

Full Length Research Paper

Novel modified release tableted microspheres of ibuprofen and misoprostol in a combined formulation: Use of software DDSolver[®]

Muhammad Akhtar^{1*}, Mahmood Ahmad¹, Shujaat Ali Khan² and Ghulam Murtaza²

¹Department of Pharmacy, Faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur, Bahawalpur, 63100, Pakistan.

²Department of Pharmacy, COMSATS Institute of Science and Information Technology, Abbottabad, Pakistan.

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The current study was aimed to develop a stable sustained release drug delivery system for ibuprofen and a cytoprotective agent misoprostol in a combined dosage form. Non-aqueous emulsion solvent evaporation method was used to prepare ibuprofen microspheres. Ethylcellulose (EC) and Hydroxypropyl methylcellulose (HPMC) were used as the release retarding polymers in combination. Ibuprofen microspheres were prepared separately and then compressed into tablet dosage forms with misoprostol dispersions in HPMC. For surface topography of microspheres, Scanning Electron Microscope (SEM) was used. Fourier transformed infrared (FTIR) spectroscopy and X-ray diffractometry (XRD) were employed to evaluate pharmaceutical incompatibility and physical state of drug in formulation. The mechanism and pattern of drug release were determined by applying kinetic models. Tableted microspheres were also assessed for accelerated stability study for three months. SEM showed spherical shape microspheres. FTIR and XRD data for developed formulation indicated stability and compatibility of drugs with excipients. After 10 h, 86.97 and 89.33% of ibuprofen and misoprostol were released from micro particles while 75.43 and 77.65% from tableted microspheres, respectively. Non-aqueous emulsion solvent evaporation was found to be a suitable method to prepare stable sustained release tableted microspheres of ibuprofen and misoprostol in combination.

Key words: Ibuprofen, misoprostol, hydroxypropyl methylcellulose (HPMC), ethylcellulose (EC), tableted microspheres, DDSolver[®].

INTRODUCTION

Ibuprofen (IBN) is a non-steroidal anti-inflammatory drug. It is an appropriate drug for oral controlled release formulation due to adverse gastro-intestinal effects and

the short biological half-life that requires administration three times a day (Brunton et al., 2005; Sweetman, 2011; Saravanan et al., 2003). Misoprostol (MIS) is an analogue of naturally occurring prostaglandin E₁, indicated for the treatment of gastric and duodenal ulcers. It has been proven beneficial and is an approved drug by FDA in the prevention and treatment of gastric ulcer disease induced by non-steroidal anti-inflammatory drugs (Sweetman, 2011). MIS is a cytoprotective, acting directly on the gastric mucosa (Oth et al., 1992).

Ethylcellulose (EC), an ethyl ether of cellulose, is a long-chain polymer of β -anhydroglucose units joined by acetal linkages and is widely used in oral and topical pharmaceutical formulations. EC is a well-known water insoluble polymer that has long been used as rate

*Corresponding author. E-mail: muhammad.akhtar@iub.edu.pk.
Tel: +92-300-6720628.

Abbreviations: IBN, Ibuprofen; MIS, Misoprostol; IBN-M, Ibuprofen microspheres; FTIR, Fourier Transform Infra Red; EC, Ethyl cellulose; HPMC, Hydroxypropyl methylcellulose; TabM, Tableted microspheres; XRD, X-ray diffractometry; SEM, Scanning Electron Microscope; EMEA, European Medicine Agency; DEE, Drug Entrapment Efficiency; rpm, Revolutions per minute.

controlling membrane in medication dosage forms to regulate drug release. It can be dissolved or dispersed in different solvents by means of coating or granulating processes (Raymond et al., 2009; Shan-Yang et al., 2004).

Hypromellose (HPMC) is widely used as an excipient in oral, ophthalmic, nasal and topical pharmaceutical formulations. It is an odorless and tasteless, white or creamy-white fibrous or granular powder and is generally regarded as a non-toxic and non-irritating material (Raymond et al., 2009). Amongst different polymers, HPMC has been employed successfully to obtain appropriate sustained release matrix formulations of various types of materials (Velasco et al., 1999).

Microencapsulation is a means of encapsulation of small particles of solids or droplets of liquids and dispersions either by applying relatively thin coatings or the formation of small spherical polymeric or waxy matrices containing drugs. It is a useful method of prolonging drug release from dosage forms and reducing adverse effects (Bolourtchian et al., 2005). Controlled drug delivery systems in comparison to immediate drug delivery systems offer desired concentration of drugs at the absorption site allowing maintenance of drug concentration within the therapeutic range, lowering frequency of drug administration and thus, enhancing patient compliance (Wahab et al., 2011). The emulsion solvent evaporation method may be employed to prepare microcapsules of water insoluble drugs within water insoluble polymers (Beck et al., 1979).

Micro encapsulation techniques have been employed to make sustained drug delivery system of IBN (Pralhad and Rajendrakumar, 2004; Perumal, 2001; Valot et al., 2009; Aerts et al., 2010; Bolourtchian et al., 2005). Similarly, different methods have also been employed to prepare stable and sustained drug delivery system of MIS (Oth et al., 1992). Fixed combination of medicinal products has been increasingly used either to improve compliance or to benefit from the added effects of two medicinal products given together (EMA, 2008).

The aim of the current study was to prepare a stable controlled release drug delivery system of ibuprofen in combination with misoprostol as tableted microspheres (TabM). Microencapsulation was used as a method to prepare microspheres. Single punch tablet machine was employed to compress prepared microspheres into tablets. This modified release combination of two drugs will be valuable for arthritis patients and combined formulation will enhance patient compliance as it will reduce the frequency of drug administration.

MATERIALS AND METHODS

Ibuprofen was received as a gift from Zafa Chemie, Pakistan; Misoprostol (misoprostol: HPMC dispersion in 1: 100) was donated by Searle, Pakistan. Ethanol, methanol, cyclohexane and n-Hexane of analytical grade purchased from Merck, Germany. EC (22 cps of Sigma Aldrich) and HPMC of low viscosity grade from Sigma

Aldrich. Liquid paraffin was purchased from the local market.

Method of preparation of IBN microspheres

Non-aqueous emulsion solvent evaporation method was employed to prepare IBN microspheres (IBN-M). Drug and polymers (HPMC and EC) were mixed in a mixture of dichloromethane and ethanol solvent system. The slurry was gradually poured into 30 ml of liquid paraffin containing 0.01% Tween 80 which is being stirred at 1100 rpm using mechanical stirrer equipped with three blade propellers. The process was carried out at room temperature. The solution was continuously stirred for 2 h and the solvent was allowed to evaporate completely and filtered by using filter paper of diameter of 12.5 cm. The microspheres obtained were washed with n-Hexane repeatedly to make them free from oil. After washing, microspheres were dried at room temperature and subsequently stored in desiccators.

Drug entrapment efficiency

Microspheres equivalent to 40 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and the powdered microspheres were dissolved in adequate quantity of methanol and kept for 12 h for complete drug extraction at room temperature. After making suitable dilution with methanol, the solution was filtered. Then absorbance was measured at 220 nm against appropriate blank. A validated method was used to estimate IBN concentration. A standard stock solution of 1mg/ml of IBN was prepared and then dilutions were made from this standard stock solution. Absorbance was measured at 220 nm. The method was found linear in the range of 10 to 80 µg/ml. Finally, a graph was plotted, concentration versus peak area. The amount of drug entrapped in the microspheres was calculated by the following formula (Patel et al., 2006):

$$\text{DEE (\%)} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

Yield of microspheres

The yield of microspheres was determined using following equation (Patel et al., 2006):

$$\text{Yield (\%)} = \frac{\text{Actual mass of product}}{\text{Total mass of drug and excipients}} \times 100$$

Morphological studies of microspheres

Scanning electron microscopy (SEM) was employed to assess the surface morphology of the prepared microspheres. SEM experiments were performed using a Hitachi S-3000N VP-SEM. Prior to the analysis, samples were gold sputter-coated to render them electrically conductive.

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 (Oth et al., 1992).

Preparation of tableted microspheres

IBN-M (equivalent to 400 mg ibuprofen) and MISc after breaking into smaller particles (equivalent to 400 µg misoprostol), were thoroughly mixed, magnesium stearate was added (1%) as a lubricant. The mixing was achieved by geometric dilution method using polythene bags. Then, this mixture was compressed directly by single-punch machine (EMMAY Enterprises, Pakistan) with a target weight of 970 mg/tablet 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 the mean hardness was calculated. The friability of the tablets was assessed using a friabilator (Emmay Enterprises, Pakistan). Twenty tablets were weighed before placing them in friabilator chamber and at the end of the test, their weight was also recorded. Finally, the 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.

Polymer swelling and erosion

To determine water uptake studies, one tablet was placed in each of the dissolution vessel containing 900 ml of phosphate buffer pH 6.8 at $37 \pm 0.5^\circ\text{C}$ using paddle method at 100 rpm. Tablets were taken out at predetermined time points from 0 to 10 h. The tablets were weighed after removing excess of water at the surface using filter paper.

The damped samples were then dried in hot air oven at 40°C until constant weight. The increase in the weight of the tablets is an indication of mass of liquid uptake and was determined using the following equation:

$$Q = \frac{W_t - W_0}{W_0} \times 100$$

Where, Q is the percentage of liquid uptake, and W_t and W_0 are the weights of hydrated and the initial starting dry weights of samples, respectively.

The percentage erosion (E) of the polymer content was determined at each time point using following equation:

$$E = \frac{W_i - W_t}{W_i} \times 100$$

Where W_t and W_i are weights of dry matrices at sampling time and at initial times (Avachat and Kotwal, 2007).

FTIR analysis

Fourier Transformed Infra-Red (FTIR) spectroscopy was employed to determine polymer and drug interaction. The spectra of drug, polymers, microspheres and TabM were recorded by FTIR (Bruker, Tensor 27, Germany) using KBr disc technique. The scanning range of each spectrum was 4000 to 600 cm^{-1} for a scan period of 16 s.

XRD analysis

X-ray powder diffractometry was employed to observe the effect of microencapsulation process, and then compression into tablets on crystalline state of active drug. X-ray diffraction patterns were used to identify incompatibility of active drugs with the polymers or excipients of formulation. X-ray diffraction patterns of pure drugs, polymers and TabM were recorded using X-ray powder diffractometer (Rigaku, Miniflex-II). The scanning rate employed was $2\theta/\text{min}$ over the scanning range of 5 to 40θ (2θ).

In vitro drug release

In vitro drug release pattern of IBN-M, MISc and TabM were carried out separately. *In vitro* drug release was determined using USP apparatus-II, paddle method, (Pharma-Test, Germany) at 50 rpm. The dissolution medium used was phosphate buffer pH 6.8 and the total volume in each dissolution vessel was taken 900 ml. Temperature of dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$. Samples of 5 ml each time were withdrawn at predetermined time points of 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 h with the help of an automatic sample collector. The sample volume withdrawn was replaced with equal volume of fresh dissolution medium stored at $37 \pm 0.5^\circ\text{C}$. All the samples were appropriately diluted with dissolution medium (Bushra et al., 2008). After filtration with 0.45 µm cellulose acetate filter using micro-filtration assembly, samples were analyzed employing an HPLC with UV detection (Agilent 1200 series, Germany) at 220 nm. Reverse phase C18 column with 5 µm particle size, 4.6 µm internal diameters and 150 mm length was used for this purpose. The mobile phase was composed of Water: Methanol: Acetonitrile (35: 15: 50) and pH 3.5 was adjusted with glacial acetic acid. The dissolution analysis was carried out in triplicate for IBN-M, MISc and TabM. DDSolver[®] software was employed for the analysis of the dissolution data.

In vitro drug release kinetic studies

Drug release kinetics was assumed to reflect different release mechanisms of sustained release matrix system. The dissolution data of TabM were fitted to zero order ($Q_t = k_0 t$) and Higuchi

($Q_t = k_H t^{\frac{1}{2}}$) models. Q is the percentage of drug released at time t while k_0 and k_H are the release rate constants. Regression analysis was performed to obtain the release rate constant and the values of R^2 were also compared. Moreover, equation for drug release mechanism from the matrix system was also used as explained by Korsmeyer Peppas model ($M_t/M_\infty = kt^n$), where M_t/M_∞ is the fractional drug release at time t, k is kinetic constant and n is the so called diffusion exponent, indicative of the mechanism of the drug release. Drug release kinetics studies were conducted using DDSolver[®] software.

Stability study of tablets

TabM were evaluated for their stability. The tablets were packaged in amber glass bottles with polypropylene caps and silica gel desiccant, stored at $40 \pm 2^\circ\text{C}/75\% \pm 5\%$ relative humidity for up to 3 months. In each bottle, 24 tablets were packed and twenty one tablets (18 for dissolution and 3 for drug contents) were used at predetermined time points at 1, 2 and 3 months. Similarity factor (f_2) was used to compare dissolution profiles each time. Equation of similarity factor is given and was determined by using DDSolver[®]

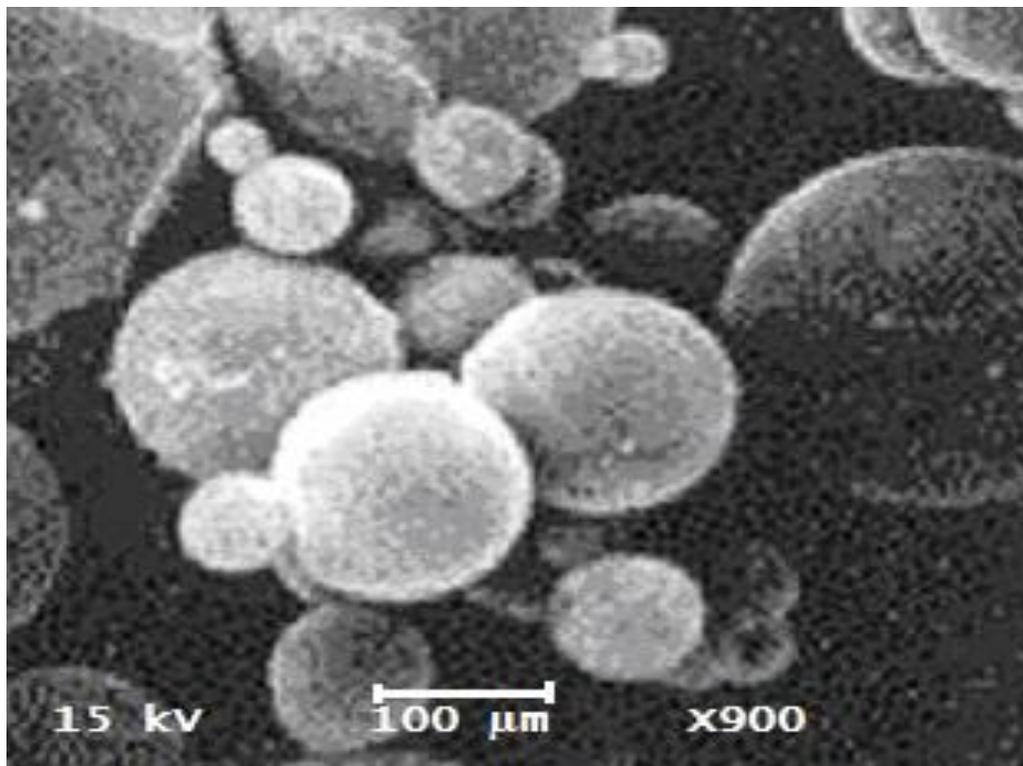


Figure 1. SEM photographs of ibuprofen microspheres (IBN-M).

software (Patel et al., 2006):

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \right] \times 100 \right\}$$

Where R_t and T_t are percent of drugs which were dissolved at each time point for the reference and test products, respectively, n is the number of time points considered.

Statistical analysis

Computer based MS-Excel software was employed to calculate mean and standard deviation. Results were presented as mean \pm S.D.

RESULTS AND DISCUSSION

Shape, drug entrapment efficiency and yield of micro particles

The resultant microparticles of IBN were spherical in shape with smooth surface as shown by the scans of electron microscope in Figure 1. Few drug crystals appeared on the surface of the microspheres. Mean drug entrapment efficiency ($n=3$) was $91.08 \pm 1.05\%$ while mean yield of the prepared microspheres of IBN observed was $71.33 \pm 2.55\%$.

Tablet hardness, friability and weight variation

Mean hardness, friability and weight variation of the tablets were 9.01 ± 1.21 kg, $\leq 0.5\%$ and $\pm 0.3\%$, respectively.

Liquid uptake and erosion of polymer

Tablets consisting of polymeric matrices developed a gel layer when they come in contact with water. The drug release then is controlled by this gel layer. Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets were determined. Simultaneously, with the liquid uptake study, the degree of polymer erosion was measured. During swelling of the tablets, an anisotropic swelling phenomena (that is, more swelling in the axial direction than in the radial direction on exposure to water) was seen. In previous studies conducted by Lopes et al. (2006) and Papadimitriou et al. (1993) similar phenomenon were observed. The reason for such preferential swelling in an axial direction may be due to the need for directional stresses imposed during tableting to relax. It follows that the area change in the swollen

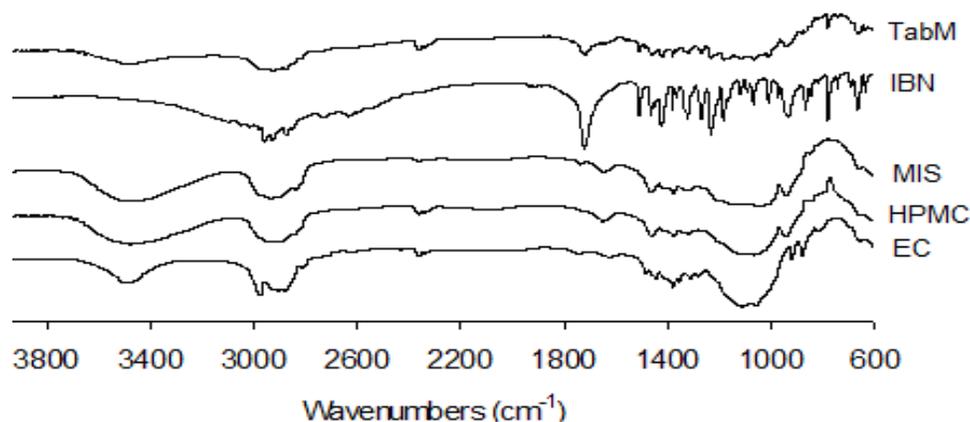


Figure 2. FTIR Spectra of polymers (EC and HPMC), misoprostol: HPMC (MIS), ibuprofen (IBN) and tableted microspheres (TabM).

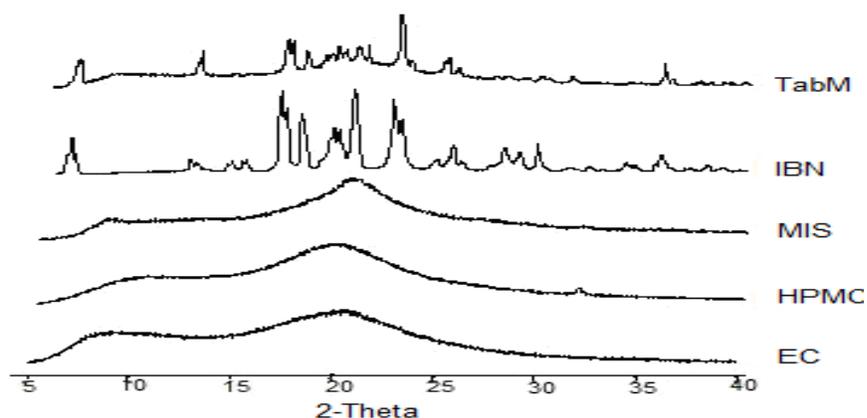


Figure 3. XRD Spectra of polymers (EC and HPMC), misoprostol: HPMC (MIS), ibuprofen (IBN) and tableted microspheres (TabM).

system is directly related to the area exposed to water access. Liquid uptake values starts decreasing when polymers erosion starts in the medium.

FTIR-Spectroscopy

As shown in Figure 2, there was observed no difference in the FTIR spectra of drug-loaded tableted microspheres (TabM) when compared to spectra of active drugs and the polymers in the smaller peaks in the region of 1200 to 1000 cm^{-1} are indication of benzene ring (Socrates, 1994). FTIR spectra showed the presence of free acid carbonyl peak at 1740 cm^{-1} with high intensity in pure IBN crystals but with reduced intensity in TabM. A peak with relative low intensity was observed at 1740 cm^{-1} in the spectrum of MIS due to carbonyl stretching of both the five-membered ring ketone and the ester carbonyl. The presence of all characteristics peaks of the active drugs was observed in this study, but no new band was

observed in the spectra of TabM showing that there was no chemical interaction between the drugs and the polymers. Therefore, two drugs were chemically stable in tablet formulation. Prolonged release of drugs from TabM was probably due to physical binding of polymers and drugs (Pralhad and Rajendrakumar, 2004).

X-ray diffractometry

The x-ray powder diffraction patterns of TabM along with those of raw crystals of drugs and polymers are shown in Figure 3. In XRD spectrum the pure IBN shows a number of distinct peaks at diffraction angles 2θ , 6.2, 12.32, 16.8, 21.23 and 23.73°.

Every crystalline substance has a specific crystallographic pattern which is always same for the same substance and in a mixture of substances each produces its pattern independently of the others (Prince, 2004). MIS and the polymers (HPMC and EC) expressed

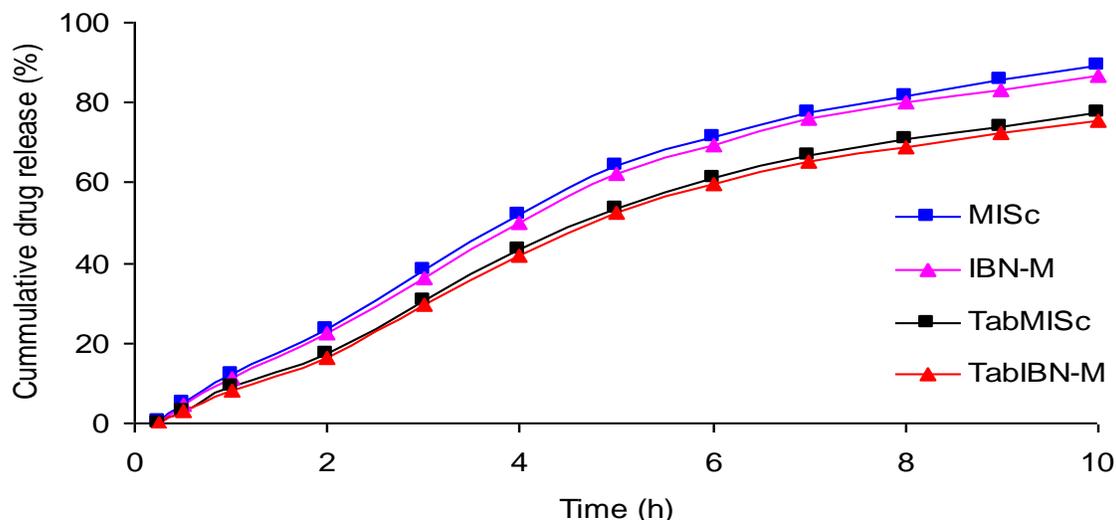


Figure 4. Dissolution profile of ibuprofen microspheres (IBN-M), misoprostol compacts (MISc), and tableted microspheres (TabIBN-M and TabMISc).

the amorphous pattern of x-ray powder diffractometry. Pure IBN showed a characteristic pattern of crystalline substance with intense peaks but decrease in intensity of signals was observed in TabM. This decrease in intensity of the signal may be due to both a dilution effect and a decrease in crystallinity of the drug. EC combination with drugs showing increased amorphous nature (Basu and Adhiyaman, 2008). The characteristics peaks in TabM were the indication that there was no chemical interaction or type of pharmaceutical incompatibility between IBN, MIS, HPMC and EC in a combined dosage form (Pralhad and Rajendrakumar, 2004).

***In vitro* drug release**

Various factors are responsible for the control of drug release from microspheres including microspheres size, drug loading and polymer composition (Pralhad and Rajendrakumar, 2004). In this study, two polymers (HPMC and EC) in a fixed ratio were used to retard the drug release. Figure 4 showed the *in vitro* drug release of IBN-M, MISc and then, after compression of these two into tablet drug delivery system and release from TabM of IBN and MIS. After 10 h, 86.97 and 89.33% of IBN and MIS were released from microspheres while 75.43 and 77.65% of IBN and MIS were released from TabM, respectively. Microspheres are smaller units and, therefore, drug would readily be released from them due to their larger surface area exposed to dissolution medium (Jinno et al., 2006). On the other hand, tablets are large compact masses of particle and sufficient time would be required for medium to penetrate into them because of their smaller area exposed to dissolution medium. The drug release rate from the microspheres was higher than that from the TabM and this may be due

to compression force applied by tablet machine during compression of the microspheres to formulated tablets (Shah, 2004). The hardness of the tablets was kept constant. After 5 h, more than 50% of the drug was released from the TabM and it was 53.81 and 52.44% for MIS and IBN, respectively.

Kinetic models

To be familiar with the *in vitro* drug release, various kinetic models were applied to the dissolution data including zero-order, Higuchi model. However, Korsmeyer-Peppas model was used to determine drug release mechanism. The release constant (k) and regression coefficient (R^2) for IBN and MIS release kinetics showed that Higuchi model was the best fit on the basis of highest linearity ($R^2 = 0.893$ for IBN and $R^2 = 0.896$ for MIS) to describe drugs release from TabM. A close relationship was also found with zero-order kinetics where $R^2 = 0.957$ for IBN and $R^2 = 0.955$ for MIS were found. Korsmeyer-Peppas plot indicated n value of 0.81 for IBN and 0.8 for MIS, both of which are showing an anomalous diffusion mechanism that is diffusion along with erosion. Therefore, the release of two drugs was controlled by more than one mechanism. The DDSolver[®] software was used for kinetic models calculations (Patel et al., 2006).

Stability study

Figure 5 shows the results for accelerated stability studies in terms of their effect on drug release. There was similarity between the release profiles of IBN and MIS after storage for 1, 2 and 3 months based on the

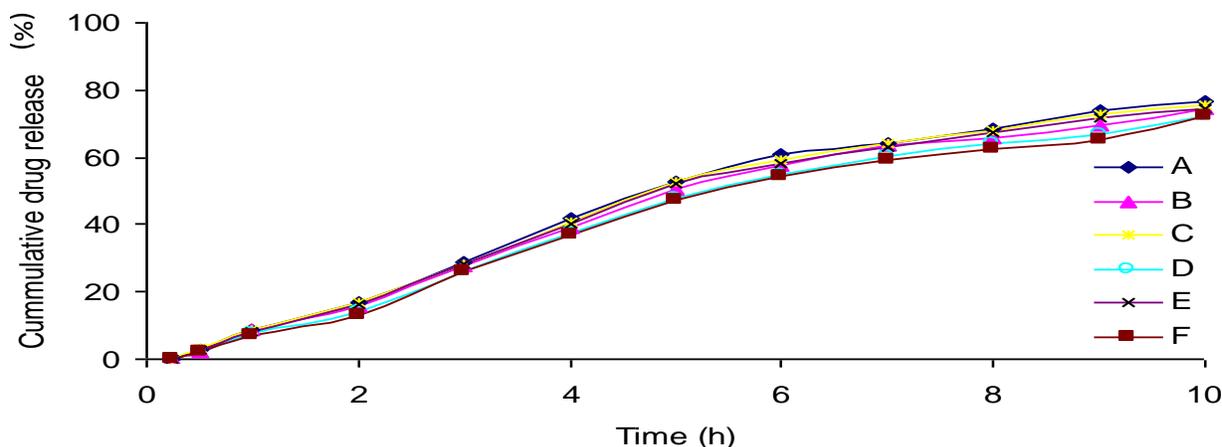


Figure 5. Stability studies: Drug release pattern of tableted microspheres of misoprostol (MISc=1) ibuprofen (TabIBN-M=2) and at 1 month (A=1, B=2), 2 month (C=1, D=2), 3 months (E=1, F=2).

calculation of similarity factor according to the guidelines provided by US Food and Drug Administration. Similarity factor (f_2) values were greater than 50 (83.46, 70.50 and 66.87 for IBN and 89.79, 84.24 and 78.78 for MIS after 1, 2 and 3 months respectively, of stability studies) thus, showing no significant change in release pattern of both drugs occurred over the period of stability studies. The drug contents of tablets were 101.3, 99.2, 98.3 and 97.5% for IBN, and 100.7, 99.0, 97.1 and 98.3% for MIS at 0, 1, 2 and 3 months respectively, of the stability studies, thereby, showing no significant degradation took place over that period. Similarity factor (f_2) was calculated using DDSolver[®] software (Patel et al., 2006).

Conclusion

Non-aqueous emulsion solvent evaporation is a suitable method to prepare tableted microspheres of ibuprofen and misoprostol in combination to make them sustained release over a period of 10 h using EC and HPMC as the drug release retarding polymers. This fixed combination of drugs will be valuable for arthritis patients, and extended release of drugs will reduce the frequency of drug administration, thereby enhancing patient compliance.

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