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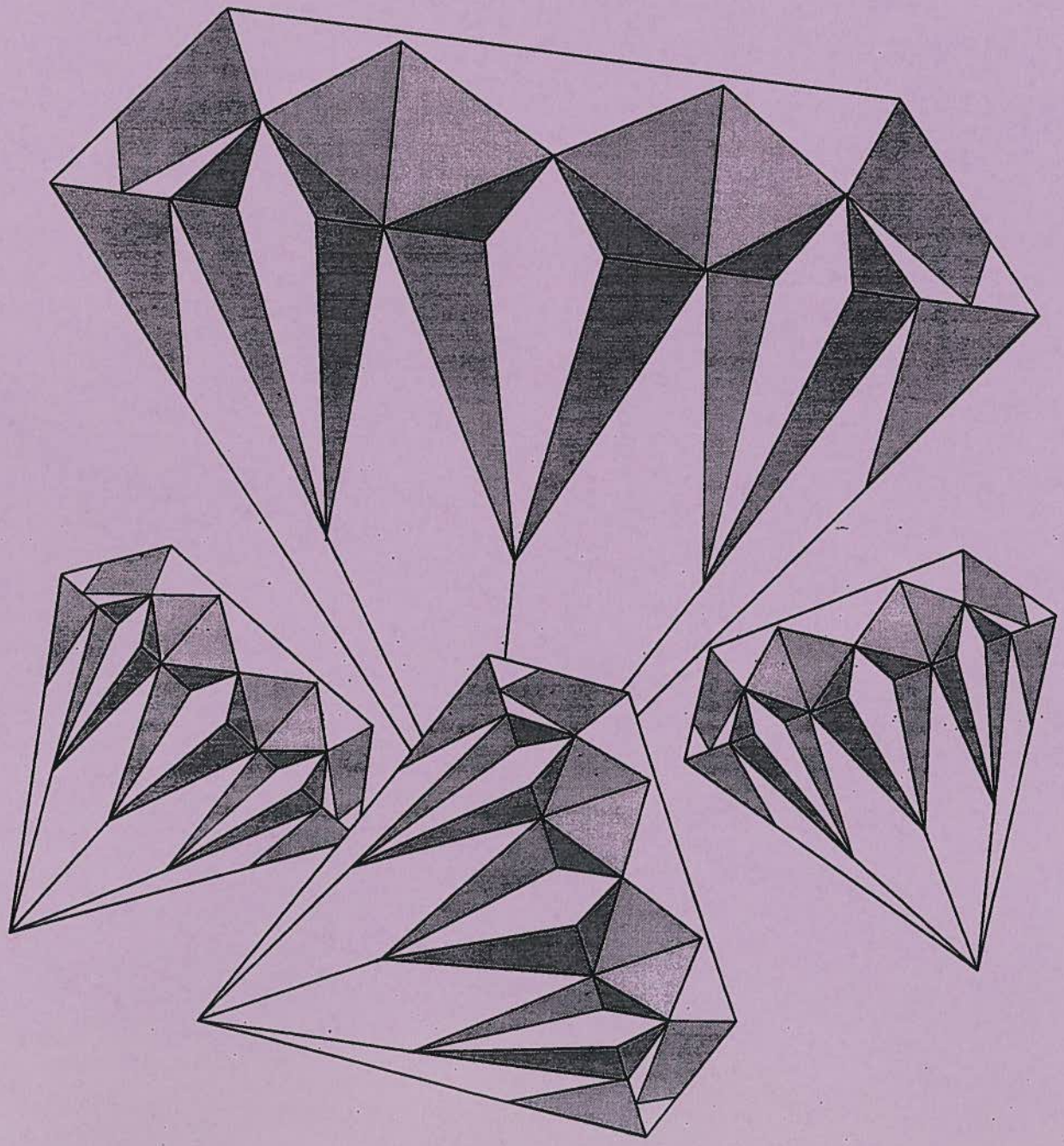

ISSN 0788-6004

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Julkaisija:
Fysikaalisen farmasian yhdistys r.y.

Tervehdys!

Fysikaalisen farmasian yhdistyksen vuosittainen symposium pidettiin tammikuussa Helsingissä. Paikalla oli lähes 100 kuulijaa ja posteriesittelyssä postereita 14. Kiitokset kaikille mukana-olleille!

Toivottavasti jokainen läsnäollut sai jotain uutta tietoa, jos ei nyt suoraan sovellettavaksi omaan työhönsä, niin ihmeteltäväksi työpaikan kahvipöytä-keskusteluihin. Luennoissa esitellyt menetelmät soveltuisivat hyvinkin monenlaisen tutkimuksen apuvälineiksi. Ehkä meidän tutkijoiden pitäisi vain useammin lähteä näistä omista ympyröistä katsastelemaan mitä muut puuhaavat ja osaavat, niin voisimme hyödyntää toistemme osaamista omissa tutkimuksissamme.

Seuraava Polymorfi ilmestyykin sitten syksyllä uuden hallituksen voimin. Olen lupautunut jatkamaan lehden toimittamista myös tulevan kauden, joten toivoisin syksyksi oikein reilua kirjoitusten satoa. Erilaiset fysikaaliseen farmasiaan liittyvät tutkimukset ja havainnot kiinnostavat yhdistyksen jäseniä ja jos joku lukijoista tekee kevään/kesän aikana mielenkiintoisia tutustumismatkoja farmasian alan kohteisiin, niin kirjoittakaa ja kertokaa kokemuksistanne meille muillekin tiedonjanoisille.

Aurinkoista kevättä kaikille!

Satu Åkerman
päätoimittaja

Puheenjohtajan palsta

Fysikaalisen farmasian yhdistystoimintaa 10 vuotta

Tänä vuonna tulee kuluneeksi 10 vuotta siitä, kun tieteellinen yhdistystoiminta fysikaalisen farmasian alalla käynnistettiin Suomessa. Yhdistyksen perustamiskokous pidettiin 18.11.1988 Turussa, ja perustajajäseninä olivat 8 alamme johtavaa tutkijaa ja vaikuttajaa: Eeva Kristoffersson, Liisa Turakka, Harry Jalonen, Paavo Kahela, Ensio Laine, Petteri Paronen, Juhani Posti ja Jouko Yliruusi. Heidän ansiostaan kiinnostus fysikaaliseen farmasiaan lisääntyi maamme yliopistoissa, tutkimus laitoksissa ja lääketeollisuudessa, ja yhdistyksen jäsenmäärä kasvoi jo yhdistyksen toiminnan alkuvaiheessa lähes nykyiselle tasolle. Fysikaalisen farmasian yhdistyksen hallitus on päättänyt huomionosoituksena yhdistyksen perustajajäseniä kohtaan esittää tulevassa juhlavuoden kokouksessa heidän nimeämistään yhdistyksen kunniajäseniksi.

Fysikaalisen farmasian yhdistys juhlistaa 10-vuotista taivaltaan kuluvana vuotena sekä vakiintunein että uusin toimintamuodoin. Hallituksen tekemän toimintasuunnitelmaesityksen mukaisesti yhdistys järjestää mm. esitelmätilaisuuksia, tukee alan perus- ja jatkokoulutusta, julkaisee omaa jäsentiedotetta (ja teemanumeroa) ja kehittää kansainvälisiä suhteita fysikaalisen farmasian alan tutkimuslaitoksiin. Yhdistys panostaa myös toimintavuoden keskeisen toimintatapahtuman eli Fysikaalisen farmasian X juhlasymposion järjestämiseen ja kiinnostavuuteen. Kaikessa juhlavuoden tapahtumiin liittyvässä ideoinnissa toivotaan jäsenkunnan aktiivista mukanaoloa ja vaikuttamista.

Nykyinen hallitus on hyvillä ja luottavaisin mielin jättämässä yhdistyksen luotsaamista uuden hallituksen "vankoille hartioille". Kuluneen toimintavuoden aikana paljon mielenkiintoisia yhdistyksen toimintaan liittyviä kehittämisajatuksia ja suunnitelmia tuli hallituksessa esille; suurin osa näistä ideoista toteutui, mutta osa jäi vielä hautumaan ja kypsymään myöhemmin toteutettaviksi. Tässä yhteydessä haluan kiittää kaikkia nykyisen hallituksen jäseniä, ja erityisesti sihteeri Sari Isokirmoa ja päätoimittaja Satu Åkermania, aktiivisuudesta ja luottamustehtävän ansiokkasta hoitamisesta.

Fysikaalisen farmasian yhdistyksen vuosikokous pidetään 26.3.1998 Kuopiossa ja toivotan kaikki yhdistyksen jäsenet lämpimästi tervetulleiksi mukaan kokoukseen ja sen jälkeen tutustumaan savolaiseen "sutjakkaan" elämänmenoon.

Jyrki Heinämäki
puheenjohtaja

STARCH DERIVATIVES AS NOVEL DIRECT COMPRESSION TABLET EXCIPIENTS WITH pH-DEPENDENT PROPERTIES

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Introduction

There is always an aspire to improve the properties of tablet formulations by developing new, better behaving pharmaceutical excipients or by modifying old excipients for new applications. Drug release from tablets is typically controlled by the aid of film coating. This procedure demands, however, lot of time and energy due to the several manufacturing steps. The coating can also break down, for example, during transportation, or it can contain drying induced cracks or even holes, which can cause unpredictable drug release. These disadvantages can be avoided by making the controlled release tablet utilizing direct compression technique.

During the last few years some studies on the suitability of pH-dependent controlled release materials for direct compression have been presented (Lin and Kao, 1990; Simon, 1994). The aim of this study was to clarify if the two examined starch derivatives, namely starch acetate and starch succinate, were useful in pH controlled tablet formulations made by direct compression. The goal was to retard the release of model drug, theophylline anhydrate, as much as possible in acidic conditions. The drug should, however, be released controlled at basic environment. Thus the optimum formulation would resemble the gastro-resistant or entero tablet formulation.

The effects of amount of starch succinate and theophylline anhydrate in starch acetate tablets as well as compression forces on drug release were evaluated. Breaking strength and disintegration time of the tablets were also tested in this study.

Materials and methods

Starch acetate (Degree of substitution, ds 2.9) (VTT Chemical Technology, Rajamäki, Finland) was used as a former of tablet matrix and starch succinate (ds 2.0) (VTT Chemical Technology, Rajamäki, Finland) functioned as a pH depended dissolution agent. In this evaluation theophylline anhydrate was chosen to be a model drug, due to its pH-independent solubility (Hussein and Friedman, 1990). Probable differences in drug release in different pH conditions are thus in consequence of the tablet formulation properties only.

Starch acetate tablet formulations were evaluated with starch succinate proportions of 5, 10 and 15 % (m/m) and with theophylline anhydrate proportions of 12.5 and 25 % (m/m).

Tablets were compressed with the instrumented eccentric tablet press (Korsch, EK-0, Berlin, Germany) using 10 mm flat faced punches at the compression speed of 30 rpm. Radial breaking strength of tablets was measured by CT5-loading equipment (Engineering Systems; Nottingham, England) and disintegration times were done according to the test of Ph. Eur. 2nd Ed., which is defined for gastro-resistant tablets. Drug release from tablets was evaluated with the rotating basket-method (Sotax AT6, Sotax AG, Basel, Switzerland) using USP phosphate buffer solutions pH 1 and 8 as dissolution medias.

Results and discussion

Tablet breaking strength

Measurements of tablet breaking strength showed that the starch acetate is capable to form strong matrix structures even with moderate compression forces (Figure 1). By increasing the compression force further the tablets became even stronger. The increase of proportion of starch succinate decreased slightly the breaking strength. That indicates incapability of starch succinate to form as strong bonds between particles as starch acetate does.

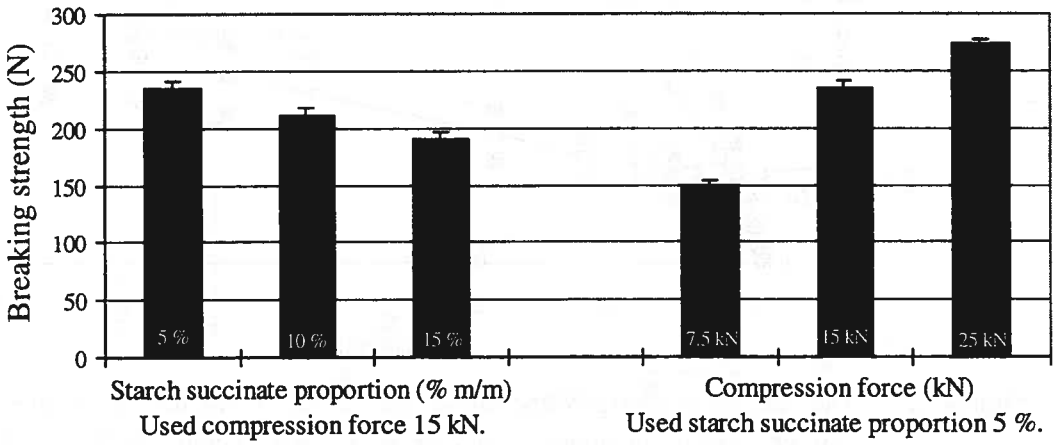

Figure 1. Effects of starch succinate proportion and compression force on the breaking strength of starch acetate tablets containing 25 % theophylline anhydrate (SD as bars; n = 6)

Tablet disintegration time

The disintegration test was carried out in a gastric fluid (pH 1.2) for two hours and after that the same tablets were transferred to a media whose pH was 6.8. All the tablets remained intact in acid conditions. In intestinal fluid tablets with 15 percent of starch succinate disintegrated within 15 minutes. When the tablet contained less than 15 % of pH controlling agent, disintegration took from 45 to 90 minutes. Differences in disintegration times are due to the greater amount of starch succinate which confirms its pH-dependent properties. Increase of starch succinate proportion also caused an increase in porosity of the tablets - porosities of starch succinate with proportions of 5 and 15 % (m/m) were 18.4 and 19.5 %,

respectively. That is another reason why tablet disintegrate faster with greater starch succinate proportions.

Drug release studies

Drug release studies showed that increase of starch succinate proportion accelerated drug release in both acid and basic environments (pH 1 and 8) (Figure 2). However, drug release rate was about seven times faster in basic media than in acid dissoluting media. The release of theophylline anhydrate in the acid media could not been prevented completely because drug particles on the tablet surface can be dissolved freely according to the intrinsic solubility of the drug to the dissoluting media without a control of matrix structure. This is due to the direct compression method which allows drug particles to exist uncovered on the tablet surface.

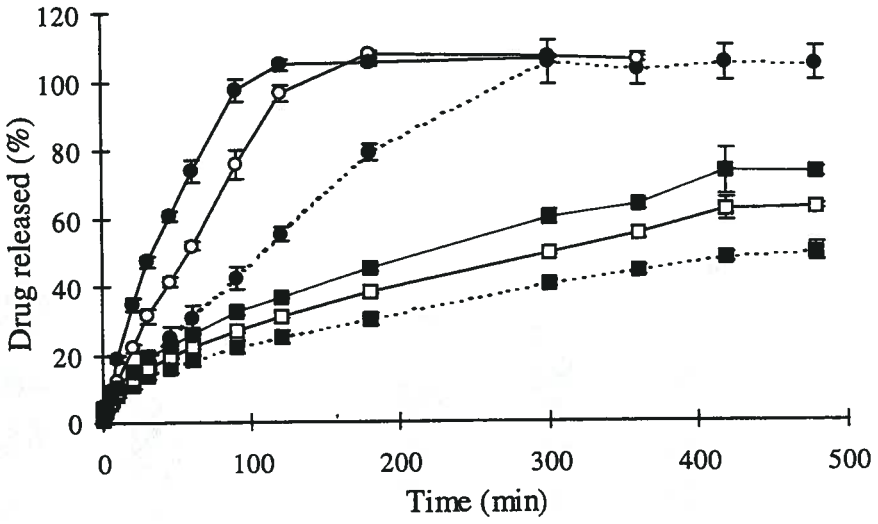

Figure 2. The release of theophylline anhydrate (25 %) from starch acetate tablets which contain starch succinate 5 % [pH 1 (...■...) and pH 8 (...●...)], 10 % [pH 1 (-□-) and pH 8 (-O-)] or 15 % [pH 1 (-■-) and pH 8 (-●-)]. Used compression force was 15 kN. (SD as bars; n = 3)

Increase of compression force retarded drug release in pH 1 but also in basic environment (Figure 3). By greater compression forces strong bonds between polymer and drug particles and intact matrix can be obtained. Thus dissoluting media can not penetrate as effectively through pores into the tablets. This results in retarded drug release. However, even if compression force greater than 15 kN was used the rate of drug release did not slow down essentially anymore. That was due to the block-like structure of tablet matrix which entirely formed already at about compression force of 15 kN. Release studies indicated also that due to the dissolution of drug particles on tablet surface compression force had no effect on drug release during the first 30 minutes of the test.

Drug release studies showed that proportion of theophylline anhydrate had no effect on the release rate on the examined compositions (12.5 % and 25 %) (Figure 4). That indicates intactiness of tablet structure which was independent of the studied amount of the drug.

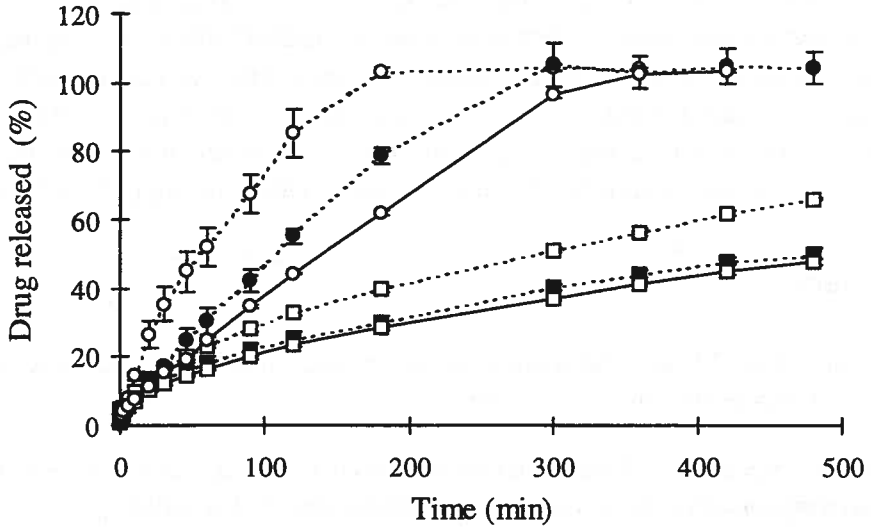

Figure 3. The release of theophylline anhydrate (25 %) from starch acetate tablets which contain 5 % of starch succinate. Tablets have been compressed using different forces: 7.5 kN [pH 1 (...□...) and pH 8 (...O...)], 15 kN [pH 1 (...■...) and pH 8 (...●...)] or 25 kN [pH 1 (-□-) and pH 8 (-O-)]. (SD as bars; n = 3)

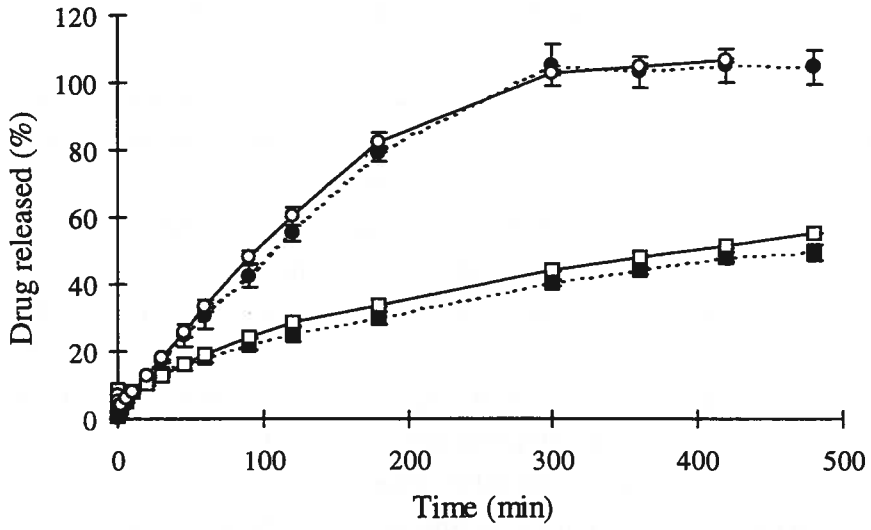

Figure 4. The release of theophylline anhydrate 12.5 % [pH 1 (-□-) and pH 8 (-O-)] or 25 % [pH 1 (...■...) and pH 8 (...●...)] from starch acetate tablets containing starch succinate 5,83 and 5 %, respectively. Used compression force was 15 kN. (SD as bars; n = 3)

Conclusion

Results pointed out that starch succinate behaved properly as a pH depended dissolution agent in direct compressed tablet formulation; drug release was accelerated when the environmental pH was above dissociation-pH of starch succinate (about pH 5.6) (Campbell,

1995). Due to the manufacturing method of tablets drug release could not been prevented completely at low pHs. Direct compression method allowed drug particles on the tablet surface to dissolve freely to the media. According to the results of this study using starch succinate / starch acetate tablet formulation there is possibility to reduce side effects caused by gastric mucosa irritating drugs. Addition of starch succinate into the starch acetate tablet gives us excellent possibilities to tailor the drug release through the whole GI-system.

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TOXICITY OF AMPHIPHILIC COMPOUNDS RESULTING FROM AMPHIPHILE-INDUCED CHANGES IN LIPID DOMAINS OF CELL MEMBRANES

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AMPHIPHILIC COMPOUNDS

The term amphipathy was first described by Hartley in 1936. Recently the term amphipathy has generally been replaced by the term amphiphilicity (Lichtenberg *et al.* 1983). Amphiphiles are molecules which contain a polar head and a hydrophobic tail. The hydrophobic regions usually consist of saturated or unsaturated hydrocarbon chains, or heterocyclic or aromatic rings. The hydrophilic moieties can be anionic, cationic or non-ionic (Florence and Attwood 1988). The hydrophobic portions are poorly soluble in water due to the 'hydrophobic effect'. Water forces hydrophobic groups together in order to minimize their disruptive effects on the hydrogen-bonded water network (Lichtenberg *et al.* 1983).

The most important amphiphilic compounds can be divided into four groups: synthetic surfactants, natural surfactants, membrane lipids and proteins. Synthetic surfactants are widely used in the study of biological membranes to solubilize membrane components. Products of cholesterol metabolism, bile salts and saponins, are the best known natural surfactants, and they have an important role in solubilizing lecithin and cholesterol from food. The amphiphilicity of these compounds is partly due to their stereochemistry (Jones and Chapman 1995).

The lipids of cell membranes can be divided as follows: phospholipids (the major structural components of cell membranes), sphingolipids, glycolipids and sterols (*e.g.* cholesterol). The phospholipids consist of long chain fatty acids in positions 1 and 2 of glycerol bridge and of polar head group in position 3 (New 1990). The amphiphilicity of proteins is related to the properties of amino acid residues forming the polypeptide chains. Amino acids in polypeptide chains may have polar or nonpolar side chains and these amphiphilic properties play an important role in the conformation and stability of the native state (Jones and Chapman 1995).

Many drugs are amphiphilic having surface active properties (*e.g.* phenothiazine tranquilizers, tricyclic antidepressants, antihistamines, local anesthetics, ß-blockers) (Florence and Attwood 1988; Joshi *et al.* 1988). Compared to typical surfactants, the hydrophobic part of these molecules is more complex containing aromatic or heterocyclic ring systems. In contrast to their diverse pharmacological actions, they have several physico-chemical similarities. A hydrophobic ring structure and a hydrophilic side chain

with charged cationic amine group in their molecular structures impart amphiphilicity to them, and these classes of drugs are often termed cationic amphiphilic drugs (Kodavanti and Mehendale 1990).

SURFACE ACTIVITY

Amphiphilic compounds have an affinity for both polar and non-polar solvents. In aqueous solutions, the amphiphiles are adsorbed at the air-water interfaces. The water molecules at the surface are replaced with non-polar groups leading to the contraction of the surface and to the decrease in surface tension. Many amphiphiles form aggregates, micelles, when the concentration is increased (the critical micelle concentration, cmc). (Florence and Attwood 1988). Several methods have been used to determine the cmc, *e.g.* surface tension, conductivity, dye solubilization, ultraviolet absorption, optical rotation and light scattering. The value of cmc can vary depending on the method used for determination (Lichtenberg *et al.* 1983). In theory, the micellization may lead to the changes in biological activity of the drugs. This may be due to the decreased transport rate or decreased ability to permeate biological membranes or to the reaction of aggregated species with other biological components (Attwood and Florence 1983).

Surface activity of the drug and its pharmacological activity only rarely correlate. Primary pharmacological actions of drugs are usually mediated via their specific binding to receptor proteins in membranes. Attwood and Agrawal (1979) showed a limited correlation between the surface activity of ß-blocking agents and their local anesthetic action. Some drugs, like anesthetics and tranquilizers, involve nonspecific binding to membrane lipids before eliciting their pharmacological actions (Seeman 1972). In contrast, surface activity of drugs correlates with their membrane damaging properties. Capability to cause epithelial damage to rabbit cornea was related to the surface activity of nonsteroidal anti-inflammatory drugs (Ellingson *et al.* 1992). Lee (1976) obtained a good correlation ($r = 0.89$) between the degree of hemolysis of human red cells and the surface tension of ellipticine solutions. However, low surface tension or high degree of hemolysis were not related to the antitumour potential of ellipticine. A positive correlation was found between the surface activity of tricyclic antidepressants (Yasuhara *et al.* 1979) and erythromycin derivatives (Dujovne 1978) and their capacity to induce cellular damage to liver cells. The ability of antiglaucoma drugs (timolol, betaxolol, dipivefrin and pilocarpine prodrugs) to lower the surface tension was correlating with the lipophilicity of the drugs (*i.e.*, octanol-water partition coefficient) (Saarinen-Savolainen *et al.* 1996). Surface activity may determine the extent of absorption onto cell membranes and membrane damage may be related to surface activity. Sometimes amphiphilic derivatives of drugs (*e.g.* palmitoyl prodrug of timolol) have been synthesized in order to improve their transport through biological membranes (Pech *et al.* 1993).

INTERACTIONS OF AMPHIPHILES WITH THE LIPID BILAYER

Biological membranes are complex lamellar structures consisting of insoluble amphiphiles, like phospholipids, neutral lipids (*e.g.* cholesterol) and membrane proteins. Lipids have many functions in cell membranes; they act as a binding surface for proteins; they separate two aqueous compartments and regulate the transfer of ions between these compartments; they provide a hydrophobic medium for processes requiring nonpolar environment and dissolve lipid-soluble molecules such as cofactors; and they modulate the function of membrane-bound enzymes (Lenaz 1979).

Biomembranes are exposed to a wide variety of small molecules which affect their structure and function (Jain and Wu 1977). Partition of amphiphilic compounds into the bilayer alters the fluidity of the membrane thereby disturbing the function of ion channels and other membrane-mediated processes. The region of the phase-transition temperature of lipids in membranes is sensitive to changes in drug uptake. Below the phase transition temperature (T_c) the fatty acid chains in phospholipids are packed together in an ordered, crystalline form; above T_c the chains become more disordered due to the movement of the chains at the higher temperature. The phase-transition temperature is characteristic for each fatty acid chain length and degree of saturation. Further, phospholipid head group and other membrane components, such as cholesterol and protein, may affect the phase-transition temperature (New 1990).

The interaction of amphiphilic compounds with lipid bilayers is dependent on the concentration of the solute amphiphile. At low concentrations the amphiphile is associated with the phospholipid bilayers without solubilizing the membranes. At high amphiphile concentrations the lamellar bilayer structures break down and mixed micelles of amphiphile and membrane components are formed. Mixed micelles are formed after lipid bilayers become saturated with the surfactant. The ratio of lipid to surfactant in bilayer must exceed a critical ratio until solubilization occurs. The disruption of the lamellar structures may involve various stages (Alonso *et al.* 1987; Elorza *et al.* 1997). The existence of pure surfactant micelles is not critical in formation of mixed micelles (Lichtenberg 1985).

Drugs that possess surface active properties in aqueous systems would be expected to behave like surfactants. However, very few drugs are able to solubilize membranes at the commonly used concentrations. Direct or indirect interaction of drugs with phospholipids may lead to several alterations in cellular structure and function which are often related to the manifestation of cytotoxicity.

Very high octanol/water partition coefficients (log P) of cationic amphiphilic drugs are indicative of a high solubility in biological membranes (Seeman 1972; Lüllmann and Wehling 1979). Hydrophobicity is known to be a major determinant of their binding to phospholipids (Lüllmann and Wehling 1979). Hydrophobic interactions involve van der Waal's forces which are known to increase in proportion to the molecular area available for the interaction (Arrowsmith *et al.* 1983). The cationic amphiphilic drugs interact electrostatically with the negatively charged phosphates of phospholipids which anchors

that part of the molecule in the polar head group region of the lipid bilayer. The depth of penetration into the bilayer depends on the length of the compound, which in part affects its effects on phase transition temperature (Borchardt *et al.* 1991). The incorporation of cationic amphiphilic drugs decrease the T_c of membrane lipids (Seeman 1972). The intensity of drug effects on transition temperature is concentration dependent and varies with the individual drugs. Binding of these drugs to the lipid bilayer is governed by two forces: the hydrophobic attraction and the electrostatic repulsion and the different potency of cationic amphiphilic drugs to depress the T_c is explained by the charge and the hydrophobicity of the drug molecules (Kursch *et al.* 1983). Binding of drugs with membranes is reversible depending on the ionic charge of the drug, hydrophobicity of the bilayer, partition coefficient, pH and pK_a of the amphiphile (Kodavanti and Mehendale 1990). Hydrophilic interactions of drugs are important with negatively charged phospholipids such as phosphatidylserine and gangliosides (Lüllmann and Wehling 1979).

Recent studies with nonsteroidal anticancer drugs (Custódio *et al.* 1993), calcium channel blockers (Mason and Trumbore 1996) and ß-blockers (Herbette *et al.* 1983) have demonstrated that lipid-mediated physical effects may play an important role in their nonspecific mechanisms of action. An important factor affecting the potency of nonspecific interactions is the localization of the drug in the lipid bilayer which in part is affected by the size, the shape and the lipophilicity of the drug molecule, and the charge carried by the drug (Mason and Trumbore 1996).

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VUOSIKOKOUSKUTSU

Fysikaalisen farmasian yhdistyksen sääntömääräinen vuosikokous pidetään torstaina 26. Päivänä maaliskuuta 1998 klo 16 alkaen Kuopiossa MedFiles Oy Ltd tiloissa, Sammonkatu 10 (p.017-2881200).

Vuosikokouksen esityslista:

1. Kokouksen avaus
2. Kokouksen puheenjohtajan ja sihteerin vaali
3. Kahden pöytäkirjan tarkastajan ja heidän varamiehiensä sekä kahden ääntenlaskijan vaali
4. Kokouksen laillisuuden ja päätösvaltaisuuden toteaminen
5. Hallituksen kertomus edelliseltä toimintavuodelta
7. Esitetään tilinpäätös, vuosikertomus ja tilintarkastajien lausunto
8. Päätetään tilinpäätöksen vahvistamisesta ja vastuuvapauden myöntämisestä hallitukselle ja muille tilivelvollisille
9. Vahvistetaan toimintasuunnitelma
10. Vahvistetaan tulo- ja menoarvio sekä jäsenmaksun ja kannattajajäsenmaksun suuruus
11. Valitaan uuden hallituksen puheenjohtaja ja sihteeri
12. Valitaan neljä hallituksen jäsentä sekä yksi varamies erovuoroisten tilalle
13. Valitaan kaksi tilintarkastajaa ja heille kaksi varamiestä
14. Kunniajäsenet
15. Muut asiat
16. Kokouksen päättäminen

Ennen vuosikokousta saamme tutustua MedFiles Oy:n tiloihin ja toimintaan klo 14.30
Vuosikokouksen jälkeen illallinen.
Vuosikokoukseen osallistuvia henkilöitä pyydetään ilmoittautumaan 19.3. 1998 mennessä Satu Åkermanille p. 017-162453, fax. 017-162456, email.Satu.Akerman@uku.fi tai Sari Isokirmolle p. 09-70859160, fax. 09-70859144 email. sari.isokirmo@helsinki.fi

TERVETULOA !
Hallitus

Sihteerin palsta

Jäsenasioita

Yhdistyksen uusiksi jäseniksi on hyväksytty Mika Aarnio Turusta, Elof Sacharias Ferm, Katja Koistinen, Niklas Laitinen, Juha Lappalainen ja Leena Petäjä Helsingistä, Juha Lappalainen Maskusta, Antti Laine, Satu Matilainen, Mirja Simonen ja Seppo Pohja Kuopiosta.

FYSIKAALISEN FARMASIAN YHDISTYS **Jäsenhakemus/ Henkilötietojen muutos**

Haluan liittyä Fysikaalisen farmasian yhdistyksen jäseneksi

Varsinaiseksi jäseneksi ☐
Opiskelijajäseneksi ☐

Henkilötietoni ovat muuttuneet ☐

Nimi _____
Oppiarvo _____
Tehtävänimike _____
Osoite (koti) _____
_____
Osoite (työ) _____
_____
Puhelin (koti) _____
Puhelin (työ) _____

Päiväys ja
allekirjoitus _____

Palautus osoitteella: Sari Isokirmo, Farmasian teknologian osasto, PL 56, 00014 Helsingin Yliopisto