BAPA

Annual Journal 2010 - Volume 19

Bangladeshi-American Pharmacists' Association

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BAPA Journal is published by Bangladeshi-American Pharmacists' Association.

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Program

Program

Day 1	Friday, November 05, 2010
4:00 pm – 8:00 pm	**Registration, Hotel Lobby**
	CONTINUING EDUCATION
6:30 pm – 8:30 pm	**ESAP & The Important Role of Pharmacists [Pacific Ball Room]** 0170-9999-10-076-L04-P, 0.2 CEU Wesley E. Badillo, MD, MPH Expanded Syringe Access Program (ESAP) coordinator & NYS Latino HIV Testing Month Coordinator NYS Department of Health AIDS Institute Dr Badillo will provide the three reasons why pharmacies are so important to ESAP and its requirements, ways to create awareness in the community about ESAP, disposal of used hypodermic needles and syringes, impact of two recent changes that occurred in the Penal Code 220.45 and discuss at least two ways in which a partnership with community agencies can be established.
8:30 pm – 9:30 pm	**Welcome and Dinner [Main Dining Room]**
9:30 pm – 12:00 pm	**Cultural Program [Atlantic Hall]**

Day 2	Saturday, November 6, 2010
7:30 am – 9:30 am	**Breakfast [Main Dining Room]**
8:00 am – 12:00 pm	**Registration [Hotel Lobby]**
	CONTINUING EDUCATION
9:00 am – 12:00 noon	**Making the Case for Quality & Safety [Pacific Ball Room]** 0170-0000-10-087-L05-P, 0.3 CEU Craig Burridge, M.S, CAE, PSSNY Executive Director At the completion of this activity, the participant will be able to: Assess the impact of chronic constipation in the elderly as it relates to quality of life, psychological effects and healthcare economics; Describe ways to tailor management strategies and treatment plans for the various etiologies of chronic constipation often encountered in residents of long-term care, including medication-related causes; Evaluate the role of traditional and newer pharmacologic treatment options for chronic constipation in elderly patients with various comorbid conditions; Apply principles of an interdisciplinary approach to monitor treatment progress and to assess the efficacy and safety of chronic constipation therapies in elderly adults.
12:00 pm – 12:45 pm	**Education in Bangladesh [Pacific Ball Room]** Dr. David Taft, Dean of Arnold and Marie Schwartz College of Pharmacy, Bob Bellantone, Ph.D and Dr. JMA Hannan, Chairman, Pharmacy Department, North South University, Dhaka, Bangladesh

1:00 pm – 2:00 pm	**Lunch [Main Dining Room]**

CONTINUING EDUCATION

Day 2	**Saturday, November 6, 2010**

PHARMACEUTICAL SEEMINAR

10:00 am – 11:00 am	**Role of First-Time-in-Human Studies in Drug Development [Summit 3]** Mohammad Hossain, PhD Director, Clinical Pharmacology Modeling and Simulation (CPMS)
11:00 am – 12:00 pm	**Melt Granulation using Twin-screw Extruders: How It Can Revolutionize the Future of Granulation Technology for Tablets** *Abu T. M. Serajuddin, Ph.D* Professor Department of Pharmaceutical Sciences College of Pharmacy & Allied Health Professions, St. John's University **[Summit 3]**
3:50 pm – 4:50 pm	Regulatory Aspects of Generic Drug Development Sharif Ahmed, MS **[Summit 3]**

CONTINUING EDUCATION

2:00 pm - 5:15 pm	**Preventing Fraud, Waste & Abuse [Pacific Ball Room]** 0170-9999-10-079-L04-P, 0 .3 CEU Craig Burridge, M.S, CAE, PSSNY Executive Director This program offers an explanation of laws and regulation related to fraud, waste and abuse, describe the elements of a company's fraud, waste and abuse policies and procedures, summarize your protections when reporting suspected fraud, waste and abuse.
3:35 pm – 3:50 pm	**Coffee Break [Lower Lobby]**
7:30 pm – 9:00 pm	**Dinner [Main Dining Room]**
9:15 pm – 1:00 am	**Cultural Program [Atlantic Hall]**

Day 3	Sunday, November 7, 2010
7:30 am – 9:30 am	**Breakfast [Main Dining Room]**
	CONTINUING EDUCATION
9:00 am – 11:00 am	**Flu Vaccine Update 2010-2011 [Pacific Ball Room]** 0170-9999-10-088-L01-P, 0.2 CEU Joseph Manganelli, PharmD, MPA, Dicussion of populations most at risk for contracting flu, immunization options available, differentiate between available antiviral treatments.

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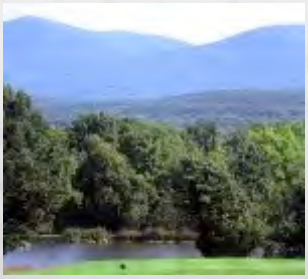
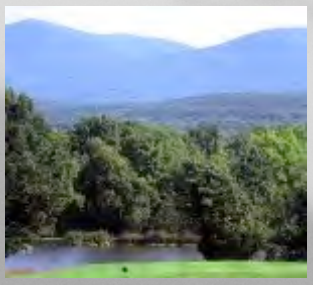






Bangladeshi-American Pharmacists' Association
1596 Dale Avenue
East Meadow, NY 11554
Telephone: (646) 325-5441

Message from the President

Dear Colleagues and Friends,

The Bangladeshi-American Pharmacist's Association Convention, as always, poses a significant challenge while deciding on the agenda!

On one hand, this is the event of a unique group of professionals, who also have diverse interests from retail pharmacy to manufacturing to regulatory affairs to R&D and so on. Putting together an agenda that would cater to the needs of each of these segments is a stimulating challenge.

But that's not the end of it. In the spirit of celebrating the achievements and success of our community, this Convention is also about our families and friends who join in and provide a unique flavor & color to the event.

Finally, in the true spirit of Bangladeshi "nostalgia" and most of all, the sense of responsibility in all of us, this Convention always focuses on the state of affairs surrounding Pharmacy education and Pharmacy profession in Bangladesh.

The above, dear friends and family, provides for an extremely busy program and some stimulating interactions and I hope that the preparations we have made to address these priorities will meet your expectations.

As we move forward, the further growth in our community would depend on the alignment of the Pharmacy curriculum in Bangladesh with the current PharmD program in USA. This is a significant challenge and will need support from our members to collaborate with the Universities in Bangladesh to make appropriate changes in their curriculum.

In conclusion, I congratulate the executive committee members and office bearer for the work for convention, I must also announce my gratitude and thanks all the sponsors of this year's event for making this program possible. The success of the program, however, will depend on the active participation of the members & their families. With this unique platform for communication, socializing & networking, I see no reason for any of us not enjoying the proceedings.

Please join in & enjoy.

Mahmud Hossain, MS, RPh

Message from the Vice President

Dear BAPA Members and Participants,

Welcome to the 19th BAPA Annual Convention. My sincere thanks to all the members, spouses, children, guests, advertisers and sponsors for attending this annual convention. I would like to congratulate our editor for the publication of the BAPA Annual Journal. I would also like to congratulate the executive committee for organizing such a huge event in a very short period of time. I know this was only possible due to our member's unconditional love and support for this great organization. BAPA is our umbrella and we all are united under this with only one goal of improving the pharmacy profession for ourselves and for our next generation. I believe the executive committee under the leadership of our president is committed to achieve this goal. I like to take this opportunity to invite all our children who graduated or are enrolled in different pharmacy schools to join this wonderful professional organization and take it to next level. Finally, I wish your stay at this convention is safe, enjoyable and pleasant.

Mohammed Daud Bhuiyan, MS, R.Ph

Vice President

Message from the General Secretary

Dear BAPA Members,

I am humbled and honored by your support for electing me as your general secretary. Thank you for the trust you have place in me and know that I will work hard to live up to that trust. I would also like to thank the previous administration for helping to make the transition so smooth.

I would like to outline my goals as general secretary for the year. The primary goal is to increase new membership, especially among new practitioners, while maintaining our core member base. Secondly, I want to increase communication with our affiliate members in the state. Our profession is at a critical time right now. So many changes in the law and additional rules and regulations, can be a real challenge, especially for independent owners. This is why it's so important to that all pharmacy organizations work together for better outcomes in the future. The last goal, and perhaps most ambitious one, is to help begin the process that will implement the Doctor of Pharmacy degree as the standard degree of the profession in Bangladesh. I assure you that as general secretary of the Bangladeshi-American Pharmacists Association, we will do our best to fulfill the promises we have made.

I joined BAPA with a vision that this organization would take its place among the strong pharmacy organizations in New York State. Since the Doctor of Pharmacy degree (Pharm.D.) has become the education standard in the US, pharmacists from Bangladesh are no longer permitted to take the Foreign Pharmacy Graduate Examination (FPGE) certification program due to the difference of equivalency between the two nations. Many universities from neighboring countries like India, Pakistan, Thailand and the Philippians each have at least one university that offers the Doctor of Pharmacy degree program; now is the time for Bangladesh to do the same. Many bright students in Bangladesh, if given the opportunity; would choose to practice in America and we would all be the beneficiaries of their contributions. Expediting the implementation of the Pharm.D. as the standard degree of the profession in Bangladesh is the next step we need to take for pharmacists who want to practice in the U.S., as well as in Bangladesh.

I am fortunate to be a part of this organization of professional healthcare practitioners and, like many of you, recognize our obligation to give back to our country. In addition to implement the Pharm.D. program there, we also want to collaborate with other organizations to improve healthcare as well as policies and systems that will provide better care for Bangladeshi citizens. While this is a daunting and long-term challenge, with dedication and commitment I am confident that we will accomplish our goals.

As a new practitioner, I want to encourage and motivate students and recent pharmacy graduates to become involved in our organization. I encourage you support our mission and our vision to work towards a better to implement a better health care system in Bangladesh, I urge you to become involved and together we can make a difference for hope and change in Bangladesh.

Mohammed Shabbir Taher

Message from the Treasurer

It is a privilege and an honor to hold the office of the Treasurer of BAPA and I wish to take this opportunity to welcome all the participants at BAPA Convention 2010.

Honor's Haven Resort and Spa, located at Ellenville, New York has been unanimously selected to be the center stage for this year's Convention. We believe that this location will do justice to the Convention's free spirited endeavors.

I would like to thank all the participants who have taken time off their busy schedules to be with us and make the event worthwhile. I also wish to thank all the Sponsors and Patrons, who have time and again supported our Association freely through their unprecedented financial help. Without this support and their participation, this event cannot achieve the success that it so deserves.

We look forward to the years ahead and firmly believe that this support will remain intact.

Any organization needs active participation by its members to succeed. We have been fortunate that BAPA has its fold unlimited number of such members that make this a vibrant and positive Organization. For this we are grateful to them. I am sure that BAPA will be stronger and will continue to make invaluable contributions to our community in the days to come.

From the Treasurer's desk, I wish you all a most enjoyable and successful Convention.

Md Mohiuddin

Treasurer, BAPA

From the Editor's Desk

I would like to welcome all the participants to the 19th Annual Convention of BAPA. With the support of the members and patrons, BAPA emerged as a very successful organization. We should contribute this phenomenal success to our members and the leadership that did set us in the right direction. The challenge that we face right now will be to sustain its vibrant growth by attracting new generation of pharmacists interested in its leadership.

This issue is dedicated to the the members, its patrons, their families and the committed leadership. Undoubtedly, our organization is one of the most successful community in North America.

This year the committee started late, so there was a lot of work cut out for us in a very short time, including this Journal. I thank all of the contributors who made such a 1st turn around. Also I thank all the patrons and advertisors who have been a constant support to foster the growth of this organizaton.

I am thankful to our President, Mahmud Hossain(Milton)who put in so much effort for this convention. I also thank our Executive Committee members who were also very helpful by giving us their input on various issues.

Have a most memorable and wonderful convention.

Devabrata Mondal, M.S., R.Ph.

From PSSNY President

The most important concept I can relay to BAPA is to get behind your state organizations and respond as one voice to issues. Do not let politicians or policy makers get the idea that pharmacy is fragmented in its support of legislation that may affect its financial stability. NCPA has achieved great successes on the national level in recent years by employing this strategy as well as raising money for Political Action Contributions. Many re-imbursement issues as well as issues enhancing scope of practice have their genesis in respective state legislative houses and enough lobbying must be done to insure we have our favorable outcomes as pharmacists.

Finally, get to know your representatives personally. This relationship can be cultivated and the goodwill garnished from it can lead to measureable results in the future in the progression of our agendas.

David Stachnik, Pres.

PSSNY

From NYCPS President

As President of the New York City Pharmacist Society (NYCPS), I offer my greetings and best wishes to the officers and members of BAPA at your annual convention. I truly appreciate the invitation extended to me to address your members, but I am unable to attend in person, due to a family function.

The survival of our industry is facing unprecedented difficulties; among them are: the cuts that we have withstood with Medicaid reimbursements, the unfair audits conducted by the Office of Medicaid Inspector General (OMIG), excessive regulations imposed by the state, the abuses of the PBMs and insurance companies, and Mandatory Mail Order Rx programs that prevent customers from even entering our pharmacies. That list can go on endlessly, but I'm sure you get the point. Our profession/business is under assault from many sides, and in order to be informed and able to protect ourselves, we must work together!

NYCPS is the regional affiliate of the state society (PSSNY), being the voice of pharmacy in the five boroughs. There are currently about 1,000 independent pharmacies in New York City – my goal is for all those pharmacy owners to become members, so that when we approach legislators about our issues, NYCPS would have credibility because of our numbers. NYCPS now has its own lobbyist in Albany (answerable to our board), supplementing the work done by the PSSNY lobbyist. NYCPS was instrumental in organizing the "Independent Pharmacy Lobby Day" conducted in March the last two years. Many BAPA members went to Albany with us, and I hope more will on March 2nd 2011. Our voices have certainly been heard by the senators and assemblymen, especially as it regards our goal of "Differential Medicaid Reimbursement for Independent Pharmacies". But, the fact that New York State is facing a huge budget deficit prevents us from being successful, at this time. But we must continue the fight..... and we will!

Lastly, I want you all to know that we are currently working hard on a project to combat Mandatory Mail Order Rx Programs. That project's goal is to let the legislators know about the public's outrage with Mail Order Rxs, by having a highly organized public relations campaign, culminating at our Pharmacy Owners Lobby Day in Albany on March 2, 2011. Your society's leadership will inform you of what you will need to do to actively participate in this project. Remember.....we can only be successful if we work together.

I thank you for this opportunity to address you, and hope you enjoy the balance of your convention.

Hoping to see you soon,

Ray Macioci

NYCPS President

Article

Article

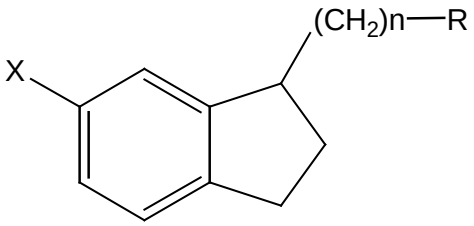
Synthesis and Biological Evaluation of Halo-Substituted Indan-1-Acids and its Derivatives.

Sitesh C. Bachar

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

Abstract

A number of halo substituted indan-1-acids, -amides, nitriles and tetrazoles have been synthesized and reported. The structures of the compounds were elucidated with UV, IR, MS, ^{1}H-NMR and ^{13}C-NMR spectral analyses. The compounds were studied for their various biological activities as plant growth regulatory, analgesic and anti-inflammatory agents.



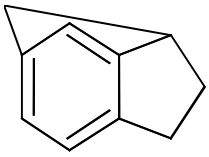
X = F, Cl, Br; n = 0 or 1; R = -COOH, -$CONH_2$, -CN, -CHN_4 (Tetrazole)

Keywords: Indan-1-acids, Indan-1-carboxylic acids, Indan-1-acetic acids, amides, nitriles, tetrazoles, plant growth regulator, analgesic, anti-inflammatory agent.

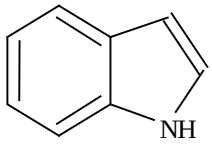
Corresponding authors: Sitesh C Bachar, Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000. Bangladesh

Introduction

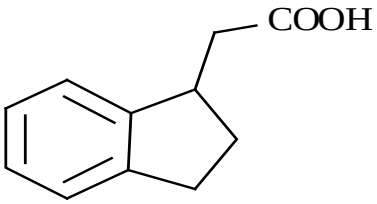
Indan ring system (A), a isostere of indole ring system (B), has been regarded as an ideal carrier associated with various biological activities (Ganellan CR 1967)[1].



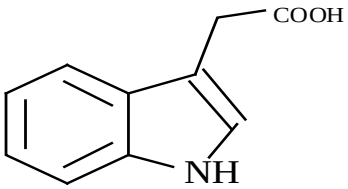
(A)



(B)



Indan-1acetic acid (D)



Indole-3-acetic acid (C)

Natural auxin has been characterized chemically as indole-3-acetic acid (D) that regulates plant growth especially by acting on root elongation (Marumo *et al* 1968). Indan-1-carboxylic acid was found to cause root elongation of wheat seedlings (Bustrom and Hansen 1956) [3] and its L-ispmers appeared to be more active than D-isomers (Fredga 1956). There are five groups of plant growth regulators namely auxins, giberelins, cytokinins, absisic acid and ethylene are regarded as phytohormones. These plant growth regulators mainly modify the crop's growth pattern by changing its response to internal and external factors that govern crop's development from germination to senescence. Auxin, the indole-3-acetic acid C), regulates plant growth and specially acts on root elongatoion[2]. The indan-1-acetic acid (D) is structurally similar to that of indole-3-acetic acid. The plant growth regulatory activity or the auxin like activity of the indan-1-acids with halo substitutions was evaluated on different bioassay models like roots and shoots elongation of Mustard (Brassica juncea L.) seedlings, hypocotyls growth inhibition of Chinese cabbage (Brassica pekinensis L.) and pea (Pisum sativum L.) and hypocotyls swelling and lateral root formation of Mung bean (Vigna radiata L.)[3,4] using indole-3-acetic acid (IAA), 2,4-dichlorophenoxy acetic acid (2,4-D) and naphthalene acetic acid (NAA) as the reference standards (Bachar and Lahiri, 1994; Bachar and Lahiri 1999 and Bachar and Lahiri 2000).

Compounds containing indan ring systems, especially with carboxylic acid functionality, possess anti-inflammatory activity. Among indan derivatives 1*H*-indene-3-acetic acid -5-fluoro-2-methyl-1-[4-(methylsulfonyl)-phenyl] methylene (Sulindac) and indan-1,3-dione are well know anti-inflammatory agents (Shen 1972). Significant anti-inflammatory activity was among a series of substituted indan-1-carboxylic acid (Juby *et al* 1972). Moreover a number of methoxy indan-1-alkanoic acids were synthesized with considerable anti-inflammatory properties

(Mukhapadhya and Lahiri 1992). With the advent of clindac (6-choloro-5-hexyl-indan-1-carboxylic acid) (Juby *et al* 1984) as anti-inflammatory agent of indane derivatives established for therapeutic use, various hlao substituted indanyl tetrazoles and indayl methyltetrazoles have been synthesized. Indane derivatives, with halo substitution could be a responsible means of increasing the analgesic and anti-inflammatory activities and widening the margin of safety (Bachar and Lahiri 2000, Bachar and Lahiri 2004, Das et al 2008, Yasmin et al 2009). Analgesic and anti-inflammatory drugs that are in use today show considerable variations in potency, incidence of side effects and individual patient responses. Because of the major limitations of existing NSAIDs it has become necessary to develop more effective and less toxic new analgesic and anti-inflammatory agents. The most common serious drawback of all analgesic and anti-inflammatory drugs is that they cause serious acidity problems which limits their use in many cases. As a result most of the patients were unable to continue these drugs for their ailment from diseases. To circumvent the acidity or gastrointestinal effects of anti-inflammatory drugs several newer templates or leads were selected which include indole nucleus, arylalkyl acid nucleus, pyrazolone, indan etc. and attempt has been taken to discover novel anti-inflammatory agent without or less gastrointestinal effects (Winter C.A. *et al*, 1963 and Remington, 1990). These nuclei were undergone some structural or molecular modifications either by introducing functional groups or ring fusion. Both the modifications resulted many promising anti-inflammatory agents. It was already established that tetrazole, an aromatic azapyrrole group, is metabolically stable (Fidgor *et al, 1967)* and has acidic characteristics closely similar to that of the carboxylic group (Herbst, 1956). At the same time it has been reported that anti-inflammatory and related biological activities have been improved or abolished by the substitution of a 5-tetrazole group in place of carboxyl function (Ganellin, 1967). In this context a number of indanyltetrazoles have been synthesized and encouraging anti-inflammatory activity has been noted (Roy *et al.,* 1983, Ray *et al.*, 1990, and Roy *et al.*, 1985. The remarkable achievements were 5-(6□-methoxyindan-1□-yl)tetrazole and 5-(5□,6□-dimethoxyindan-1-yl)tetrazole. The present communication deals with the reports of the plant growth regulatory, analgesic and anti-inflammatory activities of the halo substituted indan-1-acids and their amide, nitrile and tetrazole derivatives

Experimental

General

The chemicals and solvents used in various reactions were purchased from Merck (Germany), BDH (India) or SD Fine Chemicals (India), and used without purification. The melting points were determined by using Adco Melting Point Apparatus and were uncorrected. Thin-layer chromatography was performed using Kieselgel 60 F254 plates (Merck). The absorption maxima (lmax) of all the newly synthesised compounds were determined in absolute methanol by using Genesis-2 spectrophotometer. By using 8010M

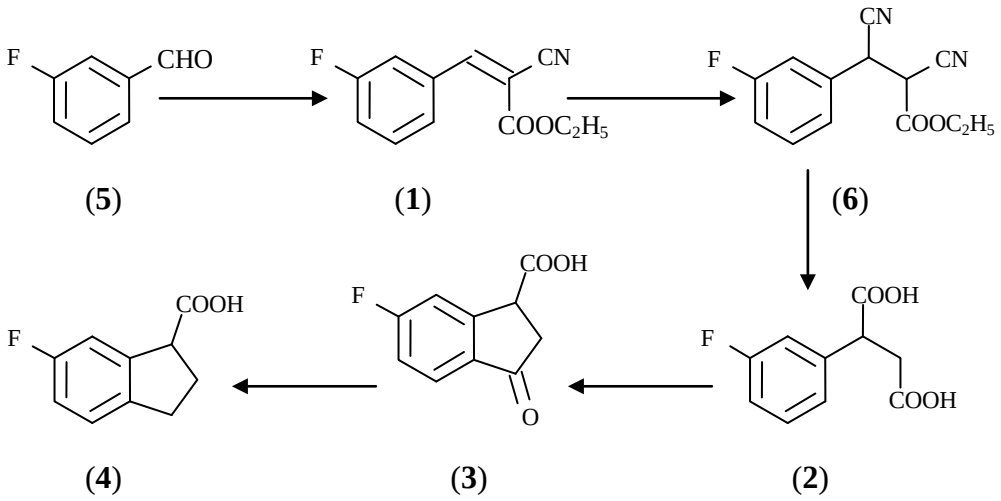
FTIR spectrometer, the characteristic absorption bands (nmax) of the newly synthesised compounds were recorded on KBr disk. NMR spectra were recorded in CD_3OD on a Bruker AVANCE 500 MHz NMR spectrometer

(500 MHz for 1H and 125 MHz for 13C) using the residual solvent peaks as internal standard. MS analyses were performed, on a Finnigan MAT95 spectrometer. HMBC spectra were optimised for a long range JH–C of 9 Hz and NOESY experiment was carried out with a mixing time of 0.4 s.

Synthesis of 6- fluoroindan-1-carboxylic acid (4)

6-Fluoroindan-1-carboxylic acid (6) was conveniently synthesized from 3-fluorobenzaldehyde (5) in six steps with an overall 24% yield (Scheme I). The five intermediates were 3-fluorophenylcyanoethylacrylate (1), 3-fluorophenyl-a,b-dicyanoethyl propionate (6), 3-fluorophenyl succinic acid (2), 3-fluorophenyl succinyl chloride (7, not shown in the scheme) and 6-fluoro-3-oxo-indan-1-carboxylic acid (3). Among these intermediates, compounds 1–3 were isolated in pure form. The structures of compounds 1–4 were elucidated by spectroscopic means (Das *et al* 2008), notably, UV, IR, HRMS and extensive 1D and 2D NMR analyses (1H and 13C NMR, 1H–1H COSY, 1H–13C HSQC and 1H–13C HMBC).

Scheme-I

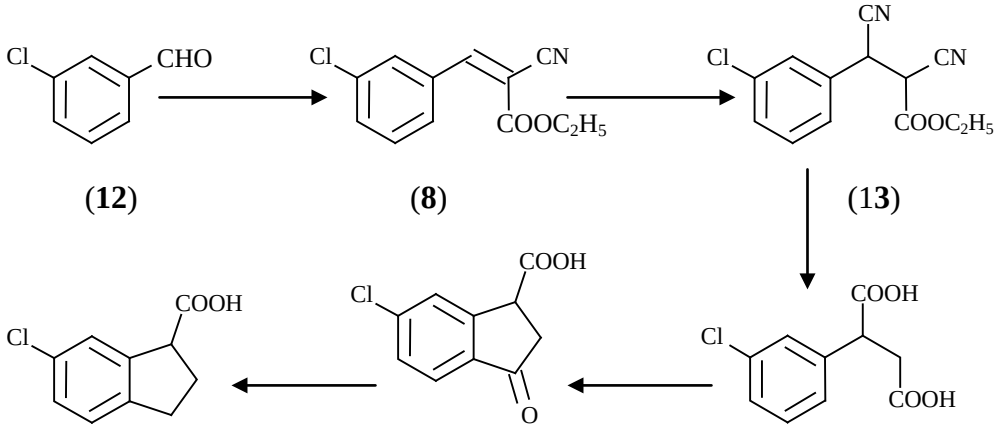


After removal of the solvent under reduced pressure, the resulting solid mass was recrystallised from alcohol–water to give 6-fluoroindan-1-carboxylic acid (**4**) (1.36 g, 76%).

Synthesis of 6- chloroindan-1-carboxylic acid (11)

For the synthesis of 6- chloroindan-1-carboxylic acid, 3-chlorobenzaldehyde (**12**) was condensed with ethyl cyanoacetate in presence of pyridine following Knoevenagel reaction (Scheme-II). The condensed product (8) was cyanated to get dicyanoderivative (**13)**, which was hydrolyzed to get 3-chlorophenyl succinic acid (**9**). The compound **9** was cyclized to 6-chloro-3-oxo-indan-1-carboxylic acid (**10**). The compound 6- chloroindan-1-carboxylic acid (**11**) was obtained by Clemmensen reduction of compound **10**.

Scheme II

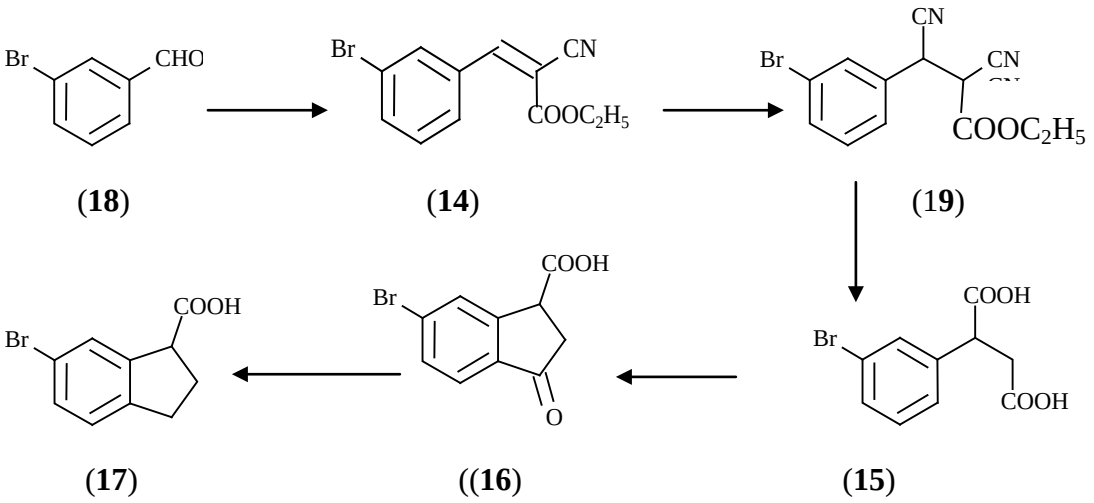


The 6-chloroindan-1-carboxylic acid (Khishimoto et al and Bachar and Lahiri 2000) thus obtained was recrystallized from ethanol water in 60-62% yield, mp-126-128°C. The structure of the compound **11** and its intermediates were elucidated through spectral analyses (Bachar and Lahiri 2000).

Synthesis of 6-bromoindan –1-caboxylic acid (17)

For the synthesis of 6- bromoindan-1-carboxylic acid, 3-bromobenzaldehyde (**18**) was condensed with ethyl cyanoacetate in presence of pyridine following Knoevenagel reaction (Scheme-III). The condensed product (14) was cyanated to get dicyanoderivative (**19**) which was hydrolyzed to get 3-bromophenyl succinic acid (**15**). The compound **15** was cyclized to 6- bromo-3-oxo-indan-1-carboxylic acid (**16**). The title compound, 6- chloroindan-1-carboxylic acid (**17**) was obtained by Clemmensen reduction of compound **16**.

Scheme III

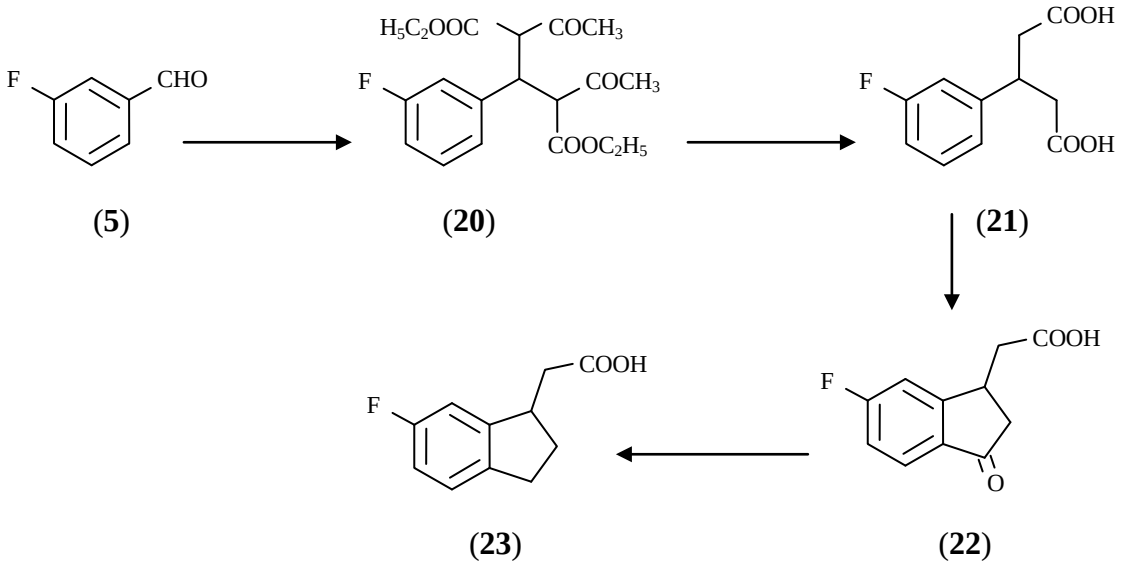


After removal of the solvent, 6-bromoindan-1-carboxylic acid (**17**) thus obtained was re-crystallized from ethanol water in 65-67% yield, mp-134-135°C. The structure of the compound **11** and its intermediates were elucidated through spectral analyses (Bachar and Lahiri 2000).

Synthesis of 6-fluoroindan-1-acetic acid (23)

6-Fluoroindan-1-acetic acid (**23**) was conveniently synthesized from 3-fluorobenzaldehyde (**5**) in five steps with an overall 30.1% yield (Scheme **VI**). The four intermediates were 3-fluorobenzylidine-*bis*-acetoacetate (**20)**, 3-fluoro-β-phenyl glutaric acid (**21**), 3-fluorophenyl succinyl chloride (**24,** not shown in the scheme) and 6- fluoro-3-oxo-indan-1-acetic acid (**22**). The structures of compounds **20, 21, 22** and **23** were eluci dated unambiguously by spectroscopic means, particularly by comprehensive 1D and 2D NMR analyses, e.g. ^{1}H-NMR, ^{13}C- NMR, ^{13}C- DEPT-135, ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC (Yasmin *et al* 2009). The UV spectral analyses of **20, 21, 22** and **23** revealed the presence of aromaticity in these molecules. The IR spectra revealed the presence of ester and ketonic carbonyl functionalities and a C-F in **20**; a C-F and a carboxylic acid (COOH) moieties in **21**; a COOH, a ketonic carbonyl and a C-F groups in **22**; and a COOH and a C-F moieties in **23**.

Scheme VI



(**5**) (**20**) (**21**) (**22**) (**23**)

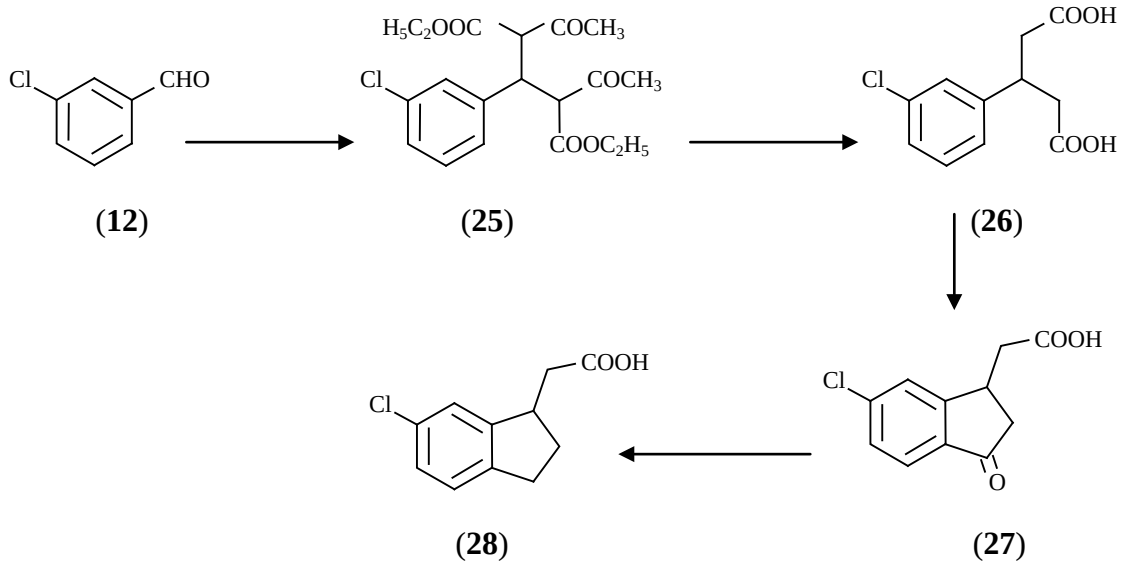
After removal of the solvent *in vaccuo*, a brownish oily liquid was obtained. Compound **23** (7.3 g; mp 48-50°; yield 75.5%) was obtained as a crystalline solid (from alcohol water) from this oily liquid.

Synthesis of 6-chloroindan-1-acetic acid (16)

For the preparation of 6-chloroindan-1-acetic acid (**28**), 3-chlorobenzaldehyde (**12**) was condensed with ethylacetoacetate) in presence of piperidine (Scheme-V). The condensed product, 3-chlorobenzylidine-*bis*-

actoacetate (**25**) was hydrolysed with 25%koholic KOH solution by refluxing on water bath. The hydrolyzed product, 3-chloro-β-phenylglutaric acid (**26**), was cyclized using polyphosphoric acid to get 6-chloro-3-oxo-indan-1-acetic acid (**27**). Clemmensen reduction of the compound **15** resulted 6-chloroindan-1-acetic acid (**28**).

Scheme V

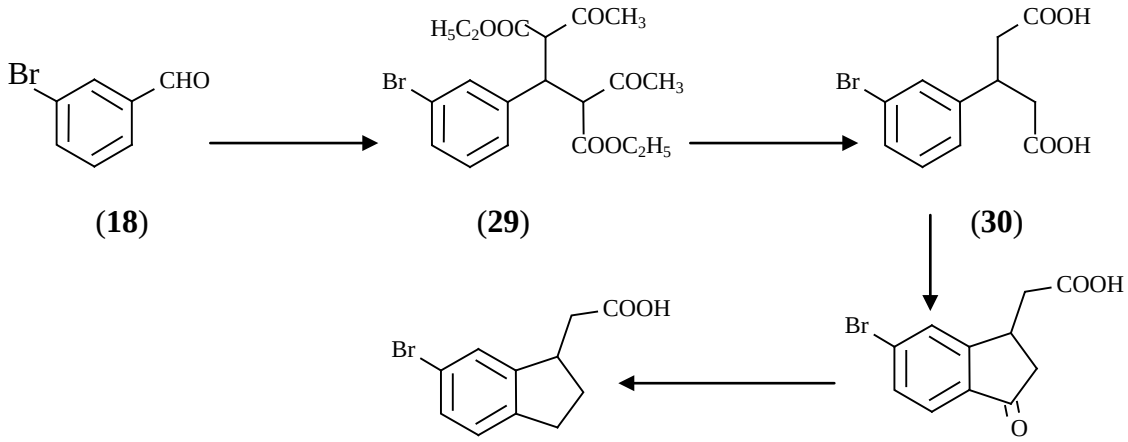


The title compound **28** as oil was distilled at 146-148°C/2.0mm-Hg (η_{32}=1.5545) and solidified on cooling. The product was re-crystalized from ethanol-water (yield 61%), mp-51-52°C. The structure of the compound **28** and its intermediates were elucidated through spectral analyses (Bachar and Lahiri 2000).

Synthesis of 6-bromoindan –1-acetic acid (32)

For the preparation of 6-bromoindan-1-acetic acid (**32**) , 3-bromobenzaldehyde (**18**) was condensed with ethylacetoacetate) in presence of piperidine (Scheme-VI). The condensed product, 3-bromobenzylidine-*bis*-actoacetate (**29**) was hydrolyzed with 25% alcoholic KOH solution by refluxing on water bath. The hydrolyzed product, 3-bromo-β-phenylglutaric acid (**30**), was cyclized using polyphosphoric acid to get 6-bromo-3-oxo-indan-1-acetic acid (**31**). Clemmensen reduction of the compound **31** resulted 6-chloroindan-1-acetic acid (**32**).

Scheme VI



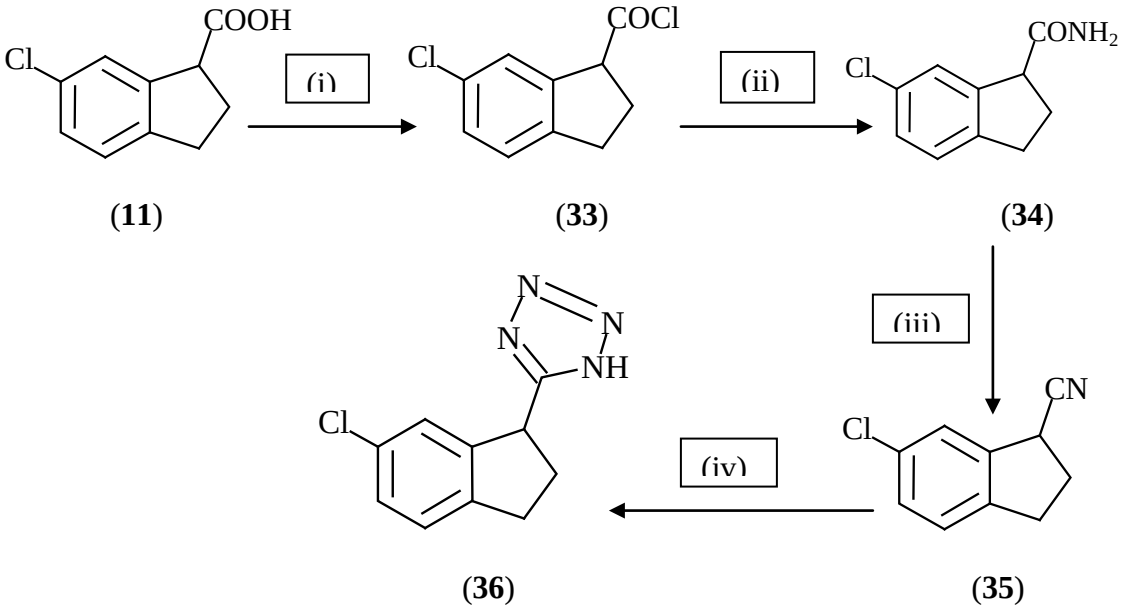
(**18**) (**29**) (**30**) (**31**) (**32**)

The title compound **32** as oil was distilled at 128-130°C/1.0mm-Hg (η_{32}=1.5622) and solidified on cooling. The product was re-crystallized from ethanol-water (yield 66%), mp-47-49°C. The structure of the compound **32** and its intermediates were elucidated through spectral analyses (Bachar and Lahiri 2000).

Synthesis of 5-(6'-chloroindan-1-yl)tetrazole (36)

The compound 5-(6'-chloroindan-1-yl)tetrazole (**36**) was synthesized from 6-chloroindan-1-carboxylic acid (**11**) as shown in **Scheme-VII**. The compound **11** was treated with thionyl chloride in dry benzene and refluxed for 1.5h. The 6-chloroindan-1-carboxylic acid chloride (**33**) thus obtained was immediately added to ammonia solution at 1-5° to give 6-chloroindan-1-carboxamide (**34**, 85%) following Schotten-Baumann reaction as colorless crystalline needles. The compound **34** was then dehydrated with P_2O_5 in dry benzene refluxing for 1.5h. After decomposing the reaction mixture and working up made the compound **35** (6-chloroindan-1-carbonitrile, 78%) as a colorless crystalline solid. Subsequently, 6-chloroindan-1-carbonitrile (**35**) was allowed to react with activated NaN_3 in presence of NH_4Cl in DMF at 130-140° for 46h to afford 5-(6'-chloroindan-1'-yl)tetrazole (**36**) (50%) as a white crystalline powder.

Scheme-VII



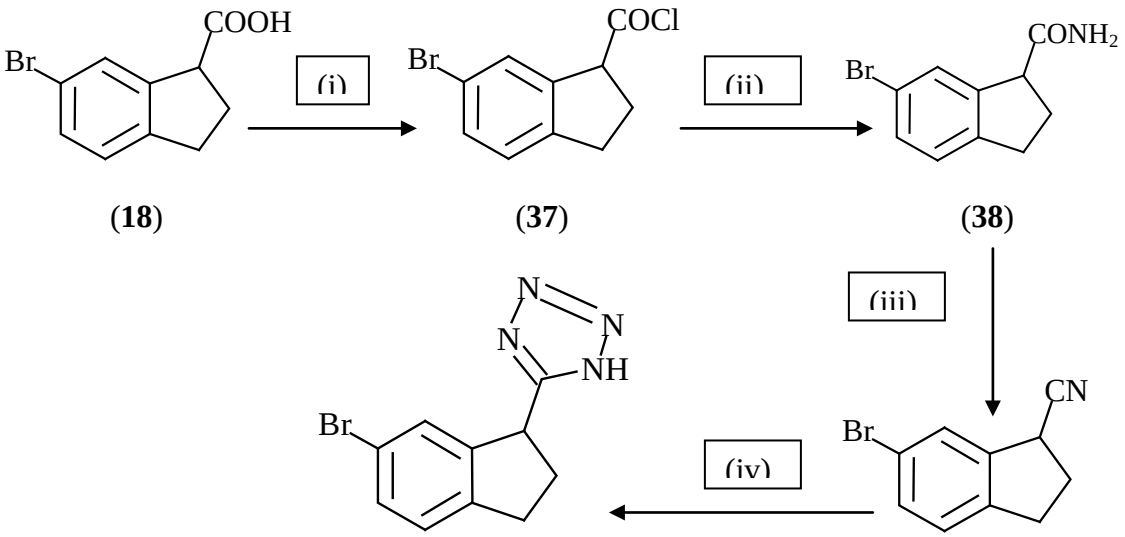
Reaction condition: (i) $SOCl_2$, Dry C_6H_6, 1.5h; (ii) NH_4OH, Dry C_6H_6, Stirring 1.0h, 1-5°; (iii) $POCl_3$, $Na_2S_2O_3$, or P_2O_5, Dry C_6H_6, 2.0h; (iv) activated NaN_3, NH_4Cl, Dimethylformamide (DMF), 130-140°, 46h.

The structure of the compounds **34**, **35** and **36** were confirmed by various spectral analyses (Bachar and Lahiri 2004). Compound **36** was established by fast atomic bombardment mass spectroscopy (FAB-MS) and ^{13}C-NMR data consistent with the molecular formula $C_{10}H_{10}ONCl$, having molecular ion peak at m/z 196.0534 (M+1). In ^{1}H-NMR spectroscopy, compound **34** also exhibited characteristic singlets at δ 6.99 and 6.36 ppm due to two primary amine protons, which were dropped by D_2O exchange spectrum. Compound **35** was ascertained by FAB-MS and elemental microanalyses data corresponding to $C_{10}H_8NCl$ having molecular ion peak at m/z 178.0231 (M+1). The IR spectrum of the compound showed an absorption band at 2236 cm^{-1} ascribable to the nitrile functional group. Compound **36** was also established by EIMS and elemental microanalyses data corresponding to the molecular formula $C_{10}H_9N_4Cl$, having molecular ion peak at m/z 220.3(M^+). The ^{1}H-NMR data of compound **36** were almost similar to those of **34** and **35**. Only the tetrazole proton of the compound was not shifted in the spectrum due to tautomerisation.

Synthesis of 5-(6'-bromoindan-1-yl)tetrazole (40)

Compound **38**, **39** and **40** were obtained starting from 6-bromoindan-1-caboxylic acid (**18**) in **Scheme-IX** following the same procedure as mentioned for compounds **34**, **35** and **36**.

Scheme-XI



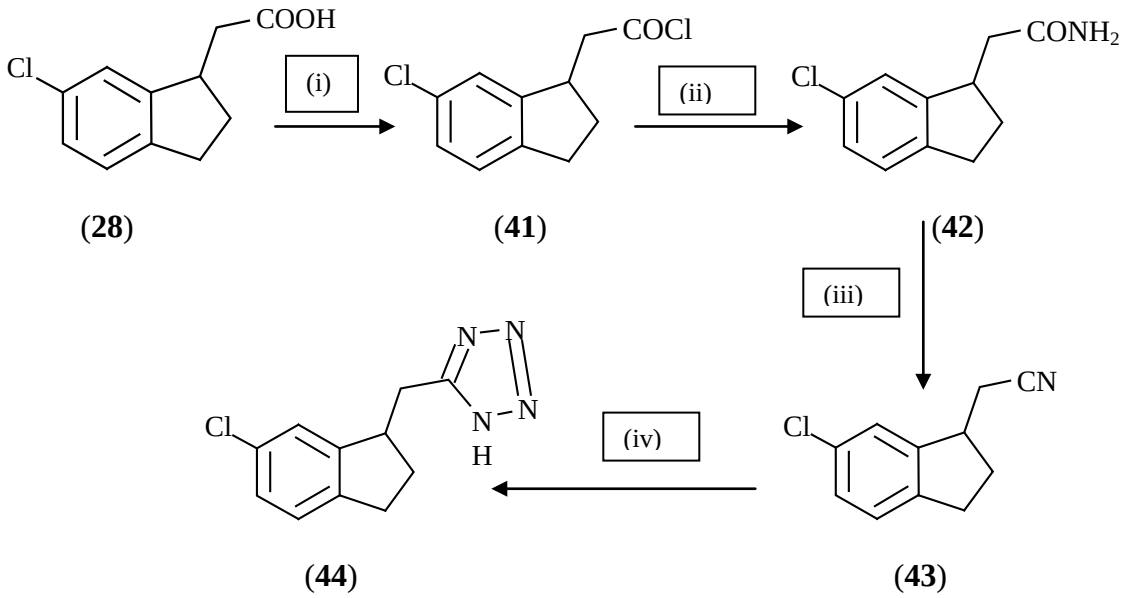
Reaction condition: (i) $SOCl_2$, Dry C_6H_6, 1.5h; (ii) NH_4OH, Dry C_6H_6, Stirring 1.0h, 1-5°; (iii) $POCl_3$, $Na_2S_2O_3$, or P_2O_5, Dry C_6H_6, 2.0h; (iv) activated NaN_3, NH_4Cl, Dimethylformamide (DMF), 130-140°, 46h .

Compound **38** was colorless needles obtained in 88% yield and was established by FAB-MS and ^{13}C-NMR spectroscopy to molecular formula $C_{10}H_{10}ONBr$ having molecular ion peak at m/z 240.0018 (M+1). In ^{1}H-NMR spectroscopy the compound exhibited characteristic two primary amine protons as separate singlet at δ 7.00 and 6.37ppm respectively, which were dropped by D_2O exchange spectrum. Compound **39** obtained as yellowish crystals in 82% yield and was ascribed by FAB-MS and elemental microanalyses data consistent with the molecular formula $C_{10}H_8NBr$, having molecular ion peak at m/z 222.0764 (M+1). Compound **40** was obtained as brownish crystalline solid in 52% yield. It was also established by EIMS and elemental microanalyses corresponding to molecular formula $C_{10}H_9N_4Br$, having molecular ion peak at m/z 264.3(M^+). The ^{1}H-NMR spectrum of the compound **40** was similar to those of **35** and 36. Only the tetrazole proton of the compound was not shifted in the spectrum due to its tautomeric nature (Bachar and Lahiri 2004).

Synthesis of 5-(6'-chloroindan-1-yl)methyltetrazole (44)

Compound **42**, **43** and **44** were obtained starting from 6-chloroindan-1-acetic acid (**28**) in **Scheme-X** following the same procedure as mentioned for compounds **34**, **35** and **36**.

Scheme-X



Reaction condition: (i) $SOCl_2$, Dry C_6H_6, 1.5h; (ii) NH_4OH, Dry C_6H_6, Stirring 1.0h, 1-5°; (iii) $POCl_3$, $Na_2S_2O_3$, or P_2O_5, Dry C_6H_6, 2.0h; (iv) activated NaN_3, NH_4Cl, Dimethylformamide (DMF), 130-140°, 50h.

Compound **42** was synthesized from 6-chloroindan-1-acetic acid [10] (**28**) following the method as those of **34** and **38**. The compound was obtained as white crystalline needles in 87% yield. The structure was determined by FAB-MS and ^{13}C-NMR data consistent with the molecular formula $C_{11}H_{12}ONCl$, having molecular ion peak m/z at 210.0698(M+1). In the ^{1}H-NMR spectroscopy compound **42** showed characteristic two primary amine protons as separate singlet at δ 6.85 and 6.24ppm respectively, which were dropped by D_2O exchange spectrum. Compound **43** was obtained by dehydrating the compound **42** using P_2O_5 in dry benzene. Then after decomposition with water and subsequent extraction of the reaction mixture with C_6H_6, the solvent was evaporated, the material was subjected to column chromatography with silica gel and the compound was obtained as yellowish oil in 79% yield (Bachar and Lahiri 2004).

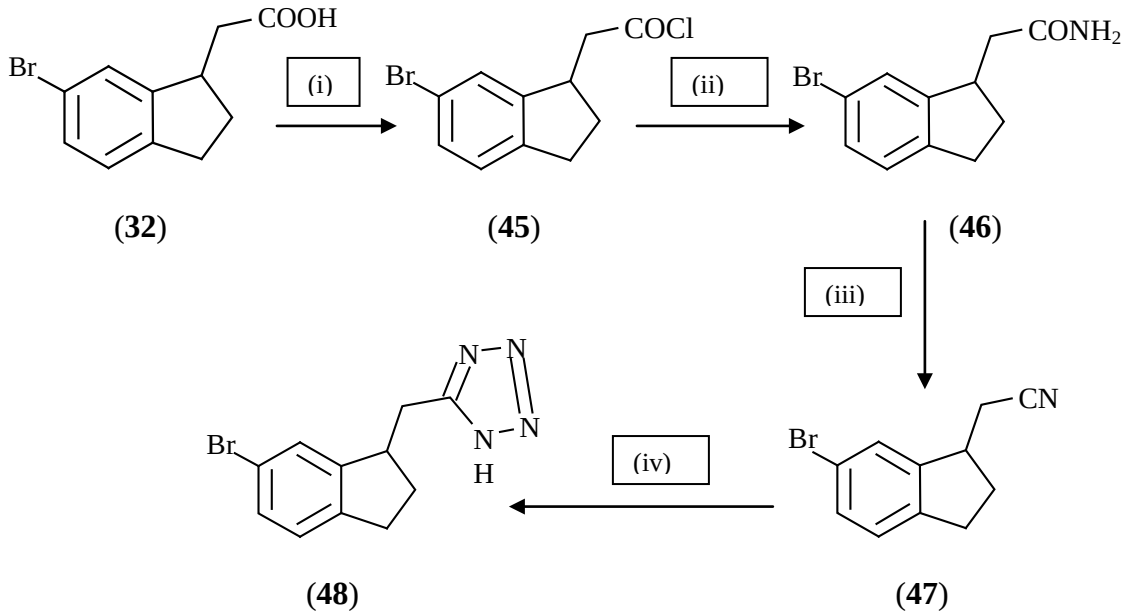
Compound **43** was ascertained by FAB-MS and elemental micro analyses data indicating the molecular formula $C_{11}H_{10}NCl$, having molecular ion peak m/z at 192.0813. The IR spectrum of the compound **43** showed characteristic absorption band at 2252 cm^{-1} ascribable to the nitrile functional group. Compound **44** was synthesized following the method as those of **36** and **40**, only the changing in reaction time for 50h. The compound obtained as light brown crystalline powder in 53% yield. The structure of the compound **44** was determined by EIMS and elemental microanalyses data confirming the molecular formula $C_{11}H_{11}N_4Cl$, having molecular ion peak m/z at 234.2 (M^+).

The ^{1}H-NMR spectrum of the compound was almost similar to those of **42** and **43**. Only the tetrazole proton of the compound **32** was not shifted in the spectrum due to tautomerisation.

Synthesis of 5-(6'-bromoindan-1-yl)methyltetrazole (48)

Compound **46**, **47** and **48** were obtained starting from 6-chloroindan-1-acetic acid (**28**) in **Scheme-X** following the same procedure as mentioned for compounds **42**, **43** and **44**.

Scheme-VIII



Reaction condition: (i) $SOCl_2$, Dry C_6H_6, 1.5h; (ii) NH_4OH, Dry C_6H_6, Stirring 1.0h, 1-5°; (iii) $POCl_3$, $Na_2S_2O_3$, or P_2O_5, Dry C_6H_6, 2.0h; (iv) activated NaN_3, NH_4Cl, Dimethylformamide (DMF), 130-140°, 48h .

Compound **46** was synthesized from 6-bromoindan-1-acetic acid (**32**) following the method as those of **34**, **38** and **42**. The compound **46** was obtained as white crystalline needles in 90% yield. The structure was determined by FAB-MS and ^{13}C-NMR data consistent with the molecular formula $C_{11}H_{12}ONBr$, having molecular ion peak m/z at 254.0190 (M+1). In the ^{1}H-NMR spectroscopy compound **46** showed characteristic two primary amine protons as separate singlet at δ 6.82 and 6.23ppm respectively, which were dropped by D_2O exchange spectrum. Compound 47 was prepared by dehydrating the compound **46** using P_2O_5 in dry benzene. Then after decomposition with ice water the reaction mixture was worked up followed by column chromatography with silica gel, as that of **43** and the compound **47** was obtained as yellowish oil in 84% yield. The structure of compound **47** was confirmed by ^{1}H-NMR and elemental microanalyses data indicating the molecular formula $C_{11}H_{10}NBr$, having molecular ion peak m/z at 235.0533. The IR spectrum of the compound showed characteristic absorption band at 2252 cm^{-1}

ascribable to the nitrile function. Compound **48** was synthesized following the method as that of **44** in 50% yield as a light brown crystalline powder. The structure of the compound **48** was determined by EIMS and elemental microanalyses data confirming the molecular formula $C_{11}H_{11}N_4Cl$, having molecular ion peak m/z at 278.3 (M^+). The ^{1}H-NMR spectrum of the compound was almost similar to those of **46** and **47**. Only the tetrazole proton of the compound **36** was not shifted in the spectrum due to tautomerisation (Bachar and Lahiri 2004).

Plant growth regulatory activity on mustard (Brassica junceae L.) seedlings

The synthesized compounds **6**, **12**, **16** and **20** were investigated for their activity on rots and shoots elongation of mustard seedlings. Healthy mustard seedlings were collected and allowed to germinate on filter paper containing distilled water for 24 h at roon temperature. Ten grown seeds taken on a filter paper wee placed in a petridish (.5cm dia) containing 5ml of aqueous solution of each test sample at 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, and 10^{-4} M concentration levels separately and were allowed to grow in day light for 72 h at 28 ± 2°C day temperature in laboratory conditions. The experiment was repeated three times with three replicates for each sample and the length of the roots and shoots were measured for respective concentrations. The growth obtained in terms of promotion and inhibition on the basis of water content was compared with reference standard indole-3-acetic acid (IAA) and naphthalene acetic acid (NAA). (Table-1&2).

The percentage of growth was obtained by using the formula -

$$\% \text{ growth} = \frac{\text{Elongation of pea segments in treatment solutions}}{\text{Elongation of pes segments in buffer control}} \text{ x100}$$

Hypocotyl growth inhibition of Chinese cabbage (Brassica pekinensis L.)

Healthy Chinese cabbage seeds were allowed to germinate and grow on filter paper in a petridish containing distilled water for 24h at room temperature. The primary grown seeds taken in a petridish (6.0 cm dia) containing 4ml of aqueous solution of each test sample at 10^{-6}, $5x10^{-6}$, 10^{-5}, $5x10^{-5}$ and 10^{-4} M concentrations wee incubated and allowed to grow in the dark at 25±0.1°C for 72h. The experiments were repeated three times with three replicates for each sample and length of hypocotyls was measured for respective concentrations. Here IAA, 2,4-dichlorophenoxy acetic acid (2,4-D) and NAA were used as reference standard and compared (Table-3).

Effect on elongation of pea (Pisum sativum L.) epicotyl segments.

The test compounds were further studied to observe their effect on elongation of pea *(Pisum sativumL)* epicotyl segments. Peas wee allowed to grow on wet cotton sheet in a petridish for seven days up to third internode

stage in the dark at room temperature 27 ±2 °C in laboratory conditions. Ten 1cm ections, taken 5mm below the apical hook of the seedlings, were incubated, in duplicate, in 5ml of each test solution containing 5mM K-maleate buffer pH 5.5 at concentrations of 5x10-8, 5x10-7, 5x10-6 and 5x10-5M separately for 16h at 25±0.1°C with gentle shaking. The experiment was repeated three times with three replicates. Final length of the epicotyls were measured and expressed as a percentage of growth obtained in buffer control. IAA, 2,4-D and NAA were used as reference standards.

The percentage of growth was obtained by using the formula

$$\% \text{ growth} \quad \frac{\text{Elongation of pea segments in treatment solutions}}{\text{Elongation of pes segments in buffer control}} \text{ x100}$$

Plant growth regulatory activity on hypocotyls swelling and lateral root formation of mung bean (Vigna radiata L.)

Mung bean seeds were primarily grown on wet cotton bed in a petridish for 24h at room temperature and laboratory conditions. Six grown seeds were incubated in a petridish (5 cm dia) on a cotton sheet containing 3ml of aqueous solution of each sample at concentration of 10^{-6}, $5x10^{-6}$, 10^{-5}, $5x10^{-5}$ and 10^{-4}M separately in the dark at 25±0.1°C for 72h. The experiment was replicated three times using IAA, 2,4-D and NAA as reference standards and water as control. IAA, compound 16 and 20 were studied only at concentration 10^{-3}M to compare their effect on lateral root formation and hypocotyls swelling.

Evaluation of analgesic activity

Adult *Swiss albino* mice (4 to 5 weeks) weighing 20 to 25 g were used to study the analgesic activity by the acetic acid-induced writhing test as described by Vogel and Vogel with slight modifications. Animals were divided into different groups consisted of five in each. Test drugs were given orally to the respective groups of animals at dose levels of 25 and 50 mg/kg body weight and the standard drugs phenylbutazone and indomethacin were given at doses of 100 and 10 mg/kg body weight, respectively. Control mice were treated with normal saline only. After 45 min of drug administration, acetic acid solution (0.7%, 0.10 mL/10g) was administered intraperitoneally (i.p.) to the each group of animals. After an interval of ten minutes, numbers of writhing were counted for another 10 min. The percent inhibition of writhing was measured using the following formula.

$$\text{Percent inhibition} = \frac{W_c - W_t}{W_c} \text{ x 100}$$

Where W_C represents the average writhing produced by the control group and W_t represents the average writhing produced by the test group, respectively. The result of the study was represented in Table-5.

Evaluation of anti-inflammatory activity

The synthesized compounds were evaluated for anti-inflammatory activity by carrageenan induced rat paw edema model on Long *Evans* rats. The test compounds and the reference standard phenylbutazone were dissolved in suitable solvents, which were administered orally to the animals in the test group. After 1 hour of oral administration of the drugs, 1% carrageenan suspension (0.1ml) were injected to the sub planter region of the hind paw. Paw volumes were measured before and after 1, 2, 3, 4 and 24 hour of carrageenan administration up to the fixed mark at the level of lateral mallcolus. The average percent increase in paw volume calculated and compared against that of control group. Percent inhibition were calculated using the formula-

$$\%\text{Inhibition} = (Vc - Vt)x100/Vc$$

where, Vc and Vt were the average edema volumes of control and tested groups respectively. The results of the study were represented in Table-6.

Result and Discussion

As a part of investigation for the evaluation of various biological activities halo substituted indan-1-carboxylic acids, indan-1-acetic acids, 5-(indan-1'-yl)tetrazole and 5-(indan-1'-yl)methyltetrazole were synthesized. The results obtained were reviewed and discussed. On the basis of the previous history and types of the compounds they were evaluated in plant growth regulatory activity, analgesic and anti-inflammatory activity.

From the results of the different plant bioassay models it was evident that the growth promoting and inhibiting activity i.e. the growth regulatory activity of the compounds 11, 17, 28 and 32 were dependent on concentration, being growth retardation at higher concentration and growth promotion at lower concentration in comparison to the IAA, 2,4-D and NAA. Among the test compounds, 6-chloroindan-1-carboxylic acid **(11**) and 6-bromoindan-1-carboxylic acid **(17**) exhibited significant auxin like activity in comparison to 6-chloroindan-1-acetic acid **(28**) and 6-bromoindan-1-acetic acid **(32**). The 5-(6'-chloroindan-1'-yl)tetrazole (**36**), 5-(6'-bromoindan-1'-yl) tetrazole (**40**), 5-(6'-chloroindan-1'-yl)methyltetrazole (44) and 5-(6'-bromoindan-1'-yl)methyltetrazole (**48**) did not exhibited better plant growth regulatory activity as was observed in compounds **28** and **32** (Bachar and Lahiri 1999, Bachar and Lahiri 1994). The experimental results indicated that the chlorine, the more electronegative substitution at the benzenoid part of the indan nucleus, potentiates the auxin like activity of the indan molecule (Table 1, 2, 3, and 4). The fluoro substituted compounds were not evaluated for plant growth regulatory activity.

On the basis of previous study the anti-inflammatory and analgesic activity of Clindac, indan-1,3-dione and the marketed product Sulindac, compound **4**, **23, 36, 40, 44** and **48** were also evaluated for their analgesic and anti-

inflammatory activity due their structural similarities. The analgesic activity for acetic acid induced writhing on *albino* mice was measured for compounds **4**, **23**, **36**, **40**, **44** and **48.** Compounds **4** (Das *et al* 2008*)* and **23** (Yasmin *et* al 2009) exhibited significant analgesic activity than those of compounds **36, 40, 44** and **48** in different experiment (Bepary *et al* 2008). The significant ($p<0.001$) analgesic activity, exhibited by the compound 6-fluoroindan-1-carboxyc acid **(4)** and 6-fluoroindan-1-aceic acid (**23)** at a dose of 50mg/kg body weight, was comparable to that of aminopyrine with 47.89 % ($p<0.0005$) inhibition at a dose of 30mg/kg body weight, indomethacin with 48.50% ($p<0.0005$) inhibition at 8mg/kg body weight and diclofenac Na with 62.88% ($p<0.0005$) inhibition at 10mg/kg body weight. Among the two compounds 6-fluoroindan-1-aceic acid (**23)** showed the maximum effect. So, a one carbon chain length increase between the carboxyl function and indan ring system increased analgesic activity was observed. The effect of substitution at the benzenoid part of the indan nucleus and chain lengthening on analgesic activity was approximately in the following order respectively: fluoro > bromine > chlorine and tetrazole > methyltetrazole (Table-5a and 5b). Compounds **11, 17, 28** and **32** were not reported, but a significant analgesic and anti-inflammatory were observed which will be communicated in near future.

The writhing reflex in mice induced by acetic acid is a sensitive procedure to evaluate the potential analgesic activity of drugs. It has been suggested that acetic acid acts by releasing endogenous mediators, which stimulate the nociceptive neurons in mice (Collier et al 1968). Acetic acid is sensitive to cyclooxygenase inhibitors and has been used to evaluate the effect of analgesic agents, which primarily inhibit the cyclooxygenase involved in prostaglandin synthesis. Acetic acid is also sensitive to non-steroidal anti-inflammatory drugs (NSAIDs) and to narcotics and other centrally acting drugs (Santos et al 1998; Reichert et al 2001). Recently it has been found that the nociceptive activity of acetic acid may be due to the release of cytokines, such as TNF-a, interleukin-1b and interleukin-8, by resident peritoneal macrophages and mast cells (Ronaldo et al 2000). Based on this report, it can be assumed that in the present
study the antinociceptive action showed by compounds **4** and **23** in the acetic acid induced writhing test might be due to inhibition of the release of TNF-a, interleukin-1b and interleukin-8, by resident peritoneal macrophages and mast cells.

The anti-inflammatory activity was studied with 5-(6'-chloroindan-1'-yl)tetrazole (**36**), 5-(6'-bromoindan-1'-yl)tetrazole (**40**), 5-(6'-chloroindan-1'-yl)methyltetrazole (**44**), 5-(6'-bromoindan-1'-yl)methyltetrazole (**48**) at 100mg/kg body weight, in comparison to the positive control PBZ also at 100mg/kg body weight. In this study both the compound 5-(6'-chloroindan-1'-yl)methyltetrazole (**44**) and 5-(6'-bromoindan-1'-yl)methyltetrazole (**48**) exhibited better activity than compound **36** and **40**. For better evaluation both the compounds **44** and **48** were further evaluated for anti-inflammatory activity at 50 mg/kg body weight on the experimental animals. In this study it was observed that compound **44** exhibited 24.92% ($p<0.001$) inhibition and 39.98 % ($p<0.001$) inhibition at 50 and 100mg/kg body weight, which is comparable to the phenylbutazone with 29.98% ($p<0.001$) inhibition

and 41.71% ($p<0.001$) inhibition at 50 and 100mg/kg body weight respectively at third hour of the study. An interesting feature was observed that when a one carbon chain length is increased between the indan nucleus and tetrazole ring the activity was increased. So, the effect of substitution at the benzenoid part of the indan nucleus and chain lengthening on analgesic activity was approximately in the following order respectively: chlorine > bromne and methyltetrazole > tetrazole (Table-6a and 6b).

The time course of edema development in carrageenan induced paw edema in rats is generally represented by a biphasic curve (Vinegar et al 1969). The first phase occurs within an hour of carrageenan injection and is partly due to the trauma of injection and also to histamine and serotonin components. Prostaglandins play a major role in the development of second phase of reaction with bradykinin, protease and lysozyme, which is measured around third hour time (Crunkhorn and Meacock 1971). The presence of PGE_2 in the injected paw can be demonstrated at third hour and period thereafter. The carrageenan induced paw edema model in rats is known to be sensetive to cyclooxygenase inhibitor and has been used to evaluate the effect of anti-inflammatory agents, which primarily inhibit the cyclooxygenase involved in prostaglandin synthesis (Di Rosa and Willoughby 1971). Based on this report it can be inferred that the antiinflammatory activity showed by the compounds 5-(6'-chloroindan-1'-yl)methyltetrazole (**44**), 5-(6'-bromoindan-1'-yl)methyltetrazole (**48**) may be due to inhibition of enzyme cuclooxygenase leading to inhibition of prostaglandin biosynthesis.

Reference:

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The Effects of Ethanol on Dissolution of Various Types of Oral Modified Release Dosage Forms

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Introduction

One of the potential benefits of modified release (MR) dosage forms over the conventional dosage systems is that the former one requires less frequent administration than the other one. In order to provide this benefit to the patient, the MR dosage forms should contain a significantly higher amount of active drug to be released over a longer time period. If the release controlling mechanism of the MR system is compromised, exposure to toxic level or "dose dumping" may occur.

"Dose dumping" from dosage form-alcohol interactions has become a concern following the fatal events with Palladone™, a hydromorphone containing product, in 2005. The drug was formulated as modified release pellets using ethylcellulose, Eudragit RS, and stearyl alcohol. Administration of a single Palladone™ capsule dose was characterized by biphasic absorption, a relatively rapid rise to an initial peak concentration, followed by a second broader peak with therapeutic plasma concentrations maintained over the 24-hour dosing interval. Co-ingestion of alcohol with Palladone™ could increase maximum plasma concentrations (C_{max}) of hydromorphone by several folds as compared to the one when it was taken with water. Significant increase in C_{max} caused serious and potentially fatal adverse reactions in some patients, which became a great concern to the FDA. Thereafter the agency asked the maker of the drug to withdraw it from the market (FDA News Release).

Per capita consumption of ethanol in the US from all alcoholic beverages combined is about 2.2 gallons; and over 110 million Americans are classified as current drinker (Lean about alcoholism). Regular beer, wine, and spirits usually contain 5%, 15%, and 40% (v/v) ethanol, respectively. Absorption of alcohol from the upper gastrointestinal tract is fast, when the alcohol strength is 20-30%. Spirits containing 40% alcohol delay gastric emptying and the absorption of alcohol (Paton A. 2007). Since the cases of Palladone™ were reported, the potential effect of alcohol to accelerate drug release and thereby enhanced rate and extent of drug absorption from MR oral dosage forms has been a concern to the manufacturers as well as to the regulatory agencies. A number of research articles on the effects of alcohol on drug release from oral solid dosage forms have been published over the last few years (Levina M, et al. 2007; Roberts M, et al 2007; Walden M wt al. 2007). Those works, however, do not consider the different types of MR based on their mechanisms of drug release which may be affected by the co-ingestion of alcohol. The purpose of this study was to explore the *in-vitro* effect of alcohol on drug release from various types of MR oral dosage systems including delayed and sustained release formulations.

Methods

Delayed release products, such as, Naproxen EC 250mg tablets, Ecotrin® 81mg tablets, and Asacol® 400mg tablets, and prolonged release dosage forms, namely, Nifedipine ER 30mg tablets, Proranolol ER 80mg capsules, Venlafaxine XR 37.5mg capsules, and Pentasa® 400 mg capsules were obtained from a local drug store. *In-vitro* evaluations of release characteristics of the dosage forms were conducted in 900 ml of USP simulated gastric fluid without the enzyme (SGF) for 2 hours followed by dissolution in simulated intestinal fluid without the enzymes (SIF) in a VanKel USP apparatus I at 50 rpm using on-line UV spectrophotometric detection. To evaluate the effect of alcohol, the dissolutions were carried out in SGF with different levels of ethyl alcohol (5%, 10%, and 20%) for 2 hours followed by dissolution in SIF for 10 hours.

Results and Discussions

Presence of 5% and 10% ethanol in dissolution media did not produce significant difference in drug release as compared to that in SGF alone. When 20% alcohol was employed in the dissolution media, the delayed release dosage forms, Naproxen EC, Ecotrin®, and Asacol® did not release their contents in 2 hours. Nifedipine ER tablets, a prolonged release system, released about 4% more of their contents in presence of alcohol than in the SGF alone in the first two hours. This behavior is attributed to the higher solubility of the drug in hydro-alcoholic solution than in aqueous media. From multi-particulate sustained release product, Pentasa®, the drug release was reduced by about 4% in first two hours in the presence of alcohol. This is apparently due to the lower solubility of 5-aminosalicylic acid in ethanol. The release characteristics, however, of propranolol LA capsules were significantly influenced by alcohol. In presence of 20% ethanol in the dissolution media, almost two folds increase in drug release was noticed from Propranolol LA capsules in 2 hours. Another multi-particulate system, Venlafaxine XR® capsules, did not exhibit noticeable difference in their release behaviors in presence of alcohol.

After 2 hours of dissolution in SGF with or without 20% ethanol, the dosage units were further evaluated in SIF for 10 hours. Enteric coated dosage forms, Naproxen EC, and Ecotrin® tablets began resealing their contents within half-hour of dissolution in SIF. Those dosage forms are coated with a functional coat of methacrylic acid derivatives with usual pH threshold of above 5.5 to impart enteric characteristics. The functional coat was resilient enough to withstand the effect of 20% ethanol in dissolution media for 2 hours. The coat eroded and the system began releasing the drugs in contact with SIF, as the pH of the dissolution media was 6.8 (Figures 1 & 2). On the other hand, the pH threshold of Eudragit-S®, the coating agent used in Asacol® tablet, is 7.0. Ideally drug release should not take place from Asacol® at pH 6.8. Apparently some defects on the coat on one of the tablets caused it to release its contents after four hours and another after five hours of dissolution in SIF (Figure 3).

Nifedipine ER tablets have been developed as osmotic pump system. The semi-permeable coat on the tablet was not susceptible to 20% ethanol. Presence of alcohol, however, feebly accelerated the dissolution of the drug as a result of its higher solubility in alcohol than in water. Thus in 2 hours, about 4% increase in drug release was observed in SGF with ethanol (Figure 4). In case of Pentasa®, an opposite effect of alcohol was observed. Pentasa beads are coated with ethylcellulose and drug release takes place by diffusion. 5-Amino salicylic acid is more soluble in water than in hydro-alcoholic solution. In figure 5, the multi-particulate system exhibited difference in release rates for the first 2 hours when the media contained ethanol; but overall dissolution in 12 hours was not significantly different. The release characteristics from propranolol LA capsules, as presented in figure 6, were influenced by alcohol. The drug is soluble in water as well as in alcohol; but the release controlling mechanism was affected by alcohol. Thus, 100% drug release took place in about 8 hours

in presence of ethanol in SGF, while it took about 11 hours in absence of alcohol. Release characteristics of Venlafaxin XR capsules were not influenced by ethanol. Drug release from the beads is controlled by diffusion through cellulose derivative coating membrane. Venlafaxine hydrochloride is a highly water soluble salt and its solubility is not affected by ethanol, as such, there is no appreciable differences in the profiles as presented in figure 7.

Conclusions

The degree of influence by alcohol on drug release from various types of modified release dosage forms is not same. Drug release controlling mechanisms, the solubility of the drug in ethanol, duration of exposure to alcohol all are important considerations in evaluating the effects of alcohol on their dissolution behaviors. In general, an enteric coat of methacrylic acid derivatives is resilient enough to withstand 20% ethanol for two hours. In case of diffusion or diffusion-dissolution controlled systems, solubility of the active in ethanol can play a significant role in release behavior of the product. In order to protect patients from alcohol induced toxicity from oral modified release dosage forms, further studies, especially the *in-vivo* animal studies, are warranted on this issue. Nevertheless, pharmacists need to acknowledge the fact that co-ingestion of alcohol with certain dosage forms may cause fatal reactions and their interventions can help patients avoid such serious adverse reactions from the very same drug that can save life.

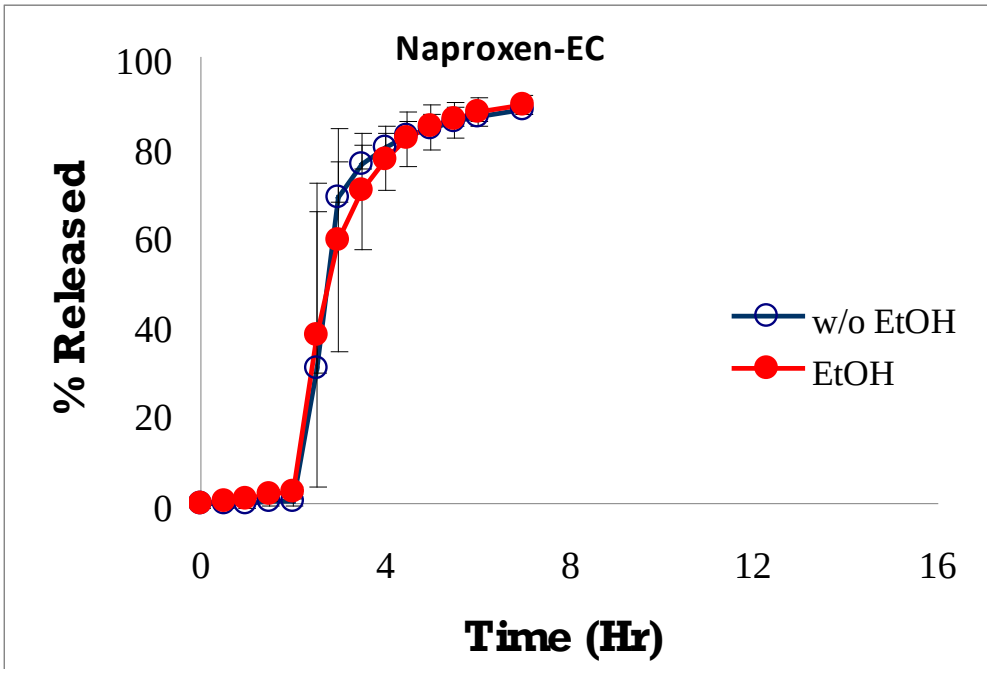

Figure1.

Dissolution of Naproxen EC 250mg tablets in SGF alone and with 20% ethanol (EtOH) for 2 hours followed in SIF (n=6)

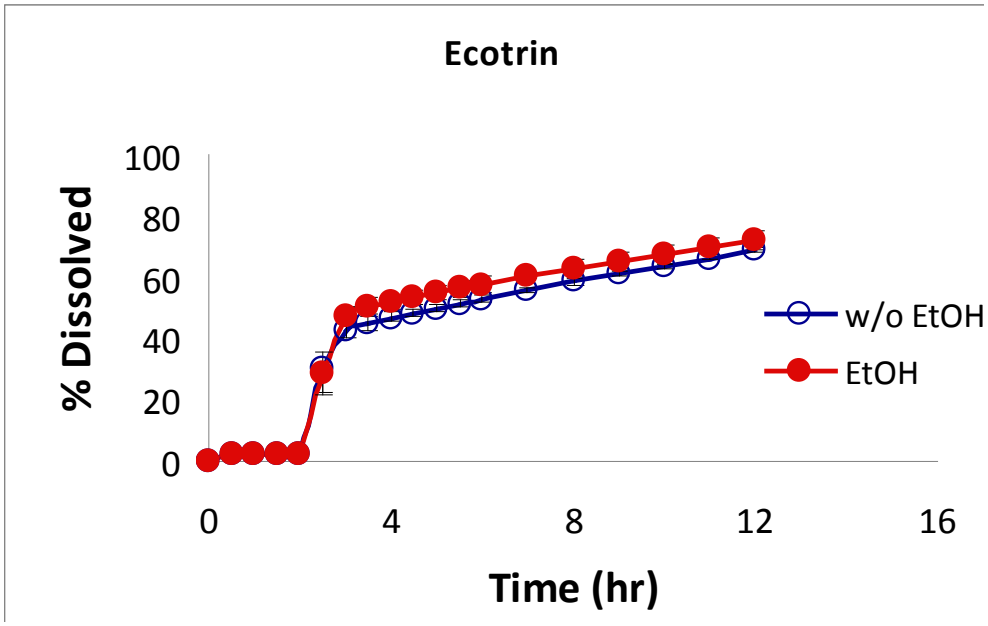

Figure 2.

Dissolution of Ecotrin® 81mg tablets in SGF alone and with 20% ethanol (EtOH) for 2 hours followed in SIF (n=6)

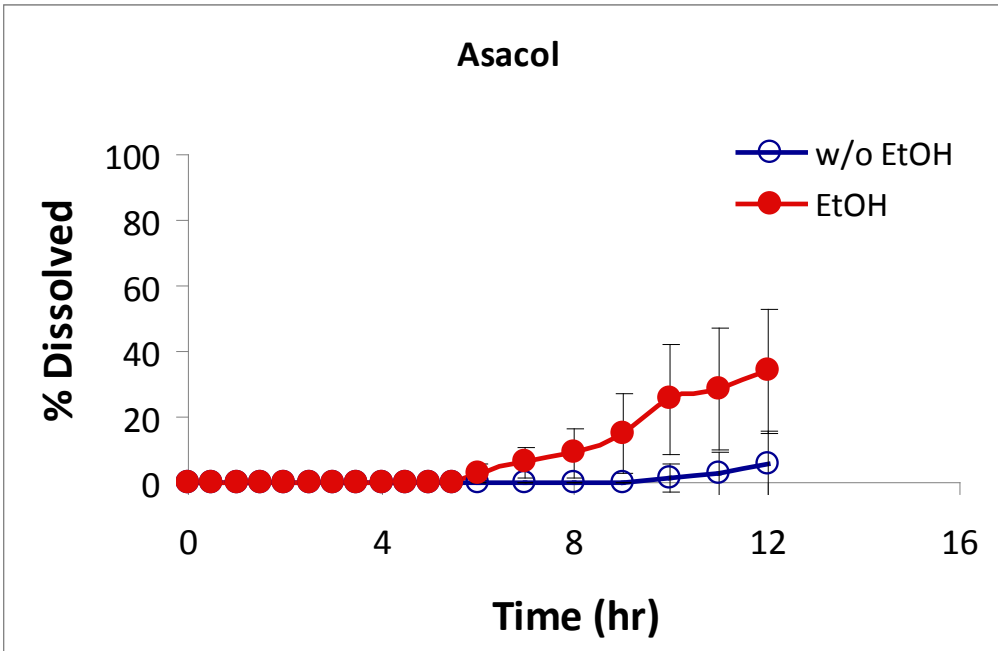

Figure 3.

Dissolution of Asacol® 400mg tablets in SGF alone and with 20% ethanol (EtOH) for 2 hours followed in SIF (n=6)

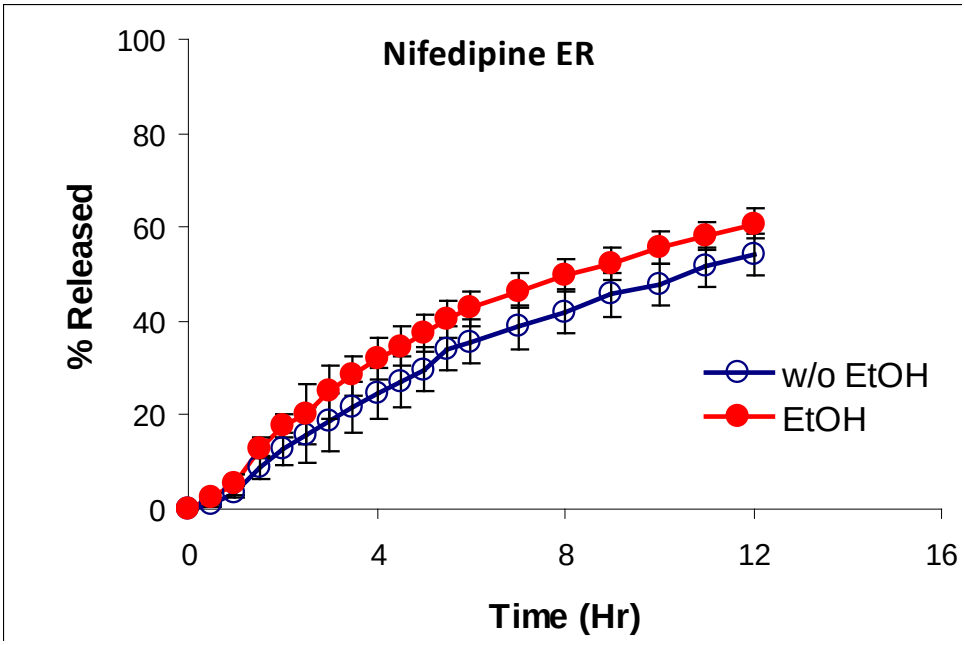

Figure 4.

Dissolution of Nifedipine ER 30mg tablets in SGF alone and with 20% ethanol (EtOH) for 2 hours followed in SIF (n=6)

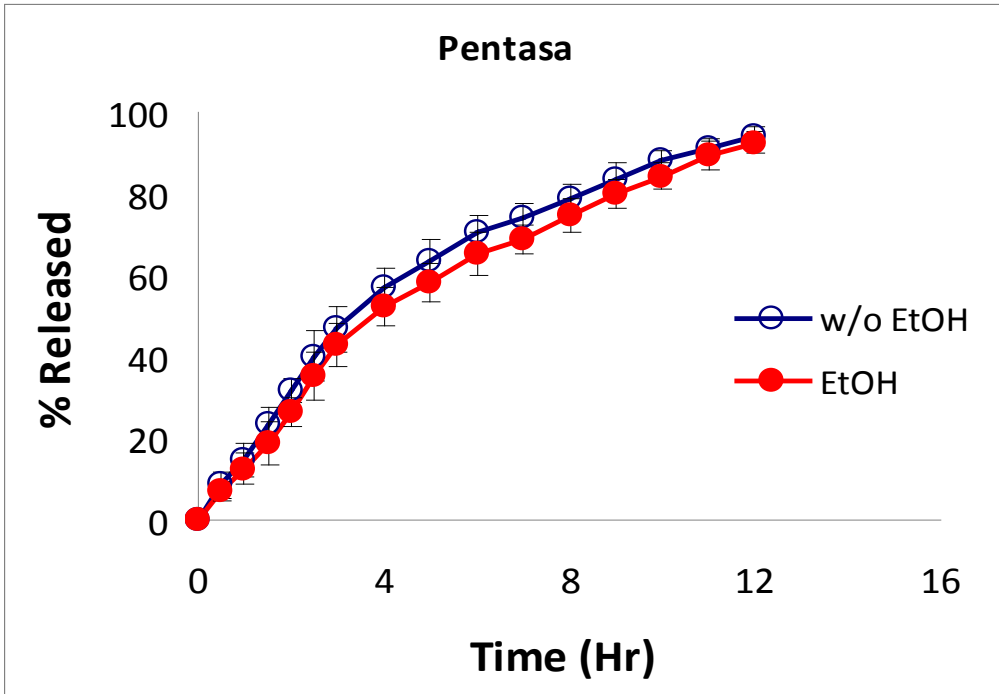

Figure 5.

Dissolution of Pentasa® 400mg-capsules in SGF alone and with 20% ethanol (EtOH) for 2 hours followed in SIF (n=6)

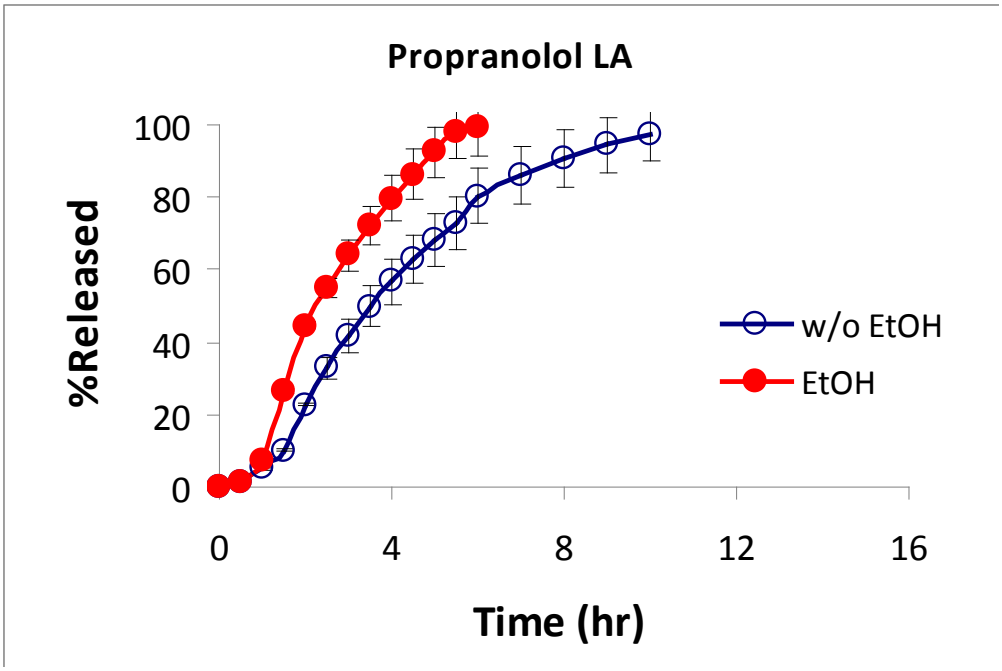

Figure 6.

Dissolution of Propranolol LA 80mg Capsules in SGF alone and with 20% ethanol (EtOH) for 2 hours followed in SIF (n=6)

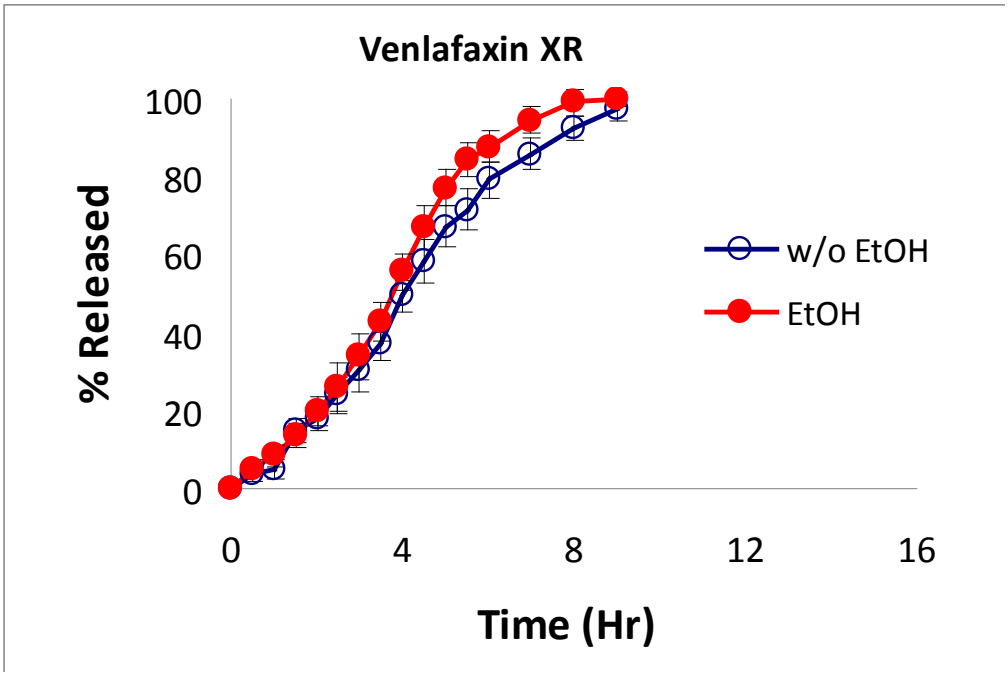

Figure 7.

Dissolution of Venlafaxine XR 37.5mg Capsules in SGF alone and with 20% ethanol (EtOH) for 2 hours followed in SIF (n=6)

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Acetaminophen Assay in

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Purpose

The need for compounding is obvious, as there will always be situations that require tailoring medication for individuals who have special needs. However, there is genuine concern about the quality of the compounded products. Although most compounding is done at a physician's request to meet prescription specifications, compounded products, when analyzed, often fail their objectives. In this article, the authors assess the impact of content analysis on the quality of compounded products, as the Appalachian College of Pharmacy faculty introduced product assay in the compounding course.

PHA 0175 is a core non-sterile compounding course at the Appalachian College of Pharmacy during the first professional year. The duration of the course is 14 weeks during which a series of seven extemporaneous products are compounded. Students are aware that two of their products will be assayed for drug content. The students are oriented to the regulations of compounding (USP Chapters <795> and <1075>) during pre-lab lecture sessions.

The purpose is to enforce quality of the compounded product and to raise compliance awareness among students.

The methods of determination of acetaminophen (APAP) in two product matrices are further discussed.

Methods

Students compounded APAP suspension and solution based on the prescriptions:

Rx 1. APAP 2 gr/tsp
Flavor 1.5 mL
Syrup NF 30 mL
Methocel E4M 2% gel qs to 60 mL

Rx 2. APAP Solution 120 mg/tsp
Disp 50 mL
Sig: 1 tsp q 4-6 h prn for fever

For two successive years students were instructed to prepare and submit analytical samples using acetaminophen suspension and acetaminophen solution.

Results within 100 ±10% of the prescription quantity received a full score, and points were deducted when results fell beyond the limits.

Students used an electronic balance to dilute their suspension 500 times in two successive steps:

- 1 g suspension to 10 g solution
- 1 g solution to 50 g solution

Standard solutions within 100 ±50% range of the expected concentration of the diluted suspension were prepared using APAP powder. Samples were analyzed by measuring absorbance at 290 nm using UV Spectrometer.

Similarly students were asked to prepare and submit samples using their APAP solutions after diluting by a factor of 160.

Compounding Laboratory

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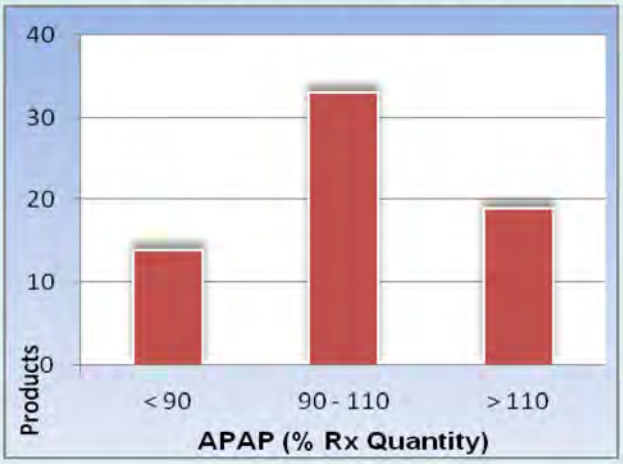
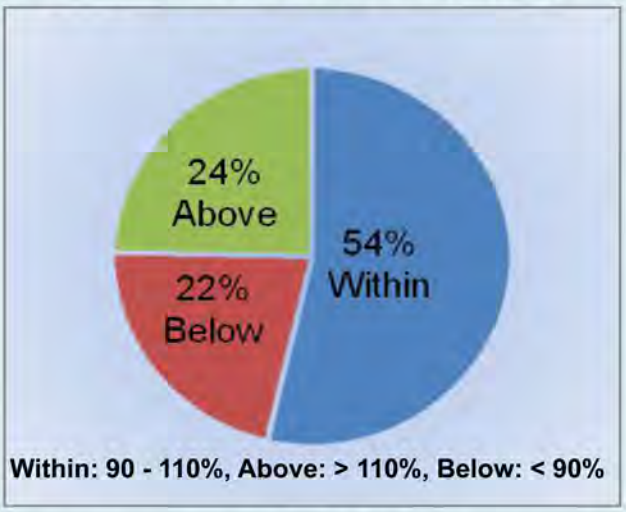
Results

APAP Content in Suspension



APAP Content in Solution



- Assay results reflect gradual improvement
- Students learned good laboratory practice
- Students maintained compounding records
- Students appreciated the process
- Analytical results integrated their learning
- Regulation awareness was generated

Conclusions

- Limited surveys conducted by FDA revealed that a significant percent of the compounded products fail to meet quality[1-2].
- Imposing accountability in compounding courses in pharmacy school may improve the quality of compounded products[3].
- At the Appalachian College of Pharmacy, compounded product quality has been improved due to imposing product assay.

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Acknowledgement

The authors would like to acknowledge the class of 2011 and 2012 for their participation in this project.

The authors would also like to thank Dr. Rodney Siwale for his assistance as a course faculty participant.

Gastroesophageal Reflux Disease (GERD): Overview and Treatment Options

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Introduction

Gastroesophageal reflux disease (GERD), also known as acid indigestion, refers to chronic symptoms or mucosal damage due to backward flow of stomach contents into the esophagus. It is generally considered as a benign disease in most cases. Nevertheless, it is a chronic condition that often requires long term treatment. Clinical studies over the past decade have helped us understand the disease. There are a number of different approaches to its management. A brief overview of GERD and its treatment modalitites cvan help the pharmacist make appropriate recommendations for this common condition.

Epidemiology

GERD is the most common upper gastrointestinal disorder in the western world. However, many patients with active symptoms do not seek medical attention, making it difficult to estimate its prevalence in the world. In the US more than 20% of the population experience acid indigestion at least once a month, and more than 5% experience it daily.[1] In France, about 30% either occasionally or frequently experience reflux symptoms.[2] Approxmately 12% of Japanese patients admitted to having symptoms more frequently than once a month.[3] In Pakistan, 24% of the population surveyed reported that they had experienced symptoms.[4]

GERD can occur in both sexes at all ages, but more women report it than men. The incidence is especially high in elderly and pregnant patients.[5] Approximately 35% of newborn babies in the U.S. have difficulties with reflux within the first few months of life. Chronic heartburn is the most common of many manifestations of GERD. If GERD is left untreated, the quality of life of the patient will be significantly compromised and serious complications may arise. Above all, GERD is associated with a significant health-related cost. The direct and indirect costs for every German patient per

year with non-erosive reflux disease have been reported to be €342(±864) and €40(±473); the costs for patients with erosive reflux disease are significantly higher.[6]

Pathophysiology

GERD can be caused by various physiological disorders. For example, the patient may have lower espophageal sphincter (LES) inefficiency, transient LES relaxation, and impaired expulsion of gastric contents into the esophagus.[7,8,9] Other conditions can contribute to GERD, including hiatal hernia, Zollinger-Ellison Syndrome, excess weight, and hormonal imbalance during pregnancy.[10.11,12]

Food as a Trigger of GERD

Small amounts of gastric acid normally pass into the esophagus without causing symptoms. However, when the frequency and amounts of acid increase, symptomatic damage to the esophagus begins. Certain foods and eating habits can trigger the symptoms. The common dietary triggers of GERD include eating large, fatty and/or spicy meals, chocolate, peppermint, citrus fruits and also drinking coffee, tea, citrus fruit juices, alcohol, and carbonated beverages. Smoking and lying down after a meal can also trigger the symptoms.[9,13]

Symptoms

Heartburn, a burning sensation behind the sternum (breastbone), is the most common symptom of GERD.[10,11,12] Many people notice their heartburn worsens after eating. Regurgitation is also a sign of GERD, and occasional regurgitation is common for many people. Other symptoms include a sore, raw throat or a hoarse voice, a frequent sour taste of acid (especially when lying down), a feeling of burping acid into the mouth, the misperception that food is stuck in the throat, persistent dry cough, and waterbrash (sudden excess of saliva).[14,15]

Immature digestive systems of newborns are a common cause of GERD.[16] In general, children outgrow reflux by their first birthday. GERD may cause caughing, repeated vomiting, and gentle spilling from the mouth. Diagnosing GERD in children and infants is usually difficult, as there is no universal single pediatric symptom and different children may have one isolated symptom or any combination.

Diagnosis

Early diagnosis and treatment can help reduce or even eliminate uncomfortable symptoms of GERD. However, diagnosis of GERD may be difficult due to the lack of a gold standard in assessing the disease. Moreover, patients may be asymptomatic, or may present with multiple symptoms. Furtther, the severity of the symptoms is often unrelated to the severity of the disease. Symptoms may be treated with antacids, H2 blockers or proton pump inhibitors. If the heartburn remits after treatment, it will most likely be diagnosed as GERD.[17]

It must be noted that while chest pain is a symptom of GERD, it is difficult to differentiate between GERD-related chest pain and chest pain due to morbid cardiac conditions. For this reason, all patients with chest pain should initially be evaluated by a physician.

In severe and persistent cases patients must eventually consult a physician. Diagnostic exmainations include barium x-rays, esophageal manometry (which determines how well muscles in the esophagus move food into the stomach and how effectively the lower esophageal sphincter closes), 24 hour esophageal pH monitoring, and esophagogastroduodenoscopy (EGD). An EGD is performed when the patient does not respond well to treatment, or when symptoms include dysphagia, anemia, blood in the stool, wheezing, and/or voice changes.[18,19]

Long term complications of chronic GERD

Untreated GERD can cause serious complications apart from reduced quality of life. They include esophagitis (irritation and inflammation of the esophageal lining caused by stomach acid), permanent esophageal damage, dysphagia (difficulty in swallowing), Barrett's esophagus (changes in the cells of the esophagus that may be precancerous caibnduced by chronic exposure to refluxate), esophageal cancer, etc.[20,21] Patients with chronic GERD also experience lung and breathing problems, ear, nose, and throat problems, coughing, wheezing, frequent pneumonia, bronchiectasis (permanent widening and damage to the air passages in the lungs), chronic asthma, laryngitis, and voice hoarseness.[22]

Treatment

Treatment of GERD depends on the severity of the symptoms. For some patients, especially those with mild symptoms, effective treatment may consist solely of lifestyle changes, such as changes in their diets (i.e., avoiding the food or feeding habit that may trigger the symptoms).[23] Patients with moderate and persistent symptoms often require

pharmacological intervention, and in very rare but severe cases surgery is the best possible choice.[24,25,26] Table 1 presents medical therapies, from the most simple to the most complex cases.

GERD in babies usually reduces with time.[16] However, the mother should attempt to reduce the frequency of episodes by burping the baby a few times during each feeding, keeping the baby upright for 30 minutes after each feeding, avoiding feeding too much at one time, and giving the baby smaller meals more often.

Nonprescription antacids (e.g., Mylanta, Maalox, Rolaids, and Tums) neutralize stomach acid and can be recommended for the management of mild GERD symptoms. Nonprescription and prescription H-2 blockers (ranitidine, famotidine, cimetidine, and nizatidine) block the production of stomach acid, and are useful in mild to moderate GERD. The relative potencies of the H-2 blockers are presented in table 2. Proton pump inhibitors reduce the amount of acid the stomach produces, and are usually prescribed in moderate to severe cases.[27] They are available as nonprescription omeprazole (e.g., Prilosec OTC) and as prescription drugs (e.g., omeprazole [Prilosec], pantoprazole [Protonix], lansoprazole [Prevacid], rabeprazole [Aciphex], esmosprazole [Nexium]).[28]

In most cases, GERD relapses if therapy is discontinued; therefore, patients with GERD require long-term drug therapy.

In severe or persistent GERD, when medications are ineffective or adverse effects limit their utility, surgery may be recommended.[29] The most common surgical procedure is known as fundoplication, which strengthens the valve between the esophagus and stomach. However, the procedure is not curative; many patients still require medications after surgery.

Conclusions

GERD is a common gastrointestinal disorder triggered by a variety of factors. Changes in lifestyle and eating habits can help alleviate the symptoms for many who experience GERD. Patients with mild to moderate symptoms may be managed with antacids or acid-reducing agents, whereas those with severe and persistent cases should consult their physicians. However, early diagnosis and treatment of GERD can significantly improve the quality of life of patients and reduce its health cost.

Table 1. Medical therapies for GERD (in order of potency)

-Lifestyle modification
-Nonprescription antacids
-H-2 receptor blockers
-Proton pump inhibitors
-Surgical Intervention

Table 2. Potencies of H-2 Receptor Blockers Related to Cimetidine by Weight

Drug	Daily dose (mg)	Relative potency
Cimetidine	800	1
Ranitidine	300	4-8
Famotidine	40	40-60
Nizatidine	300	4-8

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