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Preparation and characterization of taste masked valsartan by ion-exchange resin approach

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Abstract:

The bitter taste is one of the most important drug formulation problems. The unpleasant taste leads to noncompliance, which consequently decreases the therapeutic efficacy of the drug. Therefore, masking of bitter taste is very important in drug formulation. In this study an antihypertensive drug, valsartan, which is a weak acid with bitter taste, was used as a model drug to mask its taste with dowex2 (weak base anion exchange resin). The taste masking of a drug using ion exchange resin basically depends on the complex formation between the drug and a specific type of resin. Complex formation under various preparation conditions including; the ratio of drug to resin, mixing time, the pH of the processing medium and the concentration of valsartan was investigated in this study. Optimum conditions for complex formation and maximum drug load were obtained at a drug-resin ratio 1:8, mixing time 4 hours, pH 6.8, temperature 50º C and drug concentration 0.02% w/v. The drug resin ate complex was evaluated for the drug content, taste, drug release and molecular properties. The resinate formation was confirmed using different analytical techniques like thermal analysis using differential scanning calorimetry (DSC), spectroscopic method like Fourier transform infrared spectroscopy (FTIR) and by X-ray powder diffraction analysis (XRPD).

Key words: valsartan, dowex2, ion exchange resin, valsartan-dowex2 complex

تحضير وتقييم مادة الفالزرتان بعد اخفاء طعمها المر باستخدام رزن التبادل الايوني

صفاء هلول محمد*

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الخلاصة:

الطعم المر هو من اكثر مشاكل تصييغ الادوية. ان الطعم الغير مرغوب يؤدي الى عدم تقبل الدواء من قبل المريض وبالتالي يقلل من فعاليته العلاجية. لذا يعتبر اخفاء الطعم المر من الامور المهمة جدا في تصييغ الادوية. في هذه الدراسة تم استخدام الفالسارتان، الدواء المضاد لارتفاع ضغط الدم والذي يعتبر حامض ضعيف ذو طعم مر كنموذج لاخفاء طعمه المر باستخدام داويكس 2 (رزن التبادل الايوني القاعدي الضعيف). أن مبدأ اخفاء الطعم للادوية بأستخدام رزن التبادل الايوني يعتمد على تكوين المعقد بين الدواء ونوع معين من الرزن. لقد تم في هذه الدراسة تكوين المعقد تحت ظروف تحضيرية متنوعة والتي شملت نسبة الدواء الى الرزن، مدة المزج، الدالة الحامضية لمحيط التفاعل وتركيز الفالسارتان وتقيم النتائج. الظروف المثلى لتكوين المعقد وأعلى تحميل للدواء تم الحصول عليها عند نسبة الدواء-الرزن 1-8، مدة المزج 4 ساعات، الدالة الحامضية 6.8، درجة الحرارة 50 درجة مئوية وتركيز الدواء0.02% نسبة وزن/حجم. وقد تم تقييم معقد الدواء-الرزن لمعرفة كمية الدواء المحملة، تحرير الدواء والخصائص الجزيئية. تم التاكد من تكون المعقد بأستخدام طرق تحليل مختلفة كالتحليل الحراري بأستخدام المسعر التحليلي التفاضلي، وطرق التحليل الطيفي باستخدام الاشعة تحت الحمراء وحيود الاشعة السينية.

الكلمات المفتاحية : الفالسارتان، داويكس2، رزن التبادل الايوني، معقد فالسارتان-داويكس2.

Introduction:

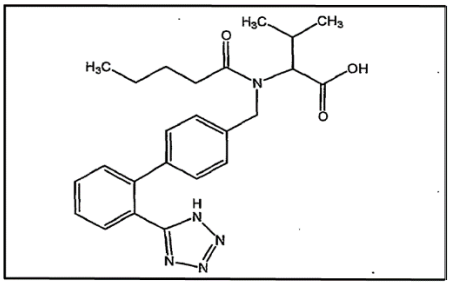
Several taste masking methods are available such as chemical modification (like a prodrug), coating the particle surface, physical masking by additives and using of ion exchange resins [1]. Ion-exchange resins are widely utilized in the formulation of bitter drugs for oral use like taste masking of clarithromycin and

levetiracetam [2, 3]. These agents adsorb on drug surface and hide the bitter taste. An ion exchange resin is formed from small diameter beads (1 to 2 mm) which is unsolvable matrix. It has various colors, such as white and yellowish, made-up from an organic polymer substrate structure. The structure of these substances is very complicated, consisting of porous surfaces, from which the ions are confined or released. The catching of ions occurs with the immediate discharge of other ions. This method is termed ion exchange. The following characteristic properties govern in the selection of ion-exchange resins; the chemical nature of functional part of the resin, resin swelling property, biocompatibility and biodegradability of resin [4-7]. Since resins comprise about 60 percent or higher of drug form complex with resin, it is essential to assess the degree of resins toxicity. Commercial resin products cannot be used directly. A careful purification of ion exchange resin is necessary. Resin is not absorbed via body tissue and nontoxic for human intake. The test for toxicological tolerance revealed that it does not have any physiological effect and is non-toxic [8]. Valsartan is an antihypertensive medication belong to the angiotensin receptor blockers (ARB) [9, 10]. Therefore, it is consumed in the controlling of hypertension, heart failure and to decrease the cardiac mortality in patient have left ventricular dysfunction after myocardial infarction [11]. The aim of this study is to mask the bitter taste of valsartan via complexation with ion-exchange resin (dowex2), investigate different factors (drug: resin ratio, temperature, pH, mixing time and drug concentration) that could affect the complex formation, confirmation of the resinate formation by different techniques (like differential scanning calorimetry, Fourier transform infrared spectroscopy and X-ray powder diffraction analysis(and evaluation the release of valsartan from drug-resin complex at different pH media.

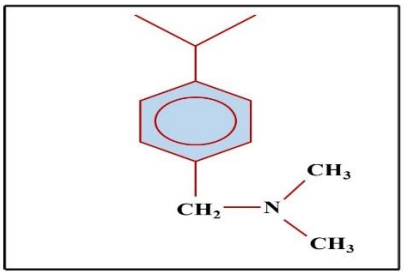
Materials and Methods:

Materials:

Valsartan was purchased from Provizer pharma, India. Weak base anion-exchange resin (dowx2) was purchased from ion exchange resin company, Ltd (India). All other chemicals were of analytical reagent grade and used as received. The chemical structures of valsartan and dowex2 are shown below:



Chemical structure of valsartan [12]



Chemical structure of dowex2

2.2 Construction of Valsartan Calibration Curve

The calibration curves of valsartan in different buffer solutions of pH (0.7, 1.2, 2, 4.6, 5, 6.8, 8 and 9) were constructed using serial diluted solutions of the drug in each buffer. They analyzed at the previously determined λ_{max} of drug using UV-visible spectrophotometer, and the recorded absorbance for each sample was plotted versus the concentration in order to obtain specific valsartan calibration curve.

2.3 Preparation of Drug-Resin Complex (DRC)

2.3.1 Purification of Ion Exchange Resin

Purification of (dowex2) was accomplished through rinsing the resin with distilled water followed by activation the resin with 0.1 N HCl, about 300 ml of

0.1 N HCl was added then the activated resin rinsed with sufficient quantity of distilled water followed by drying step which was accomplished at 50° C in an oven of automatically controlled hot air temperature. The resultant dry resin was kept away from the contact of atmospheric air by packing inside tightly closed glass vial [13].

2.3.2 Formation of Valsartan-Dowex2 Complex

Valsartan was mixed with dowex2 in the ratio (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 and 1:8). Deionised distilled water (about 200 ml) was used to disperse the mixtures with continuous stirring for 4 hours with magnetic stirrer to allow a complete complex formation between the drug and resin. The drug-resin complex (DRC) obtained was subjected to filtration then was washed with sufficient quantity of distilled water. The prepared resinate was allowed to dry in a hot air oven [2]. The best or selected ratio (according to loading percent) was further investigated using different mixing time, pH, temperature and concentration.

2.3.3 Valsartan Content and Loading Percent

Drug loading in the prepared ion exchange resin complex was determined by analyzing the supernatant for the free drug by measuring uv absorbance of drug at 250 nm, then the amount of valsartan loaded into complexes was determined from the difference between the initial and free amount of valsartan in the supernatant [3].

2.4 Conditions Affecting Complexation

2.4.1 Effect of Mixing Time

For optimization of mixing time the stirring of the drug: resin mixture at 1:8 ratio was carried out for 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 and 4h on a magnetic stirrer to allow maximum possible loading. The sample was then evaluated for drug loading after each time interval [14] .

2.4.2 Effect of pH on Drug Loading

A mixture of valsartan and dowex2 at 1:8 weight ratio was stirred in different buffer solutions of pH values (0.7, 1.2, 2, 4.6, 5, 6.8, 8 and 9) using a magnetic stirrer [2, 15].

2.4.3 Effect of Temperature on Drug Loading

Mixtures of valsartan and dowex2 at 1:8 weight ratios were stirred in deionised distilled water at three elevated temperatures (30º C, 40º C and 50º C) by a magnetic stirrer [15].

2.4.4 Effect of Drug Concentration on Drug Loading

Different valsartan concentrations (0.002 % w/v, 0.004 % w/v, 0.008 % w/v and 0.02 % w/v) and dowex2 at 1:8 weight ratios were stirred in deionised distilled water by a magnetic stirrer [15].

2.5 Studies on Drug-Resin Complex

2.5.1 In-Vitro Dissolution Studies

- **Drug Release at Salivary pH (6.8)**

To determine the amount of valsartan that might be released in the mouth during the administration of the drug: resin complex formulation; in-vitro release study was first performed at the salivary pH (6.8). Any amount of drug that might be released in the mouth results in the sensation of the bitterness taste of the drug by the patient. Drug resin complex equivalent to (40 mg) of valsartan was placed in beaker and 25 ml of a representing salivary solution (pH 6.8 phosphate buffer) was added, and then magnetically stirred for about one minute, then filtered. The filtrate was analyzed spectrophotometrically at 250 nm [16].

- **Dissolution studies in Buffer Solution pH 1.2 (stomach media)**

United States Pharmacopoeia dissolution apparatus (type II) was used to study the release of valsartan from DRC at pH 1.2 dissolution media. Accurately weighted amount of DRC equivalent to 40 mg of valsartan was added to 900 ml (pH 1.2 dissolution media) that maintained at 37±0.5° C [3]. Dissolution medium was rotated at 50 rpm and the release of drug

was tested for 2 hours. At different time interval of 2, 5, 10, 15, 20, 30, 45, 60, 75, 90 and 120 minutes, five milliliters of aliquots were periodically withdrawn and analyzed for the amount of drug released spectrophotometrically at 250 nm. Five milliliters of fresh dissolution medium were added after each withdrawal to keep a sink condition. The test was carried out in triplicate [2, 13, 17].

- **Dissolution Studies in Buffer Solution pH 6.8 (Intestinal Media)**

After completing the dissolution studying in stomach media, the DRC was filtrated and transferred to the intestinal media (900 mL of buffer solution pH 6.8) maintained at 37±0.5 °C, using the same type II USP dissolution apparatus. Drug release was performed at 50 rpm for 2 hours. Five milliliters samples were periodically withdrawn at different time interval of 2, 5, 10, 15, 20, 30, 45, 60, 75, 90 and 120 minutes. The samples were analyzed for the amount of drug released at various time intervals spectrophotometrically at 250 nm. Five milliliters of fresh dissolution medium was added after each withdrawal to keep a sink condition. The test was carried out in triplicate [2]. The same dissolution media (pH 1.2 and 6.8) were used to test the release of pure drug for comparison.

2.5.2 Differential Scanning Calorimetry (DSC)

DSC is one of the thermal analysis techniques usually used for characterization the thermal behavior of drug substance in pure state and in pharmaceutical mixture and to determine its molecular state. In this study, the thermal behavior of untreated drug, and the effect of drug-complex preparation on the molecular state of the drug was assessed by DSC analyses. About 5 mg of sample was placed in crimped aluminum pans and scanned from 20° to 200°C at 10°C/ min under a nitrogen atmosphere, purge at 50 ml/ min [3].

2.5.3 Fourier Transform Infrared (FTIR)

FTIR spectroscopy was used to investigate molecular interaction between the drug (valsartan) and the resin (dowex2) that could be occur during physical mixing and/ or by complexation. Samples of (untreated valsartan, resin, physically treated drug with resin and complexed drug-resin) were mixed with sufficient quantity of KBr and compressed into a disk then analyzed using a FTIR spectrometer (Shimadzu 8300, Japan). Scanning range was 4000-400 cm^{-1} [3].

2.5.4 X-Ray Powdered Diffraction (XRPD)

XRPD is a technique used to obtain information about the structure of crystalline materials [3]. In this study, valsartan, dowex2, valsartan-dowex2 complex, and a physical mixture were analyzed by an automated X-ray diffractometer with monochromatic Cu ka radiation, voltage 40 kV, current 30 mA at a scan speed of 5 deg/min.

3. Results and discussion

3.1 Construction of Valsartan Calibration Curves

Calibration curves of valsartan in D.W and different buffer solutions of pH (0.7, 1.2, 2, 4.6,5, 6.8, 8 and 9) at λ_{max} 250 nm are shown in Figure (1). Straight lines with high regression coefficient were gotten when the value of absorbance plotted versus the concentration, indicating that the calibration curves obey Beer's law within the concentration range used.

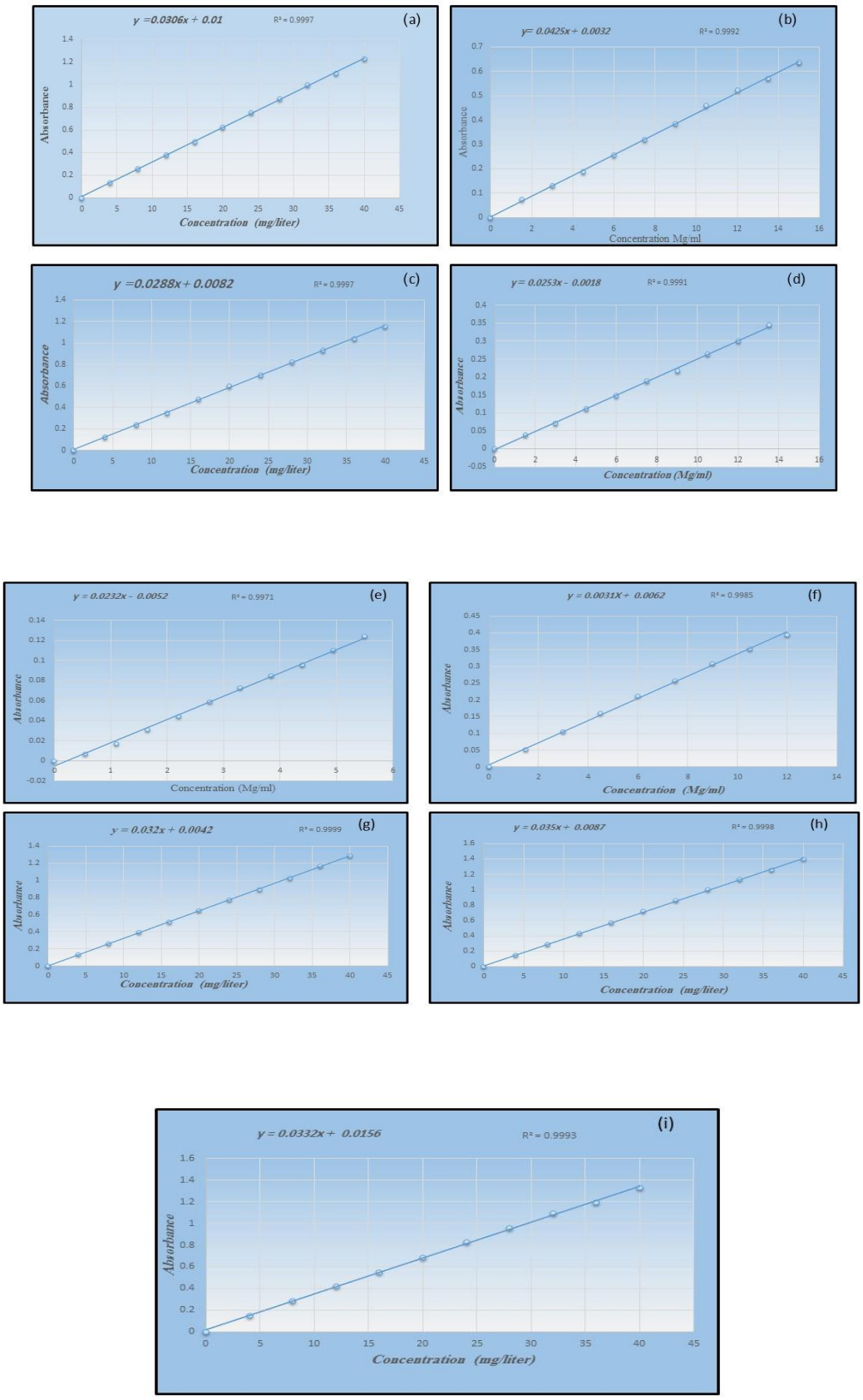


Figure-1: calibration curves of valsartan at (a)D.W,(b)pH 0.7, (c) pH 1.2,(d) pH 2,(e) pH 4.6,(f) pH 5,(g) pH 6.8,(h) pH 8 and (i) pH 9.

3.2 Preparation of Drug-Resin Complex (DRC)

3.2.1 Purification of Ion Exchange Resin

Dowex2 was washed with distilled water to remove any impurities may be found. Dowex2, which is a weak base anion exchange resin, to react it must first be ionised. Protonisation of amine group of resin could be achieved by reacting with a strong acid (like HCl), by which the amine group transformed into a quaternary ammonium[18].

$$R\text{-}CH_2\text{-}N(CH_3)_2 + H^+Cl^- \rightarrow R\text{-}CH_2\text{-}NH^+(CH3)_{2+}Cl^-$$

3.2.2 Formation of Valsartan-Dowex2 Complex

Valsartan: dowex2 complexation was optimized for various drug: resin ratios. In each case, 40 mg of valsartan was stirred with varying amount of resin in deionised water using magnetic stirrer at 400 rpm[15]. A plot of mean for three determinations for percentage drug loaded at different resin ratios was plotted in figure (2 a). The best ratio of complexation was 1:8 giving 98.28 % of drug loading at temperature 50º C, pH 6.8, mixing time 4 hours and drug concentration 0.02 % w/v.

3.3 Conditions Affecting Complexation

3.3.1 Effect of Mixing Time on the Drug Resin Complexation

Figure (2 b) shows that the maximum drug has been complexed in 4 hours due to the optimum ions exchange completed in this period. This result is in agreement with those obtained for taste masking of clarithromycin using complexation with ion exchange resin [2].

3.3.2 Effect of pH on the Drug Loading

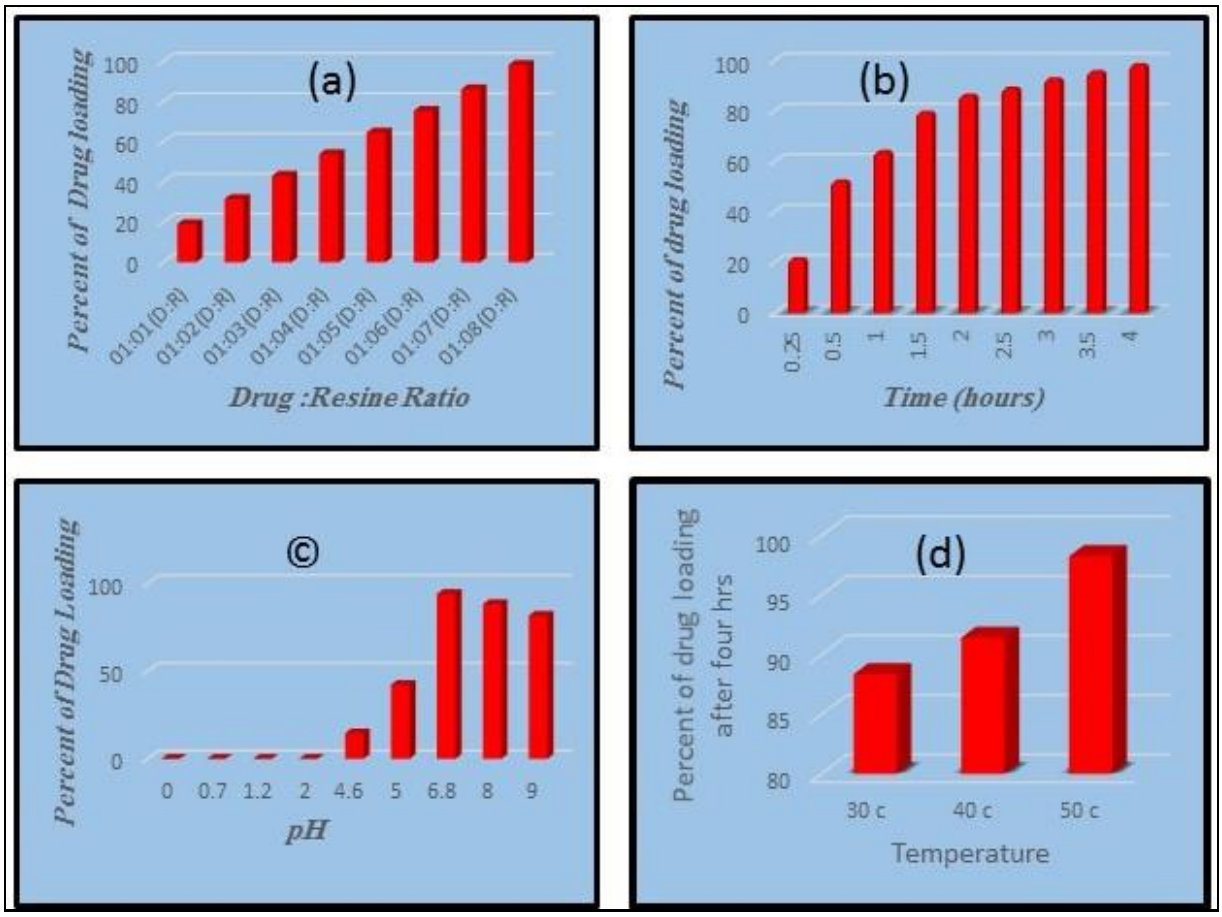
The effect of pH on drug loading is shown in Figure (2 c). At acidic pH valsartan is available as unionized free acid which results in decreased drug loading. When the pH increases above 4, an increase in drug loading is observed. This is attributed to the liberation of hydrogen ions by the valsartan carboxyl group and protonation of the resin. As a result, a complex form through an ionic bond between protonated resin and carboxylic group of valsartan. The maximum loading efficacy (about 94.06 %) was observed at pH 6.8 as both the drug and resin are ionized adequately. On the other hand, loading efficiency decreased as the pH of the media increased, due to the presence of unionized resin at alkaline pH [13, 15].

3.3.3 Effect of Temperature on the Drug Loading

Figure (2 d) shows that the temperature affected the complexation process. Highest drug loading on resin occurred at temperature 50º C. Increase in the temperature during complexation process, could increases kinetic and ionization of drug and resin. It was suggested that high temperature may also increase swelling of resin, and also lead to an increase in the diffusion rate of ions by diminishing the thickness of exhaustive exchange zone. This result is in agreement with the result founded by Puttewar T who studied formulation and evaluation of or dispersible tablet of taste masked doxylamine succinate using ion exchange resin [15].

3.3.4 Effect of Drug Concentration on Drug Loading

Drug concentration per milliliters of loading solution was found to affect the loading time and had no significant effect on extent of uptake. Highest drug loading obtained at highest drug concentration, as shown in Figure (2 e), probably due to efficient competition for binding site with other ions in solution. Thus, higher drug concentration used to reduce the time required for complexation [15]. Highest drug loading obtained at (0.02 % w/v). Therefore, the concentrated drug-resin solution showed the best result.



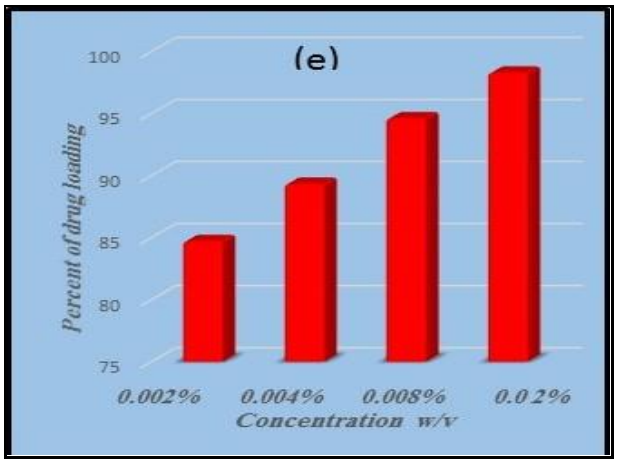


Figure-2: factors affecting complexation;(2 a) effect of drug-resin ratio, (2 b) effect of time, (2 c) effect of pH,(2 d) effect of tem
*** Drug: resin ratio in figure (2 b), (2 c), (2 d) and (2 e) was 1:8perature and (2 e) effect of concentration.**

3.3.5 Optimized Conditions

The optimum conditions for the preparation of valsartan-dowex2 complex were obtained with drug: resin ratio (1:8), time (4 h.), pH (6.8), temperature (50º C) and drug concentration (0.02 % w/v).

3.4 Studies on Drug-Resin Complex

3.4.1 In-Vitro Dissolution Rate Studies

➢ **Drug Release at Salivary pH (6.8)**

The results showed that there is no release of valsartan from valsartan-dowex2 complex powder in an average salivary pH of 6.8 within 60 seconds. The DRC is

stable in salivary pH for a period of administration where the contact time of drug with taste buds will be very short. This retardation of drug release is very significant. Therefore, the retardation of dissolution rate of valsartan from the complex is responsible for reduction of the bitterness of the drug. As the DRC passes through the mouth to further parts of the gastrointestinal tract, the complex will start to exchange the drug with ions and thus permit the drug to be released [2, 15, 17].

- **Dissolution studies in Buffer Solutions pH 1.2 and 6.8**

The percentage of valsartan released within 120 minutes at gastric media (pH 1.2) was 49.202 %, and the remaining amount of valsartan was released within 30 minutes at intestinal pH 6.8 (as shown in figure 3). Release of drug from the complex could be a result of hydration of valsartan- dowex2 complex by water absorption then swelling of hydrated complex by dissolution process, and then exchange process of the drug with ions. The ion exchange process controls valsartan release from DRC [15, 17]. The percentage of valsartan (as a pure drug) released within 120 minutes at gastric media (pH 1.2) was 10.103 %, and the remaining amount was released within 120 minutes at intestinal pH 6.8. The results display a significant difference ($P<0.05$) in the percent of valsartan released and indicating that DRC gave fastest dissolution process.

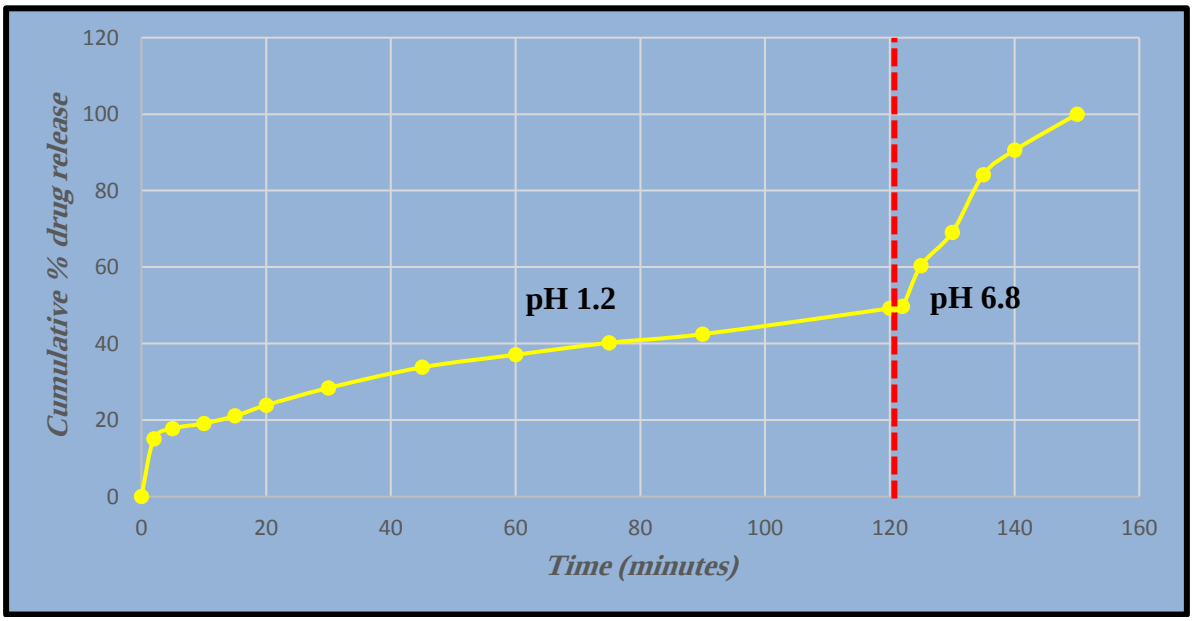
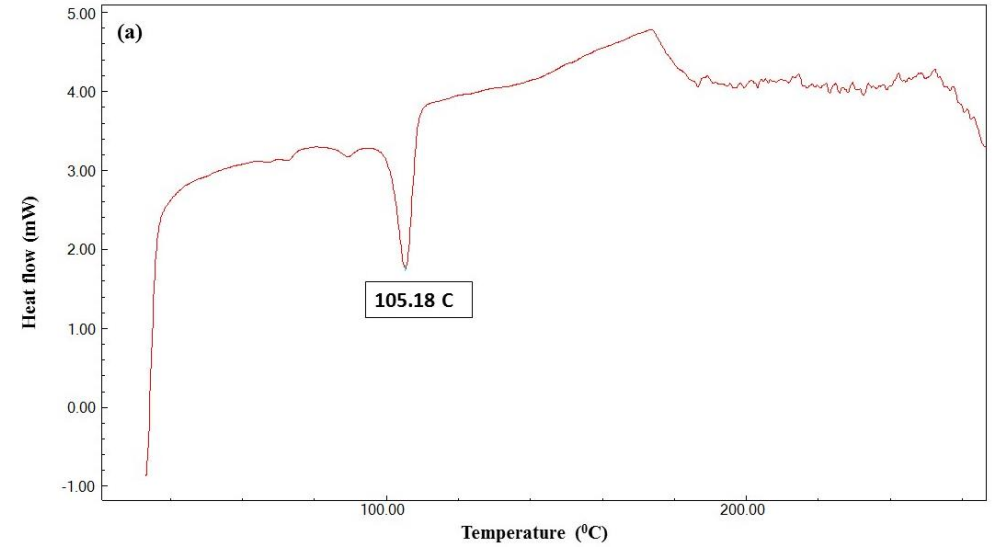
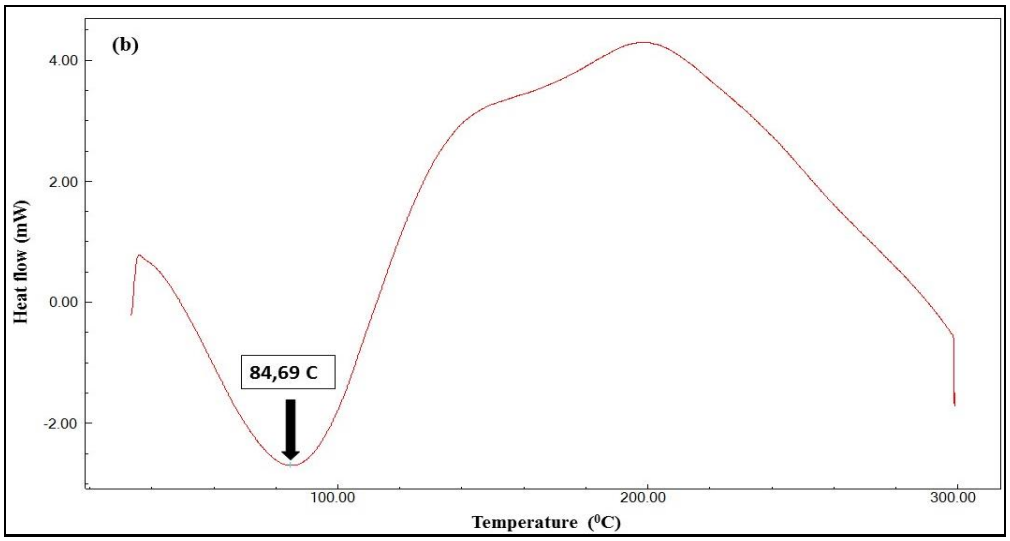


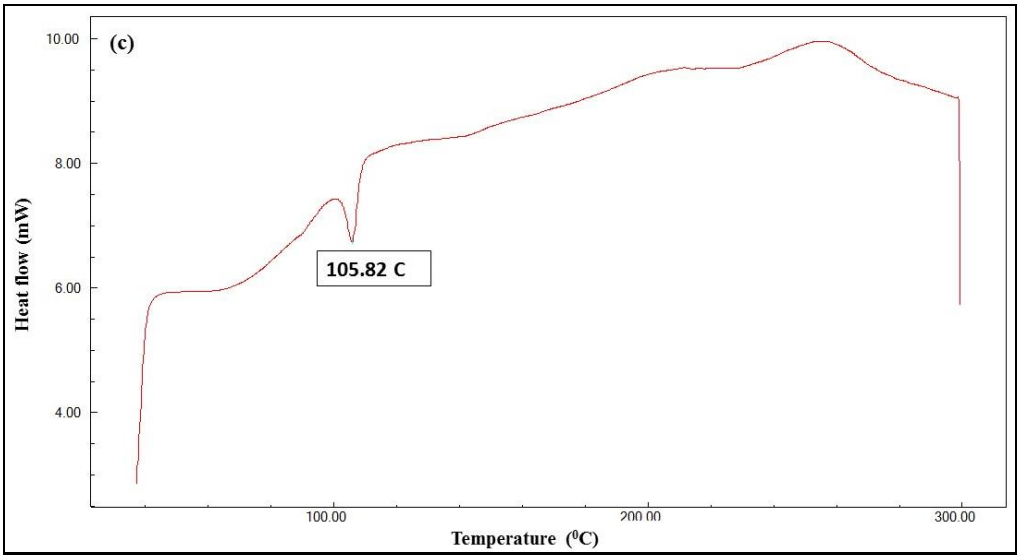
Figure -3: Cumulative Percent of the Drug Release from D: R Complex Powder in pH 1.2 and 6.8

3.4.2 Differential Scanning Calorimetry (DSC) Characterization of Sample

The thermogram of pure valsartan exhibited a sharp endothermic peak at 105.18 ºC (see Figure 4 a). The dowex2 showed broad endothermic peak at 84.69º C (see Figure 4 b) and physical mixture of valsartan-dowex2 exhibited two peaks related to drug and resin (see Figure 4 c). The valsartan-dowex2 complex exhibited a broad endothermic peak related to the resin at 74.56ºC and absence of drug endothermic peak, indicating that the drug is uniformly dispersed and in amorphous state (see Figure 4 d).


(a)
Heat flow (mW)
5.00
4.00
3.00
2.00
1.00
0.00
-1.00
105.18 C
100.00
200.00
Temperature (⁰C)


(b)
Heat flow (mW)
4.00
2.00
0.00
-2.00
84,69 C
100.00
200.00
300.00
Temperature (⁰C)


(c)
Heat flow (mW)
10.00
8.00
6.00
4.00
105.82 C
100.00
200.00
300.00
Temperature (⁰C)

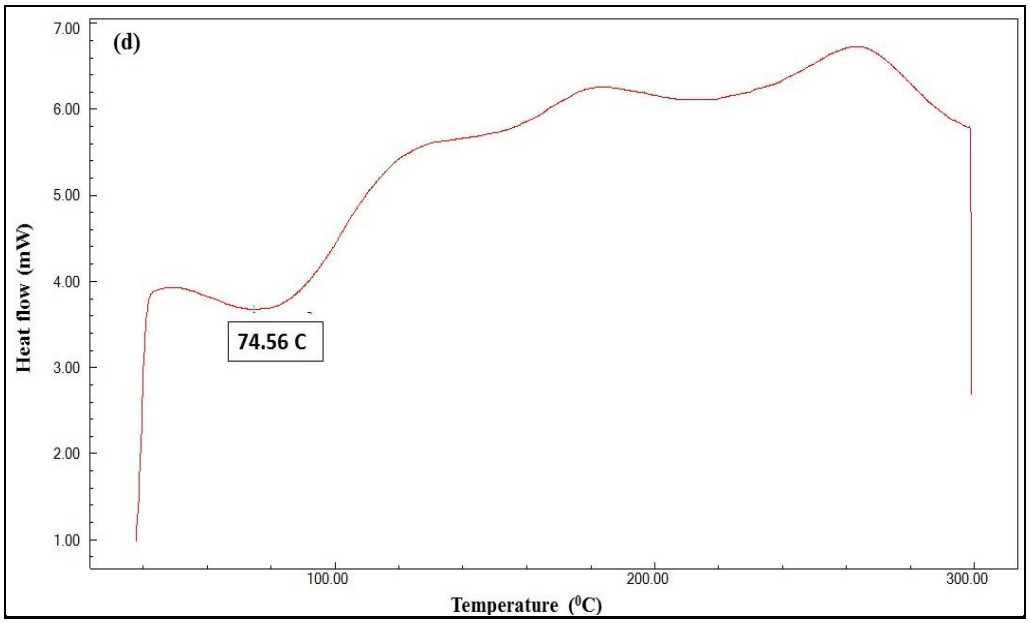


Figure-4: DSC thermograms of the (a) pure valsartan, (b) dowex2, (c) physical mixture and (d) valsartan-dowex2 chemical complex.

3.4.3 Fourier Transform Infrared Spectral (FTIR) Study

The FTIR spectra of the pure valsartan is shown in Figure (5 a), the spectra displayed peaks at 3452 and 2963cm^{-1} which are related to stretching vibration of NH and aliphatic C-H groups respectively. The characteristic peak at 1730 cm^{-1} representing the carboxylic acid C=O stretching, whereas the sharp peak at 1602 cm^{-1} resulted from bending vibration of N=N bond. The peaks 1468 and 1409 cm^{-1} were due to the N=N stretching in tetrazole ring (CN_4). The peak at 1204 cm^{-1} is attributed to stretching vibration of C-O bond. The characteristic peak at 1730 cm^{-1} representing the carboxylic acid C=O stretching, whereas the sharp peak at 1602 cm^{-1} resulted from bending vibration of N=N bond. The peaks 1468 and 1409 cm^{-1} were due to the N=N stretching in tetrazole ring (CN_4). The peak at 1204 cm^{-1} is attributed to stretching vibration of C-O bond. The characteristic peak at 759 cm^{-1} is related to aromatic C-H bending out plane [19-22].

The FTIR spectra of the dowex2, as presented in Figure (5 b) showed a peak at 3433 cm^{-1} as a result of stretching vibration of aliphatic C-H, while the peak at 2940 cm^{-1} is related to aromatic C-H stretching vibration. The peak at 1636 cm^{-1} representing the aromatic C=C stretching, whereas the peak at 1507 cm^{-1} is related to stretching vibration of C-N bond.

The FTIR spectra of the physical mixture (valsaetan-dowex2) showed all characteristic peaks related to the drug and resin (see Figure 5 c). This indicated that light mixing for short periods of time is not enough to cause an interaction between valsartan and dowex2.

The FTIR spectra of the valsaetan-dowex2 complex (as illustrated in Figure 5 d) showed a peak at1636 cm^{-1} related to amide C=O stretching vibration and disappearance a peak at 1730 cm^{-1} related to carboxylic C=O stretching of the pure valsartan. This indicated formation of valsartan-dowex2 complex by the ionic bond formation between the carboxylic group of valsartan and amide group of dowex2. The other peaks of the FTIR spectra of the valsaetan-dowex2 complex were similar to the spectra of pure valsartan and the resin.

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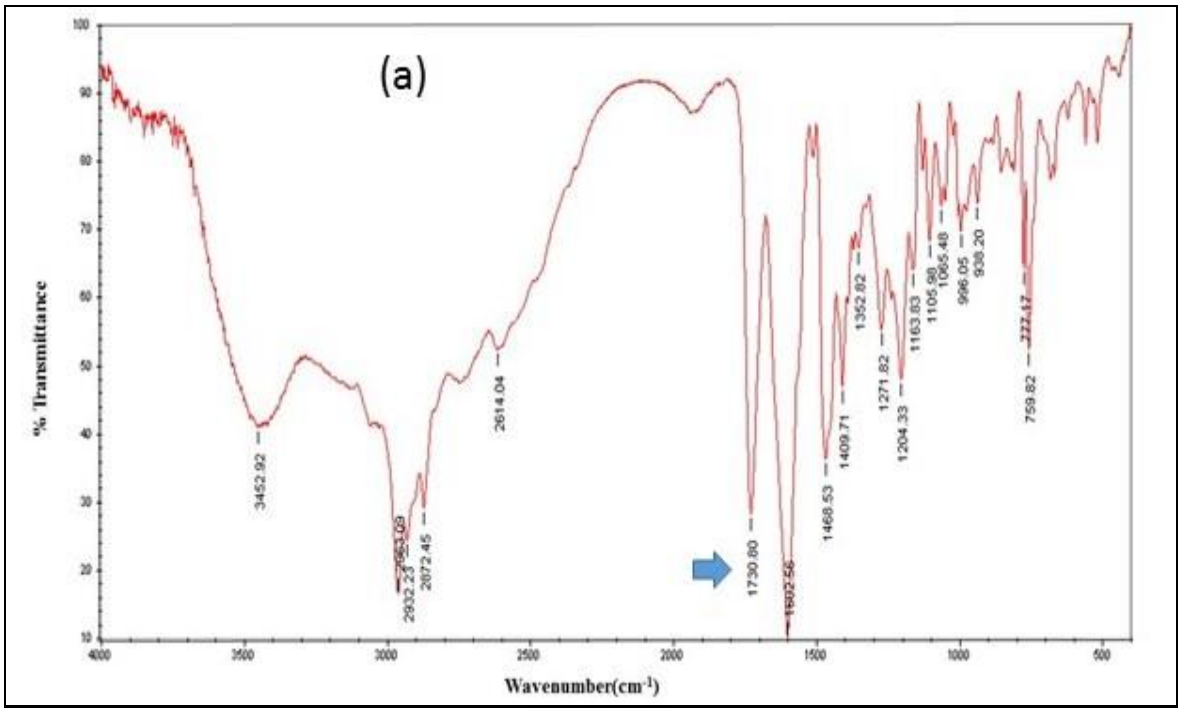
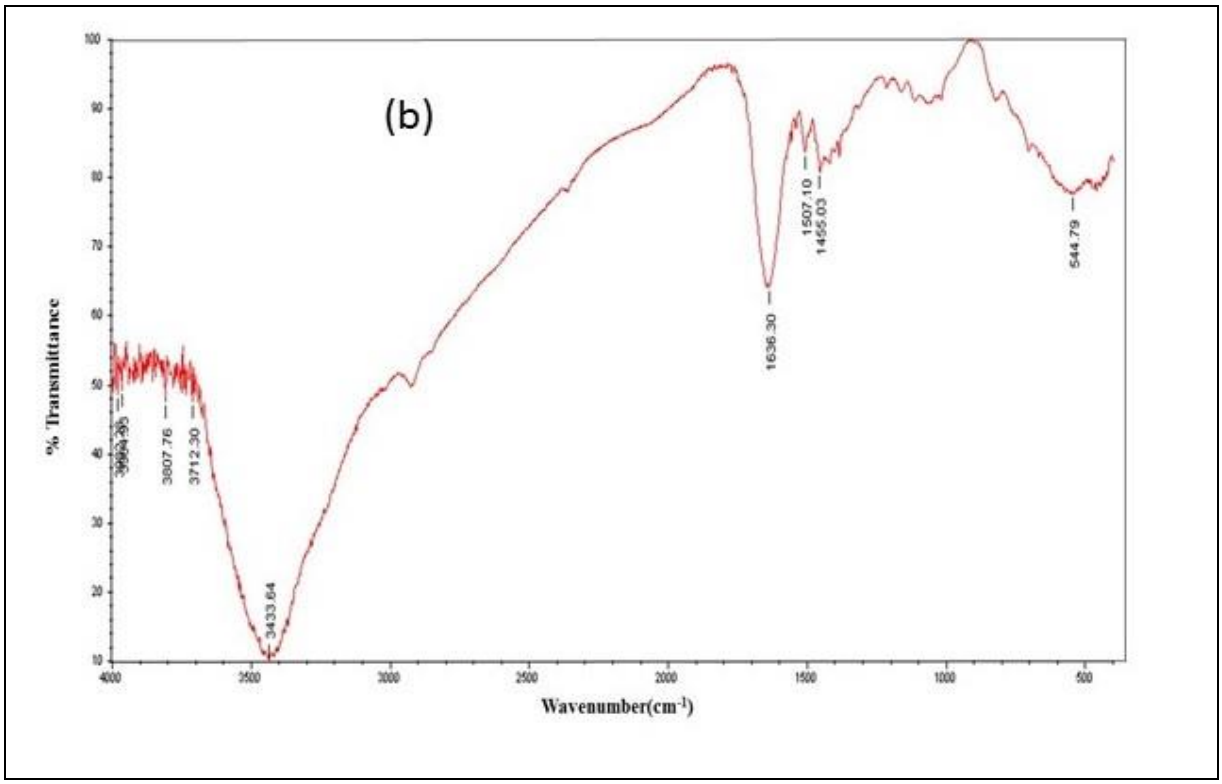

(a)
% Transmittance
Wavenumber(cm-1)
3452.92
2932.23
2872.45
2614.04
1730.60
1468.53
1409.71
1352.82
1271.82
1204.33
1163.63
1105.98
1065.48
996.05
938.20
759.82


(b)
% Transmittance
Wavenumber(cm-1)
3807.76
3712.30
3433.64
1636.30
1507.10
1455.03
544.79

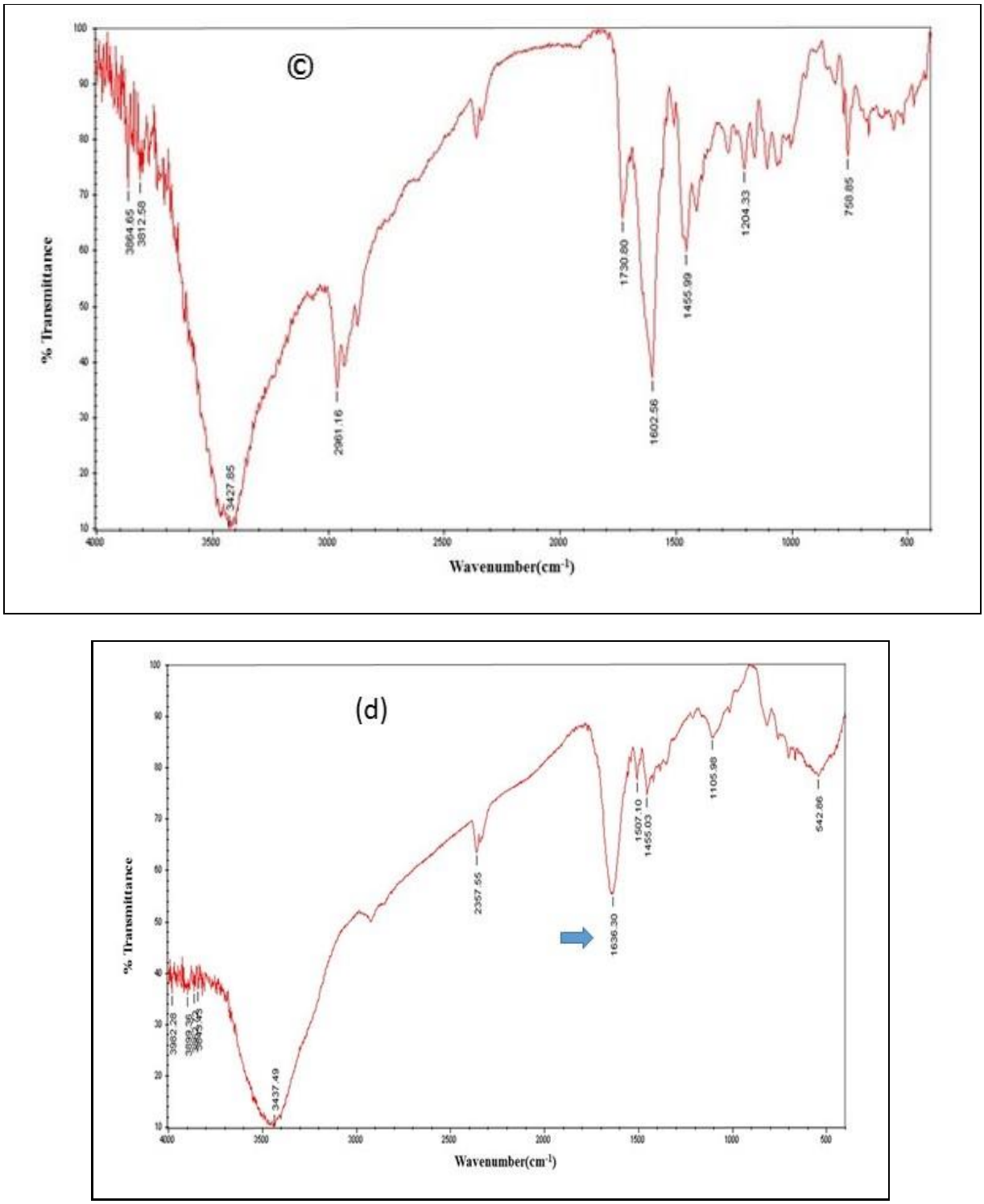


Figure-5: FTIR spectra of the the (a) pure valsartan, (b) dowex2, (c) physical mixture and (d) valsartan-dowex2 chemical complex.

3.4.4 X-ray Powder Diffraction (XRPD) Characterization of Samples

The X-ray powder diffractogram pattern of valsartan showed several diffraction peaks for example at diffraction angles (2theta) 3, 13.5, 20, 22, 43.5, 64.5 and 77.5 degree, which are indicative of its crystalline character (as displayed in Figure 6 a). The diffractograms pattern of dowex2 and physical mixture of valsartan-dowex2 are

shown in the figures 6 b and 6 c, respectively. On the other hand, the diffraction pattern of the valsartan-dowex2 complex showed a marked decrease in the intensity of the diffraction peaks at diffraction angles 3, 13.5, 22 and 43.5 degree, which could be attributed to partially conversion of the drug to the amorphous form during complexation with the resin (see figure 6 d).

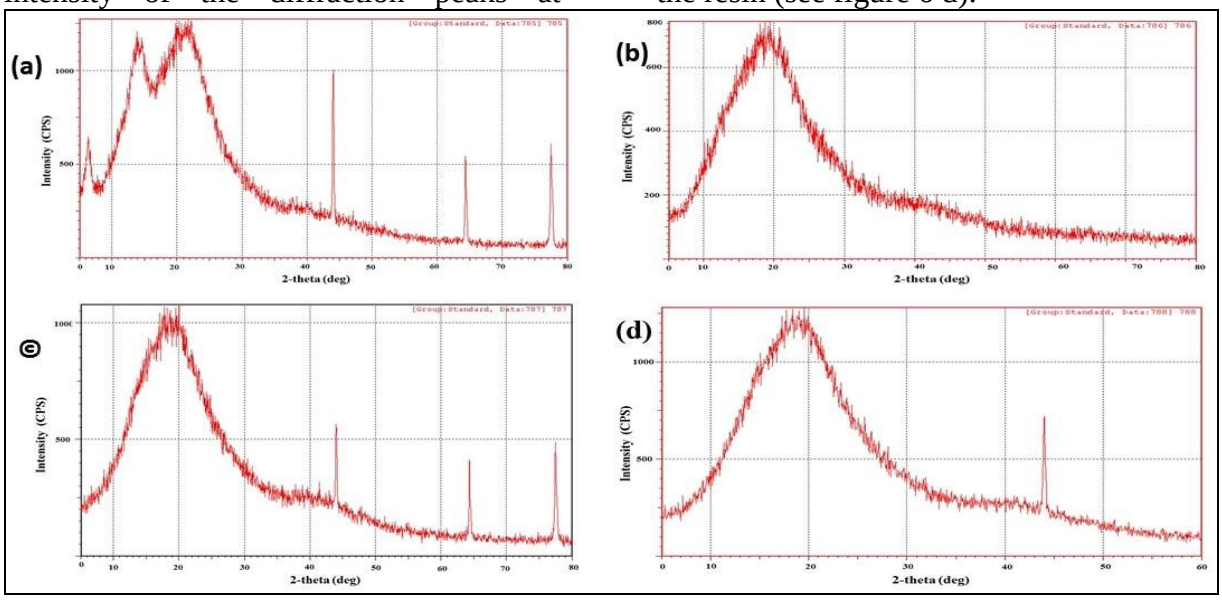


Figure-6: X-ray diffractograms of (a) pure valsartan, (b) dowex2, (c) physical mixture and (d) valsaetan-dowex2 chemical complex.

Conclusion

Based on results of this study, it can be conclude that dowex2, an anionic exchange resin, could be used for masking the bitter taste of valsartan. The optimum conditions for the preparation of valsartan-dowex2 complex are drug-resin ratio (1:8), time (4h), pH (6.8), temperature (50º C) and drug concentration (0.02 % w/v) which provided best contact between drug and resin. Also, the release of valsartan from drug-resin complex is highly increased in stomach and intestinal media.

Recommendation

It is recommended to use valsartan-dowex2 complex for the preparation of or dispersible tablets (ODTs) of valsartan and comparing the taste and release profile of conventional marketed valsartan Diovan® with the prepared ODTs.

References:

1- S. Tongay, T. Schumann, X. Miao, B. Appleton, and A. Hebard, "Tuning Schottky diodes at the many-layer-graphene/semiconductor interface by doping," Carbon, vol. 49, pp. 2033-2038, 2011.

2- A. Kumar, N. Singh, and D. Kaushik, "Taste Masking of Clarithromycin using Complexation with Ion exchange resin," Int J Pharm Tech Res, vol. 6, pp. 203-211, 2014.

3- S. Sivaneswari, E. Karthikeyan, D. Veena, P. J. Chandana, P. Subhashree, L. Ramya, et al., "Physiochemical characterization of taste masking levetiracetam ion exchange resinates in the solid state and formulation of stable liquid suspension for pediatric use," Beni-Suef University Journal of Basic and Applied Sciences, vol. 5, pp. 126-133, 2016.

4- M. E. Aulton, Pharmaceutics: The science of dosage form design: Churchill Livingstone, pp. 322-334, 2002.

5- V. Suhagiya, A. Goyani, and R. Gupta, "Taste masking by ion exchange resin and its new applications: a review," Int J Pharm Sci Res, vol. 1, pp. 22-37, 2010.

6- N. Shet and I. Vaidya, "Taste Masking: A Pathfinder for Bitter Drugs," International Journal of Pharmaceutical Sciences Review and Research, vol. 18, pp. 1-12, 2013.
7- M. Bhalekar, J. Avari, and S. Jaiswal, "Cation-exchanger in pharmaceutical formulation," Indian J Pharma Educ, vol. 38, pp. 184-8, 2004.
8- D. Bhowmik and K. S. Kumar, "Recent Trends in Ion Exchange Resins Used In Pharmaceutical Formulations-An Updates," The Pharma Research (T. Ph. Res.), vol. 4, pp. 138-148, 2010.
9- M. Dekivadia, A. Gudigennavar, and B. Umarji, "Development & optimization of fast dissolving tablet of levocetirizine HCl," International Journal of Drug Development and Research, vol. 4, pp. 2, 2012.
10- B. S. Raj, I. Punitha, and S. Dube, "Formulation and Characterization of Fast Disintegrating tablets of Amlodipine using Super-disintegrants," journal of Applied Pharmaceutical Science, vol 8,pp. 118-123, 2012.
11- Kalpana P, Manish S. Vipin S., and M. K., "mouth dissolving tablets; approach, technology involved, marketed formulation and recent trend.," International journal of pharmaceutical sciences, vol. 1, pp. 1-10, 2012.
12- R. Panigrahi, S. Behera, P. K. Choudhury, K. Chowdary, and G. Mishra, "Effect of Combination of Superdisintegrants on Fast Dissolving Tablet of Gliclazide,"International Journal of Pharmaceutical Research & Allied Sciences, vol 1, pp. 73-78 , 2012.
13- K. Bhise, S. Shaikh, and D. Bora, "Taste mask, design and evaluation of an oral formulation using ion exchange resin as drug carrier," AAPS PharmSciTech, vol. 9, pp. 557-562, 2008.
14- D. Douroumis, "Practical approaches of taste masking technologies in oral solid forms," Expert opinion on drug delivery, vol. 4, pp. 417-426, 2007.
15- T. Puttewar, M. Kshirsagar, A. Chandewar, and R. Chikhale, "Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin," Journal of King Saud University-Science, vol. 22, pp. 229-240, 2010.
16- Anand V, Kandarapu R, Garg S, "Ion-exchange resins: carrying drug delivery forward," Drug Discovery Today, vol. 6, pp. 905-914, 2001.
17- Swapnil umakant wani, Prashant Shamkuwar, Ashwini Nagnath Yerawar, and Ramandeepsingh Bedi, "Formulation of Drug-Resin complex and evaluation of its molecular property & release kinetics," Scholars Research Library, vol. 2, pp. 155-164, 2010.
18- P. Akkaramongkolporn, K. Terada, and E. Yonemochi, "Molecular properties of propranolol hydrochloride prepared as drug-resin complexes," Drug development and industrial pharmacy, vol. 27, pp. 359-364, 2001.
19- E. G. C. Clarke, Isolation and identification of drugs in Pharmaceuticals, body fluids, and post-mortem material. Vol. 2: The Pharmaceutical Press, 17 Bloomsbury Square, London WC1A2NN., pp. 873-1258, 1975.
20- N. Chella, N. Shastri, and R. R. Tadikonda, "Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan," Acta Pharmaceutica Sinica B, vol. 2, pp. 502-508, 2012.
21- A. K. Mahapatra, P. Murthy, S. Biswal, A. P. Mahapatra, and S. P. Pradhan, "Dissolution Enhancement and Physicochemical Characterization of Valsartan in Solid Dispersions with β-CD, HP β-CD, and PVP K-30,"

Dissolution technologies, vol. 18, pp. 39-45, 2011.

22- W.-J. Xu, H.-J. Xie, Q.-R. Cao, L.-L. Shi, Y. Cao, X.-Y. Zhu, et al., "Enhanced dissolution and oral bioavailability of valsartan solid dispersions prepared by a freeze-drying technique using hydrophilic polymers," Drug delivery, vol. 23, pp. 41-48, 2016.