BAPA

Bangladeshi-American Pharmacists' Association

Annual Journal 2012 - Volume 21

Exercising Care When Dispensing Controlled Substances

- Drug Development for the Geriatric Population
- Comparative dissolution studies of pioglitazone
- Immune System Function

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Contributors:

Joseph J. Bova, R.PhI
Mohammad Hossain Ph.D
Kazi Anam, MS, R.Ph.
Sitesh C. Bachar Ph.D

Contact: bapapresident2012@gmail.com

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30-12 36th Ave, Long Island City, NY 11106,
Telephone: 516 650 7937
Fax: 718 729 0165
email: bapapresident2012@gmail.com

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Message from the President

Since the end of the fees-for-service policy by New York State Medicaid in October, 2011, pharmacists are on life support. The Pharmacy Benefit Managers control the class of drugs local pharmacists may dispense as well as the reimbursement amount. The PBM exclude local pharmacies from dispensing expensive drugs that they have labeled Specialty Drugs. But according to the New York State Board of Pharmacy, there is no separate license to become a Specialty Drugs pharmacist. Patients who had been receiving so-called Specialty Drugs from local pharmacies all along are now forced to mail their prescriptions to the PBMs' own specialty mail order pharmacies.

All fields in pharmacy are now subject to more regulation and oversight. Those of us working in retail and hospitals are having difficulty dispensing controlled drugs to needy patients. New York State just passed the I-Stop legislation to curtail the abuse of controlled drugs. These bills are going to place extra burdens on the pharmacist. For the first time, the bills allow pharmacists to receive controlled drugs prescriptions electronically only. On top of that, pharmacists have to report their dispensing record to the NYS controlled drug database at the time of dispensing. This requires pharmacists to upgrade their software. The introduction of user fees by FDA for ANDA makes it harder for small generic companies to compete with multi-national companies. With decreased competition, manufacturers' generic drug prices have sky rocketed.

On behalf of BAPA, I thank the PSSNY leadership Dr. Judaianne Slish, current president, and Craig Burridge, Executive Secretary of PSSNY, and other affiliate board members for their effort and time devoted to passing the AMMO and Specialty Drug bills. Some interest groups and the PBM are looking for loop holes in these bills. They are trying to make mail order for NYS Medicaid prescriptions mandatory, especially with regard to the expensive so-called Specialty Drugs. We need to challenge these measures. I urge all of our member pharmacists to contribute a minimum of $3,500.00 to the PSSNY legal fund to stop the PBM's attack on local pharmacies.

As we age and our metabolism slows down without our having time to exercise and burn the calories, our sugar and cholesterol levels are getting ever higher. We, the BAPA executive committees, decided to teach our fellow members how to identify and prevent diabetic complications. At end, our members will be able to implement these techniques in their own practices to help improve their patients' health.

We thank our members for joining us here with your family after Ramadan and hope you enjoy yourself and make new friends.

I thank Barbara Trimarchi of PSSNY and Diane Mangano for helping us in our C.E courses. I am grateful to my executive committee members, specially Devabrata Mondal, Mahmud Hossain Milton, Mustaque Chowdhury, Md. Mohiuddin, and Enamul Kabir. I also thank my coworker Syed Hadi for helping me with data-entry and for mailing letters to our members.

We at BAPA are grateful to Kinray for their support. We also thank Liaquot Hossain of Advance Pharmaceuticals, Abu Kabir of Kabco and Monir Ahmed of Pharbest. We thank BAPA's younger generation, especially Dr. Safinaz Rahman and Dr. Tasmiya Khan for helping in our Continuing Education program. We also thank Dr. Abu T. M. Serajuddin and Dr. Salah U. Ahmed for sharing their ideas and expertise with our members engaged in manufacturing.

I am grateful to my wife, Ruksana Shirin Ahmed, and our children for allowing me to share their time with BAPA.

I hope that you have a great time with us and that you join us again next year.

Shahab Ahmed

Message from the Vice President

Dear BAPA members, guests and participants,

It is my pleasure and honor to welcome you all to the 21st Annual BAPA Convention.

I would like to extend my gratitude for giving our executive committee the opportunity and privilege to serve you all. Let us truly embrace the concepts of new thinking and fresh focus in all that we do. Let us strengthen our organization so that pharmacists and pharmaceutical scientists working within various disciplines of pharmacy will be recognized as experts in health promotion and disease prevention. Let us all work together to realize and achieve this vision.

BAPA is the only organization where we can simultaneously show respect to our working professions as well as our cultural heritage. It allows us to value ourselves as contributing citizens of the American society while staying true to our Bangladeshi roots.

We welcome constructive criticism and suggestions so that we can better serve you and work hard to carry the profession to next level. We especially encourage the younger generation of pharmaceutical graduates and working professionals to engage and participate in our programs. After all, they are the faces of this generation and we hope that they carry on our legacy in the future.

In closing, let me thank the executive committee members for their hard work in hosting this platform for us to learn and network with one another. I would also like to extend my profound thanks to the editor for his splendid work in publishing this journal.

I wish you all an enjoyable, meaningful and enlightening time together at this convention.

Thank you.

Qamrul Ahsan (Kanchan)

Vice President

Message from the General Secretary

Dear BAPA Members,

First of all, I would like to thank you for giving me this opportunity. It's an honor to serve as your General Secretary and hope I am performing to your expectations. I would also like to thank the Executive Board for putting me in this position.
It is my privilege to invite you all to our 21st Annual Convention at the exotic Sea View Resort. The weekend will feature a wide variety of events, making the experience enjoyable both socially and educationally. Like every year, we get together and exchange our views professionally and personally, this year we also hope you will enjoy all the events as it has been well laid out by our most dynamic executive committee members.

We all know that BAPA is a unique organization through which most of us have not only enhanced our professional communication but also now know each other as family. Since its inauguration in 1991 we are maintaining its integrity by implementing constructive suggestions to improve BAPA to its best level. Feel free to leave us tips and suggestions on how to run this organization the way you see fit. This is YOUR organization and your feedback is valuable to us.

I've been a member of BAPA since its inception. I've seen it grow from a group of Pharmacists to what it is today; a large network of Bangladeshi American Pharmacists who use our resources to better their own careers. BAPA has grown to be more than a professional network. Our families have become heavily involved in this organization. The entire social aspect of our organization would not be the same without them. Consequently, we need to extend these advantages to the next generation. We highly encourage recent pharmacists to become active in the BAPA Community.
This Convention, I encourage further participation by our families so BAPA can be as strong as ever.

I would like to thank all of our executive committee members for their dedication toward the successful organization of this Convention. I would also like to thank the sponsors for their continuous support as without you, we would be nowhere near as successful as we are today.

And finally on behalf of the executive committee I am wishing you all the best for years to come. Let's make this Convention a success.

Respectfully,

Enamul Kabir

Article

Article

Drug Development for the Geriatric Population

Mohammad Hossain

Introduction:

Geriatric labeling information is of increasing importance because of the growing proportion of elderly population and the significant use of medications by this age group. The geriatric population has been arbitrarily defined by regulatory agencies as comprising patients aged 65 years or older [1-4]. Age-related physiological changes can affect the pharmacokinetics of the drug, and the pharmacodynamic response to the drug, both of which can influence the drug-response and the dose-response relationship.

Effect of Aging on Drug Pharmacokinetics:

PK differences associated with aging are important for drug absorption (deglutition disorders, low efficiency of esophageal and sphincter peristalsis, changes in gastric pH, decreased gastrointestinal and splanchnic blood flow, reduction of surface area of small intestine, intestinal blood permeability and drug transporters), distribution (decrease of lean body mass, water, serum albumin concentration, binding serum proteins, increased total body fat, increased blood-brain barrier permeability) and elimination (reduced renal function due to age-related decrease in renal blood flow and glomerular filtration rate; reduced hepatic drug clearance due to age–related changes in hepatic blood and liver mass)[5-8].

Effect of Aging on Drug Pharmacodynamics:

Age-related changes in pharmacodynamics may occur at the receptor or signal-transduction level or homeostatic mechanisms may be attenuated [5,7,8]. Drug effects are attenuated less in the elderly, the reactions may be stronger than in young subjects and the incidence of adverse drug effects is higher. It is well-known that immune function, particularly cell-mediated immunity, decreases with aging [9].

Regulatory Requirements:

In 1997, FDA established the *Geriatric Use* subsection, as a part of the PRECAUTIONS section, in the labeling for human prescription drugs to include more complete information about the use of a drug or biological product in the elderly (persons aged 65 years and over) (21 CFR 201.57(f)(10)). As a result, many application holders are required to submit geriatric labeling supplements under 21 CFR 314.70 or 601.12 [3]. Data to support geriatric use labeling may include efficacy, safety and PK/PD. The ICH E7 guideline states, “for drugs used in diseases not unique to, but present in the elderly, a minimum of 100 patients would usually allow detection of clinically important

differences"[2]. Depending on the numbers of patients, data should be presented for various age groups (for example <65, 65-74, 75-84 and > 85) to assess the consistency of the treatment effect and safety profile in these patients with the non-geriatric patient population [10]. The Clinical Pharmacology section of the labeling should cite any limitations on the geriatric indication, need for specific monitoring, specific hazards associated with the geriatric indication, any dose adjustment and other information related to the safe and effective use of the drug in the geriatric population.

Clinical Considerations:

Evaluation of the effects of age or age-related conditions on the PK of drugs in geriatric patients (over the entire spectrum of the geriatric patient population) include effects of renal impairment, hepatic impairment, drug-drug, drug-food and drug-disease interactions and are often assessed in studies with non-geriatric subjects [1-2]. Evaluation of age-related differences in the PK of a drug can come either from a PK screen in conjunction with the main Phase 3 studies or from formal PK studies in the elderly. The formal PK study can be done in healthy geriatric subjects or in patient volunteers with the disease to be treated by the drug. It may be necessary to develop galenic formulations that facilitate dose adjustment, eliminate difficulty in chewing or swallowing, reduce the risk of medication errors and to improve compliance in the elderly [4]. Besides non-compartmental analysis of Phase 1 PK study in the elderly, the population PK approach can also be used in Phase 2-3 of drug development to gain information on drug pharmacokinetics and safety/efficacy in the elderly provided a sufficient number of patients in different age ranges (including patients >65 and >75 years) are included in the clinical trials. Depending on the mechanism of action of the drug and/or the characteristics of the disease, certain specific adverse events and age-related efficacy endpoints should be actively sought in the geriatric population, e.g., effects on cognitive function, balance and falls, urinary incontinence or retention, weight loss and sarcopenia.

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Comparative dissolution and *in-vitro –in-vivo* correlation (IVIVC) studies of pioglitazone 30 mg IR tablets.

Sajal K. Saha[1], Suman Saha[2], Md Aftab Uddin[3], A. K. Azad Chowdhury[1], Sitesh C. Bachar[4]*

[1]Department of Clinical Pharmacy & Pharmacology, University of Dhaka, Dhaka-1000.
[2]AristoPharma Ltd, Shampur-Kadamtali, Dhaka – 1204
[3]Department of Genetic Engineering and Biotechnology, University of Dhaka, Dhaka-1000.
[4]Department of Pharmaceutical Technology, University of Dhaka, Dhaka-1000. Bangladesh.

Abstract

Dissolution study is used to predict the *in-vivo* performance of a solid oral dosage form of pharmaceutical product. There have various trades of same dosage form of a generic available in Bangladesh pharmaceutical market although having scanty of IVIVC and bioequivalence data. The main objective of present study was to conduct the comparative dissolution testing of various trades of pioglitazone 30mg IR tablet with evaluation of IVIVC and treatment of dissolution data obtained by using Analysis of Variance (ANOVA) to determine whether all the formulations used were equivalent or significantly different. Four different brands as test products from different manufacturers in Bangladesh and reference product of pioglitazone 30 mg IR tablets from Takida pharmaceuticals, USA were selected in the study. In-vitro release data were obtained for Test and Reference formulation using the USP paddle method (apparatus 2) at 50 rpm and a temperature of 37°C in the dissolution medium of 0.1N hydrochloric acid at pH 1.2. Blood samples were collected over 24 hours period and analyzed by a simple, fast and precise reverse phase binary HPLC method with UV detection to establish a correlation between in-vitro release and in-vivo absorption. Percent drug release at each time interval was calculated for total 30 tablets (5X6) and the data obtained was treated with statistical technique –ANOVA. It was concluded from the study that all the formulations taken were equivalent and there was no intra and inter variation between each and every formulation. A non-linear IVIVC established for a local product of immediate release (IR) pioglitazone tablet. As absorption profile was found out only for a local product it may be concluded that the *In-vitro–In-vivo* correlation is well established and justified for only a local (T1) product by level A correlation. The findings may lead to further study to evaluate a comparative IVIVC profile for reference and Bangladeshi brand products of pioglitazone.

Key words: Pioglitazone, dissolution, release kinetics, similarity factor, *IVIVC*.

*Corresponding author: Sitesh C Bachar, [4]Department of Pharmaceutical Technology, University of Dhaka, Dhaka-1000. Bangladesh. Email: bacharsc63@yahoo.com

Introduction

Oral drug administration is the most user-friendly form of drug delivery; remains the preferred route of drug administration with the highest degree of patient compliance and the majority (84%) of the 50 most-sold pharmaceutical products in the US, European markets and Bangladesh as well are given orally.[1] For solid formulations, the dissolution process is one of the important limiting steps for the entire absorption process.[2] *In vitro* dissolution studies are an essential tool during the early and late stage drug development. The quality of the *in vitro* dissolution data are of great importance for their proper use in the evaluation of dosage form performance; the composition, volume and hydrodynamics of the contents in the gastrointestinal (GI) lumen following administration of the dosage form must be accurately simulated *in-vitro*. One of the challenges of pharmaceutical research is correlating *in-vitro* drug release information of various drug formulations to the *in-vivo* drug profiles (IVIVC). The main objective of developing and evaluating an IVIVC is to reduce the number of bioequivalence studies performed during the initial approval process as well as with certain scale-up and post approval changes. IVIVC development could lead to improved product quality and decreased regulatory burden.[3]

According to Scale-Up and Post approval Changes (SUPAC) IR guidance, a manufacturer will frequently need to demonstrate that the dissolution profiles of the pre-change product and post change product are “similar” in terms of biological properties (pharmacodynamic and pharmacokinetic) and physicochemical properties of the drug product containing the drug substance. In Bangladesh all local manufacturers produce generic products by changing manufacturing process and equipments compare to the innovators products after getting approval from Drug Administration .That’s why SUPAC are required for those local and generic products. SUPAC IR suggest that dissolution profiles may be compared by determining similarity and dissimilarity factor (f_2 and f_1 metric) that are recently introduced by Moor and Flanner.[4] SUPAC IR also states that an f_2 value between 50-100% suggests that the two dissolution profiles of local and reference formulations are similar.[5] For doing so, we made an attempt to find out the similarity of our local products with reference products in terms of comparative dissolution profiles and to establish *in-vitro–in-vivo* correlation. This present communication deals with the comparison of release kinetics profile, similarity and dissimilarity among four local products, and with reference product of pioglitazone 30 mg IR tablet with evaluation of IVIVC.

Pioglitazone has been widely used in the last decade and is now considered a relatively safe and effective anti diabetic agent. The structural formulation of pioglitazone hydrochloride is (±)-5-[p-[2-(5-ethyl-2-pyridyl) ethoxy]-2, 4 thiazolidine dione hydrochloride. The empirical formula is $C_{19}H_{20}N_2O_3S.HCl$.The molecular weight is 392.90. As the case of pioglitazone, in the fasting state, after oral administration, it was first measurable in serum within 30 minutes. After absorption from the gastrointestinal tract, peak plasma concentrations were observed within two hours.[6] It was rapidly absorbed within one hour, achieved peak concentrations at 2 - 3 h. The absolute bioavailability ranged between 70 - 96% with a mean value of 83%.[7] Food slightly delays the time to peak serum concentration 3 - 4 h, but does not alter the extent of absorption.[8]

Pioglitazone is highly bound to plasma proteins (> 99%) mainly to serum albumin. It is metabolized mainly by CYP3A4 and CYP 2C8/9.[9] Pioglitazone and its metabolites were excreted via urine (15-30%). The remainders were excreted into bile and feces.[10]

Methods

In vitro dissolution test

Six immediate release tablets of each test (T1-T4) and reference (R) products of pioglitazone were taken in the *in-vitro* release kinetic study. The dissolution test was carried out according to the procedure described in the USP paddle method (apparatus 2).The paddle rotation speed was maintained at 50 rpm at 37°C. The release test was carried out in 900 ml of dissolution medium (0.1N hydrochloric acid) using a dissolution tester. Samples of 5 ml were withdrawn at time 0, 5, 10, 15, 30, 45, 60, 75, 90, 105, and 120 minutes, filtered, and were analyzed by UV spectrophotometer at a detection wave length 269 nm.[11]

In vivo absorption study

Subjects

Fifteen healthy Bangladeshi adult volunteers ranging in age from 21 to 30 y (mean age ±SD, 23.93±2.73), in weight from 58 to 76 kg (mean weight ± SD, 61.40±7.98) and height from 166 to 185cm (mean height ±SD, 164.93 ±4.87) producing a body mass index (BMI) of 22.57±1.47 were enrolled in this study.

Study Design

The study was conducted according to the declaration of Helsinki (1964). Each volunteer signed an informed consent document before entering the study. Ethical permission was taken to approve the protocol and consent form of this study from the institutional ethical review committee (Faculty of Pharmacy, University of Dhaka). Fifteen healthy male volunteers received a single oral dose of pioglitazone 30mg in the *in-vivo* study. Before enrollment, each subject was determined to good health through medical history, physical examination, electrocardiogram (ECGs) and routine laboratory tests.

Sample Collection

Venous blood samples (6mL) were collected in heparinized tubes at fasting hour and at 0.5 1.0, 1.5, 2.0, 2.5, 3.0, 5.0, 8.0, 12 & 24.0 hour after dosing. The centrifugations of the collected samples were done at 3000 rpm/min for 20 minutes followed by isolation of the plasma. Plasma samples were stored in tubes at -20℃ until analysis. Blood sampling of the volunteers was done in the BIRDEM hospital, Shahbag, Dhaka, Bangladesh.

Bioanalytical method

A simple, fast and precise reverse phase binary HPLC method was developed for the separation and quantification of pioglitazone from plasma. This quantification was carried out using Luna C_{18} (250x4.6mm, 5μ) column and mobile phase comprised of acetonitrile and ammonium acetate (pH 4.5; 20 mM) in the ratio of 60:40 (v/v). The flow rate was 1.0 ml/min and the effluent was monitored at 269nm. The retention time was 6.1 ±0.2 min. The method was validated in terms of linearity, precision, accuracy and specificity, limit of detection and limit of quantification. The inter-day and intra-day assay coefficient of variances (CVs) for pioglitazone was less than 6.4% for all quality control concentrations.

Data Analysis

The area under the plasma concentration-time curve to 24 hour ($AUC_{0–24}$) was determined by the trapezoidal rule, and the area under the serum concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) was calculated according to the following formula: $AUC_{0-\infty} = AUC_{0-t} + C_t/K_{el}$, where C_t is the last quantifiable serum level. [12]

The percent of drug absorbed was calculated by means of model dependent techniques such as Wagner-Nelson procedure. According to Wagner – Nelson equation,

$$\frac{A_t}{A_0} = \frac{C_t + K_{el} \times AUC_0^{\,t}}{K_{el} \times AUC_0^{\,\infty}}$$

Here,

A_t / A_0 denotes the fraction of drug absorbed at time t, C_t is the plasma drug concentration at time t, K_{el} is elimination rate constant, $AUC_0^{\,t}$ and $AUC_0^{\,\infty}$ are the area under the plasma concentration – time profile curve at time t and ∞ respectively.

Similarity factor (f_2) and difference factor (f_1) were also determined by using the equation (Eq.-2 and Eq.-3) developed by Moore and Flanner. [4]

$f_2 = 50 \log [\{1+1/n (Rt-Tt)\ 2\}-0.5 \times 100]$ --- (Eq.-2)

$f_1 = [\{| Rt - Tt | / Rt\} \times 100]$ ---------- (Eq.-3)

Where Rt and Tt are the percent drug dissolved at each time point for the reference and test products, respectively; n is the number of dissolution sample times and t is the time points for collecting dissolution samples. [3]

The Mean Dissolution Time (MDT *in-vitro*), was also calculated both for test and reference formulations by using equation- 4. [13, 14]

$MDT_{in\ vitro} = t_{mid}\ \Delta M / \Delta M$ --------- [Eq. 4].

Analysis of Data by ANOVA

To the obtained DE values, ANOVA was applied at 95 % confidence interval (0.05% LS) .Total three sum of squares were calculated named SS_{total}, $SS_{between}$, and SS_{within} according to the formulae given below.

Let a, b, c …..,k be the k groups to be compared among themselves, n_1, n_2, n_3, …..nk samples in each group and N, the grand total of all the samples.

Correction Factor = $[(\Sigma X)^2/N]$

SStotal = ΣX^2 – Correction Factor (CF)

SSbetween= $[(\Sigma X_a)^2/n_a] + [(\Sigma X_b)^2/n_b] + [(\Sigma X_c)^2/n_c] +------+ [(\Sigma X_k)^2/n_k] – CF$

$SS_{within} = SS_{total} - SS_{between}$

Results and Discussion

The dissolution results for test and reference tablets are listed in Table 1 and presented graphically in the Figure 1. From the graphical presentation it was observed that the dissolution pattern of reference (R) product was almost similar to that of those test products (T1-T4). Similarity factor (f_2) and dissimilarity factor (f_1) for reference and test products were presented in Table 2. For all the products percent of drug released was calculated from dissolution profiles. Percent of drug absorbed for a test formulation (T1) at different time interval were obtained from the equation 1 and have been shown in fig. 2. Table 2 describes the similarity factor (f_2) for 5, 10, 15, 30, 45, 60, 75, 90, 105 and 120 minutes and the obtained values were 65.17, 59.37, 63.62, 66.61, 68.89, 70.73, 72.27, 73.59, 74.65 and 75.67percent and 9.43, 9.00, 5.42, 3.86, 3.07, 2.56, 2.20, 1.94, 1.82, and 1.65 percent for dissimilarity factor (f_1) at respective time intervals. As similarity factor (f_2) was within the acceptable range of 50% to 100%, the test formulations are similar to reference formulation [4]. Dissimilarity factors (f_1) were obtained 9.43, 9.00, 5.42, 3.86, 3.07, 2.56, 2.20, 1.94, 1.82, and 1.65 percent for the same time intervals. The values for f_1 were also within the acceptable range (less than 15%) [4].

In-vitro–in-vivo relationship

Determination of level A correlation

Level A correlation is the highest category of correlation and represents a point-to-point (1:1) relationship between *in-vitro* dissolution rate and *in-vivo* input rate of the drug from the dosage form.[4] For level A correlation, percent of drug released from immediate release film coated tablet was determined, for both reference and local products, according to compendia dissolution method using Apparatus II (paddle apparatus) which has been discussed earlier and the results are presented in the Table 1. Percent of drug absorbed was calculated from the mean serum drug concentrations, using Wagner - Nelson equation (Equation-1) for test product (T1). Then the values of percent of drug released were plotted against the percent of drug absorbed to find out the relationship (Figure 3).

Conclusion

Comparison of dissolution profiles in terms of similarity and dissimilarity factors the test (generic) and reference formulations are similar. In level A correlation, we might conclude that there is no linear correlation between percent of drug release and percent of drug absorbed for test product. Pioglitazone film coated tablet is an Immediate Release formulation. As dissolution is not a rate limiting step in IR products, the fraction of drug absorbed against the fraction of drug released profile would be non-linear type which was obtained in our present study. Since absorption cannot "keep up" with dissolution, a nonlinear relationship between the fractions of drug absorbed and the fractions of drug released was obtained. As absorption profile was found out only for a local product it may be concluded that the *In vitro - In vivo* correlation is well established and justified for only a test (T1) product by level A correlation. The findings may lead to further study to evaluate a well established and justified IVIVC profile for reference and all the products of pioglitazone manufactured by Bangladeshi pharmaceutical companies.

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Table 1. Dissolution profile for test and reference products of Pioglitazone 30 mg IR Tablets.

Time (Min)	Average % Release				
	R	T1	T2	T3	T4
0	0	0	0	0	0
5	51.5±2.1	45.82±1.13	38.58±1.17	45.36±2.10	41.52±1.52
10	87.22±1.01	79.59±1.02	65.24±0.95	69.85±0.99	62.58±1.05
15	95.54±0.62	92.58±0.38	87.57±0.85	91.48±0.88	86.78±0.96
30	98.45±0.96	96.62±0.98	96.49±0.99	99.54±0.88	95.89±0.85
45	100.01±0.29	100.95±0.68	99.54±0.45	100.05±0.17	99.85±0.34
60	101.58±0.96	101.19±0.54	100.12±0.45	100.56±0.38	100.87±0.48
75	101.83±0.99	101.56±0.87	100.5±0.78	100.85±0.76	100.87±0.45
90	101.5±0.52	101.77±0.62	101.54±0.89	100.1±0.97	100.95±0.87
105	101.19±0.1	102.14±0.45	101.62±0.43	101.35±0.62	100.96±0.95
120	101.76±0.08	102.03±0.07	101.77±0.09	101.36±0.08	100.99±0.06

Table2: Similarity and dissimilarity factor between test and reference products

Similarity factor (f_2) & Dissimilarity factor (f_1)										
f_2(%)	65.17	59.37	63.62	66.61	68.89	70.73	72.27	73.59	74.65	75.67
f_1(%)	9.43	9.00	5.42	3.86	3.07	2.56	2.20	1.94	1.82	1.65

Table 3: Dissolution efficiency of all 30 tablets

Tablet No	R	T1	T2	T3	T4
Tab1	63.33	63.33	50.00	53.33	45.00
Tab2	56.67	63.33	46.67	56.67	46.67
Tab3	56.67	60.00	53.33	46.67	48.33
Tab4	60.00	66.67	50.00	50.00	45.00
Tab5	56.67	60.00	46.67	56.67	46.67
Tab6	53.33	73.33	53.33	46.67	48.33

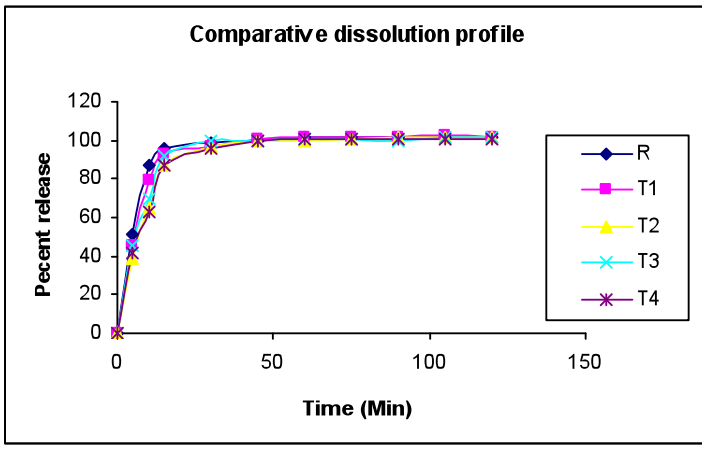

Figure 1.Comparison of mean dissolution rate among test (T1-T4) and reference (R) products.

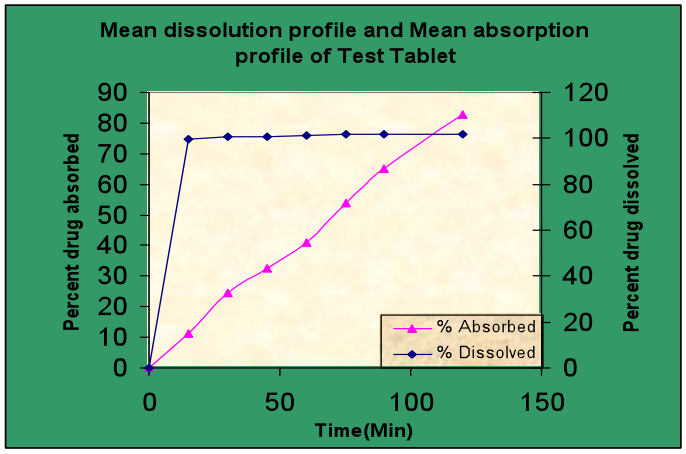

Figure 2: Pattern of changes of percent of absorption and dissolution at different time points.

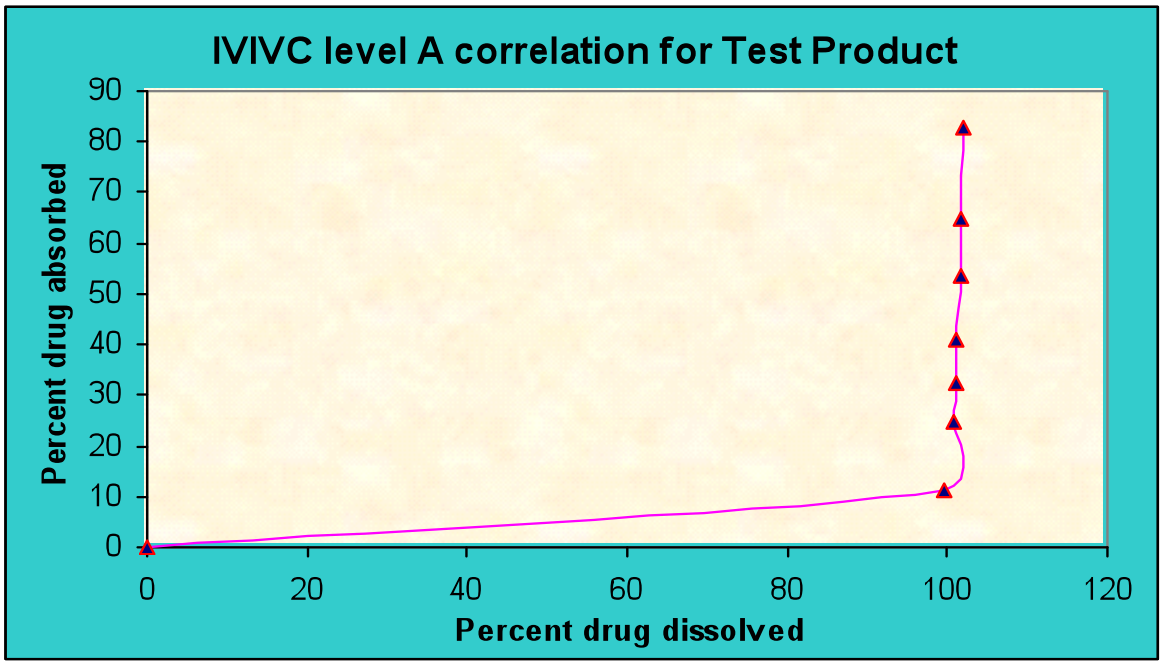

Figure 3: Nonlinear Level A correlations (IVIVC) for test product.

Statistical analysis
ANOVA

Source of Variation	SS	df	MS	F
Between the Groups	1200	5	240	15.43
Within the Groups	466	30	15.56	
Total	1666.67	35		

Note: 'F' Value from the table, at 0.05 Level of significance and (DF 5, 35) is 4.50

Immune System Function: How We Can Optimize It To Prevent Diseases

Kazi Anam MS, R.Ph.

It is past midnight. I look at the young physician's face. He is on duty tonight. He looks a bit puzzled and hesitant when I advise him to just follow my mother's wish. I look at the face of my mother and all the gadgets of modern-day medicine illustrating her vitals, which occasionally dropped below the normal range. She looks fairly peaceful and slightly oblivious to her surroundings.

The young physician pleads once more for me to reconsider resuscitation should her heart or breathing cease. I understand his frustration because he needs to feel that he is doing something. He still does not have the experience to understand that at this stage, when her immune system is almost nonfunctional, those efforts might extend her life only temporarily and with a great deal of discomfort. I just look at him and continued with my prayers.

She did not have a stroke or heart failure. She had a hospital acquired infection and developed sepsis despite all the IV antibiotics.
This is where we are vulnerable.

Our immune system actually keeps us alive. It is fighting for us every moment of our lives to keep us alive. We must understand that when our time is up, all the doctors in the world will not be able to keep us alive.
However, we can do many things to keep our immune system functioning at its optimum.

When our immune system is not functioning well, we can develop any of these immune related conditions and diseases.
1. Allergy & Hives
2. Asthma
3. Cancer
4. Hay fever
5. HIV & AIDS
6. Infections
7. Autoimmune diseases like: Rheumatoid Arthritis,Psoriasis,Lupus, Multiple Sclerosis,Scleroderma,Celiac Disease,Sarcoidosis, Graves disease, Myasthenia Gravis etc.

How do we know if our immune system is not at its optimum?
* Allergies
* Hives
* Cold sore outbreaks
*Frequent colds and flu

*Chronic diarrhea
*Candida yeast overgrowth
* Various inflammatory disorders
* Psoriasis and eczema
*Parasite infections etc

Basic understanding of our immune system.

The immune system is the best example of a teamwork. In an orchestra, all the musicians play their roles which results in perfect harmony. Same holds true for the immune system. It is amazing how a reasonably functional immune system protects us from invasion by various pathogens as well as cancer cells which are produced in our body routinely.

The major components of our immune system are:
Skin : Healthy and intact skin forms a formidable barrier for a pathogen to enter our bloodstream.

Mucous membranes: Secretory immunoglobulin(SIgA) is secreted which defends the whole body against invasion by pathogens.

Saliva : When we secrete saliva in our mouths, it contains an enzyme known as lysozyme which kills bacteria.

Probiotics: Friendly microbial colonies in our gut which play a major role in maintaining optimum immune function while destroying invading pathogens.

Interferon: Interferons are the immune system's first line of defense against most viruses.There are several types of interferons: gamma, beta and alpha interferons. Interferons helps cells that are not infected with a virus to develop resistance against it.

Natural killer cells (NK cells): Natural killer cells plays a major role in our immune system by killing the invading bacteria,fungi,microorganism,parasites and viruses.These cells also kill cancer cells before they can anchor and multiply.

White Blood Cells:These cells play a vital role in defending us.WBC's generally circulate in the blood attacking invading bacteria,parasites and any other foreign cells that somehow makes its way in the bloodstream.

Helper T cells: Which is also known as T4 cells alert the immune system about a possible invasion by foreign objects and assists the Cytotoxic T cells in their action.

Cytotoxic T cells: Also known as killer T-cells usually arrives at the site of invasion where they attach to cancer cells or infected cells.They then inject a cytokine that destroys the antigen.

Suppressor T- cells: The function of these cells is to shut down certain activities of the immune response a few weeks after the activation.This way, homeostasis is maintained until the next invasion.
Cytokines: These are proteins that are secreted by the cells.Cytokines interacts with the cells of the immune system to control our response to disease and infection.

Antibodies: These are also known as immunoglobulins produced by a type of white blood cells known as plasma cells.There are five classes of antibodies each having different response.

In general, Immunoglobulin E (IgE) is involved in allergic reactions.
Factors that influences our immune system:

1. Stress and emotional state: This plays a big role in the proper function of the immune system. In modern society, there are many stressors and we need to find ways to cope with them. A positive outlook of life helps the immune system to function better.
1. Lifestyle : Needless to say, lifestyle impacts the immune system either positively or negatively. Adequate sleep,good nutritious meals, exercise,prayer,laughter,social gatherings in general affect the immune system positively.
2. Pollution and environmental toxins: These create a great deal of extra work for our immune system. A good strategy must be adopted for internal cleansing of the toxins that accumulate over time. I recommend fasting and using Dr.Natura detox products.
3. Excessive antibiotic use : Gut flora (friendly bacteria) is almost destroyed after an antibiotic use. Repeated use of the antibiotic makes it impossible to maintain gut flora, which is extremely important for immune function. That's why it is recommended to use a broad spectrum probiotic after each antibiotic use.
4. Nutrition and Supplements: Nutrition and supplements plays a huge role in maintaining our immune system. There are many immune boosters that optimizes the immune function. These are specially helpful when someone's immune system is not functioning well and to fight cancer. Here are few immune boosting supplements that I recommend: Vitamin C,Vitamin D,Selenium,Zinc,Glutathione,Beta Glucans,Mushroom products,Broad spectrum probiotics,Colostrum,Epicor etc.
5. Genetic makeup : This has some influence in the immune function. However, adopting a better lifestyle and taking proper supplements we can circumvent some negative gene expressions.

6. Age: As we get older, our immune system starts to decline due to malnutrition, dysbiosis and lack of secretion of enzymes and certain hormones.

To conclude, a healthier lifestyle, proper management of stress, an optimistic outlook on life, nutrition and supplementation along with good detoxification will positively impact the immune system.

Exercising Care When Dispensing Controlled Substances

Joseph J. Bova, R.PhI

A community pharmacist is faced with many challenges in performing day to day activities. We are licensed by our respective states and have the duty to follow laws, rules and regulations. In order to do this, we must know what these laws, rules and regulations are. This article will focus on the dispensing of controlled substances and the pharmacist's obligation in the exercising of "due diligence". No matter what state you work in and no matter where you work, the regulations that describe a prescription as defined by the Drug Enforcement Administration (DEA) apply. Regulations part 1300.01(b)(35) define a prescription as an "order for medication which is dispensed to or for an ultimate user but does not include and order for medication which is dispensed for immediate administration to the ultimate user (i.e.- an order to dispense a drug to an in-patient for immediate administration in a hospital is not a prescription).

The purpose of a prescription is defined in section 1306.04:

(a) A prescription for a controlled substance to be effective must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. An order purporting to be a prescription issued not in the usual course of professional treatment or in legitimate and authorized research is not a prescription within the meaning and intent of section 309 of the Act (21 U.S.C. 829) and the person knowingly filling such a purported prescription, as well as the person issuing it, shall be subject to the penalties provided for violations of the provisions of law relating to controlled substances.

(b) A prescription may not be issued in order for an individual practitioner to obtain controlled substances for supplying the individual practitioner for the purpose of general dispensing to patients.

(c) A prescription may not be issued for "detoxification treatment" or "maintenance treatment," unless the prescription is for a Schedule III, IV, or V narcotic drug approved by the Food and Drug Administration specifically for use in maintenance or detoxification treatment and the practitioner is in compliance with requirements in §1301.28 of this chapter. For example, in NY, only a prescriber registered with the NYS Dept. of Health may treat outpatients for drug addiction and may only prescribe buprenorphine (Suboxone®) for this

purpose. The prescriber is issued a special DEA number that begins with an “X” when authorized to treat drug addiction.

It is important for the pharmacist to understand the language above especially the words, “The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription”. This puts the burden on the dispensing pharmacist to take any actions to be sure the prescription is legitimate. Also important is the prohibition against supplying controlled drugs to prescribers for office use. (paragraph b). All prescriptions must be in the name of the ultimate user.

Pharmacists are often faced with the task of evaluating a prescription and determining its legitimacy. The DEA provides this guidance for pharmacists:

Types of Fraudulent Prescriptions

Pharmacists should be aware of the various kinds of fraudulent prescriptions which may be presented for dispensing.

- Legitimate prescription pads are stolen from physicians' offices and prescriptions are written for fictitious patients.

- Some patients, in an effort to obtain additional amounts of legitimately prescribed drugs, alter the physician's prescription.

- Some drug abusers will have prescription pads from a legitimate doctor printed with a different call back number that is answered by an accomplice to verify the prescription.

- Some drug abusers will call in their own prescriptions and give their own telephone number as a call back confirmation.

- Computers are often used to create prescriptions for nonexistent doctors or to copy legitimate doctors' prescriptions.

The following criteria may indicate that the purported prescription was not issued for a legitimate medical purpose.

- The prescriber writes significantly more prescriptions (or in larger quantities) compared to other practitioners in your area.

- The patient appears to be returning too frequently. A prescription which should have lasted for a month in legitimate use, is being refilled on a biweekly, weekly or even a daily basis.
- The prescriber writes prescriptions for antagonistic drugs, such as depressants and stimulants, at the same time. Drug abusers often request prescriptions for "uppers and downers" at the same time.

- Patient appears presenting prescriptions written in the names of other people.

- A number of people appear simultaneously, or within a short time, all bearing similar prescriptions from the same physician.

- Numerous "strangers," people who are not regular patrons or residents of your community, suddenly show up with prescriptions from the same physician.

Characteristics of Forged Prescriptions

- Prescription looks "too good"; the prescriber's handwriting is too legible;

- Quantities, directions or dosages differ from usual medical usage;

- Prescription does not comply with the acceptable standard abbreviations or appear to be textbook presentations;

- Prescription appears to be photocopied;

- Directions written in full with no abbreviations;

- Prescription written in different color inks or written in different handwriting.

Prevention Techniques

- Know the prescriber and his or her signature;

- Know the prescriber's DEA registration number;

- Know the patient, and

- Check the date on the prescription order. Has it been presented to you in a reasonable length of time since the prescriber wrote it?

When there is a question concerning any aspect of the prescription order, call the prescriber for verification or clarification.

Should there be a discrepancy, the patient must have a plausible reason before the prescription medication is dispensed.
Any time you are in doubt, you should request proper identification. Although this procedure isn't foolproof (identification papers can also be stolen or forged), it does increase the drug abuser's risk.

If you believe that you have a forged, altered, or counterfeited prescription -- don't dispense it -- call your local police.

If you believe that you have discovered a pattern of prescription abuses, contact your State Board of Pharmacy or your local DEA office. Both DEA and state authorities consider retail-level diversion a priority issue.

Proper Controls

Loose or routine dispensing procedures, without controls and professional cautions, are invitations to the drug abuser. Proper controls against fraudulent prescriptions can best be accomplished by following **common sense, sound professional practice, and using proper dispensing procedures and controls.**

Have your pharmacy staff help protect your practice from becoming a source for prescription drug diversion. Become familiar with which drugs are popular for abuse and resale on the streets in your area. Drug abuse prevention must be an ongoing staff activity.

Encourage local pharmacists and physicians to develop a network, or at least a working relationship, which promotes teamwork and camaraderie. Discuss abuse problems with other pharmacists and physicians in the community. Most drug abusers seek out areas where communication and cooperation between health professionals are minimal because it makes their work so much easier.

Best wishes to

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