Research Article

# Optimization and Formulation of Bilayer Floating Tablets of Indomethacin with the Mixed-Solvency Concept

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**ABSTRACT**

**Objective**: The present study investigates the use of indomethacin–solubilizers solid dispersions for the development of controlled-release bilayer floating tablet formulations. **Materials and Methods:** The physical state of the dispersed indomethacin in the solubilizers mixture was characterized by Scanning electron microscopy, differential scanning calorimetry, powder X-ray diffraction, and IR spectroscopy. The mixture proportions of hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), ac-di-sol, sodium bicarbonate; polyvinyl-pyrrolidone (PVP) and indomethacin was optimized in relation to % drug release at first 30 min, and the percent cumulative drug released after 12 hours and floating properties (tablets floating lag time), employing a 17-run optimization study design combined with statistical and response surface analysis and numerical optimization. **Results and Discussion:** It was found that indomethacin exists microcrystals in the solid dispersions. The tablets showed good floating properties and controlled-release profiles, with drug release proceeding via the concomitant operation of swelling and erosion of the polymer matrix. **Conclusions:** Box-Behnken designs proved to be efficient tools in the optimization of the tablet formulation, and the global optimum formulation suggested by the design expert software.

**Keywords:** Solid Dispersion, Indomethacin, Bilayer Floating Tablet, In-silico optimization.

## 1. INTRODUCTION

Indomethacin is a methylated indole derivative and a member of the arylalkanoic acid and is a non-steroidal anti-inflammatory drug. It is potent antipyretic, analgesic, and anti-inflammatory drug (Tripathi, 1999; Martindale, 1996 ; British Pharmacopoeia, 2007). Oral administration of indomethacin is associated with certain problems such as frequent dosing (25 mg two-three times daily), varying half-life and fluctuating plasma concentration. Problems that can possibly be addressed by the preparation of a controlled-release formulation (Wu et al., 1997; Wie et al., 2007; Barmpalexis et al., 2010). Oral solid dosage forms are the preferred route for many drugs and are still the most widely used formulations for new and existing modified release (MR) products (Jain, 2008). GR-DDS is designed based on delayed gastric emptying and controlled-release principles. As rapid GI transit can prevent the complete drug release in absorption zone and reduce efficacy of the administered dose, these systems are intended to restrain and localize the dosage form in the stomach or within the upper parts of the small intestine, for a prolonged and predictable period of time, until the system is devoid of the drug (Singh & Kim, 2002; Li & Jasti 2006; Jain, 2002). These formulations usually consist of swellable polymers, such as methylcellulose or chitosan and various effervescent compounds, such as sodium bicarbonate, tartaric acid and citric acid. GRDDS is not feasible for drugs that have solubility or stability problems in the gastric fluid and drugs which have nonspecific, wide absorption sites in the GIT, drugs that are well absorbed along the entire GIT are unsuitable candidates for GR-DDS e.g. nifedipine (Singh & Kim, 2002).

The term solid dispersion is defined as the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states (Vasanthavada et al., 2008). A number of investigators have demonstrated that the formation of solid dispersion of water insoluble drug with various hydrotropic agents can significantly increase in vitro dissolution rates and in vivo absorption (Law et al., 1992). In the context of drug-delivery systems, bilayer tablets allow for the modification of release profiles, by combining layers with different release profiles, i.e. by combining slow-release with immediate release layers (Zerbe & Szabo, 2006). Bilayer tableting technology has been specially developed to provide two different release rates or biphasic release of a drug

from a single dosage form. To fulfill the specific therapeutic needs of the different diseases, new drug delivery devices are required for a more accurate time-programmed administration of the active ingredients (Maggi et al., 1999). According to the recent FDA initiative in the industry, regulatory status of the excipients used (Castillo et al., 2002 ; Rowe et al., 2006) systematic optimization techniques based on experimental design, combined with the use of novel and highly efficient model-fitting methods.

The objective of this study was to use of mixed solvency concept in the development of indomethacin GR-bilayer tablets. The physical states of indomethacin in the dispersion are characterized by SEM, powder X-ray diffraction and IR spectroscopy and DSC. The mechanism of drug release from polymer matrix and floating time of tablet was evaluated and optimizing the composition of the solid dispersion and floating layer. The overall approach for conduct of an optimization studies in pharmaceutical dosage forms can be described by an optimization plan such as experimental designs, and it is based on the principles of randomization, replication and error control (Schwartz & Connor, 1996; Lewis et al., 1996).

## 2. MATERIALS AND METHODS

### 2.1 MATERIALS

Indomethacin supplied by Taj Pharmaceuticals, Ltd. India was used as an active pharmaceutical ingredient (API). Following solubilizers were selected on the availability basis and solubility studies were performed to select the solubilizers among them. Sodium acetate (SA), Sodium benzoate (SB), Sodium citrate (SC), Urea (U), Niacinamide (N), PEG-4000 (P4K) and PEG-6000 (P6K) purchased from Himedia, Mumbai, India. Hydroxypropyl methylcellulose (HPMC, Himedia, India) was selected for the development of sustained release floating tablet of indomethacin. Lactose as diluent, sodium bicarbonate as gas generating agent, polyvinylpyrrolidone (PVP K30, Himedia, India) solution as binder, magnesium stearate as lubricant, and aerosil as glidant were selected and obtained from Himedia, Mumbai, India. All other materials and reagents were of analytical grade and used as received from CDH, New Delhi, India.

### 2.2 Preparation of Immediate Release Solid Dispersion

Solid dispersion technology using the mixed-solvency concept precludes the use of organic solvent. A salient feature of this method is that the solubilizers (carrier) are water-soluble whereas the drug is insoluble in water. For preparation of solid dispersion accurately weighed niacinamide, sodium benzoate, and PEG-6000 were taken in a 100 ml beaker and were mixed properly. Then, minimum possible quantity of hot (70-80°C), demineralized water sufficient to dissolve the above mixture was added. After complete dissolution of solubilizers, one gm of indomethacin was dissolved in the foregoing solution, and temperature was maintained in the range of 55- 60ºC so as to facilitate the evaporation of water. As evaporation proceeded, speed of rice bead automatically decreased, and it stopped stirring when most of the water was evaporated. The wet solid dispersion thus obtained was spread on petri-dish and kept in hot air dry oven maintained at 50±2ºC so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through a sieve # 60 and were finally stored in an air-tight glass bottle until use.

### 2.3 Preparation of Sustained Release Floating Layer and Tableting

The present investigation was carried out to design and develop the gastro-retentive floating layer which could provide controlled delivery of indomethacin up to 12 hours, and, which shall be used as a second layer of the proposed bi-layer tablet. For the preparation of the sustained-release layers, three different viscosity grades of HPMC were chosen: HPMC K100LV, HPMC K4M and HPMC K15M. All the ingredients except magnesium stearate and aerosil were sifted through a 60-mesh sieve. The ingredients were mixed by geometric dilution technique. After blending, granulation was done using sufficient quantity of alcoholic polyvinyl pyrrolidone (PVP K-30) solution. The wet mass was first passed through a 12-mesh sieve and then granules were dried in an oven at 45°C for 90 min. Then, the granules were passed through a 25-mesh sieve.

For bilayer tablet punching, single punch hand driven tableting machine was utilized (Pharmaceutical Machinery Mfg. Works). Bilayer tablets were punched on 10 mm concave die and punches set. Appropriate amounts of sample containing, therefore, 20 mg of drug was taken in immediate release layer and 55 mg in sustained-release layer were compressed on a manually operated hydraulic press equipped with a 10 mm

diameter flat-faced punch and die set, pre-lubricated with magnesium sterate and aerosil at a compression pressure of 1561 Nt/cm$^2$ applied for few seconds (Srivastava et al., 2005).

### 2.4 Characterisation of Solid Dispersion

#### 2.4.1 Scanning Electron Microscopy

SEM was used to investigate the solid state physical structure of the prepared solid dispersions. SEM. photographs of indomethacin, its physical mixture with hydrotropic agents and its solid dispersions were obtained using a scanning electron microscope (JEOL-JSM 5600, Japan) with accelerating voltage from 0.5 to 30 KV.

#### 2.4.2 Powder X-Ray Diffraction Studies

The powder X-ray diffraction spectra was obtained using RU-$H_3$R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo). The graticule containing powder was placed in sample holder and exposed to $C_uK_\alpha$-radiation (40 KV, 50 MA), $2\theta = 5^o$ to $40^o$ at a scanning speed $4^0$/min and step size $0.02^o$ $2\theta$. The X-ray diffractograms of indomethacin, 1:6 solid dispersion and 1:6 physical mixture.

#### 2.4.3 Differential Scanning Calorimetric Studies

In order to obtain the DSC thermograms of the drugs and their formulations (SD and PM), a thermal analysis instrument, Pyris-6 (Perkin elmier, USA) was employed. To carry out these studies, 4 mg of drug or formulation of drug was weighed accurately and placed in aluminium pan. The pan was sealed and placed on the heating cell and covered with a glass bell jar. Heating at a rate of $10^o$C/min with a continuous purge of nitrogen (45 CC/min) was done with recording of energy changes in the sample with respect to the reference for the temperature range of 40-450°C.

#### 2.4.4 Infrared Study

A large number of solid dispersions have been characterized by IR studies using a IR spectrophotometer (Shimadzu, Japan) to assess the possibility of interaction between drugs and water-soluble carriers (3). Attempt was made to assess the possible interaction of solubilizers with indomethacin by conducting IR studies on the prepared solid dispersion.

#### 2.4.5 Dissolution Rate Studies

Solid dispersion or physical mixture equivalent to 20 mg of indomethacin was tested in dissolution rate studies using an U.S.P. XXIV (type II) dissolution test apparatus (Model TDT6P, Electrolab Mumbai, India) with paddle rotation at 75 rpm. Dissolution studies were conducted in two media, 900 ml of 0.1 N HCl (pH 1.2) and pH 7.2 phosphate buffer. Temperature was maintained at 37±0.5°C. At definite time intervals 10 ml of the sample was withdrawn and analyzed for drug content spectrophotometrically.

### 2.5 Optimization of Floating Layer

In order to achieve a desirable flotation and release profile, the effects of three formulation factors, namely the proportion of HPMC K4M, sodium bicarbonate and ac-di-sol, were evaluated on three response variables: one variable characterizing the total floating time of the tested formulation and two describing the release profile (drug release at 30 min and % cumulative drug release after 12 hours).

Box-Behnken designs are a class of rotatable or nearly rotatable second-order designs based on three-level incomplete factorial design (Yang et al., 1999). This design is suitable for exploration of quadratic response surfaces and constructs a second order polynomial model, thus helping in optimizing a process using a small number of experimental runs. Design expert software (7.1.6 version) of Stat-Ease, Inc. Minneapolis, USA was used for the optimization study.

#### 2.5.1 Preparation of the Optimization Batches

The box-behnken design, including five centre points provided a total of seventeen trial batches. The granules of trial batches were prepared by the similar procedure which was used for the pre-optimization batches. The amount of excipient other than the independent variables, i.e., lactose, was varied from batch to batch so as to maintain a constant tablet weight (200 mg). The amount of magnesium stearate (2 mg) and aerosil (2 mg) was kept constant. The 5% alcoholic PVP solution was used as a binder.

#### 2.5.2 Statistical and Response Surface Analysis

The best model for each response was selected on the basis of the $R^2$ value. The model showing the highest $R^2$ value was selected for the response. ANOVA was performed to identify insignificant terms in model ($p > 0.1$) and generate the polynomial equations to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative). The polynomial equations were

used to demonstrate the relationship between the formulation ingredients and the responses.

**2.5.3 Numerical Optimization**

Numerical optimization of the factors was done by setting the criteria in the design expert software. For the above-mentioned criteria, design expert software 7.1.6 predicted eight solutions with desirability value ranging from 0.730 to 0.722. The solution with maximum desirability value was selected as optimized formulation.

**2.6 Validation of Predicted Optimized Formulation**

Three batches of selected optimum formula were prepared. The granules were evaluated as earlier for bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose. The tablets were prepared and evaluated for weight variation, friability, hardness, drug content, total floating time and in vitro release profile (Zhenphing et al., 2002).

**2.6 *In vitro* Drug Release from Bilayer Tablet**

Release of the prepared tablets was determined up to 12 hr. using an U.S.P. XXIV (type II) dissolution rate test apparatus (Model TDT 6P Electrolab Mumbai, India). Nine hundred ml of 0.1 N HCl containing 0.5% SLS was used as a dissolution medium. The rotation of a paddle was fixed at 75 rpm and the temperature of 37 ± 0.5ºC was maintained throughout the experiment. The samples were analyzed spectrophotometerically for drug contents on double beam UV/Visible spectrophotometer (Shimadzu 1700) at 320 nm (Indian Pharmacopoeia, 2007).

The drug release data obtained from the dissolution study of the indomethacin bilayer tablet was analyzed with respect to zero order model, first order model, Higuchi model and Korsmeyer-Peppas model. The value of slope for Korsmeyer-Peppas equation and regression coefficients for other models are recorded.

**3. RESULT AND DISCUSSION**

**3.1 Characterisation of solid dispersion**

The drug crystals seemed to be irregular in shape and size. The physical mixture of the drug and solubilizers showed the presence of drug in the crystalline form. It was easy to recognize the solubilizer particles from that of drug despite the reduction in size of particles of solubilizers during mixing and its presence in the high amount (1:6 ratios). The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the solubilizers.

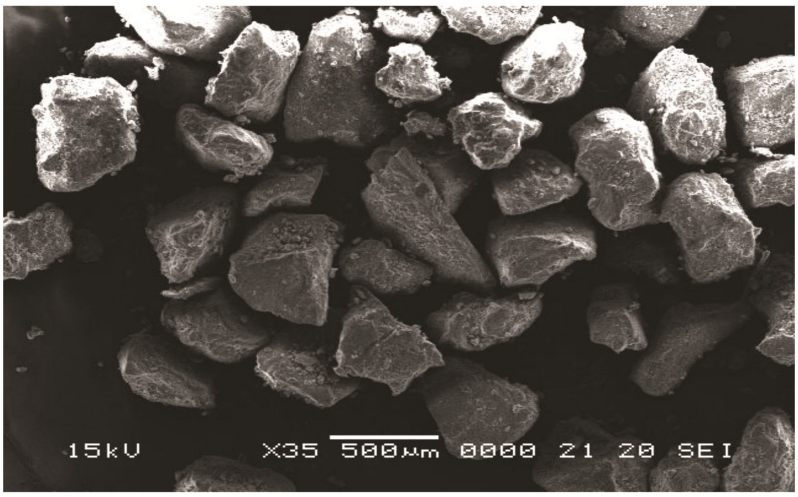


**Fig. 1: S.E.M. photograph of solid dispersion of indomethacin**

The X.R.D. pattern of indomethacin shows intense and sharp peaks at 6.6°, 11.66°, 14.58°, 16.78°, 21.6° which prove crystalline nature of indomethacin. Diffraction patterns of physical mixtures show a lesser degree of crystallinity and lesser number of characteristic peaks of indomethacin, which suggest that the crystalline nature of the drug is changed. The patterns of solid dispersion are completely diffused indicating a new amorphous solid phase.

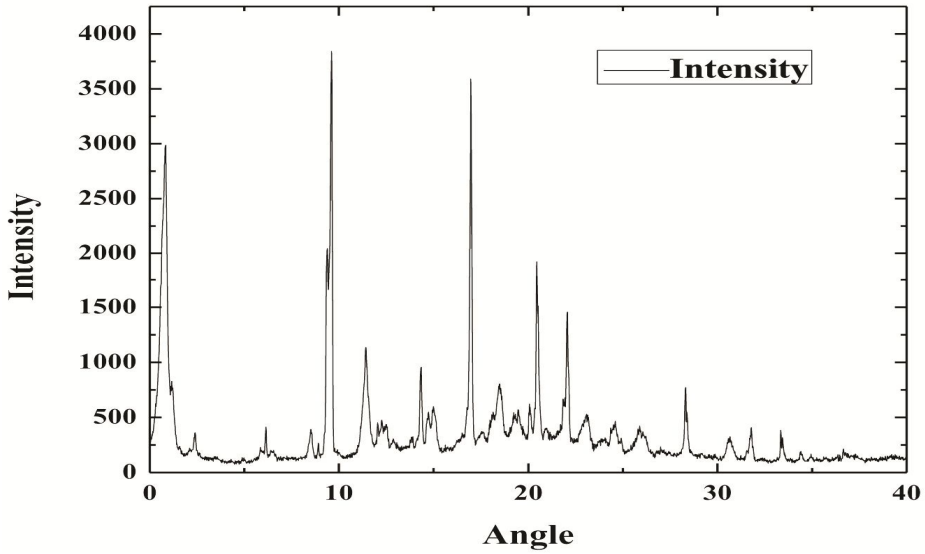


**Fig. 2: X.R.D. spectra of (1:6) solid dispersion**

The DSC curve of the crystalline form of indomethacin showed a sharp endothermic peak at 161.8°C attributable to melting. However, the curves of the solid dispersion showed an endothermic peak at 115.9°C and 215.15°C (Bogdanova et al., 1998). IR spectrum of a physical mixture showed peaks at wave numbers 3100-3300, 1765, 1687, 1325, 1257, 1217 and 600-400 whereas IR spectrum of solid dispersion showed peaks at wave numbers 3100-3300, 1800, 1687, 1323, 1257, 1217 and 600-400. The patterns of physical mixture and solid dispersion showed approximately superimposition of indomethacin spectra showed in (Figure 3). This is indicative of absence of complex formation between drug and solubilizers.

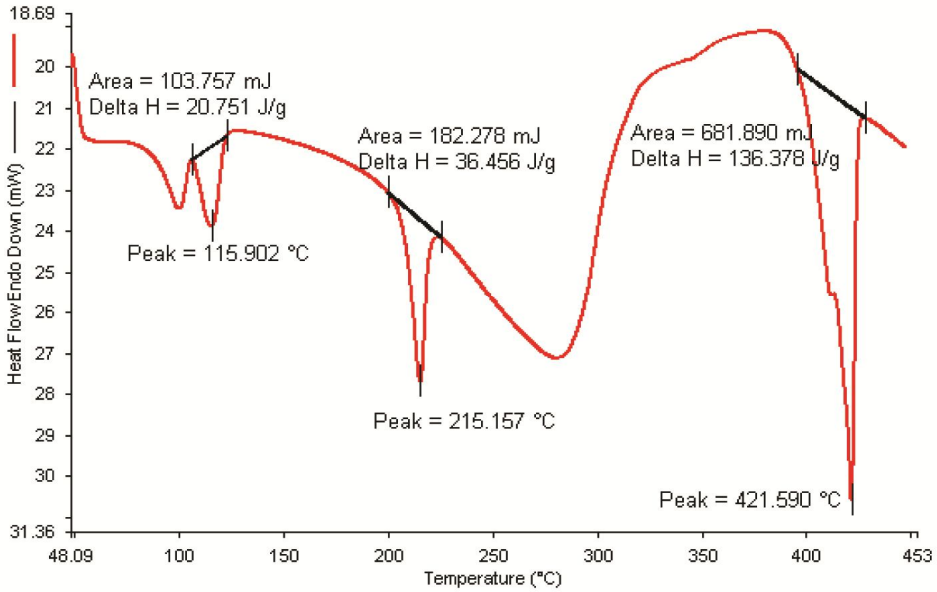


**Fig. 3: D.S.C. curve of solid dispersion (1:6)**

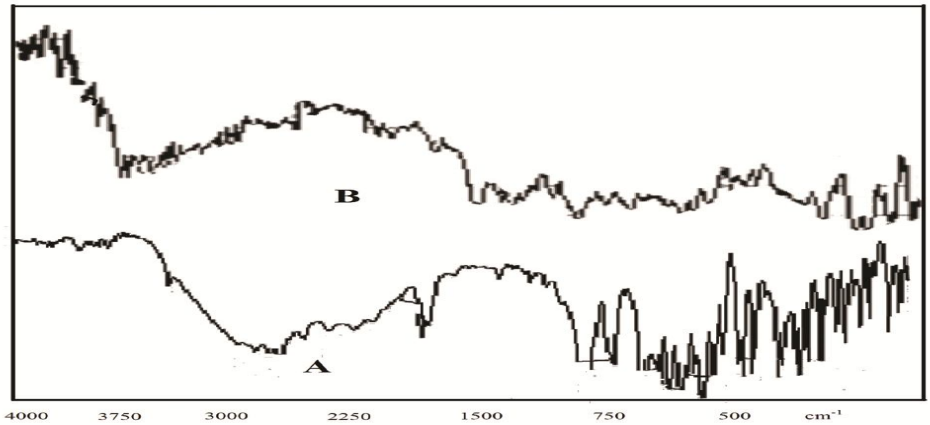


**Fig. 4: (A) IR spectra of solid dispersion; (B) FTIR Spectrum of indomethacin drug sample.**
**All solid dispersions showed good dissolution rate. Since there was no significant difference in dissolution rate among different ratios of solid dispersions, therefore 1: 6 ratio was considered as optimum and was used for further studies**

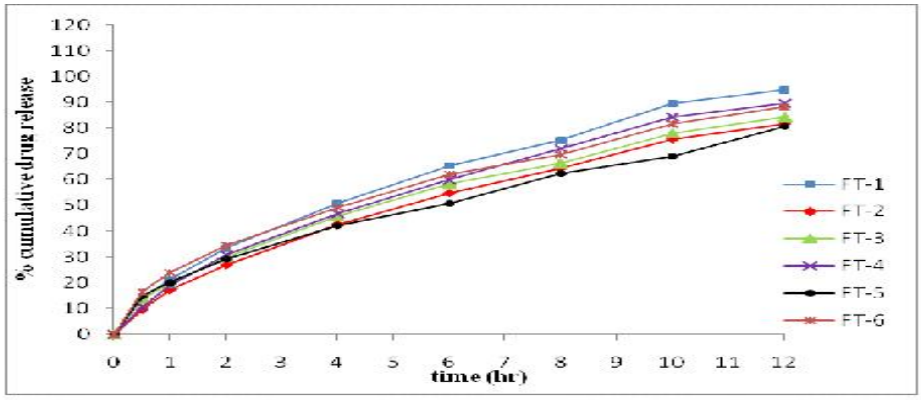


**Fig. 5: % cumulative drug released v/s time plot of optimization batches (FT-1-FT-6)**

### 3.2 Optimisation of Floating Layer

The results obtained from the experiment were statistically analysed for response variables by using Design Expert 7.1.6. Version (Stat-Ease Inc., Minneapolis, USA). The 3-D response surface diagrams and their respective contour maps facilitate an understanding of the contribution of the variables and their interactions, so they were used for analysing the results.

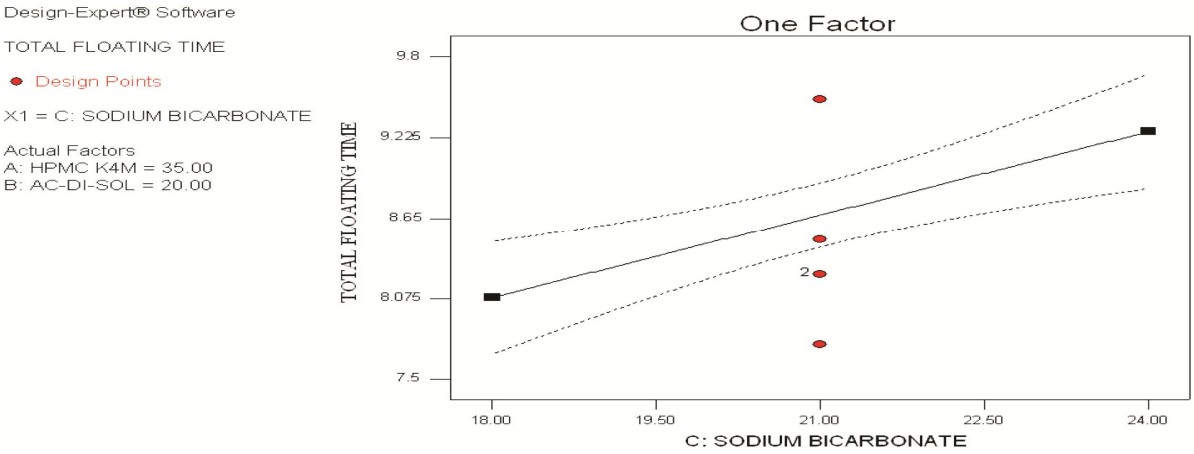


**Fig. 6: Model graph showing the influence of factor C on total floating time**

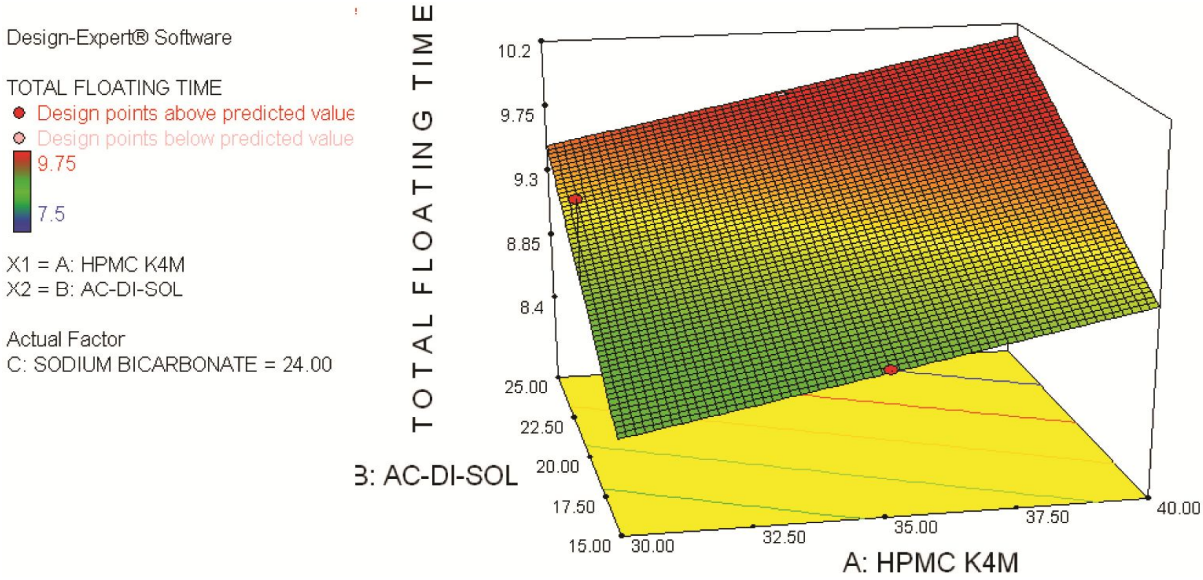


**Fig. 7: Response surface plot showing the influence of factor A and B on response R1**

### 3.2.1 Evaluation of the Optimization Batches

Three batches of selected optimum formula were prepared. Tablets were evaluated for following parameters: weight variation, hardness, friability and in vitro drug release profile. The results of these tests are shown in Table 1.

**Table 1: Evaluation of tablets of optimization batches**

| Formulation Code (s) | Weight variation (Mean ±SD) | Hardness ($kg/cm^2$) | Friability (%) |
|---|---|---|---|
| FT-1 | 201.2± 1.7 | 4.5-5.5 | 0.64 |
| FT-2 | 199.3± 2.1 | 4.5-5.5 | 0.42 |
| FT-3 | 201.1± 0.8 | 4.5-5.5 | 0.23 |
| FT-4 | 202.5± 1.2 | 4.5-5.5 | 0.38 |
| FT-5 | 199.6± 1.1 | 4.5-5.5 | 0.21 |
| FT-6 | 200.2± 2.3 | 4.5-5.5 | 0.17 |
| FT-7 | 201±2.9 | 4.5-5.5 | 0.47 |
| FT8 | 203± 0.5 | 4.5-5.5 | 0.54 |
| FT-9 | 198.9± 1.2 | 4.5-5.5 | 0.67 |
| FT-10 | 200.8± 0.9 | 4.5-5.5 | 0.45 |
| FT-11 | 200.4± 1.9 | 4.5-5.5 | 0.57 |
| FT-12 | 201.2± 2.7 | 4.5-5.5 | 0.72 |
| FT-13 | 202±0.9 | 4.5-5.5 | 0.34 |
| FT-14 | 201.6± 2.1 | 4.5-5.5 | 0.57 |
| FT-15 | 201± 1.8 | 4.5-5.5 | 0.27 |
| FT-16 | 202.7± 1.4 | 4.5-5.5 | 0.55 |
| FT-17 | 201.5± 1.3 | 4.5-5.5 | 0.18 |

### 3.2.2 Statistical and Response Surface Analysis

From the model, graphs showed it can be concluded that total floating time increases with an increase in amount of sodium bicarbonate and ac-di-sol. However, the effect of sodium bicarbonate is slightly more prominent than ac-di-sol. As per design point scale on L.H.S. of a response surface plot in Figure 12, total floating time increases from a blue region to a red region. Therefore, in order to obtain maximum buoyancy, only those combinations should be used, which corresponds to a red region of the response surface plot or contour plot. So, it can be concluded that with the increase in a total amount of ac-di-sol and HPMC, there is an increase in total floating time of tablet.

The drug release at 30 min was directly influenced by the amount of ac-di-sol and sodium bicarbonate. Wicking action of ac-di-sol and effervescence produced by sodium bicarbonate can be accounted for such results. HPMC showed non-linear relationship with the response R2.

HPMC showed inverse relationship with the percent cumulative drug released after 12 hours (R3) as shown in Figure 17 and Figure 18. This result is validated by the high negative coefficient (-5.57) of HPMC in the polynomial equation for R3. Figure 19 shows the effect of sodium bicarbonate (C) and HPMC simultaneously on the response R3. As per design point scale, the higher amount of C favours higher drug release. Ac-di-sol showed non-linear behavior with the response R3.

### 3.2.3 Numerical Optimization

As per the design point scale on the L.H.S. of the response surface plot in Figure 22 and Figure 23, desirability function increases from 0 to 1 as we go from a blue region to a red region. Therefore, in order to get the

desirability function of 0.73, combinations, which correspond to a
dark-green region should be selected. It was observed that proposed levels of the independent variables (by the software) were those corresponding to a dark-green region only.

Proposed levels of HPMC K4M, ac-di-sol and sodium bicarbonate were used to prepare the sustained release floating layer so that desired results of the selected response variables could be obtained. The composition of sustained release floating layer is shown in Table 2.

**Table 2: Predicted optimized formula of sustained release floating layer**

| S. No. | Ingredient | Quantity/tablet (mg) |
|---|---|---|
| 1 | Indomethacin | 55.00 |
| 2 | HPMC K4M | 30.00 |
| 3 | Ac-di-sol | 19.42 |
| 4 | Sodium bicarbonate | 22.53 |
| 5 | Lactose anhydrous | 69.00 |
| 6 | PVP- K30 | q.s. |
| 7 | Magnesium stearate | 2.00 |
| 8 | Aerosil | 2.00 |

### 3.3 Validation of Predicted Optimized Formulation

The flow properties of granules of all three batches were found to be good. Weight variation, friability and assay were found to be within acceptable limits. Hardness was also within the desired limits (Chinam et al., 2007). The results are shown in Table 6. Comparison of the experimentally observed and software predicted response variables showed a good agreement between the observed and predicted values. This demonstrated that the optimization technique was successful in designing the indomethacin sustained release floating tablet formulation.

**Table 3: Responses of optimized formulation**

| Response | Value predicted by software | Value obtained from optimized formulation batches | | |
|---|---|---|---|---|
| | | Batch I | Batch II | Batch III |
| Total floating time (hrs) | 8.60 | 9.00 | 8.25 | 8.75 |
| Drug released at 30 min (%) | 13.50 | 14.24 | 12.44 | 12.78 |
| % Cumulative drug released after 12 hrs | 90.0 | 92.42 | 91.38 | 88.58 |

### 3.4 *In vitro* drug Release

The final indomethacin bilayer tablet showed the desired in-vitro release profile. Two different drug release phases were observed. The tablet provided around 25 mg of dose during first 30 minutes and sustained the release of remaining dose for the next 12 hours. The regression coefficients for various plots of bilayer tablets showed that the release data best fitted in the first-order model. In Korsmeyer-Peppas plot, the value of slope is 0.3108, which suggests that Quasi- Fickian diffusion is the mechanism of drug release. The release of indomethacin from bilayer tablet.

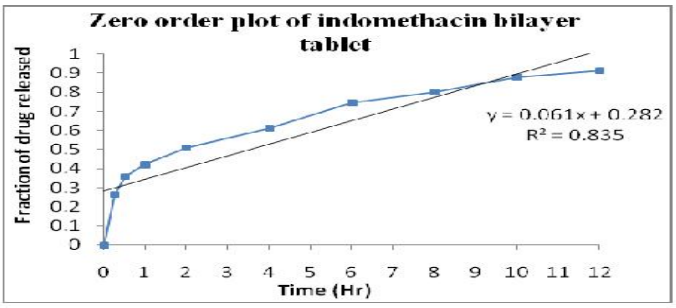


**Fig. 8: Zero order plot of the indomethacin bilayer tablet**

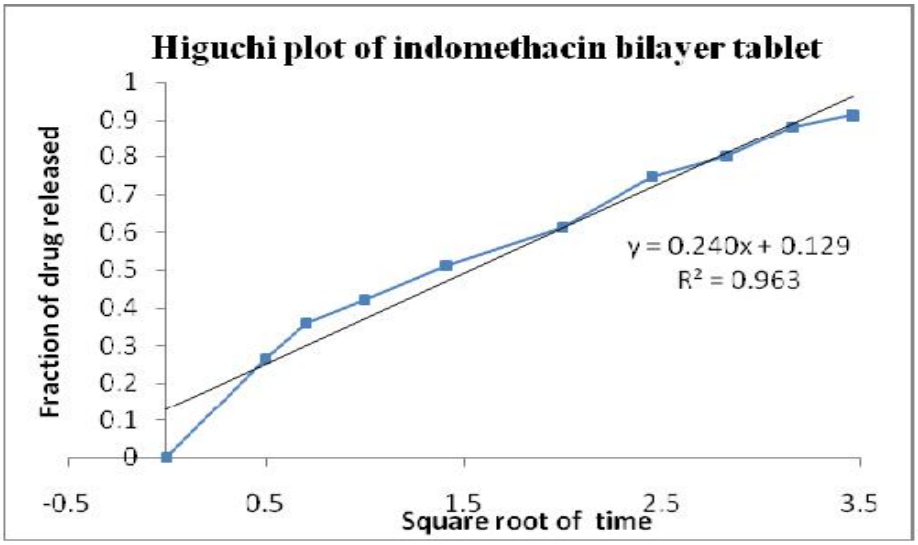


**Fig. 9: Higuchi plot of the indomethacin bilayer tablet**

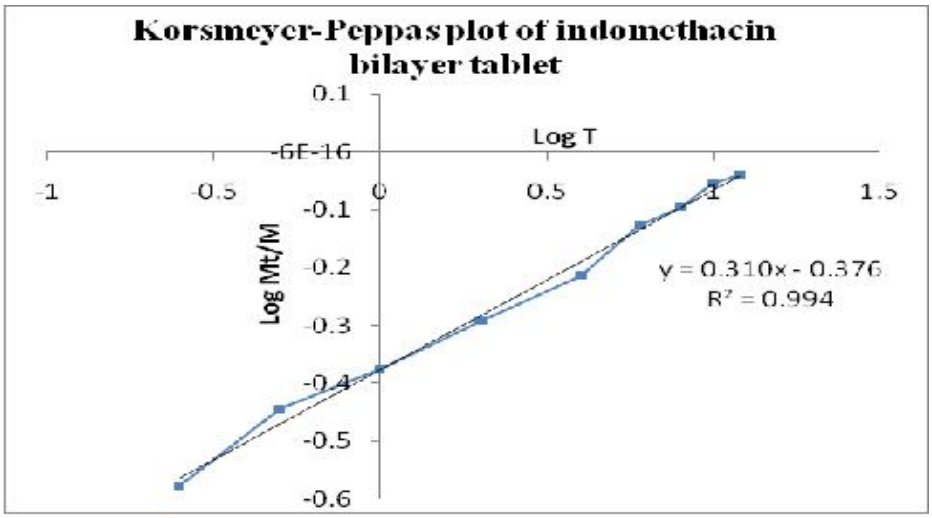


**Fig. 10: Korsmeyer-Peppas plot of the indomethacin bilayer tablet**

### 3.6 Stability testing of bilayer Tablet

The formulated indomethacin bilayer tablets were kept at different storage conditions. The control samples were kept at 2-8$^0$C and test samples were kept at room temperature and at 40$^o$C. The drug content of the tablets was determined initially and then at the interval of 15 days and one month. The drug content of the optimized formulation at zero days was found to be 98.24%. The indomethacin bilayer tablet formulation was found to be stable under the conditions of room temperature and 40ºC for the period of one month at least (Mathews, 1999).

## 4. CONCLUSION

From the above studies, it can be concluded that the approach of mixed-solvency is novel, safe, cost-effective and user friendly. It also eliminates the problem of toxicity associated with high concentration of water-soluble solubilizers. So, it can be employed in dosage form development of drugs where the fast onset of action desired. Furthermore, successful development of gastro-retentive sustained release tablet was done using in-silico optimization technique. Based on these findings, it can be said that modified release tablet formulations with desired attributes can be developed using computerized optimization technique.

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from Chemistry Department of Dr. H. S. Gour University.

**Declaration of Interest**

The authors report no declarations of interest.

**Appendices**

Figures with essential colour discrimination, some figures used in this article are difficult to interpret in black and white.

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