2.1             | 2.22 ± 0.17  |
| CP                               | 62.1 ± 1.4             | 1.63 ± 0.07  |
| P C <sub>3</sub> E <sub>4</sub>  | 64.0 ± 2.1             | 1.61 ± 0.11  |
| P C <sub>1</sub> E <sub>2</sub>  | 58.8 ± 1.2             | 1.69 ± 0.09  |
| P C <sub>1</sub> E <sub>4</sub>  | 51.0 ± 2.1             | 2.17 ± 0.33  |
| E                                | 67.8 ± 2.3             | 1.47 ± 0.33  |
| M C <sub>1</sub> X <sub>1</sub>  | 50.1 ± 0.3             | 1.68 ± 0.15  |
| M C <sub>1</sub> CP <sub>1</sub> | 29.4 ± 0.1             | 2.86 ± 0.20  |
| M C <sub>1</sub> E <sub>4</sub>  | 99.1 ± 1.6             | 0.94 ± 0.02  |

The values of diffusion exponent of Peppas equation and the correlation coefficient of release data of bupropion hydrochloride tablets in water were used to determine the drug release mechanism from tablets. The results are seen in Table IV.

**Table IV**

The values of the diffusion coefficient (exponent of *n* in Peppas equation) and the regression coefficient (*r*<sup>2</sup>) of bupropion HCl release data from different tablet formulations in water fitted to the Peppas equation (n=3)

| Formulation                      | <i>r</i> <sup>2</sup> ± SD | <i>n</i> ± SD |
|----------------------------------|----------------------------|---------------|
| C                                | 0.8147 ± 0.0851            | 0.056 ± 0.025 |
| P C <sub>1</sub> X <sub>1</sub>  | 0.9569 ± 0.0161            | 0.212 ± 0.009 |
| P C <sub>3</sub> X <sub>4</sub>  | 0.9573 ± 0.0223            | 0.170 ± 0.015 |
| P C <sub>1</sub> X <sub>2</sub>  | 0.9701 ± 0.0133            | 0.324 ± 0.006 |
| P C <sub>1</sub> X <sub>4</sub>  | 0.9668 ± 0.0041            | 0.379 ± 0.011 |
| X                                | 0.9523 ± 0.0134            | 0.023 ± 0.489 |
| P C <sub>1</sub> CP <sub>1</sub> | 0.9772 ± 0.0025            | 0.515 ± 0.012 |
| P C <sub>1</sub> CP <sub>2</sub> | 0.9842 ± 0.0011            | 0.396 ± 0.026 |
| CP                               | 0.9784 ± 0.0091            | 0.230 ± 0.009 |
| P C <sub>3</sub> E <sub>4</sub>  | 0.9706 ± 0.0167            | 0.191 ± 0.014 |
| P C <sub>1</sub> E <sub>2</sub>  | 0.9583 ± 0.0115            | 0.025 ± 0.230 |
| P C <sub>1</sub> E <sub>4</sub>  | 0.9103 ± 0.0966            | 0.216 ± 0.020 |
| E                                | 0.9314 ± 0.0203            | 0.241 ± 0.005 |
| M C <sub>1</sub> X <sub>1</sub>  | 0.9143 ± 0.0069            | 0.421 ± 0.010 |
| M C <sub>1</sub> CP <sub>1</sub> | 0.9950 ± 0.0000            | 0.569 ± 0.017 |
| M C <sub>1</sub> E <sub>1</sub>  | 0.8141 ± 0.1410            | 0.079 ± 0.010 |

The release profiles of bupropion HCl from tablets in three different media were performed to see the pH dependency of drug dissolution in the designed tablets. The P C<sub>1</sub>X<sub>4</sub> containing polyelectrolyte complex of chitosan: xanthan (1:4) released more than 80 % of its drug content within 8 h which is acceptable based on standard values in USP [23], while the formulation of X containing pure xanthan

released only 65 % of its drug content within 8 h (Figure 5a).

According to Table III the maximum value of MDT is related to  $P C_1X_4$  which is significantly ( $p < 0.05$ ) higher than other formulations containing chitosan and xanthan or pure chitosan. Moreover,  $DE_8$  % for  $P C_1X_4$  is significantly lower than other formulations containing pure chitosan, pure xanthan and their complex. Conclusively, reduction of the chitosan ratio in the complexes, results in increasing the MDT and reduction of the  $DE_8$  %.

In acidic medium formulations of X and  $P C_1X_4$  demonstrated maximum and minimum dissolution and in the medium containing phosphate buffer saline the results were the same as in water medium (Figure 5a). Among the pure carbomer, pure chitosan and their complexes, the  $P C_1CP_1$  (the formulation containing polyelectrolyte complex of chitosan:carbomer (1:1) and C had the maximum and the minimum dissolution rate, respectively (Figure 5b). 90 % of the drug is released within 8 hours. According to MDT and  $DE_8$  % values, the formulation  $P C_1CP_1$  demonstrated the best release profile acceptable based on USP standards (Table III). The results obtained in acidic medium were similar to water however, in medium containing phosphate buffer saline,  $P C_1CP_1$  and CP had the maximum and minimum dissolution rate, respectively (Figure 5b). Among the pure Eudragit L100, pure chitosan and their complexes, the  $P C_1E_4$  i.e., the formulation containing polyelectrolyte complex of chitosan:Eudragit L100 (1:4) and E had the maximum and the minimum dissolution rate, respectively (Figure 5c). The MDT and  $DE_8$  % values of the  $P C_1E_4$  formulation are significantly higher and lower than formulations containing pure chitosan and pure Eudragit L100, respectively (Table III).

The results of acidic medium were similar to water medium. The release was not acceptable in the medium containing phosphate buffer saline since, except for the formulation containing pure chitosan; other formulations released more than 60 % of their drug content within 1 hour which is not according to USP standards [23].

The mechanism of drug release from the formulations containing pure chitosan, pure xanthan, their complexes and their physical mixtures in different media was studied by the Peppas equation shown in Table IV. The diffusion exponent ( $n$ ) shows that in water medium all the tablets follow Higuchi kinetic model and have non-Fickian diffusion except pure chitosan which shows Fickian diffusion. In acidic medium all formulations show Higuchi kinetic and non-Fickian diffusion and in the phosphate buffer saline medium the Higuchi kinetics model and Fickian

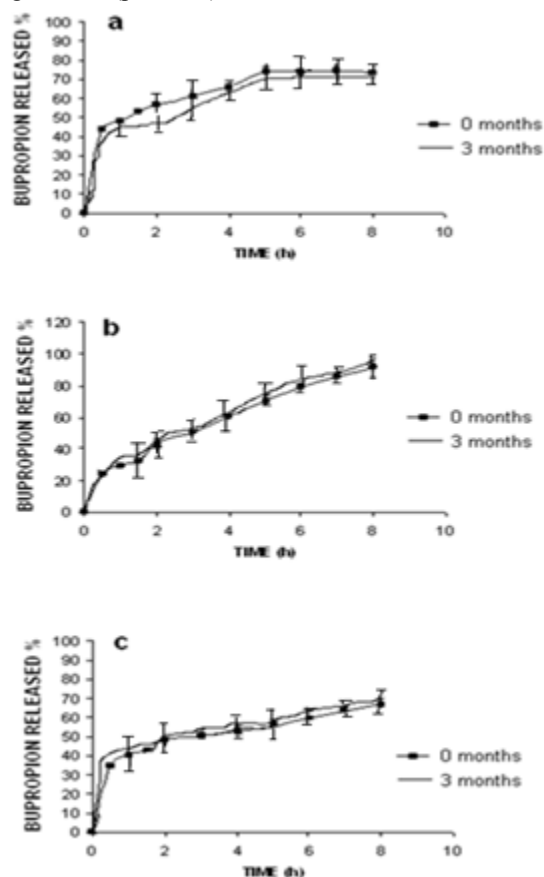
diffusion is dominant except for the formulation X that contained pure xanthan, and shows non-Fickian diffusion.

The physical mixture of chitosan with all polymers followed the Higuchi kinetics model and the non-Fickian diffusion (Table IV).

No significant difference was found between the drug release profiles of the stored samples of  $P C_1X_1$ ,  $P C_1CP_1$  and  $P C_1E_4$  after three-month storage under accelerated conditions. There were no signs of visually distinguishable changes in appearance and colour of tablets. The drug content was comparable with that of the control samples and within acceptable limits ( $\pm 10$  %). On the basis of these results, it can be concluded that the formulations had enough stability under accelerated stability test conditions for three months.

#### Accelerated stability study

Figure 7 shows the release profiles of optimum formulations ( $P C_1X_1$ ,  $P C_1CP_1$  and  $P C_1E_4$ ) at preparation time (zero time storage) and during 3 months storage period. As this figure indicates, the statistical differences of the release profiles after 3 months and at the time of preparation were not significant ( $p > 0.05$ ).



**Figure 7.**

*In vitro* dissolution profiles of bupropion hydrochloride from sustained release tablets containing polyelectrolyte complex of a)  $C_1X_1$ , b)

C<sub>1</sub>CP<sub>1</sub> and c) C<sub>1</sub>E<sub>4</sub> in water at zero time and after 3 months storage at 40°C / 75 % RH

## Conclusions

Polyelectrolyte complexation between amine groups of chitosan and anionic polyelectrolytes of Eudragite L100, xanthan gum and carbopol 934 led to sustained release of bupropion HCl from the matrix tablets. The formulations of polyelectrolytes obtained from 1:1 ratio of chitosan and xanthan gum (*P* C<sub>1</sub>X<sub>1</sub>), 1:1 of chitosan and carbopol (*P* C<sub>1</sub>CP<sub>1</sub>) and 1:4 of chitosan:Eudragit (*P* C<sub>1</sub>E<sub>4</sub>) had better results in providing sustained release pattern for bupropion HCl than pure polymers or the physical mixture of the polymers. They released the drug in water medium by a Higuchi kinetic model and the non-Fickian diffusion mechanism. These tablets showed acceptable stability during storage under stress conditions of 40°C / 75 % RH for 3 months. Polyelectrolyte complexes obtained from chitosan and polyanionic polymers are promising in production of sustained release matrix tablets.

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