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Design, synthesis, and biological evaluation of some new charge transfer complexes as a combination model

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ABSTRACT

The present work includes design and synthesis a new model of charge transfer complexes from simvastatine which is antihyperlipidemic drug as acceptor with angiotensin receptor blockers(candesartan, losartan, valsartan, telmisartan, irbesartan) as donors and characterization the models by UV, FT-IR, HNMR spectrophotometry, it shows change in spectral peaks which refer to formation of charge transfer complexes. And study the effect of interaction on availability of drugs with the time, different PH and different concentrations. Which shows the variability in availability of drugs in combination (charge transfer complexes) due to PH, concentration, and time changing, this variability in availability mostly effect on simvastatine which mean decrease or absence the availability of simvastatine and increase the availability of angiotensin receptor blockers (mostly not absolutly). Beside this we study the evaluation of biological activity of combinations and compare with the biological activity of simvastatine alone on the lipid profile of rabbits , by induced hypercholesterolemia in rabbits for two weeks (except the positive control group) and gave the drugs for four weeks and measuring the lipid profile changing in order to improve the change in the efficacy of simvastaine alone and simvastatine in combinations and this variability due to donor-acceptor interaction (charge transfer interaction)

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INTRODUCTION

The term charge transfer complex (CTC) was first used by Mulliken. He describes a new type of adduct to describe the behavior of certain molecular groups, which do not adhere to the traditional patterns of ionic, covalent, and hydrogen bonding components. While these adducts generally retain some of the component properties, some changes are obvious. For example, its solubility, its diamagnetic and paramagnetic susceptibility. Charging interactions within a molecular complex consisting of an electron donor D and an electron acceptor A include resonance with charging transfer from D to A (Abdulredha, 2015).

It is important phenomenon in the process of biochemical and bioelectrochemical energy. The term charge transfer gives kind of complex resulting from donor and acceptor interactions with the formation of weak bonds and widely discussed by Foster. In molecular interactions between electron donors and receivers are correlated with formation of strongly colored charge Transfer complexes (CTCs) which absorb radiation in visible region. Important processes in biological systems are molecular complexation and structural recognition. Drug action, catalysis of enzymes and movement of ions

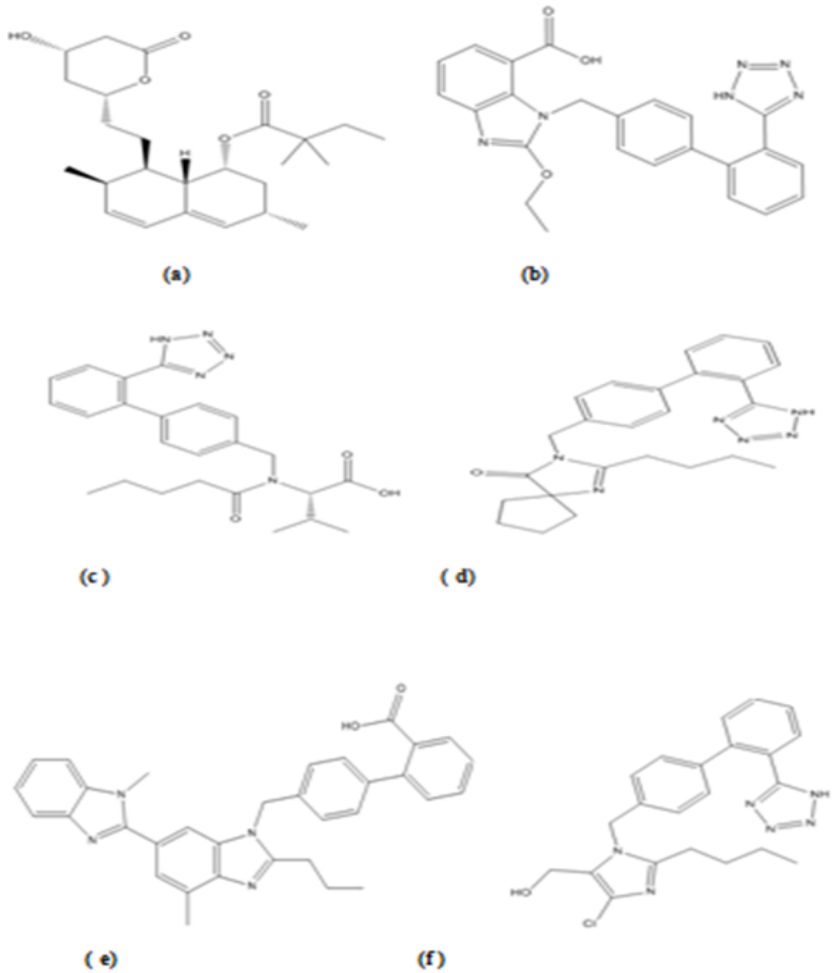

Figure 1: Chemical structures of (a) simvastatine (b) candesartn (c)valsartan (d) irbesartan (e) telmisartan (f) losartan

via lipophilic membranes all require complexation.

The key directors of the specificity, rate regulation and reversibility are the characteristics in many biochemical reactions (Arslan and Duymus, 2007). Many drugs are easily identifiable by spectrophotometry on the basis of complex color transfer charges formed between electron acceptors and electron donors. Methods of analyzing many drugs are recorded mainly by direct UV spectrophotometry, fluorometry, polarography, colorimetry and HPLC (Duymus *et al.*, 2006). The charging-transfer (CT) reaction between electron-donating and electron-accepting molecules is of considerable importance in various fields of chemistry due to their existence in biological systems, widespread applications as organic electrical conductors, the study of drug-receptor interaction mechanisms, the storage of solar energy and the study of thermodynamics and pharmacodynamics In medical molecules. CT reactions are generally associated with the development of strongly colored CT complexes, which normally absorb radiation; however, a new light-absorbing band exists at much longer wavelengths than in the CT complex component spectrum. The rapid creation of these complexes results in their comprehensive usefulness in the production of spectrophotometric methods for analyzing many organic and/or pharmaceutical molecules (Darwish *et al.*, 2014), spectrophotometric assays offer significant economic advantages over gas chromatography and high-performance liquid chromatographic techniques (Shahdousti *et al.*, 2008). Obtain quantitative estimates of drugs in pure form or in cheaper, faster, quicker and more precise pharmaceutical preparations. Plays important roles in many biological fields such as DNA-binding, antibacterial, antifungal and insecticidal Some CT drug complexes exhibit antimicrobial activity against gram-positive and gram-negative bacteria and fungi (Adam, 2014)

Chemistry of CT or H-bonding interactions between either drugs or biological compounds and small organic or inorganic solid-state molecular acceptors In recent years, the solution has attracted growing

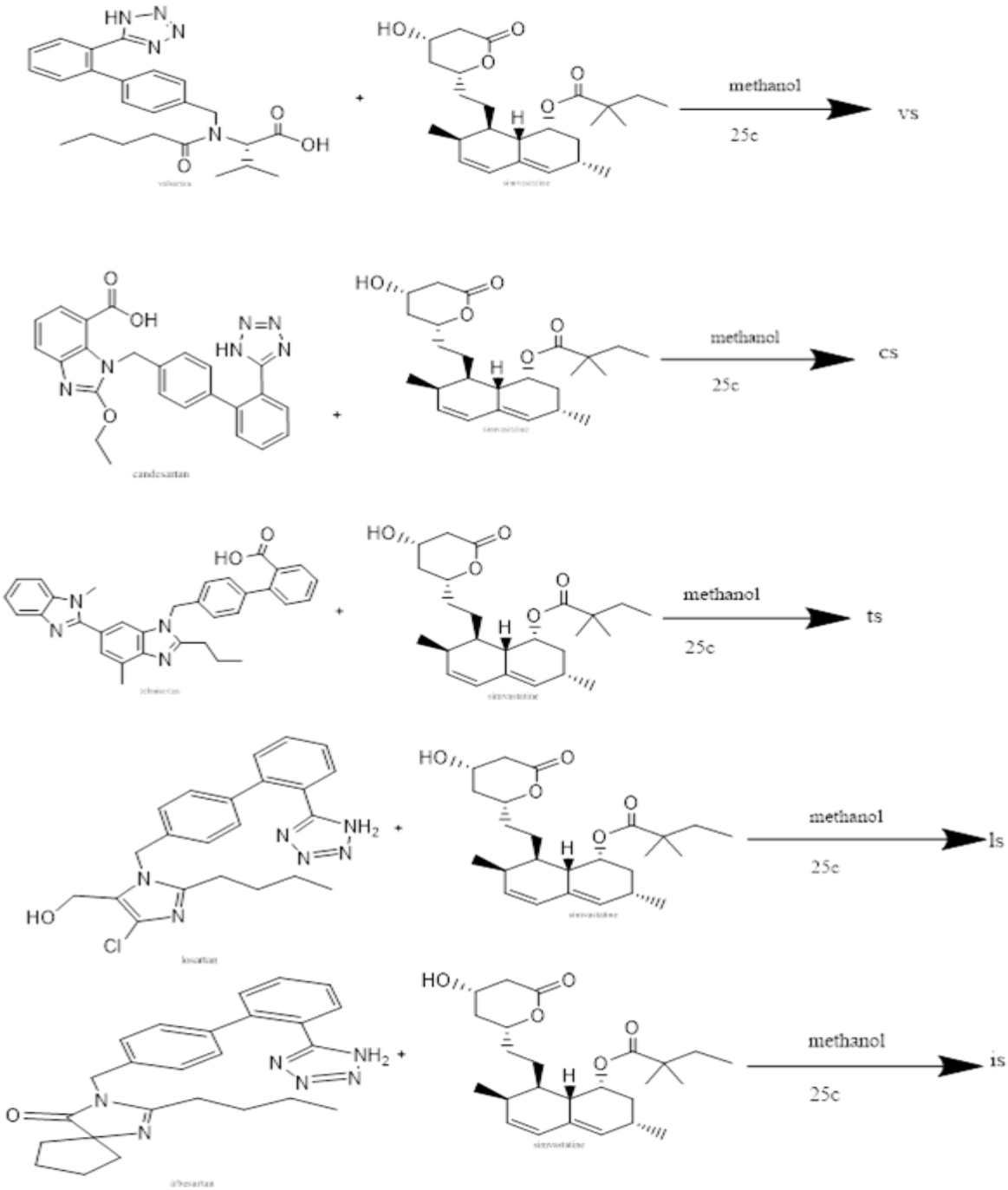

Figure 2: Synthesis of complexes

attention, considerable interest and increasing significance and has become a common research area. There are many examples for charge transfer complex such as cloxacillin sodium with riboflavin (Roy *et al.*, 2006), vitamin K with quinine and quinidine (Dozal *et al.*, 2000), losartan with iodine (Darwish, 2005), losartan with antidiabetic (Mirza *et al.*, 2013), determination of dapson by charge transfer complex formation with chloranil (Al-Ennizi *et al.*, 2020), complex formation with metals (Nawar *et al.*, 2020).

Objective of the work

1. Synthesis a complex model from combination of two drugs by a charge transfer complex formation.
2. Study the effect of solvents on complex.
3. Study the effect of time on complex.
4. Study the effect of temperature and PH on complex.

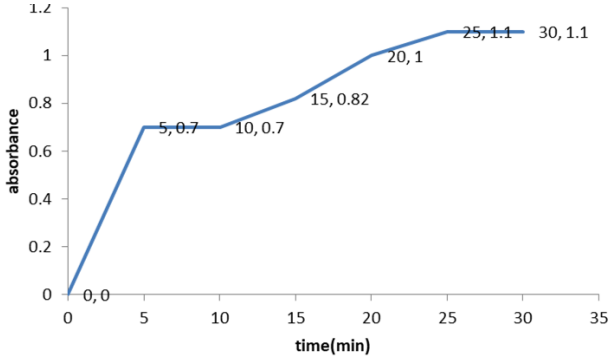

Figure 3: Asorbance of complex 1 spectra versus time

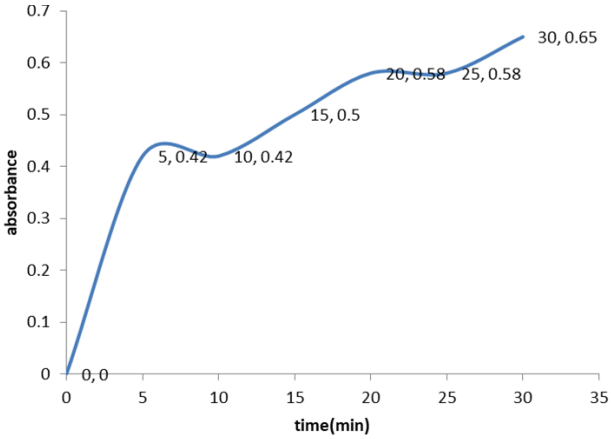

Figure 4: absorbance of complex 2 spectra versus time

5. Evaluation the bioavailability of each drug in complex.

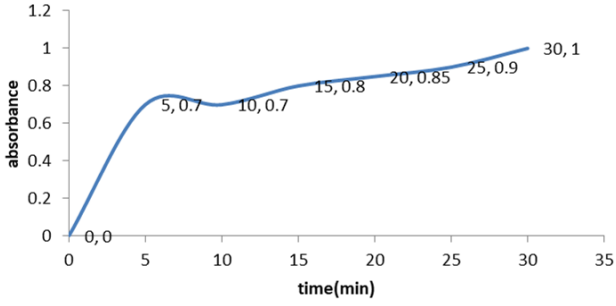

Figure 5: Absorbance of complex 3 spectra versus time

MATERIALS AND METHODS

Chemicals

1. Candesartan, sigma –aldrich Germany.
2. valsartan, sigma –aldrich Germany.
3. irbesartan, sigma –aldrich Germany.

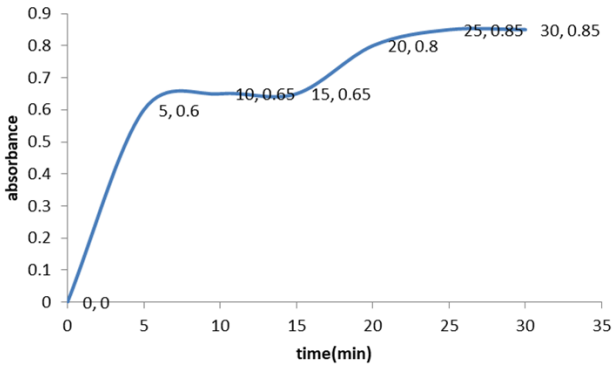

Figure 6: Absorbance of complex 4 spectra versus time

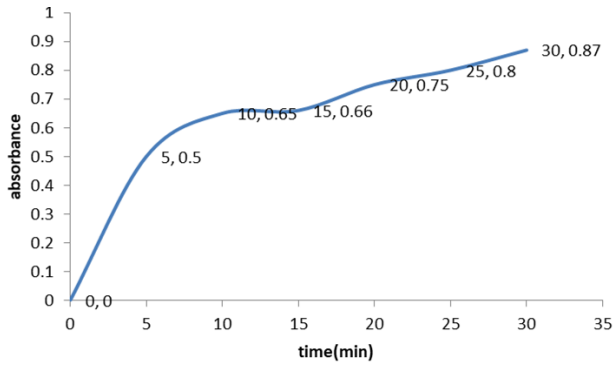

Figure 7: Absorbance of complex 5 spectra versus time

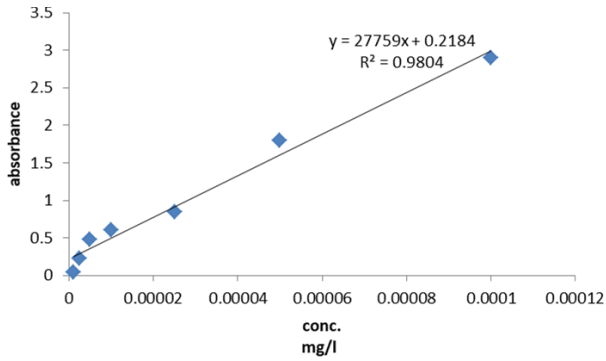

Figure 8: Absorbance of complex 1 spectra versus conc

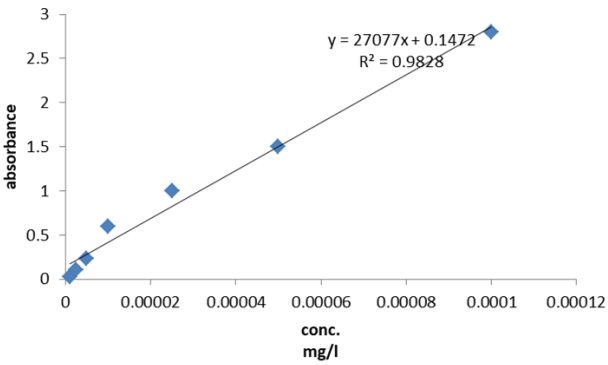

Figure 9: Absorbance of complex 2 spectra versus conc

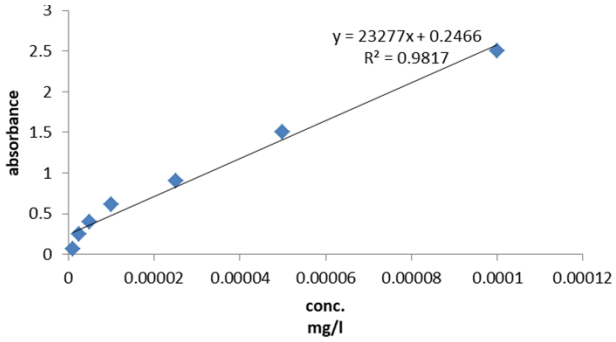

Figure 10: Absorbance of complex 3 spectra versus conc

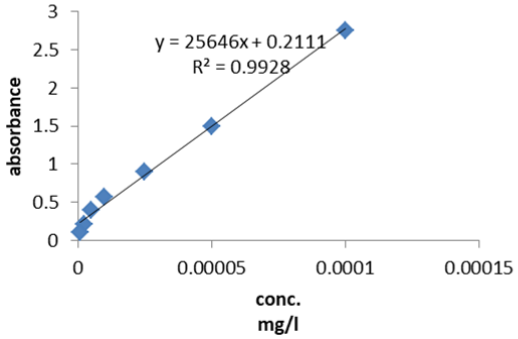

Figure 11: Absorbance of complex 4 spectra versus conc

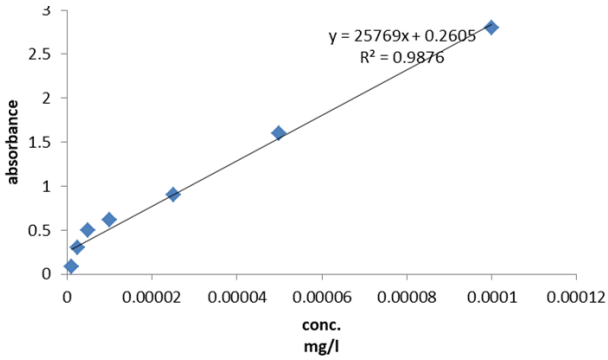

Figure 12: Absorbance of complex 5 spectra versus conc

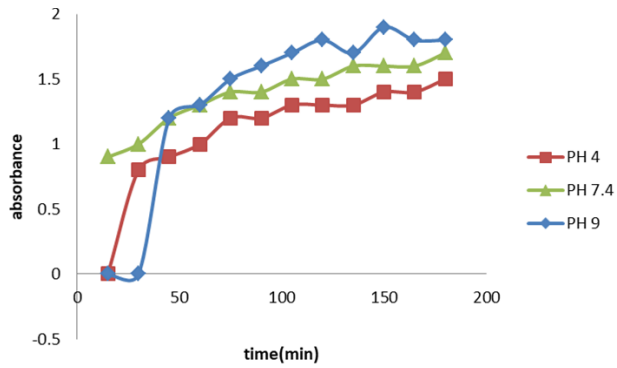

Figure 13: Effect of PH on simvastatine in complex 1

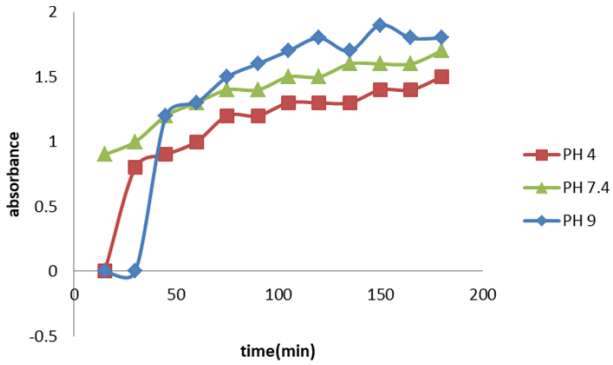

Figure 14: Effect of PH on simvastatine in complex 2

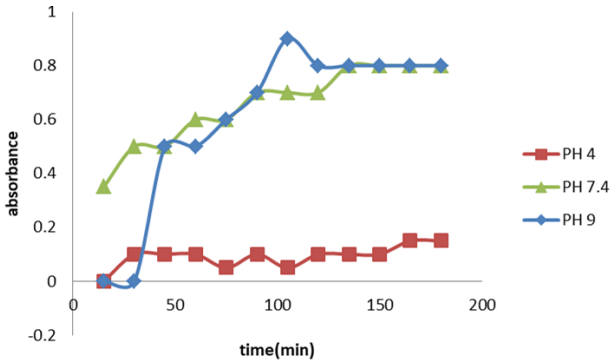

Figure 15: Effect of PH on simvastatine in complex 3

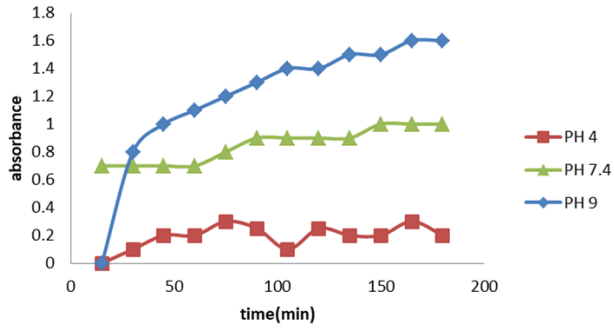

Figure 16: Effectof PH on simvastatine in complex 5

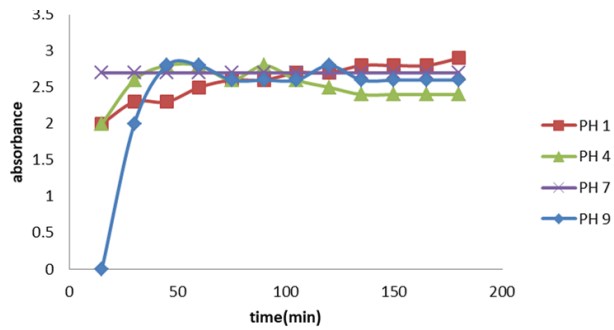

Figure 17: Effectof PH on candesartan in complex 1

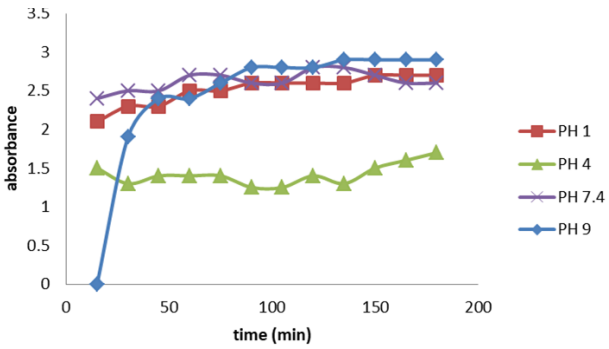

Figure 18: Effect of PH on valsartan in complex 2

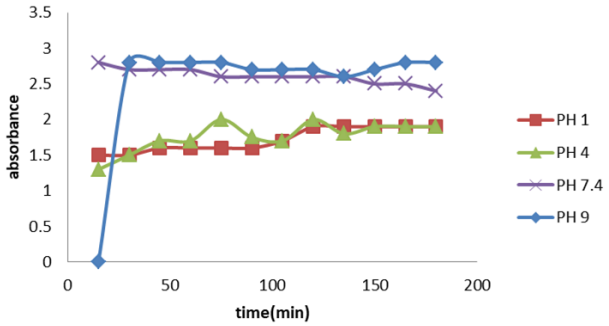

Figure 19: Effect of PH on irbesartan in complex 3

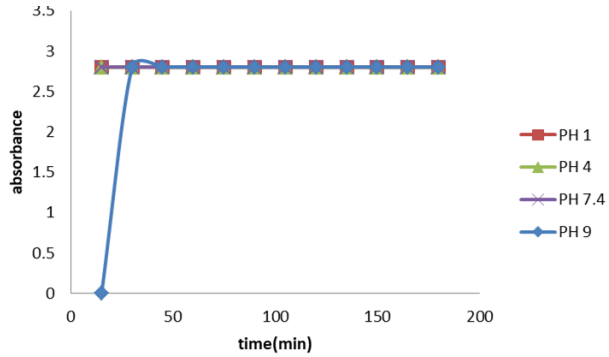

Figure 20: Effect of PH on telmisartan in complex 4

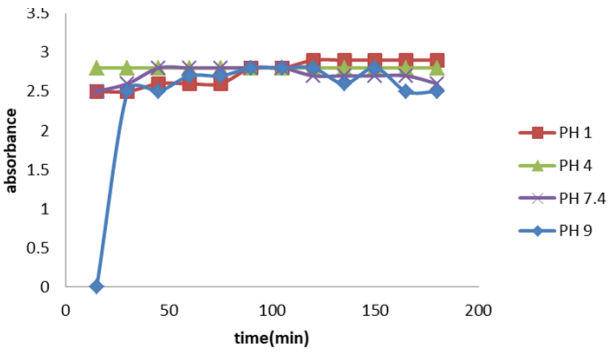

Figure 21: Effect of PH on losartan in complex 5

4. telmisartan, sigma –aldrich Germany.
5. Losartan potassium, sigma –aldrich Germany.
6. simvastatine, sigma –aldrich Germany.
7. Acetone,
8. Sodium hydroxide, Merck Germany.
9. Ethanol,
10. Methanol, sigma –aldrich Germany.
11. Ethyl acetate,
12. Dmso India
13. Dichloromethane, Ajax chemical Australia
14. Chloroform India
15. Hexane, Merck Germany.
16. Hydrochloric acid, Merck Germany.
17. Sodium carbonate.

Synthesis

Dissolve (1mmole) (0,41857 gm) of Simvastatin (acceptor) in 40ml of methanol. Dissolve (1mmole) of sartans (donors): 0,44045 gm candesartan/0,43552 gm valsartan/0,4285 gm irbesartan/0,5146 gm telmisartan/0,42291 gm losartan (as seen in Figure 1) each of these sartans in 40 ml of methanol separately. The solutions have been mixed (each donor has an acceptor) with regular stirring and reflux in a round bottom flask. TLC had monitored and tracked the progress of the reaction. Solvent was evaporated after the reaction was completed. Re-crystallization of the compounds in methanol purified the products: chloroform (8:2) (Arayne *et al.*, 2009). The products of reaction seen in Table 1, Figures 2 and 22.

RESULTS AND DISCUSSION

Ultraviolet spectra

Use Cecil 7200 spectrophotometer at the department of pharmaceutical /collage of pharmacy /university of Basrah. from UV analysis lambda max of drugs 230.5, 237.5, 246 nm for simvastatin. and for sartan from (1 to 5), and 251, 252, 246, 293 and 246.5 nm respectively. For candesartan, valsartan, irbesartan, telmisartan and losartan.

FT.IR spectrum

Infrared spectra of the synthesized compounds were recorded by FT-IR. 8400S Shimadzu. spectrophotometer (Japan) using KBrdisk in range 4000-400 cm^{-1} at Department of pharmaceutical chemistry /collage of pharmacy /university of Basra.

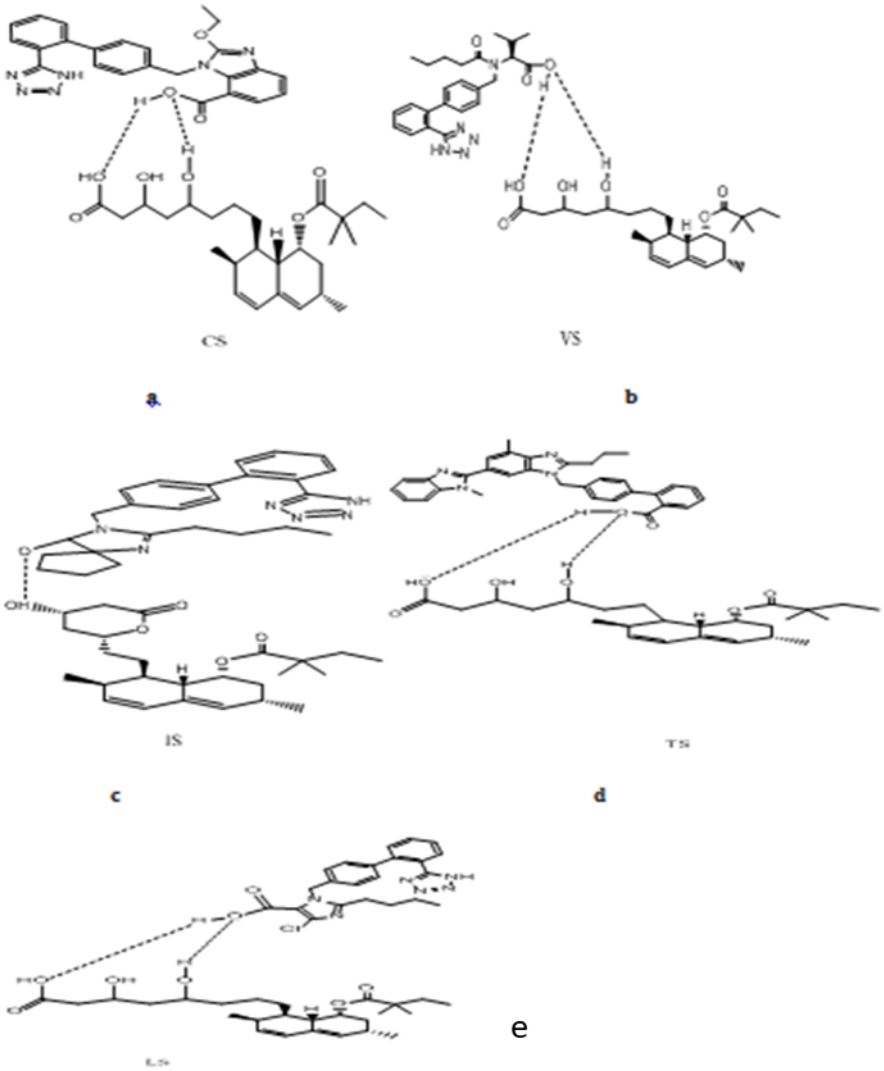

Figure 22: (a)complex1 (b) complex 2 (c) complex 3 (d) complex 4 (e) complex 5

Table 1: Features of Complexes

Compound	Combination	Molecular formula	Molecular weight	Colour	Melting point °C.
Complex1	candesartan	C49H58N6O8	859.02	White powder	174-176
Complex2	valsartan	C49H67N5O8	854.09	White powder	100-102
Complex3	irbesartan	C50H66N6O6	847.07	White powder	157-159
Complex4	telmisartan	C58H68N4O7	933.17	White powder	150-152
Complex5	losartan	C47H61N6O6	841.47	White powder	160-167

Complex 1

Show strong broad at 3475 cm^{-1} refer to O-H, at 3444 cm^{-1} attributed N-H, strong band at 3059 refer to C-H aromatic, C-H aliphatic at 2966,2931,2873 cm^{-1}, strong band at 1716 cm^{-1} refer to C=O, and C=N, C=C, C-O, C-N at 1624, 1473, 1261, 1056 cm^{-1} respectively.

Complex 2

Show strong broad at 3444 cm^{-1} refer to O-H, at 3066 cm^{-1} attributed N-H, C-H aromatic overlap by O-H, C-H aliphatic at 2970, 2935, 2877 cm^{-1}, strong band at 1705 cm^{-1} refer to C=O, and C=N, C=C, C-O, C-N at 1612, 1480, 1242, 1037 cm^{-1} respectively.

Complex 3

Show strong broad at 3383 cm^{-1} refer to O-H, C-H aromatic overlap by O-H, C-H aliphatic at 2931, 2877 cm^{-1}, strong band at 1728 cm^{-1} refer to C=O, and C=N, C=C, C-O, C-N at 1620, 1462, 1253, 1060 cm^{-1}

Table 2: Lipid Profile Results

Group	Cholestrol 0	Cholestrol 2	Cholestrol 4	TG 0	TG 2	TG 4	LDL 0	LDL 2	LDL 4	HDL 0	HDL 2	HDL 4
s	58	106	30	80	110	70	31	46	39	29	25	25
s	69	110	19	140	167	115	32	40	40	27	30	20
s	61	98	15	90	146	80	40	42	35	29	30	20
c+s	82	95	36	92	105	95	37	42	38	29	31	29
c+s	65	67	30	105	100	90	34	35	29	26	24	22
c+s	77	100	52	80	110	75	31	35	30	23	22	24
v+s	80	90	25	62	90	80	34	39	40	25	20	19
v+s	72	85	40	94	98	80	38	43	33	22	25	23
v+s	35	76	32	66	114	86	30	42	39	25	21	25
l+s	36	60	45	60	100	100	31	41	39	26	25	19
l+s	47	85	30	75	118	95	39	43	40	30	31	23
l+s	52	112	70	56	122	105	30	31	33	25	23	24
i+s	43	80	32	50	95	80	36	42	37	29	26	20
i+s	36	60	30	140	162	140	32	34	36	26	26	22
i+s	22	63	39	75	120	95	29	31	32	28	24	23
t+s	47	78	40	95	109	109	28	36	42	29	25	27
t+s	43	69	20	80	97	97	27	35	36	28	24	20
t+s	80	105	70	90	110	90	25	30	25	27	26	25
c+	34	35	38	73	85	110	42	40	40	27	30	32
c+	29	25	15	65	68	70	37	34	37	25	22	25
c+	18	25	15	60	70	90	32	33	37	23	25	22
c-	32	90	75	115	123	120	31	40	43	23	30	35
c-	32	27	80	80	110	170	36	49	65	26	23	25
c-	100	104	115	125	155	155	41	45	50	32	27	25

respectively.

Complex 4

Show strong broad at 3383cm^{-1} refer to O-H, C-H aromatic overlap by O-H, C-H aliphatic at 2928cm^{-1}, strong band at 1712 cm^{-1} refer to C=O, and C=N, C=C, C-O, C-N at 1658, 1454, 1084, 1045cm^{-1} respectively.

Complex5

Show strong broad at 3378 cm^{-1} refer to O-H, C-H aromatic overlap by O-H, C-H aliphatic at 2928, 2877 cm^{-1}, strong band at 1716 cm^{-1} refer to C=O, and C=C, C-O, C-N at 1462, 1257, 1026cm^{-1} respectively.

As a result of all complexes peaks ; there is a broad OH band, shift C=O band of carbonyl to the right, decrease the intensity of C=C, C-O, and C-N bands.

^{1} H-NMR Spectra

The compounds were studied for ^{1}H-NMR Spectra at the analytical Laboratory of Tehran University, College of Sciences, Chemistry Department, using 500MHz NMR (INOVA Switzerland). DMSO-d_6 was used as a solvent and TMS as an internal standard. As a consequence of all HNMR complex peaks Most peaks are moved to the right (shielding).

Study the effect of solvents on charge transfer complexes

Dissolve 1* 10-5 molar concentrations of each complex (1 to 5) in 10 ml of each solvent (acetone, dichloromethane, chloroform, methanol, ethanol, dmso) and watch the effect by UV spectroscopy. The Study shows that the use of ethanol and methanol as solvents is ideally suited to stability of complexes.

Study the effect of time on charge transfer complexes

Dissolve 1* 10^{-5} molar concentration of each complex (1 to 5) and determine the effect by UV-spectroscopy within 5 to 30 min, with 5 min as interval.

As seen in Figures 3, 4, 5, 6 and 7 and this is mostly referred to raise the concentration of complexes after 5 min of addition or mixing.

Study the effect of concentration on charge transfer complexes

Various concentrations of complexes versus absorbance. As in Figures 8, 9, 10, 11 and 12 and this to improve the concentration is located with the linearity which is $1^{*}\ 10^{-5}$ according to beer's law (Ibezim, 2012).

Study of interaction

Using Caleva dissolution tester at Department of pharmaceutical /collage of pharmacy /university of Basrah. simvastatin interaction with sartan was performed in vitro in the same set of dissolution media. Simvastatin was added to the dissolution medium already established at 37 ° C at zero time in each set of experiments, while sartan was added after 15 minutes of time interval. aliquots were removed and assayed. Absorbance of each drug versus time In each experiment set was determined (Arayne *et al.*, 2006). As in Figures 13, 14, 15, 16, 17, 18, 19, 20 and 21 and from this study we see the availability of sartan increase mostly while availability of simvastatine decrease or absent at PH 1,4, 7.4 and 9. (availability of simvastatine in complex 4 is zero). So the effect of PH on complexes is various due to acidity and basicity

Biological activity

Using 24 white rabbits (male) (weight 1.5 to 2 kg) divided into 8 groups each one includes 3 rabbits five group for five complexes and one negative control and one for positive control and one for simvastatine alone ,induce hypercholesterolemia for two week to all groups (except the positive control group). After this period the drug model was given to each category as a classification for four weeks, then the lipid profile (cholesterol, triglyceride, LDL, HDL) was calculated and the difference in availability was found between the complex and simvastatin alone (Mohammadi *et al.*, 2009; Mehta *et al.*, 2003; Cavallini *et al.*, 2009)as seen in Table 2.

Abbreviations For Table 2 is given below,

1. TG= triglyceride
2. LDL = low density lipoprotein
3. HDL=high density lipoprotein
4. 0 = zero time
5. 2 = after 2 weeks
6. 4 = after 4 weeks
7. S = simvastatine
8. C+S = complex 1
9. V+S = complex 2
10. i+s= complex 3
11. t+s= complex 4
12. l+s= complex 5
13. c+ = positive control
14. c- = negative control

CONCLUSIONS

Charge transfer complexes (1,2,3,4 and 5) characterized by the UV, IR, HNMR spectrophotometry studies. The effect of CT interactions that decrease or increase the availability of acceptor or donor and this depends mostly on temperature and PH. In this study, the availability of simvastatin (acceptor) is shown to be decreased or absent and increased for donors (1,2,3,4 and 5). Dose adjustment for both drugs (acceptor and donor) is required if both drugs are given at the same time or in conjunction with two drugs. The biological activity of the combinations is not clear because the sample is small (three rabbits in each group) and a large sample (at least 10 rabbits in each group) is required for further studies. To get a good picture of the difference between combinations and simvastatin alone for the effect on the lipid profile.

ACKNOWLEDGEMENT

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Funding Support

Nil.

Conflict of Interest

Nil.

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