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COMPARATIVE PHARMACOKINETICS OF A RAPIDLY DISINTEGRATING TABLET FORMULATION OF IBUPROFEN AND ENTERIC-COATED IBUPROFEN: CLINICAL SIGNIFICANCE FROM A PILOT STUDY

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Abstract- Ibuprofen is among the most frequently used NSAIDs (nonsteroidal anti-inflammatory drugs) for treatment of pain and inflammation. A novel rapidly disintegrating tablet (RDT) formulation of ibuprofen, 100 mg, was developed as a fast-acting, quick-dissolving formulation. The purpose of this study was to evaluate, comparatively, the pharmacokinetics of ibuprofen from the RDT product and enteric-coated (EC) ibuprofen, 200 mg, with emphasis on clinical significance. Following a cross-over pharmacokinetic study design, healthy volunteers received a single oral dose of the RDT or EC ibuprofen and absorption-related pharmacokinetic parameters were determined using WinNonlin®. Quantifiable plasma concentrations of ibuprofen from the RDT were detected within 3-10 minutes post-dose, with maximum concentration (C_{max}) of 8.89 ± 1.74 µg/mL occurring at 1.38 ± 0.43 hours (t_{max}). Corresponding values for EC ibuprofen were 30-60 minutes, 17.17 ± 1.31 µg/mL and 1.83 ± 1.01 hours, respectively. The bioavailability of ibuprofen from the RDT relative to EC ibuprofen was 1.52. Study results have demonstrated that the RDT possessed faster onset of action, higher bioavailability on a per mg basis and more consistent plasma levels of ibuprofen. Due to its significantly lower ibuprofen content and rapid disintegration, this RDT could be viewed as a safer alternative to EC ibuprofen.

Key words- Ibuprofen, pharmacokinetics, absorption, relative bioavailability, rapidly disintegrating tablet

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Introduction

Ibuprofen is one of the most frequently administered NSAIDs (nonsteroidal anti-inflammatory drugs) worldwide today for the treatment of pain and inflammation whether as a prescription-only medication or an over-the-counter (OTC) product. It was the first in its class to become available in the U.S., which was subsequently joined by naproxen, fenoprofen, ketoprofen, flurbiprofen and oxaprozin as NSAIDs of the propionic acid derivatives subclass. As a member of this subclass, ibuprofen possesses anti-inflammatory, analgesic and antipyretic activity. It can also alter the platelet function and prolong bleeding time [1, 2]. The mechanism of action of ibuprofen involves inhibiting the cyclooxygenase (COX) enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects. Like aspirin, indomethacin and all other NSAIDs, ibuprofen is considered a nonselective COX inhibitor; that is, it inhibits both COX-1 and COX-2. The analgesic, antipyretic and anti-inflammatory activity of NSAIDs appears to be achieved mainly through inhibition of COX-2, whereas inhibition of COX-1 would be responsible for the unwanted effects on platelet aggregation and the gastrointestinal tract [1,3].

As typically the case with pain medications whether for acute or chronic use, the onset of action becomes a valuable parameter when assessing treatment success; the shorter the onset of action, the more desirable the drug formulation is. Another attribute to pain medications is the consistency with which their analgesic effect(s) are produced. Less variability in the absorption characteristics from a given dosage form is associated with more consistent pain relief. Moreover, achieving the analgesic effect with the minimum required dose is desirable and common-sense practice as this will minimize any potential for toxicity even for a drug with a longstanding and favorable safety record such as ibuprofen [4].

A novel, rapidly disintegrating tablet (RDT) formulation of ibuprofen, 100 mg, was developed with the intent to enhance the overall therapeutic response to ibuprofen. This formulation was designed as a fast-acting, quick-dissolving solid oral dosage form which might be especially valuable in situations when a fast onset of action is desirable. Furthermore, this RDT was designed to contain only 100 mg of ibuprofen, which is half of the lowest available OTC strength

of ibuprofen oral tablet. The intent of this dose reduction was to enhance the safety particularly upon long-term administration of ibuprofen while still maintaining the clinical efficacy of ibuprofen.

Therefore, the purpose of this pilot study was to evaluate, comparatively, the pharmacokinetics of ibuprofen from this RDT and enteric-coated (EC) ibuprofen, 200 mg, with emphasis on the onset of action, relative bioavailability and consistency in ibuprofen absorption. Furthermore, the clinical significance of administering ibuprofen in the form of a RDT compared to an EC formulation is discussed in light of the growing evidence that repeated exposure to EC NSAIDs is still harmful to the gastrointestinal tract as the enteric coat seems to only transfers the site of injury from the stomach to the small intestine [5,6]. As of today, this is the first attempt to characterize the pharmacokinetics of this RDT formulation of ibuprofen.

Methods

Pharmacokinetic Study

The pharmacokinetics of ibuprofen from the RDT and the EC formulation was studied in healthy adult volunteers. The study was approved by the Ohio Northern University Institutional Review Board as a single-center, open-label, single-dose, two-period cross -over pharmacokinetic study. Study subjects included both males and females with an average age of 23.4 ± 4.3 years; range: 21-31 years (n = 4 for the RDT product. As for EC ibuprofen, data was available for 3 of the 4 study subjects; fourth subject was not available for administration of the EC ibuprofen). All female subjects had a negative pregnancy test on study day. Subjects were not taking any medications and had not received any ibuprofen or ibuprofen-containing products within at least 48 hours of the study day. Study subjects were instructed to fast for at least eight hours prior to administration of the RDT or EC products.

On the scheduled study day, each subject reported to the research center and was placed in the supine position with the upper torso inclined at 30 to 45 degrees. Venous access was gained through the insertion of an 18- or 20- gauge venous catheter into an antecubital vein. The RDT product, Fasprofen®, was supplied by Applied Medical Research, Austin, TX, while the EC formulation, Advil® EC, (Wyeth Consumer Healthcare, Madison, NJ; Lot No. C13829) was purchased from a local community Pharmacy. On the first of two occasions, each subject received a single dose of either one of the two study drug products. For the RDT product, each subject placed a single tablet on the tongue and allowed saliva to totally disintegrate the dosage form. Subjects indicated to the investigators the time at which the drug had completely disintegrated (no grittiness). As for EC ibuprofen, study subjects were instructed to swallow the tablet as a whole with 240 mL of water.

Plasma and HPLC Analysis

Prior to product administration, 2 mL of plasma was collected from each subject (baseline) through the venous catheter. After product administration, 4 mL of blood was collected at 3, 5, 10, 15, 20, 25, 30, 35, 45, 60, 75, 90, 120, 180 and 240 minutes for the RDT and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225 and 240 minutes for EC ibuprofen (by design, blood samples were collected frequently during the early phase after the RDT administration to accurately characterize the time to reach quantifiable levels of ibuprofen in the blood from this dosage form. As for EC ibuprofen, a 15-minute sampling interval throughout the entire sampling duration was deemed appropriate for pharmacokinetic characterization). Blood was collected into pre-heparinized tubes which were placed in ice-water bath. The blood was centrifuged within 30 minutes of collection at 3,500 rpm for 10 minutes. Plasma was then transferred into storage tubes and placed at -80°C until analysis for ibuprofen content was performed (within 90 days of collection; no evidence of significant drug degradation under these storage conditions).

A reverse-phase HPLC (high performance liquid chromatography) assay for quantification of ibuprofen in human plasma was employed based on the method of Farrar H. et al. [7], with slight modification. The method consisted of ultraviolet detection at 220 nm (Waters, Milford, MA, USA) and Waters Symmetry® C_{18} column (4.6 X 150 mm). Mobile phase consisted of 40% water (pH adjusted to 2.6 with phosphoric acid) and 60% acetonitrile in isocratic mode at a flow rate of 1.0 mL/min. Assay linearity was established over the full concentration range for ibuprofen. For preparation of calibration curves in human plasma, 160 µL of blank human plasma, obtained from the healthy volunteers, was mixed with 40 µL of varying concentrations of an ibuprofen-containing solution in DMSO (dimethyl sulfoxide). To that, 400 µL of acetonitrile was added to precipitate the plasma proteins. The mixture was first mixed for 20 seconds then centrifuged at 13,000 rpm for 1 minute. Three hundred µL of the clear supernatant was withdrawn and evaporated to dryness by blowing nitrogen gas at 50 psi. The residue was reconstituted with 100 µL of the mobile phase and mixed with an equal volume of the internal standard (o-anisic acid, 0.25 µg/mL) and injected into the HPLC. Peak base-line resolution was achieved and the method was validated with an intra- and inter-day coefficient of variation of 1.92% (n = 3) and 3.49% (n = 6), respectively. For preparation of ibuprofen-containing samples for HPLC analysis, 200 µl of plasma was mixed with 400 µl of acetonitrile. The remainder of the procedure was similar to that for the preparation of the calibration curve samples described above.

Pharmacokinetic Data Analysis

Noncompartmental pharmacokinetic analysis of the plasma concentration versus time data for ibuprofen was performed using WinNonlin® (v.2.1; Pharsight Corporation, Mountain View, California). For pharmacokinetic analysis of individual patient data, the labeled strength of the RDT product and EC ibuprofen were assumed to be 100%. In this analysis, the maximum concentration (C_{max}) and the time of the maximum concentration (t_{max}) were the observed values from the plasma concentration-time profiles. The elimination rate constant (lz) was estimated using linear regression of the terminal ln (concentration)-versus-time data (minimum of 3 data points). The t½ was calculated as 0.693/lz. The pharmacokinetic analyses for ibuprofen included calculation of the area under the plasma concentration-time curve from time zero until the time of the last measurable plasma concentration (C_{last}; $AUC_{0\rightarrow t}$) using the linear trapezoidal rule. The area under the plasma concentration-time curve from the time of the last measurable ibuprofen concentration to infinite time ($AUC_{t\rightarrow\infty}$) was calculated as C_{last}/ lz and the area under the curve from zero to infinity ($AUC_{0\rightarrow\infty}$) was calculated as the sum of $AUC_{0\rightarrow t}$ and $AUC_{t\rightarrow\infty}$. The relative bioavailability (F_{rel}) of ibuprofen from the RDT product relative to that from EC ibuprofen was calculated as:

$F_{rel} = (AUC_{0\rightarrow\infty}/Dose)_{RDT\ Product}/(AUC_{0\rightarrow\infty}/Dose)_{EC\ ibuprofen}$

Statistical Data Analysis

The statistical significance of differences in the pharmacokinetic parameters of C_{max}, t_{max}, $AUC_{0\rightarrow\infty}$ and t½ from the two dosage forms was evaluated by student's paired t-test using GraphPad Software, Inc. P value of < 0.05 were considered statistically significant.

Results

Subjects were requested to indicate to the investigators when they perceived that the RDT formulation had completely disintegrated on their tongue. The average time for complete disintegration was 70.4 ± 19.2 seconds, ranging from 51 to 94 seconds (n = 5). For the RDT, quantifiable plasma concentrations of ibuprofen were detected within 3-10 minutes after drug administration. In comparison, it took 30-60 minutes for concentrations to start showing up in plasma upon oral administration of EC ibuprofen (Fig. 1).

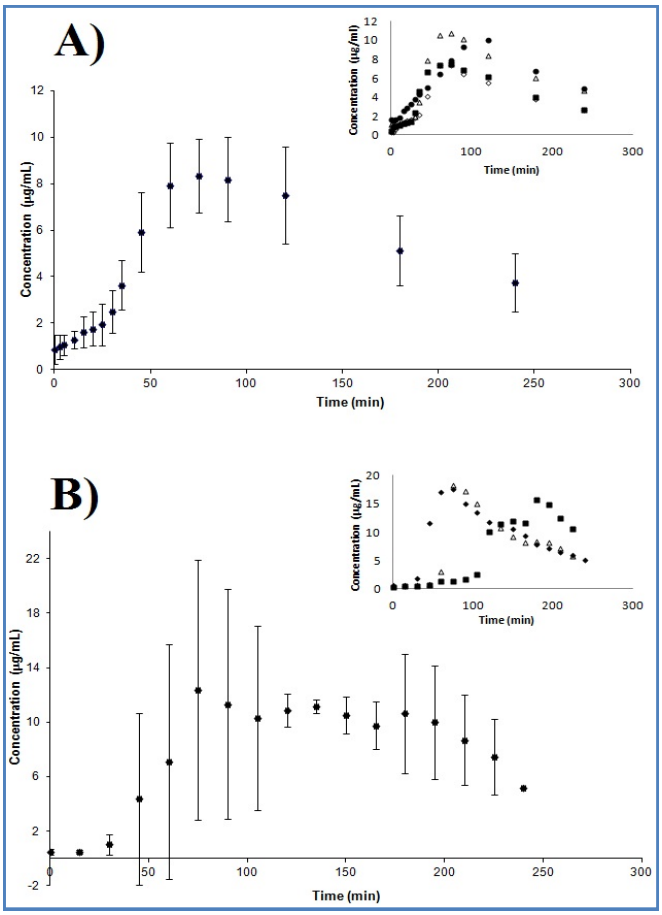

Fig. 1- Plasma concentration vs. time profile upon single oral administration of the RDT product (A; n = 4) and EC ibuprofen (B; n = 3) to healthy human subjects. Bars denote S.D. Inserts show individual subject data.

In general, the concentrations of ibuprofen upon the RDT administration increased with time, as typically seen with extravascular dosing and that was followed by the concentrations decreasing with time in a monoexponential fashion with a maximum concentration (C_{max}) of 8.89 ± 1.74 µg/mL (mean ± standard deviation) occurring at 1.38 ± 0.43 hours (t_{max}). As for EC ibuprofen, the corresponding values for C_{max} and t_{max} were 17.17 ± 1.31 µg/mL and 1.83 ± 1.01 hours, respectively (Table 1).

Table 1 - Pharmacokinetic parameters for ibuprofen upon single oral administration of the RDT product (ibuprofen, 100 mg) and EC ibuprofen (ibuprofen, 200 mg)

		Parameter			
		C_{max} (µg/mL)	t_{max} (hr)	$AUC_{0\rightarrow\infty}$ (µg.hr /mL)	$t_{1/2}$ (hr)
RDT Product (Ibuprofen, 100 mg)	Mean ± S.D.[a]	8.89 ± 1.74	1.38 ± 0.43	33.2 ± 9.5	1.97 ± 0.25
	C.V. (%)[b]	19.6	31.5	28.6	12.9
Advil® EC (Ibuprofen, 200 mg)	Mean ± S.D.	17.17 ± 1.31*	1.83 ± 1.01	43.7 ± 5.5	1.25 ± 0.36
	C.V. (%)	7.6	55.1	12.6	28.8

[a] *S.D.: standard deviation*
[b] *C.V. (%): coefficient of variation, defined as (S.D./mean) x 100%*
**Denotes statistical significance; student's paired t-test, P = 0.0086.*
$AUC_{0\rightarrow\infty}$ = area under the plasma concentration-time curve from time zero to infinite; C_{max}= maximum observed plasma concentration; t_{max} = time to C_{max}; t½ = terminal elimination half-life

The area under the ibuprofen plasma concentration vs. time curve from time zero to infinity ($AUC_{0\rightarrow\infty}$) was 33.2 ± 9.5 and 43.7 ± 5.5 µg. hr/mL from the RDT product and EC ibuprofen, respectively. That corresponded to a bioavailability of ibuprofen from the RDT product relative to that from the EC formulation, F_{rel}, of 1.52, i.e., the RDT product provided 52% more ibuprofen than EC ibuprofen on a per mg basis. As for the t½, values were calculated to be 1.97 ± 0.25 and 1.25 ± 0.36 hours for the two drug products, respectively (Table 1).

Discussion

The RDT is a rapidly disintegrating tablet of ibuprofen that was formulated to produce a fast onset of action, by dissolving in the mouth, relative to EC ibuprofen. The purpose of this pilot study was to evaluate, comparatively, the pharmacokinetics of ibuprofen upon single oral administration of the RDT and EC ibuprofen, with emphasis on onset of action, relative bioavailability and consistency in ibuprofen absorption. The rationale behind choosing EC ibuprofen as the reference formulation is because it is still the most frequently utilized form of ibuprofen, especially for chronic administration.

Upon oral administration of the RDT formulation, the tablet disintegrated within just over one minute. While this disintegration time exceeds the FDA recommended designation for an ODT (orally disintegrating tablet) of 30 seconds or less, it is still consistent with the defining characteristics for an ODT product which include disintegration in saliva without the need for chewing or liquids [8]. This rapid disintegration time does bear clinical significance. Martinez M.N. and Amidon G.L. [9] demonstrated that the initial rise of the plasma concentration, following oral administration, is critical with regard to time of onset of the desired pharmacological effect. While ibuprofen shows low solubility in the aqueous acidic media, it is highly permeable through physiological membranes [10]. Consequently, drug absorption in this case, will be governed by tablet disintegration and subsequent drug dissolution, both of which are formulation related parameters. The results of our study show that the onset of absorption, which correlates with the onset of pharmacological action, of ibuprofen from the RDT is fast and much faster

than that from EC ibuprofen, as evident by quantifiable plasma levels of ibuprofen after only few minutes following oral administration. It is likely that the absorption of ibuprofen from the RDT starts in the oral mucosa although based of the t_{max} values comparison with EC ibuprofen, it seems that the majority of absorption still takes place from the GI (gastrointestinal) tract. While statistically insignificant, t_{max} seems to be shorter with the RDT compared to EC ibuprofen. This can be attributed to, at least in part, the rapid disintegration and subsequent dissolution of the RDT. However, larger number of subjects is required to confirm this observation.

Upon evaluating the extent of ibuprofen absorption from the RDT, as represented by C_{max}, the value for this parameter was twice as much for EC ibuprofen, which was not surprising since the latter contained twice as much ibuprofen. Analysis of the $AUC_{0\rightarrow\infty}$ revealed an interesting finding, though. Doubling the dose from 100 mg, with administration of the RDT, to 200 mg, with the administration of EC ibuprofen, resulted in only 32% increase in exposure to ibuprofen, as represented by the increase in $AUC_{0\rightarrow\infty}$. Translated into bioavailability terms, the RDT represents a 52% increase in oral bioavailability over that from EC ibuprofen, upon dose normalization (F_{rel} of 1.52). Simply put, administering half of the ibuprofen dose, with the RDT, still maintained 76% of the exposure to the drug from EC ibuprofen. Although in our study we did not evaluate the desired pharmacodynamic effect (relief/reduction of pain perception), it can be reasonably assumed that quicker availability of ibuprofen in plasma, as shown for the RDT, will also provide quicker analgesic efficacy [11]. Interestingly, these results for the rate and extent of ibuprofen absorption from the RDT product are comparable to those from another independent study evaluating the absorption kinetics of ibuprofen extrudate; a novel, rapidly dissolving ibuprofen formulation, upon dose normalization since 400 mg of the latter was administered [12].

Ibuprofen serum concentrations and its analgesic effect have been shown to correlate [13]. Therefore, consistent absorption from a given dosage form is a prerequisite for a consistent analgesic affect. Our results, even with this small number of subjects, have demonstrated a more predictable, consistent and low inter-individual variability in the absorption characteristics of ibuprofen from the RDT, which was not the case with EC ibuprofen. Literature well documents a variety of physiological, pathological and pharmacological factors that influence the gastric emptying rate [14] and the rate of drug absorption from an EC tablet formulation will be impacted by those factors. While the absorption extent may not to be altered, those multitude of factors could significantly alter the onset of action and t_{max}; two key parameters for a pain relief medication. On the other hand, within a minute of administration of the RDT, ibuprofen will be in the form of solution/suspension, so when it comes in contact with the absorptive surfaces whether in the oral cavity or GI tract, it will therefore be readily available for absorption, resulting in a more consistent absorption profile upon each administration.

Although statistically insignificant, the RDT seems to possess a prolonged ibuprofen t½ relative to that from EC ibuprofen. This prolonged t½ may be a consequence of the dosage form design since the RDT contains glucosamine which acts as a mucoadhesive [15]. It could as well be a consequence of repetitive swallowing of some of the disintegrated tablet particles over time, such that the input of the dose continued, even in slight proportions, for some time after administration and possibly within the early portion of the elimination phase. In previous work [16], we observed similar pattern of prolonged t½ upon oral administration of an orally disintegrating tablet formulation of low-dose aspirin, Fasprin®, which is currently available as an OTC product on the U.S. market.

Over the past few decades, significant body of literature has documented the adverse drug reactions of NSAIDs with the most prevalent being GI disturbances [17]. More importantly, these harmful effects have been associated even with EC formulations. In a review article, Davies N.M. demonstrated that while EC and sustained-release formulations of NSAIDs have attempted to improve therapeutic efficacy and reduce severity of upper GI side effects, it is possible that these formulations may increase the exposure of the active drug to the mucosa distally to the duodenal bulb and thereby increase toxicity to distal GI regions where these effects are difficult to monitor [5]. These harmful effects to the intestinal mucosa have been demonstrated even in younger, healthier population where small bowel injuries as well as reduced blood flow to the small intestine upon oral administration of EC low dose aspirin (100 mg) were observed within as little as 14 days [6]. Based on these reports, it can be concluded that EC NSAIDs seem to only shift the site of injury from stomach to small intestine. In addition to their documented GI toxicity, treatment failure has been reported with the use of EC NSAIDs. In a study comparing coated versus uncoated aspirin as an anti-coagulant, 65% of patients taking coated aspirin, irrespective of the strength, had no reduced clotting compared with 25% for those taking the uncoated formulation [18]. One explanation for this observed "aspirin resistance" was poor absorption from the EC formulation, which was substantiated by the enhanced therapeutic effectiveness upon switching to an uncoated aspirin preparation. Although our study did not evaluate any pathological/toxicological outcomes, it is reasonable to believe that the RDT possesses a lower potential for harmful effects on the GI mucosa such as bleeding, lesions and ulcerations due to its significantly lower ibuprofen content and rapid disappearance of the intact tablet within the GI tract. Last but not least, the more consistent and predictable absorption characteristics from the RDT formulation will increase the chance of treatment success with ibuprofen; a highly efficacious NSAID with long history of effective pain relief.

Conclusion

The rapidly disintegrating tablet (RDT) formulation of ibuprofen, 100 mg, has been shown to possess favorable absorption-related kinetics compared to EC ibuprofen, including faster onset of action, higher bioavailability on a per mg basis and more consistent plasma levels. Due to its significantly lower ibuprofen content and rapid disintegration within the GI tract, this RDT product could be viewed as a safer alternative to EC ibuprofen with higher long-term tolerability.

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References

[1] Harvey R., Champe P., Finkel R., Cubeddu L. and Clark M. (2009) *Lippincott's Illustrated Reviews: Pharmacology*, 4*th Edition, Baltimore*, 501-507.

[2] Moore N. (2003) *Int. J. Clin. Pract. Suppl.,* 135, 28-31.

[3] Praveen R. and Knaus E.E. (2008) *J. Pharm. Pharm. Sci.*, 11 (2), 81s-110s

[4] Rainsford K.D. (2003) *Int. J. Clin. Pract. Suppl.*, 135, 3-8.

[5] Davies N.M. (1999) *J. Pharm. Pharm. Sci.*, 2(1), 5-14.

[6] Nishida U., Kato M., Nishida M., Kamada G., Yoshida T., Ono S., Shimizu Y. and Asaka M. (2011) *World. J. Gastroenterol.*, 17(2), 226-230.

[7] Farrar H., Letzig L. and Gill M. (2002) *J. Chromatogr. B.*, 780 (2), 341-348.

[8] FDA/CDER, *Guidance for Industry: Orally Disintegrating Tablets*.

[9] Martinez M.N. and Amidon G.L. (2002) *J. Clin. Pharmacol.*, 42, 620-643.

[10] Levis K.A., Lane M.E. and Corrigan O.I. (2003) *Int. J. Pharm.,* 6, 49-59.

[11] Seibel K., Schaffler K., Reeh P. and Reitmeir P. (2004) *Arzneimittelforschung*, 54, 444-451.

[12] Klueglich M., Ring A., Scheuerer S. Trommeshauser D., Schuijt C., Liepold B. and Berndl G. (2005) *J. Clin. Pharmacol.*, 45(9), 1055-1061.

[13] Laska E.M., Sunshine A., Marrero I., Olson N., Siegel C. and McCormick N. (1986) *Clin. Pharmacol. Ther.*, 40(1), 1-7.

[14] Benet L.Z., Massoud N. and Gambertoglio J.G. (1985) *Pharmacokinetic Basis for Drug Treatment*, 2*nd Edition*, 0-33.

[15] Gautier S., Arpagaus C., Schafroth N., Meuri M., Deschamps A. and Maquet V. (2010) *Drug Delivery Technology,* 10(8), 30-37.

[16] Rojeab Y., Martin B.S., White R., Montenery S., McWilliams M., Walker M. and Kisor D. (2011) *Int. J. Med. Clin. Res.*, 2(2), 72-77.

[17] Fries J.F., Williams C.A. and Bloch D.A. (1991) *Arthritis Rheum.*, 34(11), 1353-1357.

[18] Alberts M.J., Bergman D.L., Molner E., Jovanovic B.D., Ushiwata I. and Teruya J. (2004) *Stroke*, 35(1), 175-178.