Title: Enhancement of the Dissolution and Permeation Rates of Meloxicam by Formation of its Freeze-Dried Solid Dispersions in Polyvinylpyrrolidone K-30

Authors: M. El-Badry, M. Fathy

Source: *Drug Development and Industrial Pharmacy, 32, 141-150 (2006)*

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Freeze-drying (FD) and solvent evaporation (SE) were used to prepare solid dispersions (SDs) of meloxicam (MX) in polyvinylpyrrolidone K-30 (PVP). The SDs were prepared at different ratios, namely 1:1, 1:3, and 1:5 MX:PVP weight ratio. Differential scanning calorimetry (DSC), infrared absorption spectroscopy (IR), and x-ray powder diffractometry (XPD) were utilized to characterize the physicochemical properties of the SDs. Meloxicam (MX) in the solid dispersions appeared with less crystallinity form and was present in a complete amorphous form at higher PVP ratio. Dissolution rates of MX as a pure drug, physical mixtures (PMs), and SDs indicated a marked increase of the dissolution rate of MX in presence of PVP. The increase in the dissolution rate was dependent on the ratio of PVP and the method of preparation. In addition, the permeability of the drug through standard cellophone membrane and hairless mouse skin was also evasluated. The permeation rate of MX was significantly increased in the case of SDs and was dependent on the ratio of PVP. The results were primarily due to increase wettability, the solubilization of the drug by the carrier, and formation of MX amorphous form.

Title: Ca-alginate Beads Loaded With Meloxicam: Effect of Alginate Chemical Composition on the Properties of the Beads and Ulcerogenicity of the Drug

Authors: M. Fathy

Source: *J.* Drug Del. Sci. Tech., 16 (3), 183-189 (2006)

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Ca-alginate beads loaded with melocicam (MX) were produced by dripping dispersion of MX in sodium alginate solution into gently stirred CaCl2 solution. Alginates having different mannuronic-block to guluronic-block (MM/GG) ratios were utilized in bead preparation. The gelation of the beads continued for a long time and was dependent on the MM/GG ratio as well as the alginate fraction. Swelling and erosion of Ca-alginate beads were observed in phosphate buffer (pH 7.4). MX release in 0.1 N HCl was scarce while, in phosphate buffer (pH 7.4), the release was dependent on MM/GG ratio and drug content. With the increase in MM block fraction, the MX release increased. The release was consistent with the swelling of the beads and alginate release from the beads (erosion). Scanning electron microscopy (SEM) photographs showed that the prepared beads were nearly spherical in shape and small (about 1 mm diameter). The surface of the beads showed cracks and fissures. Differential scanning calorimetry (DSC) indicated that MX was present in the beads in crystalline form. The gastric mucosa of the rat administered free MX showed complete disappearance of mucosal surface with marked ulceration. On administration of the beads loaded

with MX, no ulceration or even inflammation was observed. In conclusion, alginate beads loaded with MX gave different patterns of release according to MM/GG ratio and MX:Alg ratio. Taking into account that MX is NSAIDs, variation in release pattern is important and could be used to protect the GIT from its side effects.

Title: Excellent Absorption Enhancing Characteristics of NO Donors for Improving the Intestinal Absorption of Poorly Absorbable Compound Compared with Conventional Absorption Enhancers

Authors: Gihan Fetih[1,2], Fawsia Habib[2], Hidemasa Katsumi[1], Naoki Okada[3], Takuya Fujita[1], Mohammed Attia[2], Akira Yamamoto[1]

Source: *Drug, Metab. Pharmacokinet., 21 (3), 222-229 (2006).*

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The characteristics of NO donors, NOC5 [3-(2-hydroxy-1-(1-methylethyl-2-nitrosohydrazino)1-propanamine), NOC12 [N-ethyl-2-(1-ethyl-2-hydroxy-2-nitrosohydrazino)-ethanamine] and SNAP [S-nitroso-N-acetyl-DL-penicillamine] as absorption enhancers for poorly absorbable drugs were examined in rats using an in situ closed loop method. They were compared with a group of conventional absorption enhancers including sodium glycocholate (NaGC), sodium caprate (NaCap), sodium salicylate (NaSal) and n-dodecyl-β-D-maltopyranoside (LM). 5(6)-carboxyfluorescein (CF) was used as a model drug to investigate effectiveness, site-dependency, and concentration-dependency of the tested enhancers. Overall, the NO donors can improve the intestinal absorption of CF at

low concentration (5 mM), whereas higher concentration was required for the conventional absorption enhancers to elicit the absorption enhancing effect. In the small intestine, SNAP was the most effective absorption enhancers, although its concentration (5 mM) was lower than the conventional absorption enhancers (20 mM). On the other hand, LM and NaCap as well as the three NO donors were effective to improve the colonic absorption of CF. In the regional difference in the absorption enhancing effects, the NO donors showed significant effects in all intestinal regions, whereas we observed a regional difference in the absorption enhancing effect of the other conventional absorption enhancers. In the conventional enhancers, the absorption enhancing effects were generally greater in the large intestine than those in the small intestine. LM and NaCap were ineffective in the jejunum, although they were effective for improving the absorption of CF in the colon. NaSal was ineffective in both the jejunum and the colon. The absorption enhancement produced by NO donors was greatly affected by increasing the enhancer concentration from 3 to 5 mM, but only a slight increase was obtained when the concentration was raised to 10 mM. Similar results were obtained for the other enhancers over the range of 10 to 20 mM, but the absorption enhancing effects of these enhancers were almost saturated above these concentrations. These results suggest that NO donors possess excellent effectiveness as absorption enhancers for poorly absorbable drugs compared with the conventional enhancers. They can enhance intestinal absorption of CF from all intestinal regions and they are effective at very low concentrations.

Title: Colon-Specific Delivery and Enhanced Colonic Absorption of [Asu[1,7]]-eel Calcitonin using Chitosan Capsules Containing Various Additives in Rats

Authors: Gihan Fetih[1,2], Fawsia Habib[2], Naoki Okada[1], Takuya Fujita[1], Mohammed Attia[2], Akira Yamamoto[1]

Source: *Journal of Drug Targeting,14(3), (2006)*

Address: [1]Department of Biopharmaceutics, Kyoto Pharmaceutical University, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan [2]Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt

The objective of this study was to estimate the colon-specific delivery of [Asu[1,7]]-eel calcitonin (ECT) using chitosan capsules in rats. The intestinal absorption of ECT was evaluated by measuring the plasma calcium levels after oral administration of the chitosan capsules containing ECT and different combinations of additives. The same combinations were investigated by an in situ absorption experiment prior to in vivo administration of capsules. A marked decrease in plasma calcium levels was observed following the oral administration of chitosan capsules containing ECT, S-nitroso-N-acetyl-DL-penicilIamine (SNAP), sodium glycocholate, bacitracin and aprotinin (pharmacological availability (PA)% = 6.344%), as compared with capsules containing only ECT (PA% = 0.551%) or capsules containing ECT with SNAP only (PA% = 1.651 %). The hypocalcemic effect started 6-8 h after oral administration of capsules and sustained for 24 h. These findings suggest that colon-specific delivery of ECT can be achieved using chitosan capsules and these additives may be useful for

improving the colonic absorption of ECT in rats.

Title: Physicochemical Characterization of Ibuprofen/ Hypromellose Acetate Succinate Solid Dispersions

Authors: Mohamed Fathy

Source: *MJPS, 22 (2), 224-237 (2006)*

Address: Department of Pharmaceutics, Faculty of Pharmacy, Assiut University 71526, Assiut, Egypt

The main purpose of this investigation was to evaluate hypromellose acetate succinate (HPMCAS), a cellulosic enteric coating agent, as a carrier in a solid dispersion (SD) of ibuprofen (IBN). Solid dispersions of IBN were prepared by solvent evaporation at different polymer: drug weight ratios; 1:1, 1:3, 1:5, 1:10. The drug-carrier interactions in the solid state were investigated using scanning electron microscopy (SEM), infrared spectroscopy (IR), differential scanning calorimetry (DSC), and X-ray powder diffraction analysis (XRPD). No important and well-defined chemical interaction was found between the drug and the polymer at various ratios indicating compatibility between the drug and the polymer. The solubility of IBN was not affected by the presence of the polymer. The in vitro release study was performed in 0.1 N HCl and phosphate buffer pH 7.4. The presence of IBN in the form of solid dispersion displayed slower release than that of physical mixture or pure drug. However, the SD showed high release rate, in phosphate buffer pH 7.4, particularly with high content of drug. The kinetic of drug release from SD was influenced by the dissolution medium and polymer concentration. The results indicated that, HPMCAS could be used as an enteric carrier for ibuprofen.

Title: Interaction of Tiaramide Hydrochloride with Amberlite Resins: Characterization of the Interaction and Modulation of the Release Through Microencapsulation of the Prepared Resinates

Authors: Mohamed Fathy

Source: *Bull. Pharm. Sci., Assiut University, 29 (1), 111-126 (2006)*

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Tiaramide HCl (TAM), a basic NSAID, has high water solubility and short biological half life. The study was undertaken to prolong TAM's activity. TAM resinates were prepared by a batch process and using two resins, namely Amberlite IRP-69 (RI) and Amberlite MB-1 (RII). The resinates (RI/TAM & RII/TAM) were examined by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), infrared spectrometry (IR) and scanning electron microscopy (SEM). A modified emulsion solvent evaporation method was used to produce TAM-resinates coated with cellulose acetate butyrate (CAB) for more drug retardation. The microcapsules were examined using SEM. The results from DSC and XRD showed that the molecular state of the drug in the resinates changed to become amorphous instead of its original crystalline form. The IR spectroscopy revealed the presence of an interaction between the drug and resin. The dissolution behavior for the resinates in 0.1 N HCl or phosphate buffer (pH 7.4) was compared. TAM release was affected by the dissolution medium and resin type and was slower than that from drug powder or physical mixture. TAM release from microcapsules was slower than the uncoated resinates. Additionally, the anti-inflammatory activity, using carrageenan–induced rat hind paw edema, displayed prolonged pattern in comparison with uncoated resinate or free drug.

Title: Interaction of Rofecoxib With β-Cyclo-Dextrin and HP-β-Cyclodextrin in Aquoues Solution and in Solid State

Authors: A. E. Abou-Taleb, A. A. Abdel-Rhman, E. M. Samy, H. M. Tawfeek

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 236-252 (2006)*

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The interaction between rofecoxib (ROF), an analgesic anti-inflammatory drug, with β-cyclodextrin and HP-β-cyclodextrin was evaluated in aqueous environment and in solid state. The solubility of ROF with β-CyD and HP-β-CyD in aqueous solution was determined and the stability constants were calculated from the phase solubility studies at different temperatures. Binary systems of ROF with the investigated CyDs were prepared by co-grinding and solvent evaporation methods. The formation of inclusion complexes with β-CyD and HP-β-CyD in the solid state was investigated by differential scanning calorimetery, infrared spectroscopy and X-ray diffractometry. Dissolution rate of ROF binary systems was determined and compared with those of the physical mixture and the pure drug. It was found that the solubility of ROF increased as a function of both CyDs concentration and temperature showing an A_L- type diagram indicating the formation of 1: 1 stoichiometric inclusion complexes. The apparent association constants were found to be 104.45 M^{-1} and 121.65 M^{-1} for β-CyD and HP-β-CyD; respectively. Co-grinding method led to enhancement of ROF dissolution rate in comparison to the other preparation methods. The in vitro dissolution rate of ROF at pH 7.4 could be ranked in the following order: ground mixture, coevaporate, physical mixture and pure drug. Ground mixture of ROF with HP- β-CyD and β-CyD has a $t_{50\%}$ = 7 min and 50 min, respectively.

Title: Helicobacter Pylori Extract Induces Nuclear Factor-Kappa B, Activator Protein-1, and Cyclooxygenase-2 in Esophageal Epithelial Cells

Authors: Mohamed M.M. Abdel-Latif[1], Henry Windle[2], Ana Terres[2], Déirdre Ni Eidbin[2], Dermot Kelleber[2], John V. Reynolds[1]

Source: *J. Gastrointest Surg., 10, 551-562 (2006)*

Address: [1]Department of Surgery and Clinical Medicine and [2]Dublin Molecular Medicine Center, Trinity Centre for Health Sciences, St. James's Hospital, Dublin, Ireland

Helicobacter pylori infection is recognized as the major cause of gastritis and gastric cancer; however, its role in the development of gastroesophageal reflux disease and Barrett's adenocarcinoma is unclear. The expression of NF-κB, AP-1, and COX-2 may be important in inflammation and tumorigenesis in the esophagus. The aim of this study was to examine the effect of live H pylori or H pylori extract (HPE) on these factors in the esophageal epithelial cell lines SKGT-4 and OE33. NF-κB and AP-1 activity were assessed by gel shift assay and COX-2 by western blotting. Coculture of SKGT-4 and OE33 with live H pylori and HPE induced NF-κB and AP-1 DNA-binding activity, and also decreased IκB-α levels. Treatment with the specific MEK1/2 MAPK inhibitor PD98059, but not the p38 MAPK inhibitor SB203580, inhibited NF-κB and AP-1 activity. The antioxidant vitamin C inhibited H pylori-induced NF-κB activation, but increased AP-1 expression. Moreover, HPE induced COX-2 expression and IL-8

production, and PD98059 inhibited COX-2 expression, ERK1/2 phosphorylation, and IL-8 production. These data demonstrate that both live H pylori and HPE induce NF-κB and AP-1 expression in esophageal epithelial cells. The induction of such transcription factors may play a role in the specific immune response within Barrett's mucosa and may indirectly cause inflammation of the gastric cardia and the distal esophagus.

Title: Ursodeoxycholic Acid Inhibits Interleukin Beta 1 and Deoxycholic Acid-Induced Activation of NF-$_k$B and AP-1 in Human Colon Cancer Cells

Authors: Syed A. Shah, Yuri Volkov, Qamrul Arfin, Mohamed M. Abdel-Latif, Dermot Kelleher

Source: *Int. J. Cancer, 118,532-539 (2006)*

Address: Department of Clinical Medicine and Dublin Molecular Medicine Centre, Trinity Centre for Health Sciences, St. James's Hospital, Dublin, Ireland

Deoxycholic acid (DCA) has been implicated in colorectal carcinogenesis in humans with effects on proliferation and apoptosis, mediated at least in part by activation of transcription factors nuclear factor kappa B (NF-κB), activator protein 1 (AP-1) and protein kinase C (PKC) enzymes. Ursodeoxycholic acid (UDCA) is reported to reduce the frequency of colonic carcinogenesis in ulcerative colitis patients. Hence, we postulated that it might differ from DCA in its regulation of these transcription factors. The aim of the study was to determine effects of DCA and UDCA on NF-κB and AP-1 activation and explore its relationship to PKC. Human colonic tumour cell lines HCT116 were treated with DCA, UDCA, alone or pretreated with UDCA followed by DCA or IL-1β. In other experiments, cells were pretreated with PKC inhibitors and then stimulated with DCA and IL-1β or PMA. Gel shift assays were performed in nuclear extracts of the cells for NF-κB and AP-1 analysis. Western blot analyses and immunofluorescence were performed for Rel A (p65) and IκB-α levels on the

treated cells. DCA increased NF-κB and AP-1 DNA binding. UDCA did not increase DNA binding of NF-κB and AP-1 and UDCA pretreatment inhibited DCA-induced NF-κB and AP-1 DNA binding. PKC inhibitors blocked DCA-induced NF-κB and AP-1 activation. These results were validated by Western blot analysis for RelA and IκB-α. In conclusion, UDCA did not induce NF-κB and AP-1 DNA binding but also blocked DCA-induced NF-κB and AP-1 activation. These findings suggest a possible mechanistic role for UDCA in blocking pathways thought to be involved in colon carcinogenesis.

Title: Low pH Induces Co-ordinate Regulation of Gene Expression in Oesophageal Cells

Authors: Shane P.Duggan[1], William M.Gallagher[3], Edward J.P.Fox[3], Mohammed M.Abdel-Latif[1,2], John V.Reynolds[2], Dermot Kelleher[1]

Source: *Carcinogenesis, 27 (2), 319-327 (2006)*

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The development of gastro-oesophageal reflux disease (GORD) is known to be a causative risk factor in the evolution of adenocarcinoma of the oesophagus. The major component of this reflux is gastric acid. However, the impact of low pH on gene expression has not been extensively studied in oesophageal cells. This study utilizes a transcriptomic and bioinformatic approach to assess regulation of gene expression in response to low pH. In more detail, oesophageal adenocarcinoma cell lines were exposed to a range of pH environments. Affymetrix microarrays were used for gene-expression analysis and results were validated using cycle limitation and real-time RT-PCR analysis, as well as northern and western blotting. Comparative promoter transcription factor binding site (TFBS) analysis (MatInspector) of hierarchically clustered gene-expression data was employed to identify the elements which may co-ordinately regulate individual gene clusters. Initial experiments demonstrated maximal

induction of EGRl gene expression at pH 6.5. Subsequent array experimentation revealed significant induction of gene expression from such functional categories as DNA damage response (EGRl-4, ATF3) and cell-cycle control (GADD34, GADD45, p57). Changes in expression of EGRl, EGR3, ATF3, MKP-l, FOSB, CTGF and CYR61 were verified in separate experiments and in a variety of oesophageal cell lines. TFBS analysis of promoters identified transcription factors that may co-ordinately regulate gene-expression clusters, Cluster I: Oct-I, AP4R; Cluster 2: NF-kB, EGRF; Cluster 3: IKRS, AP-IF. Low pH has the ability to induce genes and pathways which can provide an environment suitable for the progression of malignancy. Further functional analysis of the genes and clusters identified in this low pH study is likely to lead to new insights into the pathogenesis and therapeutics of GORD and oesophageal cancer.

Title: Phenylpropanoid and Phenylethanoid Derivatives from *Kigelia pinnata* DC. Fruits

Authors: Yaser G. Gouda[1], Afaf M. Abdel-Baky[1], Khaled M. Mohamed[1], Faten M. Darwish[1], Ryoji Kasai[2], Kazuo Yamasaki[2]

Source: *Natural Product Research, 20 (10), 935-939 (2006)*

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Further phytochemical investigation of the fruits of Kigelia Pinnata DC has yielded a new phenylpropanoid derivative identified as 6-p-coumaroyl-sucrose (1) together with ten known phenylpropanoid and phenylethanoid derivatives (2-11) and a flavonoid glycoside (12). The structures of the isolated compounds were elucidated using various techniques of NMR and MS spectral analysis.

Title: Phenolics of *Cyperus alopecuroides* Rottb. Inflorescences and Their Biological Activities

Authors: H. M. Sayed[1], M. H. Mohamed[2], S. F. Farag[1], G. A. Mohamed[2], R. Ebel[3], O. R. M. Omobuwajo[4], P.Proksch[3]

Source: *Bull. Pharm. Sci., Assiut University, 29 (1), 9-32 (2006)*

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*Sixteen phenolic compounds, scopoletin (**1**), isoliquiritigenin 4′-methyl ether (**2**), luteolin 5,3′-dimethyl ether (**3**), luteolin 7,3′-dimethyl ether (**4**), aureusidin 4-methyl ether (**5**), apigenin (**6**), luteolin (**7**), trans-ferulic acid (**8**), luteolin 4′-O-β-D-gluco-pyranoside (**9**), luteolin 7-O-β-D-glucopyranoside (**10**), quercetin 3-O-β-D-glucopyranoside (**11**), apigenin 7-O-neohesperidoside (**12**), kaempferol 3-O-rutinoside (**13**), quercetin 3-O-rutinoside (**14**), kaempferol 3-O-[2-O-D-xylopyranosyl-6-O-α-L-rhamno-pyranosyl]-β-D-glucopyranoside (**15**) and kaempferol 3-O-[2-O-D-glucopyranosyl-6-O-α-L-rhamnopyranosyl]-β-D-gluco-pyranoside (**16**) were isolated from the methanolic extract of the inflorescences of Cyperus alopecuroides Rottb. for the first time. Their structures have been*

established on the basis of physical, chemical and spectroscopic methods in addition to comparison with literature data and/or authentic samples. The antioxidant and cytotoxic activities in addition to α-amylase inhibitory activity of the isolated compounds have been studied.

Title: A New Flavonol Glycoside from *Polygonum bellardii* ALL. Growing in Egypt

Authors: M. H. Mohamed[1], Z. Z. Ibraheim[2], A. M. A. Abd El-Mawla[2], A. M. Abd El-Kader[1]

Source: *Bull. Pharm. Sci., Assiut University, 29 (1), 203-213 (2006)*

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A new flavonol glycoside named myricetin-3-O-(5''-acetyl α-arabinofuranoside) has been isolated from Polygonum bellardii All. F. Polygonaceae growing in Egypt, together with quercetin-3-O-(5''-acetyl α-arabinofuranoside), quercetin-3-O-rutinoside (rutin), α-amyrin, β-sitosterol and β-sitosterol-3-O-β-glucoside. Their structures were elucidated using different spectral techniques.

Title: Phytochemical and Biological Study of *Grevillea robusta* A. Cunn Cultivated in Egypt

Authors: Amany Sayed Ahmed

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 272-288 (2006)*

Address: Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut, Egypt

The alcoholic extracts of the leaves and bark of Grevillea robusta A.Cunn cultivated in Egypt were subjected to preliminary anti-inflammatory screening. The results showed that, the alcoholic extracts showed a significant anti-inflammatory activity using carrageenan-induced edema. The alcoholic and aqueous extracts of the bark were tested as anti-HIV-1 protease, where they showed a moderate HIV-1 protease (1 PR) inhibitory activity at conc. 200 µg/ml. The ethyl acetate fraction of the bark showed a significant HIV-RT inhibitory activity, the n-butanol fraction showed a moderate activity, while the chloroform fraction showed no activity at conc. 200 µg/ml. On the other hand the chloroform and ethyl acetate fractions of the fruit showed a weak HIV-RT inhibitory activity. From the chloroform-soluble fraction of the total alcohol extract of the bark 2,6-dimethoxy-1,4-benzoquinone, β-sitosterol, 4-(1-hydroxy ethyl) anisol, robustol and β-sitosterol glucoside were isolated. Four phenolic glycosides were isolated from the n-butanol-soluble fraction of the bark and identified as arbutin, arbutin 2'-O-β-apiofuranoside, 4-hydroxyphenethyl alcohol 8-O-β-apiofuranosyl(1''→2')- β-glucopyranoside and 4-O-trans-p-coumaroyl{β-glucopyranoside}8-O-β-apiofuranosyl-(1''→6')}-O-β-glucopyranosyl. The identification of the isolated compounds was carried out using different methods including physical, chemical and spectral analysis.

Title: Macro- and Micromorphology of *Sanchezia nobilis* Hook. Cultivated In Egypt: Leaf, Stem and Flower

Authors: Ahmed E. Abd-Ellah[1], Khaled M. Mohamed[2], Enaam Y. Backheet[2], Mahmoud H. Mohamed[1]

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 300-327 (2006)*

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The detailed macro- and micromorphological characters of the leaf stem and flower of Sanchezia nobilis Hook. were studied with the aim to find out the diagnostic elements of these organs, which facilitate their identification in both entire and powdered forms.

Title: Phytochemical and Biological Studies of *Emex spinosa* (L.) Campd. Growing in Egypt

Authors: A. M. Abd El-Kader[1], A. M. A. Abd El-Mawla[2*], M. H. Mohamed[1], Z. Z. Ibraheim[2]

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 328-347(2006)*

Address: [1]Department of Pharmacognosy, Faculty of Pharmacy, Al-Azhar University, Assiut 71524, Egypt and [2]Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt

Thirteen compounds; α-amyrin, β-sitosterol, chrysophanol, physcion, aloe-emodin, 6´-O-palmitoyl-3-O-β-sitosterol glucoside, β-sitosterol-3-O-β-glucoside, aloe-emodin-8-O-β-glucoside, emodin-8-O-β-glucoside, torachryson-8-O-β-glucoside, caffoeyl-9-O-β-glucoside, kaempferol-3-O-rutinoside and quercetin-3-O-rutinoside (rutin) were isolated from the aerial parts of Emex spinosa (L.) Campd. growing in Egypt. Their structures were elucidated using different spectral techniques. The LD_{50} of various plant extracts were determined. Preliminary biological studies of different extracts revealed that the ethyl acetate extract was the most effective as antibacterial, ethyl acetate and chloroform extracts gave potent anti-inflammatory effects; whereas both ethyl acetate and total alcohol extracts exhibited analgesic activities. The best extracts that gave antipyretic activity were ethyl acetate and total alcohol extracts.

Title: Phytochemical and Biological Investigations of *Flacourtia cataphracta* Roxb. Cultivated in Egypt

Authors: Hanaa M. Sayed[1], Mahmoud H. Mohamed[2], Faten M. Darwish[1], Ahmed M. Mohamed[2]

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 371-387 (2006)*

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The concentrated 70% ethanolic extracts of the air-dried powdered leaves and stem bark of Flacourtia cataphracta were subjected separately to solvent fractionation by partitioning using n-hexane, chloroform and ethyl acetate respectively. Each concentrated fraction was subjected to TLC followed by isolation, purification and identification of the available constituents.

Fourteen compounds were isolated and identified by different spectral tools (UV, IR, ^{1}H-NMR, ^{13}C-NMR, MS) and comparison with corresponding literature data. β*-amyrin (**1**),* α*-amyrin (**2**), and a mixture of* β*-sitosterol and stigmasterol (**3**) were isolated from n-hexane fraction of both leaves and stem bark. 2-Oxo-18-benzolyloxy-13(16), 14-tetrahydrocleroda-3-ene (**4**), 3-*β*-acetoxy-D:A friedo oleanan-27,16*α*-lactone (**5**), 4,4'-dihydroxychalcone (**6**), apigenin (**7**) and kampferol (**8**) were isolated from chloroform fraction of the stem bark.* β*-Sitosterol-3-O-*β*-D-glucoside (**9**), 5-O-caffeoylquinic acid (**10**) were isolated from the ethyl acetate fraction of the leaves in addition to vanillin (**11**), benzoic acid (**12**), protocatechuic acid (**13**) and flacourtin (**14**) from the ethyl acetate fraction*

of the stem bark. The different leaf extracts were subjected to biological study which revealed that n-hexane, ethyl acetate and methanol fractions of Flacourtia cataphracta Roxb. are safe to be used as antidiarrheal, anti-inflammatory and antipyretic drug.

Title: Macro- and Micromorphology of the Leaf, Stem and Inflorescence of *Cassia bicapsularis* L. Cultivated in Egypt

Authors: M. A. Makboul, M. A. Abd El-Hafiz, E. K. Desoky, I. A. Mahmoud

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 446-487 (2006)*

Address: Department of Pharmacognosy, Faculty of Pharmacy, Assiut University, Assiut, Egypt

The macro- and micromorphology of the leaf, stem and inflorescence of Cassia bicapsularis L. family Fabaceae, cultivated in Egypt have been studied in order to determine the diagnostic features which can help in the identification of the plant in both entire and powdered forms.

Title: Novel 5-(2-Hydroxyphenyl)-3-Subastituted-2,3-Dihydro-1,3,4-Oxadiazole-2-Thione Derivatives: Promising Anticancer Agents

Authors: Ahmed S. Aboraia, Hamdy M. Abdel-Rahman, Nadia M. Mahfouz, Mahmoud A. EL-Gendy

Source: *Bioorganic & Medicinal Chemistry, 14, 1236-1246 (2006)*

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A series of 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives was synthesized and 13 of them were selected by the National Cancer Institute (NCI) and evaluated for their in vitro anticancer activity. Seven of the investigated compounds, ***3i, 3j, 3k, 3o, 3p, 3q*** *and* ***3r*** *displayed high anticancer activity in the primary assay. These compounds have been selected for a full anticancer screening against a 60-cell panel assay where they showed non-selective broad spectrum and prmising activity against all cancer cell lines. Compounds* ***3j*** *and* ***3k*** *proved to be the active members in this study compared to 5-flurouracil and cyclophosphamide as reference drugs, respectively. Compounds* ***3j*** *and* ***3k*** *were identified as promising lead compounds.*

Title: Synthesis of 5-Phenyl-1-(3-Pyridyl)-1H-1,2,4-Triazole-3-Carboxylic Acid Derivatives of Potential Anti-Inflammatory Activity

Authors: Safwat M. Rabea, Nawal A. El-Koussi, Hoda Y. Hassan, Tarek Aboul-Fadl

Source: *Arch. Pharm. Chem. Life Sci., 339, 32-40 (2006)*

Address: Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Assiut Uniuversity, Assiut, Egypt

A series of 5-phenyl-1-(3-pyridyl)-1H-1,2,4-triazole-3-carboxylic acid derivatives 4-10 were synthesized by rearrangement of 4-(3-pyridyl)-hydrazono-2-phenyl-2-oxazolin-5-one 3 in the presence of different nucleophiles to afford derivatives 4, 7 and 8, while hydroxamic acid derivative 6 was prepared from reaction of methyl ester 4 with hydroxylamine hydrochloride. Semicarbazide 9 and thiosemicarbazide 10, derivatives of the 5-Phenyl-1-(3-pyridyl)-1H-1,2,4-Trizole-3-carboxylic Acid, were synthesized via hydrazide 8 with potassium cyanate and appropriate isothiocyanate, respectively. The structures of the synthesized compounds were confirmed by elemental analyses, IR, ^{1}H-NMR, and mass spectra. The results of the anti-inflammatory activity of the synthesized derivatives showed that most of the tested compounds 4-10 showed significant inhibition against carrageenan-induced rat paw edema in albino rats. Dervatives 4 and 8 showed promising results and were found to be equipotent or more potent than Indomethacin and Celecoxib as reference drugs at two dose levels, 5 and 10 mg/kg, and they have no ulcerogenic activity.

Title: Synthesis and Biological Evaluation of Some Hydroxypyrazole Derivatives as Anti-inflammatory-Antimicrobial Agents

Authors: Adnan A. Bekhit[1], Hamdy M. Abdel-Rahman[2], Aida A.Guemei[3]

Source: *Arch. Pharm. Chem. Life Sci., 339, 81-87 (2006)*

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Some hydroxypyrazole derivatives 2-7 were synthesized by cyclocondensation of the keto-ester 1 with hydarzines hydrate or substituted hydrazines followed by reduction and acylation with acetic anhydride or trifluoroacetic anhydride. The newly synthesized compounds were evaluated for their anti-inflammatory, antimicrobial activities. In addition, the ulcerogenic and acute toxicity profiles were determined. Compounds N-(4-(5-hydroxy-1-trifluoroacetyl-1H-pyrazol-3-yl)phenyl) trifluoroacetamide 4b, 3-(4-nitrophenyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-ol 5b, and N-(4-(5-hydroxy-1-methyl-1H-pyrazol-3-yl)phenyl) trifluoroacetamide 7b were proved to be the most active anti-inflammatory, antimicrobial agents in the present study with a good safety margin and minimal or no ulcerogenic effect.

Title: Synthesis of β-Hydroxypropanoic Acid Derivatives as Potential Anti-Inflammatory, Analgesic and Antimicrobial Agents

Authors: Hamdy M. Abdel-Rahman[1], Mostafa A. Hussein[2]

Source: *Arch. Pharm. Chem. Life Sci., 339, 378-387 (2006)*

Address: [1]Department of Pharmaceutical Medicinal Chemistry and [2]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut, Egypt

A series of new 3-(substituted) 3-hydroxy-propanoic acid ethyl esters 1a-c, hydrazides 2a-c, thiosemicarbazides 3a-f, and semicarbazides 3g, 3h has been synthesized. Cyclization of compounds 3a-d in basic mediun Yielded 1,2,4-triazole-5-thiones 4a-d. On the other hand, reaction of hydrazides 2a-c with CS_2 in basic medium afforded 1,3,4-oxadiazole-5-thiones 5a-c. All the synthesized compounds were characterized by their physical and spectral analyses data. The synthesized compounds were characterized by their physical and spectral analyses data. The newly synthesized compounds were evaluated for their anti-inflammatory, analgesic, and antimicrobial activities. Compounds 1c, 3g, 4a, 4b, 4c and 5c exhibited comparable anti-inflammatory activity to that of indomethacin and compounds 1c, 4c and 5c were more analgesics than acetyl salicylic acid. Compounds 4b, 4c and 5c showed superior GI safety profile (33.3%, 33.3% and 50.0% ulceration) than that of indomethacin (100% ulceration) at 100 mg/kg oral dose. Compounds 4b, 4c and 5c were also non-toxic with a median lethal dose (LD_{50}) up to 200 mg/kg. The antibacterial and antifungal screenings identified compounds 3c, 4b, 4d, 5a and 5b as the most effective against a variety of tested microorganisms.

Title: Design and Synthesis of Potent β-Secretase (BACEI) Inhibitors with P_1' Carboxylic Acid Bioisosteres

Authors: Tooru Kimura[1], Yoshio Hamada[1], Monika Stochaj[1], Hayato Ikari[1], Ayaka Nagamine[1], Hamdy Abdel-Rahman[1], Naoto Igawa[1], Koushi Hidaka[1], Jeffrey-Tri Nguyen[1], Kazuki Saito[2], Yoshio Hayashi[1], Yoshiaki Kiso[1]

Source: *Bioorganic & Medicinal Chemistry Letters, 16, 2380-2386 (2006)*

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Recently, we reported potent and small-sized β-secretase (BACE I) inhibitors KMI-420 and KMI-429 in which we replaced the Glu residue at the P_4 position of KMI-260 and KMI-360, respectively, with a 1H-tetrazole-5-carbonyl. DAP (L-x, β-diaminopropionic acid) residue. At the P_1' position, these compounds contain one or two carboxylic acid groups, which are unfavorable for crossing the blood-brain barrier. Herein, we report BACEI inhibitors with P_1' carboxylic acid bioisosteres in order to develop practical anti-Alzheimer's disease drugs. Among them, tetrazole ring-containing compounds, KMI-570 (IC_{50} = 4.8 nM) and KM!-684 (IC_{50} = 1.2 nM), exhibited significantly potent BACEI inhibitory activities.

Title: Novel 1,2,4-Triazole-3-Mercaptoacetic Acid Derivatives as Potential Anti-Mycobacterial and Antimicrobial Agents

Authors: Nawal A. El-Koussi, Hamdy M. Abdel-Rahman

Source: *Bull. Pharm. Sci., Assiut University, 29 (1), 127-136 (2006)*

Address: Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt

Novel Schiff bases of 4-methyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide were synthesized. Their chemical identities were elucidated by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. The percentage of the geometrical isomers was also elucidated using the ^{1}H-NMR. The synthesized compounds were selected for screening at the Tuberculosis Antimicrobial Acquisition and Coordination Facility (TAACF) against Mycobacterium tuberculosis $H_{37}R_{v}$ strain in which they showed moderate activity at a concentration of 6.25 µg/ml. Moreover, antimicrobial screenings against E. coli (ATCC 25922), S. aureus (ATCC 19433) and C. albicans identified compound ***4g*** *as the most effective showing similar antibacterial activity as ampicillin against S. aureus.*

Title: A New Synthesis of Sulfonamides by Aminolysis of p-Nitrophenylsulfonates Yielding Potent and Selective Adenosine A_{2B} Receptor Antagonists

Authors: Luo Yan[1], Daniela C. G. Bertarelli[1], Alaa M. Hayallah[1,2], Heiko Meyer[1], Karl-Norbert Klotz[3], Christa E. Miiller[1,3]

Source: *J. Med. Chem., 49, 4384-4391 (2006)*

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I-Propyl- and 1,3-dimethyl-8-p-sulfophenylxanthine (PSB-1115 and SPT) were used as starting compounds for the development of adenosine A_{2B} receptor antagonists with a sulfonamide structure. Since standard reactions for sulfonamide formation failed or resulted in very low yields, we developed a new method for the preparation of sulfonamides. p-Nitrophenoxide was used as a suitable leaving group with well balanced stability-reactivity properties. A large variety of amines, including aniline, benzylamine, phenethylamine, propylamine, butylamine, 2-hydroxyethylamine, aminoacetic acid, and N-benzylpiperazine reacted with p-nitrophenoxysulfonylphenylxanthine derivatives yielding the desired sulfonamides in satisfying to very good yields. The obtained sulfonamides were much more potent at A_{2B} receptors than the parent sulfonates. The most active compound of the present series was 8-[4-(4-benzylpiperazide-l-

*sulfonyl)phenyl]-1propylxanthine (**11**, PSB-601) exhibiting a K_i value of 3.6 nM for the human A_{2B} receptor combined with high selectivity versus the other human adenosine receptor subtypes (575-fold versus A_1, 134-fold versus A_{2A}, and >278-fold versus A_3).*

Title: Characterization of Human and Rodent Native and Recombinant Adenosine A_{2B} Receptors by Radioligand Binding Studies

Authors: Daniela C. G. Bertarelli[1], Martina Diekmann[1], Alaa M. Hayallah[1], Dorothee Rüsing[2], Jamshed Iqbal[1], Birgit Preiss[1], Eugen J. Verspohl[2], Christa E. Müller[1,3]

Source: *Springer Science + Business Media, B.V., 2, 559-571 (2006)*

Address: [1]Pharmaceutical Institute, Pharmaceutical Sciences Bonn (PS B), Pharmaceutical Chemistry Poppelsdorf, University of Bonn, Bonn, Germany, [2]Institute of Pharmaceutical and Medicinal Chemistry, Department of Pharmacology, University of Münster, Münster, Germany and [3]Pharmazeutisches Institut, Pharmazeutische Chemie Poppelsdorf, Kreuzbergweg 26, 53115 Bonn, Germany,

Adenosine A_{2B} receptors of native human and rodent cell lines were investigated using [^{3}H]PSB-298 [(8{4-[2-(2-hydroxyethylamino)-2-oxoethoxy]phenyl }-I-propylxanthine] in radioligand binding studies. [^{3}H]PSB-298 showed saturable and reversible binding. It exhibited a K_D value of 60 ± I nM and limited capacity (B_{max} = 3.511 fmol per milligram protein) at recombinant human adenosine A_{2B} receptors expressed in human embryonic kidney cells (HEK-293). The addition of sodium chloride (100 mM) led to a threefold increase in the number of binding sites recognized by the radioligand. The curve of the agonist 5'-N-ethylcarboxamidoadenosine (NECA) was shifted to the right in the presence of NaCl, while the curve of the antagonist PSB-298 was shifted to the left,

indicating that PSB-298 may be an inverse agonist at A_{2B} receptors. Adenosine A_{2B} receptors were shown to be the major adenosine A_2 receptor subtype on the mouse neuroblastoma x rat glioma hybrid cell line NG108-15 cells. Binding studies at rat INS-1 cells (insulin secreting cell line) demonstrated that [^{3}H]PSB-298 is a selective radioligand for adenosine A_{2B} binding sites in this cell line.

Title: Synthesis and Pharmacological Activities of Novel 1-Alkyl-4-Aryl-6-Hydroxyperhydro-1,4-Diazepine-2,3-Diones

Authors: A. M. Abdel-Alim[1], M. A. Hussein[1], A. A. El-Shorbagi[1], A. A. Abu-ElMagd[1], B. S. El-Menshawi[2]

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 253-271 (2006)*

Address: [1]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Assiut University, Assiut-71526, Egypt and [2]Department of Pharmacognosy, National Research Centre, Dokki, Giza, Egypt

The present work involves the synthesis of 1-alkyl-4-aryl-6-hydroxyperhydro-1,4-diazepine-2,3-diones through the reaction of epichlorohydrin with some selected arylamine followed by the reaction of the formed intermediates with the corresponding cyclohexyl, alkyl, or aralkyl amines. The resulting N,N'-disubstituted-1,3-diamino-2-propanols were cyclized with diethyl oxalate to afford the target compounds. The structures of the obtained compounds were verified by spectral and elemental methods of microanalysis. Fifteen of the final compounds were subjected to preliminary pharmacological screening as regards their anticonvulsant activity. In addition, evaluation of the hypotensive activity of twenty two compounds was performed. Most of the tested compounds gave 100% protection against pentylenetetrazole-induced convulsions with a faster onset of action (15 min) than diazepam (30 min). On the other hand, most of the tested compounds gave mild to ~ 50-80% reduction in blood pressure in comparison to that of propranolol. Moreover, the cytotoxic activity of twenty eight final compounds was determined and only three of them elicited mild cytotoxic effects. Also, the median lethal dose (LD_{50}) of four target representative

compounds was determined and was found to range between 10-20 mg/kg (i.p.).

Title: Synthesis and Biological Activity of Certain New Indole Derivatives via the Utility of 2-Acetylindole

Authors: Alshaimaa A. Bakr[1], Mostafa A. Hussein[1]*, Samia G. Abdel-Moty[1], Abdel-Hamid N. Kafafy[1], M. M. Hamdy[2]

Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 348-370 (2006)*

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The present work involves synthesis of 1-substitutedindole-2,3-dione-2-thiosemicarbazone derivatives in order to evaluate their antimicrobial, anti-inflammatory, analgesic, and anticonvulsant activities. The target compounds were prepared through oxidative deacetylation of 1-substituted-2-acetyl-3-hydroxyindole, which followed by the condensation with different thiosemicarbazide derivatives. The purity of all the newly synthesized compounds was checked by TLC and elucidation of their structures was confirmed by IR, ^{1}H-NMR, and some representatives by mass spectrometry along with elemental microanalyses. Preliminary in-vitro antimicrobial evaluation (MIC) against some gram-positive and gram-negative bacteria as well as some fungi revealed that the tested compounds showed variable degrees of antibacterial activity, with little antifungal activity in comparison to chloramphenicol and fluconazole as reference drugs respectively. In addition, some of the tested compounds showed anti-inflammatory activity comparable to that of indomethacin. The most active

compounds were further evaluated for their analgesic activity; results showed that these compounds were more active than indomethacin. Three compounds were tested for their ulcerogenicity; two of them were safer than indomethacin. Furthermore, in-vivo anticonvulsant evaluation of the tested compounds at 2.8, 2.0 and 1.4 mmol/Kg concentrations showed comparable anticonvulsant activity to that of diazepam using pentylenetetrazole induced seizure protocol. Moreover, LD_{50} *of the most active compounds* ***4b*** *and* ***4h*** *were found to be 250 and 300 mg/Kg; respectively in comparison to the reported one for indomethacin 13 mg/Kg (i.p.). Moreover, the study involved the docking of the most active compound in the active site of COX-2 enzyme.*

Title: Spectrophotmetric Analysis of Selective Serotonin Reuptake Inhibitors Based on Formation of Charge-Transfer Complexes with Tetracyanoquinodimethane and Chloranilic Acid

Authors: Ibrahim A. Darwish, Ibrahim H.Refaat

Source: *Journal of AOAC International, 89 (2), (2006)*

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A simple, accurate, and sensitive spectrophotometric method for analysis of selective serotonin reuptake inhibitors (SSRIs) has been developed and validated. The analysis was based on the formation of colored charge-transfer complexes between the intact molecule of SSRI drug as an n-electron donor and each of tetracyanoquinodimethane (TCNQ) or p-chloranilic acid (Pca) as electron acceptors. The formed complexes were measured spectrophotometrically at 842 and 520 nm for TCNQ and pCA, respectively. Different variables and parameters affecting the reactions were studied and optimized. Under the optimum reaction conditions, linear relationships with god correlation coefficients (0.9975-0.9996) were found between the absorbances and the concentrations of the investigated drugs in the concentration ranges of 4-50 and 20-400 μg/ml with TCNQ and pCA, respectively. With all the investigated drugs, TCNQ gave more sensitive assays than pCA; the limits of assay detection were 2.5-4.8 and 20-40 μg/ml with TCNQ and pCA, respectively. The intra-and interassay precisions were satisfactory; the relative standard deviations did not exceed 2%. The proposed

procedures were successfully applied to the analysis of the studied drugs in pure form and pharmaceutical formulations with good accuracy; the recovery values were 98.4-102.8±1.24-1.8%. The results obtained from the proposed method were statistically comparable with those obtained from the previously reported methods.

Title: Generic Nonextractive Spectrophotometric Method for Determination of 4-Quinolone Antibiotics by Formation of Ion-Pair Complexes with β-Naphthol

Authors: Ibrahim A. Darwish[1], Ibrahim H.Refaat[1], Hassan F. Askal[1], Mostafa A. Marzouq[2]

Source: *Journal of AOAC International, 89 (2), 334-340 (2006)*

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[2]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Al-Azhar University, Assiut 71524, Egypt

This paper describes the development of a generic spontaneous nonextractive spectrophotometric method for determination of 13 pharmaceutically important 4-quinolone antibiotics. The method was based on the formation of yellow-colored water-soluble ion-pair complexes between 2% (w/v) β-Naphthol reagent and each of the studied drugs in sulfuric acid medium at room temperature. The formed ion-pair chromogens have maximum absorption peaks in the range of 365-391 nm. The concentrations of the reagents and the experimental conditions affecting the reaction were optimized. Under the optimum conditions, linear relationships with good linear coefficients (0.9987- 0.9995) were found between the absorbance and concentration of the investigated drugs in the range of 10-350 μg/mL. The assay limits of detection and quantitation were 1-9.9 and 3.4-32.9 μg/mL, respectively. The precision of the method was satisfactory; the values of relative standard

deviations did not exceed 2%. The proposed method was successfully applied to the analysis of the investigated drugs in pure and pharmaceutical dosage forms with good accuracy and prescision; the percentages of label claim ranged from 97.8-102.8 ± 0.35-1.60%. The results obtained by the proposed spectrophotometric method were comparable with those obtained by the official or reported methods. The proposed method is superior to all the previously reported ion-pair formation-based methods in terms of simplicity because it did not involve extraction procedures for the ion-pair complex. Therefore, this method might be recommended for routine use in quality control laboratories for analysis of the investigated 4-quinolone antibiotics in their pure forms, as well as in pharmaceutical dosage forms.

Title: Application of Inorganic Oxidants to the Spectrophotometric Determination of Ribavirin in Bulk and Capsules

Authors: Ibrahim A. Darwish[1], Alaa S. Khedr[1], Hassan F. Askal[1], Ramadan M. Mohamed[2]

Source: *Journal of AOAC International, 89 (2), 341-351 (2006)*

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[2]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Al-Azhar University, Assiut 71524, Egypt

Eight spectrophotometric methods for determination of ribavirin have been developed and validated. These methods were based on the oxidation of the drug by different inorganic oxidants: ceric ammonium sulfate, potassium permanganate, ammonium molybdate, ammonium metavanidate, chromium trioxide, potassium dichromate, potassium iodate, and potassium periodate. The oxidation reactions were performed in perchloric acid medium for ceric ammonium sulfate and in sulfuric acid medium for the other reagents. With ceric ammonium sulfate and potassium permanganate, the concentration of ribavirin in its samples was determined by measuring the decrease in the absorption intensity of the colored reagents at 315 and 525 nm, respectively. With the other reagents, the concentration of ribavirin was determined by measuring the intensity of the developed colored reaction products at the wavelengths of maximum absorbance: 675, 780, 595, 595, 475 and 475 nm for reactions with ammonium molybdate,

ammonium metavanidate, chromium trioxide, potassium dichromate, potassium iodate, and potassium periodate, respectively. Different variables affecting the reaction conditions were carefully studied and optimized. Under the optimum conditions, linear relationships with good correlation coefficients (0.9984-0.9998) were found between the absorbance readings and the concentrations of ribavirin in the range of 4-1400 μg/mL. The precision of the methods were satisfactory; the values of relative standard deviation did not exceed 1.64%. The proposed methods were successfully applied to the analysis of ribavirin in pure drug material and capsules with good accuracy and precision; the recovery values were 99.2-101.2 ± 0.48-1.30%. The results obtained using the proposed spectrophotometric methods were comparable with those obtained with the official method stated in the United States Pharmacopeias.

Title: A Validated Spectrofluorometric Assay for the Determination of Certain Macrolide Antibiotics in Pharmaceutical Formulations and Spiked Biological Fluids

Authors: Nawal EL-Rabbat, Hassan F. Askal, Pakinaz Y. Khashaba, Noha N. Attia

Source: *Journal of AOAC International, 89 (5), (2006)*

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This paper describes a simple spectrofluorometric method for the analysis of 4 macrolide antibiotics. The method is based on the condensation of 10% (w/v) malonic acid and acetic acid anhydride under the catalytic effect of tertiary amine groups of the studied macrolides. The relative fluorescence intensity of the condensation product was measured at 397/452 nm (excitation/emission) for azithromycin dihydrate and at 392/445 nm (for clarithromycin, erythromycin ethylsuccinate, and roxithromycin. All variables affecting the reaction conditions were studied. The effects of potential interference due to common excipients, such as starch, lactose, sucrose, glucose, gum acacia, and magnesium stearate, as well as trimethoprim and sulfisoxazole acetyl formulated in primomycin capsules and pediazole oral suspension, respectively, were studied. A validation study for the proposed method was carried out according to U.S. Pharmacopeia 2002. The linearity ranges were 3-80 ng/mL for all the cited macrolides. The limit of detection range was 0.74-1.20 ng/mL, while the limit of quantitation range was 2.47-4.02 ng/mL. The method was applied for the assay of the studied macrolides in pure pharmaceutical formulations and in spiked biological fluids. Results were

compared with those obtained from the reported method, where calculated t- and F-values indicated high accuracy and good precision for the proposed method.

Title: Simple and Sensitive Spectrophotometric Methods for Determination of Amantadine Hydrochloride

Authors: Ibrahim A. Darwish[1], Alaa S. Khedr[1], Hassan F. Askal[1], Ramadan M. Mohamed[2]

Source: *Journal of Applied Spectroscopy, 73 (6), (2006)*

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Three simple and sensitive spectrophotometric methods (A-C) for determination of amantadine hydrochloride has been developed and validated. The first method (A) based on the oxidation of the drug by ammonium molybdate. The second method (B) was based on the charge-transfer complexation reaction between the amantadine base as an electron donor and iodine as an σ-acceptor. The third method (C) was based on the reaction of N-alkylvinylamine formed from the interaction of the free ammonia group in amantadine molecule and acetaldehyde with chloranil to give colored vinylamino-substituted benzoquinone. The colored reaction products of these reactions were carefully studied and optimized. Under the optimum conditions, linear relationships with good correlation coefficients (0.9993 0.9998) were found between the reading and the corresponding concentration of the drug in the ranges of 2- 90 μg.ml^{-1}. The limits of detection ranged from 0.16 - 1.91 μg.ml^{-1}. The precision of the methods was

satisfactory; the value of relative standard deviations did not exceed 1.63%. The proposed methods were successfully applied to the analysis of amantadine HCl in its capsules with good accuracy and precisions; the label claim percentages ranged from (99.8 - 100.5) ± (0.52 - 1.22)%. The results obtained by the proposed spectrophotometric methods were comparable with those obtained by the official method.

Title: Immunoassay Methods and their Applications in Pharmaceutical Analysis: Basic Methodology and Recent Advances

Authors: Ibrahim A. Darwish

Source: *International Journal of biomedical Science, 2 (3), (2006)*

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Immunoassays are bioanalytical methods in which the quantitation of the analyte depends on the reaction of an antigen (analyte) and an antibody. Immunoassays have been widely used in many important areas of pharmaceutical analysis such as diagnosis of diseases, therapeutic drug monitoring, clinical pharmacokinetic and bioequivalence studies in drug discovery and pharmaceutical industries. The importance and widespread of immunoassay methods in pharmaceutical analysis are attributed to their inherent specificity, high-throughput, and high sensitivity for the analysis of wide range of analytes in biological samples. Recently, marked improvements were achieved in the field of immunoassay development for the purposes of pharmaceutical analysis. These improvements involved the preparation of the unique immunoanalytical reagents, analysis of new categories of compounds, methodology, and instrumentation. The basic methodologies and recent advances in immunoassay methods applied in different fields of pharmaceutical analysis have been reviewed.

Title: Antibodies to Heavy Metals: Isolation, Characterization, and Incorporation into Microplate Based Assays and Immunosensors

Authors: Diane A. Blake, Robert C. Blake II, Elizabeth R. Abboud, Xia Li, Haini Yu, Alison M. Kriegel, Mehraban Khosraviani, Ibrahim A. Darwish

Source: *DK9421-Chapter 4-13/11/2006-20:47-MAHESWARI-15333-XML MODEL C - pp. 93-111 (2006)*

Address: ---------

A heavy metal can be defined as any metallic chemical element with a relatively high density. At certain sites, heavy metals, including mercury (Hg), cadmium (Cd), lead (Pb), uranium (U); and copper (Cu) have been released into the soil or groundwater at levels that are toxic to plant and animal life. Unlike carbon-based environmental contaminants that will eventually be degraded and removed, metals that are deposited in the environment can persist for very long periods of time. When bound to soils and sediments, metals are relatively non-toxic except to bottom-feeding aquatic life [1]. Unfortunately, any number of ill-defined episodes, including changes in weather patterns and hydrology, changes in soil or water pH, or release of organics into the environment can mobilize metals and greatly increase their toxicity. Sites contaminated with heavy metals require long-term stewardship that includes regular monitoring for heavy metal mobilization.

Of the analytical techniques [2-6] currently used to measure metal ions, inductively coupled plasma atomic emission spectroscopy (ICPAES) is the most

commonly employed [7,8]. This technique routinely affords good sensitivity; however, the analysis is expensive, and large sample volume is often required to achieve maximum sensitivity. In addition, the time required for analysis can be prolonged because the samples must be analyzed sequentially and may sit in a queue for long periods of time. Unless coupled with mass spectrometry, high performance liquid chromatography, or capillary electrophoresis [9,10], ICPAES cannot provide information on metal ion speciation. Analyses conducted using such coupled instruments are particularly expensive and often less sensitive than those conducted using each individual instrument.

Antibody-based techniques are alternative approaches for metal ion analyses. These approaches are attractive to local and governmental agencies because they have significant advantages over the traditional analytical methods. Immunoassays are remarkably quick, reasonably portable to the analysis site, and simple to perform. Because most of the technology of an immunoassay is built into the antibody that is at the core of this detection system, sample pretreatment is usually minimal, and the instrumentation designed to transduce the antibody binding event to a measurable signal can be relatively small and inexpensive. The immunoassay and instrument can also be formatted for high throughput analysis. In addition, studies have shown that the use of immunoassays during remediation processes can reduce analysis costs by 50% or more [11]. Although most of the commercial immunoassays are directed toward complex organic chemicals, peptides, and proteins [12-17], this technique is theoretically applicable to any analyte, including a metal ion, if a suitable antibody can be generated.

Over the past ten years, this laboratory has generated over 20 monoclona1 antibodies directed toward different chelated metal ions by immunizing mice with the corresponding metal-chelate complexes. This article reviews the techniques used to generate and characterize these antibodies and describe how they may be formulated into field portable assays designed to provide inexpensive, portable,

near real-time analyses of heavy metals in environmental samples.

Title: Selective Determination of Quinones by High-Performance Liquid Chromatography with On-Line Post Column Ultraviolet Irradiation and Peroxyoxalate Chemiluminescence Detection

Authors: Sameh Ahmed[1,2], Shuu Fuji[1], Naoya Kishikawa[1], Yoshihito Ohba[1], Kenichiro Nakashima[1], Naotaka Kuroda[1]

Source: *Journal of Chromatography A, 113, 76-82 (2006)*

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A new HPLC method was developed for the simultaneous determination of quinones with peroxyoxalate chemiluminescence (PO-CL) detection following on-line UV irradiation. Quinones [i.e., 1,2-naphthoquinone, 1,4-naphthoquinone, 9,10-anthraquinone, 9,10-phenanthrenequinone] were UV irradiated (254 nm, 15 W) to generate hydrogen peroxide and a fluorescent product that were determined via PO-CL detection. Generation of hydrogen peroxide from quinones with on-line UV irradiation was confirmed using FIA system whereby incorporating an enzyme column reactor immobilized with catalase. Moreover, the structure of the produced fluorophore was confirmed using LC-MS, IR and ^{1}H-NMR. Afterwards, the conditions for UV irradiation and PO-CL detection were optimized. The separation of four quinones by HPLC was accomplished isocratically on an ODS column within 25 min. The detection limits (signal-to-

noise ratio=3) were 6.0 pmol/injection for 1,2-naphthoquinone, 4.4 pmol/injection for 1,4-naphthoquinone, 0.2 pmol/injection for 9,10-anthraquinone and 0.45 pmol/injection for 9,10-phenanthrenequinone.

Title: Spectrophotometric and Spectro-Fluorimetric Determination of Certain Diuretics in Pure Forms and in Their Pharmaceutical Formulations

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Three Simple and selective spectrophotometric and spectrofluorimetric methods were developed for the quantitative determination of certain diuretics (bendroflumethiazide, benzthiazide, chlorthalidone, clopamide, hydrochlorothiazide, hydroflumethiazide, indapamide and xipamide) in pure forms as well as in their pharmaceutical formulations through their hydroxamate formation and subsequent complexation with iron (method I), reaction with potassium ferricyanide (method II) and reaction with 4-chloro-7-nitrobenzofurazan (method III). The conditions for different reactions were studied and optimized. The methods have been validated and successfully applied to the analysis of bulk drugs and their tablets with good recoveries ranging from 97.93 (±1.46) to 100.6 (±1.75) for method I, 98.49 (±1.43) to 99.86 (±0.87) for method II, and 98.98 (±1.11) to 99.90 (±0.86) for method III. No interference

was observed from common pharmaceutical adjuvants. The results obtained compare well with those of reported methods.

Title: Quantitative Fluorescence Intensity-Structure Relationships of Certain Quinolone-Metal Chelates

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Source: *Bull. Pharm. Sci., Assiut University, 29 (2), 289-299 (2006)*

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A quantitative relationship was found between the relative fluorescence intensities of certain metal chelates of some quinolone antibacterials and their physicochemical parameters namely: the pKa_1 (corresponding to the ionisation of the 3-carboxylic group) and the calculated stability constants of the formed chelates as well as the second order connectivity indexes ($^2\chi^v$), Hammett constant (σ_m), polar constants (F) and resonance constants (R) for the substituent at position 1 of the quinolone nucleus. The studied quinolone antibacterials are amifloxacin, difloxacin, ciprofloxacin, nalidixic acid, norfloxacin, lomefloxacin, ofloxacin and pefloxacin and the metals involved are zirconium, molybdenum, vanadium and tungsten.

Twenty highly significant regression equations were obtained and used to calculate the unreported values of σ_m, F and R for the substituent at position 1 of ofloxacin. Two correlation equations were used also to predict the fluorescence intensity of molybdenum chelates of the studied quinolones.

Title: Spectrofluorimetric Determination of Macrolide Antibiotics Using Eosin-G Dye

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A fully validated and simple spectrofluorimetric method was developed for the determination of azithromycin, clarithromycin, erythromycin ethylsuccinate, erythromycin stearate and roxithromycin in bulk powders and their dosage forms. The proposed method was based on ion pair formation of either one of the cited drugs with eosin-G dye in presence of McIlvaine buffer and the resultant complex was extracted by chloroform. All variables affecting the intensity of the developed fluorescence products were studied and optimized. Straight line correlation was found over concentration ranges of 0.04–0.2, 0.4–6.4, 4.0–16, 1.6-12, 0.4–4.0 μg ml^{-1} for azithromycin, clarithromycin, erythromycin ethylsuccinate, erythromycin stearate and roxithromycin respectively, with good correlation coefficients (0.9973 – 0.9994). The limits of detection and quantitation for this method ranged from 0.01 to 1.74 μg ml^{-1} and from 0.04 to 5.79 μg ml^{-1} respectively. The relative standard deviations were 1.54–2.15%. The proposed method was applied successfully for the determination of the cited drugs in different pharmaceutical dosage forms as tablets, capsules, granules as well as suspension without

interference from common encountered additives with overall percentage recoveries ranged from 94.74 ± 1.17 to 100.20 ± 1.57. In addition no interference was observed due to other active ingredients as trimethoprim and sulfisoxazole acetyl. The results were compared favorably with those of reported method.