ChemTech
International Journal of ChemTech Research
CODEN (USA) : IJCRGG ISSN : 0974-4290, ISSN(Online):2455-9555
www.sphinxsai.com
Vol. 10, No. 02, 2017
This website is best viewed in 1024 x 768

INDEX Page-1.

Abstract Full Text PDF Full Text XML

(56-61)

The Effect of Mannanolytic Fungi and Humic Acid Dosage to Improve the Nutrient Content and Quality of FermentedPalm Kernel Cake

Mirnawati, G. Ciptaan, Ferawati

Abstract Full Text PDF Full Text XML

(62-69)

Synthesis of TiO2/Chitosan Photocatalyst, TiO2/Bentonite and Adsorption of Zeolite to Purify Unnes's Water Reservoir

Emas Agus Prastyo Wibowo, Navela Rahma Aji,Nuni Widiarti

Abstract Full Text PDF Full Text XML

(70-75)

Preparation and Solid State Characterization of Binary Mixtures of Acyclovir – Succinic Acid

Agnes Nuniek Winantari, Dwi Setyawan, Siswandono, Sundani Nurono Soewandhi

Abstract Full Text PDF Full Text XML

(76-83)

Peer Education : The Effect on Menstrual Knowledge in Early Reproductive Age Women in West Java Rural Area

Lulu Eva Rakhmilla, Ahsani Rahma Rudibianti,Vitriana Biben, Nur Amalia Rosyada

Abstract Full Text PDF Full Text XML

(84-90)

Phytochemical, TLC Profile, and Antioxidant Activity of Malinau Endemic Plant of Tabar Kedayan (Aristolochia papilifolia Ding Hou) Root Fractions

Islamudin Ahmad, Mirhansyah Ardana, Riski Sulistyarini, Wisnu Cahyo Prabowo, Muhammad Arifuddin

Abstract Full Text PDF Full Text XML

(91-98)

Method Development and Validation for the Estimation of Plerixa for by RP-HPLC Method in Bulk Drug and Pharmaceutical Dosage form

S.V.Saibaba, P.Shanmuga Pandiyan

Abstract Full Text PDF Full Text XML

(99-102)

In Vitro Test of Chive Leaves Infuse (Allium schoenoprasum, L.) on Calcium Oxalate Solubility using Atomic Absorption Spectrophotometry

Iksen, Ginda Haro, Siti Morin Sinaga

Abstract Full Text PDF Full Text XML

(103-107)

Extract Ethanol of Poguntano as Anti Diabetic in Alloxan induced Diabetic Rats

Sry Suryani Widjaja, Delfitri Munir, Rusdiana, Maya Savira

Abstract Full Text PDF Full Text XML

(108-114)

Hypoglycemic Activity of Nano Particles from Temuru Leaves and Temuru(Murraya Koenigii (L.) Spreng) Leaf Extract on Alloxan Induced rats and Antioxidant Activity

Rini Handayani, Urip Harahap, Karsono

Abstract Full Text PDF Full Text XML

(115-120) **Chronic Lead Poisoning Prevention In Children With Calcium Supplementation**

www.sphinxsai.com

ChemTech

International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.2, pp 70-74, 2017

Preparation and Solid State Characterization of Binary Mixtures of Acyclovir – Succinic Acid

Agnes Nuniek Winantari[1,2*], Dwi Setyawan[1], Siswandono[1], Sundani Nurono Soewandhi[3]

[1]Faculty of Pharmacy, Airlangga University, Jl. Dharmawangsa Dalam Surabaya 60286, Indonesia.
[2]Faculty of Pharmacy, University of Surabaya, Jl. Raya Kalirungkut, Surabaya , 60293 Indonesia.
[3]School of Pharmacy, Bandung Institute of Technology, Jl. Ganesha No. 10, Bandung 40132, Indonesia

Abstract : Physical interaction of acyclovir – succinic acid (AS) was studied. The aim of this study is to prepare and characterize binary mixture of AS. Methods of cocrystallization was solvent evaporation in equimolar ratio between acyclovir and succinic acid using ethanol and methanol. The cocrystals were characterized by Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), and Fourier Transform Infra Red (FTIR) spectroscopy. Physical characterization showed a new endothermic peak at 175.36°C according to DSC analysis. The PXRD patterns of AS binary mixture after cocrystallization are different from pure components. Furthermore, specific peaks was found at 2θ = 24,77°, 35,88° and 37,99° (AS in ethanol); 19,99° and 21,01° (AS in methanol). In addition, there are a shift in the O-H, N-H and C=O spectrum of FTIR.
Keywords : acyclovir, succinic acid , solvent evaporation, characterization, binary mixture.

Introduction

Initial R& D efforts were focused on finding new chemical entity with desired molecular structure and physical properties. Most of the active pharmaceutical ingredients (API) exists in solid state, solid does not crystallize on its own. It crystallizes several forms showing unpredictable crystal properties. There are number of approaches can be used to modify solids such as solvation, hydration, salting and polymorphism. Apart from available approaches of API modification, cocrystallization is an emerging alternative approach enhancement of physical properties[1].

Cocrystals, which refer to solid form with two or more different molecules within the same crystal lattice in a certain stoichiometric ratio, have been of great interest to the pharmaceutical industry because they have potential to enhance physicochemical properties of the API. Many cocrystals have been reported to modulate solubility, intrinsic dissolution rate, mechanical properties, compaction, purification, stability or even bioavailability compared with the API [2]. From the thermodynamic point of view, pharmaceutical cocrystals are stable and high energy forms. Therefore, they can have impact on solubility and dissolution rate of the drug. The strategy involves drug-coformer combinations that have the potential of forming energetically and structurally robust interactions[3,5,6,7]. Pharmaceutical cocrystals often rely on hydrogen bonded assemblies

between an API and coformer with well-defined stoichiometries. For a target API, we are interested in coformers with functional groups that can interact (i.e., form H-bonds) with the functional groups on the API. Common functional groups, such as carboxylic acids, amides and alcohols are typically found to interact with one another in cocrystals. Thus, carboxylic acids are considered as coformers to form cocrystals with acyclovir, including succinic acid.[3,8,9,12].

Acyclovir is a guanosine analogue antiviral drug. It is one of the most commonly used antiviral drugs because of its selectivity and low cytotoxicity. It has absorption problems mainly due to its poor solubility in water (1,62 mg/mL). This factor negatively influences its oral bioavailability which is approximately 15-30% [10,11,12,13].

Different methods have been used to produce cocrystals : solution crystallization, solid state and solvent drop grinding, and crystallization from melt. For scale up purposes, solution crystallization is the most popular [3,14,15].

Materials and Method

Materials

Acyclovir was obtained from Sigma-Aldrich (USA). Succinic acid, ethanol and methanol were purchased from Merck Chemicals (Germany) without any purification.

Preparation of binary mixture of AS by solvent evaporation

Acyclovir and succinic acid carefully weighed equimolar. Each compound was dissolved in solvent separately. The two solutions were mixed and stirred for a few minutes. Equimolar solution of both components was evaporated at room temperature for 48 hours. The obtained of solid binary system stored in a dessicator under vacuum.

Thermal Analysis by DSC

Differential Scanning Calorimetry (DSC) was performed using Mettler Toledo. About four mg of each sample was placed in crimped sample pan. The sample was heated from 30° to 300°C at a heating rate of 10°C/min under nitrogen purged.

Characterization by PXRD

Powder X-ray diffraction (Phillips X'Pert diffractometer) analysis was performed at room temperature. Condition of measurement was set as follows : Cu metal target, Kα filter, voltage of 40kV, 40 mA. The analysis was performed on the range of 2 theta of 5-40°. Sample was placed on the sample holder and flatted to prevent particle orientation during preparation.

Characterization by FTIR

Infrared spectra were recorded by using Jasco 4200-type A. The dried pure acyclovir, succinic acid, physical mixture and binary system were previously ground and mixed thoroughly with potassium bromide. The infrared spectrum was obtained using infrared spectrophotometer in wave length range of 400-4000cm^{-1}.

Results and Discussion

As shown in figure 1, an endothermic peak at 251.08°C was presented in the DSC thermogram of acyclovir. Succinic acid demonstrated an endothermic peak at 186.90 °C. In the thermogram of the AS physical mixture, it was observed an endothermic peak at 175.36 °C. The thermal behaviour of AS binary mixture showed an endothermic peak at 173.41°C (ethanol) and 172.15°C (methanol), that was distinct and unique from the individual components and physical mixture, demonstrating the formation of a new phase[16].

Differential Scanning Calorimeter (DSC) was used to evaluate the results by observing the thermal profile and arranging phase diagrams. Melting is a first order process that can be observed in the form of an

endothermic peak in DSC curves. Recall that unlike the peak temperature, the onset temperature of melting will be independent of the DSC heating rate[17].

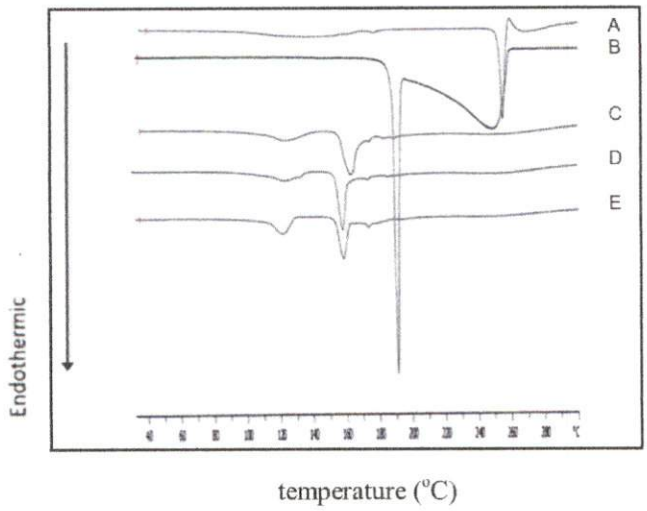
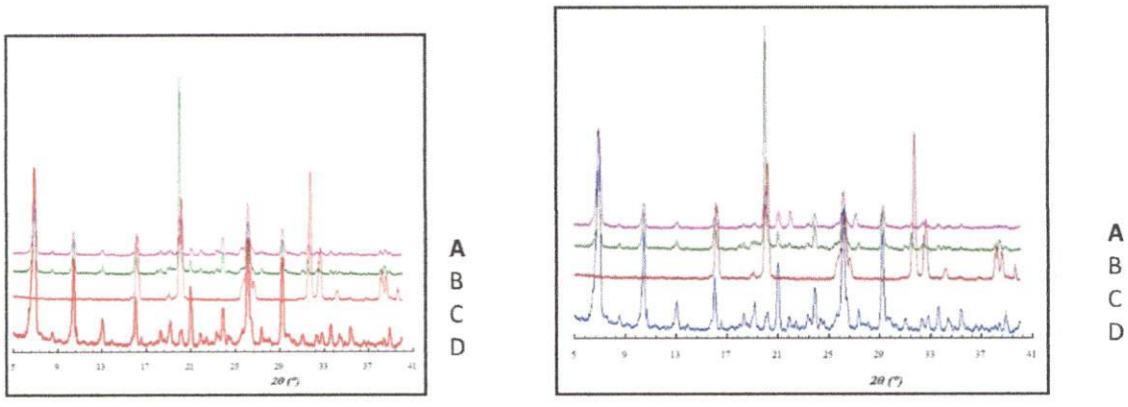


Figure 1 : DSC thermogram of A) asiklovir, B) succinic acid, C) physical mixture of AS (1:1), D) binary mixture of AS (1:1) in ethanol, E) binary mixture of AS (1:1) in methanol

PXRD is one the most powerful techniques used for the study of crystalline and partially crystalline solid-state materials. It is mainly used to characterize the crystallographic structure of pollycrystalline or powderred solid samples; different crystalline phases show distinctly different PXRD patterns. This method provides an irreplaceable technique for identifying and characterizing different solid forms of APIs (polymorphs, hydrates, solvates and cocrystals). PXRD provides fundamental structural information on the material [18].

The crystalline states for the starting materials, AS binary mixtures, and physical mixture have been presented in figure 2. In which AS binary mixtures exhibited new characteristic interference peaks at 2θ : 24.77°, 35.88°, 37.99° (in ethanol) and 19.99°, 21.01° (in methanol). The obtained binary mixtures had a unique powder pattern, different from that of the two components or their physical mixtures [16].



(a) **(b)**

Figure 2 : PXRD difractogram (a) in ethanol and (b) in methanol. A) AS binary mixture AS (1:1), B) physical mixture AS (1:1), C) succinic acid , D) acyclovir

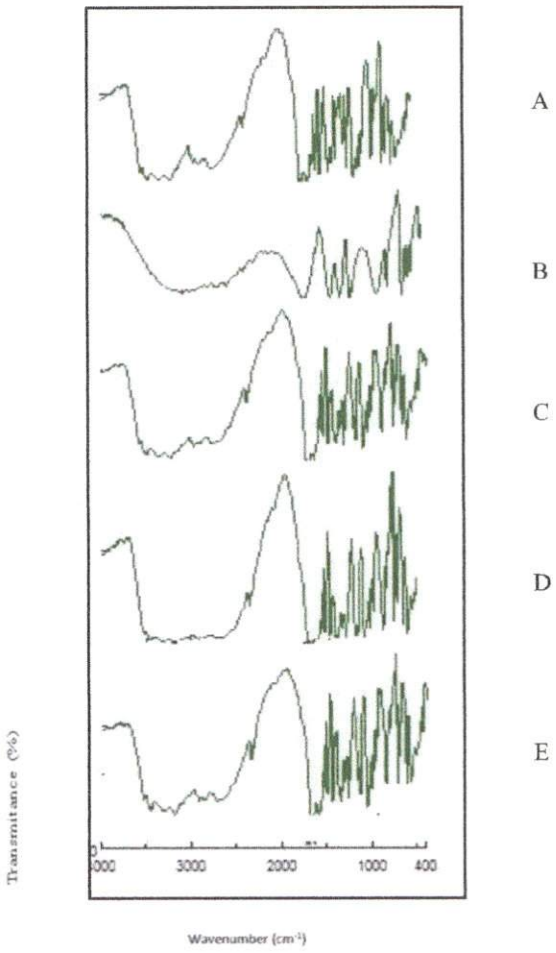


Fig. 3 : FTIR spectra of a) acyclovir, b) Succinic acid, c) AS physical mixture, d) AS cocrystals (ethanol), e) AS cocrystals (methanol)

The infra red spectrum of acyclovir had peaks in the region of 3500-3300 cm^{-1}, corresponding to primary and secondary amines, respectively, and the 1600 cm^{-1} region was represented by a band corresponding to the amide group [10]. The main absorption bands of acyclovir are a broad band 3500 cm^{-1} due to (NH,OH) , C=O stretching at 1600 cm^{-1}, CH-aliphatic stretching at 2950 cm^{-1} and CH-aromatic stretching at 3050 cm^{-1} [20]. The spectrum of succinic acid had one peak at 3439 cm^{-1} corresponding to a O-H group, and the region of 1694 cm^{-1} showed a band corresponding to C=O stretch [19]. The loss of the transmision peaks at 3500 referred to NH bending bands. Loss of C=O stretch at 1600 cm^{-1}, C-H aromatic at 3050 cm^{-1}, and O-H bending region at 3439 cm^{-1} showed the presence of hydrogen bonding between acyclovir and succinic acid due to the formation of new crystalline phase, both in ethanol either in methanol by solvent evaporation technique. This indicate the formation of cocrystal of AS.

Conclusion

Binary mixtures of acyclovir-succinic acid were formed using solvent evaporation methods in ethanol and methanol. They have been characterized by DSC, PXRD, and FTIR.

References

1. Vitthalrao M.A., Kumar F.N., Radheshyam B.K., Cocrystallization : An Alternative Approach for Solid Modification, Journal of Drug Delivery & Therapeutics, 2013, 3(4), 166-172.

2. Zhou Z., Chan H.M., Sung H.H.Y., Tong H.H.Y, Zheng Y., Identification of New Cocrystal Systems with Stoichiometric Diversity of Salicylic Acid Using Thermal Methods, Pharmaceutical Reasearch, Januari 2016.
3. Sarma B., Chen J., Hsi H., Myerson A.S., Solid Forms of Pharmaceuticals : Polymorphs, Salts and Cocrystals, Korean Journal Chemical Engineering, 2011, 28(2), 315-22.
4. Sekhon B.S., Pharmaceutical Co-crystals – An update, International Bulletin of Drug Research, 2012, 1(2), 24-39.
5. Sevukarajan M.., Thanuja B., Riyaz S. and Rahul N., Synthesis and Characterization of a Pharmaceutical Co-Crystal : (Aceclofenac : Nicotinamide), Journal of Pharmaceutical Science and Research, 2011, 3(6), 1288-1293.
6. Nanjwade V.K, F.V. Manvi, Shamrez A. M., Basavaraj K. N. & Meenaxi M. M., New Trends in the Co-crystallization of Active Pharmaceutical Ingredients, Journal of Applied Pharmaceutical Science, 2011, 1(8), 1-5.
7. Santos, O.M.M., Reis, M.E.D., Jacon, J.T., Lino, M.E.S., Simoes, J.S., Doriguetto, A.C., Polimorphism : An Evaluation of the Potential Risk to the Quality of Drug Products from the Farmacia Popular Rede Propria, BJPS, 2014, Jan/Mar, 50(1), 1-24.
8. Almarsson O. And Zaworotko M.J., Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines ? Chemical Communication, 2004, 1889-1896.
9. Najar A.A dan Azim Y., Pharmaceutical Co-Crystals : A New Paradigm of Crystal Engineering. Journal of Indian Institute of Science, 2014, 94(1), 45-67.
10. Masuda T., Yasuo Y., Etsuo Y, Kotaro F., Hidehiro U., and Katsuhide T., Cocrystallization and amorphization induced by drug-excipient interaction improves the physical properties of acyclovir, International Journal of Pharmaceutics, 2012, 422, 160-169.
11. Bruni G., Maietta M., Maggi L., Mustarelli P., Ferrara C., Berbenni V., Milanese C., Girella A., Marini A., Preparation and Physicochemical Characterization of Acyclovir Cocrystals with Improved Dissolution Properties, Journal of Pharmaceutical Sciences, 2013, 102(11), 4079-4086.
12. Yan yan, Jia-Mei C., Tong-Bu L., Simultaneously Enhancing the Solubility and Permeability of Acyclovir by Crystal Engineering Approach, Crystal Engineering Communication, 2013, 15, 6457-6460.
13. Sarkar A., & Rohani, S., Cocrystal of Acyclovir with Promising Physicochemical Properties, Journal of Pharmaceutical Science, 2014, 98-105.
14. Krisnaiah, Y.S.R., Pharmaceutical Technologies for Enhancing Oral Bioavailabilitas of Poorly Soluble Drugs, Journal of Bioequivalence & Bioavailability, 2010, 2(2), 28-36.
15. Sevukarajan, M., Thamizhvanan K., Riyaz, S., Sateesh, B.J.M., Naveen, K.B., Sreekanth, R.B., Sethu, K.J., Vivekananda, U., Sarada, K., Hyndavi, N., Hima, B.R., & Roopa L.K., Crystal Engineering Technique – An Emerging Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients, International Journal of Chemical Pharmaceutical Science, 2012, March, 3(1), 15-29.
16. Liu M., Hong C., Yao Y., Shen H., Ji G., Li G., Xie Y., Development of a pharmaceutical cocrystal with solution crystallization technology : Preparation, characterization, and evaluation of myricetin-proline cocrystals, European Journal of Pharmaceutics and Biopharmaceutics, 2016, 107, 151-159.
17. Reutzel-Edens, S.M., Analytical Techniques and Strategies for Salt/Cocrystal Characterization, In : Wouters J, Luc Q, editors, Pharmaceutical Salts and Co-crystals. RSC Drug Discovery Series No.16, Royal Society of Chemistry Publishing, 2012, 220.
18. Padrela L., Azevedo, E.G., Velaga S.P., Powder X-Ray Diffraction Method for the Quantification of Cocrystals in the Crystallization Mixture, Drug Development and Industrial Pharmacy, 2011, 1-7.
19. Ober, C.A., and Gupta, R.B., Formation of Itraconazole-Succinic Acid Cocrystals by Gas Antisolvent Cocrystallization, AAPS Pharmaceutical Science Technology, 2012,13 (4), 1396-1405.
20. Allam A.N., Naggar V.F., and El gamal S.S., Formulation and Physicochemical Characterization of Chitosan/Acyclovir Co-crystals, Pharmaceutical Development and Technology, 2013, 18(4), 856-865.

*****

Extra page not to be printed.

Always log on to- www.sphinxsai.com

For your Research References requirements.

International Journal of ChemTech Research

*****

International Editorial Board

Managing Executive Editors[Dev. A & R]

1	**Editor-in-Chief:** **Dr. Bhavik J. Bhatt,** **3041 N. Oakland Forest Drive, Apt 203, Oakland Park FL – 33309,USA**

Associate Editors

2	**Juan Pablo Rodríguez Miranda** **Distrital Francisco José de Caldas University. Faculty of Environment and Natural Resources. Bogota D.C. Colombia.** **[Official Representative of Journal in Latin America, Colombia and the Caribbean]**
3	**Dr. Nour Shafik El-Gendy,** **Egyptian Petroleum Research Institute (EPRI), 1 Ahmed El-Zomer St., Nasr City, Cairo, Egypt**
4	**Dr.Jamal Hamdo,** **Department of Chemistry- Faculty of Sciences- Damascus University, Damascus-Syria .**
5	**Dr.T.C.Koliopoulos, PhD,** **Duke University, Durham, USA.**
6	**Dr Manishabrata Bhowmick, Ph.D** **Torrey Pines Institute for Molecular Studies,11350 South West Village Pkwy Port Saint Lucie, Florida -34987, USA.**
7	**Dr. Sundarapandian Vaidyanathan,** **Professor & Dean, R & D Centre, Vel Tech University, Chennai-600062, Tamil Nadu, India.**
8	**KASMI-MIR Souad** **Faculty of Science, Saad Dahlab University Blida 1, 9000 Blida Algeria, Laboratory of Synthesis and Catalysis (LSCT), University of Tiaret 14000, Algeria.**
9	**Dr. Ashutosh Das,** **Pro-Vice Chancellor at PRIST University, Thanjavur, TN (India).**
10	**Dr. Krishna Kishore Inampudi, Ph.D** **Yale University New Haven, CT-06511 USA.**

Executive Editors[A & R]

1	**Dr. Fazlul Huq,** Head Cancer Research Group, School of Medical Sciences, Faculty of Medicine, Australia.
2	**Dr.Pavel Mokrejs,** Thomas Bata University,The Czech Republic, Europe.
3	**Dr. Adli Abdallah Hanna,** National Research Centre, Egypt.
4	**Dr. P.Y.Shirodkar,** University of Mumbai,India.
5	**Dr. M. Al-Anber,** Mu'tah University, Jordan.
6	**Dr.Saeid Amani,** Arak University,Iran .
7	**Dr.Mitu Liviu,** University of Pitesti, Romania.
8	**Dr. Nurfina Aznam,** University Negeri Yogyakarta, Indonesia.
9	**Dr. Tomasz Borowski,** Centre Lab of Chem.Tech.,Poland.
10	**Dr. Mas Rosemal Hakim bin Mas Haris,** School of Chemical Sciences Universiti Sains Penang, Malaysia.
11	**Dr.Alamdar Ashnagar,** Pasteur Institute of Iran.
12	**Dr. Abdulkareem Ismaiel Abdulraheem,** College of Health Sc.,PAAET, Kuwait.
13	**Dr. Ji-Tai Li,**

	Hebei University, China.
14	**Dr.Abdalla Shalaby,** Zigzag University,Egypt
15	**Dr. Georgia Koliopoulou,** University of Athens, Athens, Greece.
16	**Dr. A. A. Mottahedi ,** IROST,Iran
17	**Dr. Gwendoline Ee Cheng Lian,** University PutraMalaysia, Malaysia.
18	**Dr. J.V.Manwar,** GSPS.IOP, M.S.India.
19	**Dr.Miss Swastika Ganguly,** Birla Insti.of Tech.,India.
20	**Prof. Dr. Sbirna Simona-Liana,** University of Craiova, Romania.
21	**Dr Carolyn Coulter,** University of Otago, New Zealand.
22	**Dr. Konstantinos M. Kasiotis,** B P Institute, Laboratory of Pesticides Toxicology, Athens, 14561, Greece.
23	**Dr. Arun HS Kumar,** University College Cork,Ireland.
24	**Associate editors: Dr. M.Z. Kumbhare,** M.S.India. **Dr. S.R.Ninawe,** M.S.India.