Pharmacokinetic evaluation of ibuprofen controlled release matrix tablets using hydrophilic Eudragit® polymer and co-excipients

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Abstract: The present study was conducted to formulate controlled release dosage forms containing Ibuprofen with Eudragit® S 100 polymer. The tablets were formulated at three different ratios with the polymer to investigate the effect of different concentrations of polymer on *in vitro* drug release patterns/kinetics and *in vivo* absorption/pharmacokinetics. Pre-formulation studies were conducted including bulk density, tapped density, compressibility index, Hausner ratio and angle of repose. *In vitro* studies were conducted using phosphate buffer (pH 7.4) as dissolution medium. *In vivo* performance was evaluated using albino rabbits. Physico-chemical characteristics (i.e. dimensional tests, weight variation, hardness, friability and drug content determination) fell in the USP acceptable limits. The compressibility index was found to range between 12.02±0.01% and 18.66±0.03%, the Hausner ratio varied between 1.02±0.01 and 1.19±0.10 and the angle of repose ranged from 15.19±0.01 to 24.52±0.10, all indicating better flow properties than the bulk-reference standard. Both bulk and tapped densities also fell in the USP acceptable range. Ibuprofen market tablets showed T_{max} of 2.1±0.4h, which was significantly (P-value <0.05) lower compared to that of the reference standard (i.e. 4.09±1.3h). Ibuprofen test formulation has a half-life ($t_{1/2}$) of 16.9±2.5h, which was significantly (P-value<0.001) higher compared to that of the reference standard (i.e. 9.23±2.9h). Eudragit® S 100 polymers can be used efficiently to develop directly compressed prolonged release tablets.

Keywords: Eudragit, ibuprofen, *in vivo, in vitro*, controlled release, co-excipients, polymer-based formulations

INTRODUCTION

Oral drug delivery systems continue to rise in popularity and scientists are working on different methods to control the delivery of drug in the body, enhance the drug bioavailability (i.e. half-life), decrease the cytotoxicity, improve both the clinical efficacy and the patient compliance. During the few past decades and with the boost of nanotechnology in the recent years, a lot of work has been done to prepare controlled-release formulations of water-soluble drugs which is still a challenging issue to pharmaceutical technologists because water soluble drugs, if not properly designed, may suddenly release the entire drug after administration to body thereby causing rapid severe body toxicity (Artursson *et al.,* 1991).

Controlled release formulations have been designed for the delivery of drugs at a predetermined rate over wide range of different conditions and durations of therapeutic treatments. Various matrix-based systems, in which the drug is finely dispersed in polymeric and non-polymeric release modifying agents, are preferred controlled-release drug delivery systems because of manufacturing ease (Tiwari *et al.,* 2008).

Ibuprofen is a propionic acid derivative of non-steroidal anti-inflammatory group of drugs (NSAIDs), which is used as analgesic and antipyretic agent (Khan & Zhu, 1998). It has melting point ranging from 74 to 77°C. However, it is slightly soluble in water although soluble in organic solvents such as methanol, ethanol and acetone. Its half-life is only about 1.8 to 2 hours. Its dissociation rate (i.e. constant pKa) is of 5.3. Similarly to Ketoprofen, it has a chiral carbon atom on the propionic side chain and therefore, it also has two enantiomers, namely R (-)-Ibuprofen and *S* (+)-Ibuprofen. *S* (+) -Ibuprofen is pharmacologically 160 times more active than *R* (-) -Ibuprofen (Adams, 1976). Basically, almost all of the pharmacological activity of Ibuprofen comes from *S* (-) -Ibuprofen (Neupert, 1997). *In vivo*, *R* (-) -Ibuprofen is converted or inverted to *S* (+) -ibuprofen to the extent of 57-69%.

As shown in the fig. 1, Ibuprofen inhibits the synthesis of cyclooxygenase (COX) enzymes (COX_1 and COX_2), which act as catalysts in the production of prostaglandins (PGs) and thromboxanes (TXs) known to be involved in different physio-pathological processes (e.g. inflammation, blood coagulation). As PGs are responsible for the sensitization of pain receptors and also plays a role in production of inflammation and fever, ibuprofen acts then as an indirect analgesic and anti-pyretic by suppressing the continuous production of PGs.

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The aim of study was to develop *S* (+) -Ibuprofen controlled-release matrix tablets using Eudragit® polymer and other hydrophilic co-excipients including hydroxypropylmethylcellulose (HPMC), corboxymethylcellulose (CMC), Starch, Xanthan Gum and Gum Acacia as release retarding agents using simple direct compression technique. Additionally, the study also aimed to evaluate the tablets *in-vitro* and *in-vivo* using albino rabbits.

MATERIALS AND METHODS

Main ingredients and apparatus

Ibuprofen (Gratis sample by Drug Testing Laboratory (DTL), Peshawar), Ibuprofen Taiji SR® Ibuprofen (300 mg) by China Pharmaceutical Company, Chongqing (Mainland), Eudragit® (Dow Chemical Co., Midland, USA), Monobasic potassium phosphate, Sodium hydroxide, Carboxy-Methyl-Cellulose (CMC), Hydroxy-Propyl-Methyl-Cellulose (HPMC), Starch (ST), Lactose, Magnesium Stearate, Gum Acacia (GA), Xanthan Gum (XG), (Merck, Germany), Acetonitrile HPLC grade (Malinckrodt, USA), Diethyl ether, Phosphoric acid (BDH, UK), n-hexane, Triethylamine (Mal-inckrodt, USA). Local breed of male albino rabbits (mean age, 45 days) were purchased from local market (D.I.Khan, KPK, Pakistan). Differential scanning calorimetry **(**DSC) was referenced as Mettler Toledo DSC 822e (Greifensee, Switzerland), and Fourier transform infrared **(**FT-IR) was referenced as SpectrumOne spectrophotometer (Perkin Elimer, UK). The hardness tester was the Erweka Apparatus TB24 (Germany). The friability tester was the Erweka TA3R (Germany). The PharmaTest dissolution apparatus was the D-63512 (Hamburg, Germany)

Pre-formulation studies

Differential scanning calorimetry (DSC) studies

The differential scanning calorimetry (DSC) studies were performed for investigation of Ibuprofen interaction with polymers and excipients, using the DSC instrument (Mettler Toledo DSC 822e, Greifensee, Switzerland) equipped with Stare computer program. Approximately 3 to 6 mg of sample was weighed in aluminum pan and then sealed with punched lid. The temperature range was kept at 20 to 300°C, with heating rate of 10°C/min under nitrogen gas flow.

Fourier transforms infrared (FT-IR) studies

For further confirmation, FT-IR spectroscopy of pure Ibuprofen and its mixture with polymers and different excipients, using FT-IR Spectrum One spectrophotometer (Perkin Elimer, UK) in the range of 650 to 4000 cm^{-1}, was assessed in order to observe the drug-polymer and excipient interaction, The sample of several milligrams was placed on the stage of machine, and then handle of the machine was placed on the sample for generation of enough pressure. This way, sharp peaks with reasonable intensities have been obtained. The spectra obtained were the result of 6 scans at 1 cm^{-1} resolution.

Preparation of Ibuprofen-Eudragit® controlled release (IBU CR) matrix tablets

Ibuprofen-Eudragit® matrix tablets (200 mg) were prepared by direct compression method. Each tablet contained 100mg Ibuprofen and varying concentration of Eudragit® polymer in different formulations (Table 1). The controlled release (CR) tablets were prepared at several drug; polymer (D:P) ratios to check the effect of polymer concentration on drug release rates. HPMC K100 M, Na-CMC, starch xanthan gum and gum acacia were used as co-excipients to determine their influence on the release mechanism of Ibuprofen from polymers. Lactose was used as filler and magnesium stearate (0.5%) was used as lubricant in these Ibuprofen-Eudragit® matrix tablets. All the ingredients were weighed accurately and were mixed properly in a pestle and mortar. The mix powder was then passed through 80 mesh for 3 times, and was lubricated with magnesium stearate, again this mass was passed though the 80 mesh and was compressed using a single punch machine (Katikaneni *et al,*. 1995).

Physicochemical evaluation of tablets

Ibuprofen controlled-release matrix tablets were evaluated for different physicochemical and quality control tests. These parameters include dimensional tests, weight variation, hardness, friability and drug content determination. Ibuprofen CR tablets were evaluated for weight variation by taking 20 tablets which were then weighed on a digital weighing balance. Erweka hardness tester (Erweka Apparatus TB24, Germany) was used to calculate the average hardness of all matrix tablets formulations. Friability tester (Erweka TA3R, Germany) was used to calculate the average friability of 20 matrix tablets, at the constant speed of 25 rpm for 4mn. The average thickness and diameter was calculated by randomly selecting 10 tablets from each batch and measured with the help of Vernier caliper (Rao *et al.*, 2001).

Dissolution studies

The *in vitro* release of Ibuprofen from polymeric tablets was measured by United States Pharmacopeia (USP) Method-I (rotating basket method) in 900mL of dissolution media (phosphate buffer, pH 7.4) using Pharma Test dissolution apparatus (D-63512, Hamburg, Germany) at a speed of 100rpm and at constant temperature of 37±0.1°C. At specific time intervals, samples of each 5mL from each station were collected and immediately replaced with the same dissolution solvent previously stored at same temperature. These samples were filtered through a membrane filter having a pore size of 0.45µm before being analyzed though UV-Visible spectrophotometer at 221nm (Reynolds *et al.*, 2002).

Drug release mechanism

The *in-vitro* drug release kinetics of Ibuprofen-Eudragit® controlled-release matrix tablets were determined by plotting the fraction released *versus* time. The data were then fitted to the following five different kinetic models including: Zero order kinetics ($W=K_1t$), First order kinetics ($In\ (100\text{-}W) = In100\text{-}K_2t$), Higuchi kinetics ($W=K_4\ t^{1/2}$), Hixson Crowell kinetics ($(100\text{-}W)^{1/3} = 100^{1/3}\text{-}K_3t$) and Korsmeyer-Peppas kinetics ($M_t/M_\infty=K_5t^n$). In these kinetic models, the one which best described the kinetics was selected (i.e. in our study, Korsmeyer-Peppas equation, where M_t/M_∞ is the fractional drug release into the dissolution medium, *K* the constant which is a property of drug delivery system, and *n* the diffusional exponent which elucidates the drug release mechanism). In Korsmeyer-Peppas equation, when n=0.5 then it means that the drug is released from the matrix tablet with a quasi-Fickian diffusion mechanism; when n>0.5 then it means that anomalous, nearly zero order or non-Fickian release mechanism exists; thereby, when n=1, then it means thtat non-Fickian, case-II or Zero order release mechanism occurs (Fassihi, 1987).

Aging studies of test tablets

To determine the reproducibility of the manufacturing process, three different batches of selected formulations from the test were prepared at three different periods. These formulations were stored at proper accelerated storage conditions (i.e. temperature of 40±2°C, relative humidity (RH) of 75±5% in a stability chamber (Ti-Sc-THH-07-0400 Faisalabad, Pakistan), tightly air closed high density polyethylene jars.) These storage conditions were in accordance with international commission for Harmonization guidelines for a 6month period. After the due time, these tablets were evaluated for their appearance, hardness, friability and percent drug content at pre-storage (0 time) and after storage for 1, 2, 4 and 6 months (Fawcett & Morgan, 1997).

In vivo study protocol

In-vivo study for Ibuprofen CR tablets were performed on 10 healthy albino rabbits according to a randomized two way crossover design (Table 2). The average weight of rabbits was 2±0.3kg. The 12 rabbits were divided into two groups (Group A & Group B), each group having 6 rabbits. The study was conducted for a two trial periods by administering a single dose to each rabbit (Su S-F *et al.,* 2003).

The tablets were introduced into the base of rabbits tongue for ingestion though a plastic needle followed by a few drops of water (i.e. nearly 15mL). Moreover, the rabbits were having free access to water during the study period but were kept fasted for 12 hrs after the dosage administration. At specific time intervals, blood samples (i.e. each 0.7mL) were collected from the marginal ear vein of each rabbit, stored in small 3mL tubes and allowed to clot. In another 3mL glass tube, a 200µL serum was obtained after centrifugation at 3000 rpm for 10 min. The plasma from each tube was transferred to new tubes, and was kept at -20°C for further studies (Kuksal *et al.,* 2006).

High performance liquid chromatographic (HPLC) analysis of plasma Ibuprofen concentration

A reversed-phase HPLC method was used for the quantitative analysis of Ibuprofen in rabbit blood plasma. This HPLC system (Perkin Elmer Series 200, USA) included TCNav software for the operation. Briefly, this HPLC system consisted of a binary pump solvent delivery system, a UV-visible wavelength detector and an integrator NCI 900. The chromatographic separation was carried out on partition (5µm pore size), 4.0mm x 250 mm ODS Hypersil C18 stainless steel analytical column fitted with a refillable guard column. The detector was operated at 221nm wavelength. The mobile phase for HPLC analysis was constituted of 0.1M ammonium dihydrogen phosphate and acetonitrile (ratio 70: 30 v/v). To this mobile phase, triethylamine 0.08% was added before the pH was adjusted to 5.9 with 85% phosphoric acid. The plasma analysis was done at a flow rate of 1.0 mL/min and quantification was done by height of peak. In order to quantify the plasma concentration of Ibuprofen from the regression equation, the peak height ratio of Ibuprofen was determined after comparison with that of Verapamil HCl (internal standard).

Analysis of pharmacokinetic parameters

Three different pharmacokinetic parameters including plasma concentration time curve ($AUC_{0\text{-}\infty}$), peak plasma concentration (C_{max}) and time to reach peak plasma concentration (T_{max}) were estimated from the plasma concentration-time profile of individual rabbits in which C_{max} and T_{max} were calculated directly from the arithmetic plot of blood plasma concentration of Ibuprofen versus time profile of individual volunteer, and $AUC_{0\text{-}\infty}$ was estimated by trapezoidal rule. Similarly, the apparent volume of distribution (Vd/F) was calculated by Eq. (1):

$$Dose / (AUC_{0\text{-}\infty} \times K_e) \quad (1)$$

For the determination of individual absorption profile the Eq. (2) was used:

$$\%\ absorbed\ at\ time\ t = Ct + K_e\ AUC_{0\text{-}t} / K_e\ AUC_0 \quad (2)$$

Where *Ct* is plasma concentration at time *t*, K_e the elimination rate constant, $AUC_{0\text{-}t}$ the area under the plasma concentration time curve from any time zero to time *t*, and AUC_0 the total area under the plasma concentration *versus* time curve (Siepmann & Peppas, 2001).

STATISTICAL ANALYSIS

Our data were analyzed using ANOVA (ANalysis Of VAriance) in order to calculate the values of certain

pharmacokinetic parameters such as $AUC_{0-\infty}$, C_{max}, $t1_{/2}$, K_e and *Vd/f* obtained with the two preparations. This statistical test has a distinguished effect due to subjects, treatments and periods. The T_{max} values of the two preparations were analyzed using the wilcoxon signed rank test for paired samples. A statistically significant difference was considered when P-value was inferior to 0.05 ($p<0.05$).

RESULTS

Differential scanning calorimetry (DSC) studies

To investigate the interactions of Ibuprofen with polymers and different excipients, DSC studies were conducted. fig. 2 shows DSC curves of pure Ibuprofen and its physical mixtures with polymer Eudragit and different co-excipients. A sharp endothermic peak at 76.19°C was observed for pure Ibuprofen at the temperature corresponding to its melting point (fig. 2A).

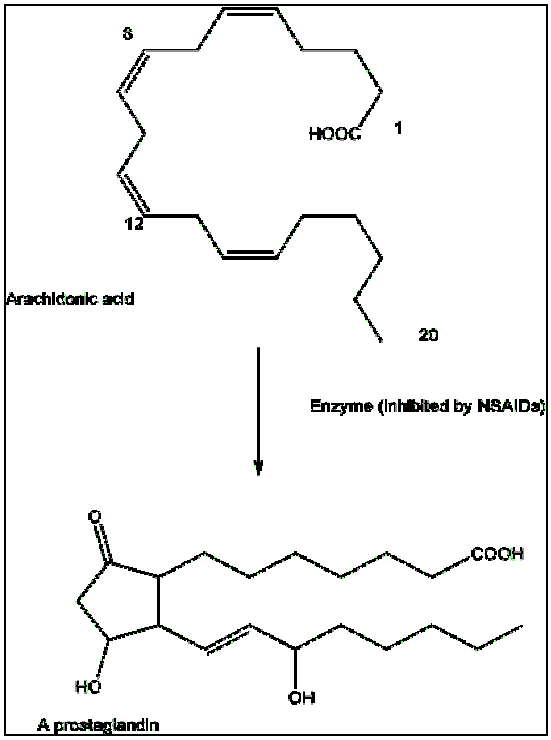

Fig. 1: Prostaglandins (PGs) synthesis *via* cyclooxygenases (COXs) catalysis. Non-steroidal anti-inflammatory group of drugs (NSAIDs), such Ibuprofen, are able to suppress the enzymatic activity of COXs.

As shown in the figs. 2A-F, the endothermic peak of ibuprofen in its mixtures with either the polymers or the co-excipients did not show any major change as compared to that of the pure drug, indicating no possible interaction.

Fourier transforms infrared (FT-IR) studies

For further analysis, FT-IR spectra of pure Ibuprofen and their respective physical mixtures were also assessed to assure the compatibility between pure drug and its physical mixtures with polymer Eudragit and different co-excipients (i.e. lactose, magnesium stearate, HPMC, starch, CMC, xanthan gum and gum acacia). The resulting FT-IR spectra are shown in figs. 3A-F. Pure Ibuprofen showed sharp characteristic peaks at 1708 cm^{-1}, which corresponds to the carboxyl acid (COOH) present in Ibuprofen. Other smaller FT-IR assignments in the region (1200 to 1000 cm^{-1}) are the indication of the benzene ring (Socrates, 1994).

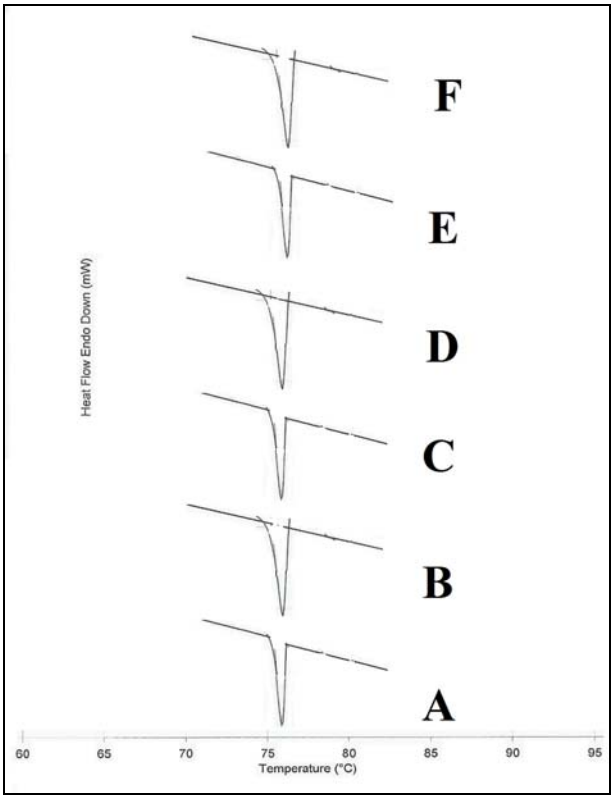

Fig. 2: DSC curves of pure Ibuprofen and its physical mixtures with polymer Eudragit and different co-excipients. A; B: C: D: E: F.

Owing to the consideration that the sharp, characteristic FT-IR peaks of Ibuprofen did not change in physical mixture with polymer and different excipients, no possible interaction can be claimed, confirming our DSC data.

As shown in Table 3, the compressibility index, Hausner Ratio and angle of repose values for pure Ibuprofen are 28±0.03%, 1.39±0.02 and 48.5±0.03, respectively. These data indicate poor flow properties. Therefore, for improvement of flow properties, 0.5% magnesium stearate, as lubricating agent, was added for all formulations during mixing of the formulation ingredients. This showed good results and improved flow properties of the powder blends. Indeed, as shown in table 3, the values of the above mentioned parameters were significantly increased (i.e. the compressibility index for Ibuprofen formulations became 12.02±0.01% to

18.66±0.03%, the Hausner Ratio as 1.02±0.01 to 1.19±0.10 and the angle of repose as 15.19±0.01 to 24.52±0.10 indicating much better flow properties. Both bulk and tapped densities also fell in acceptable range (table 3).

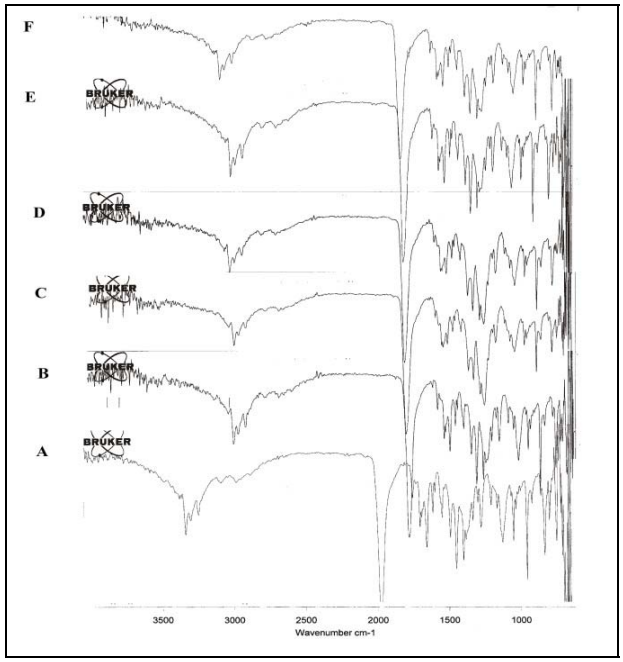

Fig. 3: FT-IR spectroscopy of Ibuprofen and its physical mixtures with polymer Eudragit and different co-excipients. A: B: C: D: E: F.

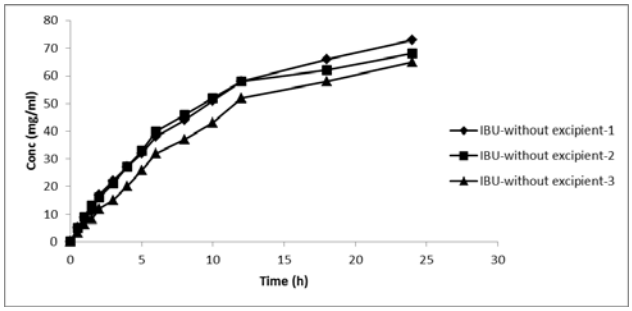

Fig. 4: *In vitro* drug release profiles of Ibuprofen-Eudragit® CR tablets in phosphate buffer pH 7.4 (Mean ± SEM, *n*=6)

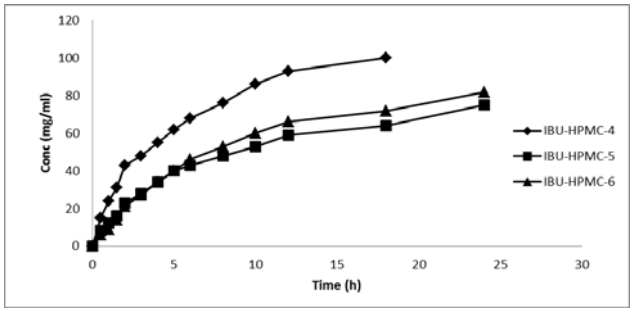

Fig. 5: Release profile of Ibuprofen from Eudragit® polymer in the presence of HPMC as co-excipient.

Tablet evaluation

Ibuprofen controlled release tablets were physically evaluated for certain physical parameters i.e. thickness, hardness, diameter, friability and weight variation in laboratory by the latest equipment's (table 4). Ibuprofen tablets were evaluated for these parameters to assess the quality of these tablets and also these parameters serve as a pointer to Good Manufacturing Practices (GMPs). The tablets were round, good looking and smooth. The weight of a tablet is a compendia standard for the quality of tablets. Thereby, the weight variation tests performed on Ibuprofen tablets revealed that these tablets were in acceptable USP limitations i.e. 197 to 204mg (>0.5), which shows good weight uniformity. The average hardness of the tablets was 6.9±0.17, which was within the acceptable USP range (5-10kg/cm^2). The average thickness was 2.09±0.03mm (USP range 2-4 mm) and average diameter was 5.86±0.06mm (USP range 4-13 mm), which also were in acceptable limits. The average friability was ranging from 0.17±0.06.

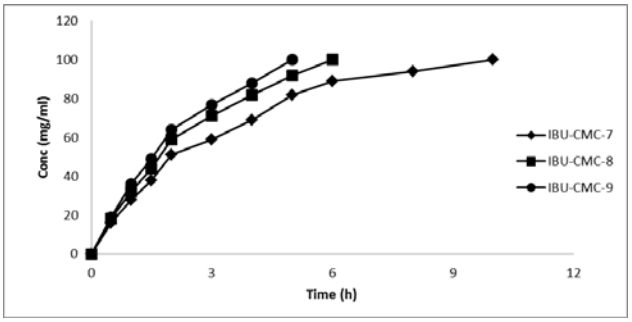

Fig. 6: Release profile of Ibuprofen from Eudragit polymer in the presence of CMC as co-excipient.

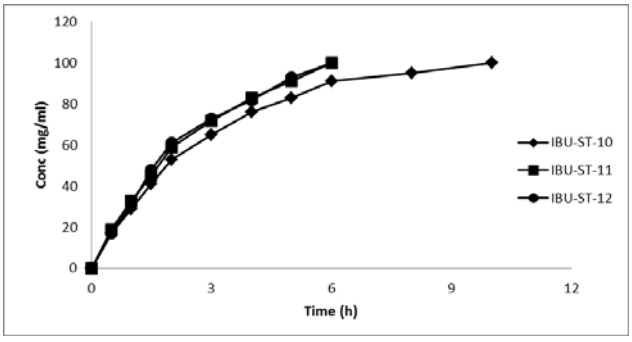

Fig. 7: Release profile of Ibuprofen from Eudragit® polymer in the presence of Starch as co-excipient.

In vitro drug release kinetics and dissolution equivalency

As shown in fig. 4, the three designed formulations (which differ in concentrations of Eudragit® as rate controlling polymer) exhibited different release profiles with respect to time. Thereby, formulation prepared at D:P ratio 10:3 was the most optimized one, releasing 65% drug in 24hs while the other formulations released 68% and 73% drug for D:P 10:2 and 10:1, respectively. It might be observed that Eudragit® polymer being

hydrophilic in nature could attractive the solvent molecules to dissolve the drug rapidly, nevertheless our concentration-dependent approach in closely densed polymer particles delayed the drug release for more than 24 hrs, which is quite valuable. Our data also suggest that a D:P ratio increasingly rich in Eudragit® could retard the drug release, and so the drug delivery *in vitro* could be controlled by playing with the D:P ratio.

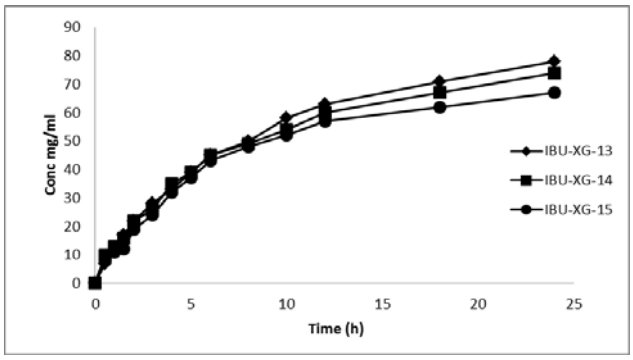

Fig. 8: Release profile of Ibuprofen from Eudragit® polymer in the presence of xanthan gum as co-excipient.

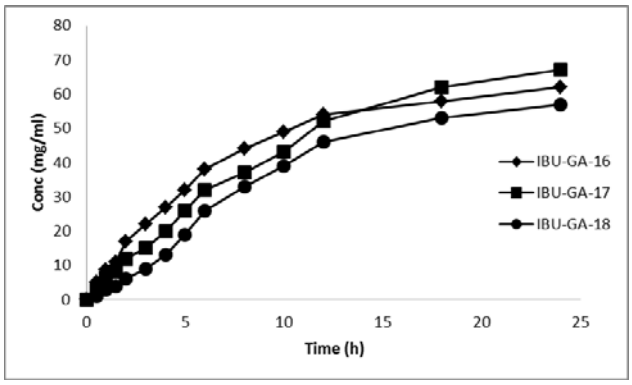

Fig. 9: Release profile of Ibuprofen from Eudragit® polymer in the presence of gum acacia as co-excipient.

Influence of co-excipients on drug release rate

The preparation of tablets may require the addition of co-excipients to obtain tablets with appropriate size and properties, or to modify the drug release rates. Therefore, the influence of different co-excipients, such as HPMC K100M, CMC Starch, Xanthan gum and Gum acacia was studied on the release rates of Ibuprofen from the matrix tablets containing Eudragit® as polymer. The release study was performed after physico-chemical evaluation of all formulations containing co-excipients. Tablets with acceptable physical properties were obtained in all cases (data is not shown). Moreover, excellent content uniformity was observed in all tablets with the above mentioned co-excipients.

Influence of HPMC as co-excipient

It could be observed that partial substitution of lactose with 30% HPMC resulted in higher release rate from IBU controlled-release matrix tablets (D:P 10: 1, 10: 2 and 10:3).. The release profiles obtained from directly compressed matrices are shown in the fig. 5. Indeed, The formulations containing Eudragit® with the co-excipient HPMC K100M showed fast release of Ibuprofen, as 90% of the drug was released after 14, 22 and 24 hours, respectively. A probable reason for these responses is that the water-soluble HPMC dissolves following water absorption, creating osmotic forces within the matrices (specify which ones). This confirms, partially, the findings of Alderman, 1984; Ford *et al*., 1987; Khan GM and Zhu, 1998a&b; Khan GM, Jiabi, 1998 that small amounts of HPMC can act as channeling agent, causing higher release rates. Swell-ability and polymer chain relaxation of HPMC plays a vital role to sustain the drug release rate (Siepmann & Peppas, 2002).

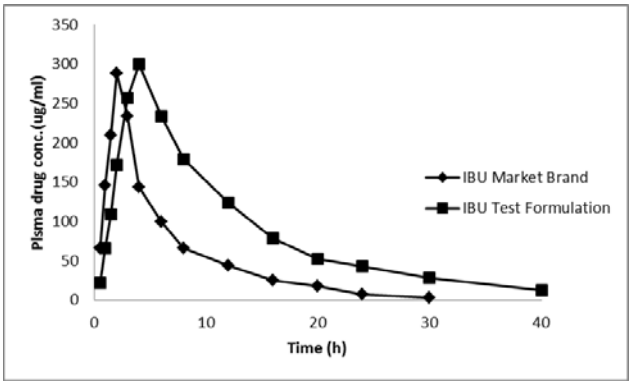

Fig. 10: Comparative release profiles of Ibuprofen reference standard and test CR formulation (D:P ratio 10:4) in phosphate buffer pH 7.4 (Mean ± SEM, *n* = 6) *in-vivo*.

Influence of CMC as co-excipient

When CMC was used as co-excipient (fig. 6), the entire drug was released within 2 hours. These drastic results might be attributed to the relatively lower viscosity of CMC, which led to low swell ability and rapid dilution and erosion of the diffusion gel layer (Alderman, 1984; Hamdy, 2007). It may also be due to the disintegrating property of CMC (Khan and Rhodes, 1975; Shah and Jarwoski, 1981), or to the water-soluble property of CMC (Khan and Zhu, 1998b). In this last case, it has been demonstrated that the water soluble co-excipient may break up the polymeric membrane around the drug contents due to the creation of osmotic forces within matrices, causing higher release rate of drug (Khan and Zhu, 1998b).

Influence of starch as co-excipient

As shown in the fig. 7, more than 90% of drug is released within 4-6 hours from the formulation containing starch as co-excipient. This result is in agreement with a previous study and can be explained by the fact that starch is insoluble in water, which subsequently may cause non-uniformity of polymeric material around the drug (Khan and Zhu, 1998b). Indeed, due to the water-swellable

Table 1: Formulations of a 200 mg Ibuprofen -Eudragit® matrix tablets

Batch	D:P	Drug (mg)	Eudragit S100	Lactose	Co-excipients
IBU-1	10:1	100	10	90	----
IBU-2	10:2	100	20	80	----
IBU-3	10:3	100	30	70	----
IBU-HPMC-4	10:1	100	10	71.2	18.8
IBU-HPMC-5	10:2	100	20	63.2	16.8
IBU-HPMC-6	10:3	100	30	55.2	14.8
IBU-CMC-7	10:1	100	10	71.2	18.8
IBU-CMC-8	10:2	100	20	63.2	16.8
IBU-CMC-9	10:3	100	30	55.2	14.8
IBU-ST-10	10:1	100	10	71.2	18.8
IBU-ST-11	10:2	100	20	63.2	16.8
IBU-ST-12	10:3	100	30	55.2	14.8
IBU-XG-13	10:1	100	10	71.2	18.8
IBU-XG-14	10:2	100	20	63.2	16.8
IBU-XG-15	10:3	100	30	55.2	14.8
IBU-GA-16	10:1	100	10	71.2	18.8
IBU-GA-17	10:2	100	20	63.2	16.8
IBU-GA-18	10:3	100	30	55.2	14.8

IBU: Ibuprofen; HPMC: Hydroxy-Propyl-Methyl-Cellulose; CMC: Carboxy-Methyl-Cellulose; ST: Starch; XG: Xanthan Gum; GA: Gum Acacia.

nature of starch, most imperfections in membranes take place, which then cause rupture of the polymeric membrane and the quick release rate of drug from tablets (Khan and Zhu, 1998b).

Influence of xanthan gum as co-excipient

The effect of xanthan gum is shown in fig. 8. As the amount of xanthan gum in the matrix increased, there would be a greater degree of hydration with simultaneous swelling which results in a lengthening of the drug diffusion pathway and reduction in drug release rate. Xanthan gum has minimum water uptake and hence minimum swelling (Al-Saidan *et. al*. 2005).

Table 2: *In vivo* drug dosing schedule, over a period of two weeks, of rabbits (n=12) divided in two equal groups.

Group	Period (weeks)	
	I	II
A (n=6)	Test formulation	Ref: ibuprofen SR tab
B (n=6)	Ref: ibuprofen SR tab	Test formulation

SR; Sustained Release

When xanthan gum is used as the only retarding polymer, drug release follows a matrix type model and so, it can be concluded that the passage of drug is through the hydrated layer (Phaechamud *et. al.,* 2007).

Influence of gum acacia as co-excipient

Gum acacia has been used as tablet binder in matrix formulation, but in hydrophilic matrix system it can act as release promoting polymer for highly hydrophilic drugs. This property of gum acacia can be correlated for its high affinity with water leading to increased water penetration into system which is responsible for polymer swelling and increased rate of erosion and finally formation of channels for drug release. It is observed from fig. 9 that increasing concentration of gum acacia has positive effect on release profile of the water-soluble drug Ibuprofen from hydrophilic matrices.

Stability and reproducibility of the manufacturing process

The best optimized formulation (D:P ratio 10:3) was selected for stability and reproducibility study owing to consideration of its average hardness of 7.04±0.11 kg/cm^2, friability of 0. 18±0.13% and drug release profile of 24 hs. This formulation having an '*n*' value of 0.913 exhibited anomalous nearly zero order release kinetics. The p-value ($P<0.05$) indicates that there was no significant difference between the drug content of all batches selected for stability studies. (i.e. hardness, friability, weight variation and physical appearance) at accelerated storage conditions after suitable time periods of 0, 1, 2, 4 and 6 months (table 5).

In vivo drug performance

In vivo drug release studies of Ibuprofen were carried out in rabbit plasma using HPLC methods. Rabbit plasma samples were withdrawn at different time intervals according to the USP specifications. The plasma sample from rabbit obtained at time zero showed no peak of Ibuprofen, which appeared for samples collected at time > 0 (fig. 10). The plasma samples after 4 hrs of drug administration showed that the retention time of

Table 3: Micromeritics of pure Ibuprofen formulation blend. The data represents a mean of 3 experiments.

Formulation	Bulk Density (g/cm^3) (Mean ± SD)	Tapped Density (g/cm^3) (Mean ± SD)	Hausner's Ratio (Mean ± SD)	Angle of Repose (θ) (Mean ± SD)	Compressibility Index (%) (Mean ± SD)
Pure Drug	-----	-----	1.39±0.02	48.5±0.03	28±0.03
IBU-1	0.323±0.02	0.339±0.07	1.11±0.01	21.22±0.01	14.23±0.07
IBU-2	0.345±0.01	0.361±0.05	1.17±0.01	22.61±0.09	16.32±0.03
IBU-3	0.341±0.03	0.371±0.01	1.14±0.09	20.27±0.01	15.07±0.02
IBU-HPMC-4	0.328±0.06	0.349±0.04	1.08±0.01	17.10±0.01	18.56±0.04
IBU-HPMC -5	0.356±0.02	0.388±0.03	1.13±0.00	17.72±0.03	15.13±0.01
IBU-HPMC -6	0.328±0.02	0.359±0.04	1.09±0.10	24.52±0.10	15.15±0.02
IBU-CMC-7	0.345±0.01	0.343±0.06	1.13±0.00	17.12±0.01	15.38±0.01
IBU-CMC-8	0.316±0.04	0.351±0.04	1.18±0.10	20.18±0.01	16.34±0.03
IBU-CMC-9	0.321±0.05	0.354±0.08	1.19±0.01	23.91±0.02	14.01±0.01
IBU-ST-10	0.323±0.02	0.383±0.06	1.14±0.01	24.18±0.07	15.03±0.05
IBU ST -11	0.346±0.01	0.344±0.04	1.08±0.01	16.61±0.09	14.39±0.01
IBU ST -12	0.353±0.09	0.371±0.05	1.06±0.09	21.21±0.01	15.17±0.02
IBU-XG-13	0.332±0.04	0.352±0.06	1.15±0.01	15.19±0.01	18.66±0.03
IBU- XG -14	0.336±0.08	0.373±0.01	1.15±0.00	18.45±0.00	17.53±0.01
IBU- XG -15	0.332±0.04	0.361±0.06	1.19±0.10	21.38±0.10	12.35±0.03
IBU-GA-16	0.335±0.03	0.343±0.04	1.12±0.00	23.52±0.01	15.18±0.01
IBU- GA -17	0.306±0.09	0.351±0.06	1.13±0.10	17.48±0.01	16.25±0.03
IBU- GA -18	0.324±0.01	0.366±0.08	1.02±0.01	15.97±0.0-	12.02±0.01

SD=standard deviation.

Table 4: Physico-chemical characteristics of Ibuprofen controlled-release tablets (Mean ± SD, n = 3).

Formulation	Thickness (mm)	Diameter (mm)	Hardness (kg)	Friability (%)	Weight Variation (mg)	Content Uniformity (%)
IBU-1	2.2±0.1	4.1±0.3	6.2±0.06	0.12±0.04	199±0.11	99.63±0.22
IBU-2	2.0±0.3	4.6±0.4	6.5±0.04	0.17±0.02	200±0.09	99.44±0.19
IBU-3	2.1±0.1	5.1±0.1	6.7±0.02	0.15±0.04	203±0.06	98.65±0.11
IBU-HPMC-4	2.1±0.7	5.3±0.4	6.2±0.04	0.16±0.06	204±0.12	99.36±0.09
IBU-HPMC-5	2.0±0.3	6.4±0.1	6.1±0.02	0.18±0.01	202±0.16	99.87±0.08
IBU-HPMC-6	2.1±0.1	7.1±0.3	7.0±0.03	0.21±0.03	198±0.08	100.0±0.13
IBU-CMC-7	2.0±0.2	5.0±0.4	6.8±0.07	0.17±0.04	201±0.06	99.56±0.22
IBU-CMC-8	2.1±0.5	5.5±0.1	6.3±0.09	0.21±0.09	203±0.11	99.67±0.16
IBU-CMC-9	2.1±0.1	6.3±0.4	6.5±0.01	0.18±0.10	201±0.12	98.19±0.09
IBU-ST-10	2.3±0.3	5.6±0.3	6.3±0.06	0.17±0.04	202±0.14	99.63±0.13
IBU-ST-11	2.0±0.2	6.7±0.1	6.2±0.04	0.15±0.09	203±0.09	98.74±0.14
IBU-ST-12	2.1±0.4	6.4±0.1	6.2±0.01	0.16±0.05	204±0.03	98.45±0.17
IBU-XG-13	2.2±0.1	6.1±0.4	6.4±0.04	0.19±0.01	200±0.07	99.66±0.14
IBU-XG-14	2.2±0.5	7.4±0.2	6.5±0.04	0.16±0.02	200±0.11	98.87±0.13
IBU-XG-15	2.1±0.6	6.3±0.1	6.3±0.01	0.17±0.05	201±0.06	99.68±0.09
IBU-GA-16	2.0±0.1	5.2±0.3	6.3±0.10	0.15±0.01	203±0.07	98.87±0.08
IBU- GA -17	2.0±0.2	6.3±0.4	6.4±0.09	0.21±0.03	201±0.01	98.78±0.11
IBU- GA -18	2.1±0.3	6.1±0.2	6.1±0.01	0.18±0.10	202±0.08	99.65±0.14

Ibuprofen was 3.99 min with no interfering peak at the retention time of Ibuprofen while the blank plasma was clean. The absolute recovery of Ibuprofen was 94% and the coefficient of determination was r^2=0.929 which showed a good linearity level of the method.

Pharmacokinetics of Ibuprofen

Ibuprofen market tablets showed a T_{max} of 2.1±0.4h while the Tmax of the reference standard was significantly (P<0.05) higher (i.e. 4.09±1.3h. Both test formulations show significantly higher Tmax values. Indeed, Ibuprofen test formulation displayed a half-life ($t_{1/2}$) of 16.9±2.5h,

Table 5: Stability parameters of Ibuprofen CR tablets prepared at D: P ratio 10: 3 (Mean ± SEM, *n*=6).

Periods of Sampling	Hardness (kg)	Friability (%)	Appearance (color)	Drug content (%)	Weight variation (%)
Pre-storage (0 time)	7.0±0.17	0.17±0.16	White	102±3.8	5±0.2
After 1 month	7.1±0.14	0.18±0.13	White	102±2.3	5±0.3
After 2 months	7.0±0.16	0.21±0.17	White	101±2.1	4±0.3
After 4 months	7.1±0.19	0.15±0.13	White	100±4.3	5±0.4
After 6 months	7.0±0.13	0.22±0.11	White	101±2.9	5±0.3

Table 6: Pharmacokinetics parameters of Ibuprofen market tablets *versus* test formulation.

Formulation	Half-Life $t_{1/2}$ (h)	Cmax (µg/ml)	Tmax (h)	AUC $_{o-t}$ (µg.h/ml)	AUCo-∞ (µg.h/ml)
Market	9.23±2.9	287.91±3.1	2.1 ±0.4	4676.7±3.2	16821±3.9
Test Formulation	16.9±2.5	299.12±1.86	4.09±1.3	8971.4±3.6	23781±4.5

which was significant higher compared to that reference standard of 9.23±2.9h (P<0.001). This data means that there was an extended absorption phase of CR formulation that caused higher *in vivo* bioavailability. The C_{max} of Ibuprofen CR test formulations was 299.12±1.86 ng/mL, which was significantly higher compared to that reference standard of 287.91.3±3.1ng/mL (P<0.05). Also, the AUC_{0-t} for Ibuprofen test CR formulation was of 8971.4±3.6ng.h/mL, which was significantly higher compared to that reference standard of 4676.7±3. 2ng. h/mL (P<0.001). Similarly, $AUC_{0-\infty}$ for Ibuprofen test CR formulation was of 23781±4.5ng.h/mL, which was significantly higher compared to that reference standard of $AUC_{0-\infty}$ 16821±3.9ng. h/mL (P<0.001) (table 6).

DISCUSSION

The *in vitro* and *in vivo* dissolution profiles of Ibuprofen formulations prepared at different D:P ratios revealed that the polymer concentration mediates the drug release control. Indeed, more the concentration of the polymer (Eudragit®) was high, more the drug release (i.e.Ibuprofen) was significantly prolonged, allowing higher bioavailability *in vivo* (i.e. in rabbits).

For *in-vivo* drug performance and kinetics of Ibuprofen CR tablets, the peak plasma levels were monitored regularly. From our *in vivo* results, we could conclude that Ibuprofen CR formulations maintain a nearly constant blood plasma level for a long period of time (> 24 hrs) as compared to the reference standard which gain its constant blood plasma level for less extended time period. The demonstrated long half life $t_{1/2}$ and time required to obtain peak plasma concentration (T_{max}) showed that the drug release was slower, and this for an extended period of time.

In our present study, Eudragit® was used as a rate controlling polymer which was found to be a significant rate controlling material. Moreover, the formulations with Eudragit® polymer were of desired friability and hardness, allowing drug release in a nearly constant manner, exhibiting nearly zero order kinetics and maintaining a constant drug plasma level in therapeutic range, eventually minimizing the chances of toxicity and side-effects while improving the patient compliance (Sastry *et al.,* 2000). In case of Ibuprofen test formulation, after oral administration, a gradual increase was observed in plasma concentration of Ibuprofen reaching peak plasma concentration in approximately 4.3hs. Moreover, this CR test formulation indicates a slow and steady rate of drug absorption into blood stream. In case of reference standard SR formulation, after oral administration the drug reaches a peak plasma concentration in approximately 2.79 hs (Fassihi, 1987).

Interestingly, a linear curve was obtained with our test Ibuprofen formulation shifting the drug transport mechanism to a nearly zero order transport. Different kinetic models were used to evaluate the drug release transport from matrix tablets. The values of *in-vitro* dissolution profiles of Ibuprofen from different formulations in phosphate buffer were fitted in these kinetic models. Korsmeyer-Peppas equation best describes the drug transport mechanism of Ibuprofen where the diffusion coefficient '*n*' was calculated though the slope of the straight line of the data. The value of '*n*' of the most optimized formulation *i.e.* prepared at D:P ratio 10:3 was 0.944 (1<0.944>0.5) indicating Case-II, anomalous non-Fickian or nearly Zero order drug transport/release mechanism (Alderman, 1984; Hamdy *et al.,* 2007; Shah & Jarwoski 1981).

Then, Fickian is the mechanism by which drug passes though small pores of the matrix tablets into the surrounding medium, zero order indicates the mechanism of drug transport though the erosion of polymer chains (possibly due to dehydratation caused to matrix material subsequently allowing progressive drug release) and anomalous transport demonstrates the drug transport mechanism though a combined effect of diffusion and

erosion. Moreover, the linearity of the regression line was determined by the coefficient of determination r^2 having a value of 0.944. Taken together, in our experimental setting, our global data demonstrate that the polymer Eudragit®, used as rate controlling material, is highly suitable for developing controlled release drug delivery systems containing Ibuprofen (or certainly other drugs) because Eudragit®, hydrophobic in nature, cannot be affected by the gastro intestinal tract fluids and related parameters (e.g. pH) (Katikaneni *et al*., 1994).

Eventually, and in agreement with our present statements, an independent *in-vitro* study that consisted to study the effect of polymers on drug release profiles of Ibuprofen matrix tablets, has reported similar results when increasing concentration of polymer (Khan & Rhodes, 1995).

CONCLUSION AND PERSPECTIVE

The results obtained from *in-vitro* dissolution studies in simulated gastric fluids concluded that the formulations of Ibuprofen controlled release tablets having 40% highest Eudragit® polymer were able to significantly increase the time period of the drug release. Also, the *in-vivo* pharmacokinetic evaluation of Ibuprofen controlled release tablets in healthy rabbits showed a significantly slow and steady drug absorption into blood stream, reflecting a good controlled release formulation which would be helpful in further clinical studies on human volunteers.

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