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Polymer co-processing of ibuprofen through compaction for improved oral absorption

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Running head: Polymeric co-processing of Ibuprofen

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ABSTRACT

Improving oral absorption remains a major challenge for the biopharmaceutical industries aiming at introducing newer drugs or prolonging product life cycle. Most of the strategies adopted to improve oral bioavailability for poorly soluble drugs employ hazardous solvents. The purpose of this study was to improve the oral absorption of ibuprofen adopting a green pharmaceutical approach without using hazardous solvents. In this study commonly used cellulosic polymers were exploited to improve the absorption of dissolution rate limited drug ibuprofen through a simple co-processing through compaction method. The un- processed, processed and co-processed ibuprofen samples were subjected to physicochemical characterization like Fourier transform infra red spectroscopy (FT IR), Differential scanning calorimeter (DSC) and Powdered X-ray Diffraction (PXRD). Further, in vitro dissolution studies and ex vivo intestinal absorption studies were also conducted. FT IR, DSC and PXRD revealed no molecular interaction of ibuprofen with the studied co-processing excipients and/or method. The co-processed ibuprofen samples exhibited significant improvement in dissolution (unprocessed samples released 56.23±2.92% ibuprofen whereas processed samples released upto 89.67±2.88%). Similar improvement in intestinal permeation was also observed. The in vitro dissolution and ex vivo permeation data showed a higher degree of correlation ($r>0.9$). The method adopted in this study may provide a lower cost, quicker, readily scalable alternative for formulating poorly water-soluble drugs.

Key words: Ibuprofen; cellulosic polymer; dissolution; intestinal permeation; FT IR; DSC; PXRD.

Introduction

Effectively delivering most of the new or already available pharmaceuticals to the human body have always been a technological challenge for the pharmaceutical industry. Poor aqueous solubility continues to impose a major hurdle for the formulation and preclinical evaluation of new chemical entities.[1-3] About 40% of pharmaceutical compounds are recognized as poorly water-soluble, and their poor solubilities lead to poor bioavailability.[4] With the increasingly lipohphilic nature of the candidate drugs, solubility and dissolution rates have become the limiting factors that affect bioavailability of oral and parenteral formulations. While advanced technologies for enhancing delivery of poorly soluble drugs have included using prodrugs,[5] polymorphs, solvates, co-crystals,[6] salt formation,[7] lipid based systems,[8] micellar solubilization including self-emulsifying drug delivery systems,[9] inclusion complexes,[10] amorphous solid forms such as spray dried dispersions,[11] etc., a green pharmaceutical approach remains particularly desirable to the pharmaceutical industry.

Among methods using polymeric substances to improve dissolution, solid dispersions are one of the most promising approaches. Melting and solvent evaporation are the most commonly employed methods for preparation of solid dispersions. Water soluble polymer like polyethylene glycol (PEG), polyvinylalcohol (PVA), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methylcellulose (MC), etc has been used as carriers for improving dissolution rate in solid dispersions. The major limitations of melting method include availability of limited water-soluble polymers which can dissolve drugs and the drugs often decompose during processing at high temperature. On the other hand, in the solvent method, mostly organic solvents are used which are highly toxic to the biodiversity imposing a significant threat to human being.

Ibuprofen is a very commonly prescribed non steroidal anti-inflammatory agent with analgesic and antipyretic activity. However, the oral bioavailability of ibuprofen is low due to

poor dissolution behavior. In the present work we are reporting an eco-friendly green pharmaceutical approach. In this study, we have used a slugging method to improve the dissolution rate and oral absorption of ibuprofen (oral absorption is dissolution rate limited) using few commonly used cellulosic tableting excipients like various grades of Hydroxy propyl methyl cellulose (HPMC). The physicochemical characterization was carried out using analytical techniques like FT IR, DSC and PXRD. In vitro dissolution studies and ex vivo intestinal permeation studies were also carried out. Finally a correlation between in vitro dissolution and ex vivo permeation was established.

Materials and methods

Materials

Ibuprofen was obtained as a gift sample from Cipla Ltd (Mumbai, India). HPMC K3LV P (Hydroxypropyl Methyl Cellulose, methoxyl content: 19 - 24%, hydroxypropyl content: 7- 12%, nominal viscosity for a 2% (w/v) aqueous solution of 3 mPa s); HPMC E3LV P (Hydroxypropyl Methyl Cellulose, methoxyl content: 28 - 30%, hydroxypropyl content: 7- 12%, nominal viscosity for a 2% (w/v) aqueous solution of 3 mPa s) and HPMC E5LV P (Hydroxypropyl Methyl Cellulose, methoxyl content: 28 - 30%, hydroxypropyl content: 7- 12%, nominal viscosity for a 2% (w/v) aqueous solution of 5 mPa s) was obtained as gift sample from Colorcon Asia Pvt. Limited (Goa, India).

Processing/co-processing of ibuprofen samples

Dry blending of a physical mixture (1:1) of ibuprofen and polymer was carried out as per Table 1. Compacts of the ibuprofen/polymer blend were prepared by using a hydraulic pellet press (PCI Analytics Ltd., Mumbai). The compacts were produced using flat faced, 10 mm diameter, round tooling. The dwell time and compression force for all the compaction processes was fixed at 1 min and 30kN respectively. The resultant compact was milled using a ball mill (Swastik Electric and Scientific Work, Ambala Cantt, India). A ball mill with a

cylindrical jar (outer diameter = 14.3 cm, inner diameter = 13.3 cm, and internal volume = 1000 ml) and stainless steel balls were used to perform the ball milling. For milling purposes 100 balls (each ball having 1.27 cm diameter) were taken. Before milling, the jar and balls were washed and cleaned properly and dried. The speed of rotation of the cylindrical jar was maintained at 100 rpm. The ball charge in the jar allows smooth cascading motion during milling. Milling was performed for 1 h at room temperature (25°C) and no significant increase in temperature of the milled material was detected at the end of the process.

Particle size may significantly influence the dissolution and mechanical behavior of drugs. To minimize the possible influence of varying particle size of powder samples on dissolution, a similar sieved fraction was collected as adopted by Kaialy et al.[12] The powdered materials were sieved separately through mesh # 100 (0.150 mm) and retained on # 140 (0.106 mm) to obtain the ibuprofen powder samples for further analysis.

Fourier Transform Infra red Spectroscopy (FT IR)

FTIR spectra of pure ibuprofen and prepared powder samples were measured for comparison using KBr pellets method. An average of at least 50 scans of each sample was collected at a scanning speed 2 U/s over a wave number region 4000–600 cm^{-1} (Model: JASCO FTIR 410, Nicolet Instrument).

Differential Scanning Calorimetry (DSC)

The solid state properties of the raw ibuprofen and prepared samples were studied using differential scanning calorimetry (DSC 822, Mettler Toledo). An accurate weight of each powder sample (5 mg) was placed in aluminium pan, sealed non-hermetically and heated (range 10–200 ◦C) at a heating ramp rate of 10 ◦C/min under a nitrogen gas (50 L/min). Before each measurement, the sample was allowed to equilibrate for 5 min at 30 ◦C. The transition temperatures and enthalpy readings were automatically calculated using Mettler Toledo software for each peak.

Powder X-ray diffractometry (PXRD)

Samples of ibuprofen in its native state and prepared powder samples were assessed for crystallinity using a X-ray diffractometer (Model: SEIFERT, C-3000, Germany) using Nickel-filtered CuKa radiation (k = 1.54 A˚). The voltage and current were 35 kV and 30 mA, respectively, and smoothed 95. Measurements were carried out in the angular range from 5° to 40° (2θ) using step size 0.05 and 0.25 s per step.

In vitro dissolution studies

Samples of ibuprofen pure drug (10 mg) and processed sample equivalent to 10 mg ibuprofen were subjected to dissolution rate studies in 900 ml distilled water (USP paddle method: Thermonic, Campbell Electronics, Mumbai, India, at 100 rpm and 37 °C). The drug content in the withdrawn aliquots was analyzed spectrophotometrically at 220 nm (UV-160, Shimadzu, Japan).

Ex vivo intestinal permeation studies

Small intestine of goat was collected from a local slaughter house for the study, kept in buffer fluid (Krebs-Ringer solution) and used immediately without storing for a prolonged period. The tissue sample was cleaned properly to separate the mesentery, rinsed with the buffer and then cut in different sections. Each section was everted on a Teflon rod, and fixed on its location by means of a thread. The experimental set up followed as mentioned by Meriani et al[13] with slight modification. Briefly, intestinal holder was cylindrical glass vessel connected to a "U" glass tube whose one portion was represented by the intestine. Intestine holders (four in one set) filled with buffer fluid represented the receiver environment (4 × 12 mL) and the holder placed in the donor environment. Both receiver and donor phases were continuously aerated to keep the intestine cells alive during experimentation. At regular interval of time, after beginning of the permeation test, 4 mL of the receiver phase were sampled from each intestine holder and replaced with pure buffer, for a time duration of 120

min. Ibuprofen concentration in each of four liquid phases sampled was estimated by UV spectrophotometer (UV-160, Shimadzu, Japan).

Histopathology for Viability of Intestinal Cells

Histopathological investigations were carried out to assess the viability of the intestinal tissue before and after the permeation study. Small pieces of the intestine (before and after the permeation study) was rinsed with buffer fluid and processed by paraffin technique and further stained with Haematoxylin-Eosin method.

Statistical analysis

The observed difference in the dissolution and permeation of ibuprofen from different powder samples were compared by using one way analysis of variance (ANOVA) followed by all pair wise multiple comparison procedure such as Tukey test at overall significance level of 0.05 using Sigma Stat software (Sigma Stat 3.5, SPSS Inc, Chicago, IL, USA). The correlation coefficients were estimated using Microsoft Excel® software.

Results and discussion

Ibuprofen-polymer interaction

FT IR investigation revealed no significant shift of the characteristic peaks of ibuprofen in the polymeric compacts indicating no interaction (Spectra not presented). However, in a previous investigation to adopt a solvent free approach using solid state milling of ibuprofen with kaolin, our research group has reported a reduction in absorbance of the free and hydrogen bound acid carbonyl peak (1719cm^{-1}) accompanied by a corresponding increase in the absorbance of carboxylate peak (1592 cm^{-1}) in the co -ground samples.[14] This change in FT IR spectrum was due to a possible acid base interaction between ibuprofen and kaolin.

Further, to investigate the solid state of ibuprofen in the polymeric compacts, DSC studies were carried out. DSC thermograms (Fig 1) revealed very slight shift in the melting endotherm of ibuprofen indicating a slight reduction in drug crystallinity. However, no

broadening of melting endotherm indicated significant preservation of drug crystallinity (absence of amorphization) unlike our previous work where we reported significant amorphization during co-milling of ibuprofen with kaolin and aluminum hydroxide.[14,15]

Powder X-ray diffraction pattern (Fig. 2) of unprocessed raw ibuprofen (Ir) revealed high intensity reflections and they corresponded to the following interplanar distances: 13.9, 7.5, 5.2, 4.6, and 4.0Å with characteristic peaks at 6.1°, 11.9°, 16.5°, 19.3°, and 22.5° (2θ), respectively. The diffraction pattern of ibuprofen processed (Ip) and co-processed (IK3, IE3, IE5, IHPC and IPEG) samples retained the original diffraction pattern of raw ibuprofen.

In Vitro dissolution studies

The raw ibuprofen dissolution in distilled water was found slow and incomplete (only 56.23±2.92%). Dissolution rate studies (Fig 3) revealed a significant improvement ($p<0.05$) in drug release from all the three co-processed ibuprofen samples (IK3, IE3 and IE5) when compared to native raw ibuprofen (Ir) and processed ibuprofen (Ip). Though initially (at 5 min.), the drug release from the co-processed and processed ibuprofen samples were low compared to the raw ibuprofen, after 30 minutes the drug release gradually improved and at the end of two hours released 58.81±3.11%, 87.32±3.81%, 89.67±2.88% and 79.55±3.09% for Ip, IK3, IE3 and IE5 respectively.

Statistical treatment of the observed data using one way ANOVA followed by post-hoc Tukey test suggested no significant difference ($p>0.05$; 95% confidence interval of difference= -11.12 to 5.964) in percent drug release between raw ibuprofen (Ir) and slugged alone ibuprofen (Ip) indicating slugging alone without polymeric component as an inefficient approach. Moreover, the difference in percent drug release was found insignificant ($p>0.05$; confidence interval of difference= -10.87 to 6.214) for IK3 vs IE3. Similarly, the difference in percent drug release was found insignificant for IKE vs IE5 ($p>0.05$; confidence interval of difference= -0.7642 to 16.32) indicating all the HPMC grades investigated in this study as

equally efficient. Moreover, percent dissolution of ibuprofen from all the co-processed samples was found significantly higher ($p<0.05$) than Ir or Ip samples. The dissolution of ibuprofen from the studied samples at the end of 120 minutes followed the order: IE3>IKE>IE5>Ip>Ir.

This result can be due to a more intimate dispersion of the drug onto the hydrophilic polymeric carrier, as a result of the mechanical treatment, that could strongly promote drug wettability by reducing the interactions among hydrophobic ibuprofen particles. On the other hand, the relatively higher cohesive forces with unprocessed ibuprofen sample could potentially influence the overall dissolution. A similar improvement in dissolution of nateglinide was observed by Maggi et al during their attempt of co-milling the drug with some hydrophilic super disintegrants and polymers. [16]

Ex vivo intestinal permeation

Intestinal permeation studies using isolated goat intestine is a standard method to assess the rate of permeation of drugs upon oral administration.[13,17] The study conducted for two hours revealed a significant ($p<0.05$) improvement of rate and extent of permeation of ibuprofen from co-processed samples when compared to raw ibuprofen and processed (alone) samples (Fig 4).

Raw ibuprofen (Ir) and processed (alone) ibuprofen (Ip) samples showed lower percent of permeation (36.52±4.905 % and 37.18±3.794% respectively). However, the co-processed ibuprofen samples exhibited significantly ($p>0.05$) higher intestinal permeation (58.82±6.519%, 66.21±8.001% and 72.10±5.673 for IE5, IK3 and IE3 respectively). The differences in percent permeation was found statistically significant at a level of significance of 0.05 when the observed data were subjected to one way ANOVA followed by post hoc Tukey test.

Drug dissolution in gastrointestinal fluid is a prerequisite step in oral absorption of drugs. The oral absorption of ibuprofen is dissolution rate limited and hence approaches to improve dissolution of such dissolution rate limited drugs will improve oral bioavailability.[18-20] The various grades of HPMC studied in this research demonstrated significant improvement in dissolution of ibuprofen which has resulted in improved intestinal permeation.

Further, attempt was made to assess the in vitro-ex vivo correlation. The percent drug permeated ex vivo at various time points were plotted against cumulative amount of drug released in vitro at the same time point. The correlation coefficients were estimated using Microsoft Excel® software.

One of the challenges of biopharmaceutical research is correlating in vitro drug release information of various drug formulations to the ex vivo and in vivo drug profiles (IVIVC). This demands the need for a tool to reliably correlate in vitro and ex vivo/in vivo drug release data. Such a tool shortens the drug development period, economizes the resources and leads to improved product quality.[21,22] The main objective of an IVIVC is to serve as a surrogate for ex vivo permeability study. IVIVC can be used in the development of new pharmaceuticals to reduce the number of human studies during the formulation development.[23]

In the present work, in vitro drug release data was attempted to correlate to ex vivo permeation pattern. The correlation coefficients (Table 2) were found above 0.9 indicating existence of a higher level of correlation between the in vitro-ex vivo datasets for all the powdered samples.

Histopathology for viability of intestinal tissues

The normal pattern epithelial tissue with intact nucleus of intestine in histology (Fig 5 a) indicated viability of cells in the intestinal tissue sample before the permeation study. After 2 h of permeation study, it is observed that the epithelial cells of intestinal villi are slightly

enlarged indicating vacuolar degeneration due to transport of ibuprofen across the membrane Fig 5b & c). The intact nuclei in almost all the cells indicated the viability of the cells even after 2 h of permeation study. In a similar investigation to evaluate alkylmaltosides as intestinal permeation enhancer, Petersen et al also reported occasional minor oedema post permeation studies.[24] However, the tissue barrier and secretory capacity were still at an acceptable level.

Conclusions

A solvent free, eco friendly and green pharmaceutical approach for improving oral absorption of dissolution rate limited drug ibuprofen is reported. The co-processing method adopted resulted in powdered ibuprofen samples with improved in vitro dissolution and ex vivo intestinal permeation. The co-processed samples retained the crystallinity and are supposed to be stable unlike transition to poorly soluble crystalline states with amorphous formulations. Moreover, the in vitro- ex vivo correlation was found to be of higher level with $r>0.9$. The histopathology revealed viability of the tissue samples during the ex vivo studies.

Conflicts of interest: The authors disclose no conflicts of interest.

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Figure legends

Figure 1. DSC thermograms of different ibuprofen samples showing sharp unchanged melting endotherm of ibuprofen.

Figure 2. PXRD pattern of different ibuprofen samples showing no significant change in diffraction pattern.

Figure 3. In vitro dissolution of ibuprofen powdered samples.

Figure 4. Ex vivo intestinal permeation of ibuprofen powdered samples.

Figure 5. Histology of intestinal tissue samples; (a) Before permeation study; (b) after permeation study with polymer co-processed ibuprofen sample and (c) after permeation study with slugged ibuprofen sample.

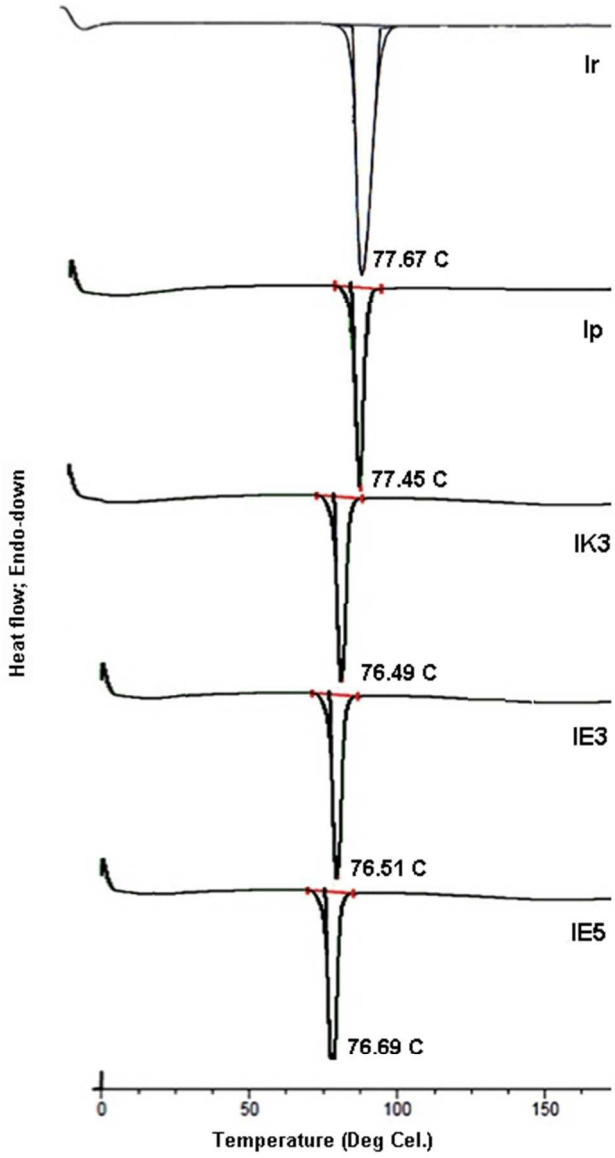

Figure 1

118x212mm (96 x 96 DPI)

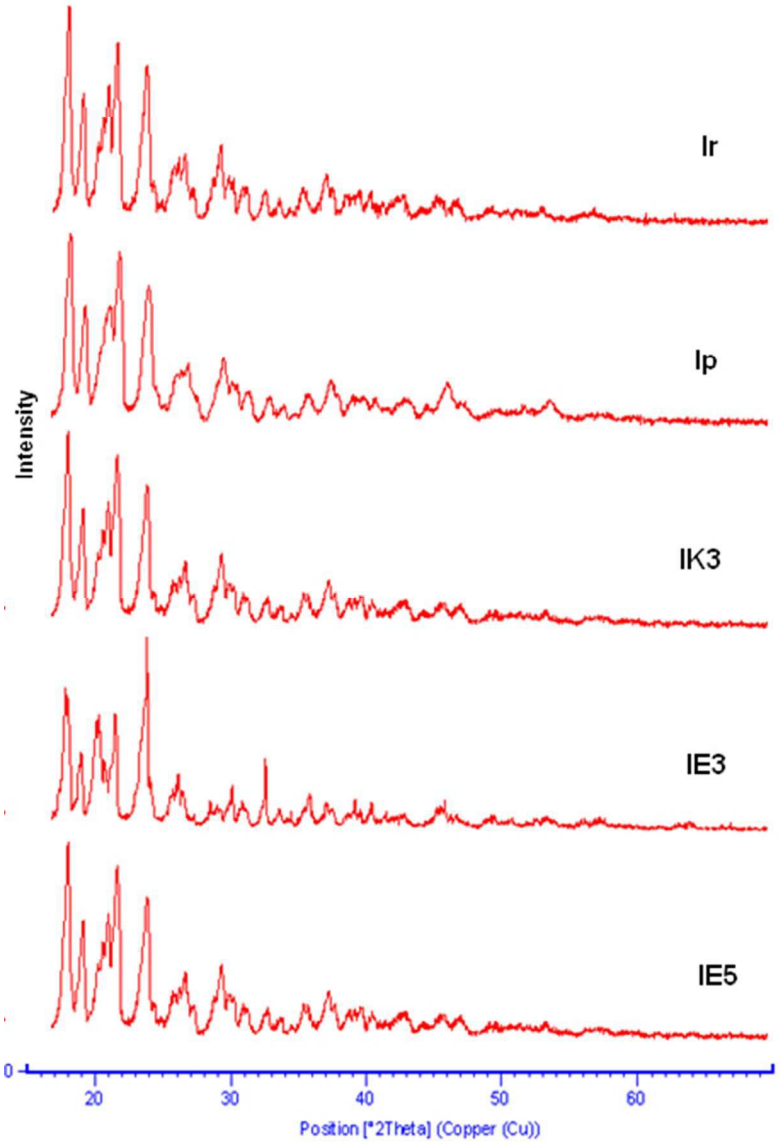

Figure 2

126x186mm (96 x 96 DPI)

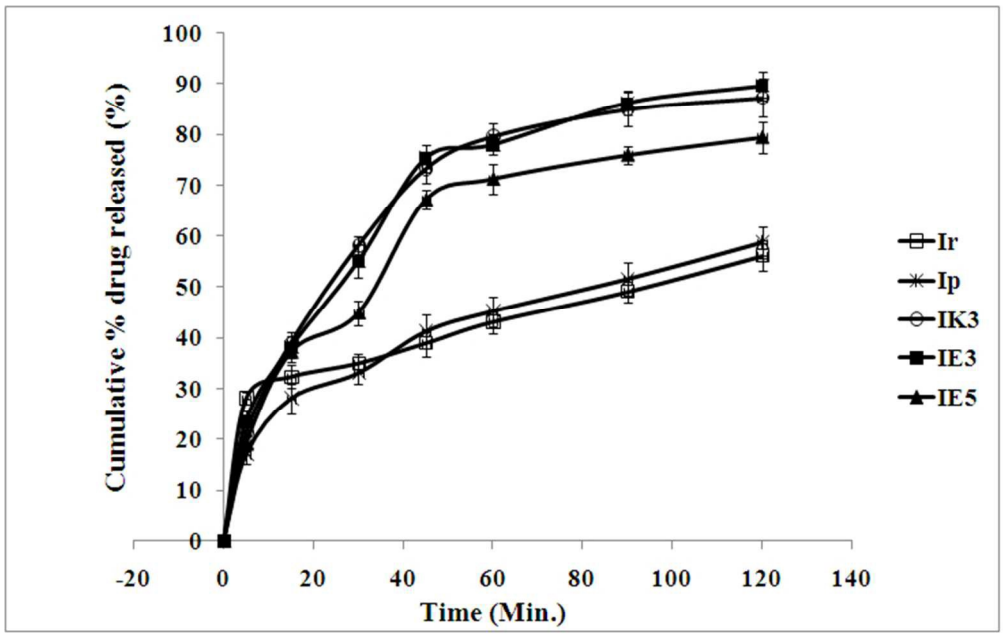

Figure 3

194x137mm (96 x 96 DPI)

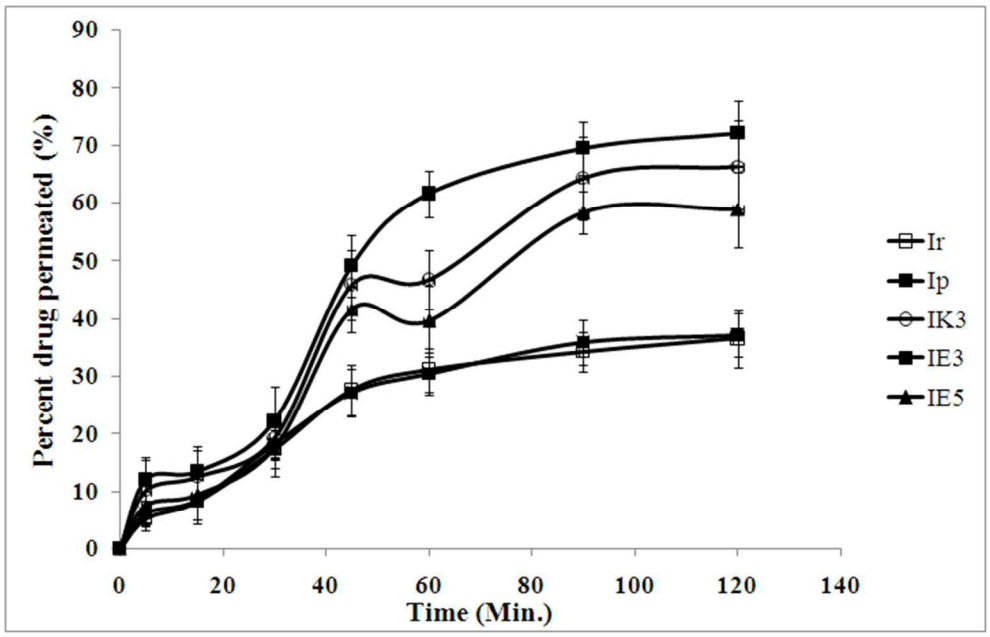

Figure 4

194x137mm (96 x 96 DPI)

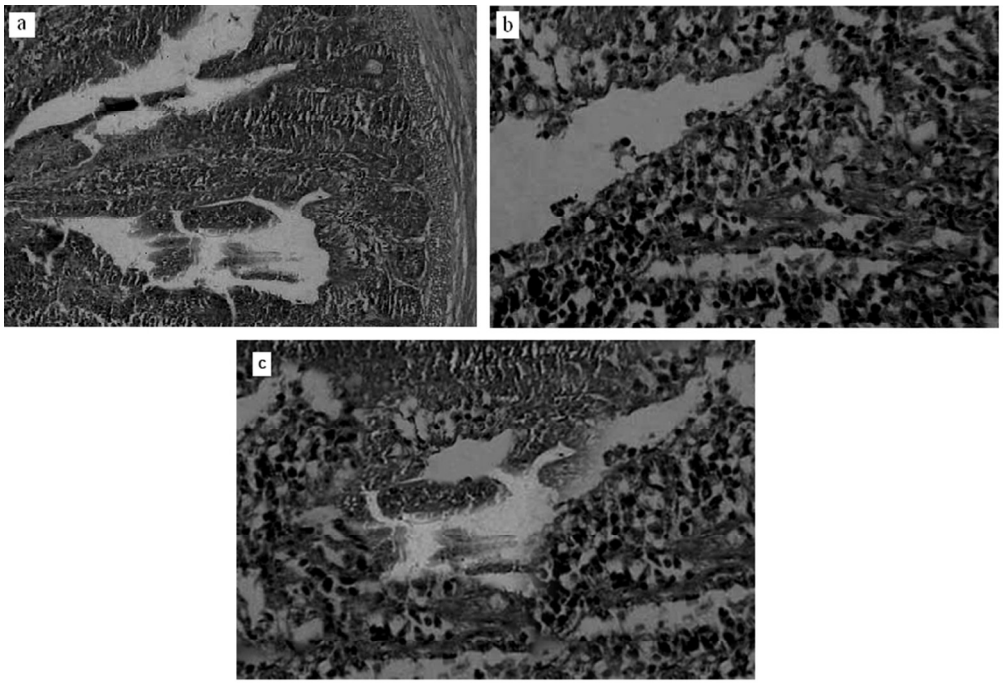

Figure 5

244x181mm (96 x 96 DPI)

Table 1. Formulation code of ibuprofen samples unprocessed/processed through polymeric compaction.

Sample code	Polymer	Ibuprofen : Polymer	Processing status
Raw Ibuprofen (Ir)	-	-	Unprocessed
Ibuprofen (Ip)	-	-	Ibuprofen alone slugged
IK3	HPMC K3LV P	1:1	co-processed by slugging
IE3	HPMC E3LV P	1:1	co-processed by slugging
IE5	HPMC E5LV P	1:1	co-processed by slugging

Table 2. Correlation of In vitro dissolution-Ex vivo intestinal permeation data

Sample code	Correlation coefficient (r)
Ir	0.8899
Ip	0.9659
IK3	0.9344
IE3	0.9534
IE5	0.9438