Preparation of modified release diltiazem HCl capsule by complexation with ion exchange resin

Jenan M. AL-Mosawi*, Alaa A. Abdulrassol,**
Eman B.H. Al-Khedairy**
*Departments of Pharmaceutics, Colleges of Pharmacy, *University of Karbala, Karbala
**University of Baghdad, Baghdad, Iraq

Received	Accepted
2.6.2010	30.1.2011

ABSTRACT

Background: Diltiazem HCl is a calcium channel blocker drug used in the treatment of angina pectoris and hypertension.

Objective: To prepare a sustained release diltiazem HCl capsule by complexation with polystyrene sulfonate strong cation exchange resin (dowex®50wx4) as a complexing and retarding agent.

Methods: The effect of stirring time and drug: resin ratio on diltiazem HCl loading on dowex®50wx4 was studied. Drug resin complexes were characterized by Fourier Transform Infrared (FT-IR) spectroscopy. The release of drug from the complexes was examined in pH 1.2 and pH 6.8 separately in comparison with pure drug and with commercially available sustained release products Tildia® 120mg capsule and BI-Tildiem® 120mg tablets

Results and conclusion: Most efficient loading was obtained using 1:2 and 1:2.5 drug:resin ratio with stirring time of 60 and 30 minutes respectively. The resultant complexes only retard the release of diltiazem HCl when compared with pure drug while the sustained release product was obtained by coating the complex with carnauba wax and the retardation increased as a function of wax concentration. 20% of wax coated complex gave the release profile approximately similar to the marketed sustained release product of diltiazem HCl, Bi-Tildiem® (Sanofi-France) 120 mg tablets.

Key words: Diltiazem HCl, sustained release dosage form, cation exchange resin, complexation

الخلاصة

الخلفية: الدلتيازيم كلورهيدرات هو دواء مثبط للكالسيوم ، يستخدم في علاج الذبحة الصدرية وارتفاع ضغط الدم.

الهدف : تحضير كبسولات مديدة المفعول لعقار الدلتيازيم كلورهيدرات كمعقد بواسطة تبادل الايونات الموجبة مع الراتنج القوي من نوع سلفونات البوليستيرين (Dowex® 50wx4)

طرق العمل: دراسة تأثير مدة الدوران و نسبة كمية الدواء الى الراتنج على تحميل الدواء على الراتنج وقد تم تشخيص المعقد الناتج باستخدام التحليل الطيفي بواسطة الاشعة تحت الحمراء. كما تمت دراسة تحرر الدواء من المعقد في وسط ذو اس هيدروجيني ١،٢ ووسط ذو اس هيدروجيني ٦،٨ بشكل منفصل وبالمقارنة مع مسحوق الدواء النقي و المنتجات التجارية المديدة المفعول الموجودة في السوق وهي تلديا ١٢٠ملغم كبسول و حبوب باي- تيلدا ١٢٠ ملغم

النتائج والاستنتاج: ان احسن تحميل للدواء على الراتنج كان باستخدام نسبة ١:٢ و١: ٢،٥ دواء: راتنج وبمدة دوران ٦٠ دقيقة و٣٠ دقيقة على التوالي وقد وجد بان المعقد الناتج أبطأ تحرر الدواء عندما تمت مقارنته مع مسحوق الدواء النقي بينما تم الحصول على ناتج مديد المفعول بواسطة تغليف المعقد بالشمع الكوبرينكي وان الاعاقة تزداد كدالة لتركيز الشمع. وقد وجد انه عند تغليف المعقد بنسبة ٢٠٪ من الشمع الكوبرينكي أعطى تحرر مقارب نوعا ما الى المنتج المسوق لحبوب باي- تيلدا ١٢٠ ملغم

Oral sustained release dosage forms have been used for improving therapeutic efficacy and patient compliance.[1] Ion exchange resins have been used as drug carriers in pharmaceutical dosage forms for taste masking[2] and for controlling release[3,4] These resins are water insoluble, cross-linked polymer networks which are attached to ionizable group. Drugs can be loaded onto the resins by an exchanging reaction resulting in formation of drug-resin complex (drug resinate) [5]. The drug is released from the resinates by exchanging with ions in the gastrointestinal fluid, followed by drug diffusion [6]. The polymeric and ionic properties of ion exchange resin will release the drug more uniformly than that of simple matrices. Moreover, ion exchange resin impart flexibility in designing a variety of delivery system ,in which the sustained release system may be formulated as simple or coated systems. [7] Dowex®50wx4 which is a polystyrene sulfonate strong acid cation exchange resin with water retention capacity of 64%-72%, containing 4% divinylbenzene (4% degree of cross linking) have been used to provide sustained release preparation for a large number of drugs.[3,4] Diltiazem HCl is a calcium channel blocker drug with short half life used in the treatment of angina pectoris and hypertension [8]. It can be considered as a good candidate for sustained release preparation to improve patient compliance. The aim of this study is to prepare an oral sustained release capsule of diltiazem HCl using Dowex®50wx4 ion exchange resin as a complexing and retarding agent.

Materials and Methods

Materials

Diltiazem HCl powder (United Pharmaceutical, Jordan), Dowex®50wx4 (ALPHA CHEMIKA, Mumbai), Lactose (PH.Eur. France), Carnauba wax (Samrra Drug Industry-SDI, Iraq), TILDIA® (Medical bahri company, Syria) 120mg capsule, BI-TILDIEM® (Sanofi Winthrop Industrie, France) 120mg tablet. All other chemicals used in the study were of analytical grade.

Methods

Preparation Drug: Resin Complex

Factors Affecting Drug Loading

1- Effect of Stirring Time

Batch method was used for the preparation of diltiazem-resin complexes , 100 mg of dowex® 50wx4 was placed in a beaker containing 25 ml of sterile water for injection (pH 6.2) with an accurately weighed 100mg diltiazem HCl (as 1:1 drug: resin ratio) and stirred for 30,60,120 minutes. The mixture was filtered and the residue was washed with 75 ml of sterile water for injection to remove any unreacted drug and other ions. Bound drug was measured indirectly by measuring the unbound drug in filtrate at λ237 nm, and the difference in weight between the initial amount of drug added and the remaining amount of drug in the filtrate was considered as the amount of drug loaded onto the resin. [9, 3]

2-Effect of drug: resin ratio

Different drug resin ratios were used for the preparation of diltiazem resin complex including 1:1, 1:2 and 1:2.5 with stirring time of 30, 60 and 120 minutes using batch method as mentioned previously. The complex with acceptable drug loading was then dried over night at 50 ºC for further study[3].

Fourier transform infrared (FT-IR) spectroscopy

The FT-IR spectra for pure drug (diltiazem HCl), resin (dowex® 50wx4) and drug resin complexes were recorded using potassium bromide disk

method. Samples were prepared in potassium bromide disk by means of a hydrostatic press. Spectral measurements were obtained by powder diffuse reflectance on a FT-IR spectrophotometer (Shimadzu, 8400S) in the wave number 400-4000 cm^{-1} to find out drug resin interaction [10].

Preparation of diltiazem HCl capsules

Accurately weighed simple or coated resinate equivalent to 120 mg of diltiazem HCl was blended with sufficient amount of lactose and filled in a hard gelatin capsule size 0.

Preparation of coated drug resin complex

A specified amount of carnauba wax 15% (w/w) and 20% (w/w) (based on the total weight of capsule content) were taken in a beaker and melted by heating (90°C). Drug resin complex was then dispersed in the melted wax with continuous stirring. The hot mass was passed through mesh size 16 sieves[11].

Assay of drug content

Twenty mg. of accurately weighed amount of simple resinate or its equivalent from coated resinate was shaken for 48 hours in 250 ml of phosphate buffer solution (pH6.8) and then filtered. The filtrate was diluted ten times and then assayed spectrophotometrically at λ_{max} 237nm for diltiazem HCl.[12]

Dissolution test

The in vitro release of diltiazem HCl from the prepared capsules containing pure drug powder, simple drug:resin complex, coated drug:resin complex and marketed sustained release products (Tildia® 120mg capsule, Bitildiem® 90mg tablet) were monitored in 900 ml. of 0.1N HCl, and phosphate buffer solution pH 6.8 at 37 ± 1°C separately [9, 12] using a USP dissolution apparatus II, at 100 rpm. Five ml. solutions were removed at predetermined times and were replenished immediately with the same volume of fresh media. The solution was diluted ten times and then assayed spectrophotometrically at λ_{max} 237 nm.[13] for diltiazem HCl.

Statistical analysis

Results are given as a mean for duplicate samples. The results were statistically analyzed using t-test, P value of less than 0.05 was considered significant.

Results and Discussion

Preparation of drug: resin complex

Factors affecting drug loading

Diltiazem HCl is highly soluble in water. The dissolved diltiazem HCl exists as protonated drug ions (since it dissolved at pH 6.2 below its pka 7.7) which can displace the hydrogen counter-ion (H^+) at the sulfonic acid functional groups on the ion exchange resin particle[14]. Batch method procedure was used to prepare diltiazem-resin complexes in this study because of simpler, quicker and more suitable for very fine particles [15]

Effect of stirring time

The percentage of drug loading (wt/wt) with a stirring time of 30, 60,120 minutes was found to be 58.8%, 64.2%and 63.4% respectively. This study revealed that as the stirring time increased the drug loading increased[16]. This finding may indicate that the significant involvement of Van der Waals forces or chemisorption taking place along with drug exchange during complexation[9, 17]. Increasing the stirring time above 60 minutes did not further increase the drug loading. Therefore this contact time (60min) between drug and resin could be considered as an optimum time for the ion exchange process to achieve maximum drug loading.

Table 1: Effect of Drug: Resin Ratio on Drug Loading

Drug: resin ratio / Stirring time (min)	1:1	1:2	1:2.5
30	58.8%	71.4%	97.4%
60	64.2%	96.7%	99.29%

Effect of drug: resin ratio

Table 1 shows the effect of drug: resin ratio on drug loading, it was found that as the amount of resin increased the drug loading was also increased, which may be due to providing a higher amount of exchangeable groups for the drug[18]. No significant differences (P>0.05) in drug loading (96.7% and 99%) was found when increasing drug: resin ratio from 1:2 to 1:2.5 respectively with stirring time of 60 minutes which may indicate that the optimum ion exchange could be completed with the lower amount of the resin at this stirring time[9]. Complex prepared using 1:2.5 drug: resin ratio, with stirring time of 30 minutes and the complex prepared using 1:2 drug resin ratio with stirring time of 60 minutes, were nomenclated as complex I and II respectively and they were subjected for further studies.

Fourier transform infrared (FT-IR) spectroscopy

The infrared of pure drug (diltiazem HCl), resin (dowex® 50wx4) and drug resin complexes (I, II) are shown in figures (1, 2, 3 and 4) respectively.The IR spectrum of diltiazem HCl exhibited the characteristic absorption peaks at 3201cm^{-1}(N-H stretching), 3001 cm^{-1} (aromatic C-H stretching),1743cm^{-1} (ester C=O stretching) and the IR spectrum of dowex®50wx4 exhibited the characteristic absorption peaks at 2928cm^{-1}(C-H stretching), 1626cm^{-1}(aromatic C=C stretching), 1344cm^{-1}(S=O stretching of sulfonic group). Since the IR spectrum of the complexes containing the same characteristic absorption peaks present in drug and the resin, therefore the exchange might occur between the protonated drug and cationic resin [10] at the protonated site by exchanging the proton of the drug with the proton of the sulfonic acid group of the resin. In addition the IR spectrum of both complexes I&II are identical which may indicate that the same complex is obtained.

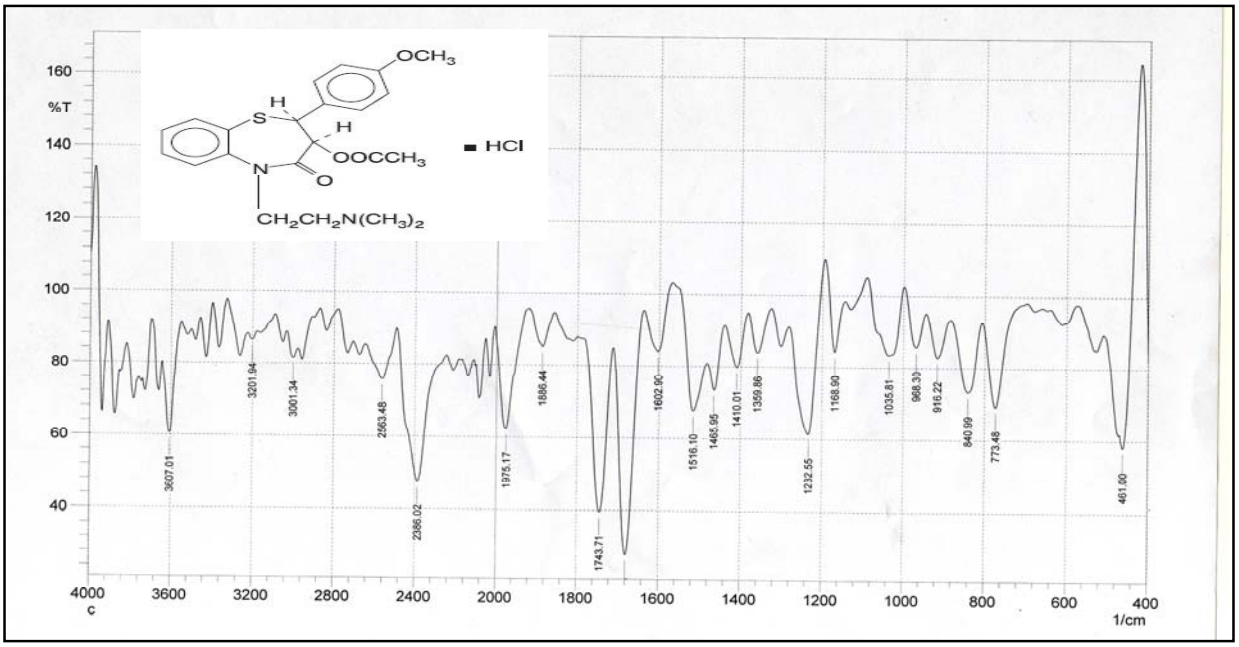

Figure 1: IR spectrum of diltiazem HCl

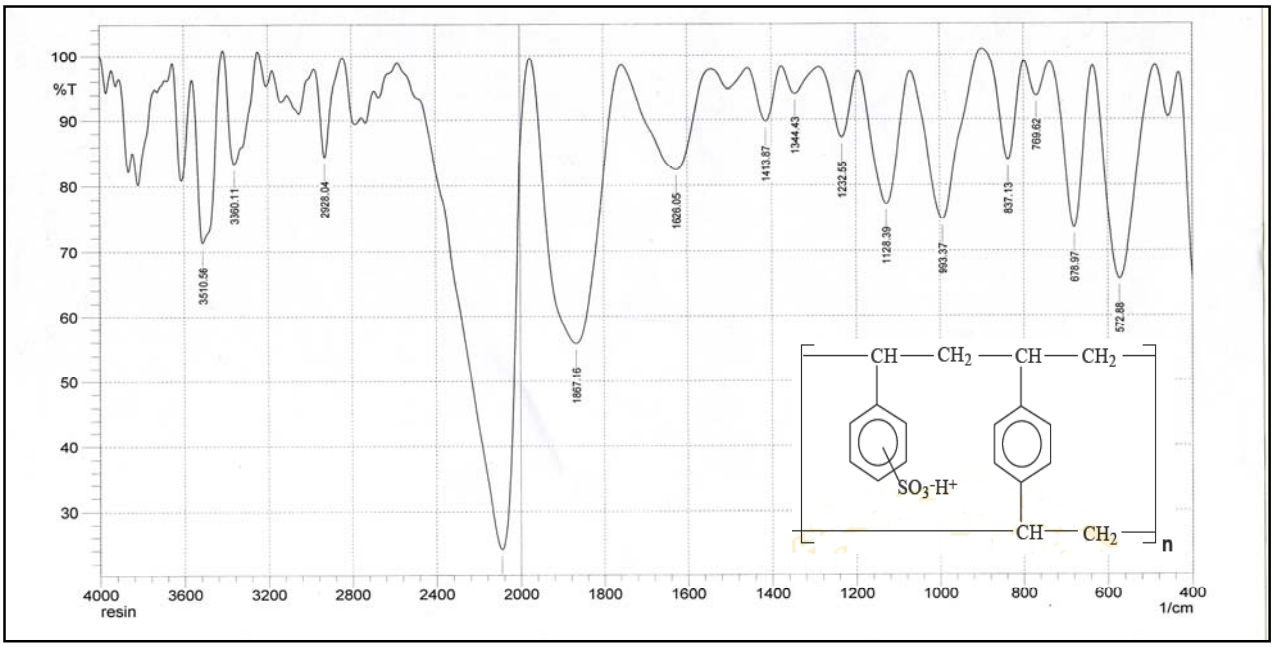

Figure 2: IR spectrum of dowex ®50 wx4

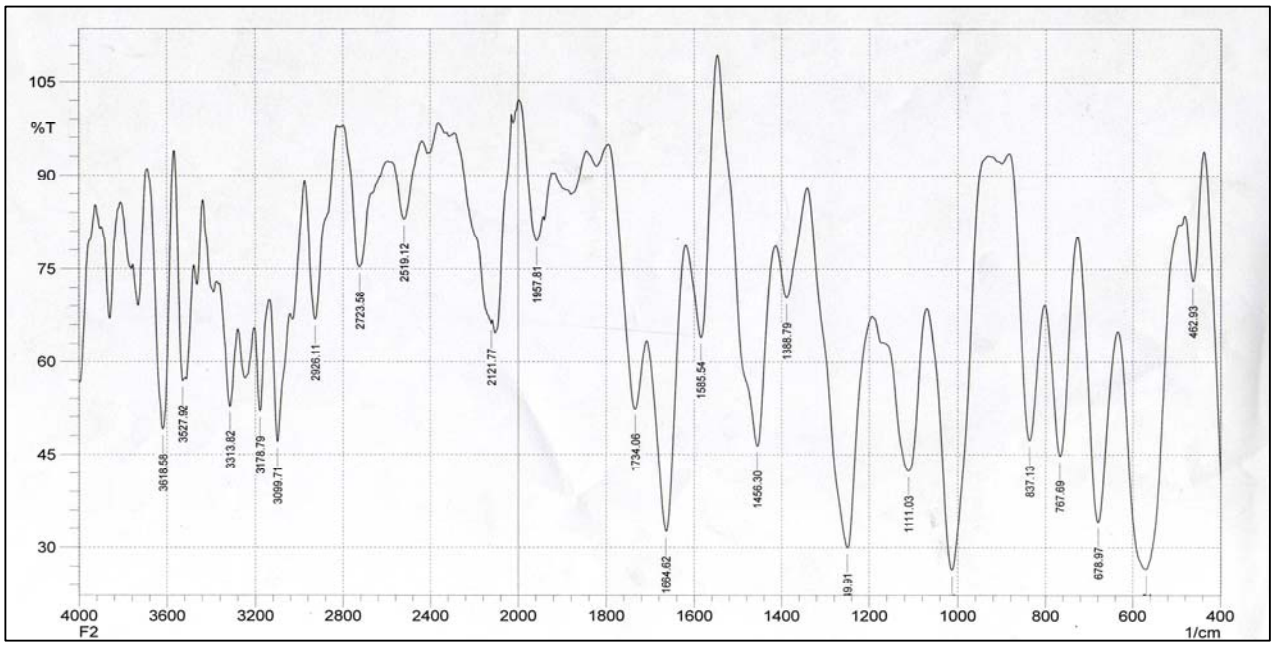

Figure 3: IR spectrum of complex

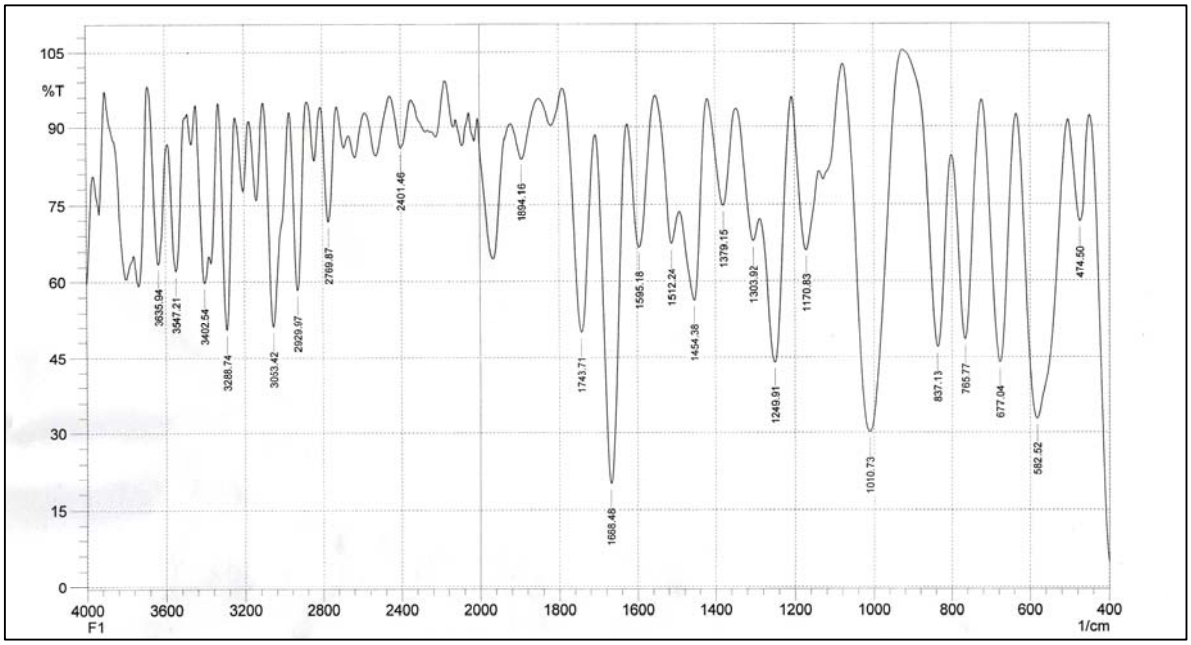

Figure 4. IR spectrum of complex II

Assay of drug content

The same drug content was found in both sample (complex I and complex II) and coated resinate which was equal to 55 %(11.1mg).

Dissolution test

The release profiles of diltiazem:resin complexes (I and II) in 0.1N HCl and in phosphate buffer pH 6.8 are shown in Figure 5. The drug release from the complexes reached equilibrium which was about 100% in 0.1N HCl and 80%

in phosphate buffer pH 6.8 at approximately after 3 hours with no significant differences between them, so it can be concluded that there was no influence of the drug:resin ratio on the release of drug from the complex. Since the release profile, drug content, and IR spectrum of both complexes (I and II) are all identical, this may indicate that actually the same complex was obtained, therefore the study was continued on one complex (complex II) . On the other hand figure 6 shows the release profile of pure diltiazem HCl in comparison with diltiazem: resin complex in 0.1N HCl and phosphate buffer pH 6.8, the release of drug from the complex was slow with a maximum release after 3 hours compared to 1 hour for pure drug, this finding is in agreement with that reported by Madgulkar et al. in which the ion exchange resin has a retarding effect on drug release[19]. More retardation was obtained after coating this complex with carnauba wax since 66% of drug was released within 3 hours from 15% and 20% wax coated complex in 0.1N HCl and 66% and 56% in pH 6.8 respectively as shown in figure 7. In addition increasing carnauba wax concentration was accompanied with decreasing initial burst release for the first hour and retards further drug release, since carnauba wax is extremely hydrophobic in nature with low wettability which makes the complete release of drug impossible because certain fraction of the dose is coated with impermeable wax[11, 20]. Figure 8 shows the release profile of 20% wax coated complex in comparison with marketed Tildia® 120mg capsule and marketed BI-Tildiem® 120mg tablet in 0.1N HCl and phosphate buffer pH 6.8 .The results revealed that there is a significant difference between the release profile of 20% wax coated complex and that of Tildia® 120mg capsule ($P< 0.05$) at 0.1N HCl and pH 6.8 while, there is a significant difference ($P< 0.05$) between the release profile of the prepared capsule (20% wax coated complex) and the marketed BI-TILDIEM® 120mg tablet at pH 6.8 only with no significant difference at 0.1N HCl , since the time required for drug release to reach equilibrium was about 3 hours for TILDIA® 120mg capsule compared to 4.5 hours for both 20% wax coated complex and BI-Tildiem® 120mg tablet in a more sustained release pattern. This difference may be due to the differences in the physical properties of the materials used in the preparation of each product.

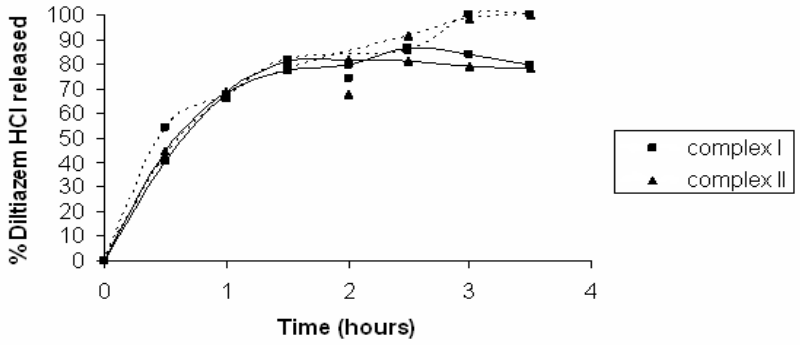

Fig (5) Release profiles of diltiazem-resin complexes (I and II) in 0.1 N HCl (- - - - -) and pH 6.8 (——) at 37 °C

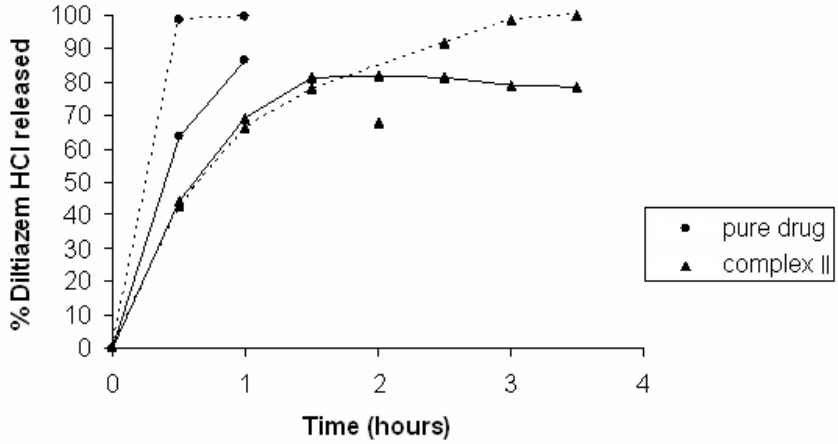

Fig (6) Release profile of pure drug and complex in 0.1 N HCl (- - - - -) and pH 6.8 (——) at 37 °C

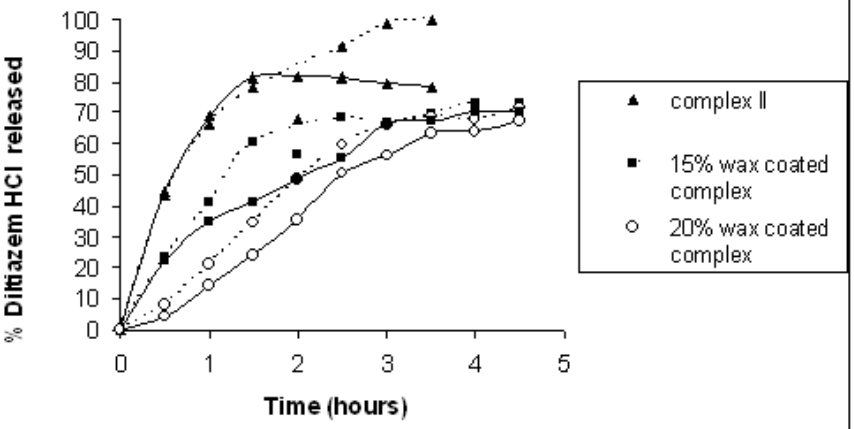

Fig (7) Release profile of complex, 15% wax coated complex and 20% wax coated complex in 0.1N HCl (- - - - -) and pH 6.8 (——) at 37°C

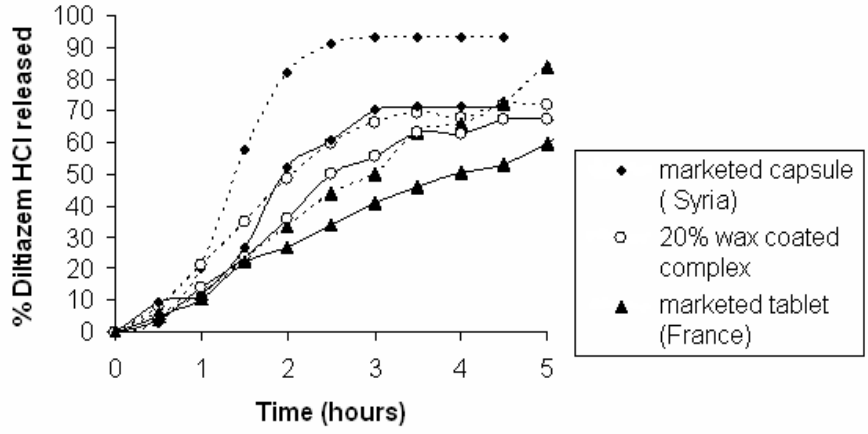

Fig (8) Release profile of 20% wax coated complex, marketed capsule (Syria) and marketed tablet (France) in 0.1 N HCl (- - - - -) and pH 6.8 (——) at 37 °C

Conclusion

The preparation of diltiazem-resin complexes were found to be affected by stirring time and drug: resin ratio to certain limit, this complex was only retard the release of drug while sustained release product was obtained after coating the complex with carnauba wax and this retardation increased as a function of wax concentration.

Acknowledgment

The authors wish to thank Dr Ahlam J. Qasir for her generous help in studying the I.R. spectra of the formulas.

References

1. Gennaro AR. Remington: The Science and Practice of Pharmacy 19th ed. Easton; Mack Publishing Co 1995. p.1662.
2. Borodkin S, Sundberg DP. Polycarboxylic acid ion-exchange resin adsorbates for taste coverage in chewable tablets. J Pharm Sci 1971;60:1523-7.
3. Pongjanyakul T, Priprem A, Chitropas P, and Puttipipatkhachorn S. Effect of polysulfonate resins and direct compression fillers on multiple-unit sustained release dextromethorphan resinate tablets. AAPS Pharm Sci Tech 2005;6(2):E190-7.
4. Junyaprasert BV, Manwiwattanakul G. Release profile comparison and stability of diltiazem-resin microcapsules in sustained release suspension. Int J Pharm 2008;352(1-2):81-91.
5. Borodkin S. Ion exchange resin and sustained release: Encyclopedia of pharmaceutical technology 8th. New York: Marcel Dekker 1993. P. 203-216.
6. Notari RE. Biopharmaceutis and clinical pharmacokinetics 4th ed. New York: Marcel Dekker;1987. P. 130-218.
7. Amsel LP. Recent advances in sustained release technology using ion-exchange polymers, Pharm. Technol 1984;4:28–48.
8. Sweetman S.C. The complete drug reference 33th. London: pharmaceutical press 2002. P. 875.
9. Pisal S, Zainnuddin R, Nalawade P, et al. Molecular properties of

ciprofloxacin-indion® 234 complexes. AAPS Pharm Sci Tech 2004;5(4):E62.
10. Silverstein RM, Francis X, Webster, Keimle DJ. Spectrometric identification of Organic Compounds 7th ed. NY: John Wiley & sons 2005;83-5.
11. Shende MA, Akare SC, Boorugu R, Patil AT. Formulation and in vitro evaluation of sustained release delivery of diltiazem hydrochloride through wax matrices. int J Chem Tech Res 2009;1(4):1359-67.
12. Halder A, Sa B. Preparation and in vitro evaluation of polystyrene-coated diltiazem-resin complex by oil-in-water emulsion solvent evaporation method. AAPS Pharm Sci Tech 2006;7(2):E46.
13. The united state pharmacopoeia, 2007.
14. Khan S, Guha A, Yeole PG, Katariya P. Strong cation exchange resin for improving physicochemical properties and sustaining release of ranitidine hydrochloride. Indian J pharm sci 2007;69(5):626-32.
15. Deasey P.B. Microencapsulation and related drug processes: Ion-exchange resin. New York: Marcel Dekker, 1984; p. 241-52.
16. Bhalekar M, Avari JG, Jaiswal SB. Cation-exchanger in pharmaceutical formulation. IJPS 2004;38(4):184-187.
17. Storm G, van Bloois L, Brouwer M, Crommelin DJ. The interaction of cytostatic drugs with adsorbents in aqueous media. The potential implications for liposome preparation. Biochim Biophys Acta 1985;818(3):343-51.
18. Chen Y, Burton MA, Codde JP, et al. Evaluation of ion exchange microspheres as carrier for the anticancer drug doxorubicin in-vitro studies. J Pharm Pharmacol 1992;44:211-15.
19. Madgulkar AR, Bhalekar MR, Kolhe VJ, Kenjale YD. Formulation and optimization of sustained release tablets of venlafaxine resinates using response surface methodology. Indian J Pharm Sci 2009;71(4):387-394.
20. Motycka S, Newth L, Nairn JG. Preparation and evaluation of microencapsulated and coated ion exchange resin beads containing theophylline. J Pharm Sci 1985;74(6):643-3.