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Separation and Pre-Concentration for the Spectrophotometric Determination of Chloramphenicol in Pharmaceutical Preparations

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Abstract : A new simple, rapid, sensitive, selective, and accurate cloud point extraction method for the spectrophotometric determination of Chloramphenicol (CAP)in different pharmaceutical preparations. Chloramphenicol **as** active antibiotic is widely used in the treatment the diseases. The spectrophotometric method is based on the condensation reaction between CAP and 1,2naphthoquinone-4-sulfonic(1,2 NQS) as reagent to formed aorange-red compound after reducing nitro group in drug into amino group by used a concentratedHCl and zinc dust. The product was extracted with triton X 114 by cloud point extraction technique to increase sensitivity of method, range-red compound was showed a maximum absorption at 489nm. Beers law was obeyed in the concentration rangeof0.1-6µg.mL^{-1} with a molar absorptivity (7.49 x 10^{4})L. mol^{-1}.cm^{-1},andsandell's sensitivity (4.31x 10^{-3}) µg.cm^{-2},respectively. The analytical parameters were optimized as the following: The best temperature is(1-60 °C), the reaction completed directly with addition NQS to drug and the best volume of NQS solutionis1mL.Limit of detection (LOD),and limit of quantification (LOQ)are0.032 ppm, and 0.097 ppm, respectively, E%, Rv and fc was 99.92, 0.3, 3.33333 respectively, the recoveries range98.53%-103.37%.Themethodwas successfully applied to the analysis of the (CAP)units pharmaceutical preparations(Eye drops ,Ointments and Capsules).

Key words: Drugs, Chloramphenicol (CAP), 1,2naphthoquinone-4-sulfonic(1,2 NQS), condensation reaction, Pharmaceutical preparation.

Introduction

Chloramphenicol is 2,2-dichloro-N-[(1R,2R)-2-hydroxy1(hydroxymethyl)-(4nitrophenyl) ethyl] acetamide. ($C_{11}H_{12}Cl_2N_2O_5$)Fig.1A white, greyish-white or yellowish-white, fine, crystalline powder or fine crystals, needles or elongated plates , a little soluble in water, freely soluble in alcohol and in propylene glycol, the melting point of this drug 149 °C to 153 °C[1]

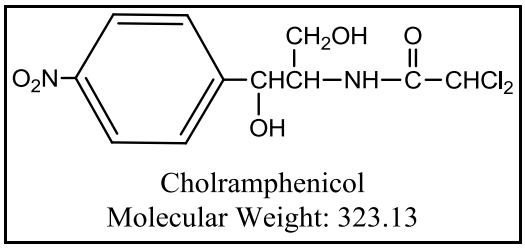


Fig. 1: Chemical structure of chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic It is active against the diseases caused by aerobic and anaerobic gram-positive also gram- negative organisms[2]. Chloramphenicol was initially obtained from Streptomyces Venezuelae in 1947, it was soon synthesized by chemical processes and the commercial product now is all synthetic [3]. Chloramphenicol is one of the few natural nitro compounds , active inhibitor of protein synthesis of microbial. It usually binds to the 50S subunit of ribosome of the bacterial and inhibits formation the peptide bond[2-6]. Chloramphenicol is distributed to body fluids and all tissues such the central nervous system also cerebrospinal fluid therefor the concentration of chloramphenicol in brain tissue usually be equal to that in serum due to the drug transfer through cell membranes readily[2].Chloramphenicol is an antimicrobial agent with restricted use. It is used to combat serious infections where other antibiotics are ineffective. Because of its risk to cause cancer, aplastic anemia and carcinogenic properties, its use in human and veterinary medicine is limited by its toxicity[7].

The adverse effects of this compound have led to restrict its use in both human and veterinary medicine[8].Severalmethodshave been used for determination of chloramphenicol in pharmaceutical dosage forms such a spectrophotometric methods[9-11,] chromatographic methods[12-14], electrochemical methods[14-16], flow-injection analysis methods[16-18.]

Cloud point extraction (CPE)

A. Basic concept of CPE

CPE techniques use a characteristic property of many nonionic surfactants that form micelles in aqueous solution: they become turbid when heated to the suitable cloud point temperature. Above the cloud point temperature, the micellar solution will separates into a larger diluted aqueous phase and a small surfactant rich phase. In the aqueous phase, the concentration of surfactant will be near the critical micelle concentration. In the surfactant-rich phase, any analyte solubilized in the hydrophobic core of the micelle in the solution will be concentrated, following the cloud point extraction.[19]

B. Surfactants

Structures of surfactants have amphiphilic property consisting of a hydrophilic and a hydrophobic part. These special structures cause their surface-active properties like concentration at surfaces, reduction of the surface tension, and formation of micelles in bulk solution. Therefore, they are widely used in formulations for washing, wetting, emulsifying, and dispersing. Laundry detergents, cleaning agents, and personal care products are by far the largest class of surfactant containing products for domestic use. [20]

C. Classification of surfactants

The most agreeable classification of surfactants is based ontheir dissociation in water.

A-Anionic Surfactants

In water, anionic Surfactants are dissociated in an amphiphilic anion, and a cation,which is an alkaline metal (Na^+, K^+) or a quaternary ammonium. Anionic surfactants account for about 50 % of the world production.

b- Nonionic Surfactants

Hydrophilic group of nonionic Surfactants of a nondissociabletype, such as phenol, alcohol, ester, ether, or amide, so nonionic Surfactants do not ionize in aqueous solution. A large proportion of thesenonionic surfactants can made hydrophilic by the existence of a polyethylene glycol chain and they obtained by the polycondensation of ethylene oxide. They are called polyethoxylated nonionics.

c- Cationic Surfactants

They are dissociated in water into an amphiphilic cation and an anion,most often of the halogen type. A very large proportion of this class agree to nitrogen compounds such as fatty amine salts and quaternary ammoniums, with several the alkyl type, often coming from natural fatty acids.

d- Zwitterionic

When a single surfactant molecule called **amphoteric** or **zwitterionic** when consist of both anionic and cationic dissociations.[21)]

Below table explain examples about these types of Surfactants.

Table 1 .Examples of types of Surfactants.[22]

Class	Examples	Structure
Anionic	Na stearate	$CH_3(CH_2)_{16}COO^-Na^+$
Cationic	Laurylamine hydrochloride	$CH_3(CH_2)_{11}NH_3^+Cl^-$
Nonionic	Polyoxyethylene alcohol	$C_nH_{2n+1}(OCH_2CH_2)_mOH$
Zwittenionic	Dodecyl betaine	$C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$

Preconcentration Factor, phase volume ratio and recovery efficiency.[23]

The preconcentration factor, (f_c) is defined as the ratio ofthe volume of bulk solution before phase separation (V_t)to that of the surfactant-rich phase after phase separation (V_s).

$$fc = \frac{v_t}{v_s}$$

Where, $V_t$and $V_S$are volumes of the bulk solutionbefore phase separation and the surfactant-rich phase,respectively.

The phase volume ratio, R_v is defined as the ratio of thevolume of the surfactant-rich phase to that of the aqueousphase. It is calculated using the following formula.

$$Rv = \frac{v_s}{v_w}$$

Where, V_S and $V_w$are the volumes of the surfactant-richphase and the aqueous phase respectively.

The recovery efficiency of solute can be characterized as the percentage of solute extracted from the bulk solution into the surfactant-rich phase. It is calculated using the following expression.

$$E\% = \frac{c_o v_t - c_w [(v]_t - v_s)}{c_o v_t} * 100$$

Where $C_0$is the initial concentration of solute in the bulksolution and $C_w$is the concentration of solute in dilutephase. $V_t$is the volume of solution and $V_s$is volume ofsurfactant rich phase after phase separation.

Application of cloud point extraction.

There are the machof method which used cloud point extraction as technique for determination drugs or other substance.[24-25]

In this method was develop for the reducing of nitro group of drug CAP by concentrated hydrochloric acid and zinc dust and then reaction with NQS reagent to form a orange-red compound and extracted the product with Triton X 114, then measured the absorbance of yield orange-red by use UV-Visible Spectrophotometer .

Experimental

Apparatus

UV-Visible Spectrophotometer, double-beam, Shimadzu model UV-1800 PC (Japan) with quartz cell

of 1 cm path length was used for all spectral and absorbance measurements.

Reagents

All reagents and chemicals used without further purification and freshly prepared.

Standard solution of reduced chloramphenicol (CAPR)100 µg.mL^{-1}

Reduced chloramphenicol(RCAP) solution (100 ppm) was prepared by dissolving of 0.01 g of its pure form with 5 ml of methanol in 100 ml beaker and was reduced by using 0.3 g zinc powder and 0.5 ml of conc. hydrochloric acid and kept aside for 5 min in bath water at 50 ^{o}C with stirring for complete reduction. The reduced solution was leted for 15 min for cooling after that was filtered to 100 ml in a calibrated flask and diluted with D.W to the mark.

Stock Solution of (0.01 M) NQS

It was prepared by dissolving 0.26 g of it in 100 ml beaker with 20 ml of D.W with stirring after that the volume was completed to the 100 ml with the same solvent after transferred it to volumetric flask.

Stock Solution of (0.01 M) Sodium bicarbonate

It was prepared by dissolving 0.84 g of it in 100 ml beaker with 20 ml of D.W with stirring after that the volume was completed to the 100 ml with the same solvent after transferred it to volumetric flask.

Stock Solution of (5% v/v) Triton x114

It was prepared by dissolving 5 ml of it in 100 ml volumetric flask with 20 ml of D.W with stirring after achieving mixing the volume was completed to the mark with the same solvent.

Pharmaceutical preparations of chloramphenicol

(i) **Eye drops:** It was prepared by mixed tow tube (50 mg ,10 ml each) then thesolution was diluted to 50 ml with methanol (equivalent to 100 mg (0. 1 g)in 50 ml).5 ml from this solutionwas transferred (equivalent to 10 mg(0.01 g) in 5 ml) to 100 ml beaker . Reducing solution of (100 ppm) CAPR was prepared by the way which was explained previously .

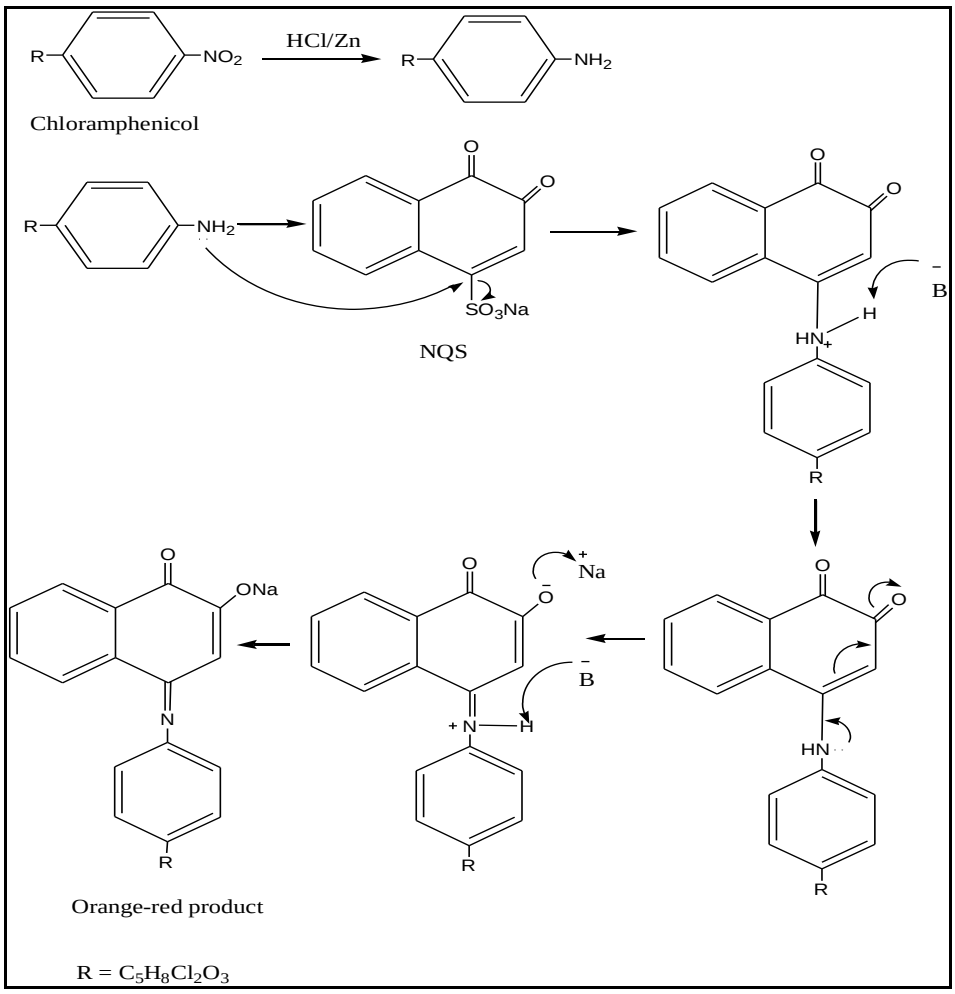
(ii)**Ointment (1 % , 5 g) ,** equivalent 50 mg of CAP**.** Two tube of ointment (1 % , 5 g) , equivalent to 100 mg of CAP was dissolved in 50 ml of petroleum ether and extracted three time with the 15 ml D.W. the total extracts were filtered and completed to 50 ml with methanol. 5 ml from this solution was transferred (equivalent to 10 mg(0.01 g) in 5 ml) to 100 ml beaker . Reducing solution of (100 ppm) CAPR was prepared by the way which was explained previously.

(iii) **Capsules (250 mg) .**ten capsules (250 mg) was took ,mixed and weighted . from the mixture was transferred 10 mg to 100 ml beaker and dissolved with 5 ml of methanol. Reducing solution of (10 ppm) CAPR was prepared by the way which was explained previously.

Results and Discussion

Suggested mechanism

The mechanism of condensation reaction was suggestion in this study showed in scheme (2) agreement with that was found in litterateurs[26]



Scheme 2: Proposed mechanism of the reaction between CAPR and NQS

Optimum conditions[27-42]

Effect of type of base

Genral process

The product consists not directly, but it needs to heating at 70 ^{0}C for 10 min. Therefore the extraction cannot take place directly, but must first prepare the product at the optimum condition then extracted it by cloud point extraction technique.

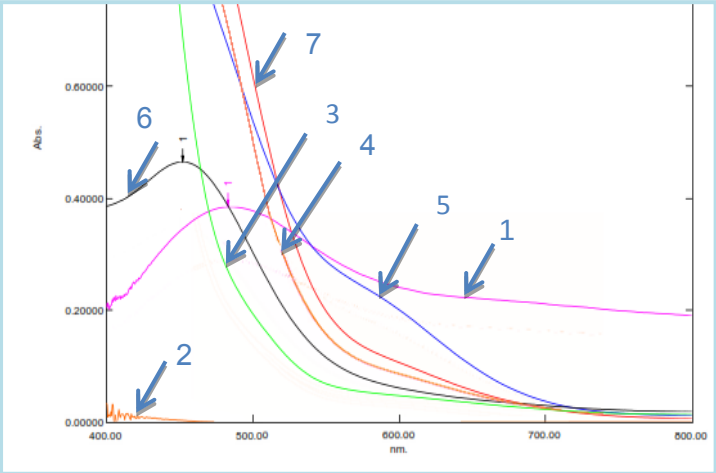
One ml of NQS (0.01 M) as regent was added to desert of CAPR (100 ppm) in 10 ml volumetric flask then 0.5 ml of sodium bicarbonate (0.1M) as base. The solution was heated at 70 ^{0}C in bath water for 10 min to form orange-red product. The colored solution was cooled then 0.5 ml of (5%) triton x114 was added and the volume was completed to the mark with D.W and was transferred to 10 ml separation tube.

Separation tube was standing in the bath water at the 50 ^{o}C for 15 min. During that appearance turned into a cloudy solution that refers to formed micelles. To separation rich –phase micelle, the solution was put in centrifuge for 10 min at 4000 rpm. Aqueous solution was removed and the precipitate was dissolved in 3 ml ethanol. Absorbance of colored product was measured against suitable blank at 489 nm.

Effect of type of alkaline solutions

Althoughthat the reaction occur in alkaline medium, but same alkaline solutions using it causes development color of the blank and its absorbance interaction with region of absorbance of product of CAP. Therefore the best alkaline solution can be used in reaction those that cause little development of color of the

blank. Therefor the best base with the smallest absorbance of blank was studded by added (1 ml, 0.1M) of different base. Absorbance of a colored solution formed was measured at 489 nm against D.W, as blank in each time.Fig (2) explain the result.



1- Product

2- $NaHCO_3$ without heating

3-$NaHCO_3$ with heating

4- KOH with heating

5- $Na_2CO_3$with heating

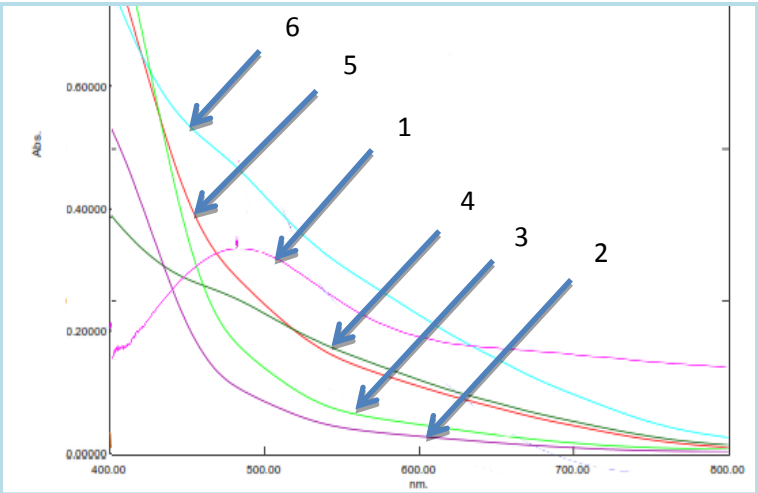
6-NaOHwith heating

Fig (2).Absorbance and ë max of blank at different types of base.

The best alkaline solution was sodium bicarbonate with smallest absorbance at 489 nm. But the absorbency of blank at 489 nm pre-heating differs after heating, so the blank must be heated at a same optimum temperature of the product solution.

When was measured optimum volume of sodium bicarbonate the pH of the solution was distinguish and was (8), Therefore the effect of buffer solutions was studied by completing the solution of colored product with certain buffer.

On the other hand, using the buffer solution was effect also on the development the color and absorbance of blank at 489 nm. Therefore the effect of buffer solution on blank also studied. The absorbance of the solutions were measured at 489 nm. The study show the absorbance of product was decrease and the absorbance of blank was increase. Fig (3) explains the result.



1, 2- Product and blank without buffer

3- Blank with (NH4Cl +NH3) buffer

4- Blank with (KH_2P0_4 + NaOH) buffer

5- Blank with (CH3COONH4 +NaOH) buffer

6- Blank with (Na2HPO4 + HCl) buffer

Fig 3.Absorbance of blank at different types of buffer.

From the figure above shows that buffer solutions reason increase absorbance of blank at same ë max of colored product. Therefor using sodium bicarbonate only without buffer gave the best condition of an alkaline medium to form colored product.

Effect of volume of sodium bicarbonate

The optimum volume of sodium bicarbonate was studied where was prepared a series of solutions contain a different volume of sodium bicarbonate with fixing the volume of drug (0.5 ml) and volume of NQS (1 ml). The absorbance against suitable blank was measured for each solution at ë $_{max}$ 489nm.Fig (4) explains the result.

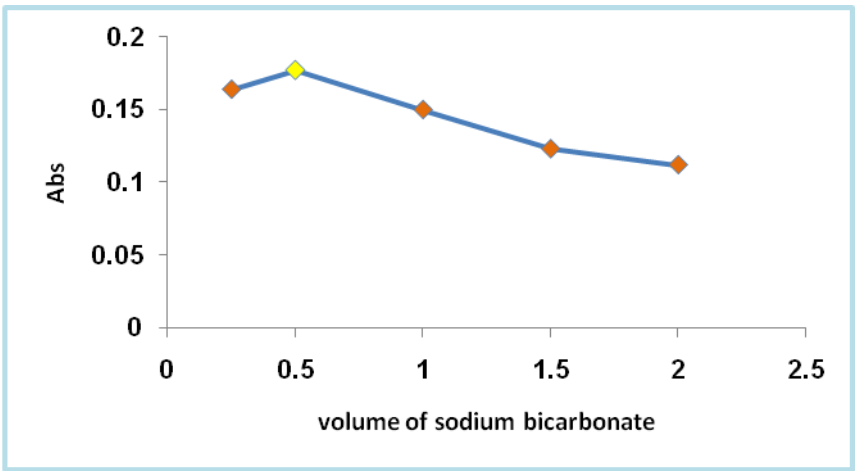


Fig 4.Absorbance of colored product at different volume of sodium bicarbonate.

Figure (411) shown the best volume of sodium bicarbonate was0.5 ml.

Effect of volume of NQS (0.01 M)

The optimum volume of NQSwas studied by preparing a series of solutions contain a different volume of reagent (0.5-2.5) with fixing the volume of CAPR (0.5 ml) and volume of sodium bicarbonate (0.5 ml). The absorbance 0f colored product against suitable blank was measured for each solution at ë $_{max}$ 489.Fig (5) explains the result.

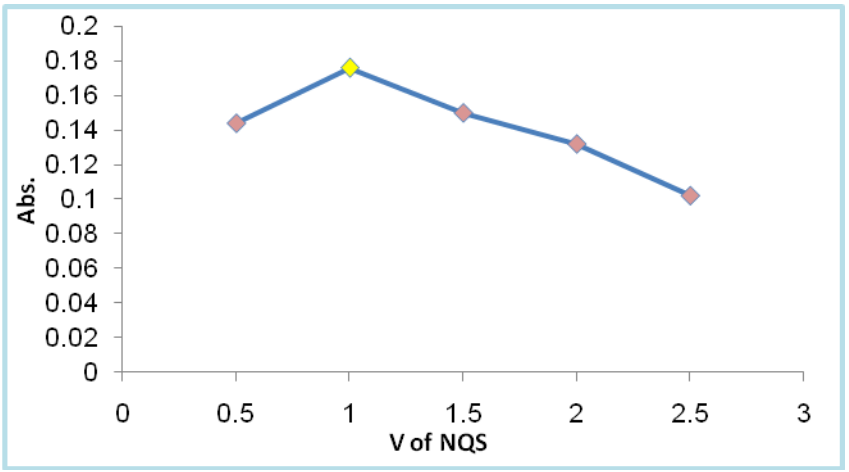


Fig 5.Absorbance of colored product at different volume of NQS.

The optimum volume of NQS can be used in reaction was 1 ml. This volume was fixing in all subsequent experiments.

Effect temperature and time of heating.

The optimum temperature of heating also was studied by preparing a series of solutions contain (0.5 ml) of CAPR, 0.5 ml of sodium bicarbonate and 1 ml of NQS. After that the solution was heated at different temperature for 10 min toform colored product.

Also the optimum time of heating was studied by the same procedure above but with fixing temperature in 70 ^{0}C and heated for different time. The absorbance against suitable blank was measured for each solution at ë $_{max}$ 489 nm. Figs (6, 7) explain the results.

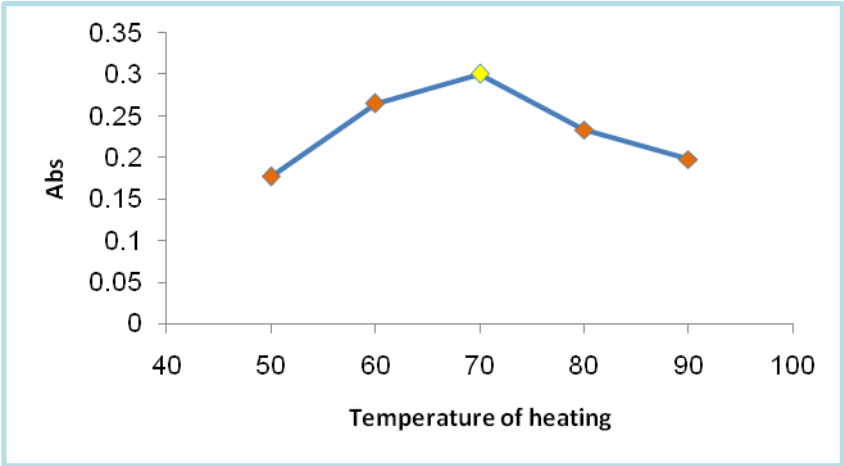


Fig 6.Absorbance of colored product at different temperature of heating.

The optimum temperature which can use in reaction was 70 ^{0}C, this temperature fixing in all subsequent experiments.

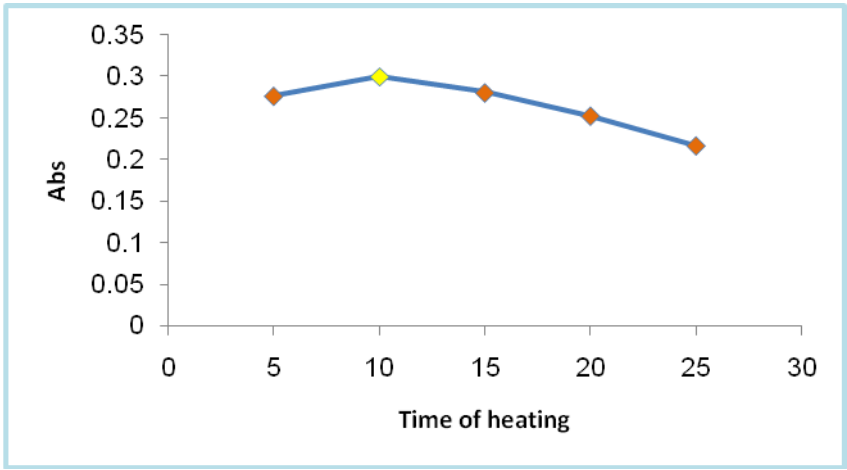


Fig 7.Absorbance of colored product at different temperatures of heating.

The optimum time can that using in reaction was 10 min.This time fixing in all subsequent experiments.

The order of addition

The order of addition was studied by providing three solutions in 10 ml volumetric flask contain 0.5 ml CAPR, 0.5 ml sodium bicarbonate and 1 ml NQS but in a different sequence in addition. The absorbance of colored product was measured against suitable blank at 489 nm after completing the volume to the mark with D.W. Fig (8) explains the results.

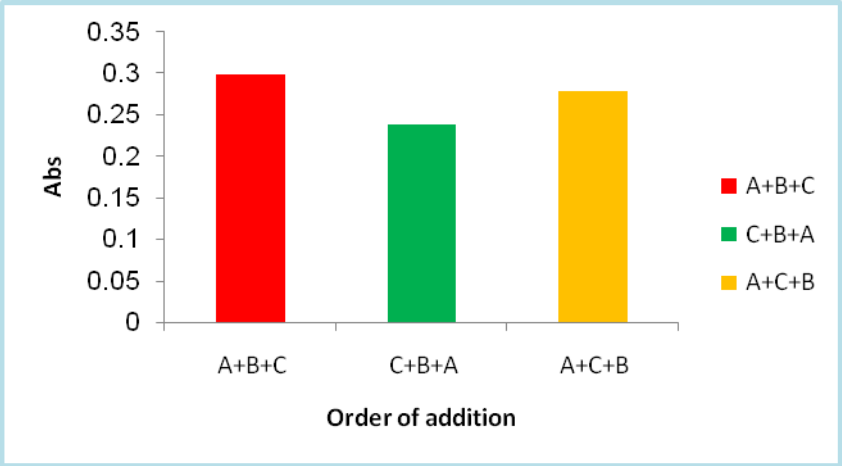


Fig 8.Absorbance of colored product in different order of addition.

Where, A is (CAPR), B is (sodium bicarbonate), C is (NQS).

The optimum order of addition was CAPR + sodium bicarbonate + NQS.

Effect of time of stability

The effect of time of stability also was studied. After prepare the solution of colored product by applying optimum conditions the absorbance of colored product was measured each five min. Fig (9) explains the result.

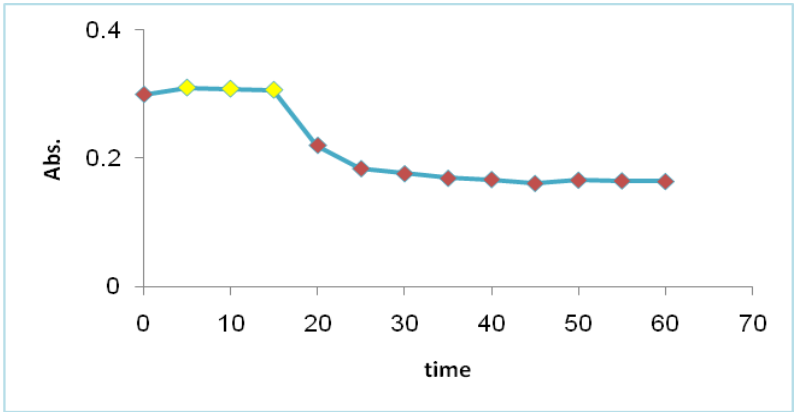


Fig 9.The absorbance of colored product at a different time.

From figure above, the absorbance was stablefor 15 minutes and then beginsto reduce. Therefore, the optimum time for measuring the absorbance was during the first fifteenminutes.Now, after we study optimum conditions of product we will extract it by cloud point extraction for increase sinsitveity of method because we see the reagent also development in basic medium and it absorbance some of radition in same weavelenghth of product therefore we will remove this interferance by cloud point extraction technqiue also by this technqiue the molar absorbativity will increase because the absorbance for all concentration will increase through preconcentration process. The optimium conditions of cloud point extraction also were studied such as.

The optimum volume oftriton x114

The optimum volume oftriton x114 was studied by providing series of 10 ml volumetric flask, every each one contains the colored product which formed in the previous step and was added different volume of triton x114, then the cloud point extraction process was completed. The absorbance of colored product after the extraction was measured to each solution against suitable blank at 489 nm. Fig (10)

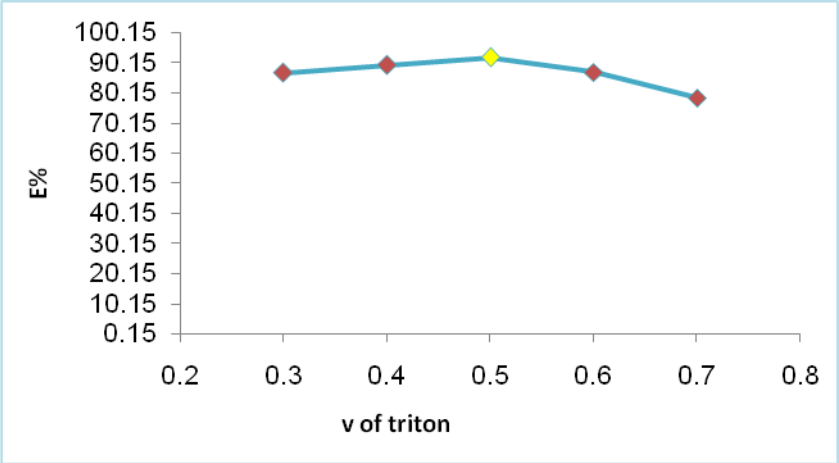


Fig 10.E% of colored product at different volumes of triton x114.

The optimum volume of triton x114 was 0. 5 ml, which it gave absorbance, equal (1.13) and extraction percent (91.98 %).

Effect of temperature of heating (Equilibrium temperature) on extraction.

The temperature of heating **was** studied by range from 30 ^{o}C to 70 ^{o}C in a search of optimum value after preparation of colored solution which will undergo to cloud point extraction to extract CAP. Absorbance of solutions was measured against suitable blank at 489 nm. Fig (11).

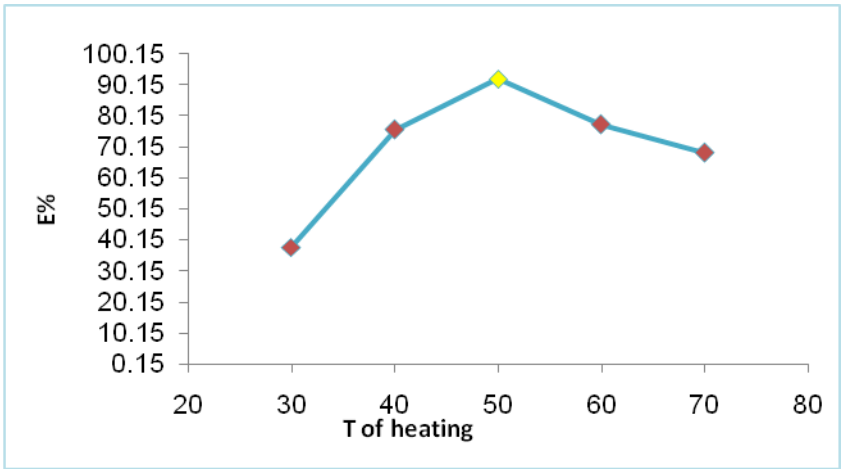


Fig 11.E% of colored product at a different temperature.

The optimum temperature was 50 ^{0}C and, which gave absorbance (1.132) and extraction percent (92.16 %) nearly.

Effect of heating time (incubation time) of extraction.

The time of heating(incubation time) **was** studied by rang (5, 10, 15, 20, 25) min in a search of optimum. Absorbance of solutions was measured against suitable blank at 489 nm. Fig (12).

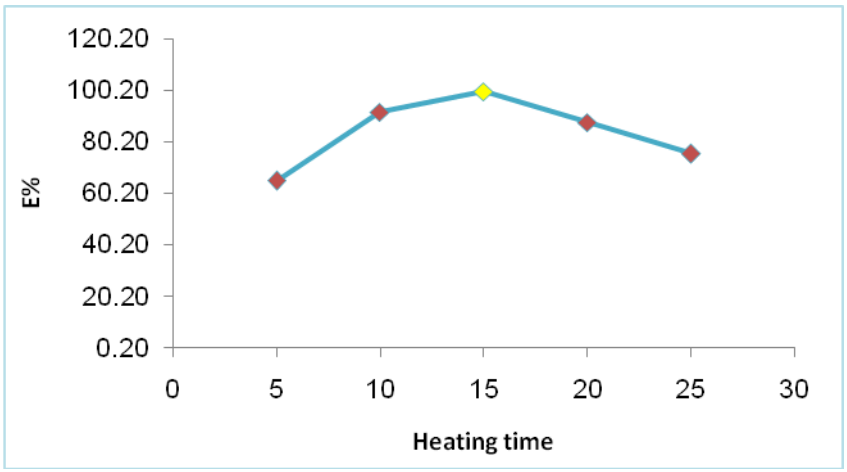


Fig 12.E% of colored product at a different time.

The optimum time was 15 ^{0}C and, which gave absorbance (1.219) and extraction percent (99.66 %) nearly.

Effect of centrifuge time of extraction

For obtaining on higher extraction to colored product from aqueous solution, Time of centrifuge was studied for this aim.

The studied was performed by using a series of 10 ml volumetric flask, every each one contains the colored product which formed in the previous step by the procedure of method Tow, and was added 0.5 ml, and then the solution was completed to the mark with D.W and was transferred to 10 ml separation tube

Separation tube was standing in the bath water at 50 ^{0}C for 15 min.The solution was put in a centrifuge for different time (2.5, 5, 10, 15, and 20) min at (4000) rpm. Aqueous solution was removed and the precipitate was dissolved in 3 ml of ethanol. Absorbance of solutions was measured against suitable blank at 489 nm.**Fig13.**

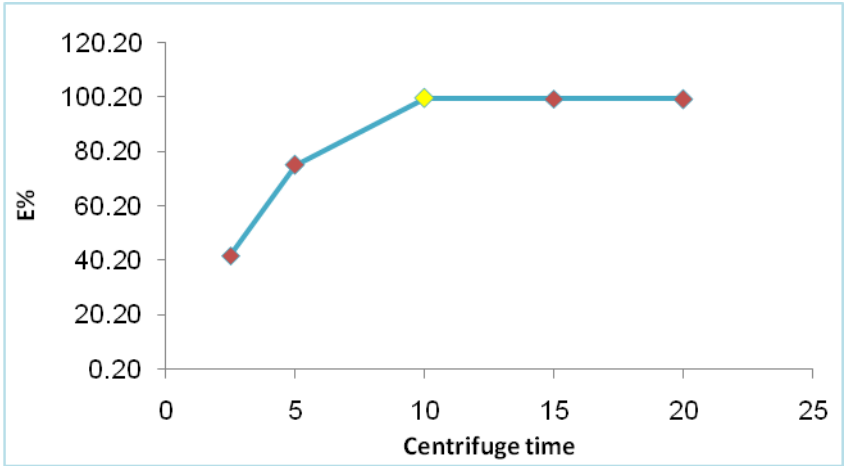


Fig 13E% of colored product at different centrifuge time.

The optimum centrifuge time was 10 min which gave absorbance (1.221) nm and extraction percent (99.84 %).

Effect of time of stability

After completing the extraction process according to the optimum conditions which illustrated above the absorbance was measured every five min for one hour to know the stability of product with time and what is the best time which we can during it recorded the absorbance. Fig (14) explain the result.

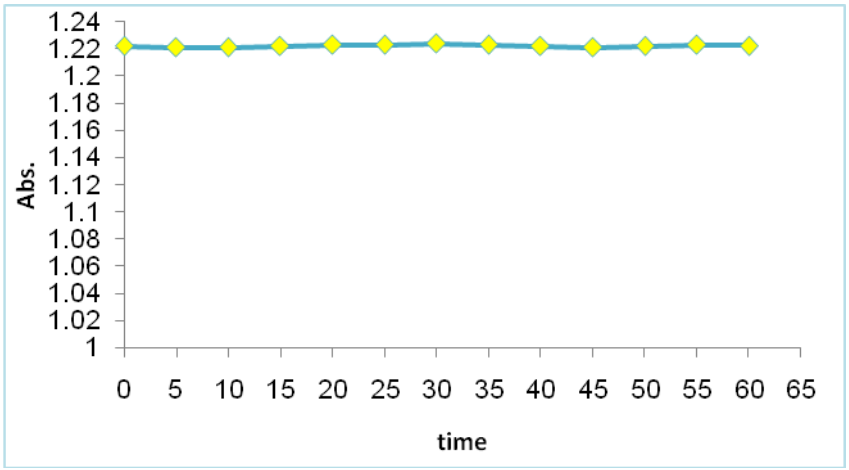


Fig 14.Abs of colored product at a different time (min).

Sandell's sensitive, Molar absorptivity, Limit of detection LOD and limit of quantification LQD which were calculated by this method by the equations which was mentioned inlitterateursand other information that has been obtained from thecalibrationcurve was included in the table (2).

Table 2. Analytical values of statistical treatments of the calibration curve.

value	**parameter**
y = 0.2318x + 0.0639	Regression equation(ppm)
0.1 – 6	Beer's law limits (mg ml^{-1})
0.9997	R^2 value
0.2318	Slope
$7.49 * 10^4$	Molar absorptivity ($l.mol^{-1}. cm^{-1}$)
$4.31* 10^{-3}$	Sandell's sensitive
0.032	LOD ($ng.ml^{-1}$)
0.097	LOQ ($ng.ml^{-1}$)
99.92	E%
0.3	Rv
3.33333	fc

Conclusion

A simple, sensitive, rapid cloud point extraction method for spectrophotometric determination of CAPdrug .It is based on condensation reaction between CAP and NQSto yield orange-red colored product that

exhibitsamaximumabsorptionat489nm.Theproposedmethodwasappliedsuccessfully to determination of drug in its pharmaceutical preparations.

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