Controlled Release Gastroprotective Combined Formulation of Two Drugs Using Hypromellose: Preparation and In Vitro Evaluation

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SUMMARY. The aim of study was to develop a stable controlled release drug delivery system of ibuprofen and misoprostol in fixed dose combination. The influence of hydroalcoholic medium on in vitro drug release properties was also investigated. Non-aqueous emulsion solvent evaporation method was used to prepare microparticles. The micromeritic properties of microparticles were assessed by particle size, bulk density, tapped density, Carr’s index, Hausner’s ratio and angle of repose measurements. Microparticles of both drugs were directly compressed to develop tableted microparticles (TMs). SEM was used to describe surface morphology of microparticles. FTIR was used to determine drug and polymer compatibility while XRD and DSC were used to assess drug’s physical state in dosage form. TMs were subjected in vitro dissolution test using three different dissolution media separately, including 0.1 N HCl at pH 1.2, phosphate buffer solution (PBS) at pH 6.8 and 40% hydroalcoholic buffer solution (40% EtOH) at pH 6.8. Various kinetic models were applied to dissolution data in order to describe drug release pattern from dosage form. TMs were also subjected for their accelerated stability for a period of three months. Microparticles possess good flow properties. Increasing polymer to drug ratio resulted in an increase in mean particle size and entrapment efficiency. DSC and XRD data revealed that crystalline behavior of ibuprofen was reduced following incorporation into the microparticles. FTIR spectra presented little change in height of peaks in formulations as compared to pure drug crystals. Drug release rate was higher in 40% EtOH at pH 6.8 than PBS at pH 6.8 and 0.1N HCl at pH 1.2. Drug release was predominantly controlled by a diffusion mechanism. TMs remained stable at harsh accelerated storage conditions. Two drugs in combined dosage form as TMs were successfully prepared using hypromellose by applying technique of microencapsulation by non-aqueous emulsion solvent evaporation.

KEY WORDS: hypromellose, ibuprofen, misoprostol, tableted microparticles, 40% EtOH.
INTRODUCTION

Ibuprofen (IBN) is a weak acidic (pKa 4.5) and widely used as a non-steroidal anti-inflammatory drug (NSAID) having analgesic and anti-inflammatory activities. Given the adverse gastrointestinal side effects associated with IBN coupled with its short biological half-life, it is a good candidate for the development of oral controlled-release formulations 1. Misoprostol (MIS) is a synthetic analogue of prostaglandin E1 and has been approved by FDA as a drug in the prevention and treatment of NSAIDs induced gastric and duodenal ulcers 2. HPMC is an odorless and tasteless, white or creamy-white fibrous or granular powder. It is generally accepted as non-toxic and non-irritating material and widely applied as excipients in oral, ophthalmic, nasal and topical formulations 3. Microencapsulation is an effective method of reducing adverse drug effects and extending drug release from dosage forms 4. Fixed dose combinations of drug products have been increasingly used either to benefit from the added effects of drugs or to improve patient compliance (EMEA, 2008) 5. Microencapsulation methods have been employed to develop extended release dosage forms of IBN 6-9. Similarly sustained drug delivery system of MIS has also been developed 10. Excipients are critical components in designing delivery systems such as swellable matrices that in principle may be used to produce zero-order kinetics 11,12. Microencapsulation is a well-recognized technique has been used to modify or retard drug release and to minimize or eliminate gastrointestinal tract irritation 8. In contrast to non-disintegrating polymer matrix tablets, multiparticulate delivery systems distribute more evenly throughout the GI tract, offer reduced local irritation, and have been shown to provide more reproducible drug absorption 13. Furthermore, since the dose consists of multi subunits, the risk of dose dumping is reduced 14. The multi particulate units can be delivered as compressed tablets or filled into hard gelatin capsules. However, the tablets formulations of multi particulate units have the advantage of preventing tempering as in the case of capsules 15.

The current study was attempted to develop a stable sustained release drug delivery system of IBN with MIS in fixed dose combination. Microencapsulation technique was employed to prepare microparticles. The dosage form was characterized for its physical and chemical stability as well as drug release characteristics. The in vitro characterizations included in this study were SEM, XRD, DSC, FTIR and Zetapotential. In addition, dissolution profiles of sustained release dosage forms were also assessed in different dissolution media.

MATERIAL AND METHODS

Materials

Ibuprofen was provided as gift from Zafa Chemie, Pakistan; misoprostol was donated by Searle, Pakistan. Dichloromethane, hydroxypropyl methylcellulose (HPMC; 40-60cps) and liquid paraffin were purchased from Sigma Aldrich (UK) while potassium dihydrogen phosphate and n-hexane from Merck (Germany). All other chemicals used were of analytical grade or equivalent quality and used as provided without further purification.

Preparation of ibuprofen microparticles

Ibuprofen microparticles were prepared at drug to polymer ratios of 1:1, 1:2, and 1:3 (M1, M2, and M3, respectively). Drug and polymer in above said proportions were co-dissolved at room temperature in dichloromethane (20 mL) with constant stirring using magnetic stirrer to produce uniform drug and polymer solutions. This mixture was then added to liquid paraffin (50 mL) containing tween 80 (0.1% v/v). The stirring was continued until complete evaporation of solvent and formation of microparticles. The formed microparticles were separated by filtration using Whatman filter paper, washed with n-hexane and air dried.

Determination of drug entrapment efficiency and yield

Drug microparticles, theoretically equivalent to 40 mg of drug were taken for evaluation. The crushed and then powdered microparticles were dissolved in adequate quantity of methanol, vortexes and kept for 12 h for complete drug extraction at room temperature. Suitable dilution with methanol was made and filtered. Absorbance was taken at 220 nm against appropriate blank. The drug entrapment efficiency (DEE) was calculated using Eq. [1]:

\[
DEE(%) = \frac{A}{T} \times 100
\]  

where \(A\) is amount of drug actually present and \(T\) is theoretical drug load. The yield of microparticles was determined using Eq. [2]:

\[
Yield(%) = \frac{P}{M_d + M_p} \times 100
\]
where $P$ is mass of microparticles, $M_D$ and $M_P$ are mass of drug and polymer, respectively, used in formulation of microparticles. Each determination was performed in triplicate and findings are given as mean ± SD.

**Micromeritic properties**

The tap density of microparticles was determined by simple tapping method using 10 mL measuring cylinder and the number of tappings was fixed to 100 tappings as it was sufficient to bring about a plateau condition with microparticles. Eq. [3] was used to calculate tap density:

$$D_T = \frac{M_T}{V_T}$$

where $D_T$ is tapped density, $M_T$ is mass of microparticles and $V_T$ is volume of microparticles after tapping. Carr’s index was calculated from bulk density ($D_B$) and tapped density ($D_T$) as in Eq. [4]:

$$\text{Carr's index} = \frac{(D_B - D_T)}{D_T} \times 100$$

Hausner’s ratio was calculated as given in Eq. [5]:

$$\text{Hausner's ratio} = \frac{D_T}{D_B} \times 100$$

Angle of repose which measures the resistance to particles flow was determined using fixed funnel method. The microparticles were passed through a funnel on horizontal surface. The height ($h$) of the heap formed and radius ($r$) of cone base were measured. Eq. [6] was used to determine angle of repose.

$$\theta = \tan^{-1} \frac{h}{r}$$

where $\theta$ is angle and $h$ is height of microparticles heap and $r$ is radius.

**Measurement of size distribution and zetapotential**

The size distribution and zeta potential measurements of microparticles were performed by Zetasizer Nano ZS (Malvern Instruments, UK). Microparticles were suspended in n-hexane (0.25% w/v) and poured into specialized charge/size cuvette. Before keeping in Zetasizer for analysis the samples were vortex for two minutes.

**Preparation of MIS compacts**

MIS compacts (MISC) were prepared by direct compression of 40 mg MIS (equivalent to 400 µg misoprostol) with 40 mg of methocel K4M and 2.5 mg of magnesium stearate. The drug assay was assumed 100% for active drug material that was supplied (1:100 of misoprostol:HPMC) as a donation by Searle-Pakistan.

**Preparation of tableted microparticles (TMs)**

IBN-M (M2 on the basis of drug entrapment efficiency and micromeritic properties was selected to be combined within a single tableted microspheres dosage form. The appropriate quantity of M2 (equivalent to 400 mg ibuprofen) was mixed thoroughly and compressed directly with and MISC that was broken into smaller particles (equivalent to 400 µg misoprostol), added magnesium stearate (1%) as a lubricant. The mixing was achieved by geometric dilution method using polythene bags. The direct compression of microparticles was carried by single-punch tablet machine (EMMAY Enterprises, Pakistan) containing 400 mg of IBN and 400 µg of MIS active drugs.

**Evaluation of tablet hardness, friability and weight variation**

An automatic hardness tester (Curio, Pakistan) was employed to determine hardness of the tablets. Ten tablets were evaluated in each test and mean hardness was calculated. The friability of tablets was assessed using a friabilator. Twenty tablets were weighed before placing them in friabilator chamber and at the end of test, their weight was also recorded. Finally, loss in weight was calculated. Weight uniformity test was conducted on twenty tablets selected randomly and weighed using a ‘Class A’ electronic weighing balance (Precisa, Switzerland) and %weight variation was estimated.

**Scanning electron microscopy (SEM)**

Morphological studies of microparticles were performed with scanning electron microscopy. SEM analyses were carried using Hitachi S-3000N VP-SEM. The samples were gold sputter coated to render them electrically conductive prior to the analysis.

**Differential scanning calorimetry (DSC)**

DSC scans of pure drugs, polymer and tableted microspheres were recorded by using a computer interfaced Differential Scanning Calorimeter (DSC 4000, Perkin Elmer). All samples were weighed (5-8 mg) and sealed in alu-
minum pans for analysis and heated at a scanning rate of 10 °C/min under constant nitrogen flow of 20 mL/min between 20 °C and 160 °C.

**Powder X-ray diffraction (PXRD)**

Powder X-ray diffraction of pure drugs, polymer and tableted microparticles were conducted using an X-ray Diffractometer (Rigaku, Miniflex-II). The diffractometer was equipped with a 20 compensating slit and was calibrated for accuracy of peaks with silicon. The scanning rate employed was 2° min⁻¹ over the range 5° to 40° (2θ).

**Fourier transforms infrared spectroscopy (FTIR)**

FTIR spectrophotometer (Jasco, FTIR/4100) was used to determine drug-polymer interactions using a KBr disk method. The scanning range of samples was from 4000 to 400 cm⁻¹ for a scanning period of 16 s. The FTIR spectra were recorded for pure drugs, polymer and tableted microparticles.

**In vitro drug release profile**

*In vitro* drug release profiles of IBN microparticles, MIS compacts and tableted microparticles were evaluated in different dissolution media including 0.1N HCl of pH 1.2, Phosphate buffer solution of pH 6.8 and 40% EtOH buffer of pH 6.8, separately. *In vitro* dissolution studies were carried out to evaluate negative effect of alcohol on drug release from prepared modified release formulations as indicated by an FDA alert in July 2005. Microparticles, equivalent to 400 mg of IBN, 400 µg of MIS and tableted microparticles were placed in dissolution medium (900 mL) at temperature of 37 ± 0.5 °C in USP XXII dissolution apparatus type-II (paddle method) operating at a speed of 100 rpm. To enhance wetting of microparticles 0.1% v/v tween 80 was added to the dissolution media. Samples were withdrawn from vessels at predefined schedule at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h. The withdrawn volume was immediately replaced with fresh dissolution media. Samples were suitably diluted and after filtering through 0.45 µm filter. The samples were subjected for analyses using RP-HPLC-UV system (Agilent 1200 series, Germany) at wavelength of 220 nm. The mobile phase was comprised of methanol: acetonitrile: water (15:50:35). The pH 3.5 of mobile phase was adjusted glacial acetic acid. DDDSolver® software was used for analyses of dissolution data. Percentage drug release was calculated and plotted as a function of time to study pattern of drug release.

**Application of kinetic models**

The data obtained from dissolution in pH 6.8 phosphate buffer solution were used to evaluate mechanism and pattern of drug release by applying important kinetics models i.e., Zero order \( Q_t = k_0 t \), First order \( \ln Q_t = k_1 t \), Higuchi \( Q_t = k_H t^{1/2} \) and Korsmeyer–Peppas \( M_t / M_\infty = k_t n \), where \( Q_t \) is amount of drug released from drug delivery system at time \( t \), \( M_t / M_\infty \) is fraction of drug released at time \( t \), \( k_0, k_1, k_H, k_t \) represent kinetic constants for zero-order, first-order, Higuchi and Korsmeyer-Peppas models, respectively and \( n \) is diffusional exponent.

**Stability studies of tableted microparticles (TMs)**

Following the guidelines of International Conference on Harmonization (ICH) to conduct stability studies TMs were kept in stability chamber (Sanyo MIR-162, Japan) maintained at controlled conditions of temperature 40 ± 2 °C and 75 ± 5% relative humidity. The samples of TMs were taken from chamber and evaluated for stability by conducting drug assay and FTIR at 1, 2, and 3 months and compared for their stability with freshly prepared i.e. control.

**Statistical analysis**

To calculate mean and standard deviation computer based MS-Excel software was used. The results were presented as mean ± SD.

**RESULTS AND DISCUSSION**

**Yield and entrapment efficiency**

The %yield of IBN microparticles was in the range 76.63 ± 1.97% to 81.21 ± 1.06% while %entrapment efficiency (%EE) of drug was from 84.26 ± 1.30% to 88.52 ± 4.21%. The percentage yield was highest in case of M2 while lowest for M1. This may be due to optimum concentration of polymer. The %EE was increased from M1 to M3 as concentration of polymer in formulation was increased. This is due, probably, to the availability of greater concentration of polymer to retain drug molecules. The high contents of IBN in microparticles were also believed due to the poor drug solubility in mineral oil. The results are presented in Table 1.

**Micromeritic properties**

The bulk density values ranged from 0.25 ± 0.01 to 0.20 ± 0.01 g/cm³ while tapped density
values ranged between 0.30 ± 0.01 and 0.24 ± 0.00 g/cm³ for M1 to M3, respectively. It was observed that bulk density decreased with increase in particle size that may probably due to increase in particle size and intrapartical space. The compressibility or Carr’s index values ranged from (mean ± SD) 15.93 ± 1.34% to 16.97 ± 1.38%. The values of Hausner’s ratio were found to lay between 1.19 ± 0.02 and 1.20 ± 0.02. All formulations showed good flowability on the basis of angle of repose (< 30°). All formulations showed similar flow properties while different particle sizes. It was due, probably, to the contribution of polymer to improve sphericity of microparticles as indicated in Table 2.

### Size distribution and zetapotential

The mean particle sizes of formulations were in range from 154.22 ± 9.68 to 244.06 ± 12.91 µm. The mean particle size of M3 was largest while smallest for M1 indicating that particle size is directly related to concentration of polymer in formulation. Increasing polymer load led to a more viscous solution. When viscous polymeric solution was poured into continuous phase, larger droplets and thus larger microparticles were formed. Zetapotential of microparticles was found for tested formulation in range of -8.9 to +9.7. Zetapotential of microparticles is the degree of electrical potential at their share plane. The stability of the colloidal dispersions is related to the value of zetapotential. The zetapotential indicates the degree of repulsion between adjacent and similarly charged particles in a colloidal dispersion. Microparticles with higher value of zetapotential (either positive or negative) will remain away from each other as dispersed particles resulting in more stabilized colloidal formulation. A negative charge value of microparticles is due to negative hydroxyl groups in polymeric film on their surface. The colloidal dispersions with value of zeta potential greater than (±) 60 are considered having excellent stability as dispersed dosage forms. On the other hand low value of zetapotential presented that microparticles will be less stable in suspension form. This indicates that for extended stability they required to be kept in solid state (Fig. 1).

### Hardness, friability and weight variation of tableted microparticles (TMs)

Mean hardness, friability and weight variation of tablets were 7.35 ± 1.37 Kg, ≤ 0.45% and ± 0.55%, respectively. Tablet hardness expressed usually as force required to crush a tablet when placed between two jaws forcing each other. Tablet hardness usually affects drug dissolution and drug release. Friability is the ability of

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<td>Actual drug loading (%)</td>
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<td>Entrapment Efficiency (%)</td>
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<td>Product yield (%)</td>
<td>76.63 ± 1.97</td>
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Each value is mean ± SD of three observations

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<th>Parameters</th>
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<tr>
<td>Mean particle size (µm)</td>
<td>154.22 ± 9.68</td>
<td>191.49 ± 5.97</td>
<td>244.06 ± 12.91</td>
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<td>Bulk density (g/cm³)</td>
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<td>Tapped density (g/cm³)</td>
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<td>Carr’s index (%)</td>
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<td>Hausner’s ratio</td>
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<td>Angle of repose</td>
<td>20.93 ± 0.15</td>
<td>21.42 ± 0.34</td>
<td>22.18 ± 0.16</td>
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Each value is mean ± SD of three observations

Table 1. Yield and entrapment efficiency of IBN microparticles.

Table 2. Micromeritic properties of IBN microparticles.
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Tablets to withstand abrasion, packaging, handling and transportation. Friability is expressed as % weight loss. The acceptable limit is 0.5% to 1%. The pharmacopoeial limit in weight variation test for percentage deviation of tablets of more than 250 mg is ±5%. The average percentage deviation of tablets was found to be within the above limit and hence passed the test for uniformity of weight as per official requirement.

Scanning electron microscopy (SEM)

The IBN microparticles of formulation M2 were found spherical in shape with smooth surface. Few drug crystals can be seen on the surface of microparticles. Nonspherical shaped rough surface MISc were observed under scanning electron microscope as indicated in Fig. 2. Smooth surface microparticles are expected to release drug in a more sustainable manner as compared to irregular shaped. This may be due to smooth and appropriate coating of polymer to core material.

X-ray powder diffractometry (XRD)

Every crystalline substance has a particular crystallographic pattern which can be used for its identification like that of human fingerprinting. The crystallographic pattern is always same for the same substance and in a mixture of substances each produces its pattern independently of the others. X-ray diffraction was conducted to assess whether drug was present in a crystalline or amorphous form in microparticles. Pure drugs, polymer and microparticles were subjected for their XRD pattern. The XRD pattern of IBN showed a number of intense peaks at diffraction angles 2θ = 6.2°, 12.32°, 16.8°, 17.9°, 21.23° and 23.73°. There were no diffraction peaks observed in MIS and polymer XRD pattern. The decrease in intensity of crystalline nature of IBN was observed in TMs and that may be due to a dilution factor or decrease in crystallinity of drug in drug delivery system. The appearance of characteristics peaks in TMs was indicated that there were no chemical interactions or pharmaceutical incompatibilities between drugs and excipients in a single dosage form as shown in Fig. 3.

Fourier transformed infrared spectroscopy (FTIR)

FTIR spectrum of IBN showed peaks at 3100-2800 cm⁻¹ (O–H stretch of carboxylic acid), 2960, 2920, 2875 cm⁻¹ (aliphatic C–H stretch), 2730, 2640 cm–¹ (C–H stretch characteristic of an acid), 1720 cm–¹ (C=O stretch of aliphatic acid), 1510 cm–¹ (Skeletal vibration of aromatic ring), 1420 cm–¹ (C=O bond and C-O stretch of carboxylic acid dimmer), 1235 cm-1 (C-O stretch). In spectrum of MIS a distinct peak was observed at wavenumber 1740 cm⁻¹ due to carbonyl stretching of both the five-membered keto
and ester carbonyl. The presence of all characteristic peaks of active drugs but no new peaks in FTIR spectrum of TMs indicating that there were no chemical interactions between drugs and excipients. Therefore, two drugs were chemically stable as tablet formulation. This confirms that the drug has good compatibility with polymer. The sustained release effect was probably due to physical binding of drugs and polymers as shown in Fig. 4.

**Differential scanning calorimetry (DSC)**

DSC thermograms of pure drugs, polymer and TMs were conducted. Sudden changes in thermal behavior of either drug or polymer may indicate a drug-polymer interaction. A sharp endothermic response was observed for IBN at temperature 78.5 °C (ΔHf = 127.57 J g⁻¹) that corresponds to its melting point. The polymer did not show any fusion peak except a broad endotherm between 60 to 80 °C. DSC thermograms of MISc solid dispersions indicated its miscibility with polymer and it could be suggested that MIS is molecularly dispersed in polymer. This dispersion could reduce mobility of MIS and water hence reduces drug degradation. The TMs presented relatively less intense peak of IBN as compared to pure drug. The decrease in intensity may be due to drug entrapment in polymer or dilution factor as shown in Fig. 5. Both the drugs remained unchanged in TMs thus indicated compatibility between two compounds and polymer.

**In vitro drug release**

The release of IBN and MIS from HPMC based microparticles and TMs was observed in 0.1N HCl pH 1.2, Phosphate buffer solution pH 6.8 and 40% EtOH buffer solution pH 6.8. Microparticle size, drug loading and polymer concentrations are factors controlling release of drug from microparticles. The maximum IBN and MIS release from microparticles was 54.87% and 56.35% while from TMs it was 53.77% and 55.86% for IBN and MIS, respectively during 12 h study in 0.1N HCl dissolution media at pH 1.2. In phosphate buffer solution at pH 6.8 the maximum release of IBN and MIS from microparticles was 79.35% and 90.59% while from TMs drug release was 76.12% and 88.27% observed for IBN and MIS, respectively. The drug release rate was observed for IBN and MIS in 40%EtOH phosphate buffer solution at pH 6.8 for period of 12 h and found maximum of 87.39% and 91.37% from microparticles while 83.53% and 88.95% from TMs, respectively. The microparticles are tiny units having larger surface area exposed to the dissolution medium that would cause rapid drug release from them. In contrast tablets are large compact masses of particles with less exposed area to dissolution medium to penetrate and to release drug. The drug release rate from microparticles was higher as compared to TMs and that may be due to compression force applied by tablet machine during compression of microparticles to formulate tablets. The smaller particles have larger surface area exposed for dissolution as compared to the bigger particles. However, percentage of drug release was shown to increase in 40% EtOH phosphate buffer solution at pH 6.8 and that indicated the reduced retardant properties of polymer by the presence of alcohol in dissolution medium. The release profiles did not show any burst effect indicating homogenous drug distribution. The analysis of data showed no clear correlation between ethanol solubility of ingredients and ethanol susceptibility of formulations. Furthermore, since each dose consists of many subunits so that the risk of dose dumping is reduced. The dissolution profiles of formulations in three different dissolution media are shown in Fig. 6.

**Application of kinetic models**

The drug release constant (k) and regression coefficient (R²) obtained from Zero order, First order, Higuchi and Korsmeyer-Peppas models are shown in Table 3. Drug release kinetics showed that release of IBN and MIS from TMs was best described by Higuchi model on the basis of highest values of regression coefficient (IBN = 0.988 and MIS = 0.985). Korsmeyer-Peppas model showed an n value of 0.514 and 0.503 of IBN and MIS, respectively. Anomalous transport by Korsmeyer-Peppas indicates that...
The mechanism of drug delivery is diffusion and macromolecular mobility (due to HPMC swelling), which was indicative of anomalous diffusion mechanism that is diffusion along with erosion. Therefore, the two drugs in combination as TMs followed more than one mechanism of release from the formulation. DDSolver® software was used to obtain values of these kinetic models.

### Stability study

The drug assays were within the acceptable range of drug products. The drug assay was 100.5%, 99.3%, 98.7%, and 98.1% for IBN and 101.5%, 101.2%, 99.4%, and 98.3% for MIS at zero (control), 1, 2, and 3 months, respectively. As observed from the FTIR spectra (Fig. 7) of TMs stored at specified conditions of temperature and relative humidity after 1, 2 and 3 months, no significant changes were seen when compared to the control.

### CONCLUSION

The current method of microencapsulation can be applied successfully to prepare sustained drug delivery system of IBN and MIS in a fixed dose combination as tableted microparticles. Prolonged release of drugs up to 12 h with biocompatible polymer will be of great importance for arthritis patients by cytoprotection, reducing frequency of drug administration and thereby increasing effectiveness of therapy by enhancing patient compliance.

### Acknowledgement

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### Conflict of interest

Authors declare no conflict of interest.

### REFERENCES


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**Table 3. Values of release rate constant and correlation coefficient of tableted microparticles.**

**Figure 6.** Drug release profile of ibuprofen microparticles (IBN-M), misoprostol compacts (MISc) and combined tableted microparticles (IBN and MIS) in 0.1N HCl at pH 1.2 (A), in phosphate buffer solution at pH 6.8 (B), and in 40%EtOH phosphate buffer solution at pH 6.8 (C).

**Figure 7.** FTIR spectra of TMs at zero (control), 1, 2, and 3 months of accelerated stability study.