550

INVESTIGATION OF ANTI-RHEUMATOID DRUGS WITHIN MICELLES OF DIFFERENT SURFACTANTS

ISLAMABAD

A dissertation submitted to the Department of Chemistry in partial fulfillment of the requirement for the degree of

Master of Philosophy in Physical Chemistry

by

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In the name of Allah,

the Beneficent, the Merciful.

DECLARATION

This thesis submitted by ***Muhammad Rafique*** is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University Islamabad, as satisfying the thesis requirement for the degree of ***Master of Philosophy in Chemistry***.

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To
those whose prayers and
encouragements paved
the way of my success.

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The words cannot describe gratitude towards my loving parents. The whole I achieved is actually their achievements and they certainly deserve more than this. The words are insufficient to express my feeling for them. Special love is for my sisters and brothers.

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Muhammad Rafique

ABSTRACT

Surfactants have amphiphatic structure. The structure of surfactant causes not only concentration of surfactant at surface and reduction of surface tension of solvent but also orientation of molecules at surface. Surfactant molecules self associate to form cluster, known as micelles and phenomenon is micellization. Solubilization of drugs by aqueous micellar solution of sodium dodecyl sulphate (SDS) and cetyltrimethyl ammonium bromide (CTAB) have been studied as the function of surfactant concentration by different methods. The depression in critical micelles concentration (CMC) of surfactants with different concentration of drugs were determined by conductivity method at 25°C.

Anti-rheumatoid drugs are pain-killer. Some of which were used as additive such as flurbiprofen, ibuprofen and aspirin. These drugs have prominent anti-inflammatory, analgesic and antipyretic action. The flurbiprofen and ibuprofen mechanism of action is by inhibitor of enzyme cyclo-oxygenase resulting in reduced prostaglandin synthesis. Flurbiprofen also potent inhibitor of platelet aggregation due to inhibition of thromboxane formation. Aspirin inhibits fatty acid cyclogenase by acetylation of active site of enzyme.

Interaction of drugs with micelles "which act as drugs carriers" of anionic and cationic surfactants were discussed by conductometric and spectroscopic methods using physical parameter like partition coefficient "K_X" and free energy change "ΔG_P". It is concluded that flurbiprofen is more incorporated/penetrated into micelles as compared to ibuprofen and aspirin.

CONTENTS

Chapter 1

INTRODUCTION

Chapter – 1

INTRODUCTION

Surfactant is an abbreviation for surface active agent which mean active at a surface. Surfactant is characterized by its tendency to adsorb at surface and interface. Thus surface active agent is therefore a substance that at low concentration adsorbs at interfaces in the system and significantly changes surface tension [1].

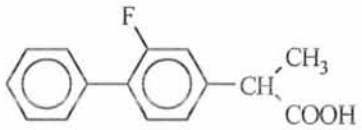
The properties of surfactant which are of great importance are micellization and solubilization. Micellization is tendency of surfactant molecule to associate themselves at a particular concentration. The process at which process of micellization starts is known as critical micelle concentration (CMC). Surface active agent has particular molecular structure known as amphipathic structure. This amphipathic structure consist of a structural group that has little attraction for solvent called lyophobic group, together with a group that has strong attraction for solvent called lyophilic group. Surface when dissolve in a solvent, the lyophobic group cause a distortion of the solvent liquid structure, therefore, increase the free energy of system. This increase in free energy means less work is needed to bring a surfactant molecule than water molecule. Micelle formation or micellization is an interfacial phenomena, such as detergency and solubilization depend on existence of micelles in solution.

Aggregation process is another way by which distortion of solvent structure can be decreased and thus the free energy of solution reduced. In micellization phenomenon surfactant molecule aggregate into clusters with their lyophobic group directed toward interior of the cluster and lyophilic groups directed toward solvent. Thus it can be said that micellizaiton is a process alternative to adsorption at interface for removing lyophobic group from contact with solvent, therefore, reducing the free energy of the system.

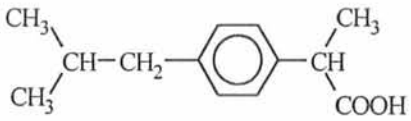
The present study is an investigation of solubilization of anti-rheumatoid drugs within micelles formed by solution of anionic and cationic surfactant i.e. SDS and CTAB respectively and about the partition coefficient "K_X" and free energy of transfer of these drugs (flurbiprofen, ibuprofen and aspirin) from aqueous medium to organic phase or micellar phase. Anti-rheumatoid drugs are pain-killer some of which are used as additive. They have prominent anti-inflammatory, analgesic and antipyretic action [2,3].

Ibuprofen is a white powder or crystalline solid and is non-hygroscopic. Flurbiprofen is white or cream powder. Both flurbiprofen and ibuprofen mechanism of action is by inhibition of enzyme cycloxygenase resulting in reduced prostaglandin synthesis. Flurbiprofen is also potent inhibitor of platelet aggregation due to inhibition of thromboxane formation [4] and can be measured in plasma either by HPLC which has sensitivity of 40 μgl^{-1} [5]. Aspirin inhibits fatty acid cycloxygenase by acetylation of active site of enzyme [6,7].

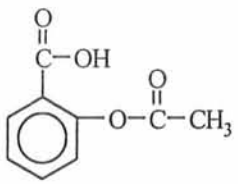
The actual purpose of this work was investigation of different drugs flurbiprofen, ibuprofen and aspirin with skin membrane. It is rather difficult to study the mechanism of interaction of these drugs with skin membrane in laboratory, therefore, we used a pseudo model here. As skin membrane consist of micelles and bilayers (lipids and proteins form micelles, we wanted to study the interaction of drugs with these micelles and bilayers. So in our pseudo model, we used surfactant i.e. anionic and cationic and relate this with skin because same type of mechanism is involved in both cases.



Flurbiprofen



Ibuprofen



Aspirin

Organic additives tend to decrease the CMC of the surfactant [8,9]. The CMC depression is due to the solubilized additives in the ionic micelles. Two factors are responsible for this depression [8].

i) Entropy of mixing in the micelles increases with solubilized additive molecule. The additive assumed to be partitioned between bulk water and micellar phase.

ii) Decrease in charge density of the surface of micelles leading to a decrease in electric work of micellization of surfactant ions.

The project was aimed to estimate the solubilization of flurbiprofen, ibuprofen and aspirin in micelles formed by anionic and cationic surfactant i.e. SDS and CTAB respectively. It was done by titration, conductometric and spectroscopic methods at room temperature. The value of partition coefficient "K_X" and hence standard free energy change of solubilization (ΔG^0_p) of these drugs within micelles and surrounding solution were also calculated and reported.

Chapter 2

THEORETICAL

Chapter – 2

THEORETICAL

PART-I

2.1 Surfactant

A surface active agent (or more briefly, surfactant) is a substance that when present at low concentration in a system, has the property of adsorbing onto the surfaces or interfaces of the system and of altering to a marked degree the surface or interfacial free energies of those surfaces. The term interface indicates a boundary between any two immiscible phases; the term surface denotes an interface where one phase is a gas, usually air.

Interfacial free energy is the minimum amount of work required to create that interface. The interfacial free energy per unit is what the measure when we determine the interfacial tension between two phases. It is the minimum amount of work required to create unit area of the interface or to expand it by unit area. A surface-active agent is therefore a substance that at low concentration adsorbs at some or all of the interface in system and significantly changes the amount of work required to expand those interfaces. Surfactants usually act to reduce interfacial free energy rather than to increase it.

Surface-active agents have a characteristic molecular structure known as amphiphathic. This amphipathic consist of two groups.

i) Lyophobic Group

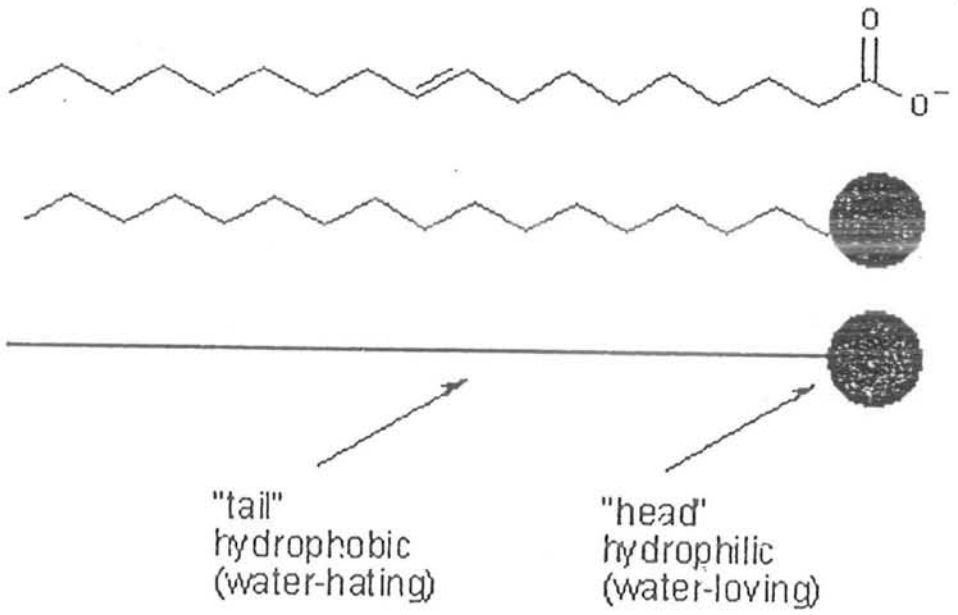
It has little attraction for solvent. In case of water, it is termed as hydrophobic group.

ii) Lyophilic Group

The group which has strong attraction with solvents known as lyophilic group. In case of water, termed as hydrophilic group.

When surfactant is dissolved in a solvent, the presence of the lyophobic group in the interior of the solvent causes a distortion of solvent liquid structure, increasing the free energy of the system. In an aqueous solution of a surfactant this distortion of the water by lyophobic (hydrophobic) group of the surfactant, and the resulting increase in the free energy of the system when it is dissolved, means that less work is needed to

bring a surfactant molecule than a water molecule to the surface. The surfactant therefore concentrates at surfaces since less work is now needed to bring molecules to the surface. The presence of the surfactant decrease the work needed to create unit area of surface. On the other hand, the presence of the lyophilic (hydrophilic) group prevents the surfactant from being expelled completely from solvent as a separate phase, since that would require desolvation of the hydrophilic group. The amphipathic structure of the surfactant therefore causes not only concentration of the surfactant at the surface and reduction of the surface tension of the solvent, but also orientation of the molecules at surface with its hydrophilic group in aqueous phase and its hydrophobic group oriented away from it.



The basic properties of surfactants are as

i) Reduction of interfacial free energy

ii) Micellization

iii) Solubilization

iv) Detergency

v) Electric double layer formation [1]

The hydrophobic group is usually a long chain hydrocarbon residues, less often a halogenated or oxygenated hydrocarbon or siloxane chain, the hydrophilic group is an ionic or highly polar group. Depending on the nature of hydrophilic group surfactants are classified as

1. Anionic surfactants
2. Cationic surfactants
3. Zwitterionic surfactants
4. Nonionic surfactants

Anionic Surfactants

The surface-active portion of the molecule bears a negative charge (2), for example

1. $R–COO–\ \bar{O}Na$ (soap)
2. $RC_6H_4SO_3^-Na^+$ (alkylbenzene sulfonate)

Cationic Surfactants

The surface-active portion bears a positive charge, for example

1. $RNH_3^+Cl^-$ (salt of a long amine)
2. $RN(CH)_3^+Cl$ (quarternary ammonium chloride)

Zwitterionic Surfactants

Both positive and negative charges may be present in the surface-active portion, for example

1) $R^+NH_2CH_2–CO^-$ (long chain amino acid)
2) $R^+N(CH_3)_2CH_2CH_2SO_3^-$ (sulfobetaine)

Nonionic Surfactants

The surface-active portion bears no apparent ionic charge, for example

1) $RCOOCH_2CHOHCH_2OH$ (monoglyceride of long chain fatty acid)

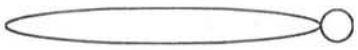
2) $RC_6H_4(OC_2H_4)_XOH$ (polyoxyethylenated alkylphenol)

2.1.1 Geometric Arrangements

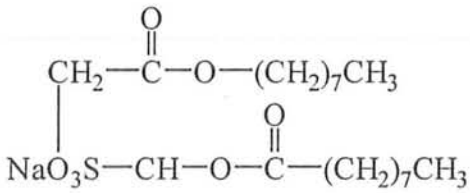
Hydrophobic and hydrophilic groups can be arranged to give surfactants with fundamentally different shapes.

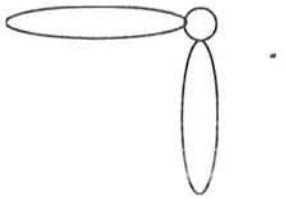
1. **Small Head, Single Tail**

   SDS $[CH_3(CH_2)_{11}SO_4^-Na]$



2. **Small Head, Two Tails**





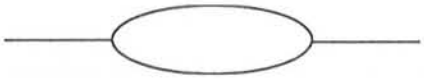
   (Aerosolot)

   American cyanamid

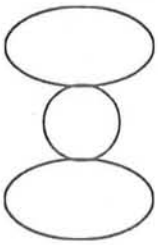
3. **Large Head, Two Tails**

   $CH_3(CH_2)_{10}COO–(CH_2CH_2–O–)_{40}–OOC(CH_2)_{10}CH_3$

   Poly(ethylene oxide)didiocanoate



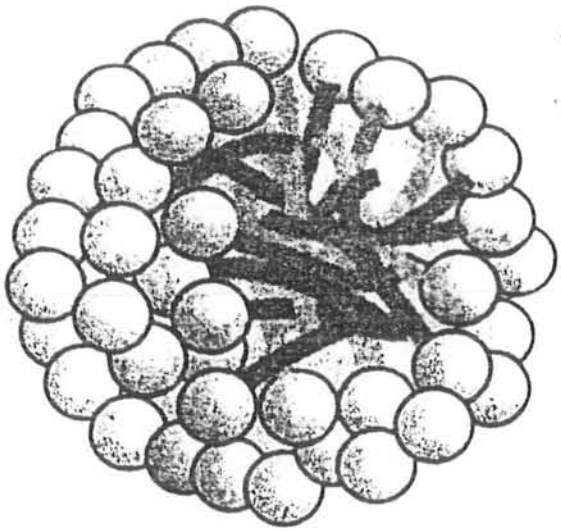
4. **Two Large Hydrophiles, One Large Hydrophobe**



   $HO–(CH_2CH_2–O)_m–[CH_2–CH–CH_{3n}–]–(O–CH_2CH_2)_m–O$

2.2 Micellization

Self association of surfactant molecules above certain concentration to form cluster, aggregates known as micelles, phenomena is micellization.



A schematic version of a spherical micelle. The hydrophilic groups are represented by spheres and the hydrophobic hydrocarbon chains are represented by the stalks, these stalks are mobile.

This property of surfactants is of prime importance as certain interfacial phenomena depend upon it. Examples of such phenomena are detergency and solubilzation which depend on presence of micelles in the solution. Micellization is of primitive importance for unusually catalysis of certain organic reaction. In certain cases, micellization has application to biochemistry where micelles have been considered to process similarity to biological membranes and globular proteins.

When a surfactant is dissolved in a solvent, the lyophilic (less) and lyophobic group in the same molecule distort the structure of the solvent and therefore increase the free energy of the system. One way to reduce distortion is adsorption on the surface. However, another way to minimize the free energy is aggregation of surface active

molecules into micelles with their lyophobic groups directed toward the interior of micelles and their lyophilic groups directed toward the solvent. Micellization is therefore a mechanism alternative to adsorption at the interfaces for removing lyophobic groups from contact with the solvent, thereby reducing the free energy of the system [1].

2.2.1 Types of Micelles

There are three main types of micelles:

i) Spherical micelles
ii) Rod like micelles
iii) Lamellar like micelles

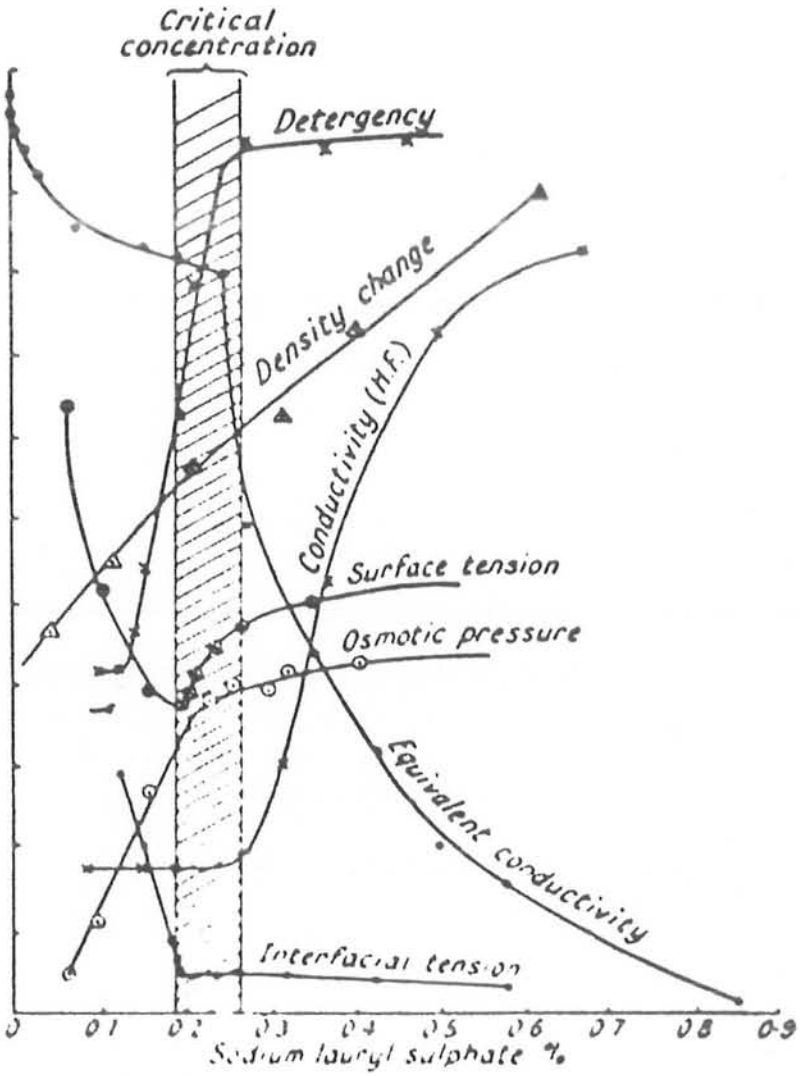
The structure of micelle is assumed to be an aggregate of 50-100 molecules with a radius approximately equal to length of the hydrocarbon chain of the surfactant. The interior of the micelle is essentially hydrocarbon in nature, while the surface consists of a layer or shell of head groups and associated counter ions solvent molecules [10].

2.3 Critical Micelles Concentration (CMC)

The concentration of surfactant in solution at which phenomenon of micelle formation occurs is termed as critical micelles concentration (CMC). It can be determined by abrupt change in measurable physical properties versus surfactant concentration. These physical properties are as:

i) Electrical conductivity
ii) Light scattering
iii) Surface tension
iv) Refractive index

These physical properties in an aqueous solution of surfactant show abrupt change in a certain narrow concentration. These sudden changes in physiochemical properties have been used to determine the critical micelle concentration (CMC) [1].



Philips defined CMC as "the concentration at which the properties of solution change in the most abrupt manner" [12].

$$\left(\frac{d^3\phi}{dC^3}\right)_{Tc=CMC} = 0$$

Where ϕ is any physical property which varies linearly with concentration of solution. It is generally the concentration of solutes at which the concentration of micelle would be zero.

2.4 Factors Affecting the Value of Critical Micelles Concentration in Aqueous Medium

There are number of factors which affect the critical micelles concentration in aqueous medium:

i) Structure of surfactant
ii) Presence of added electrolyte
iii) Organic additive
iv) Temperature of solution

1. Structure of Surfactants

Surfactants are amphiphatic in nature i.e. having hydrophilic and hydrophobic group so each component affect CMC.

a) Hydrophobic Group

CMC decrease as length of hydrophobic group increase. Aggregation number depends on the length of both hydrophobic and hydrophilic groups. Aggregation number increases with increasing the length of hydrophobic group but decreases with increasing length of hydrophilic group [13].

b) Hydrophilic Group

Increase in hydrophilicity result an increase in CMC. Surfactants having more than one hydrophilic group in the molecule show larger CMC than those with one hydrophilic group with equivalent hydrophobic group.

2. Temperature

For ionic surfactants, the CMC increase by increasing the temperature but for non-ionic surfactants the effect is of reverse mode. The effect of temperature on the CMC of surfactant in aqueous medium is complex. The value first decreases with

increase in temperature to some minima and then increase with the further increase in temperature. Increase in temperature causes decrease in hydration of hydrophilic group which favours micellization. Since temperature increase also causes disruption of structured water surrounding the hydrophobic group and effect is that favour micellization. The relative magnitude of these two opposing effects determines whether the CMC increase or decrease over a particular temperature.

3. pH

pH has a relatively small effect on the CMC of surfactants containing of long alkyl chain salts of strong acids unlike the salts of strong acids, however, the carboxylate soap surfactants exhibit a significant sensitivity to pH. Change in pH will have little or no effect on the CMC of non-ionic surfactants.

4. Electrolyte

In aqueous solution when an electrolyte is added, CMC decreases the order of electrolyte affecting the CMC is anionic > cationic > Zwitterionic surfactant. The effect on the CMC of non-ionic surfactant is least. The effect of concentration of electrolyte is given by [14]:

$$\log C_{CMC} = a \log C_1 + b$$

Where a and b are constant for a given ionic head at a particular temperature and C_1 is the total monovalent counterion concentration. CMC depression is mainly due to decrease of ionic atmosphere near the ionic heads therefore deceased the electrical repulsion between them in micelle.

For non-ionic and Zwitterionics the relationship is [15-17]

$$\log C_{CMC} = KC_s + \text{constant}$$

K is constant for particular surfactant, electrolyte, temperature and C is the concentration of electrolyte. The change in CMC of non-ionic and Zwitterionic surfactant is mainly due to salting out or salting in, when monomeric form of a surfactant is salted out by presence of an electrolyte micellization is favoured and CMC of the surfactant is decreased. When monomeric form is salting in the CMC is increased.

Hydrophilic group of the surfactant molecules are in contact with the aqueous phase in both monomeric and micellar forms of the surfactant while the hydrophobic groups are in contact with the aqueous phase only in the monomeric form. The effect of

the electrolyte on the hydrophilic group in the monomeric and micellar forms may cancel each other leaving the hydrophobic group.

5. Organic Additive

Small amount of organic materials may produce marked changes in the CMC of surfactants in aqueous medium. Some of these materials may be present as impurities in surfactants.

There are two classes of organic materials that markedly affect the CMC of the aqueous solutions of surfactants.

Class-I

These materials are those which affect the CMC by being incorporated into micelles. These include polar organic compounds e.g. alcohols and amides. They affect the CMC at much lower liquid phase concentration than those in second class. Members of this class reduce the CMC. Shorter chain members of class are probably adsorbed mainly in the outer portion of micelle close to water micelles interface. The longer chain members are probably adsorbed mainly in the outer portion of the core between the surfactant molecules.

Depression of CMC appear to be greater with increase chain length to a maximum when the length of hydrophobic group of additive approximately that of surfactant [18].

Those molecules that are most effective at reducing CMC are solubility in outer portion of micelle core and then under lateral pressure tending to force them into inner portion of core. This pressure increases with cross-sectional area of molecules. Additives that have more than one group capable of forming hydrogen bonds appear to produce greater depression of CMC than those with only one group capable of H-bonding to water. Hydrocarbons which are solubilized in the inner portion of the core, decrease the CMC only slightly.

Very short chain polar compounds e.g. dioxane, ethanol at low bulk phase concentrations also depress the CMC, but effect is small. In these compounds adsorption occurs on the surface of micelle, close to hydrophilic head. For aliphatic and alkylaryl hydrocarbon, the content of solubilization appears to increase with unsaturation or cyclization and decrease with increase in the chain length.

Class-II

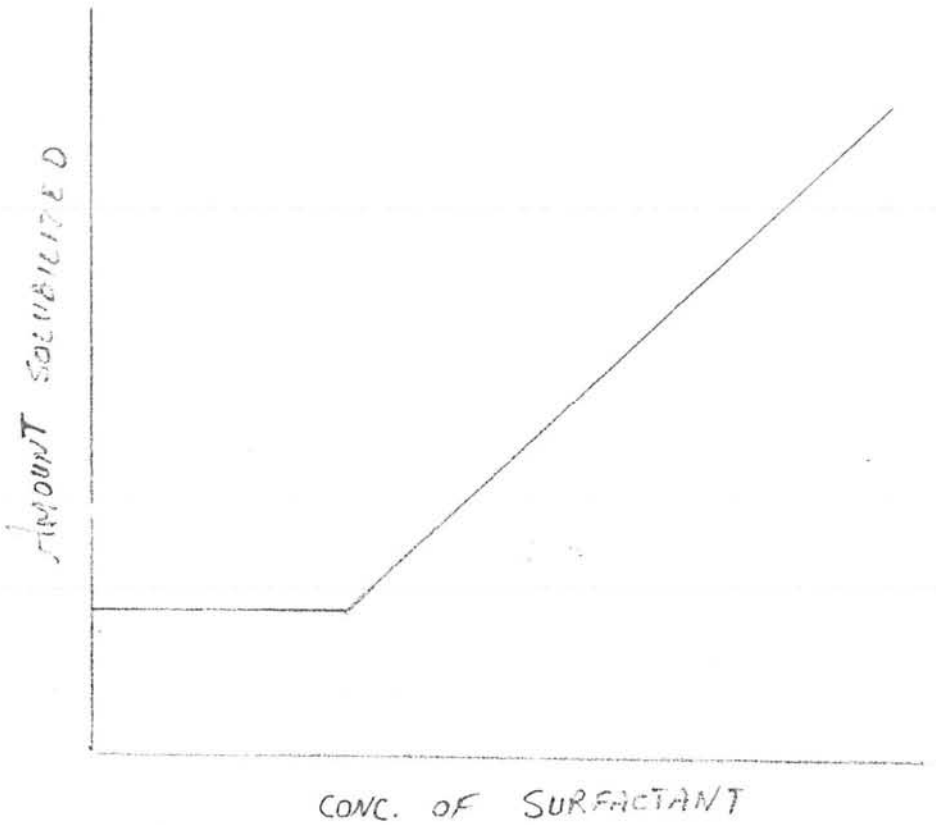
The members of this class change CMC by modifying the interaction of water with surfactant molecules or with micelles. By doing this by modifying the structure of H_2O, its dielectric constant or its solubility parameter cohesive energy density. Members of this class include urea, formamide, guanidinium salt, short chain alcohols, ethylene glycol, fructose and xylose. Urea, formamide and guanidinium salts are believed to increase the CMC of surfactant in aqueous solution especially nonionics. Materials that promote water structure such as xylose or fructose decrease the CMC of surfactant. Glycol and short chain alcohols at high bulk phase concentration may increase the CMC because they decrease the cohesive energy density of water. Thus increasing solubility of monomeric form of the surfactant and hence CMC.

2.5 Solubilization by Surfactant Solution

Solubilzation may be defined as "the spontaneous dissolving of substance by reversible interaction with micelle of a surfactant in a solvent to form a thermodynamically stable isotropic solution with reduced thermodynamically activity of solubilized material. It is one of the most important properties of aqueous micellar solutions that is directly related to micelle formation is solubilization. Solvent insoluble materials may be dissolved by solubilization mechanism. The importance of phenomenon from the practical point of view is that it makes possible the dissolving of substances in solvents in which they are normally insoluble. In solubilization, the solubilized material is in the same phase as the solubilzing solution and the system is consequently thermodynamically stable.

If solubility of a normally solvent insoluble material is plotted against the concentration of the surfactant solution that is solubilizing it. We find that solubility is very slight at concentration below the CMC of the surfactant but rises abruptly, this indicates that solubilzation is a micellar phenomenon, since it occurs only to a negligible extent at the concentration where micelles. If they exist at all, are found in significant number.

Studies of solubilization of organic solutes have been made to determine the effect of micellar structure and changes in the environment at the site of solubilization. Many investigators have used various physical methods to study solubilities of polar and non-polar organic solutes in ionic and non-ionic surfactant micelles.



In order to achieve a better understanding of phenomenon of solubilization, two major things are necessary to be understood. Firstly one would like to know what is the extent to which a particular compound can be solubilized in a given surfactant solution. The other aspect of interest is to know the region of location of solubilizate molecule within micelle. The later aspect is of particular interest in understanding the nature of catalytic activity of micellar systems. The structure of surfactant micelles is such that interior portion is highly non-polar and interfacial is relatively polar. The interior region is generally considered as locus of solubilization. For every non-polar solubilizates such as n-alkanes solubilizate molecule of relatively high polarity such as alcohols are believed to be solubilizate in the interfacial region of the micelles, so that their polar functional group could retain their contact with water. However, for molecules such as aromatic hydrocarbons which are only slightly polar, conflicting suggestions have been presented in literature concerning their location in the micelles [18,19].

Hydrophobic effects have often been considered to be dominant in determining the locus of solubilization. However, the effect of electrostatic interaction should also be considered in relation to the solubilization of organic solutes in ionic micelles. Ionic micelles ordinarily have an extensive hydrophobic core region which can interact strongly with hydrocarbon and halogenated hydrocarbon groups of solutes.

2.6 Applications of Surfactants

The applications of surface active agents are widely distributed throughout science, technology and every day life. A few of them are given here:

1. Surfactants solubilize flavour oils in beverages and improving the capacity of paper towel, to absorb H_2O.
2. In tanning of leather, they promote wetting and penetration.
3. The act as extraordinary catalysts for organic reactions in the micellar media, increasing reaction rate to many folds.
4. Surfactants play vital role in microelectronics and they are useful in fabricating a wide variety of components and materials ranging from ceramic substrates to magnetic storage media and printing inks.
5. Surfactants are used as antistatic agent in the manufacture of plastic articles and wetting agents in the formation of plastic coating.
6. They have number of applications in pharmaceutical industry. A number of drugs are in the form of emulsions. Surfactants are also used as drug carrier.
7. Surfactants are important part of pesticides.
8. No cream and lotions can exist without surfactants. So industry of pharmaceutical and cosmetics depend upon surfactants. These surfactants act as emulsifying agents.
9. They play a major role in oil drilling. The surfactants on one hand help in the formation of emulsion of water and oil. On other hand reduce friction during the drilling.

PART-II

2.7 Biological Membrane

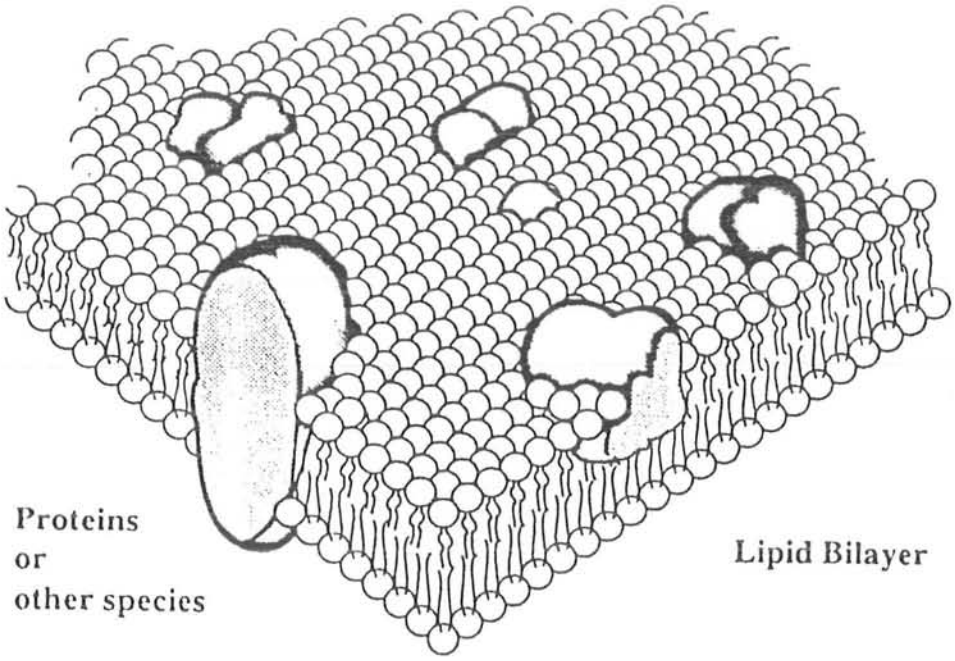
The skin membrane is bilayered phospholipid protein so their structural arrangement has close resemblance with surfactants, which when dissolved in water, form micelles at particular concentration, that particular concentration at which micelles form called critical micelles concentration. So we have used surfactants, i.e. anionic and cationic, we studied the interaction of drugs as an additive with these surfactants by titration, conductometric and spectroscopic method. We calculated the partition coefficient "K_X" and free energy of transfer (ΔG_P^o). From this we can know that how much additive incorporated into micelles of these two types of surfactants and where is greater interaction occurs.

All cells possess at their periphery a membrane, which provides the essential barrier that separate "inside" from "outside".

2.7.1 Structure of Biological Membrane

All biological membranes whether from eucaryotic or prokaryotic cells, have the same classes of chemical components. Similarly, in structure organization and a number of properties in common. There are major differences in specific lipid, protein and carbohydrate components but not in the physiochemical interaction of these molecules in membrane. Membranes have a trilaminar appearance when viewed by electron microscopy with two dark bands on each side of a light band. The overall width of various mammalian membranes is 7-10 nm but some membranes have significantly smaller widths. Intercellular membranes are usually thinner than the plasma membrane.

Membranes are very dynamic structure with a movement that permit the cell as well as subcellular structure to adjust thin shapes and to move the chemical components of the membrane that in lipids and proteins are ideally suited for dynamic role of membrane visually. The membranes are semi-structured but is a sea of lipid in a fluid state in which the various components are able to move.



Schematic representation of a biological membrane. The amphipathic phospholipid molecules form a bilayer with protein molecules embedded in it.

2.7.2 Chemical Composition

Lipids and proteins are the two major components of all membranes but the amount of each varies greatly between different membranes. The percentage of protein ranges from about 20% in the myelin sheath to over 70% in the inner membrane of mitochondria. Intracellular membranes have a high percentage of protein because of great enzymatic activity of these membranes. Membranes also contain a small amount of various polysaccharides in the form of glycoprotein and glycolipid. There is no free carbohydrate in membrane.

2.8 Micelles and Bilayer

Single-tailed amphiphiles such as soap anions form spheroidal or ellipsoidal micelles because of their trapped shapes, their hydrated head groups are wider than their tails.

The two hydrocarbon tails of glycerophospholipids and sphingolipids give these amphiphiles more or less rectangular shapes. The steric requirements of packing such molecules together yield large disk like micelles and they form bilayers.

2.8.1 Transport Protein Increase the Permeability of Membrane to Specific Molecules

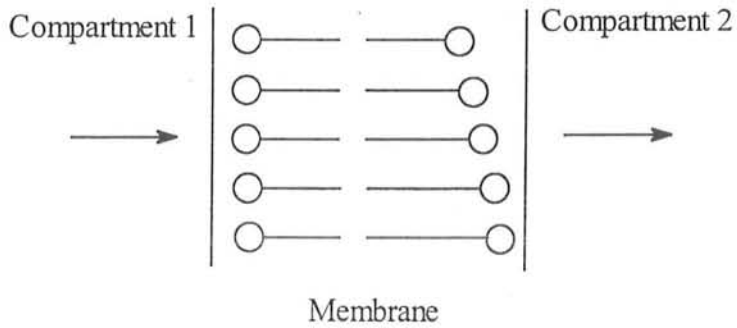
Lipid bilayers are permeable to water and neutral non-polar molecules, much less permeable to neutral polar molecules and almost impermeable to charge molecules. However, biological membranes contain protein that combine specifically with certain polar molecules and ions and facilitate their transport across the membrane.

2.8.2 Drugs Penetration to Membrane

The penetration of drugs into skin is by passive transport. The passive transport of drugs through membrane may be discussed in term of either two model process. The first is a simple diffusion model that requires the use of Fick's law. The second is the kinetic model in which simply rate laws may be derived. We shall use the latter mode because of its simplicity and the generality of the rate laws involve.

Consider the process of membrane penetration as shown in equation.

$$A_1 \underset{K_{-1}}{\overset{K_1}{\rightleftharpoons}} A_L \underset{K_{-2}}{\overset{K_2}{\rightleftharpoons}} K_2$$



Where

A_1 = Conc. of drugs in compartment 1

A_2 = Conc. of drugs in compartment 2

A_L = Conc. of drugs within the membrane

The approximate rate law is given by

$$\frac{-dA_1}{\partial t} = K_1A_1 - K_{-1}A_{-2}$$

Most frequently A_2 is not known so we write equation for rate of change of concentration of A_2

$$\frac{\partial A_L}{dt} = K_1A_1 + K_{-2}A_2 - (K_{-1} + K_2)\,A_2$$

Apply steady-state approximation. This means that the amount of drugs leaving the membrane is equal to amount of drugs entering the membrane. Thus A_2 is given by

$$\frac{dA_L}{dt} = 0$$

$$A_L'' = \frac{K_1A_1 + K_{-2}A_2}{K_1 + K_2}$$

Substitute this value in rate law, we get

$$\frac{dA_1}{dt} = \frac{K_1K_{-2}(K_oA_1 - A_2)}{K_1 + K_{-2}K_o}.$$

Where

$$K_o = \frac{K_1K_2}{K_{-1}K_{-2}}$$

This equation can be shown to be related to simplified form of Fick's law of diffusion across thin membrane:

$$\frac{dQ_A}{dt} = \frac{DM}{\Delta X_m} K_1 (A_1 - A_2)$$

Where

Q_A is quantity of A that is transported from compartment 1. It is related to the concentration by

$$A_1 = \frac{Q_A}{V_1}$$

When $A_1 >> A_2$ then rate law reduces to

$$\frac{-dA_1}{dt} = PA_1 \qquad (A)$$

Where P is permeability constant for transport of drug from compartment 1 to compartment 2.

$$P = \frac{DM}{\Delta X_m V_1} K_1 = \frac{K_1 K_{-2}}{K_1 + K_{-2}} \qquad (B)$$

Eq. (A) can be converted to linear form by integrating and taking logarithm

$$\log \frac{A_1}{A_1^o} = \left[\frac{P}{2.3}\right] t \qquad (C)$$

The plot of log A_1/A_1^o against t give a straight line with slope equal to P/2.3. Permeability constant is considered as a measure of the ability of a drug to penetrate a membrane.

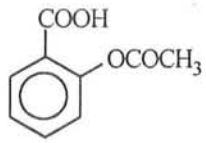
From Equation (C) it is clear that penetration of any drug through a membrane is a first-order process characterized by a rate law with the rate constant equal to the permeability constant. Higher value of "P" higher the degree of penetration for drug.

2.9 Classification of NSAIDS

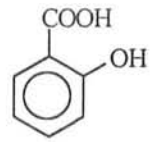
The classification of NSAIDS and other analgesic antipyretic agents based on chemical categories [28]. The vast majorities of NSAIDS are organic acids and serve as reversible, competitive inhibitors of cyclo-oxygenase activity. As organic acids, the compounds generally are well absorbed orally, highly bound to plasma proteins and excreted either by glomerular filtration or by tubular secretion. NSAIDS can be roughly divided into two groups, those with short hours (< 6 hours) and those with long hours (> 10 hours) half-lives. Because aspirin and other NSAIDS are organic acids, they accumulate at sites of inflammation which is an attractive pharmacokinetic property of drugs intended an anti-inflammatory agents.

2.9.1 Salicylic Acid Derivatives

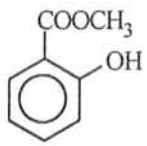
Aspirin is the most widely used analgesic antipyretic and inflammatory agent and in the standard for the comparison and evaluation of the other. Aspirin is the common household analgesic yet because the drug is so generally available, its usefulness often is underrated. It is necessary to be aware of its role in Rye's syndrome and as a common cause of lethal drug poising in young children as well as its potential for serious toxicity in used improperly.

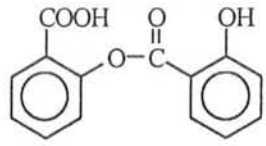


Aspirin



Salicylic acid

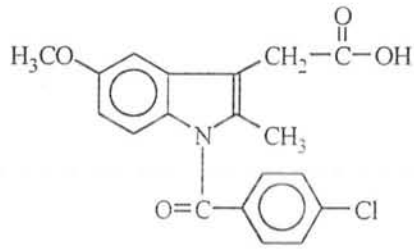




Salsalate

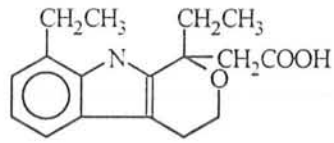
Indole and Indene Acetic Acid

Indomethyacin was the product of a laboratory search for drugs with anti-inflammatory properties. It was introduced in 1963 for treatment of rheumatoid arthritis and related disorders. Although indomethacin is used widely and is effective, toxicity often limits its use.



Indomethacin

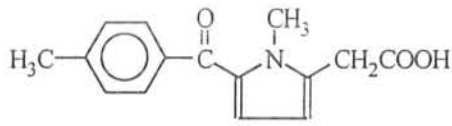
Etodolac is an anti-inflammatory drug recently approved for use in United States.



Etodolac

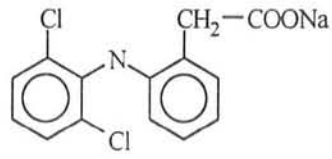
Heteroarylacetic Acids

Tolmetin and ketorolac are structurally related heteroarylacetic acid derivatives with different pharmacological features.



Tolmetin

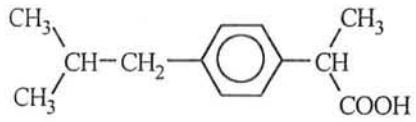
Diclofenic is phenylacetic acid derivative that was developed significantly as an anti-inflammatory agent.



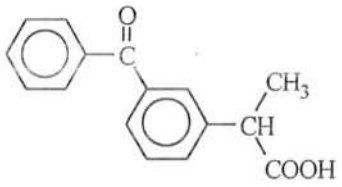
Diclofenic sodium

2.9.2 Arylpropionic Acid Derivatives

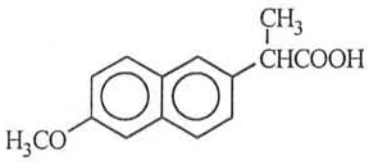
Arylpropionic acid derivative represent a group of effective, useful NSAIDS, they may offer significant advantages over aspirin and indomethacin for many patients since they usually are better tolerated. Nevertheless, propionic acid derivatives share all of the detrimental features of entire class of drugs. Furthermore, their rapid proliferation in number and heavy promotion of these drugs make it difficult for the physicians to choose rationally among members of the group and between propionic acid derivatives and more established agents. Ibuprofen was the first member of propionic acid class of NSAIDS to come into general use.



Iboprofen (Brufen)



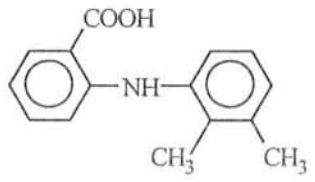
Ketoprofen



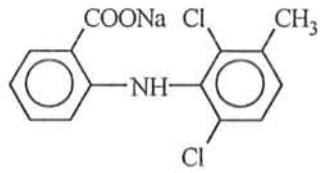
Naproxen

Anthranilic Acids

Mefenamic acid and meclofenamate are both N-substituted phenylanthranilic acids. These have anti-inflammatory antipyretic and analgesic properties. In tests of analgesic, mefenamic acid was only fenamate to display a central as well as peripheral action.



Mefenamic acid (Ponston)



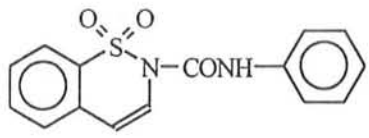
Meclofenamate sodium

Alkanones

Nabumetone is an alkanone which is anti-inflammatory agent recently approved for the use in United State. Clinical trials with nabumetone have indicated substantial efficiency in the treatment of rheumatoid. Arthritis and osteoarthritis, with a relatively low incidence of side effects. The dose typically is 1000 mg given once daily. The drug also appears to be effective in the short-term treatment of soft tissues injuries.

Enolic Acids

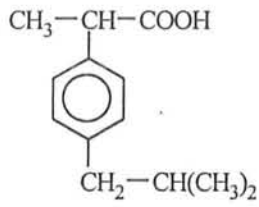
Piroxicam is one of the oxicam derivatives, a class of enolic acids that have anti-inflammatory, analgesic and antipyretic activity. It is used for treatment of rheumatoid arthritis or osteoarthritis. The principal advantage of piroxicam is its long half-life which permits the administration of a single daily dose [13].



Piroxicam

2.10 Ibuprofen

Ibuprofen is a white powder or crystalline solid with slight odour and taste. It is non-hygroscopic. It has a low water solubility but is soluble in aqueous solutions of alkali hydroxides and carbonate. Its melting point is 75°C. Ibuprofen is physically and chemically stable in the dry state. It is prepared chemically and marked as the racemic mixture of its two enantiomers.



2-(4-Isobutylphenyl)propionic acid

Chemical formula:	$C_{13}H_{18}O_2$
Melting point:	75°C
Molecular weight:	206.3

2.10.1 Pharmacology and Pharmacokinetics

Ibuprofen has prominent anti-inflammatory effects in addition to having analgesic and antipyretic action [20,21]. The analgesic effects of ibuprofen are due to both a peripheral and a central effect and are distinct from it property as an anti-inflammatory drug. Ibuprofen is a potent inhibitor of the enzyme cyclo-oxygenase which thus results in a marked reduction in prostaglandin synthesis.

Ibuprofen has similar potency in this regard to aspirin but is less potent than naproxen or indomethacin. Ibuprofen also inhibits the synthesis of some lipoxygenase products especially 11 and 15 monohydroxycicosatetrcnoic acid (HETE) but it has no effect on the generation of 5-HETE and leukotriene B4. Although some studies suggest that ibuprofen can inhibit the release of toxic radicals from stimulated leucocytes, this is probably only at concentration greater than these normally found in plasma [22,23].

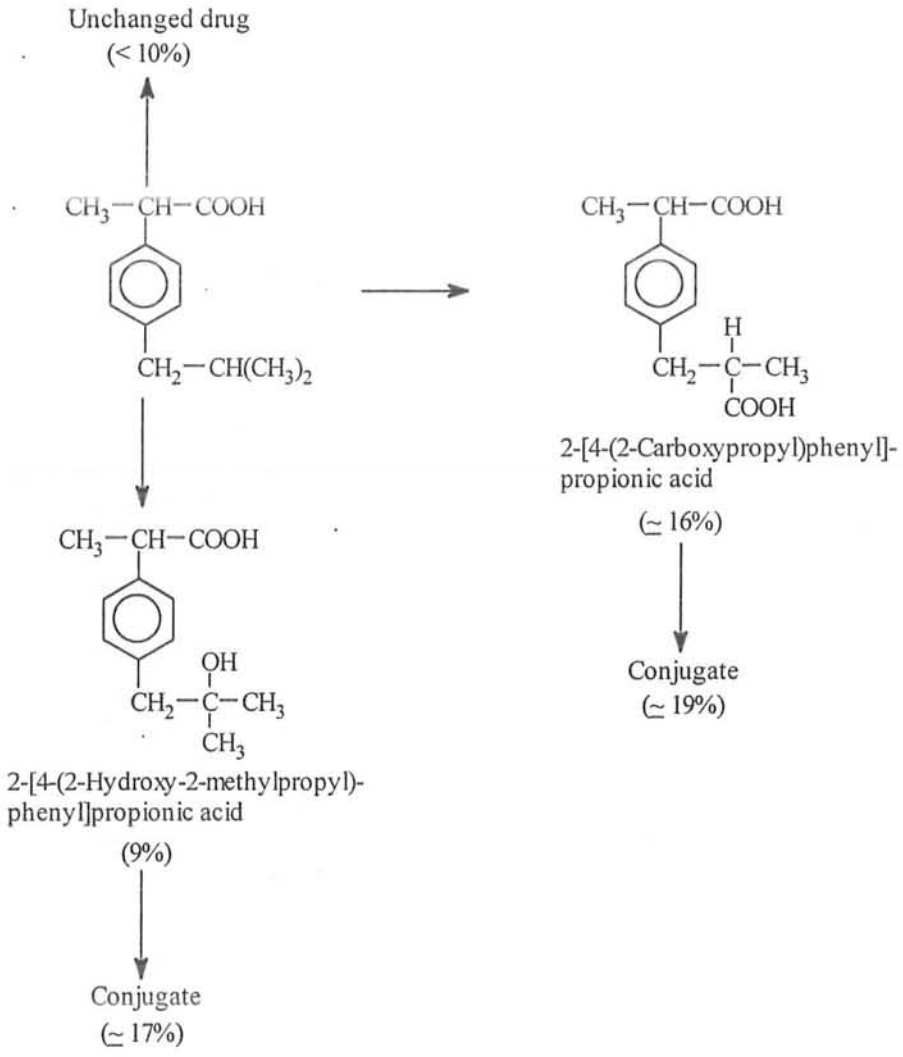
Ibuprofen is effective in relieving pain and reducing the temperature in febrile patients. The drug is also useful anti-inflammatory drug in the treatment of inflammatory

disorder. In low doses ibuprofen has predominantly analgesic properties while in higher doses the anti-inflammatory actions of ibuprofen become apparent. Ibuprofen acts on the platelets. It prevents the formation of thromboxane A_2 by platelet. It has little effect on renal function in normal individuals but can precipitate rental failure in patients who depend upon vasodilatory action.

2.10.2 Metabolism

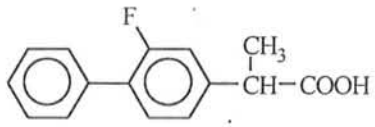
Ibuprofen is extensively metabolized in liver, with less than 10% of the dose excreted unchanged in the urine. More than 90% of dose is excreted in the urine as parent drug and metabolites, the remainder presumably being excreted in the bile and eliminated in faces.

Metabolism in Ibuprofen



2.11 Flurbiprofen

Flurbiprofen is a propionic derivative which is a potent anti-inflammatory, analgesic and antipyretic agent. It is white or cream powder which normally exists as a racemic mixture of two optical isomers, the (S)-enantiomer possessing most of biological activity, and as prepared by chemical synthesis (NIH).



2-(2-Fluorobiphenyl-4-yl)propionic acid

Chemical formula: $C_{15}H_{13}FO_2$

Molecular weight: 244.3

2.11.1 Pharmacology and Pharmacokinetics

Flurbiprofen has potent anti-inflammatory effects in addition to having antipyretic and analgesic activity. Flurbiprofen's main mechanism of action, like other non-steroidal anti-inflammatory drugs, is by inhibition of enzyme cyclo-oxygenase, resulting in reduced prostaglandin synthesis.

Flurbiprofen is also a potent inhibitor of platelet aggregation due to inhibition of thromboxane formation [4]. Flurbiprofen can be measured in plasma either by HPLC which has sensitivity [24] of 40 $\mu g l^{-1}$, or by gas chromatography and mass spectrometry, which has a sensitivity [25] of 1 $\mu g l^{-1}$.

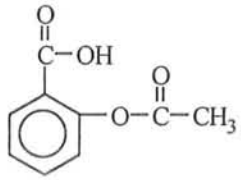
The drug is readily absorbed after oral administration, and approximately 95% of a dose is excreted in urine within 24 hours. It is extensively protein bound (99%). A single primary binding site was demonstrated with a constant of 5.32×10^5 l mol^{-1}. It has been suggested that flurbiprofen binds to a different primary site from that binding drugs such as oral anticoagulants, sulphonamides and phenylbutazone [26]. Very small amount of it are excreted in breast milk.

2.11.2 Metabolism

Approximately 95% of a dose is excreted in urine over 24 hours, 25% of which is unchanged drug. The principal routes of metabolism involve hydroxylation in the 3 and 4 positions, the resultant metabolites are excreted partly as conjugate. Unlike a number of other 2-arylpropionic acid derivatives, flurbiprofen is not subject to any significant chiral inversion (NIH).

2.12 Aspirin (Acetylsalicylic Acid)

Aspirin is a white crystalline odourless solid, prepared by chemical synthesis, e.g. by acetylation of salicylic acid with acetic anhydride using sulphuric acid as catalyst. Stable in dry air, it hydrolyses in contact with moisture.



Aspirin (2-acetyloxybenzoic acid)

Molecular weight:	180.15
Chemical formula:	$C_9H_8O_4$

2.12.1 Pharmacology

Aspirin is analgesic, anti-inflammatory, antipyretic and an inhibitor of platelet aggregation. It prolongs the bleeding time. It inhibits fatty acid cycloxygenase [6] by acetylation of active site of enzyme [7].

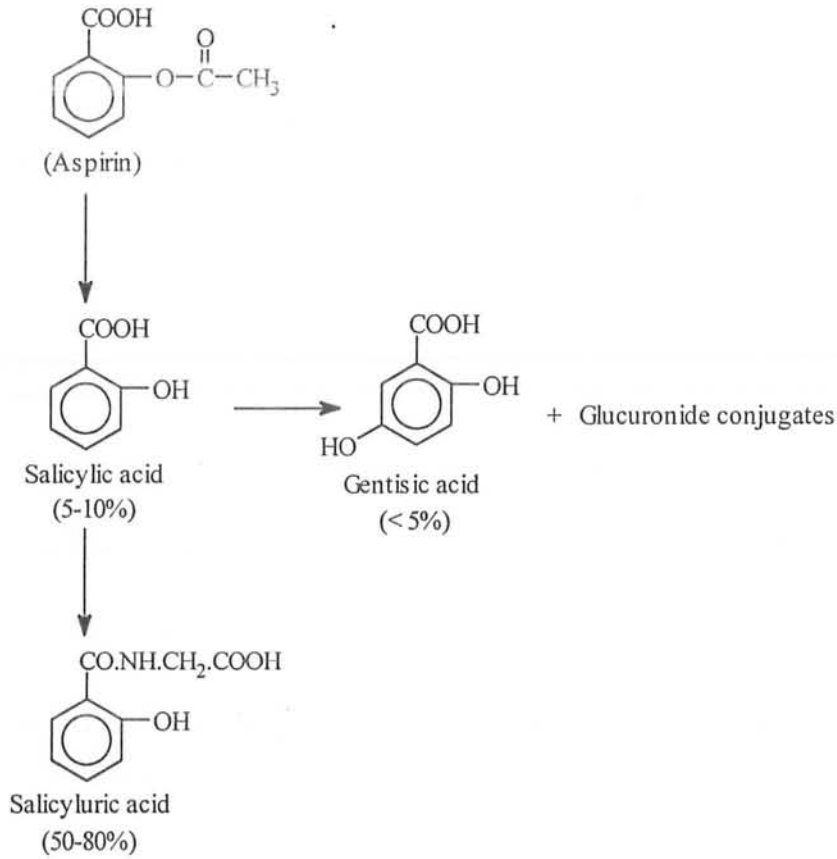
Aspirin has an active metabolite (salicylate) which, in addition to possessing some anti-inflammatory properties in its own right, also has important effects on respiration, acid-base balance and stomach.

2.12.2 Pharmacokinetics and Metabolism

The preferred analytical method is high performance liquid chromatography [27]. The sensitivity is 0.5 mgl^{-1} for both aspirin and salicylate. The blood samples are collected in the presence of potassium fluoride to inhibit plasma esterases and must be analyzed immediately if reliable information on aspirin itself is needed.

Volume of distribution of aspirin is 0.15-0.2 l/kg and that of salicylic acid is 0.13 l/kg. Protein binding of aspirin occurs to an unknown but variable extent. Aspirin is rapidly converted by esterases present in plasma and many tissues, especially liver, to salicylic acid which itself has some antipyretic, analgesic and anti-inflammatory actions. Salicyclic acid is metabolized in liver to glycine conjugate salicyluric acid. Excretion of salicyclic acid is pH dependent, approximately 80% appears unchanged in urine at pH 8, but only around 10% at pH 4.

Metabolism of Aspirin



PART-III

2.13 Conductivity

The conductance of a conductor is defined as the inverse of resistance. It is resistance between the two electrodes immersed in the solution under investigation. If A is effective cross-sectional area of electrode and these electrodes are one meter apart them.

$$R = \rho l/A$$

Where ρ (ohm m) is specific resistivity and K_s (ohm^{-1} m^{-1}) is specific or electrolytic conductivity. K_s and ρ are the intrinsic properties of the solution at given temperature and pressure. Cell constant l/A is determined by measuring the resistance, when cell is filled with solution of known specific conductivity.

Reciprocal of specific resistance is specific conductivity.

$$K_s = 1/\rho$$

Its dimension will be ohm m^{-1} or Semen's/cm.

Specific or electrolytic conductivity depends on the characteristics and the concentration "C" of the electrolyte present in the solution. Molar conductance is defined as

$$\Lambda_m = K_s/C$$

2.13.1 Equation for the CMC Based on Theoretical Consideration

As we know the organic additive is added to aqueous system. CMC of the surfactant decreased. CMC can be related to the concentration of additive "C_a". If we plot CMC Vs C_a we get a straight line with slope

$$\Delta CMC/\Delta C_a = \text{slope}$$

Whose logarithm has linear relationship with number of carbon atoms in organic additive i.e. m, therefore, a plot between $\ln CMC/C_a$ Vs m also give a straight line with slope as

$$\partial \ln \Delta CMC/\Delta C_a$$

2.13.2 Partition Coefficient

K. Shirahama and Kashiwabara proposed an equation concerning the rate of CMC depression and partition coefficient [30]. This equation is represented following which is applicable for low concentration of additives.

$$\ln(-\partial CMC/\partial C_a) = \ln(CMC^o) + \ln q + \ln K \qquad (A)$$

Where CMC^o is CMC of the surfactant without any additive. q is the constant represented interaction of additive with surfactant which depend on the surfactant chain length and related to effective micellar degree of ionization.

K_c is partition coefficient. Rearranging equation (A) we get

$$K_X = \frac{-dCMC/CMC_{(0)}}{dCa}$$

$$K_c = \frac{K_X}{n_w}$$

n_w is the number of moles of water i.e. 55.55 mole $liter^{-1}$.

Kawamura et al. give a relationship for conductance data as [31]

$$\frac{1}{\Delta A} = \frac{1}{K_c \Delta A_\alpha [C_s^{mo} - KC_a + (1+K)C_a j]} + \frac{1}{\Delta A_\alpha}$$

C_a = additive concentration

j = $\Delta A/\Delta A_\alpha$

K = $\partial CMC/\partial C_a$

2.13.3 Standard Free Energy Change of Transfer

Standard free energy change of transfer of additive from water to micelle can be calculated as

$$\Delta G^o = -RT\ln K_X$$

Where R is gas constant and T is absolute temperature.

2.14 Ultraviolet Visible Spectroscopy

Absorption of electromagnetic radiation by an organic compound in both ultraviolet and visible regions is based on same basic principle and leads to same type of molecular excitation. It is, therefore, discussed together as ultraviolet/visible spectroscopy. Since the absorption of ultraviolet/visible radiation results in the transition among the electronic energy levels of molecules. It is also usually termed as electronic spectroscopy. The wavelengths of UV/visible radiation are usually expressed in nanometer (1nm = 10^{-9} m). The UV region below 190 nm can not be studied by conventional UV spectrophotometer because oxygen in the air absorb strongly in this region. However, if oxygen is expelled out by flushing the instrument with nitrogen, the range of the instrument can be extended down to about 150 nm below which nitrogen also absorbs strongly. If the instrument is evacuated, it is possible to study whole UV region even below 190 nm. The region below 190 nm is there usually known as vacuum ultraviolet. The instrument meant for study of vacuum ultraviolet region is very expensive and only a very highly trained technician can operate it. For routine practical purposes we are mainly interested in ordinary (or quartz) ultraviolet region extending from 190 to 900 nm because atmosphere is transparent in this region as well as in visible region.

2.14.1 Absorption of Radiation and Electronic Transitions

The absorption of ultraviolet/visible radiations by molecule is associated with the excitation of valency electrons from ground state to higher energy states. In fact, the electronic transition generally occurs from the highest occupied molecular orbital (bonding or nonbonding) to the lowest unoccupied molecular orbital (anti-bonding). The wavelength of the absorbed radiation depends on the energy difference between the orbital originally occupied by electron and the orbital to which it is promoted. When a molecule absorbs UV/visible radiation of a particular wavelength, only one photon, in fact absorbed and it is assumed as a first approximation, that only one electron is promoted to a higher energy level. While other electrons remain unaffected. Furthermore, the atoms of molecule do not more during electronic transition.

In fact electronic transition occurs so rapidly that the vibrating atoms do not change their internuclear distance appreciably during this period. Electronic transitions that are associated with the absorption of UV/visible radiations are of four types

i) Sigma to sigma star "$\sigma \rightarrow \sigma^*$"

ii) $n \rightarrow \sigma^*$

iii) $\pi \rightarrow \pi^*$

iv) $n \rightarrow \pi^*$

These transitions are shown schematically as

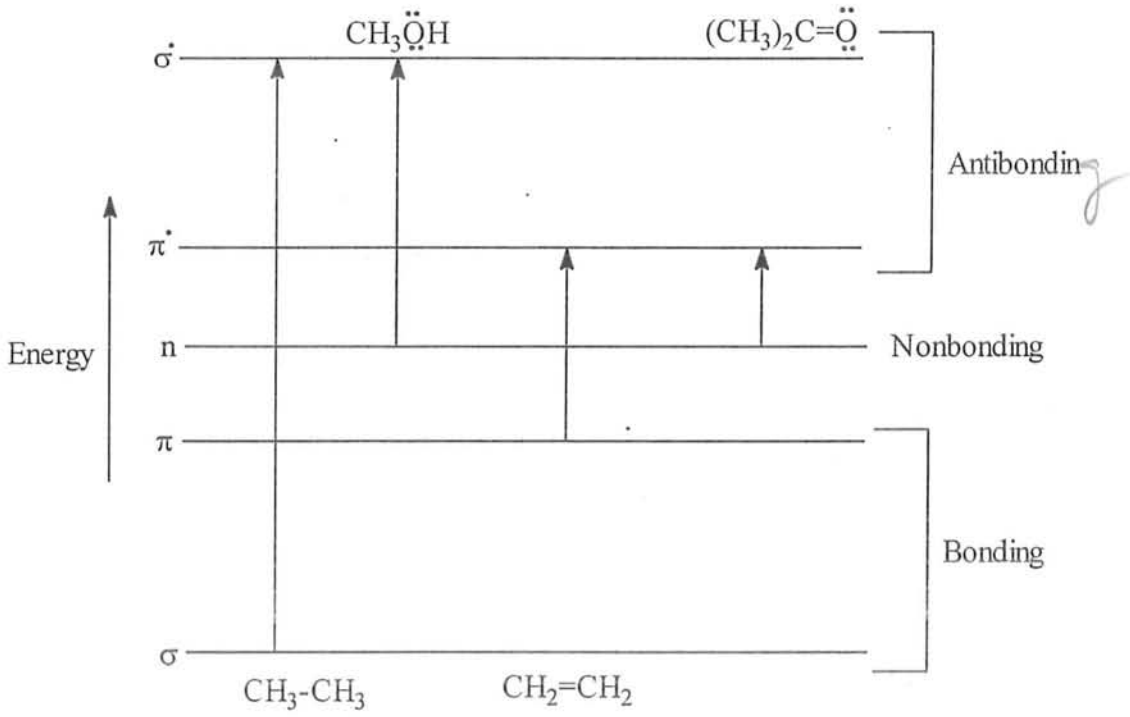


Fig. Relative energy change involved in various electronic transitions.

The $\sigma \rightarrow \sigma^*$ transitions occur in saturated hydrocarbons such as CH_3–CH_3 which contain only strongly bond sigma electrons. The excitation of these electrons from a sigma orbital to a sigma star orbital require large amount of energy necessitating absorption in the vacuum UV region, generally at wavelength below 150 nm. A C–C bond generally absorbs at about 135 nm and a C–H bond absorbs at about 125 nm. Since vacuum UV region is not accessible in most UV/Vis spectrophotometer, these transitions generally are not of use for routine analysis. So the transitions which are associated with the absorption in readily accessible UV and Vis region are mainly of the other three types.

The $n \rightarrow \sigma^*$ transitions occur in molecule containing heteroatoms such as oxygen, nitrogen, sulphur and halogen and involve the excitation of an electron from the nonbonding p-orbital of the heteroatoms to an antibonding sigma orbital of molecule. These transitions involve less energy than $\sigma \rightarrow \sigma^*$ transitions and consequently result in

the absorption at the longer-wavelength end of the vacuum UV region and shorter-wavelength end of the ordinary UV region between 150 and 250 nm of the electromagnetic spectrum.

The $\pi \rightarrow \pi^*$ transitions occur in molecule containing double or triple bonds or aromatic rings and involve the promotion of an electron from a π orbital to a π star orbital. These transitions generally absorb at 160-190 nm e.g. ethylene absorbs at 171 nm. However, a conjugated system of unsaturated bonds absorbs at a much longer wavelength e.g. butadiene absorbs at 217 nm.

The $n-\pi^*$ transitions occur in molecules that contain double or triple bonds involving heteroatoms e.g. $\rangle C{=}\ddot{O}:$, $-C{\equiv}N:$ etc. In these transitions one electron in a nonbonding atomic orbital associated with the heteroatom is excited to an antibonding π^* orbital associated with double or triple bond in the molecule. These transitions require less energy than $\pi \rightarrow \pi^*$ transitions and therefore absorb at longer wavelength, usually well within range of the ordinary UV/Vis spectrophotometers. For example, saturated aldehyde and ketones show absorption at 275-295 nm. These transitions are most useful for analysis. In given molecule, the $n \rightarrow \pi^*$ transitions require less energy and hence absorbs radiation of longer wavelength than the $\pi \rightarrow \pi^*$ transitions which in turn require less energy and hence absorb radiation of longer wavelength than the $n \rightarrow \pi^*$ transitions.

Chromophore

Any structural feature present in a molecule that is responsible for absorption of electromagnetic radiation is known as chromophore. A covalently unsaturated group responsible for electronic absorption e.g. C=C, C=O and NO_2.

Auxochrome

A saturated group with nonbonding electrons which when attached to a chromophore, alter both λ_{max} and intensity of absorption e.g. $\ddot{O}H$, NH and $:\ddot{C}l$.

Hypsochromic Shift

The shift of absorption to a shorter wavelength due to substitution or solvent effect is called blue shift or hypsochromic shift.

Bathochromic Shift

The shift of absorbance to a longer wavelength due to substitution or solvent effect is called rod-shift or bathochromic shift.

Hyperchromic Shift

An increase in absorption intensity.

Hypochromic Shift

A decrease in absorption intensity

Intensity of absorption may be measured either as transmittance (T) or as absorbance (A). The transmittance is defined as

$$T = I/I_o$$

Where I_o is the intensity of the incident radiation and I is the intensity of the transmitted radiation. The absorbance formerly known as optical density (OD) is defined as

$$A = \log (I_o/I)$$

$$= \log (1/T)$$

According to combined Bear-Lambert law

$$A = \log (I_o/I) = \varepsilon Cl \qquad (B)$$

C is concentration of sample in mole per litre of solution, l is path length of the sample solution in centimeters, ε is the molar absorptivity formerly known as the molar extinction coefficient.

$$\varepsilon = A/Cl$$

From Eq. (B), it is clear that absorbance is directly proportional to concentration "C" of sample in solution. This law is a limiting law dilute solutions i.e. ascertain that the extinction coefficient ε is independent of concentration of substance at given λ applies only to dilute solutions, ε is no longer constant for concentrated solutions but depend on refractive index of solution.

2.14.2 Double-Beam Instruments

Double-beam spectrophotometer designed to operate over a range from about 190-750 nm. The instrument is equipped with interchangeable deuterium/tungsten sources, a reflection grating monochromator and a photomultiplier detector. The beam splitter is a motor-driven circular disk or chopper that is divided into three segments, one of which is transparent, second reflecting and third opaque with each rotation. The detector receives three signals; the first corresponding to P_o and second to P and third to

the dark current. The resulting electrical signals are then processed electronically to give the transmittance or absorbance on a readout device.

An instrument of this kind shown in Fig._____ is usually provided with a motor-driven grating that is synchronized with the paper drive of a record so that automatic scanning and recording of an entire spectrum become possible [32].

2.15 Differential Spectroscopic Method

Differential absorption spectroscopic method was proposed by H. Kawamura, M. Menabe, Y. Fujita and S. Topkunage and was applied in order to determine the partition coefficient of homologues to phenyl alkanols in surfactant micellar solution. The differential absorption ΔA, depends on surfactant concentration C_s, at a given concentration of organic additive C_a. This can be explained as follows for the organic additive in water, Lambert-Beer's law holds an experimentally confirmed

$$A_w = \varepsilon^f C_a \qquad (1)$$

Where A_w is absorbance at given wavelength, ε^f is molar absorptivity.

As $\Delta A \rightarrow 0$ below CMC, it is supposed that above equation also hold in nonmicellar surfactant solution. On other hand, in the micellar region a portion of the organic region a portion of the organic additive (C_a^m) is considered to be solubilized in micelles and other (C_a^f) still remains monomerically in the bulk coater region, the total concentration, C_a is related as

$$C_a = C_a^f + C_a^m \qquad (2)$$

Assuming that the Lambert-Beer's law also holds for solubilized organic additive as well as the monomer species. The absorbance, as of a micellar solution can be expressed as

$$A_s = \varepsilon^f C_a^f + \varepsilon^m C_a^m \qquad (3)$$

Where ε^m is molar absorptivity for the solubilized organic species. The differential absorbance ΔA, corresponding to the experimentally determined quantity is represented from equation

$$\Delta A = A_s - A_w = \Delta\varepsilon C_a^m \qquad (4)$$

Where $\Delta\varepsilon = \varepsilon^m - \varepsilon^f$.

A quantity "J" is defined as

$$J = C_a^m / C_a \qquad (5)$$

The physical meaning of J is the fraction of the amount of solubilized organic additive in that of added organic additive. It is expressed that at a certain concentration C_a, J is equal to zero in the non-micellar region upto the CMC and increase with increasing C_s above

the CMC. As C_s increase upto infinity, J approach unity, since almost all added organic additive should by solubilized in micelles $C_a^m \cong C_a$. This we can write

$$J = \Delta A/\Delta A_w \qquad (6)$$

Where ΔA_w represent ΔA at infinity of C_s. The partition coefficient K_X is defined as

$$K_X = \frac{X_a^m}{X_a^f} \qquad (7)$$

Where X_a^f and X_a^m are mole fraction of organic additive in respective phase and are related with concentration of species in the solublization system.

The partition coefficient K_X is ratio of mole fraction between bulk and micellar phase

$$X_a^m = \frac{C_a^m}{C_a^m + C_s^m}$$

$$X_a^f = \frac{C_a^f}{(C_a^f + C_s^f + n_w)} = \frac{C_a^f}{n_w} \qquad (8)$$

Where C_s^f and C_s^m are concentration in monomeric and micellar states respectively. C_a^f and C_s^f in denominator of X_a^f are negligible relative to n_w. Number of moles of H_2O per litre. For convenience another partition coefficient K_c expressed in molar concentration units is defined as

$$K_c = \frac{C_a^m/(C_a^m + C_s^m)}{C_a^f} \qquad (9)$$

Where K_c related to K_X as

$$K_X = K_c.n_w$$

Using equation 5 and 6 the equation 9 can be written as

$$\frac{1}{\Delta A} = \frac{1}{K_c \Delta A_\alpha (C_s^m + C_s^m)} + \frac{1}{\Delta A_\alpha} \qquad (10)$$

Based on the present model of solubilization system, it is expected that as C_s approaches infinity, "C_a^m" approaches C_a and C_s^m to C_s^{mo} respectively.

$$C_s^{mo} = (C_s - CMC_o)$$

CMC_o is CMC of surfactant in H_2O. Thus at infinity C_s equation (10) become

$$\frac{1}{\Delta A} = \frac{1}{K_c \Delta A_\alpha (C_a + C_s^{mo})} + \frac{1}{\Delta A_\alpha} \qquad (11)$$

This equation indicate that K_c is obtained from plot of $1/\Delta A$ versus $1/(C_a+C_s^{mo})$. The intercept provides the value of ΔA_α, the slope of linear relation provides the value of partition coefficient "K_c".

An improved relationship by Kawamura et al. includes two new factors j and K in equation (11) is shown as

$$\frac{1}{\Delta A} = \frac{1}{K_c \Delta A_\alpha [C_s^{mo} - KC_a + (1+K)C_a j]} + \frac{1}{\Delta A_\alpha}$$

K is slope of CMC depression curve i.e. $dCMC/dC_a$ and j is fraction of amount of solubilized additive and can be calculated as

$$j = \Delta A/\Delta A_\alpha$$

2.16 Standard Free Energy Change of Transfer (ΔG)

Standard free energy change of transfer is given by relation

$$\Delta G^o_p = -RT\ln K_X$$

Where R&T are gas constant and absolute temperature respectively.

$$K_X = K_c \times n_w$$

n_w is number of moles of H_2O (55.55 per litre).

Chapter 3

EXPERIMENTAL

Chapter – 3

EXPERIMENTAL

3.1 Material

Sodium dodecyl sulfate (SDS), the product of Fluka was of analytical grade and is used without further purification. The molecular formula is $C_{12}H_{25}OS\ \bar{O}_3Na^+$ with molecular weight of 288.38 g $mole^{-1}$. SDS is hygroscopic, therefore, it is used in dry form. Cetyltrimethylammonium bromide (CTAB) product of Sigma, 99% purity is used without further purification. Molecular formula of CTAB is $C_{16}H_{33}N(CH_3)_3$ with molecular weight of 364.5g. CTAB is very hygroscopic, so it is used in dry form.

Flurbiprofen, ibuprofen and aspirin were used as additive. Flurbiprofen is a white or cream powder has molecular formula $C_{15}H_{13}FO_2$, molecular weight 244.3 g mol^{-1}. Ibuprofen is also white powder or crystalline solid. It is non-hygroscopic. It has molecular formula $C_{13}H_{18}O_2$ and molecular weight 206.3 g $mole^{-1}$. Aspirin is a white crystalline odourless solid has molecular formula $C_9H_8O_4$ and molecular weight 180.15 g $mole^{-1}$.

NaOH (0.001 mole/dm^3)
Oxalic acid (0.001 mole/dm^3)
Phenolphthalein as indicator
Water used was doubly distilled

3.2 The Procedure for Solubilization of Additive by Titration Method

i) Prepared different concentrations of SDS and CTAB solution distilled water range from ($30 \times 10^{-3} - 1 \times 10^{-3}$) and ($40 \times 10^{-4} - 1 \times 10^{-4}$) respectively.

ii) Added different amount of additive range from (0.1g, 0.2g, 0.3g and so on) in the different concentration of SDS and CTAB solution respectively.

iii) Stirred all flasks vigorously and filtered the flask solutions.

iv) Titrated the filtrate against standardized sodium hydroxide solution. Note volume of sodium hydroxide used.

v) Calculated strength of each solution and then amount of additive solubilized in each solution.

3.3 Conductance Measurements

The conductance measurements were made on Microprocessor Conductivity Meter (WTW), LF 2000/C model of Wissenchaftlinch Technische Werkstatten (Germany). It can detect the conductance of very dilute solution as 1 ppm accurately. It has digital range from 10^{-3} μS cm^{-1} to μS cm^{-1}. It display specific conductance references temperature selected was 25°C with ± 0.05°C.

Electrode used in this work has cell constant 0.11 cm^{-1} which was coated with platinum block in order to avoid polarization effect. There was as temperature detector immersed in the analyzing solution. Thermostat made by Coda Company, Japan, was used to control the temperature with ± 0.01°C.

3.3.1 Calibration of the Electrode

The electrode was calibrated to avoid the polarization. This can be confirmed by evaluating the cell constant of the known concentration. The aqueous solution of KCl (0.0118 mole/dm^3) were proposed and their conductance were measured at 25°C, the cell constants were calculated from relationship.

$$K = \wedge_m C/G^o \times 1000 \qquad (A)$$

Where $\wedge_m$ = molar conductance of KCl solution of concentration "C" (mole/dm^3).

G^o = Conductance of respective solution

The molar concentration in above equation calculated from equation

$$\wedge_m = 149.93\text{-}94.65\ C^{1/2} + 58.74\ ClnC + 198.4\ C^{3/2} \qquad (B)$$

The coefficients in this equation were taken from reference. This equation (B) is applicable upto 0.012 mole/dm^3 concentration of aqueous KCl solution at 25°C and with an accuracy of 0.013%. The average value of cell constant obtained from (A) and (B) was 0.1205 cm^{-1}.

3.3.2 Procedure for Conductance Measurement

Critical micelle concentration (CMC) of surfactants. SDS and CTAB was determined through specific conductivity measurement method. CMC can be obtained by plotting specific conductance Vs concentration of surfactants solution. Since conductivity of solution changed markedly with change of temperature. Therefore,

temperature is kept constant at 25°C throughout experiment by using water thermostat controlled within ±0.01°C temperature.

Prepared different concentration of SDS solution by using stock solution in distilled H_2O i.e. 30 x 10^{-3} mole/dm^3. These solutions were used to determine the CMC when no additive is used. When effect of additive at CMC of surfactant was investigated then solutions of surfactant are prepared as:

First of all prepared different concentrations of additive i.e. flurbiprofen (4 x 10^{-5}, 8 x 10^{-5}, 12 x 10^{-5}, 17 x 10^{-5} and 21 x 10^{-21} mole/dm^3). Then a portion of first concentration i.e. 4 x 10^{-5} mole/dm^3 of flurbiprofen were used for preparation of surfactant solution (SDS) with its concentration 30 x 10^{-3} mole/dm^3. Then by dilution method prepared different concentrations of SDS solution, concentrations of flurbiprofen throughout experiment remain constant but surfactant concentration changed. Therefore, corresponding change in specific conductivity was noted.

Same procedure used for other concentrations of flurbiprofen and other additives (ibuprofen and aspirin). Similarly, prepared solution of CTAB i.e. 50 x 10^{-4} mole/dm^3 and repeated the procedure.

3.4 Ultraviolet Visible Spectroscopy

Double Beam Spectrophotometer

The work was carried out on Perkin Elmer double-beam model Lambda 20 UV visible spectrophotometer at 25°C. It has two light paths, one for sample and other for the blank or reference. The detector alternately sees the reference and sample beam and output of the detector as proportional to the ratio of the intensities of the two beams I/I_o. The cells used for the UV visible spectrophotometer were square. Curettes 1 cm think (internal distance between parallel walls).

3.4.1 The Procedure for Simple Absorption Spectra Measurement

The additive solutions (flurbiprofen, ibuprofen and aspirin) with given concentration were prepared. A portion of solution was used as solvent for SDS and CTAB. The simple absorption spectra were measured by setting the curette filled with distilled water in the reference side and that of surfactant solution at same additive concentration in sample side of spectrophotometer.

3.4.2 The Procedure for Differential Absorption Spectra Measurement

The additive solutions (flurbiprofen, ibuprofen and aspirin) with given concentration were prepared. A portion of solution was used as solvent for SDS and CTAB. The differential spectra were measured by setting the curette filled with additive solution in reference side and that of SDS and CTAB solution at same additive concentration in sample side of spectrophotometer.

Chapter 4

RESULTS & DISCUSSION

Chapter – 4

RESULTS AND DISCUSSION

TITRATION METHOD

4.1 Micellization

The surfactant molecule aggregate together in such a manner that their hydrophobic tails tend to congregate and their hydrophilic heads provide protection. Hundreds of such molecules accumulate to form a micelle and phenomenon is micellization. This process take places at a particular concentration that particular concentration is known as critical micelle concentration (CMC).

Micellar systems are used as detergent. Therefore, they have an important role in industry. Micellar formation effect interfacial phenomenon in water, such as surface of interfacial tension reduction. Bulk properties are unusual and indicate the presence of colloid particle (micelles) in solution.

4.2 Solubility of Additive with SDS and CTAB Solution by Titration Method

One of the important properties of surfactant that is directly related to micelle formation is solubility. Solubilization defined as spontaneous dissolving of a substance by reversible interaction with micelles of a surfactant in a solvent to form a thermodynamically stable isotropic solution.

Tables (1,2) show relation of SDS, CTAB solution and amount dissolved of flurbiprofen, ibuprofen and aspirin in aqueous medium respectively. From Fig. (1,2) it is clear that solubility is very slight at concentration below CMC, but there is abrupt after CMC for flurbiprofen, less abrupt for ibuprofen and very less increase in solubility for aspirin.

The amount of flurbiprofen, ibuprofen and aspirin dissolved in water as 0.0244, 0.0412, 0.360 g/dm^3 respectively. The amount of material dissolve in surfactant of material depends on structure of solubilized and also nature of surfactant. Flurbiprofen is more soluble in SDS solution as compared to ibuprofen, reason behind this is that flurbiprofen behaves like straight chain or more hydrophobic as compared to ibuprofen and aspirin and ibuprofen has branch chain structure or less hydrophobic.

Hence flurbiprofen penetrate more deeply into micelles as compared to ibuprofen and aspirin.

From the titration data (as shown in Table 1,2 and Fig. 1A,2B) it is clear that there is slight solubility in pre-micellar phase and as micellar phase approach, there is abrupt change, therefore, solubility is micellar phenomenon. The increasing order of their solubility according to the hydrophobicity of the drugs as

Flurbiprofen > Ibuprofen > Aspirin

4.2.1 Solubility by CTAB

CTAB is cationic surfactant. Here both type of interactions involve i.e. hydrophobic-hydrophobic interaction between hydrophobic part of surfactant, and characteristic interaction. Therefore, all the three drugs are more dissolved in CTAB solution than SDS. In this way nature of surfactant i.e. either anionic or cationic, involved in solubilization of material. Data are shown in Table 1,2 and Fig. 1,2 respectively.

CONDUCTANCE METHOD

4.3 Effect of Additive on CMC of SDS

SDS is an anionic surfactant i.e. sodium dodecyl sulphate. The reported value of CMC for SDS is 8.27×10^{-3} mole/dm^3. The CMC value for a surfactant can be obtained by plotting specific conductance of surfactant against its concentration in aqueous solution. The addition of flurbiprofen, ibuprofen and aspirin to micellar solution is known to depression in critical micelle concentration (CMC).

Fig. 3A-3P show relation between specific conductance and concentration of SDS solution for different concentrations of flurbiprofen, iburpofen and aspirin i.e. 4×10^{-5}, 12×10^{-5}, 17×10^{-5}, 21×10^{-5} mole/dm^3 at 25°C and data is tabulated in Table (3,5).

The CMC values for SDS are determined by a break in plots of specific conductance Vs surfactant concentration. It is clear from Fig. 3A-3P that as concentration of each flurbiprofen, ibuprofen and aspirin increase. The more marked depression in CMC values are observed, data tabulated is shown in Table (6). The additive molecules are partitioned between bulk and micellar phase. Therefore,

hydrophobic-hydrophobic interaction between solubilized material and hydrocarbon part of micelles cause reduction in free energy of micelles, hence CMC decreased.

Table (6) shows that flurbiprofen depressed CMC's values for SDS more as compared to ibuprofen and aspirin. This may be due to straight chain like structure of flurbiprofen.

Sticks [33] believed that those molecules that are most effective at reducing CMC are solubilized in outer portion of the micelle core and then under the lateral pressure tending to force them into inner portion of the micelle and hence more solubilized. Flurbiprofen has straight chain like behaviour and solubilized in outer portion of micelle core and then by lateral pressure force into inner micelle, hence more solubilized. The CMC values for SDS depressed by flurbiprofen, ibuprofen and aspirin as of order

Flurbiprofen > Ibuprofen > Aspirin

The break in curve (Fig. 3A-3P) on specific conductance against concentration is primarily attribute to sharp increase in mass per unit charge of material in solution, is interpreted as evidence of the formation of micelles from unassociated molecules of surfactant. The concentration at which this phenomenon occur is called the critical micelle concentration [34-36].

4.4 Effect of Additive on CMC of CTAB

CTAB is the cationic surfactant i.e. cetyltrimethyl ammonium bromide. The CMC reported value for CTAB is 8.89×10^{-4} mole/dm^3.

Tables (11-13) show that as there is an increase in concentration of each flurbiprofen, ibuprofen and aspirin in surfactant solution, specific conducatance increase. The break in curve (Fig. 4A-4C) is due to formation of mass per unit charge of material. This break is also attributed to the binding of counterion onto the micelle surface because of high charge density. Addition of solubilized material bring about a reduction of surface charge density. In CTAB solution solubilized material depressed more CMC value as compared in SDS solution, data tabulated is shown in Tables (4,14). This may be due to presence of electrostatic and hydrophobic-hydrophobic interaction. To discuss more quantitatively, the following model is proposed. Added solubilized materials are partitioned between bulk and micellar phase and resultant entropy of mixing, in addition the hydrophobic interaction between solubilized additive and hydrocarbon part of the micelle, cause a reduction in free energy of micelles, hence CMC is lowered [37].

SPECTROSCOPIC METHOD

4.5 Anti-rheumatoid Drugs

Most of aromatic compound i.e. benzene consists of three absorption bands, all due to $\pi \rightarrow \pi^*$ transition. It absorbs at 184 nm, 202 nm and has fine structure in region between 230-270 nm with λ_{max} at 254 nm of relatively low intensity, resulting from forbidden transition, due to loss of symmetry caused by molecular vibration.

The flurbiprofen spectrum in aqueous medium (Fig. 13A), both band move towards shorter λ_{max} value from normal. Reason behind this is that there is decrease in electron density due to electron withdrawing effect of fluorine. It may be due to that polar solvent shift $n \rightarrow \pi^*$ transition to the shorter λ_{max}. Aspirin spectrum in aqueous medium, the bands are also shifted toward shorter λ_{max} from normal value due to conjugation with carboxylic group.

Ibuprofen spectrum in aqueous, the ε_2 band is shifted toward longer wavelength due to hyperconjugation of alkyl group and band shifted toward longer wavelength.

4.6 Interaction of Flurbiprofen with SDS & CTAB

There is continuum of environment from the hydrated core surface to a non-polar core. The solubilizate may be absorbed on surface oriented near the surface or it may be trapped in hydrocarbon core. Moreover, solubilization is dynamic equilibrium process and solubilizate may spend different levels between core and surface of surfactant. The absorbance values show same trend for SDS and CTAB.

Increase in the absorbance values with increase in the surfactant concentration is regarded to be caused by additive molecule tries to interact with surfactant to form complex. Although the additive molecules are incorporated in micelles, the chromophore of their molecules are still oriented near surface with negligible Van der Waal interaction with hydrocarbon core of micelles and absorb light more favourably than in bulk aqueous phase.

The absorbance Vs surfactant concentration plot of flurbiprofen at a particular concentration in the presence of various SDS, CTAB concentration are shown in Fig. 9A, 10A and respective data is shown in Tables (20,24) respectively.

4.6.1 Change in λ_{max}

Flurbiprofen molecule give maximum absorbance at 196.86 nm. Reason behind this is that $\in_2$ band is shifted toward shorter wavelength from normal due to electron withdrawing of fluorine. Tables (20,24) show effect of SDS and CTAB on λ_{max}. Flurbiprofen with increasing concentration of CTAB give an increase in λ_{max} (red-shift) from 196.86–206.10 nm. When λ_{max} increases, it means additive molecules try to interact with surfactant molecules and a complex is formed and energy for transition of electron decrease. It means electronic transition become easier. In CTAB, both hydrophobic and electrostatic interactions are involved and a complex is formed between them and then wavelength almost became constant. Wavelength Vs concentration of CTAB (C_s) plot show in Fig. 14.

In SDS there is no sharp change in λ_{max}, here less number of flurbiprofen molecules are incorporated in micelles. There is only hydrophobic interaction involved.

4.7 Interaction of Ibuprofen with SDS and CTAB

Tables (20,24) display the effect of SDS and CTAB concentration respectively on the value of maximum absorbance and λ_{max} of ibuprofen in aqueous medium. The same trend of absorbance value was observed as in flurbiprofen. Increase in absorbance value with increase in surfactant concentration is regarded to be caused by additive molecule tries to interact with surfactant molecule to form a complex. In premicellar phase absorbance increase sharply but as approach micellar phase absorbance decrease and because almost parallel to surfactant concentration. Fig. 9B, 10B which indicate level of saturation.

4.7.1 Change in λ_{max}

Ibuprofen gives maximum absorbance at 221.18 nm when there is addition of CTAB solution. λ_{max} shift toward shorter wavelength (192.17 nm) this is due to interaction of water with ibuprofen decrease and band shifted toward shorter wavelength i.e. CTAB is cationic surfactant having positively charged species. Fully charged species is more stable than partially charged species.

Ibuprofen with increasing concentration of CTAB give an increase in λ_{max} (red shift) from 192.17-203.10 nm which indicate that more additive molecules are tries to interact with surfactant molecule and form the complex. Energy for transition of electron decrease. It means electronic transition become easier. In CTAB, both hydrophobic and

electrostatic interactions are involved and a complex is formed between them. In organic phase i.e. micellar phase wavelength almost become constant which indication of maximum incorporation of molecule to micelles.

In SDS there is no sharp change in λ_{max}. There only hydrophobic interaction involved. Wavelength Vs surfactants concentration plot is shown in Fig. 13,15 respectively and data in Tables (20,24) respectively.

4.8 Interaction of Aspirin with SDS and CTAB

Tables (20,24) display the effect of SDS and CTAB concentration respectively on the maximum absorbance value and λ_{max} of aspirin. Same trend of absorbance was observed as in flurbiprofen and ibuprofen. In premicellar phase, absorbance increase sharply as surfactant concentration increase but as micellar phase approach, absorbance decrease and behave almost horizontal to surfactant concentration. Fig. 9C and 10C which indicate that maximum aspirin molecule incorporate in micelle.

4.8.1 Change in λ_{max}

Tables (20,24) display the effect of SDS and CTAB respectively on λ_{max}. Same trend of wavelength was observed as in flurbiprofen and ibuprofen with the surfactant concentration. Aspirin with increasing concentration of CTAB give an increase in λ_{max} (red-shift) from 193.98-204.17 nm which indicate additive molecule interact with surfactant molecule and form a complex. Energy for the transition of electron decrease. It mean electronic transition become easier.

At the level of maximum saturation, wavelength Vs surfactant concentration plot become almost horizontal. In CTAB solution, both hydrophobic and electrostatic interaction involve and a complex is formed between aspirin and CTAB molecule.

In SDS there is only hydrophobic interaction involve, wavelength Vs surfactant concentration plot are shown in Fig. (13,16).

4.9 Differential Absorbance "ΔA"

Tables (21,25) show data for differential absorption of flurbiprofen, ibuprofen and aspirin in the presence of SDS and CTAB. It is clear from table that differential absorbance (ΔA) increase as the surfactant concentration (C_s) increase. ΔA is considered zero at premicellar concentration of surfactant. The increase in ΔA with increase in surfactant concentration shows an increase in amount of solubilized material (drugs) in the micelles. The analysis for amount of solubilized material is made at wavelength

"λ_{max}" where highest peak observed in spectra. The shift of each peak with increasing surfactant concentration (C_s) can be ignored with experimental error ± 1.0 nm.

The ibuprofen and aspirin molecule orient near the hydrophilic surface of micelles and flurbiprofen molecule penetrate into micelle in SDS. It is due to that flurbiprofen has straight chain like behaviour and more hydrophobicity hence penetrate more deeply while ibuprofen has branch chain structure. It is due to more hydrophobic-hydrophobic interaction between solubilized material and hydrophobic part of surfactant.

In case of CTAB, more differential absorbance for flurbiprofen, ibuprofen and aspirin than SDS which indicate more penetration of these materials in micelles here both electrostatic and hydrophobic interactions involve.

4.10 Partition Coefficient by Differential Absorbance

From spectroscopic data as shown in Tables (21,25) for both SDS and CTAB respectively for all the three drugs, it is clear that as there is increase in surfactant concentration, differential absorbance increase which indicate that more and more drugs penetrate into micelles.

Differential absorbance for CTAB is more as compared to SDS which indicate more penetration of drugs within micelles of CTAB as compared to SDS. Hence more partition coefficient "K_X" for CTAB as compared to SDS.

Partition coefficient of drugs in micelles of SDS and CTAB are shown in Tables (28,29). Partition coefficient is defined as the ratio of the mole fraction concentration of additive in micelles to its mole fraction in surrounding aqueous solution. The partition coefficient for CTAB with all drugs are maximum since when drugs dissolve in water, carries negative charge and CTAB has positive charge. Therefore, there is highest interaction between them and additive (drugs) deeply penetrate in micelles.

For calculation of partition coefficient of additive, the relation proposed by Kawamura , Monabe [31] and S.S. Shah and coworkers expanded this [38,39].

$$\frac{1}{\Delta A} = \frac{1}{K_c \Delta A_\alpha [C_a + C_s^{mo}]} + \frac{1}{\Delta A_\alpha}$$

Kawamura et al., give a new relationship for conductance data as

$$\frac{1}{\Delta A} = \frac{1}{K_c \Delta A_\alpha [C_s^{mo} - KC_a + (1+K)C_a J]} + \frac{1}{\Delta A_\alpha}$$

Where

ΔA = Differential absorbance

ΔA_α = Differential absorbance at infinity value of C_s

C_a = Concentration of additive

$C_s^{mo} = C_s - CMC_{(0)}$

$K = \partial CMC/\partial C_a$

$J = \Delta A/\Delta A_\alpha$

K_c is obtained (Fig. 11A-12C) from plot $1/\Delta A$ Vs $1/C_a+C_s^{mo}$ and $1/\Delta A$ Vs $1/[(C_s^{mo}-KC_a + (1+K)C_aJ]$ by spectroscopic and conductometric method respectively. The respective data tabulated is shown in Tables 9, 17, 21 and 25.

For calculation of partition coefficient K_X, following relation was used

$K_X = K_c n_w$

n_w is the number of moles of water per cubic decimeter i.e. 55.55 mole/dm^3.

4.11 Standard Free Energy Change of Solubilization

Tables (30,31) show standard free energy change of solubilization of flurbiprofen, ibuprofen and aspirin in SDS and CTAB.

Standard free energy change of transfer was calculated using relation

$\Delta G_P^\circ = -RTlnK_X$

R = Gas constant

T = Absolute temperature

K_X = Partition coefficient

ΔG_P° is a good measuring parameter for solubiliztion, the more negative value of ΔG_P°, the more solubilization and more stabilized system.

It is clear from Tables (30,31) that value of ΔG_P° for flurbiprofen is more negative than ibuprofen and aspirin in both SDS and CTAB by conductometric and spectroscopic methods. Increase in K_X value, ΔG_P° become more negative. Flurbiprofen has most negative value of ΔG_P° which indicate flurbiprofen is most stable system. While ΔG_P° value for ibuprofen and aspirin are less than flurbiprofen. ΔG_P° values indicate that additive (drugs) in bulk environment are less stable as in organic phase (micellar phase) so they incorporate themselves inside the micelles.

TABLES & FIGURES

Table-1

Relationship between C_s and amount of flurbiprofen, ibuprofen and aspirin dissolved "ΔS" of SDS solution.

S.No.	$C_s \times 10^{-3}$	Amount dissolved "ΔS" g/dm^3		
		Flurbiprofen	Ibuprofen	Aspirin
1.	1	0.0314	0.0185	0.002
2.	2	0.0404	0.0288	0.018
3.	3	0.0435	0.0288	0.022
4.	4	0.0464	0.0330	0.030
5.	5	0.0513	0.0371	0.032
6.	6	0.0562	0.0473	0.039
7.	7	0.0904	0.0494	0.049
8.	8	0.1466	0.0639	0.063
9.	10	0.2247	0.1071	0.083
10.	15	0.2663	0.1709	0.133
11.	20	0.3420	0.2224	0.185
12.	25	0.3957	0.2822	0.215
13.	30	0.5643	0.4099	0.239

C_s = Concentration of SDS

$\Delta S = S_n - S_o$

S_o = Solubility in pure water

S_n = Solubility at different concentrations of SDS

Table-2

Relationship between C_s and amount of flurbiprofen, ibuprofen and aspirin dissolved "ΔS" of CTAB solution.

S.No.	$C_s \times 10^{-4}$	Amount dissolved "ΔS" g/dm^3		
		Flurbiprofen	Ibuprofen	Aspirin
1.	1	0.0244	0.0474	0.012
2.	2	0.0488	0.0497	0.042
3.	3	0.0633	0.0494	0.490
4.	4	0.0683	0.0535	0.0510
5.	5	0.0927	0.0803	0.550
6.	6	0.1073	0.0947	0.070
7.	7	0.1954	0.1215	0.080
8.	8	0.244	0.1483	0.148
9.	10	0.3421	0.1958	0.18
10.	15	0.4398	0.2781	0.251
11.	20	0.586	0.3729	0.313
12.	25	0.7329	0.5005	0.357
13.	30	0.8551	0.6201	0.423
14.	35	0.9528	0.7107	0.473
15.	40	1.0749	0.7972	0.543

C_s = Concentration of CTAB

$\Delta S = S_n - S_o$

S_o = Solubility in pure water

S_n = Solubility at different concentrations of CTAB

Table-3

Relationship between specific conductance and concentration of SDS in flurbiprofen water mixture at 25°C.

S.No.	C_a / C_s	Specific conductance (ms cm^{-1})				
		4×10^{-5}	8×10^{-5}	12×10^{-5}	17×10^{-5}	21×10^{-5}
1.	0	0.0616	0.0728	0.10	0.1312	0.1344
2.	2×10^{-3}	0.860	0.865	0.876	0.895	0.979
3.	3×10^{-3}	1.345	1.357	1.363	1.375	1.517
4.	4×10^{-3}	1.936	1.880	1.834	1.803	1.970
5.	5×10^{-3}	2.215	2.282	2.337	2.379	2.419
6.	6×10^{-3}	2.589	2.687	2.751	2.798	2.844
7.	7×10^{-3}	2.916	3.11	3.12	3.17	3.05
8.	8.5×10^{-3}	3.40	3.63	3.64	3.65	3.4
9.	10×10^{-3}	3.81	4.05	4.12	3.90	4.01
10.	15×10^{-3}	5.37	5.61	5.63	5.67	5.71
11.	20×10^{-3}	6.09	6.51	7.03	7.04	6.95
12.	25×10^{-3}	7.75	7.92	8.21	8.25	8.21
13.	30×10^{-3}	8.69	9.07	9.22	9.37	9.56

C_s = Concentration of SDS (mole/dm^3)

C_a = Concentration of flurbiprofen (mole/dm^3)

Table-4

Relationship between specific conductance and concentration of SDS in ibuprofen water mixture at 25°C.

S.No.	C_a / C_s	Specific conductance (ms cm^{-1})				
		4×10^{-5}	8×10^{-5}	12×10^{-5}	17×10^{-5}	21×10^{-5}
1.	0	0.0856	0.1576	0.2152	0.2968	0.3651
2.	2×10^{-3}	0.855	0.861	0.877	0.881	0.889
3.	3×10^{-3}	1.336	1.437	1.447	1.457	1.467
4.	4×10^{-3}	1.787	1.821	1.841	1.85	1.862
5.	5×10^{-3}	2.189	2.22	2.25	2.256	2.457
6.	6×10^{-3}	2.556	2.625	2.645	2.649	2.795
7.	7×10^{-3}	2.958	3.10	3.27	3.35	3.05
8.	8.5×10^{-3}	3.27	3.35	3.34	3.43	3.45
9.	10×10^{-3}	3.59	4.10	3.65	4.15	3.81
10.	15×10^{-3}	4.53	4.56	4.58	4.60	4.61
11.	20×10^{-3}	5.01	5.1	5.15	5.21	5.29
12.	25×10^{-3}	5.51	5.65	5.69	5.70	5.56
13.	30×10^{-3}	5.9	6.13	6.22	6.21	6.66

C_s = Concentration of SDS (mole/dm^3)

C_a = Concentration of ibuprofen (mole/dm^3)

Table-5

Relationship between specific conductance and concentration of SDS in aspirin water mixture at 25°C.

S.No.	C_s \ C_a	Specific conductance (ms cm^{-1})				
		4×10^{-5}	8×10^{-5}	12×10^{-5}	17×10^{-5}	21×10^{-5}
1.	0	0.087	0.158	0.215	0.297	0.379
2.	2×10^{-3}	0.891	0.975	1.053	1.138	1.174
3.	3×10^{-3}	1.445	1.468	1.548	1.633	1.659
4.	4×10^{-3}	1.938	1.948	1.992	2.067	2.104
5.	5×10^{-3}	2.390	2.410	2.421	2.482	2.529
6.	6×10^{-3}	2.817	2.827	2.835	2.853	2.914
7.	7×10^{-3}	3.17	3.20	3.21	3.20	3.30
8.	8.5×10^{-3}	3.64	3.66	3.74	3.66	3.78
9.	10×10^{-3}	4.16	4.12	4.24	4.15	4.24
10.	15×10^{-3}	5.51	5.68	5.72	5.65	5.77
11.	20×10^{-3}	7.13	6.74	6.96	6.89	6.97
12.	25×10^{-3}	8.27	8.11	7.35	7.65	7.71
13.	30×10^{-3}	9.53	8.58	8.61	8.60	8.79

C_s = Concentration of SDS (mole/dm^3)

C_a = Concentration of aspirin (mole/dm^3)

Table-6

CMC's of SDS at different concentrations of additive.

S.No.	C_a/mole dm^{-3}	CMC (mole/dm^3)		
		$A_1 \times 10^{-3}$	$A_2 \times 10^{-3}$	$A_3 \times 10^{-3}$
1.	0	8.0	8.0	8.0
2.	4×10^{-5}	7.7	7.8	7.8
3.	8×10^{-5}	7.3	7.4	7.6
4.	12×10^{-5}	6.9	7.1	7.3
5.	17×10^{-5}	6.5	6.7	7.0
6.	21×10^{-5}	6.1	6.3	6.8

Table-7

Rate of CMC's depression with additive.

S. No.	Additive	$\frac{-\Delta CMC}{\Delta C_a} = K$
1	A_1	9.55
2.	A_2	9.08
3.	A_3	6.48

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-8

J value for all additives at different concentrations of SDS ($J = \Delta A/\Delta A_\alpha$).

S. No.	$C_s \times 10^{-3}$	A_1	A_2	A_3
1.	10	0.586	0.548	0.394
2.	15	0.729	0.680	0.549
3.	20	0.796	0.775	0.619
4.	25	0.8402	0.800	0.704
5.	30	0.8623	0.835	0.746

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

J = Fraction of amount solubilized

Table-9

Relationship between C_s, $1/\Delta A$ and $1/C_s^m - KC_a + (1+K)C_aJ$ for A_1, A_2 and A_3 water system at 25°C.

S. No.	$C_s \times 10^{-3}$	A_1		A_2		A_3	
		$1/\Delta A$	$1/C_s^m - KC_a + (1+K)C_aJ$	$1/\Delta A$	$1/C_s^m - KC_a + (1+K)C_aJ$	$1/\Delta A$	$1/C_s^m - KC_a + (1+K)C_aJ$
1.	10	1.886	502.36	2.174	524.16	3.571	503.027
2.	15	1.515	142.99	1.754	144.23	2.564	143.059
3.	20	1.388	83.36	1.538	83.60	2.273	83.385
4.	25	1.351	58.83	1.493	58.09	2.00	58.840
5.	30	1.282	45.46	1.428	45.97	1.923	45.462

C_s = Concentration of SDS (mole/dm^3)

$K = -\Delta CMC/\Delta C_a$

$J = \Delta A/\Delta A_\alpha$

$C_s^m = C_s - CMC_{(0)}$

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-10

Relationship between CMC depression and partition coefficient in aqueous and micellar phase and free energy change of all additive in SDS solution at 25°C.

S.No.	Additive	$-\Delta CMC/\Delta C_a$	K_C	K_X	$-\Delta G_P$ (kJ mole^{-1})
1.	A_1	9.55	409.16	22728.93	24.85
2.	A_2	9.08	354.67	19702.21	24.49
3.	A_3	6.48	316.18	17563.98	24.21

$K = -\Delta CMC/\Delta C_a$

$K_X = K_C \times n_w$

n_w = number of moles of water per litre (55.55 mole/dm^3)

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-11

Relationship between specific conductance and concentration of CTAB in flurbiprofen water system at 25°C.

S.No.	C_a / $C_s \times 10^{-4}$	Specific conductance (ms cm^{-1})				
		4×10^{-5}	8×10^{-5}	12×10^{-5}	17×10^{-5}	21×10^{-5}
1.	2	–	–	28.5	64.5	84.7
2.	3	–	47.5	120.2	175.2	198.8
3.	4	70.1	119.1	196.1	260.2	289.5
4.	5	150	198.5	277	345	379
5.	6	200.1	250.3	357	425	462
6.	7	255	309	418	488	529
7.	8	320	374	483	552	587
8.	10	411	468	573	653	685
9.	15	559	617	735	830	860
10.	20	654	716	840	950	973
11.	25	744	807	921	1051	1075
12.	30	826	877	987	1125	1158
13.	35	905	954	1044	1183	1240
14.	40	994	1115	1050	1198	1260
15.	45	1080	1180	1154	1214	1276
16.	50	1150	1196	1196	1253	1291

C_s = Concentration of CTAB (mole/dm^3)

C_a = Concentration of flurbiprofen (mole/dm^3)

Table-12

Relationship between specific conductance and concentration of CTAB in ibuprofen water system at 25°C.

S.No.	C_a / $C_s \times 10^{-4}$	Specific conductance (ms cm^{-1})				
		4×10^{-5}	8×10^{-5}	12×10^{-5}	17×10^{-5}	21×10^{-5}
1.	3	–	33.4	63.4	120.3	161.4
2.	4	60.9	105.2	140.3	191.5	245.2
3.	5	140.4	180.3	212.6	233	328
4.	6	190.2	241.1	286.2	366	401
5.	7	260.1	302	355	434	470
6.	8	324	373	412	503	533
7.	10	432	469	510	607	637
8.	15	470	610	670	816	835
9.	20	525	706	773	933	941
10.	25	553	796	861	1023	1040
11.	30	570	865	930	1103	1125
12.	35	577	940	999	1180	1208
13.	40	590	980	1080	1199	1297
14.	45	615	1015	1153	1235	1380
15.	50	629	1055	1199	1285	1475

C_s = Concentration of CTAB (mole/dm^3)

C_a = Concentration of ibuprofen (mole/dm^3)

Table-13

Relationship between specific conductance and concentration of CTAB in aspirin water system at 25°C.

S.No.	C_a / $C_s \times 10^{-4}$	Specific conductance (ms cm^{-1})				
		4×10^{-5}	8×10^{-5}	12×10^{-5}	17×10^{-5}	21×10^{-5}
1.	2	–	63.0	149.4	218.2	265.7
2.	3	45.3	139.1	224.5	293.3	335
3.	4	124.5	213.5	296.1	367	400
4.	5	193.3	280.2	359	440	472
5.	6	267.1	353	425	497	542
6.	7	339	420	488	561	605
7.	8	401	475	540	624	660
8.	10	476	552	627	715	755
9.	15	602	675	767	880	919
10.	20	703	773	870	994	1033
11.	25	802	861	958	1102	1119
12.	30	897	941	1033	1190	1175
13.	35	996	1027	1120	1215	1243
14.	40	1093	1098	1200	1250	1275
15.	45	1155	1180	1249	1271	1321
16.	50	1230	1245	1315	1325	1343

C_s = Concentration of CTAB (mole/dm^3)

C_a = Concentration of aspirin (mole/dm^3)

Table-14

CMC's of CTAB at different concentrations of additive.

S.No.	$C_a \times 10^{-5}$ (mole dm^{-3})	CMC (mole/dm^3)		
		$A_1 \times 10^{-4}$	$A_2 \times 10^{-4}$	$A_3 \times 10^{-4}$
1.	0	9.0	9.0	9.0
2.	4	8.5	8.8	8.8
3.	8	8.0	8.3	8.5
4.	12	7.0	7.6	7.9
5.	17	6.4	7.2	7.5
6.	21	5.9	6.7	7.0

C_a = Concentration of additive (mole/dm^3)

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-15

Rate of CMC's depression with additive.

S. No.	Additive	$\frac{-\Delta CMC}{\Delta C_a}$
1.	A_1	1.539
2.	A_2	1.148
3.	A_3	0.981

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-16

J value for all additives at different concentrations of CTAB.

S. No.	$C_s \times 10^{-4}$	A_1	A_2	A_3
1.	20	0.7820	0.7558	0.6701
2.	25	0.8740	0.7812	0.7078
3.	30	0.9200	0.8267	0.7321
4.	35	0.9500	0.8739	0.7440
5.	40	1.00	0.9093	0.8438
6.	45	1.069	0.9448	0.8935
7.	50	1.104	0.9802	0.9431

C_s = Concentration of CTAB (mole/dm^3)

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

J = $\Delta A/\Delta A_\alpha$ = fraction of amount solubilized

Table-17

Relationship between C_s, $1/\Delta A$ and $1/C_s^m - KC_a + (1+K)C_aJ$ for A_1, A_2 and A_3 water system at 25°C.

S. No.	$C_s \times 10^3$	A_1		A_2		A_3	
		$1/\Delta A$	$1/C_s^m - KC_a + (1+K)C_aJ$	$1/\Delta A$	$1/C_s^m - KC_a + (1+K)C_aJ$	$1/\Delta A$	$1/C_s^m - KC_a + (1+K)C_aJ$
1.	20	1.470	907.98	1.562	879.334	1.851	907.949
2.	25	1.316	624.20	1.492	618.849	1.754	624.243
3.	30	1.250	475.20	1.429	471.958	1.695	475.765
4.	35	1.204	384.22	1.351	381.40	1.587	384.323
5.	40	1.149	322.26	1.298	320.08	1.471	322.293
6.	45	1.075	277.50	1.250	275.75	1.388	277.53
7.	50	1.041	243.67	1.205	242.20	1.315	243.69

C_s = Concentration of CTAB (mole/dm^3)

$C_s^m = C_s - CMC_{(0)}$

$K = -\Delta CMC/\Delta C_a$

$J = \Delta A/\Delta A_\alpha$

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-18

Relationship between CMC depression, partition coefficient in aqueous and micellar phase and free energy change of all additives in CTAB solution at 25°C.

S.No.	Additive	K	K_C	K_X	$-\Delta G_P$ (kJ mole^{-1})
1.	A_1	1.539	1551.63	86193.14	-28.15
2.	A_2	1.148	1242.22	69005.47	-27.60
3.	A_3	0.981	1024.00	56883.34	-27.12

K_X = Partition coefficient

K = $-\Delta CMC/\Delta C_a$ = Slope of CMC Vs C_a

Table-19

Maximum spectral values of drugs/additive in aqueous solution.

S. No.	Drug	C_a	A	λ_{max}
1.	Flurbiprofen	3×10^{-6}	0.22	196.86
2.	Ibuprofen	3×10^{-5}	0.21	221.18
3.	Aspirin	4×10^{-6}	0.27	193.98

C_a = Additive concentration (mole/dm^3)

A = Maximum absorbance

λ_{max} = Wavelength (nm) at maximum absorbance

Table-20

Relationship between C_s, A and λ_{max} for flurbiprofen, ibuprofen and aspirin.

S.No.	C_s	Flurbiprofen		Ibuprofen		Aspirin	
		A	λ_{max}	A	λ_{max}	A	λ_{max}
1.	0	0.22	196.86	0.21	221.18	0.27	193.98
2.	3×10^{-4}	0.23	195.99	0.23	221.06	0.30	193.03
3.	6×10^{-4}	0.26	195.54	0.29	220.96	0.36	192.21
4.	1×10^{-3}	0.32	195.20	0.42	219.72	0.47	193.01
5.	3×10^{-3}	0.54	194.95	0.57	222.18	0.57	193.23
6.	6×10^{-3}	0.63	195.61	0.66	221.90	0.69	194.04
7.	10×10^{-3}	0.74	196.37	0.77	221.19	0.84	194.31
8.	15×10^{-3}	0.78	196.17	0.80	222.01	0.88	193.19
9.	20×10^{-3}	0.80	195.80	0.82	222.08	0.91	193.75
10.	25×10^{-3}	0.81	195.99	0.83	221.91	0.96	192.99
11.	30×10^{-3}	0.82	196.15	0.85	221.81	1.02	193.86
12.	35×10^{-3}	0.84	196.03	0.86	220.96	1.04	194.15
13.	40×10^{-3}	0.85	196.09	0.84	221.14	1.06	193.74
14.	45×10^{-3}	0.87	195.71	0.90	221.18	1.07	193.45
15.	50×10^{-3}	0.88	195.86	–	–	1.09	193.46

C_s = SDS concentration (mole/dm^3)

A = Maximum absorbance

λ_{max} = Wavelength at maximum absorbance

Table-21

Relationship between C_s, ΔA and λ_{max} for flurbiprofen, ibuprofen and aspirin.

S.No.	$C_s \times 10^3$	Flurbiprofen		Ibuprofen		Aspirin	
		ΔA	λ_{max}	ΔA	λ_{max}	ΔA	λ_{max}
1.	10	0.53	195.08	0.46	221.75	0.28	193.03
2.	15	0.66	196.00	0.57	220.61	0.39	192.21
3.	20	0.72	194.00	0.65	221.09	0.44	192.01
4.	25	0.76	194.75	0.67	220.01	0.50	192.23
5.	30	0.78	195.11	0.71	220.53	0.53	193.04
6.	35	0.80	196.12	0.74	221.19	0.56	192.01
7.	40	0.83	195.98	0.78	220.50	0.60	194.12
8.	45	0.84	195.01	0.79	221.10	0.63	194.15
9.	50	0.86	195.25	–	–	0.65	194.71

C_s = Concentration of SDS (mole/dm^3)

ΔA = Differential absorbance

Table-22

Relation between C_s, $1/\Delta A$ and $1/C_a + C_s^m$ for A_1, A_2 and A_3.

S.No.	$C_s \times 10^{-3}$	A_1		A_2		A_3	
		$1/\Delta A$	$1/C_a + C_s^m$	$1/\Delta A$	$1/C_a + C_s^m$	$1/\Delta A$	$1/C_a + C_s^m$
1.	15	1.515	142.79	1.754	142.25	2.564	142.77
2.	20	1.388	83.31	1.538	83.13	2.273	83.31
3.	25	1.351	58.81	1.493	58.72	2.00	58.81
4.	30	1.282	45.44	1.408	45.39	1.923	45.45
5.	35	1.250	37.03	1.351	36.99	1.786	37.03
6.	40	1.205	31.24	1.282	31.22	1.667	31.25
7.	45	1.190	27.02	1.265	27.00	1587	27.02
8.	50	1.163	23.81	–	–	1.538	23.81

C_s = Concentration of SDS (mole/dm^3)

ΔA = Differential absorbance

$C_s^m = C_s - CMS_{(o)}$

C_a = Concentration of additive (mole/dm^3)

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-23

Partition coefficient of A_1, A_2 and A_3 between aqueous and micellar phase and free energy change.

S. No.	Additive	K_C	K_X	ΔG_P^o (kJ mole^{-1})
1.	A_1	325.11	18060.28	-24.28
2.	A_2	290.85	16156.92	-24.00
3.	A_3	154.70	8593.76	-22.44

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

K_X = Partition coefficient

ΔG_P^o = Free energy change of penetration (kJ mole^{-1})

Table-24

Relationship between C_s, A and λ_{max} for flurbiprofen, ibuprofen and aspirin.

S.No.	$C_s \times 10^{-4}$	Flurbiprofen		Ibuprofen		Aspirin	
		A	λ_{max}	A	λ_{max}	A	λ_{max}
1.	0	0.22	196.86	0.21	221.18	0.27	193.98
2.	2	0.23	196.17	0.25	192.17	0.29	192.01
3.	3	0.31	196.37	0.34	193.01	0.35	192.73
4.	4	0.51	197.74	0.55	193.00	0.48	192.34
5.	5	0.55	198.57	0.59	193.20	0.51	192.89
6.	6	0.60	199.23	0.63	194.01	0.57	193.15
7.	7	0.63	200.50	0.67	194.15	0.61	196.21
8.	8	0.72	201.25	0.70	194.99	0.65	199.35
9.	10	0.74	203.15	0.76	196.11	0.73	200.77
10.	15	0.77	203.45	0.77	196.55	0.75	201.9
11.	20	0.81	204.16	0.83	196.55	0.78	202.75
12.	25	0.83	204.10	0.85	197.65	0.79	202.83
13.	30	0.85	205.15	0.86	197.98	0.81	203.94
14.	35	0.86	205.45	0.87	199.86	0.85	202.04
15.	40	0.87	204.95	0.89	199.15	0.97	203.98
16.	45	0.93	205.07	0.92	201.29	0.99	203.50
17.	50	0.94	205.70	0.95	202.10	1.0	203.01
18.	55	0.95	206.10	0.96	203.15	1.02	204.97
19.	60	–	–	0.99	203.10	1.04	204.17

C_s = CTAB concentration (mole/dm^3)

A = Maximum absorbance

λ_{max} = Wavelength at maximum absorbance

Table-25

Relationship between C_s, ΔA and λ_{max} for flurbiprofen, ibuprofen and aspirin.

S.No.	$C_s \times 10^4$	Flurbiprofen		Ibuprofen		Aspirin	
		ΔA	λ_{max}	ΔA	λ_{max}	ΔA	λ_{max}
1.	10	0.51	204.01	0.49	197.15	0.32	203.93
2.	15	0.57	203.65	0.55	197.35	0.43	203.75
3.	20	0.68	203.91	0.64	196.75	0.54	204.54
4.	25	0.76	204.15	0.67	197.79	0.57	203.96
5.	30	0.80	204.12	0.70	198.18	0.59	204.01
6.	35	0.83	203.59	0.74	197.51	0.63	203.45
7.	40	0.87	204.20	0.77	198.29	0.68	202.99
8.	45	0.93	203.91	80	198.15	0.72	203.10
9.	50	0.96	203.67	0.83	197.10	0.76	203.35
10.	55	0.99	204.12	0.85	199.05	0.80	204.15
11.	60	–	–	0.87	198.32	0.82	203.75

C_s = Concentration of CTAB (mole/dm^3)

ΔA = Differential absorbance

Table-26

Relation between C_s, $1/\Delta A$ and $1/C_a + C_s^m$ for A_1, A_2 and A_3.

S.No.	$C_s \times 10^{-4}$	A_1		A_2		A_3	
		$1/\Delta A$	$1/C_a + C_s^m$	$1/\Delta A$	$1/C_a + C_s^m$	$1/\Delta A$	$1/C_a + C_s^m$
1.	20	1.470	906.618	1.562	884.950	1.851	905.797
2.	25	1.316	623.830	1.492	613.496	1.754	623.441
3.	30	1.250	475.511	1.428	469.483	1.695	475.280
5.	35	1.204	384.172	1.351	380.228	1.587	384.024
6.	40	1.149	322.268	1.299	319.488	1.471	322.165
7.	45	1.075	277.546	1.250	275.482	1.388	277.469
8.	50	1.041	243.724	1.205	242.130	1.316	243.665
9.	55	1.010	217.249	1.176	215.982	1.250	217.202
10.	60	–	195.963	1.149	194.93	1.219	195.924

C_s = Concentration of CTAB (mole/dm^3)

ΔA = Differential absorbance

$C_s^m = C_s - CMS_{(o)}$

C_a = Concentration of additive (mole/dm^3)

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

Table-27

Partition coefficient of A_1, A_2 and A_3 between aqueous and micellar phase and free energy change.

S.No.	Additive	K_C	K_X	ΔG_P^0 (kJ mole^{-1})
1.	A_1	1642.86	91261.26	-28.29
2.	A_2	1476.25	82005.69	-27.74
3.	A_3	1128.18	62670.63	-27.36

A_1 = Flurbiprofen

A_2 = Ibuprofen

A_3 = Aspirin

K_X = Partition coefficient

ΔG_P^0 = Free energy change (kJ mole^{-1})

Table-28

Spectroscopic relation between surfactant and partition coefficient of all additives.

S.No.	Surfactant	K_X		
		Flurbiprofen	Ibuprofen	Aspirin
1.	SDS	18060.28	16156.92	8593.76
2.	CTAB	91261.26	82005.69	62670.63

Table-29

Conductometric relation between surfactant and all additives at 25°C.

S.No.	Surfactant	K_X		
		Flurbiprofen	Ibuprofen	Aspirin
1.	SDS	22728.93	19702.21	17563.98
2.	CTAB	86193.14	69005.47	56883.34

K_X = Partition coefficient between aqueous and micellar phase.

Table-30

Spectroscopic relation between surfactant and free energy change of all additives.

S.No.	Surfactant	ΔG_P^0/kJ mole^{-1}		
		Flurbiprofen	Ibuprofen	Aspirin
1.	SDS	-24.28	-24.00	-22.44
2.	CTAB	-28.29	-28.03	-27.36

Table-31

Conductometric relation between surfactant and free energy change of all additives.

S.No.	Surfactant	ΔG_P^0/kJ mole^{-1}		
		Flurbiprofen	Ibuprofen	Aspirin
1.	SDS	-24.853	-24.499	-24.214
2.	CTAB	-28.155	-27.604	-27.126

ΔG_P^0 = Free energy change of penetration (kJ mole^{-1})

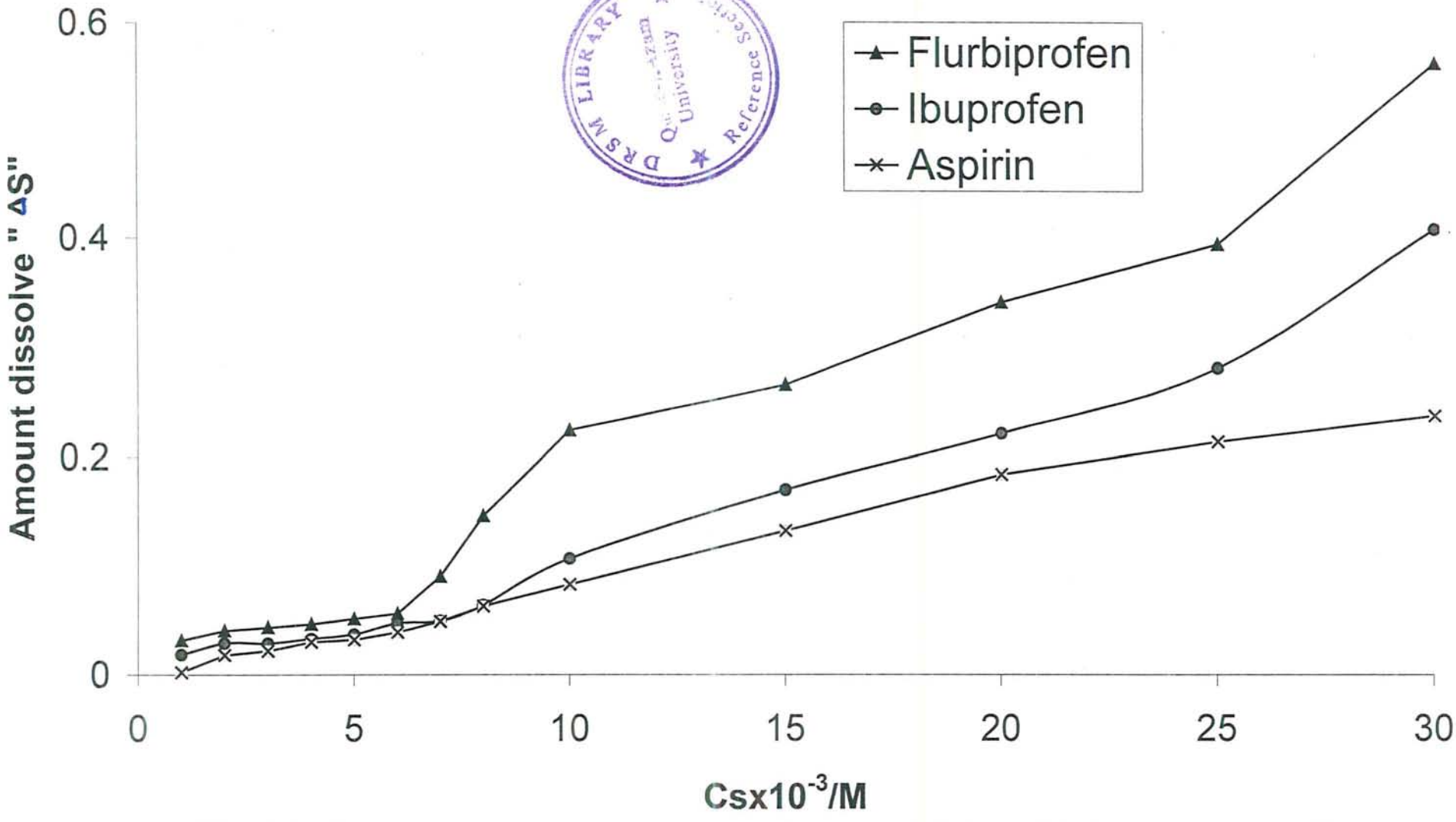


Fig.1A: Relation between amount dissolved ΔS and SDS concentration

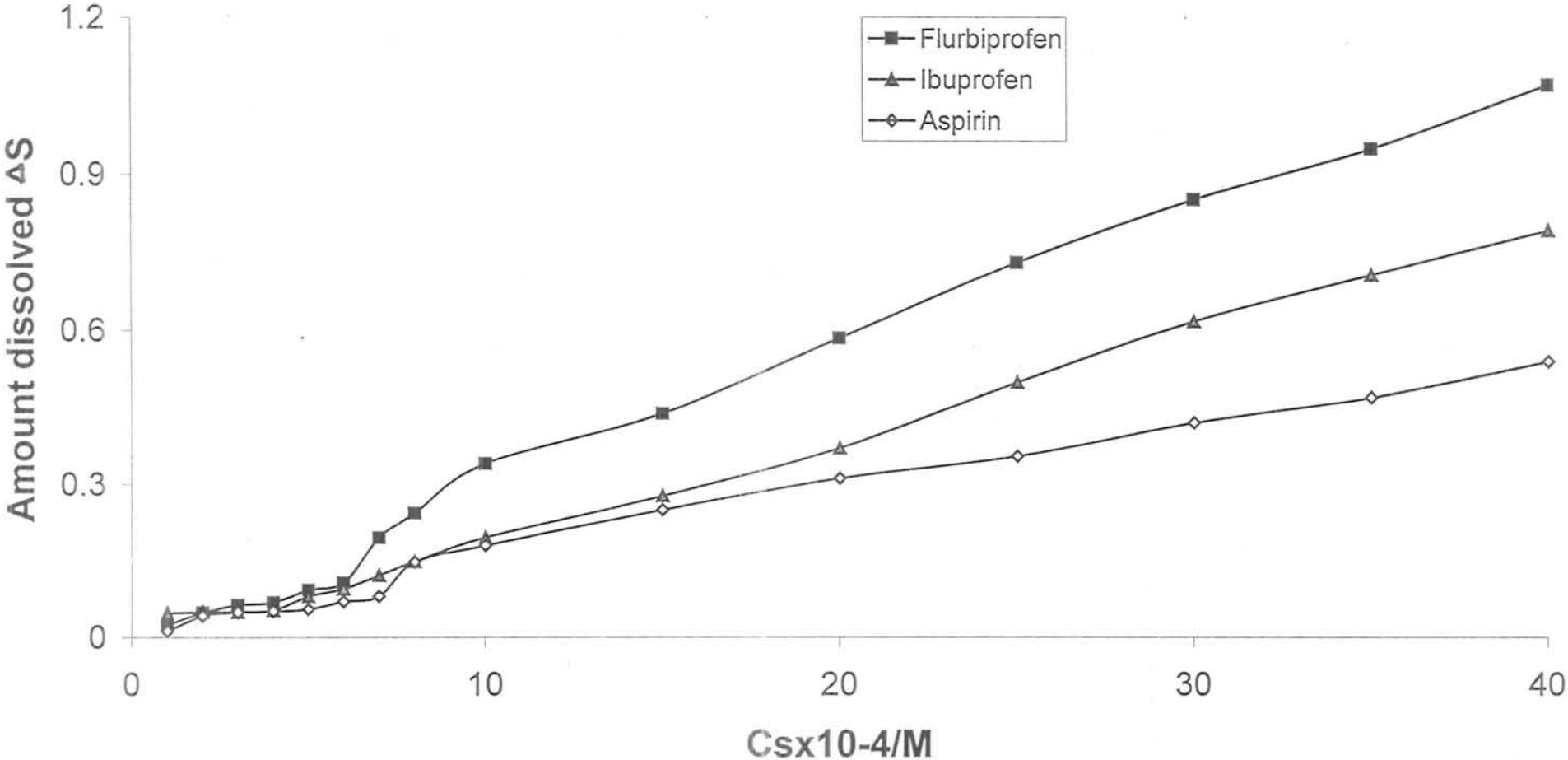


Fig.2A: Relation between amount of additive disssolved ΔS and CTAB concentration.

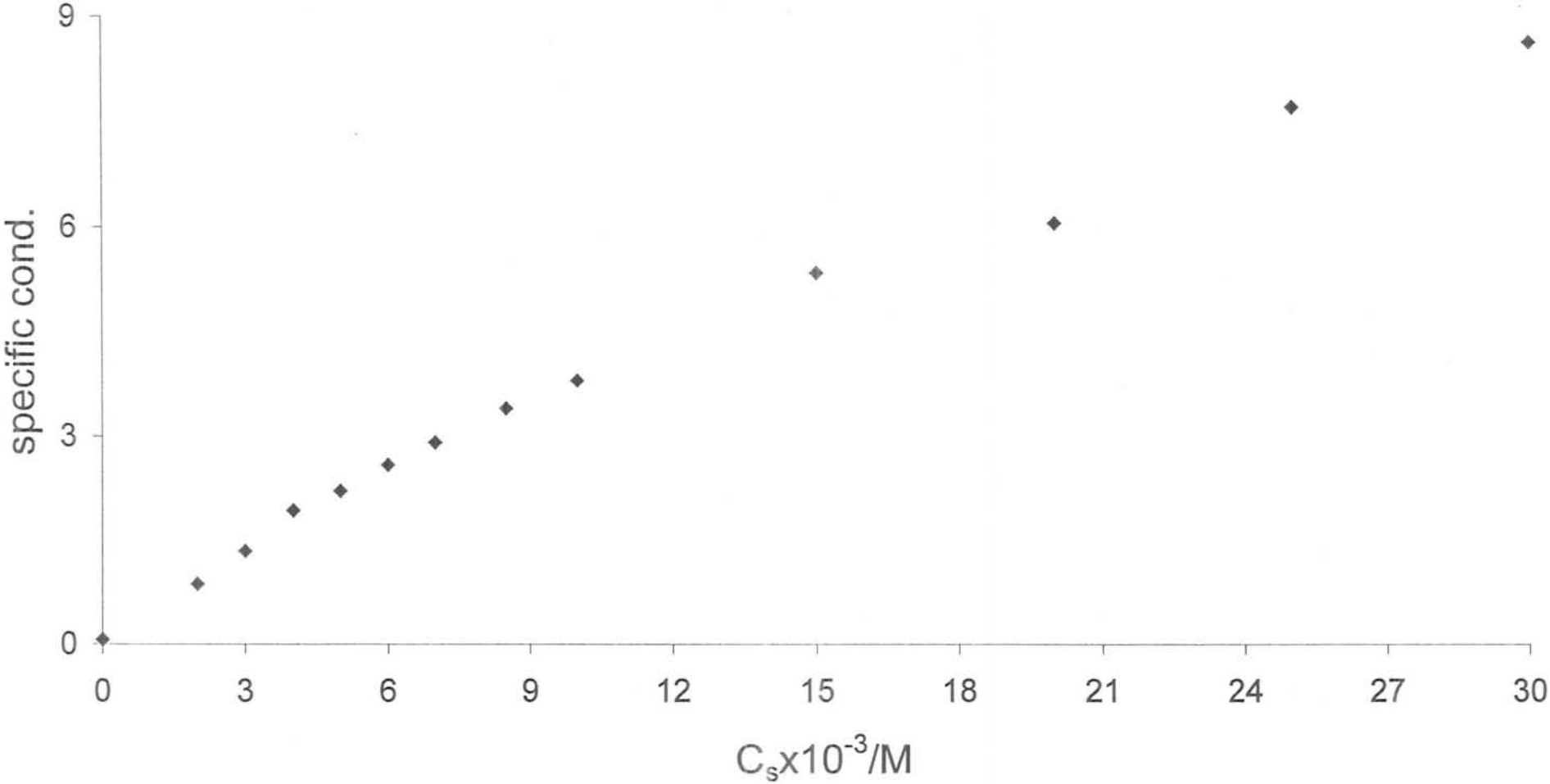


Fig.3A, Relation between specific conductance and sds concentration (Cs) for Flurbiprofin ($4x10^{-5}$M) at 25C.

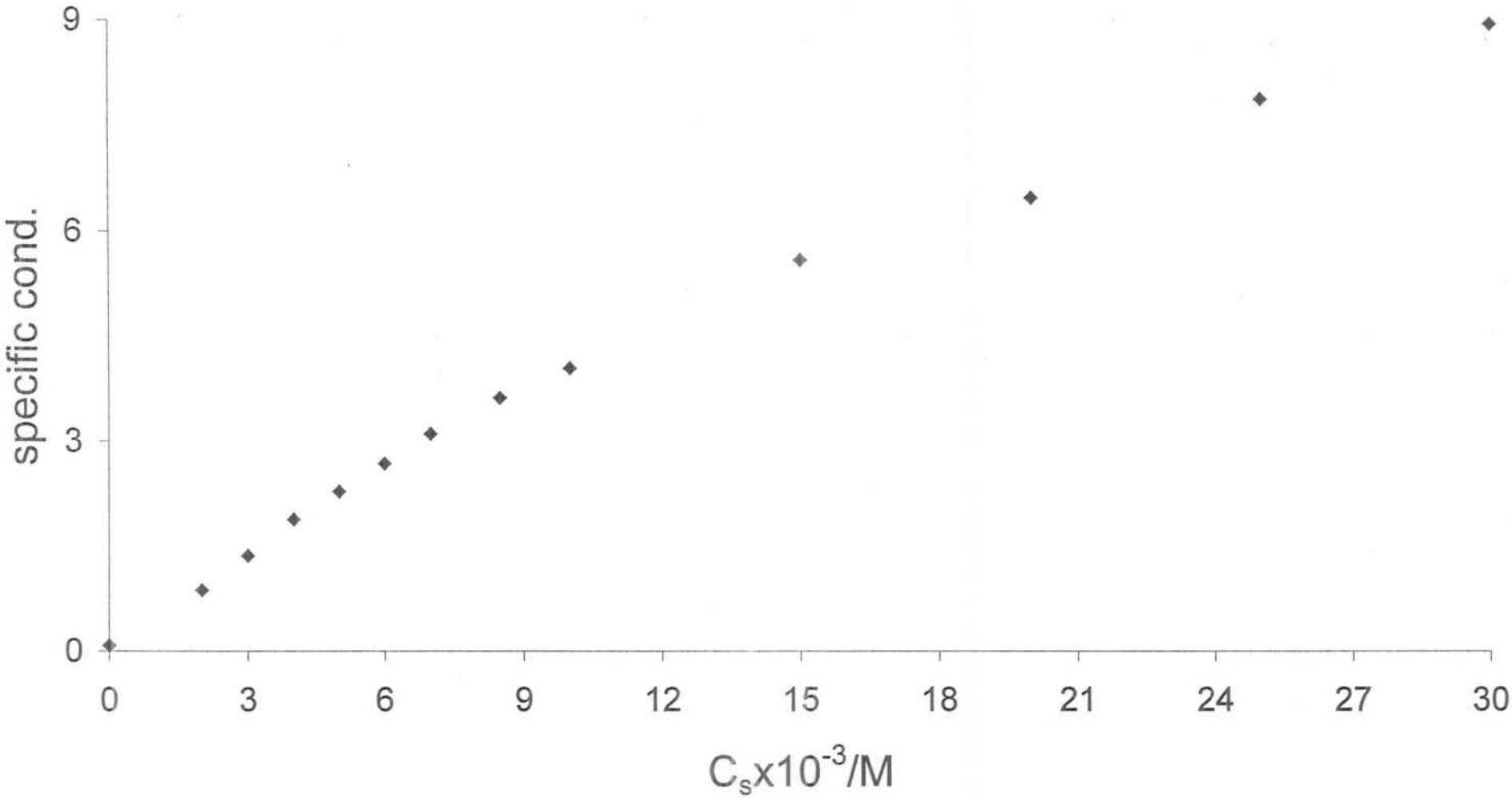


Fig. 3B, Relation between specific conductance and sds concentration (Cs) for Flurbiprofin (8X10-5M) at 25C.

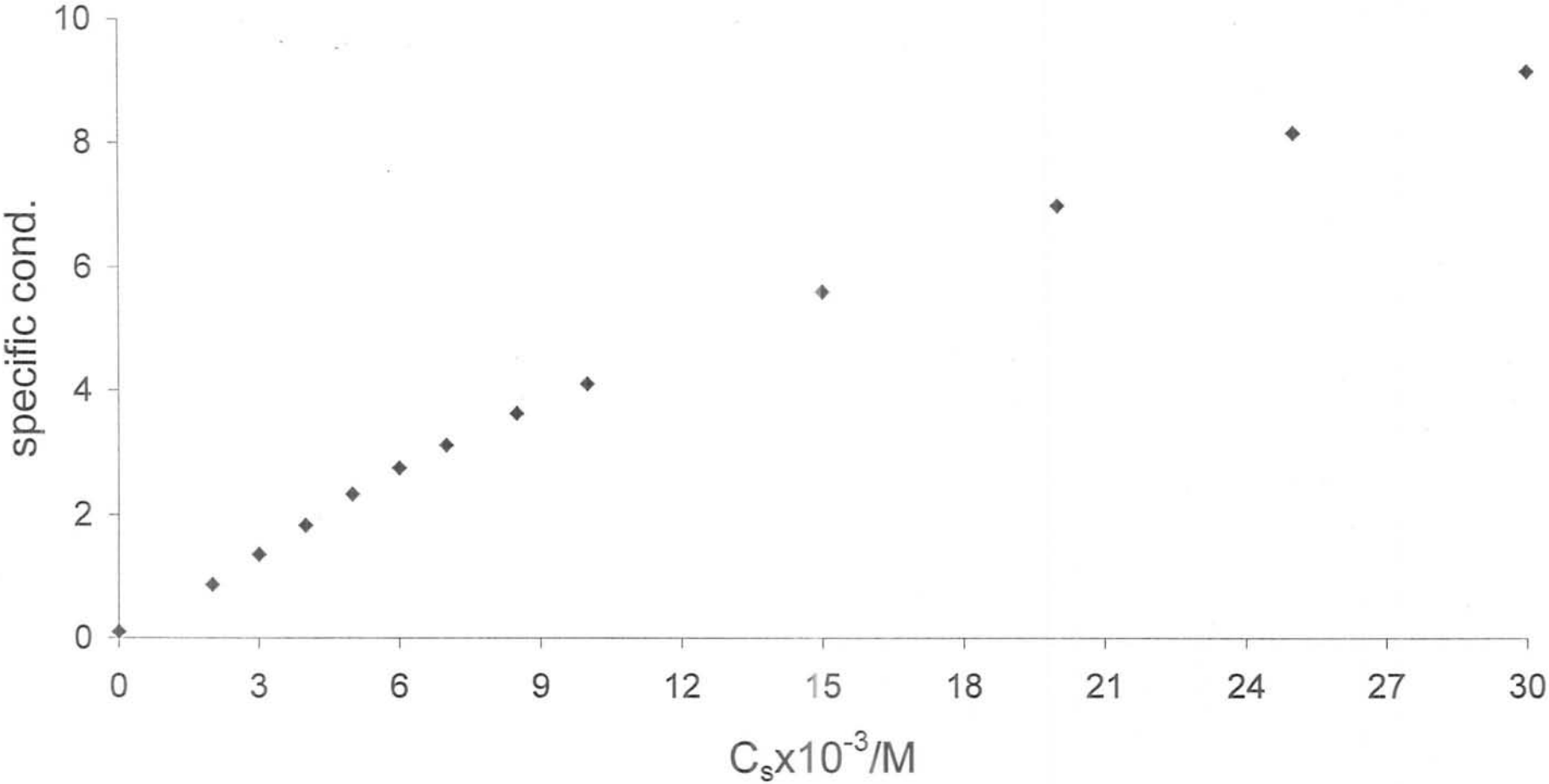


Fig.3C, Relation between specific conductance and sds concentration for Flurbiprofin(12x10-5M) at 25C.

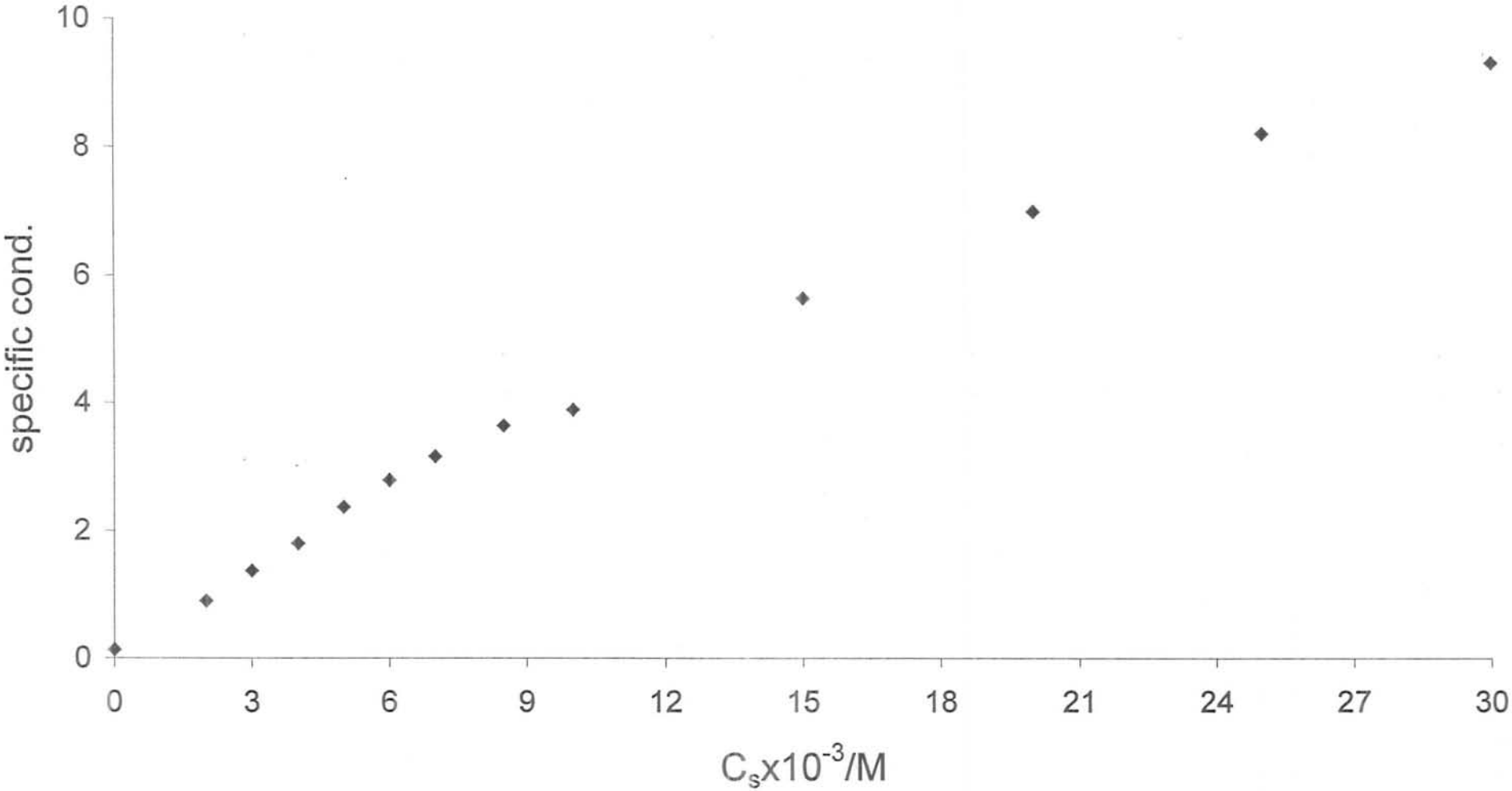


Fig.3D, Relation between specific conductance and SDS concentration (Cs) for Flurbiprofin(17x10-5M)at 25C.

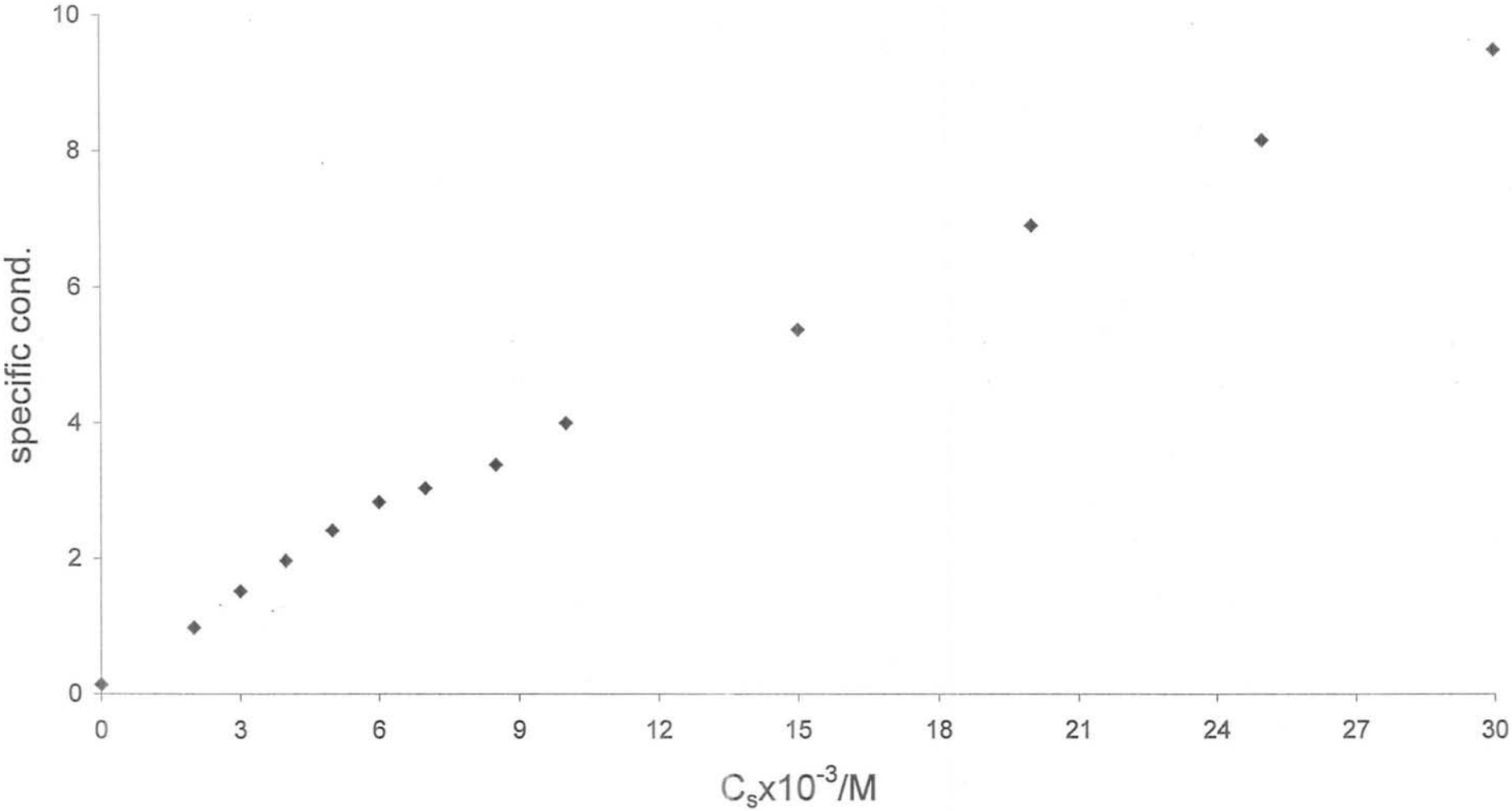


Fig. 3E, Relation between specific conductance and sds concentration(Cs)for Flurbiprofin(21x10-5M) at 25C.

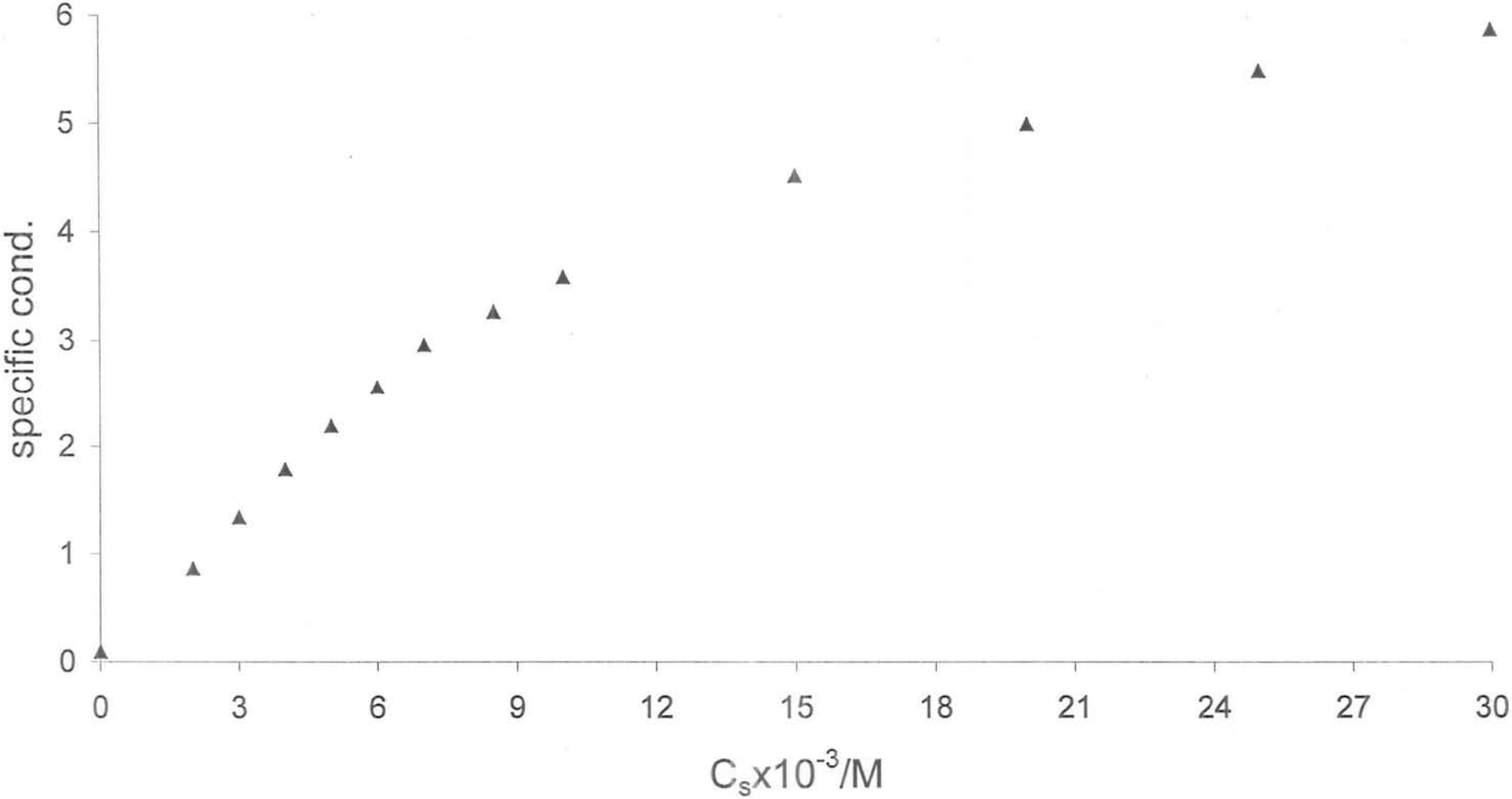


Fig. 3F, Relation between specific conductance and sds concentration (Cs) for Ibuprofen(4x10-5M)at 25C.

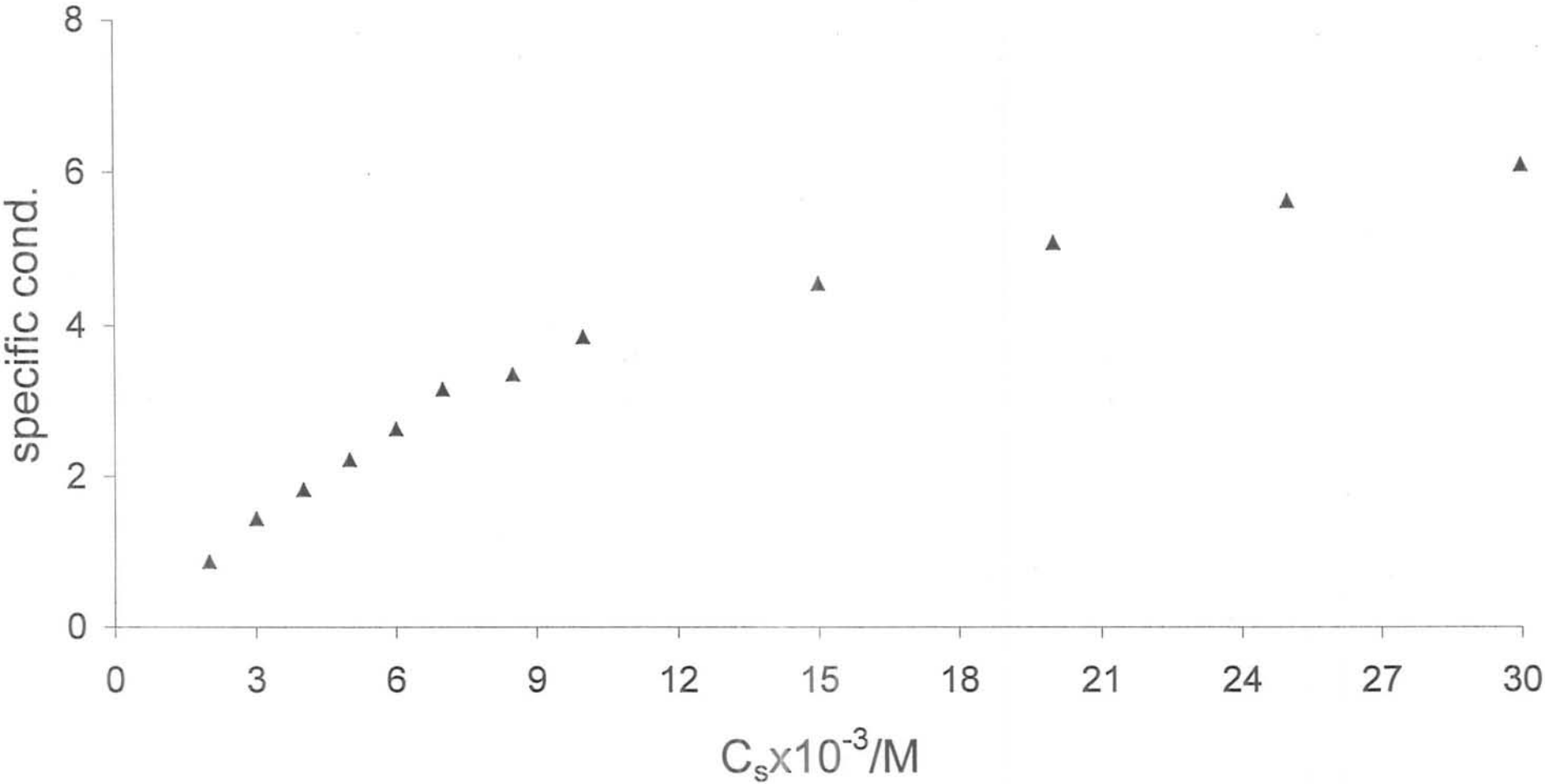


Fig.3G, Relation between specific conductance and sds concentration (Cs) for Ibuprofin (8x10-5M) at 25C.

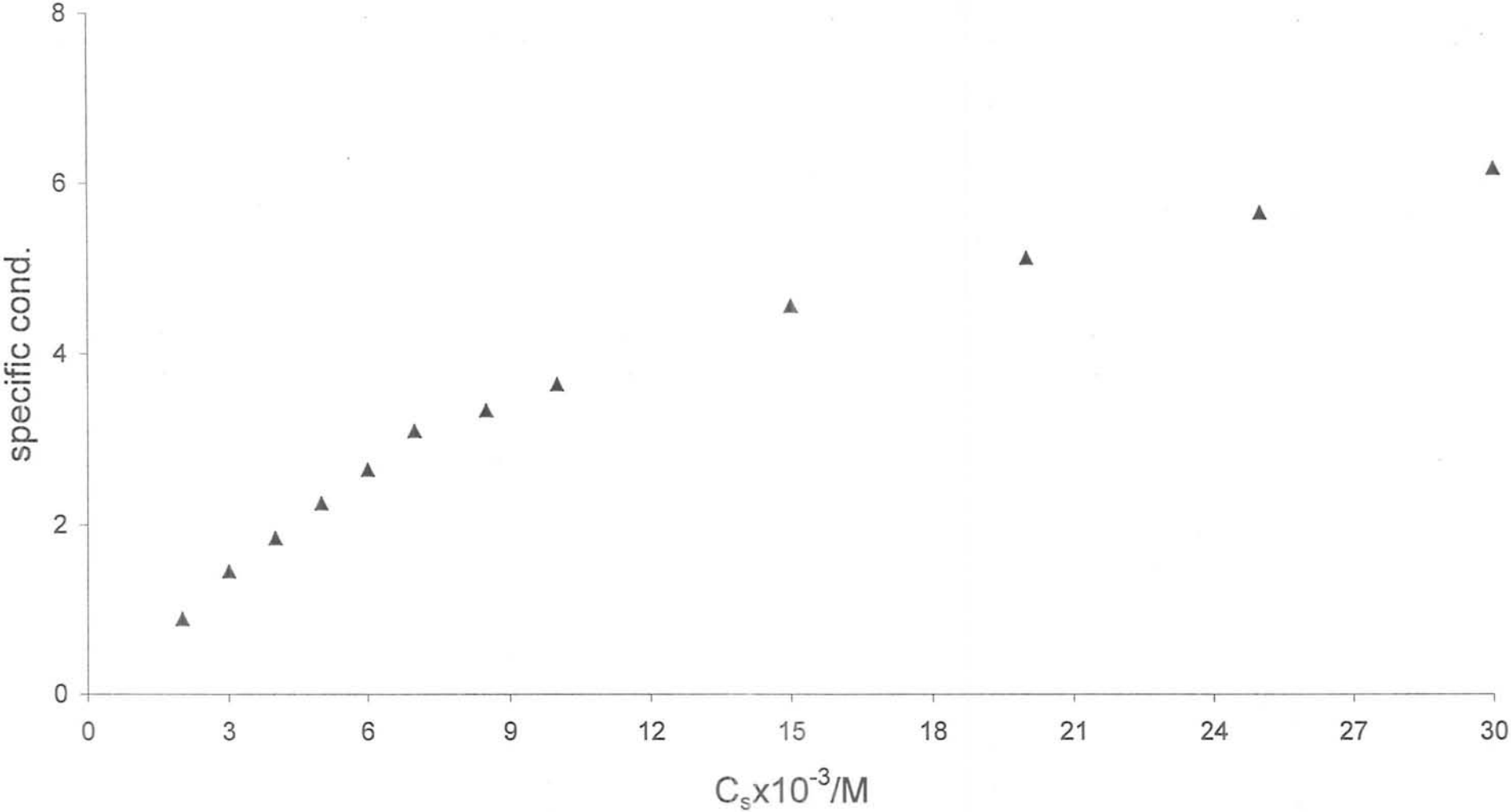


Fig.3H. Relation between specific conductance and sds concentration(Cs) for Ibuprofen(12x10-5M) at 25C.

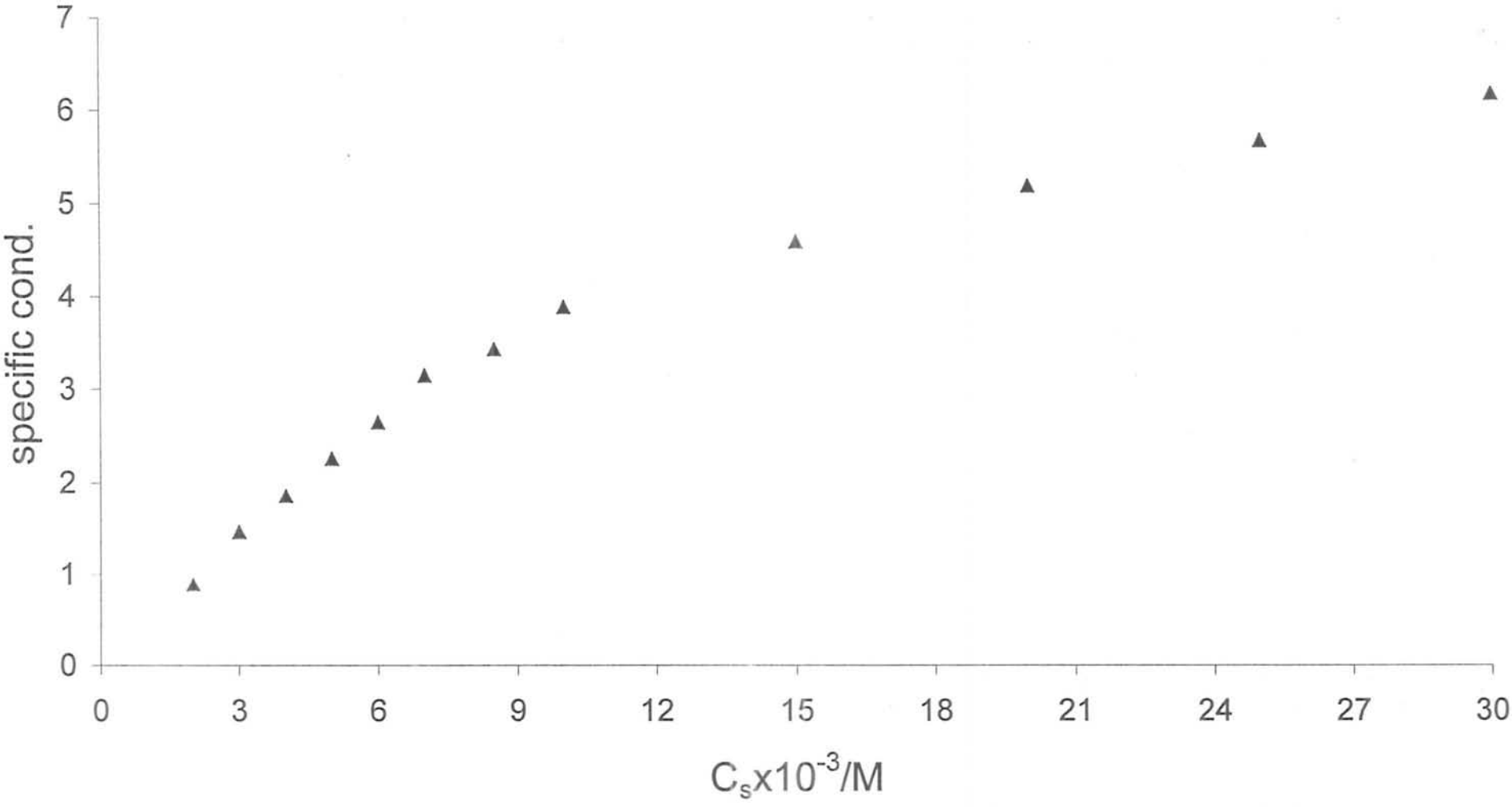


Fig. 3I, Relation between specific conductance and sds concentration (Cs) for Ibuprofen(17x10-5M) at 25C.

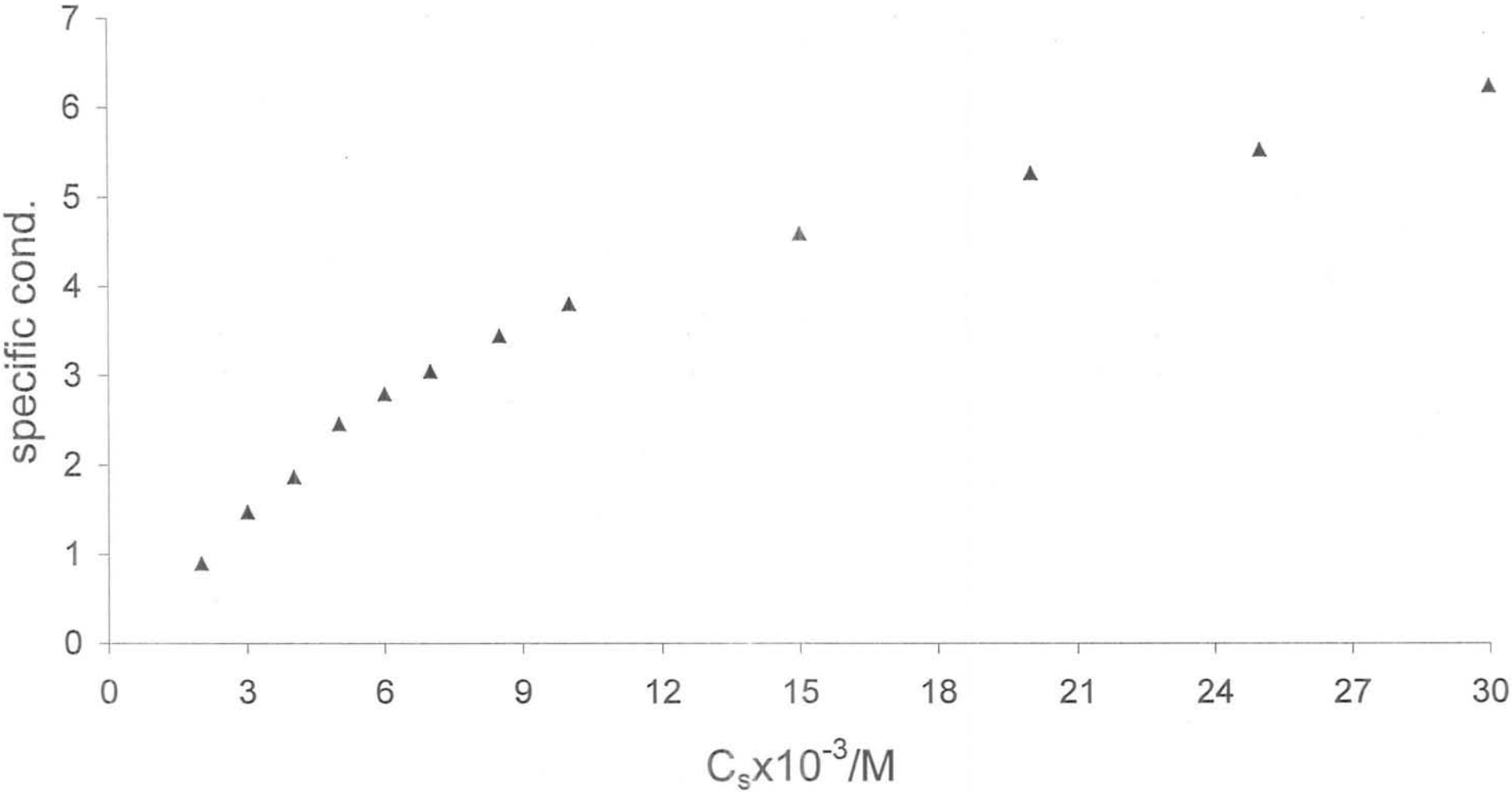


Fig. 3J, Relation between specific conductance and sds concentration (Cs) for Ibuprofen(21x10-5M) at 25C.

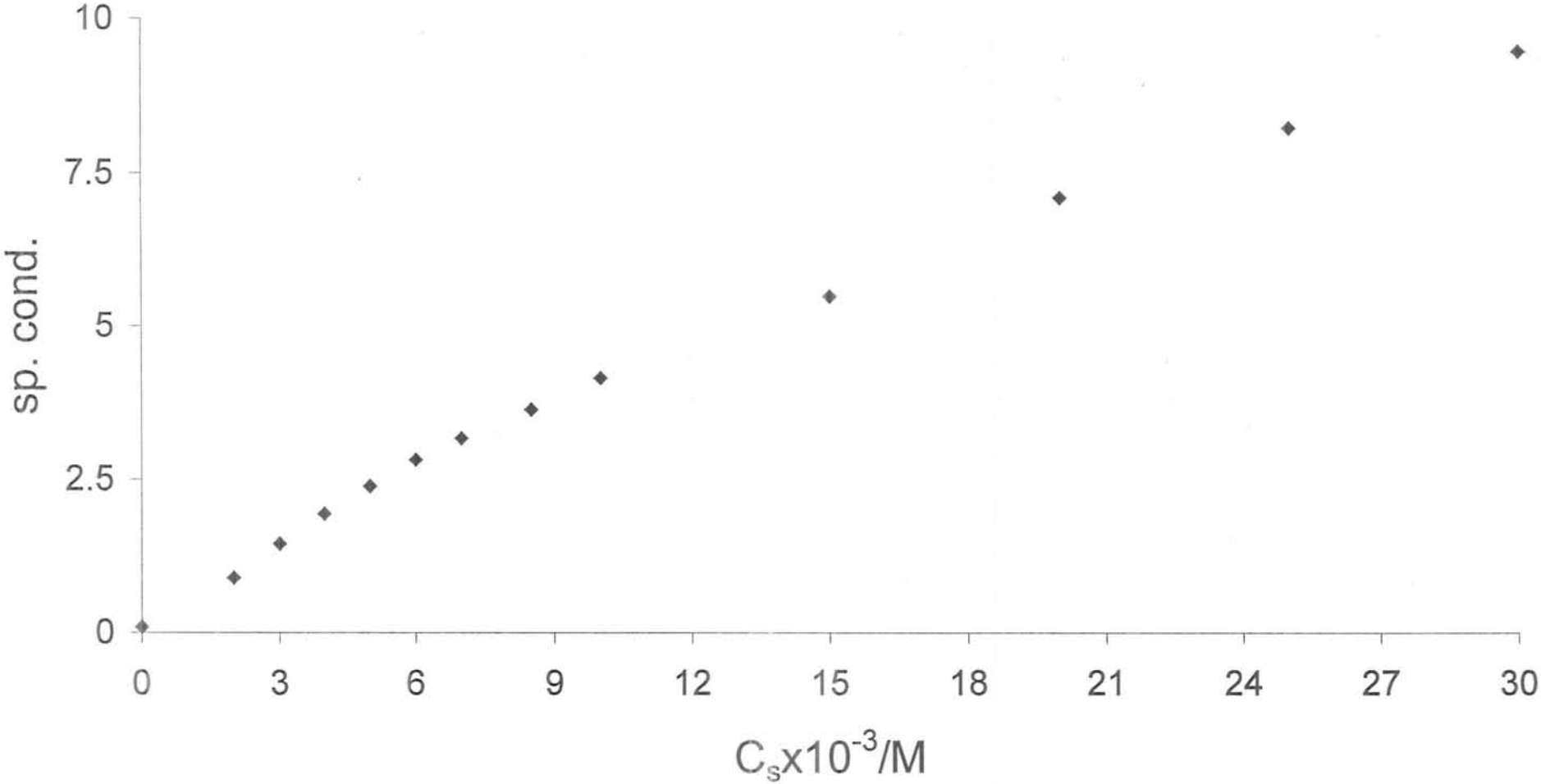


Fig.3K, Relation between spceific conductance and sds concentration (Cs) for Aspirin($4x10^{-5}M$) at 25C.

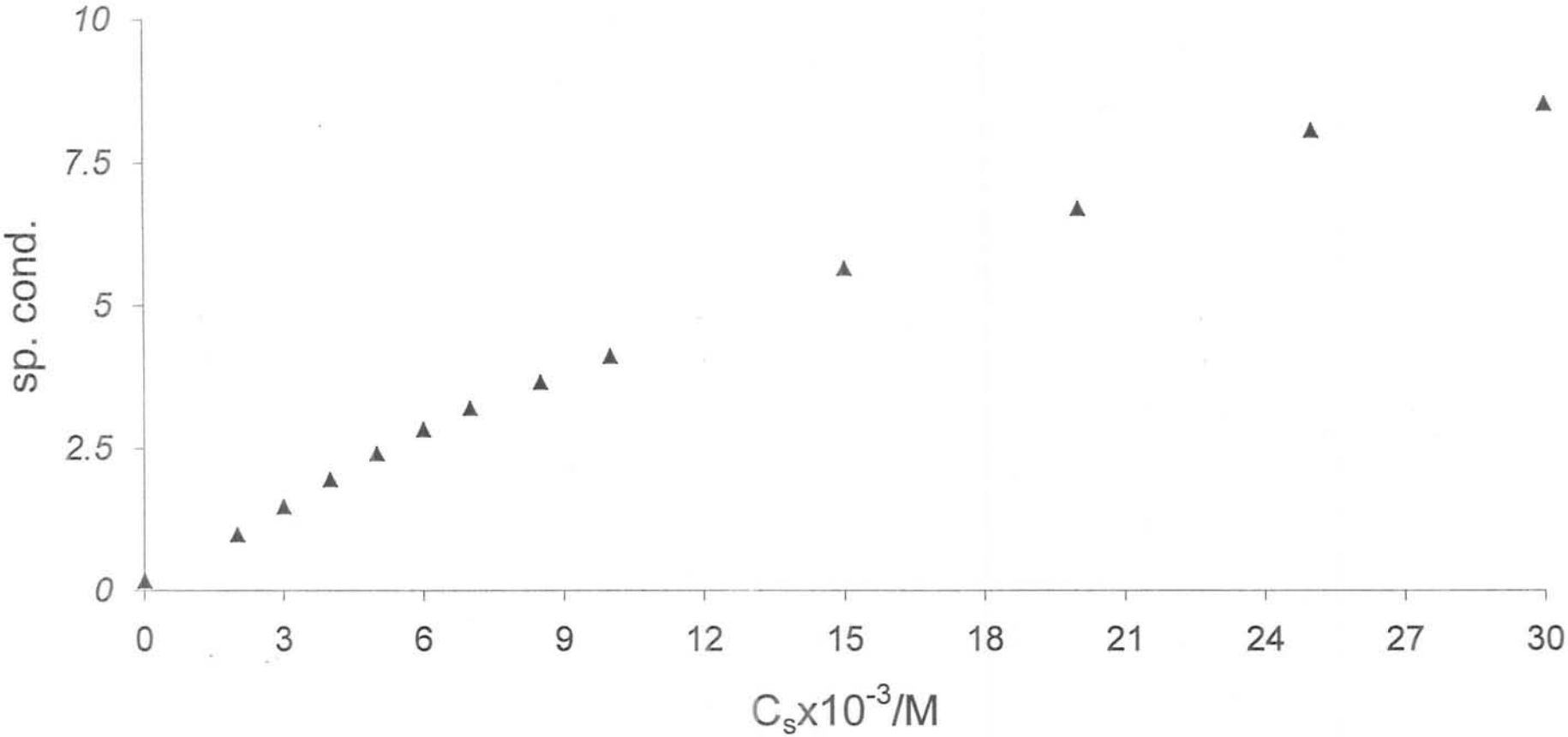


Fig. 3M, Relation between specific conductance and sds concentration(Cs) for Aspirin($8x10^{-5}$M) at 25C.

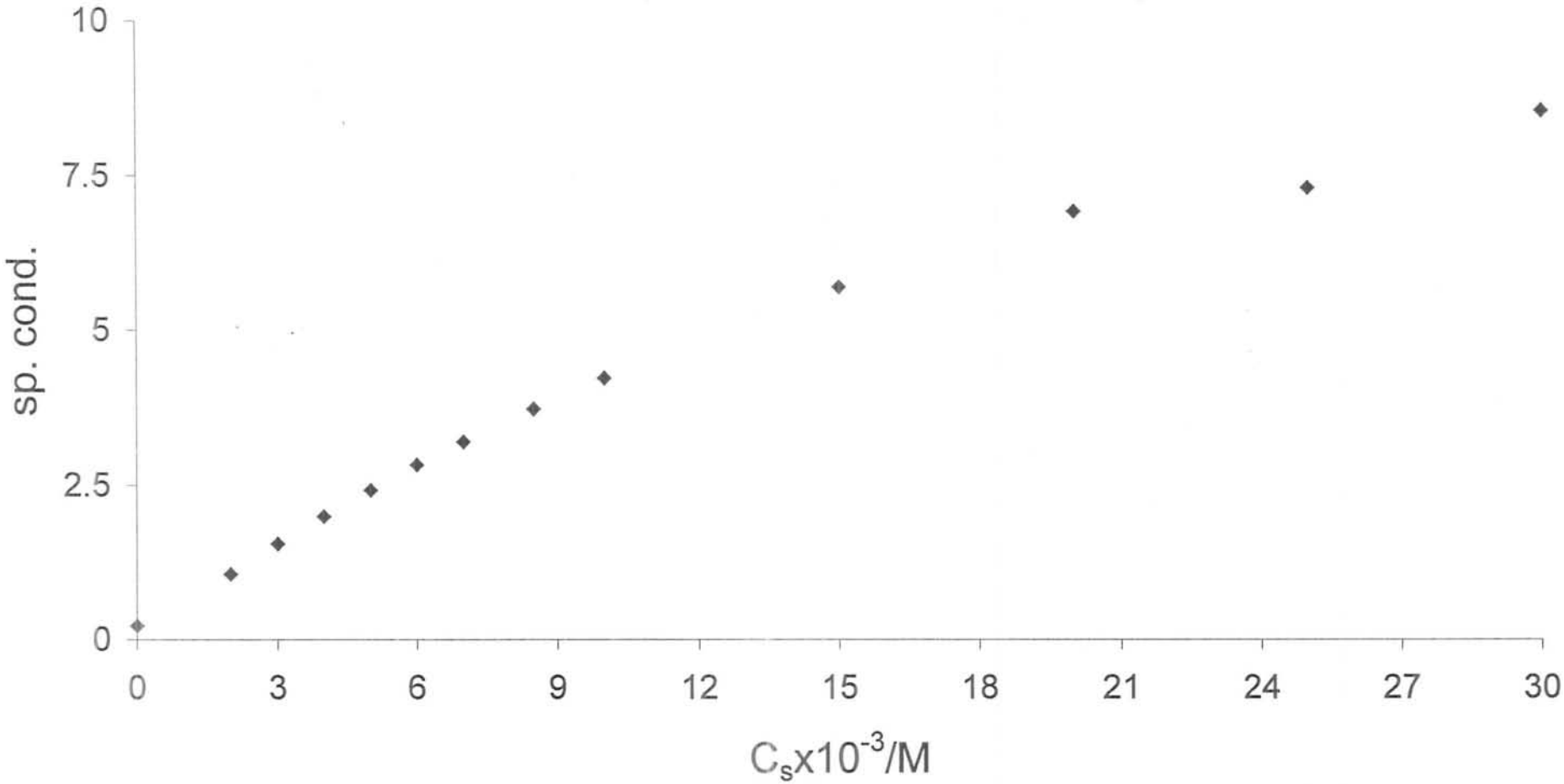


Fig.3L, Relation between specific conductance and sds concentration (Cs) for Aspirin($12x10^{-5}M$) at 25C.

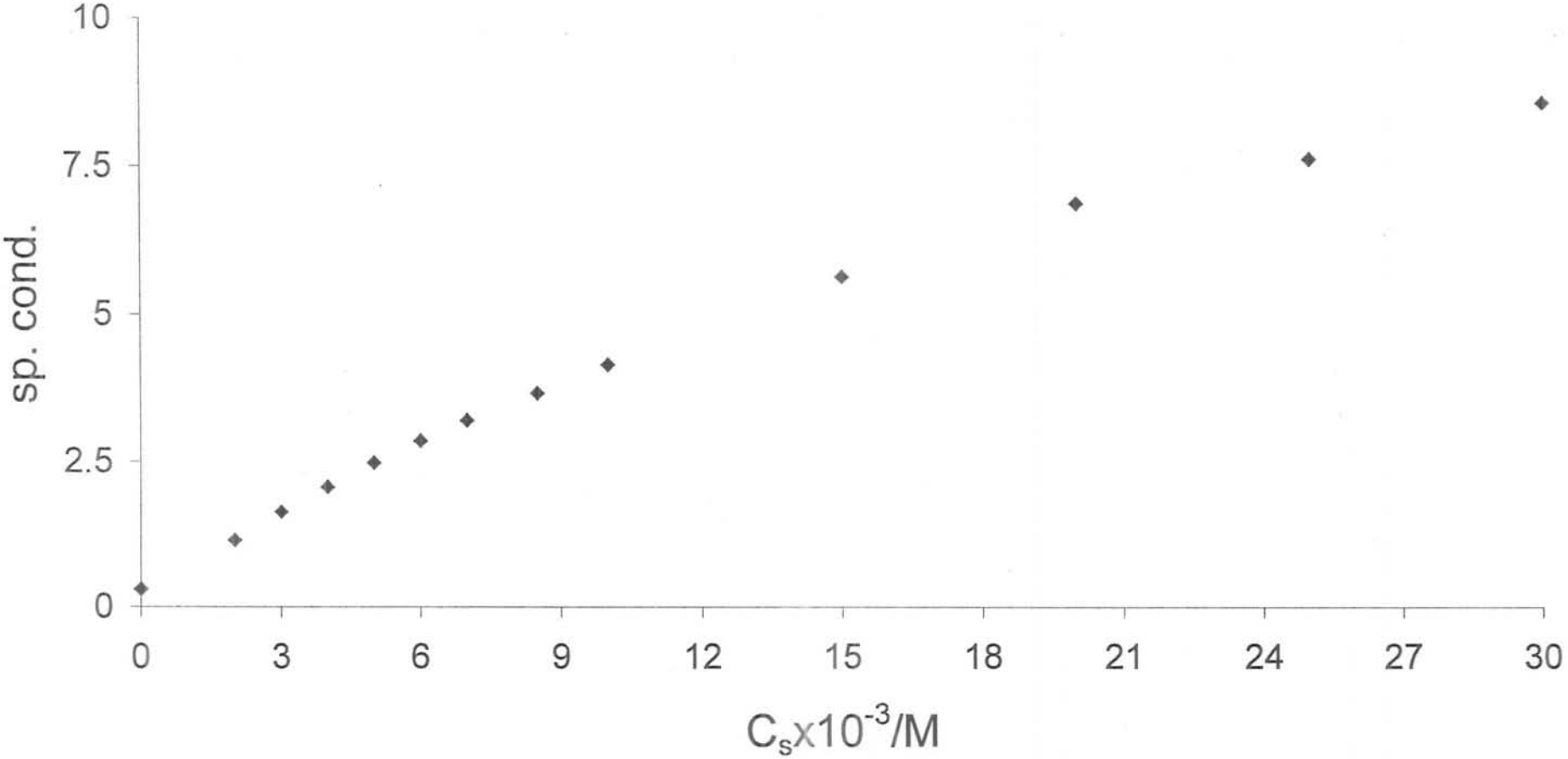


Fig. 3N, Relation between specific conductance and sds concentration (Cs) for Aspirin ($17x10^{-5}$) at 25C.

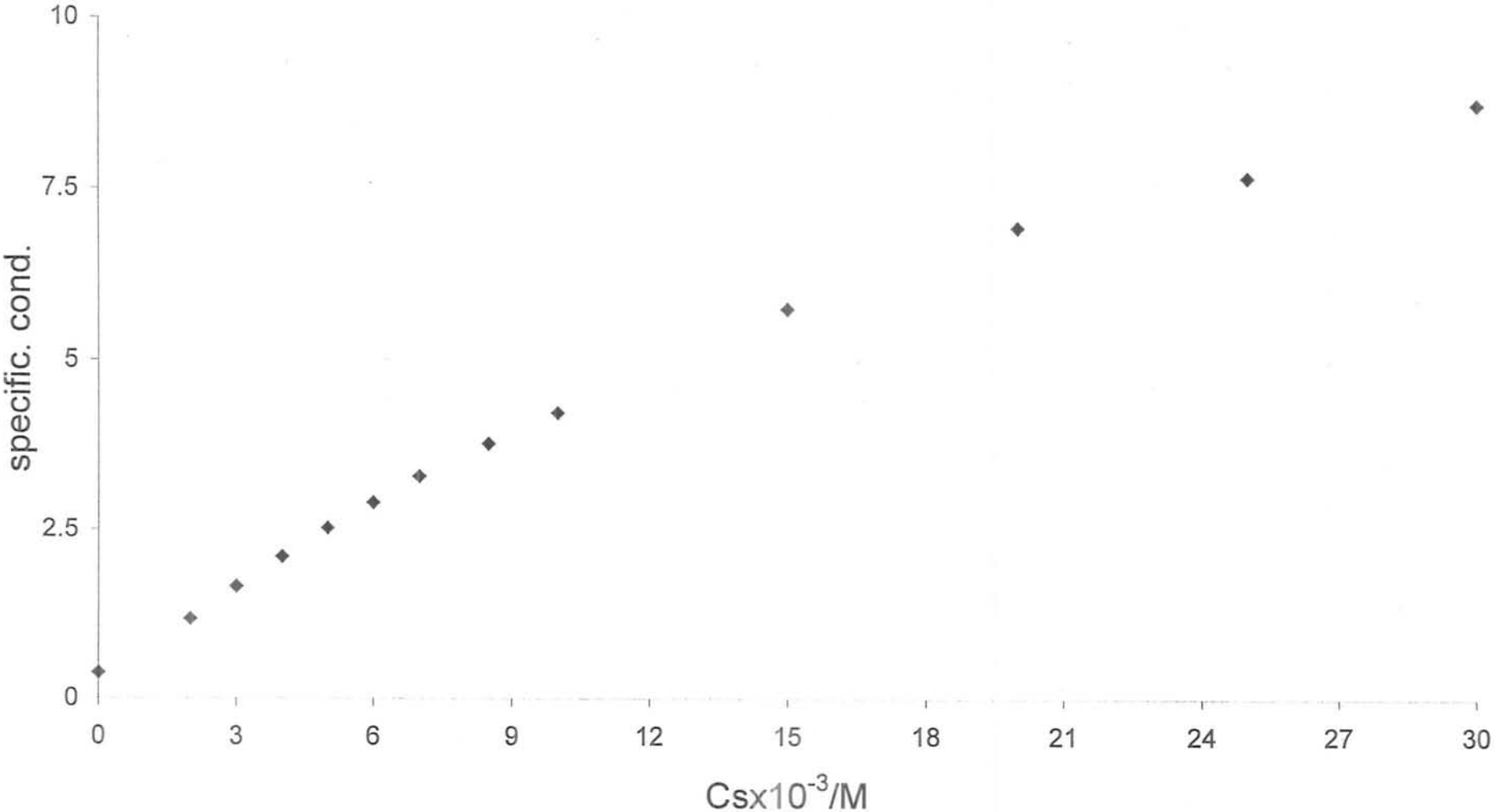


Fig. 3P, Relation between specific conductance and SDS concentration (Cs) for Aspirin($21x10^{-5}$M) at 25C.

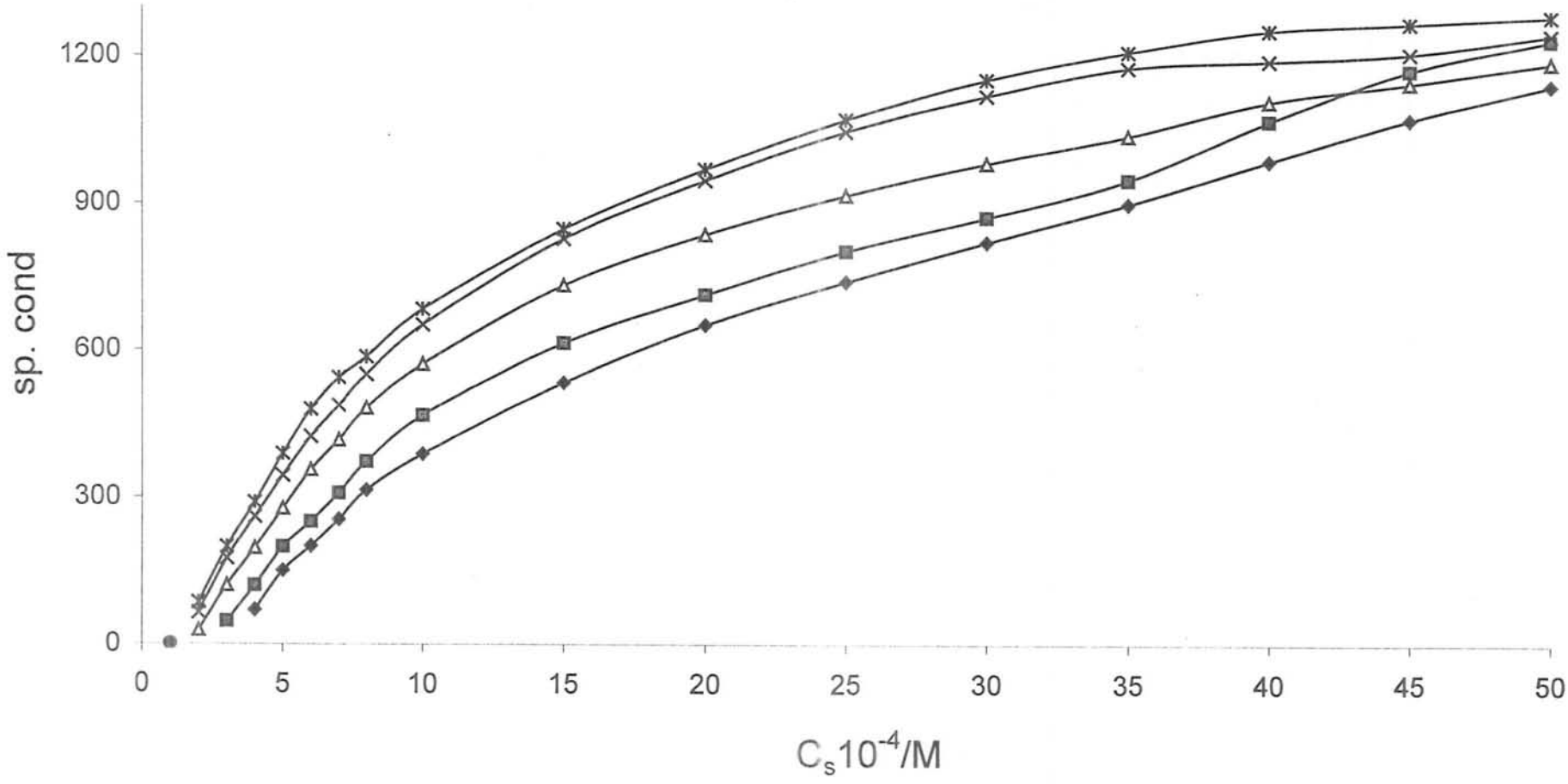


Fig.4A. Specific conductance vs CTAB concentration(Cs) for different concentration of Flurbiprofin

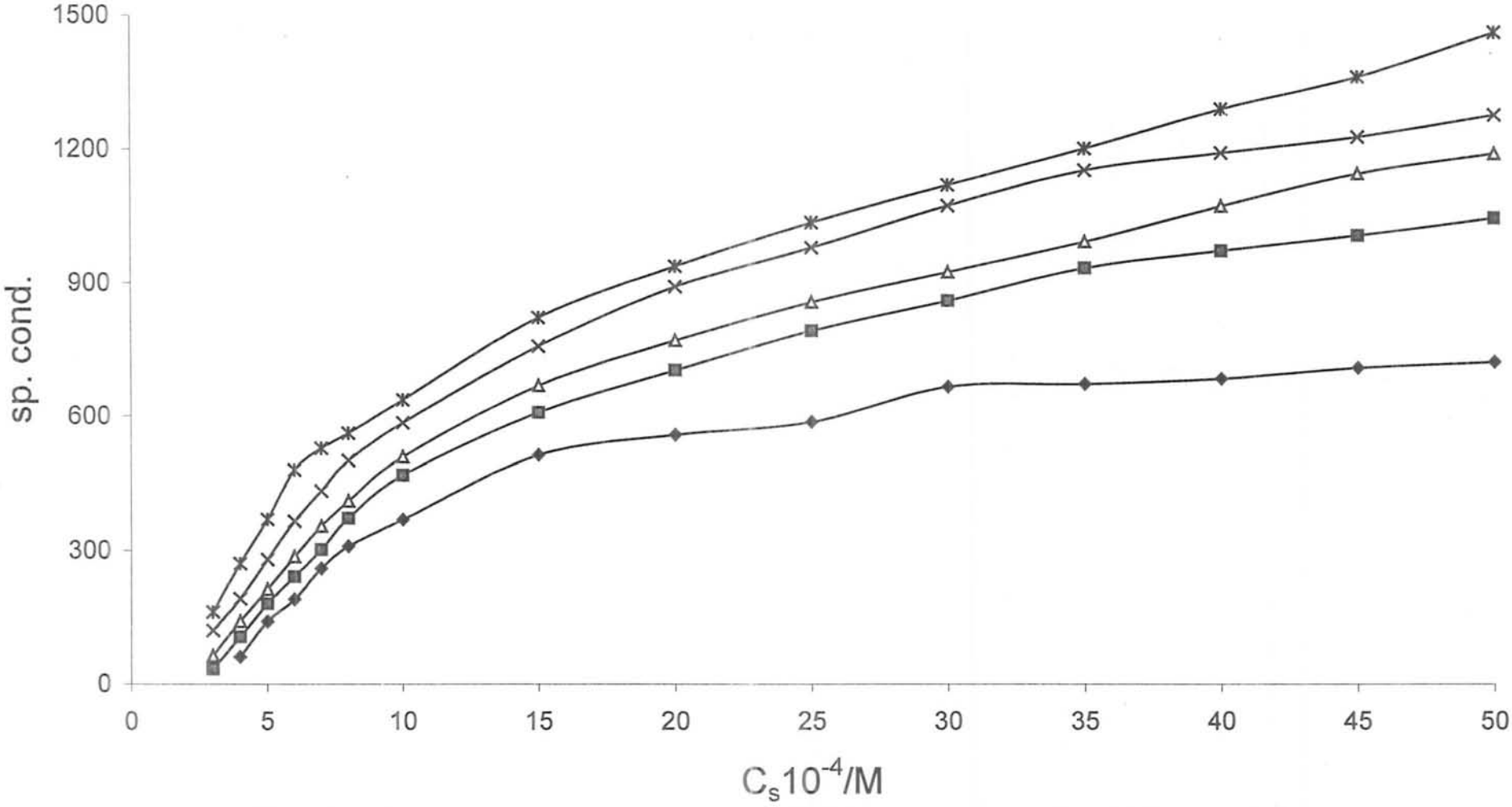


Fig.4B, Specific conductance vs CTAB concentration(Cs) for different concentration of Ibuprofin.

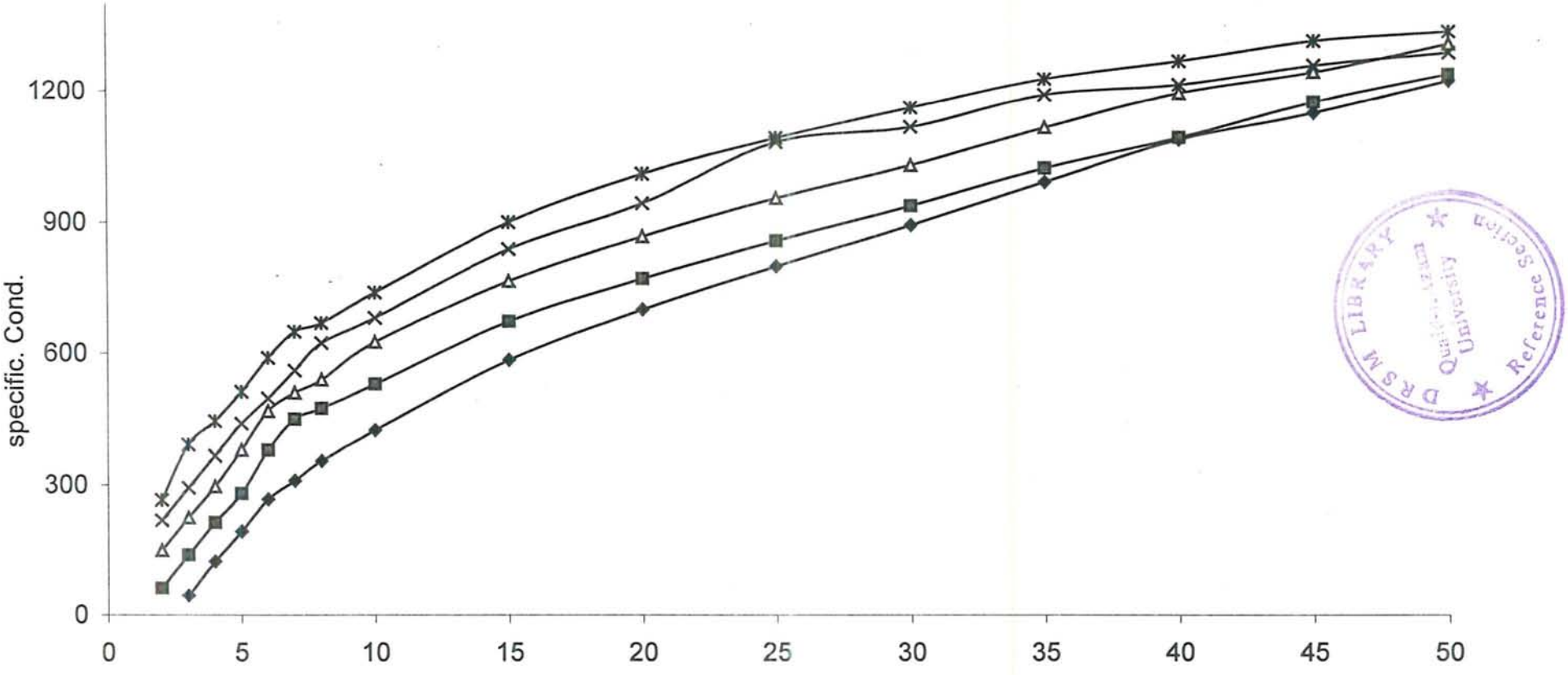


Fig.4C, Specific conductance vs CTAB concentration(Cs) for different concentration of Asprine

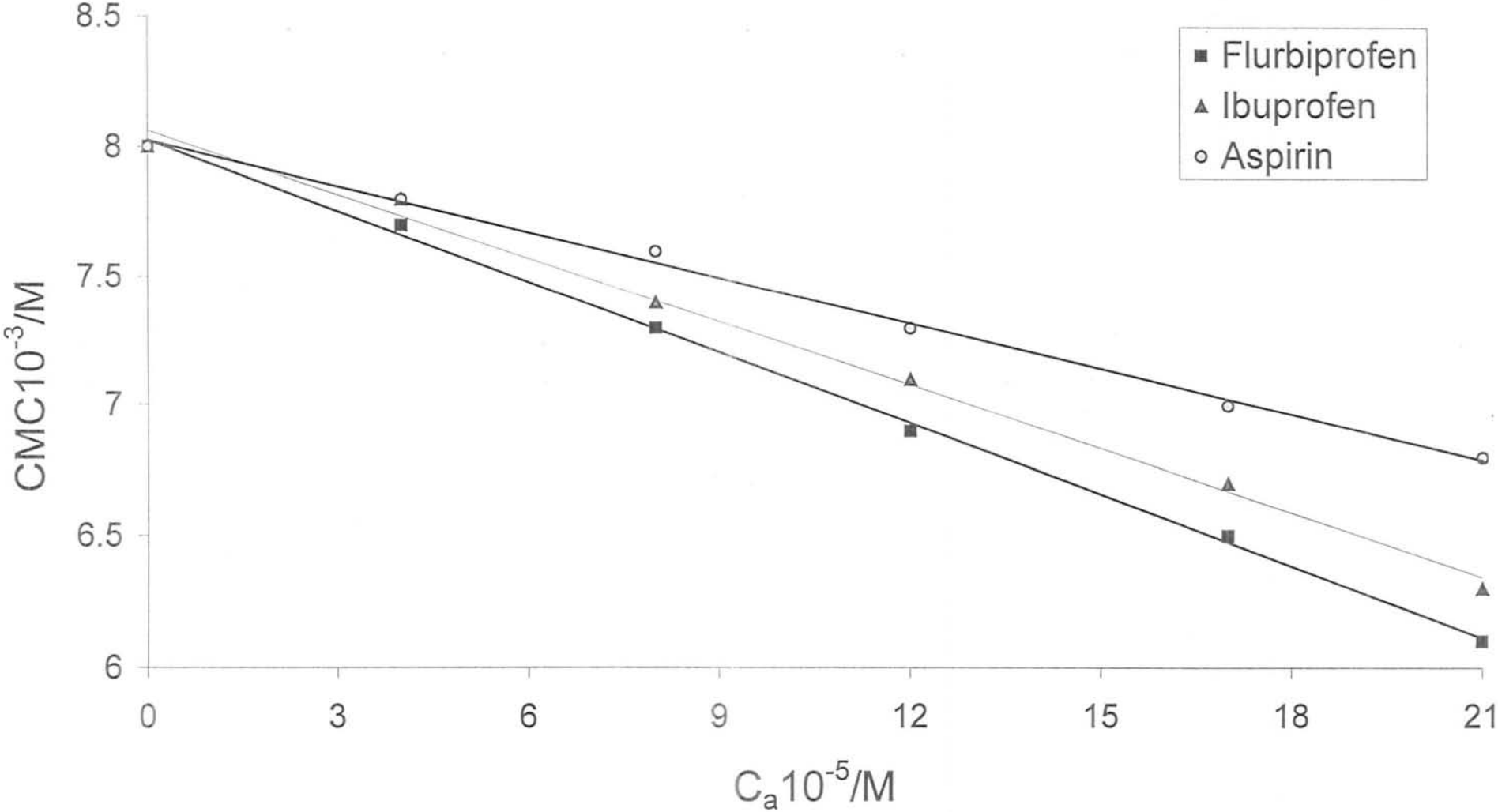


Fig.5,CMC vs concentration of additive(Ca) in SDS solution

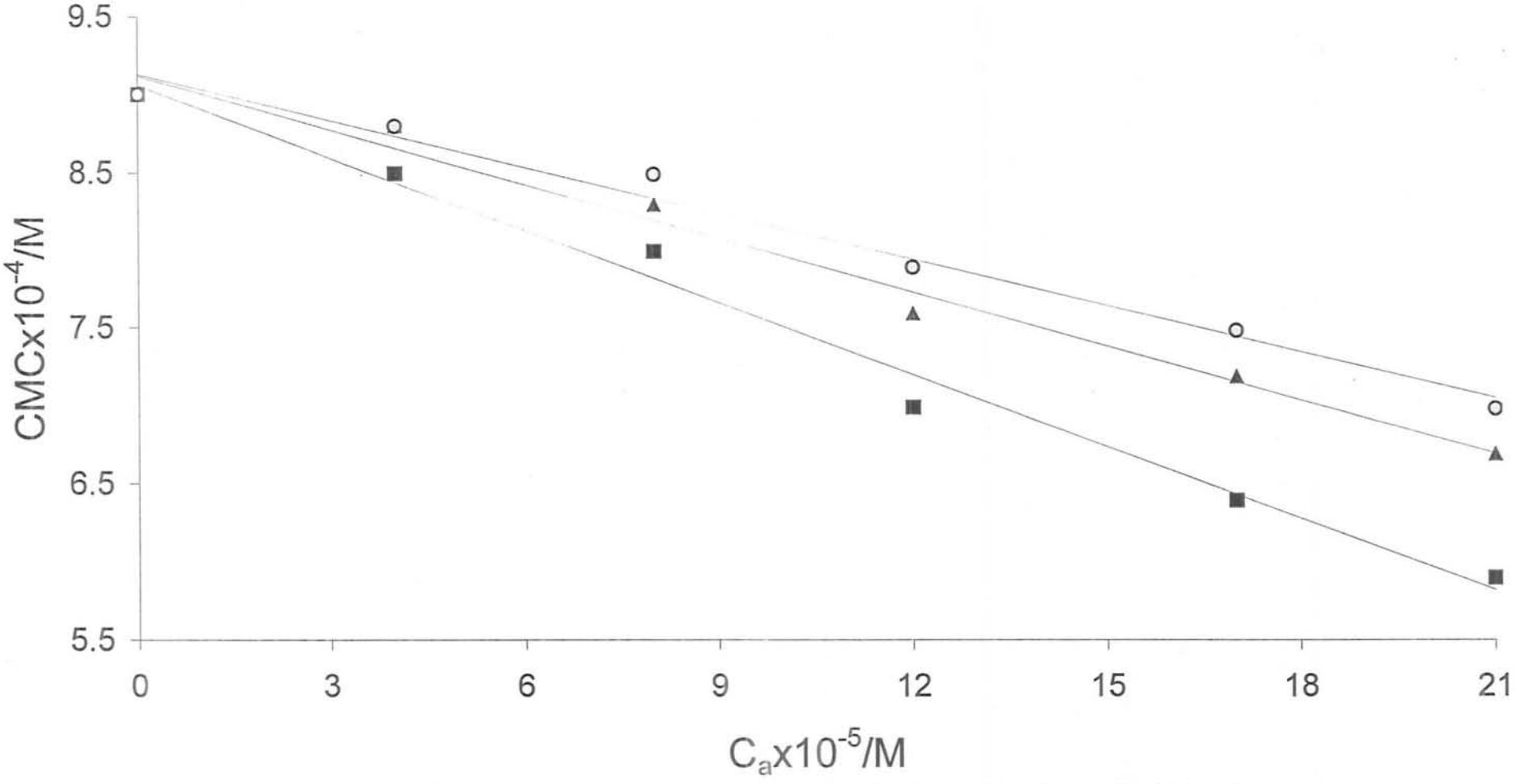


Fig.6, CMC vs concentration of additive(Ca) in CTAB solution

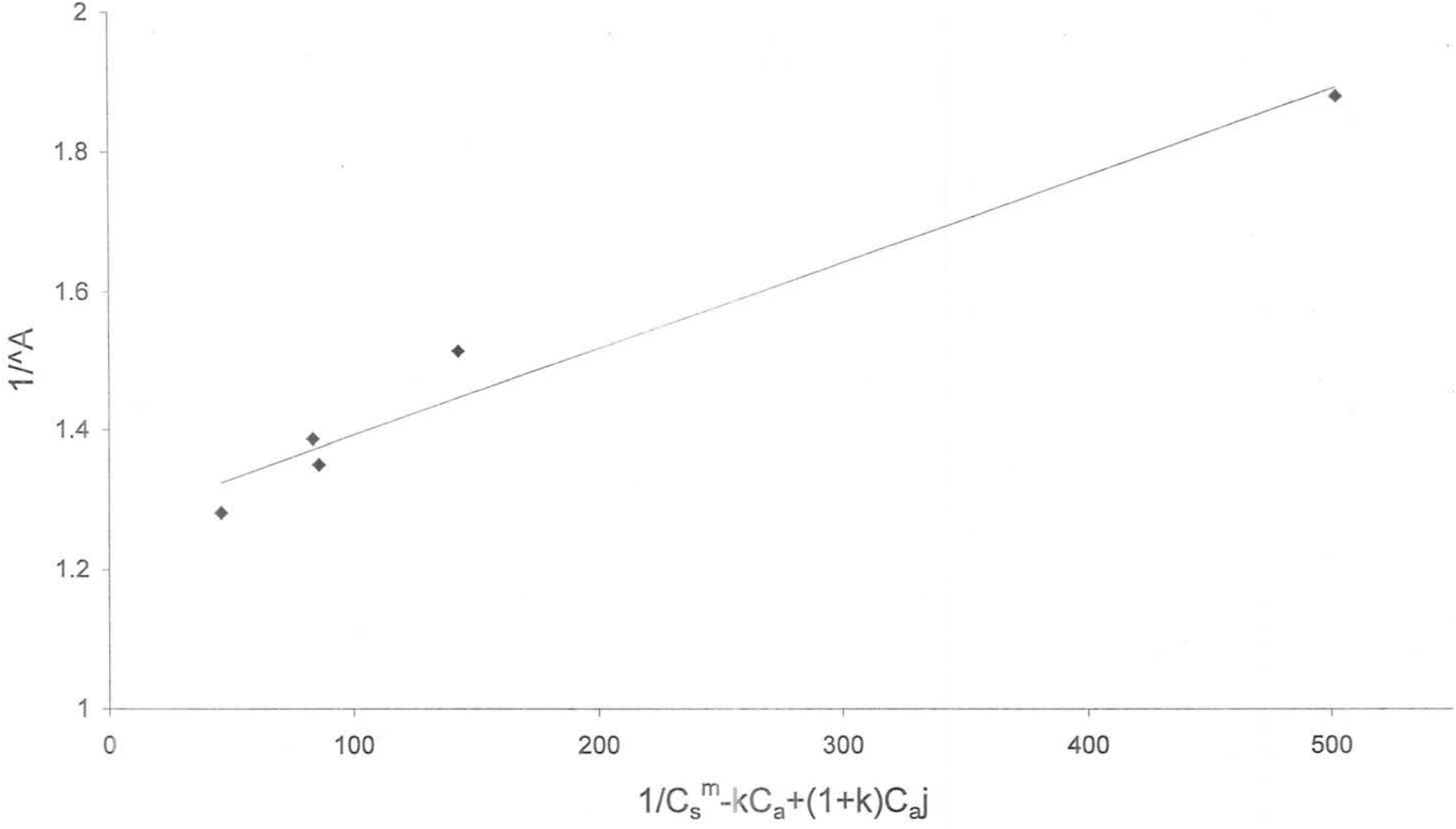


Fig.7A, 1/^A vs 1/Cs-kCa+(1+k)Caj for sds in flurbiprofin.

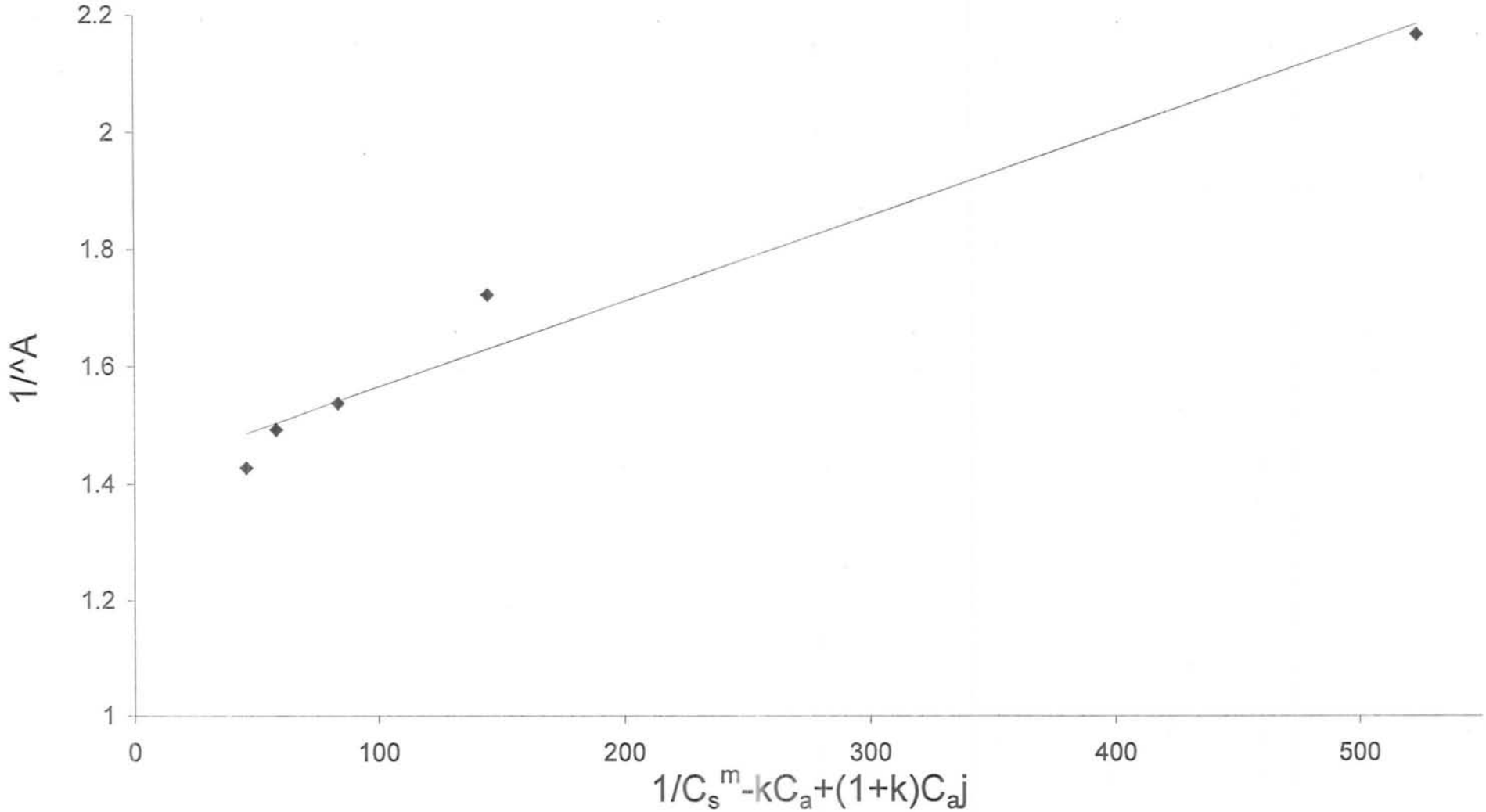


Fig.7B, 1/^A vs 1/Cs-kCa+(1+k)Caj for SDS in Ibuprofin.

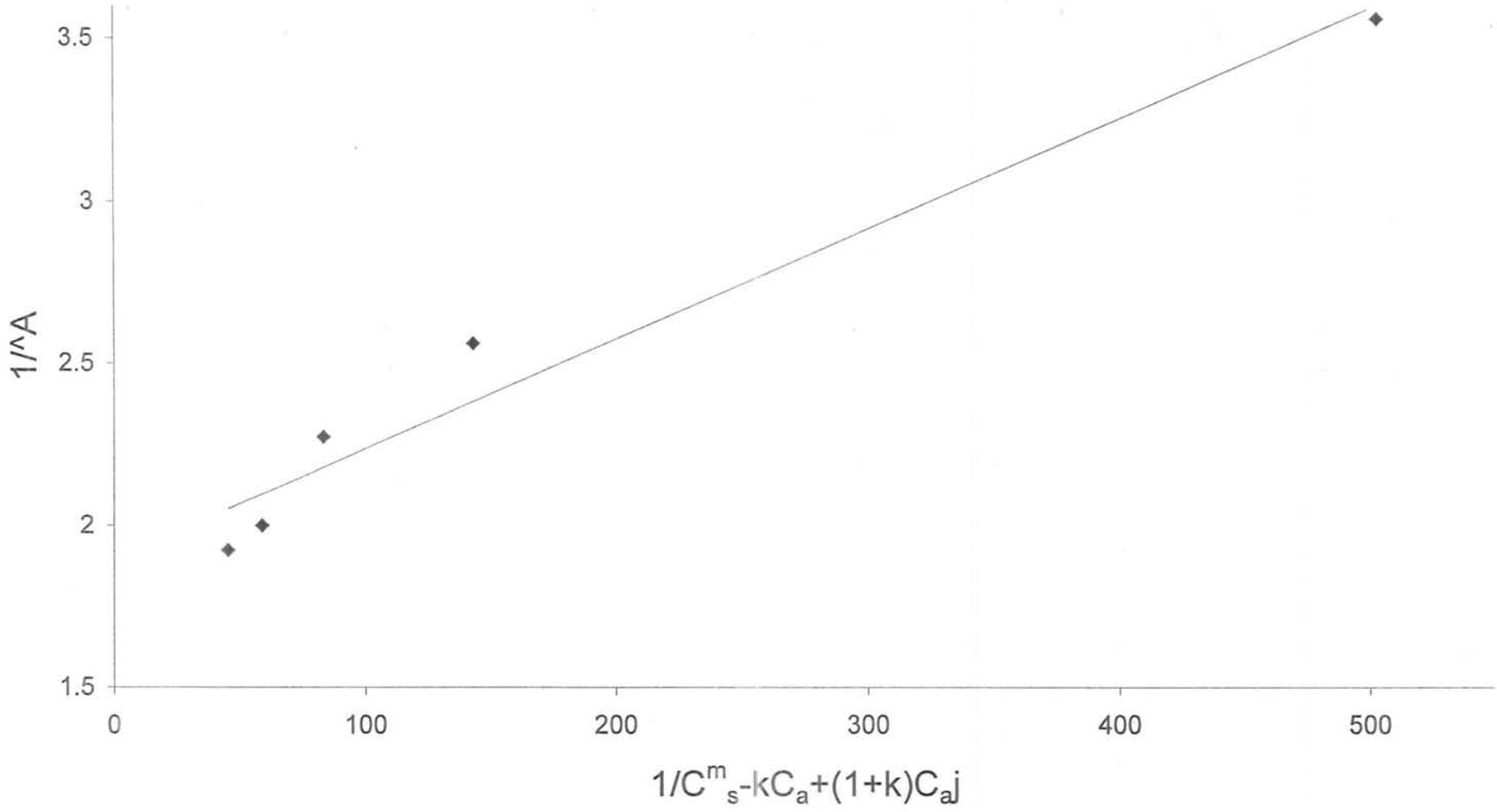


Fig. 7B 1/^A vs 1/Cs-kCa+(1+k)Caj for SDS in Aspirin

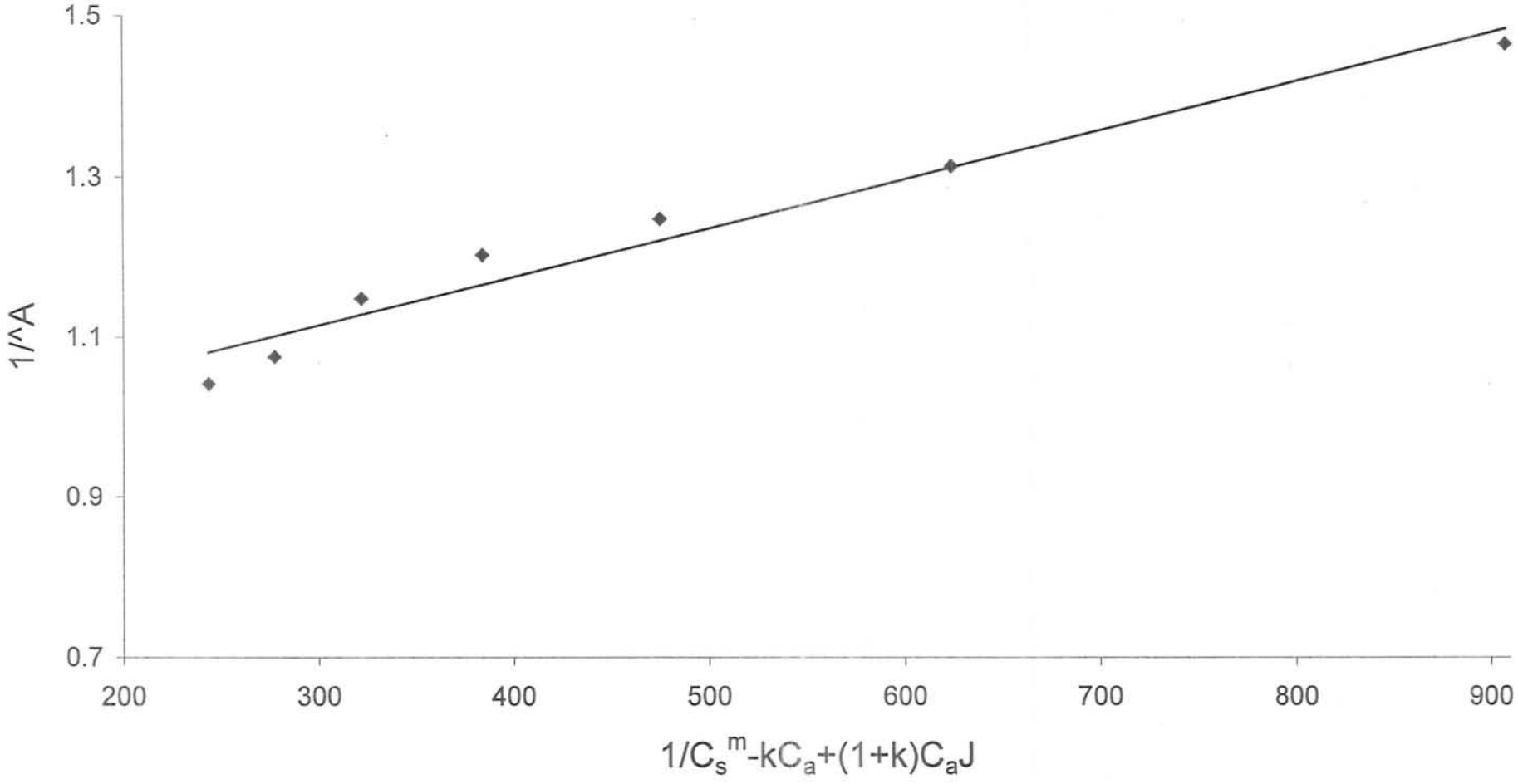


Fig. 8A, 1/^A vs 1 /Cs-kCa+(1+k)Caj for CTAB in Flurbiprofin.

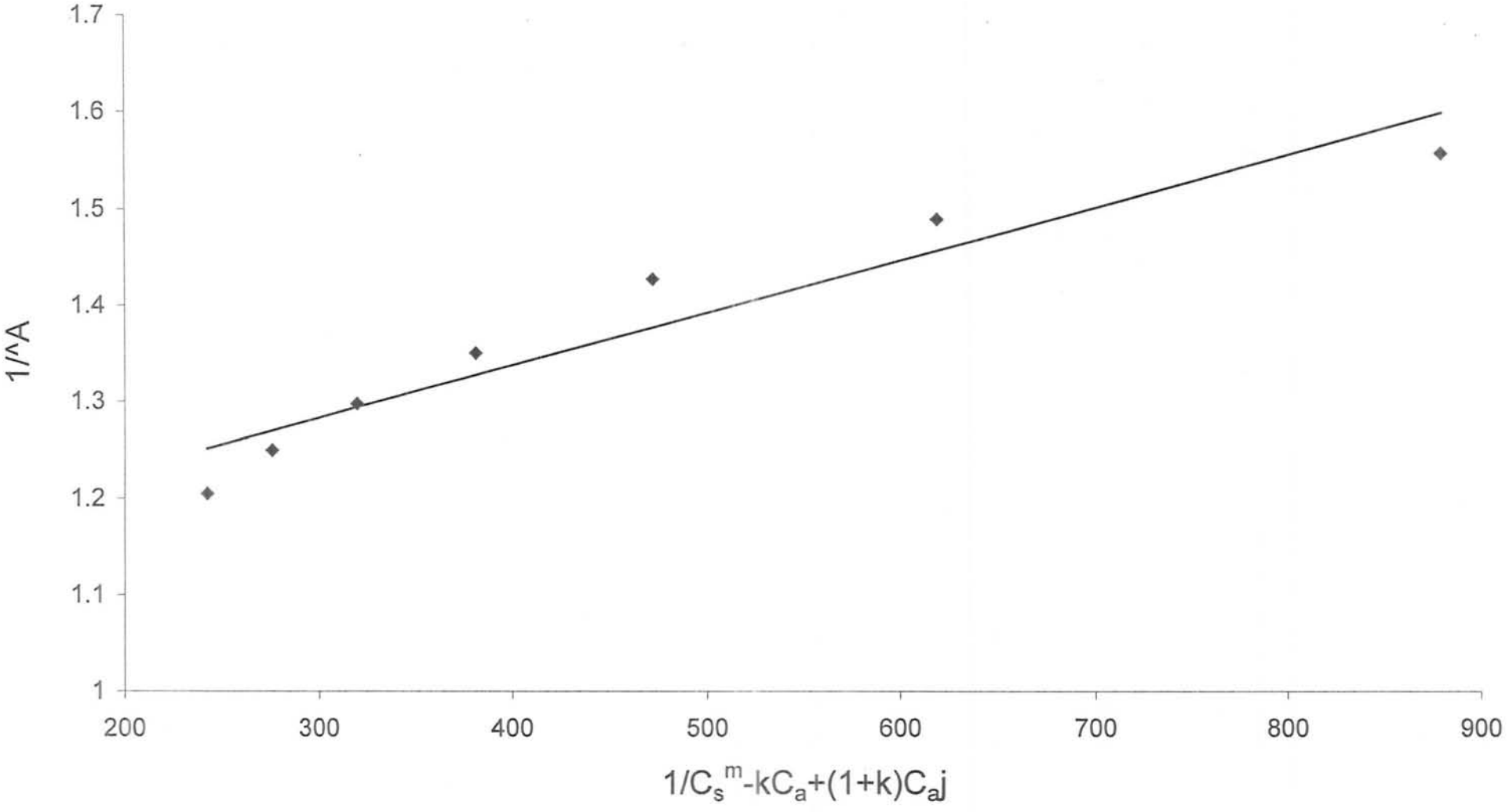


Fig.8B, 1/^A vs 1/Cs-Cak+(1+k)Caj for CTAB in Ibuprofin.

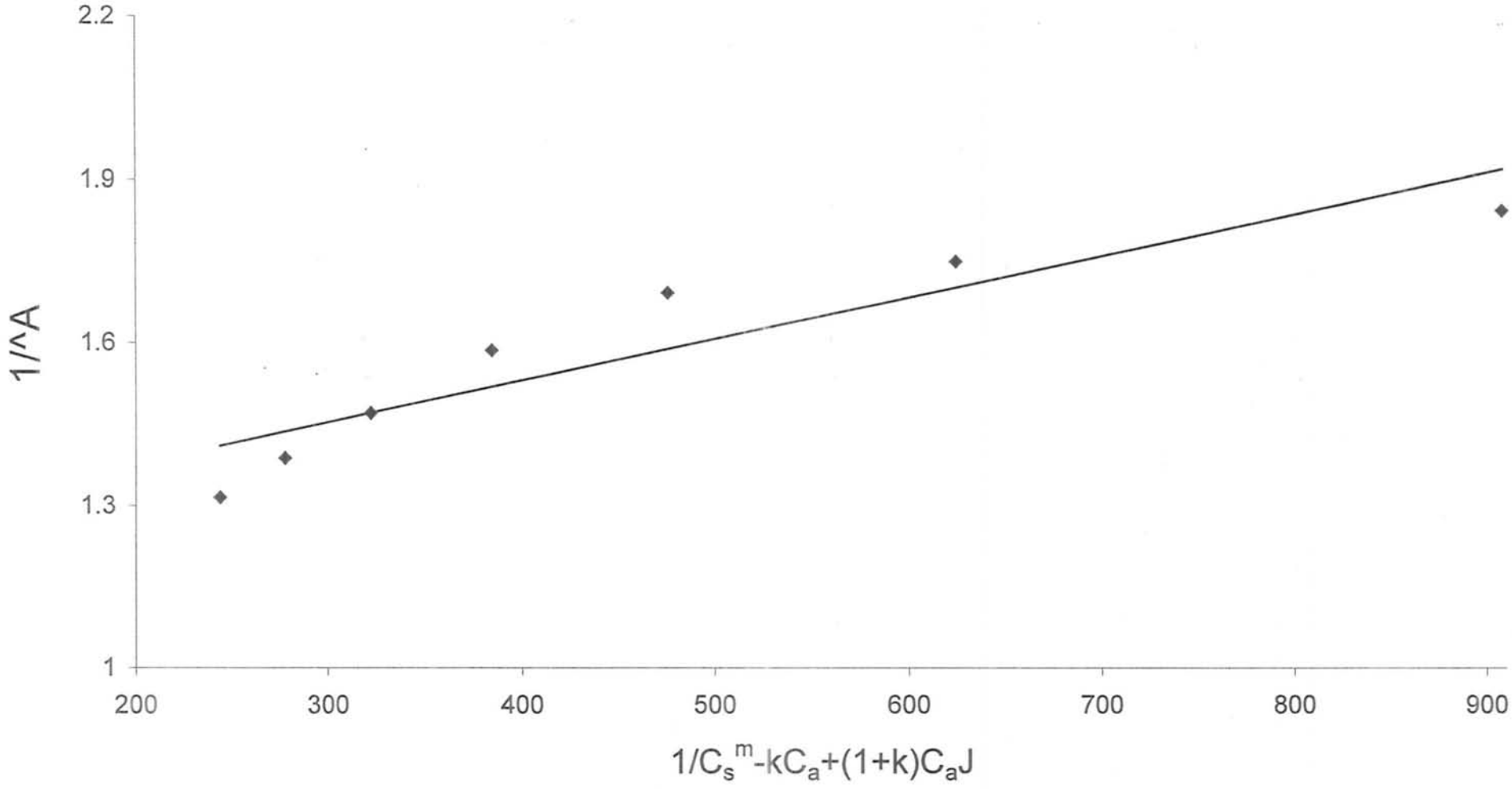


Fig. 8C, 1/^A vs 1/Cs-kCa+(1+k)Caj for CTAB in Aspirin

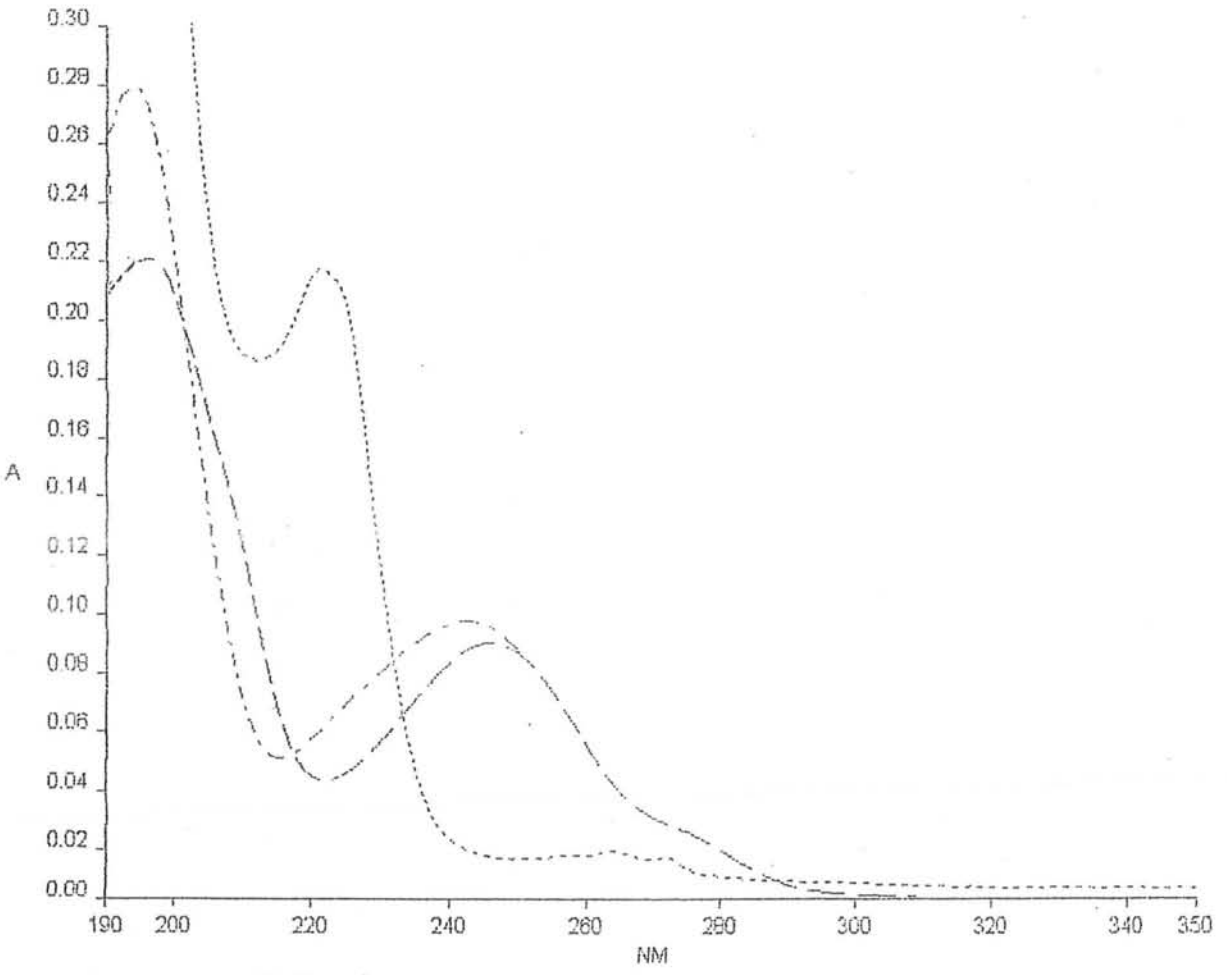


Fig. Absorbance spectra for Flurbiprofen , Ibuprofen, Aspirin in water.

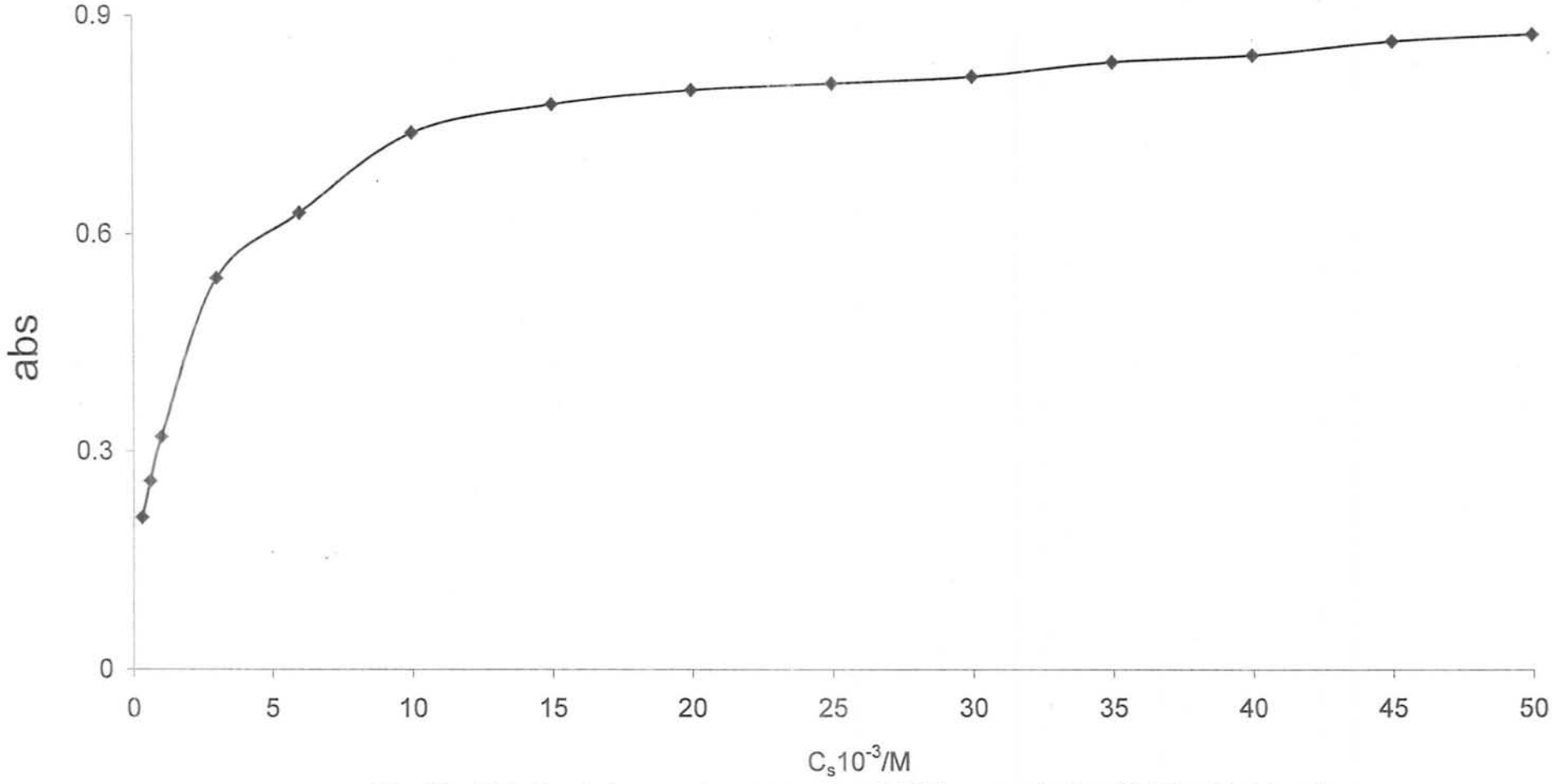


Fig. 9A: Relation between absorbance and SDS concentration(Cs) for Flurbiprofin.

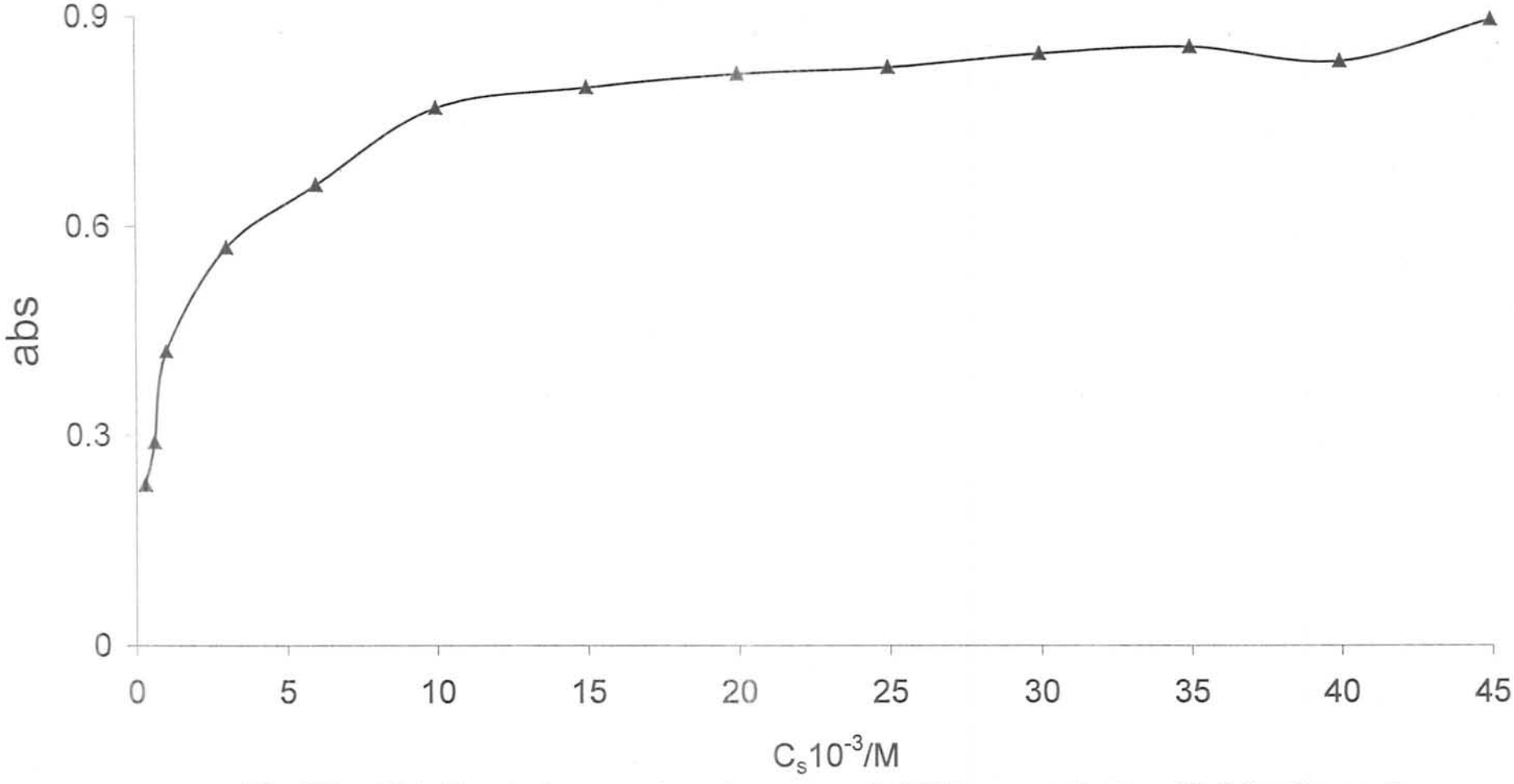


Fig.9B, Relation between absorbance and SDS concentration(Cs) for Ibuprofin.

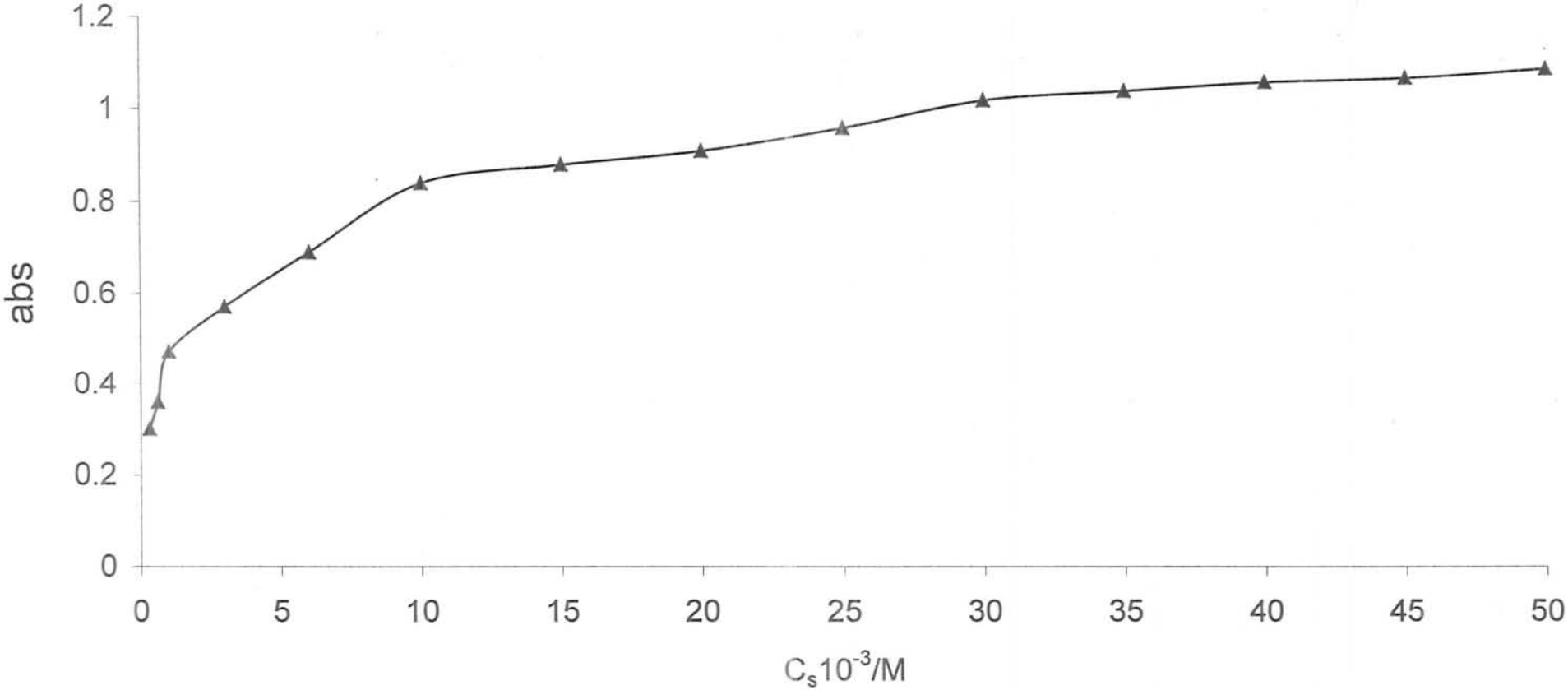


Fig.9C, Relation between absorbance and SDS concentration(Cs)for Aspirin.

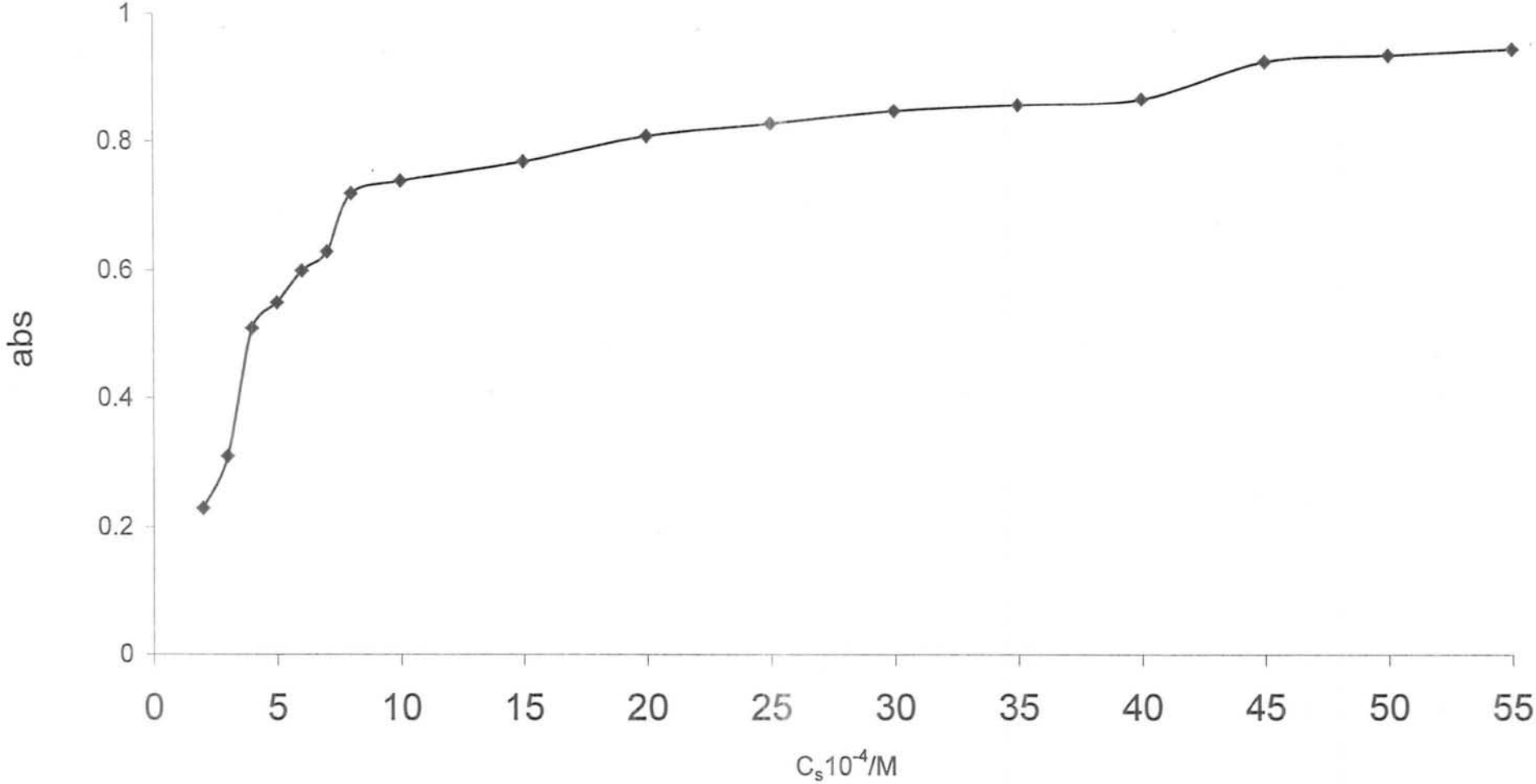


Fig. 10A, Relation between absorbance and CTAB concentration (Cs) for Flurbiprofin.

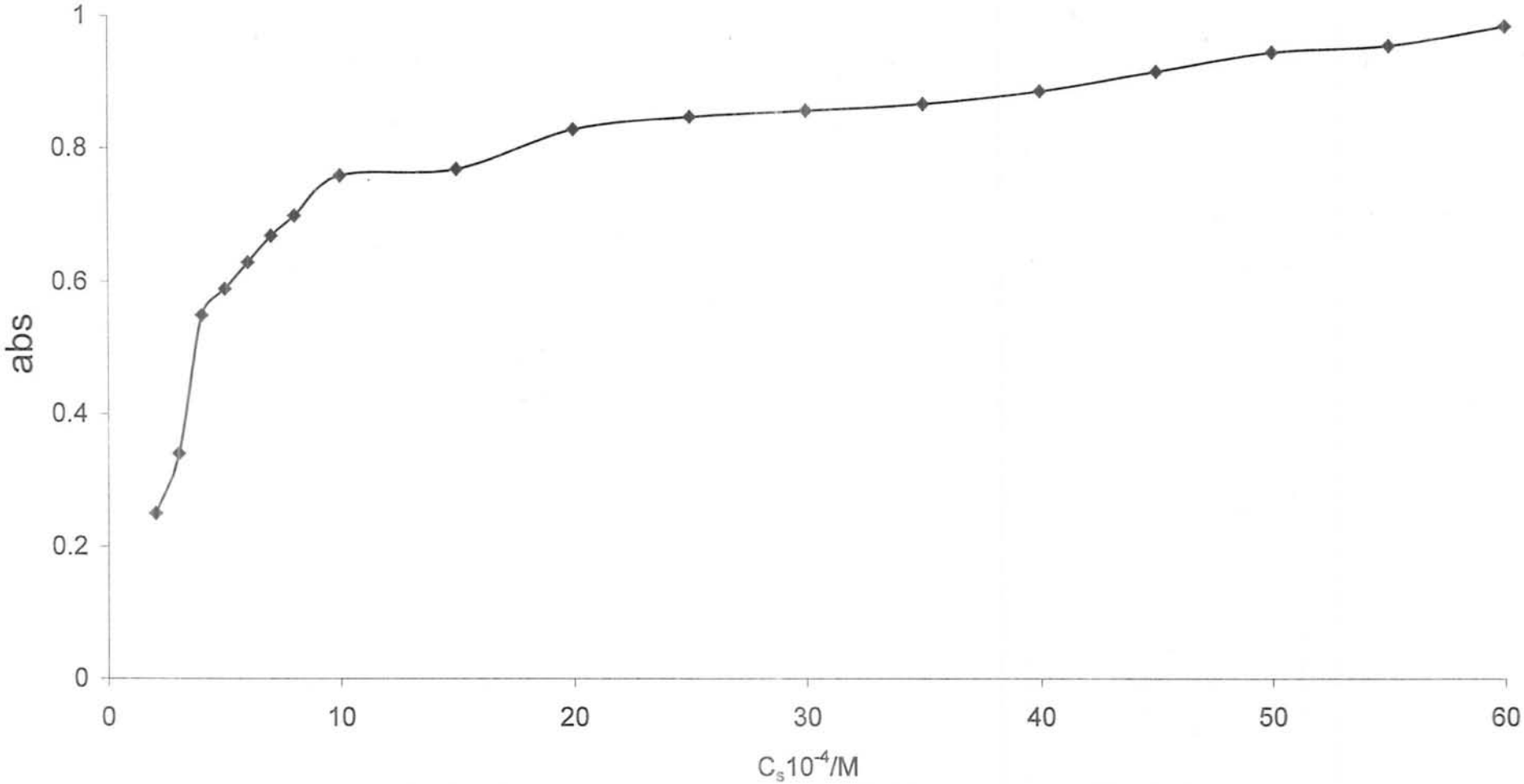


Fig. 10B: Relation between absorbance and CTAB concentration(Cs) for Ibuprofin.

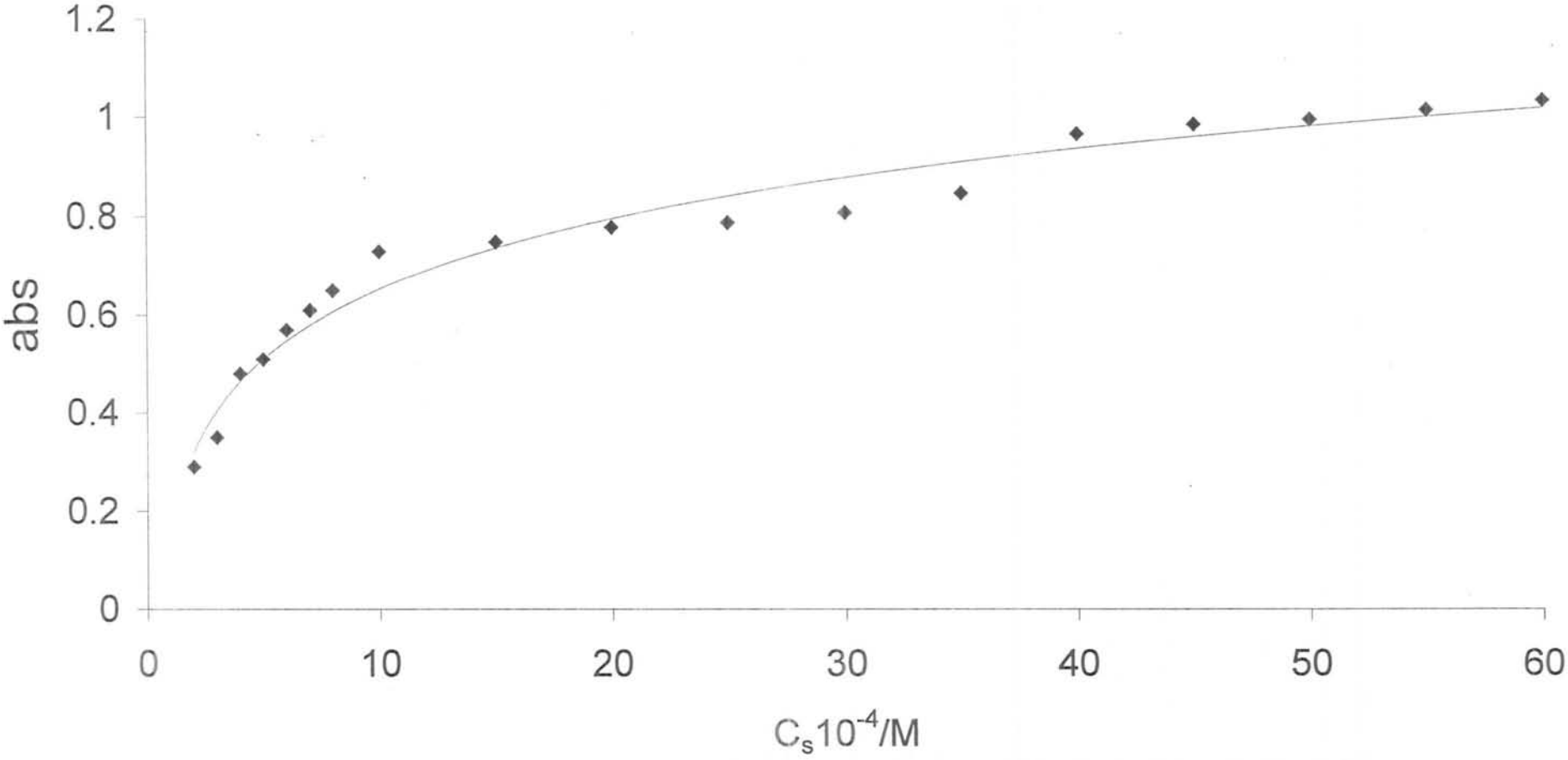


Fig. 10C: Relation between absorbance and CTAB concentration(Cs) for Aspirin.

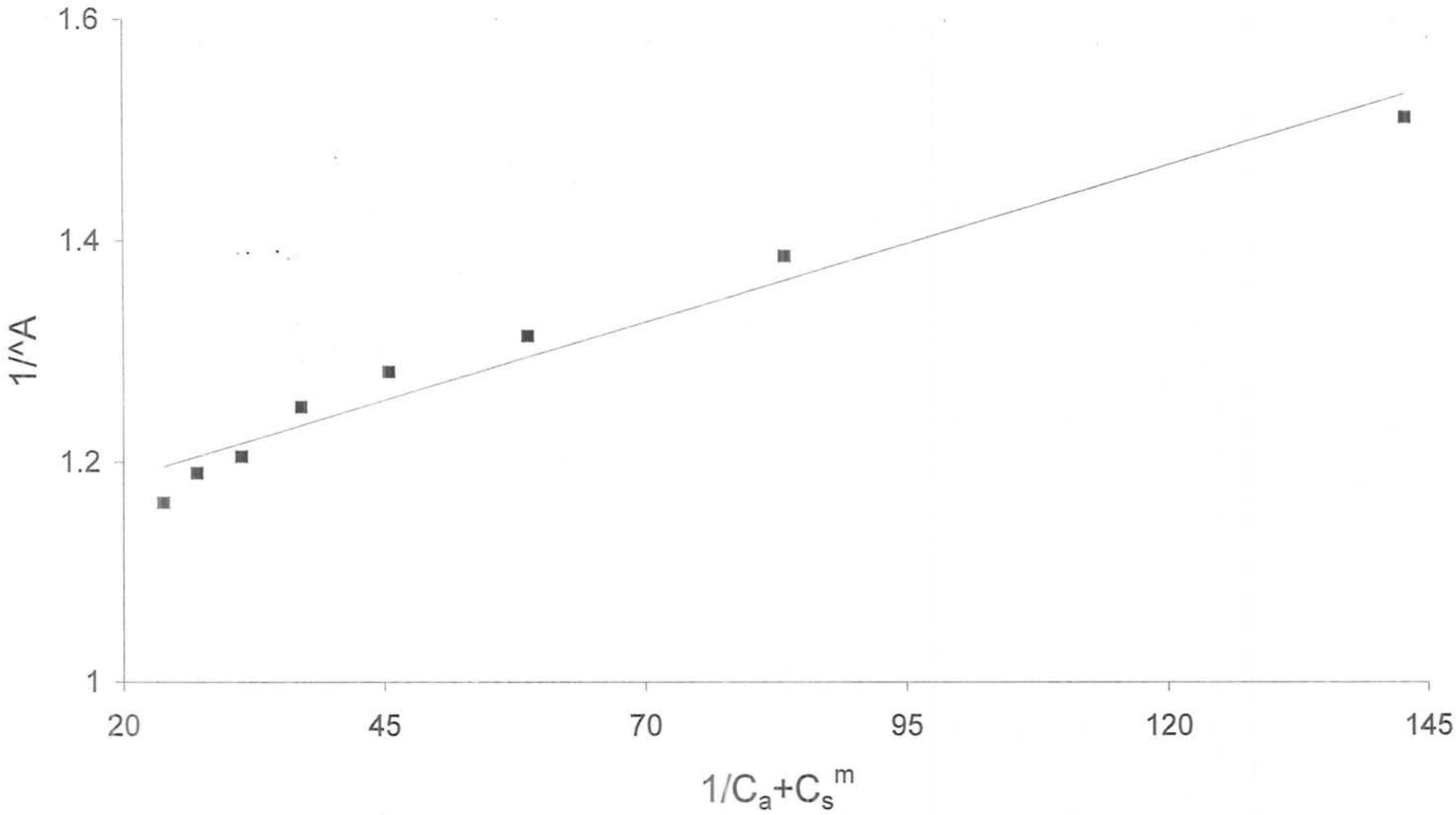


Fig. 11A, Relation between 1/^A vs 1/Ca+ Cs for SDS in Flurbiprofin.

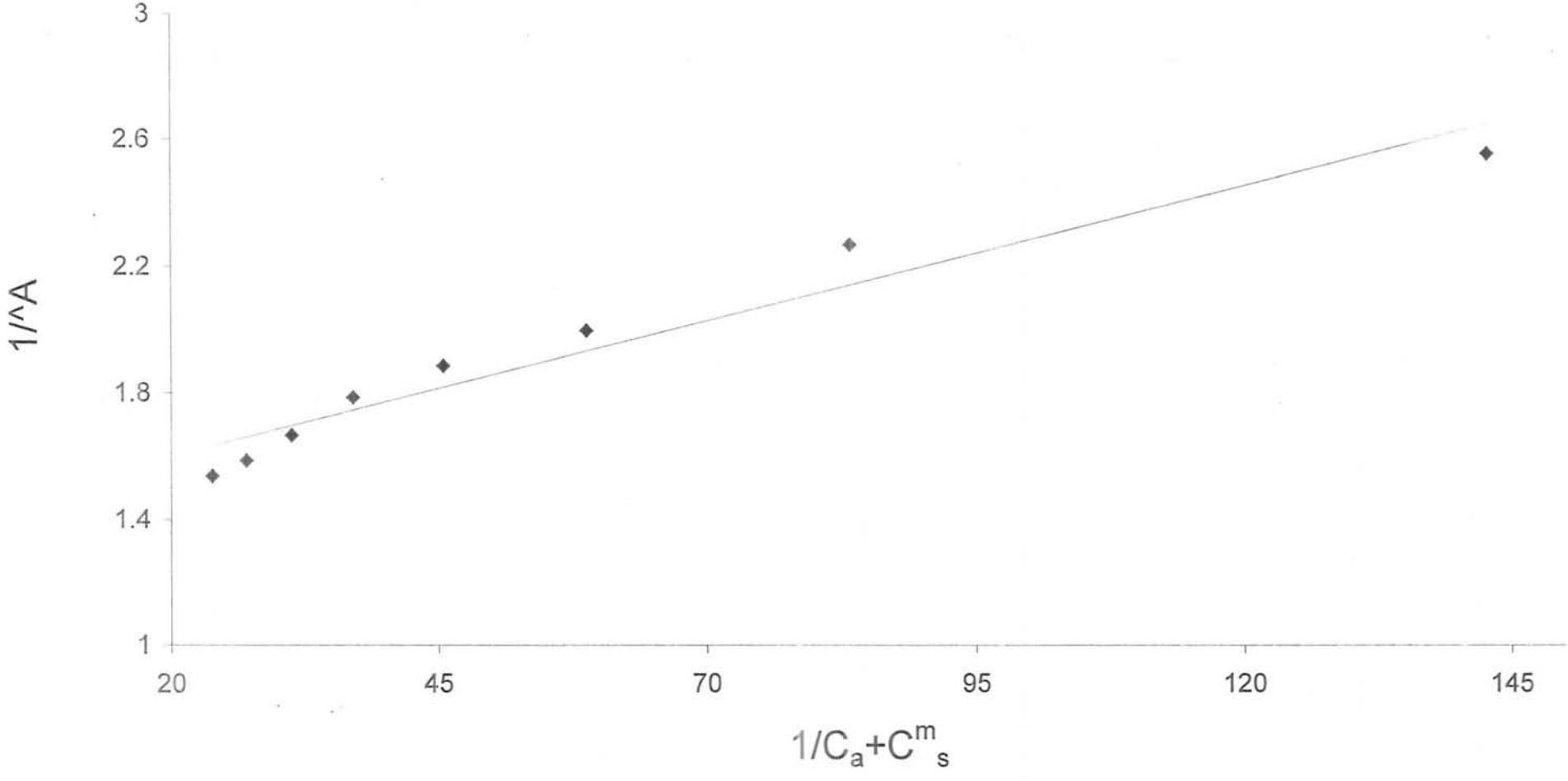


Fig. 11C. Relation between 1/^A vs 1/Ca+C$^{m}_{s}$ for SDS in Aspirin.

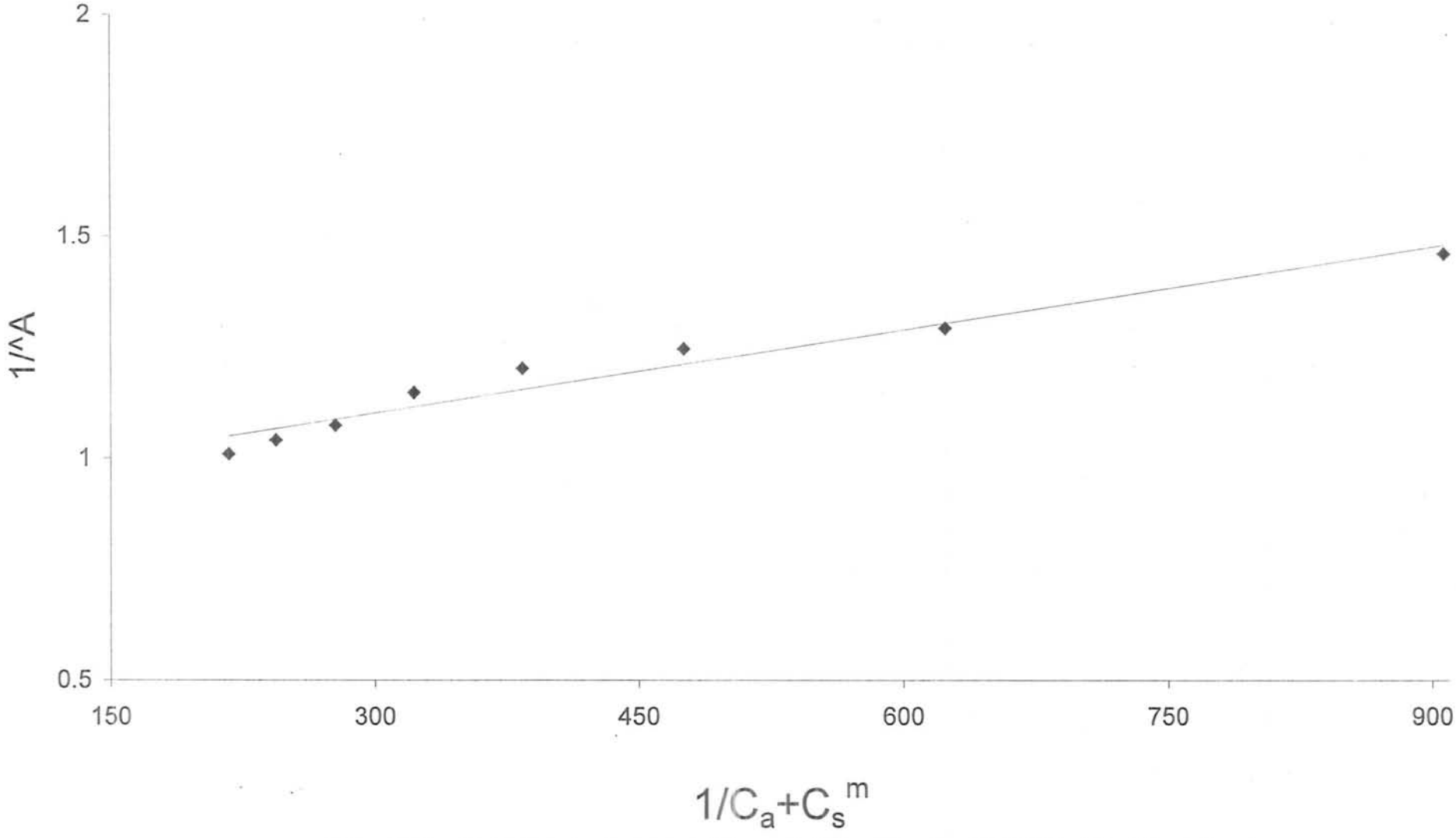


Fig. 12A, Relation between 1/^A and 1/Ca+Cs for CTAB in Flurbiprofin.

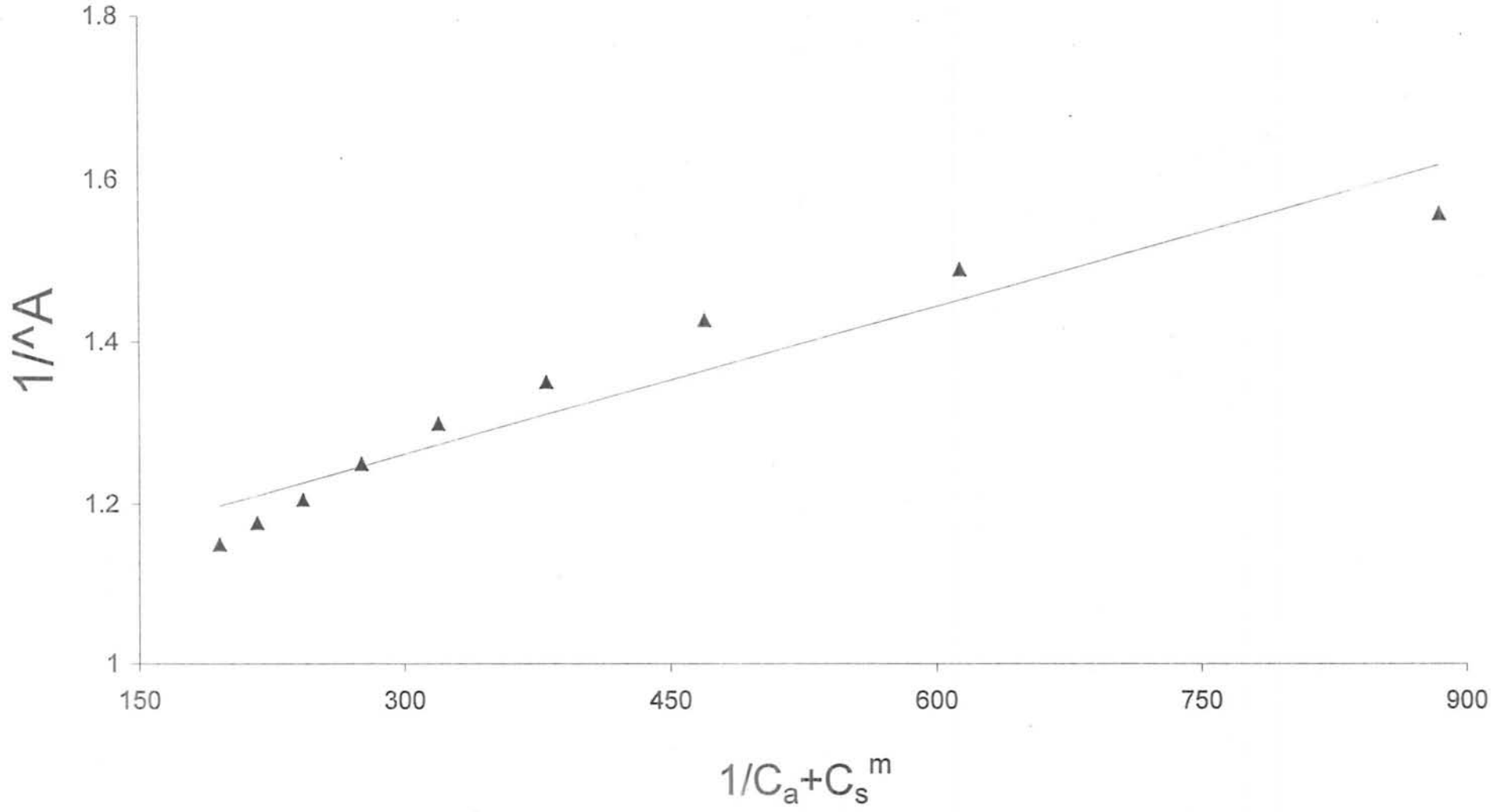


Fig. 12B, Relation between 1/^A and 1/CA+Cs for CTAB in Ibuprofin

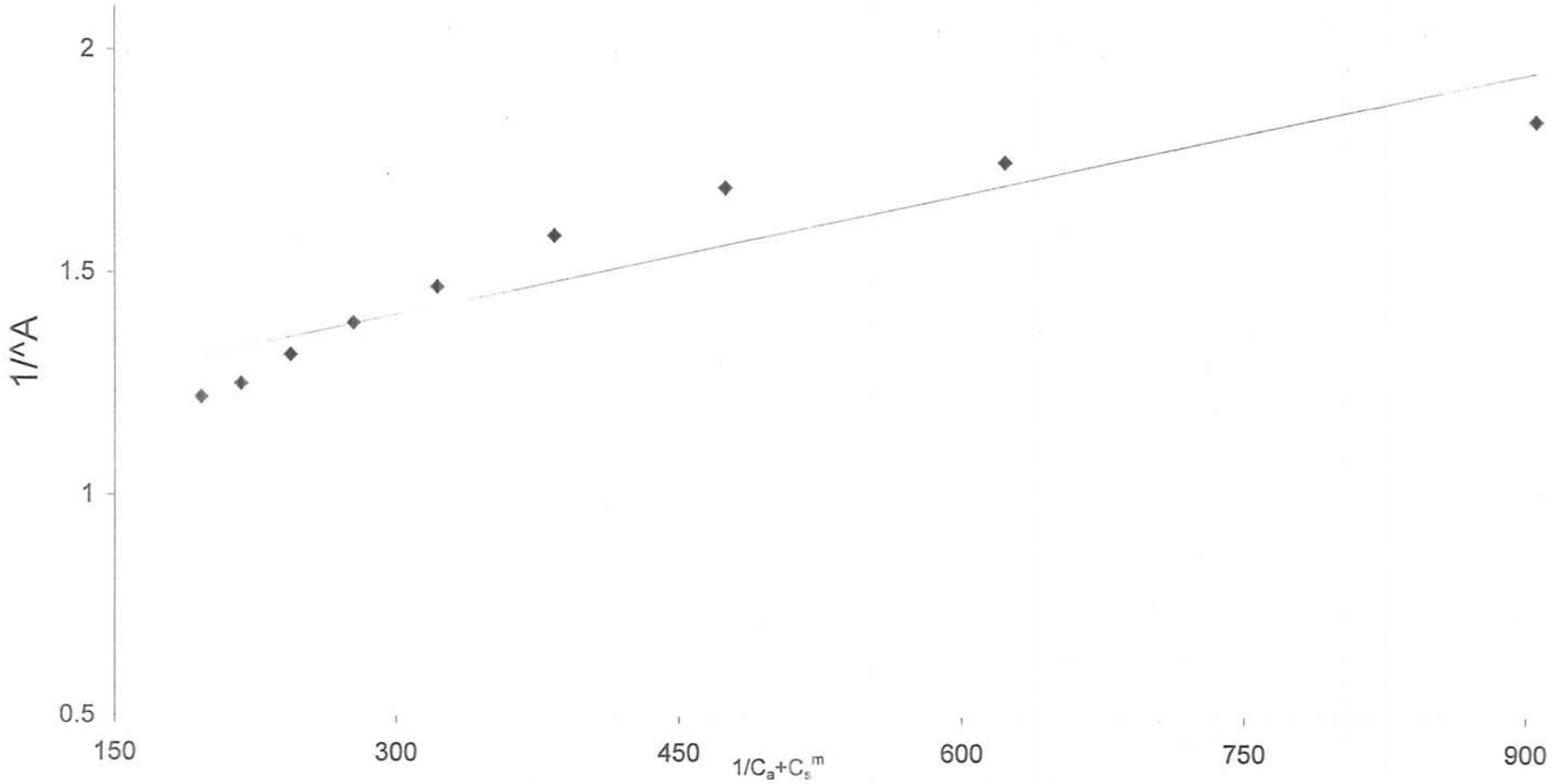


Fig. 12C, Relation between 1/^A vs 1/Ca+Cs for CTAB in aspirin.

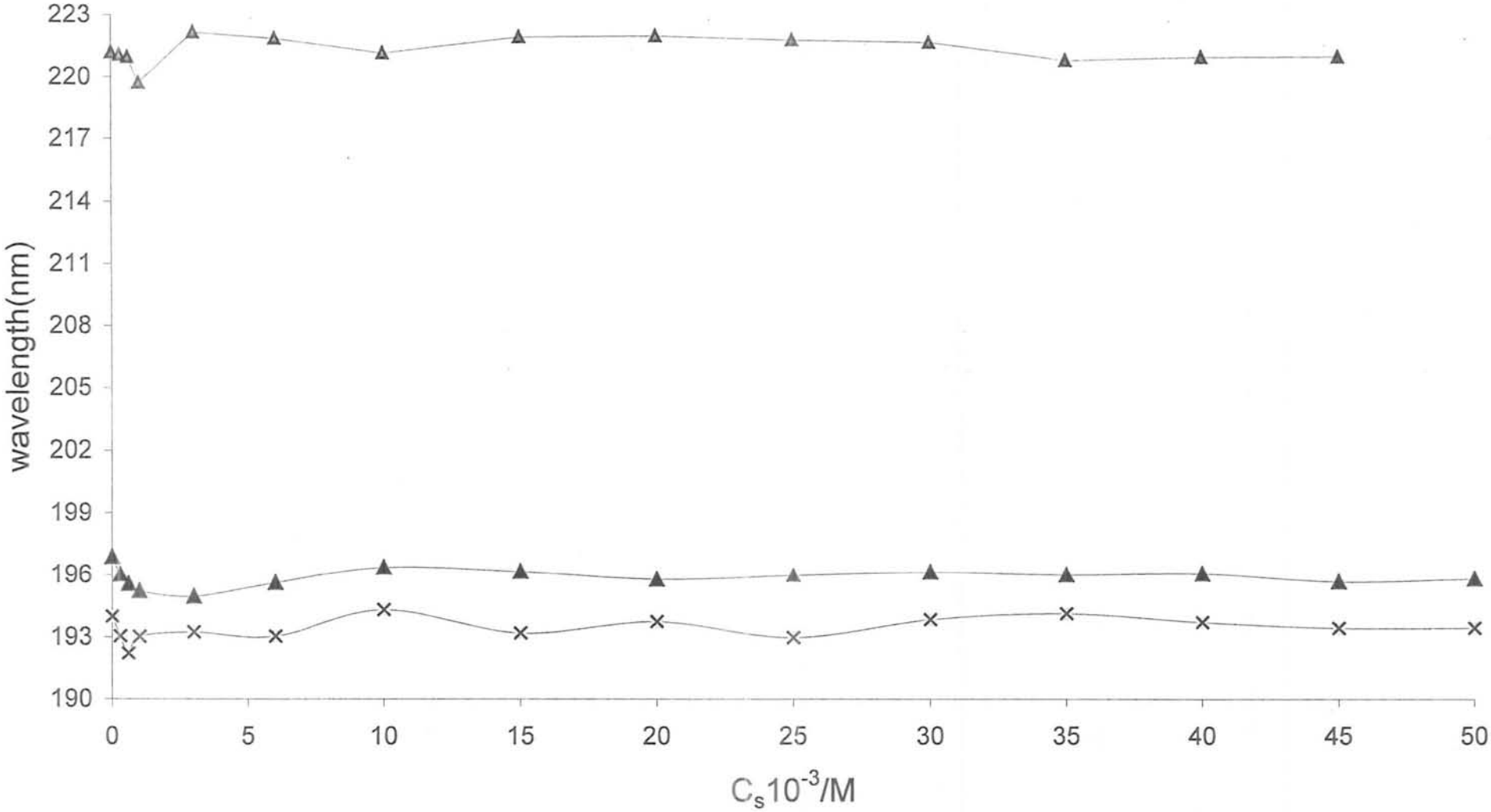


Fig.13, Relation between maxi. wavelength and sds concentration(Cs) in Flurbiprofin, Ibuprofin and Aspirin.

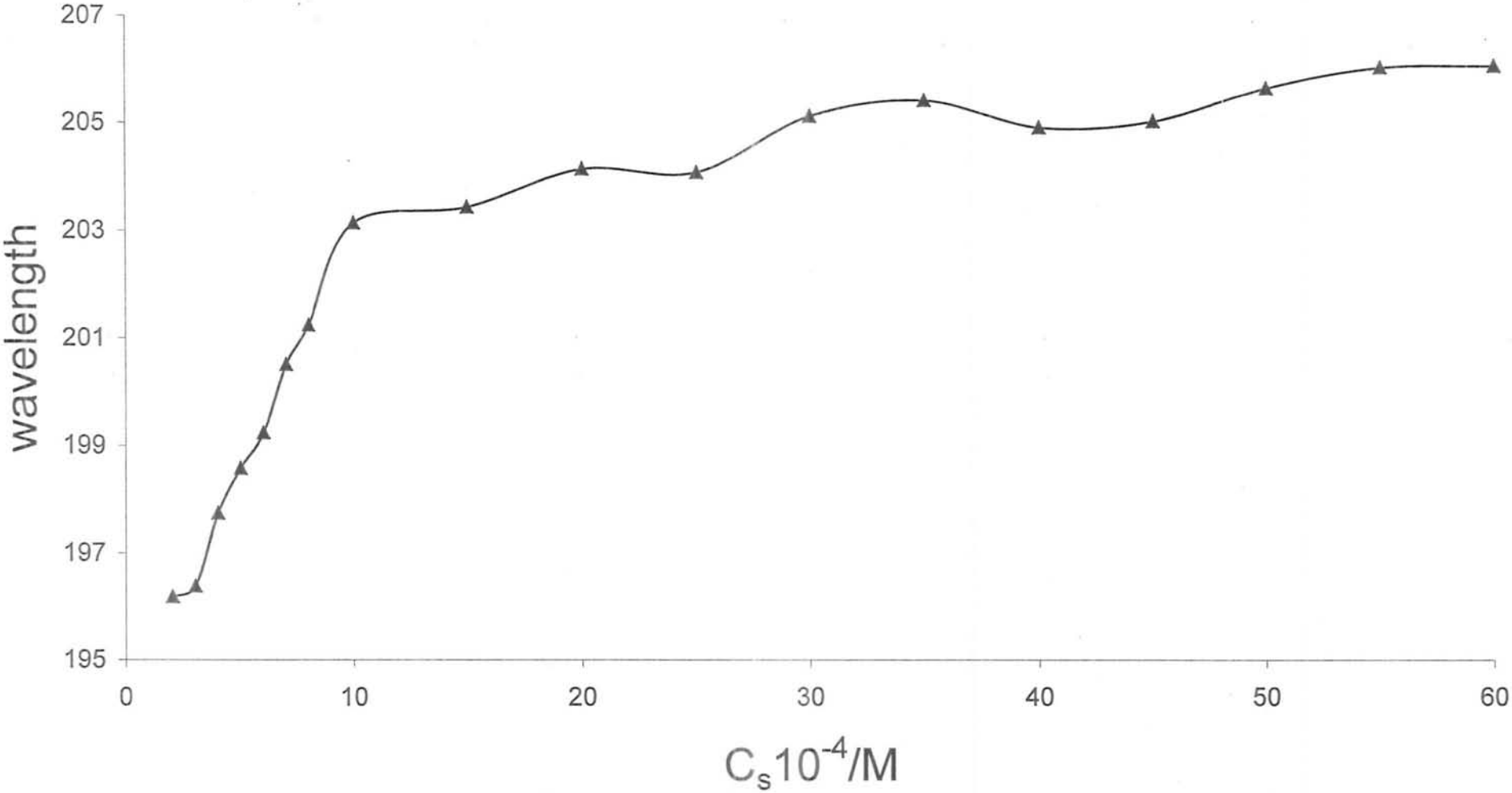


Fig. 14, Relation between maxi. wavelength and CTAB concentration(Cs) in Flurbiprofin.

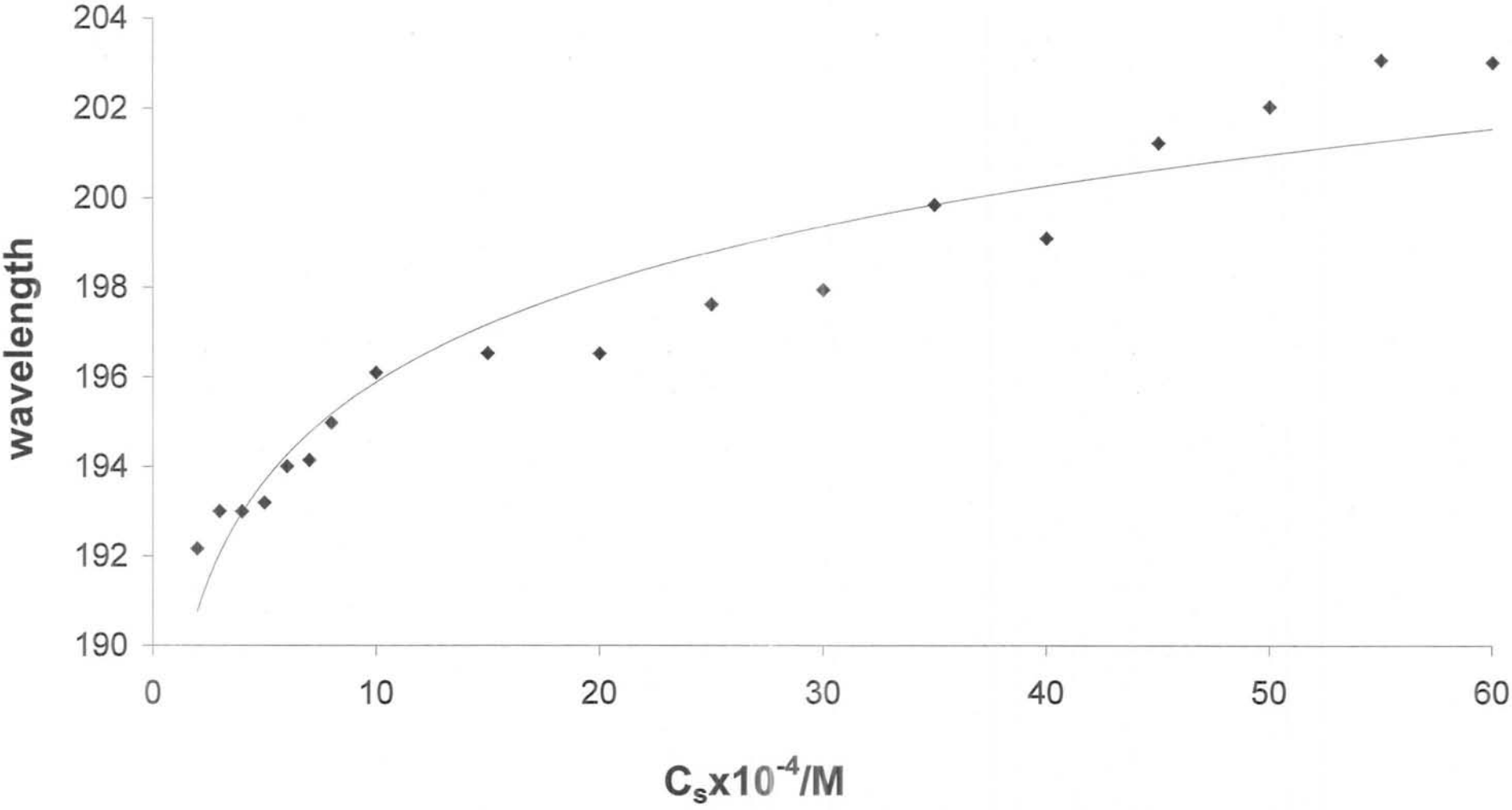


Fig.15: Relation betwean maxi. wavelength and CTAB concentration(Cs) in Ibuprofen.

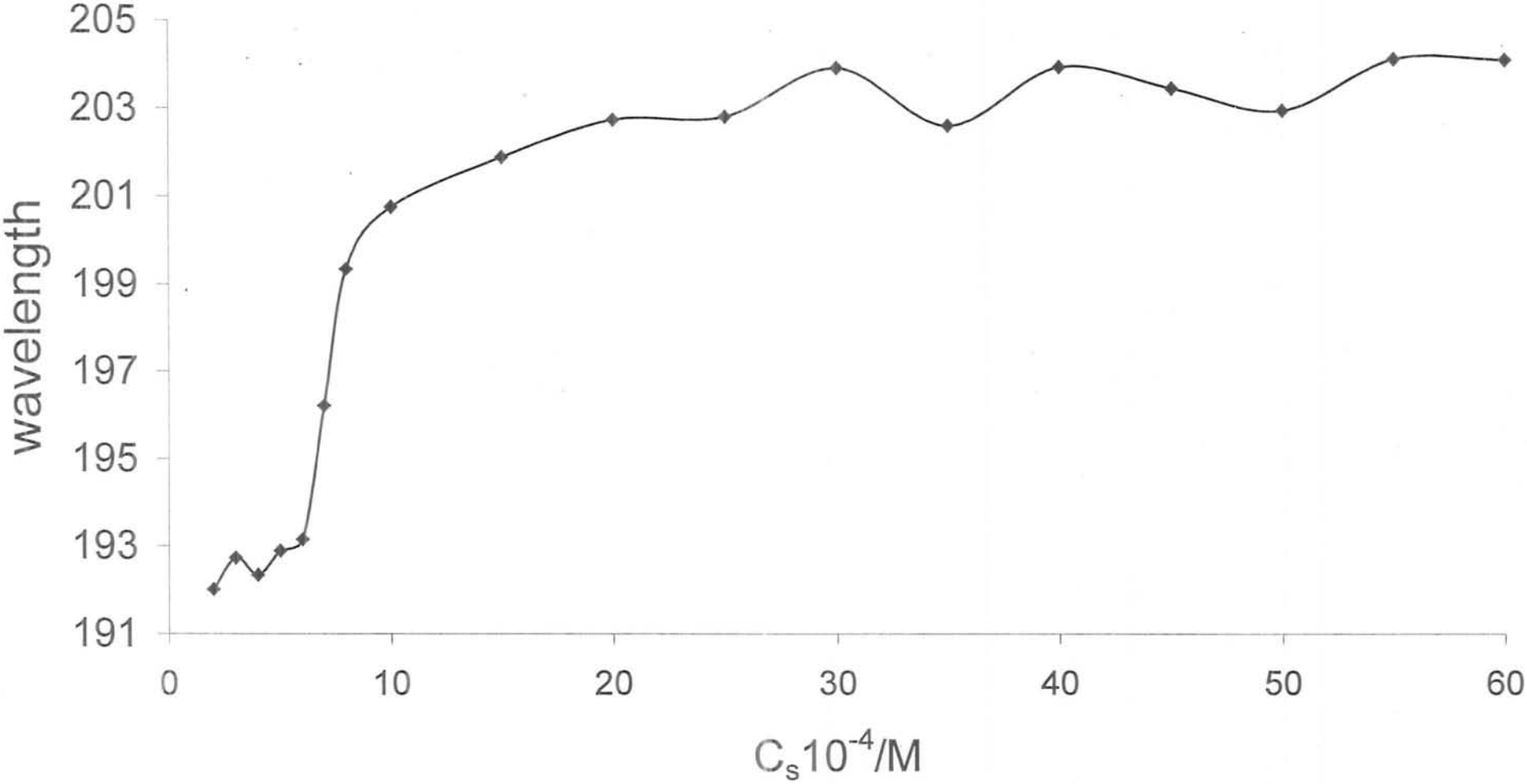


Fig.16, Relation between maxi. wavelength and CTAB concentration(Cs) in Aspirin.

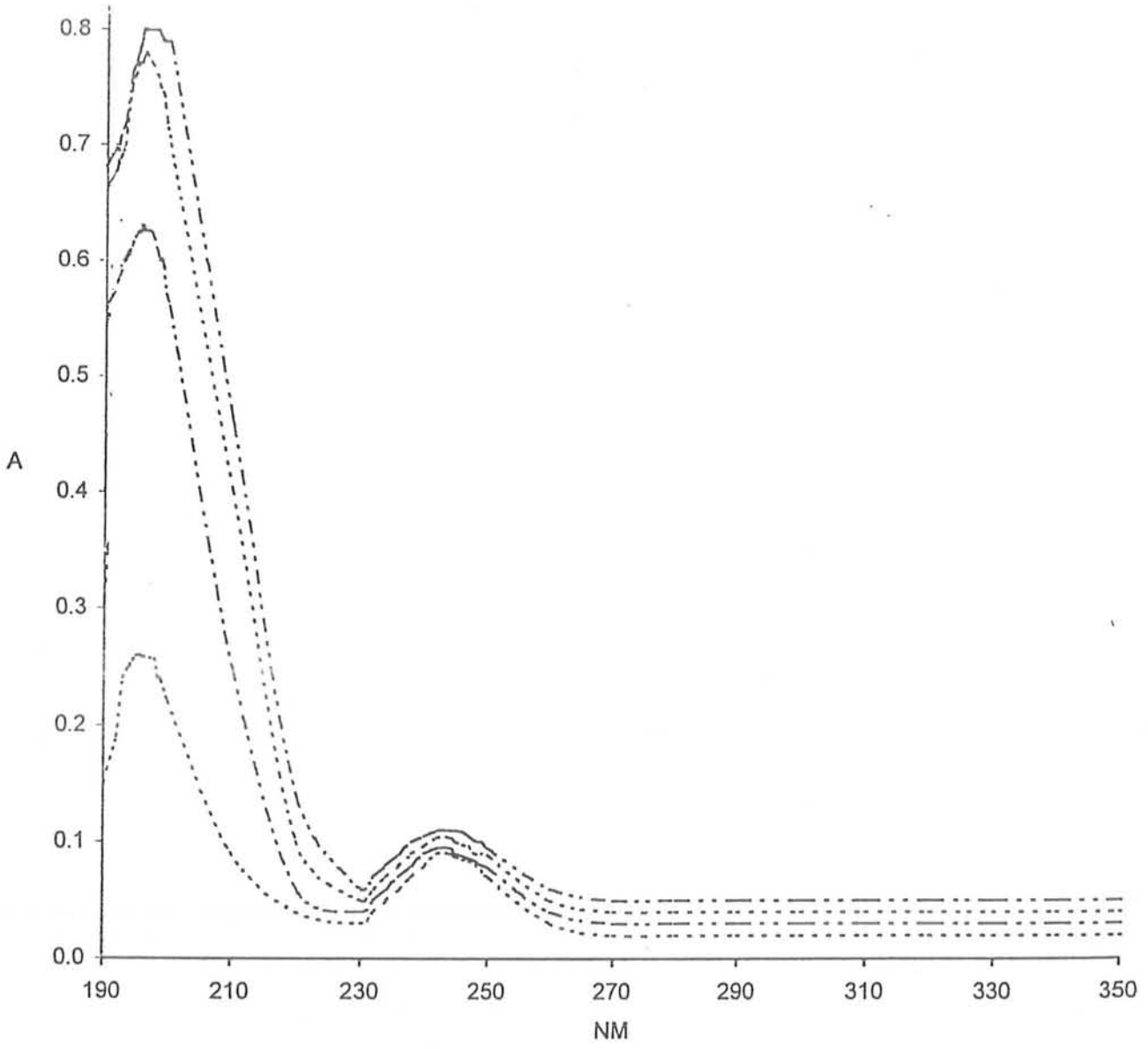
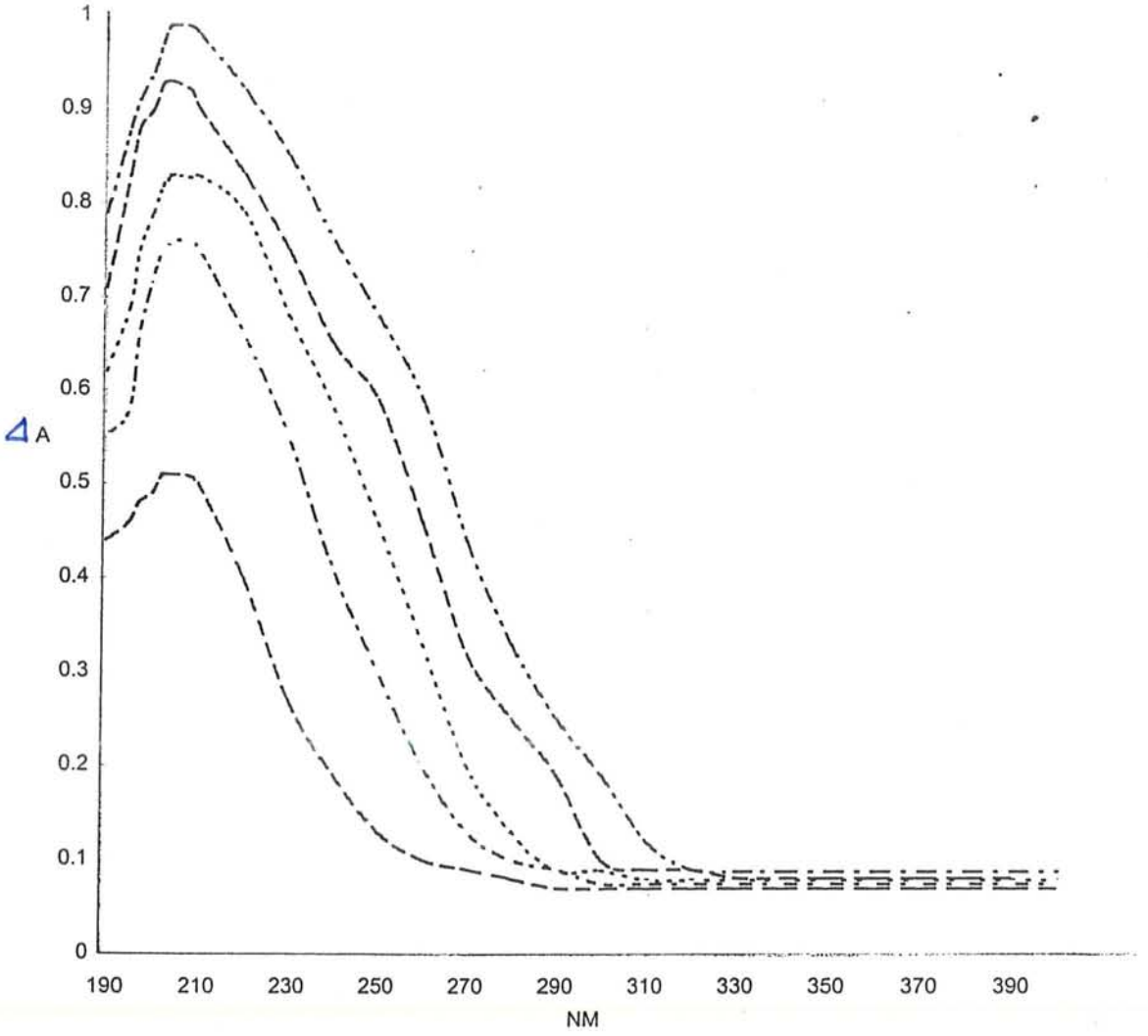


Fig. Simple absorbance spectra of Flurbiprofen in SDS.

1- $0.6x10^{-3}M$ 2- $6x10^{-3}M$ 3- $15x10^{-3}M$ 4- $20x10^{-3}M$



Fig, .Differential absorbance spectra of Flurbiprofen in CTAB.

1- $10x10^{-4}M$ -2- $25x10^{-4}M$ 3- $35x10^{-4}M$ 4- $45x10^{-4}M$ 5- $55x10^{-4}M$

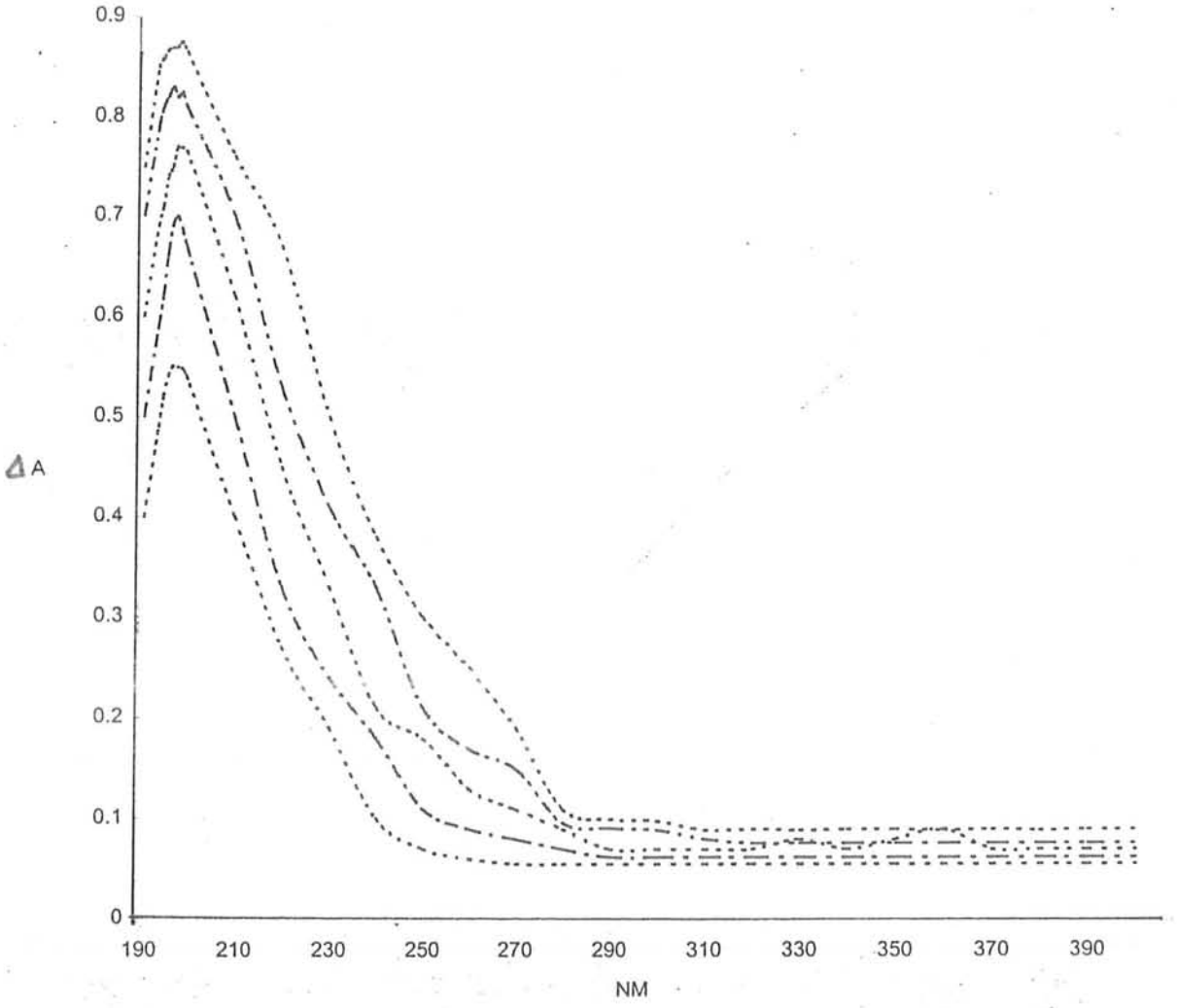
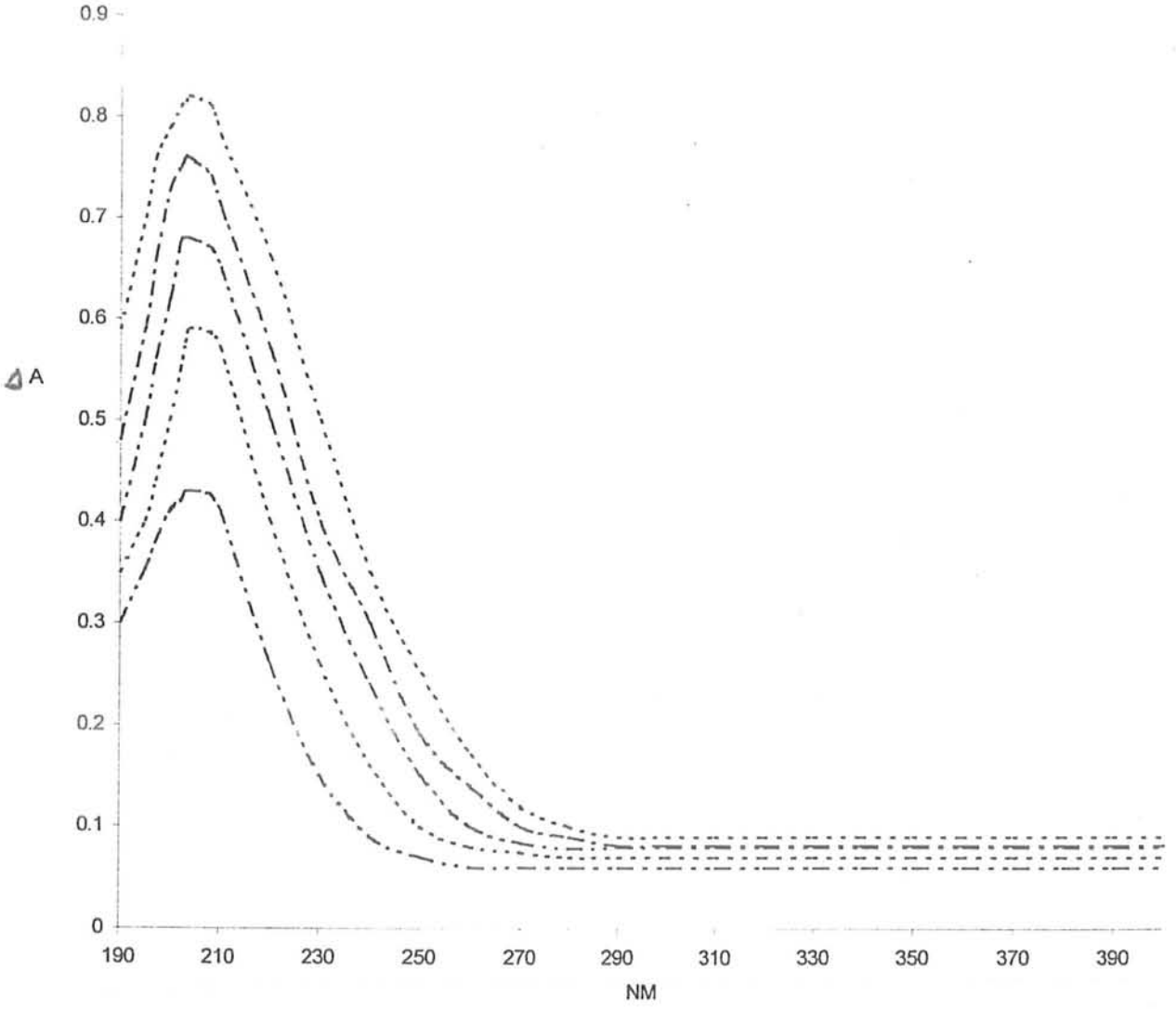


Fig. .Differential absorbance spectra of Ibuprofen in CTAB

1-15x10^{-4}M 2- 30x10^{-4}M 3- 40x10^{-4} M 4- 50x10^{-4}M 5- 60x10^{-4}M



Fig,. .Differential absorbance spcetra of Aspirin in CTAB

1-15x10^{-4}M 2- 30x10^{-4}M 3- 40x10^{-4} M 4- 50x10^{-4}M 5- 60x10^{-4}M

Conclusion

It is concluded that by conductometrically and spectroscopically partition coefficient in SDS for flurbiprofen is more than ibuprofen and ibuprofen has more than aspirin which indicate that flurbiprofen is more solubilized than ibuprofen and aspirin. The order of solubilization in SDS as

Flurbiprofen > Ibuprofen > Aspirin

In case of CTAB by conductometric and spectrometric methods, more partition coefficient of flurbiprofen, ibuprofen and aspirin as compared to SDS but order of solubilization is same as in SDS.

Flurbiprofen > Ibuprofen > Aspirin

The partition coefficient K_X, of solubilizate between bulk water and organic phase i.e. micellar phase is an important factor not only with solubilization point of view but also in understanding biological phenomenon i.e. interaction between biological membrane and drugs.

By conductometric and spectroscopic methods in SDS free energy of transfer for flurbiprofen is more negative than ibuprofen which intern more than aspirin. In CTAB, value of free energy of transfer is more and more negative as compared to SDS which indicate more solubilization and hence more stabilized system.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