www.ijrps.pharmascope.org

A novel approach for dissolution enhancement of Ibuprofen by preparing floating granules

Patel Rajanikant*[1], Patel Nirav[2], Patel N.M[3], Patel M.M[1]

[1] Kalol Institute of Pharmacy, Kalol, Gujarat, India
[2] Anand Pharmacy College, Anand, Gujarat, India
[3] Shri B.M.Shah College of Pharmaceutical Education and Research, Modasa, Gujarat, India

ABSTRACT

Ibuprofen, a weekly acidic, non-steroidal anti inflammatory drug having high permeability through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric empting time ranging from 30 min to 2 hr, after this time ibuprofen goes in to small intestine where it is solubilise but can't permeate through its membrane. To improve dissolution of such drug is challenging and rational. In present investigation, dissolution of ibuprofen improves by preparing floating granules. Floating is requiring for increasing residence time of granules in stomach. Ibuprofen must have to remain in stomach because it is mostly permeable through it. Multipurpose floating formulations was developed by preparing immediate release (for loading dose) granules containing gelucire 44/14 and sustained release floating granules containing gelucire 43/01 and small amount of gelucire 44/14. Amount of gelucire 44/14 and gelucire 43/01 was optimized using factorial design. Amount of gelucire 44/14 (X1) and amount of Gelucire 43/01 (X2) selected as independed variable. $t_{100\%}$ (time require to dissolve 100 % drug) and total floating time chosen as response or depended variable. Release kinetic of ibuprofen studied by applying different model (zero order, first order, higuchi, korsmeyer-peppas, Hixson crowell and weibull). In optimized formulation, Granules remain floated for 3 hrs. and gave 100% drug release in 150 minute. Highest R^2 and lowest Sum of square residual (calculated from AUC) was observed in Weibull model.

Keywords: Ibuprofen, Floating Granules, Gelucire 44/14, Gelucire 43/01, factorial design, physical characterization Model-Dependent Approaches.

INTRODUCTION

Recently more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water. Formulation of poorly soluble compounds for oral delivery now presents one of the interesting challenges to formulation scientists in the pharmaceutical industry. In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°), due to erratic or incomplete absorption from GIT (Swarbrick & Boylan).

Ibuprofen, a weekly acidic, non-steroidal anti inflammatory drug having high permeability through stomach because it remain 99.9 % unionize in stomach (pKa of Ibuprofen – 4.43, pH of gastric fluid - 1.2). Ibuprofen mostly permeable through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric empting time is 30 min to 2 hr. After this time ibuprofen goes in to small intestine where it is solubilised but can't permeate through its membrane (Ibuprofen having pH depended solubility and permeability). To improve dissolution of such drug is challenging and rational.

Ibuprofen available in dose of 200 mg, 400 mg and 800 mg tablets. In present work, 200 mg ibuprofen was taken. The taken amount remain practically insoluble in 900 ml, 0.1 N HCl. Dissolution study of plain ibuprofen indicated only 8% drug was release in 120 minutes. Solubility depends on amount of solute, time, amount of solvent, temperature, stirring speed, and other factors. Due to higher dose of drug, it was precipitated instead of dissolve if release quickly. If drug release was retarded then it was better solubilizes as compare to precipitation observed by fast release.

In present investigation, targeted dissolution profile achieved by incorporating gelucire 44/14 and gelucire 43/01. It was logically decided to design experiments, so as to achieve the set objectives. Thus, an attempt was made to prepare formulations which retain in stomach for more than 2 hrs because drug was not

* Corresponding Author
Email: rajnipharmacy@gmail.com
Contact: +919724323425

completely soluble within 2 hrs hence to dissolve completely in stomach region, floating dosage form must be prepared (Target selected by considering maximum gastric empting time hence minimum gastric empting time is included). These attempts improve bioavailability and consequently dose reduction would possible.

EXPERIMENTAL

Materials

Ibuprofen Gifted by Zydus Cadila, Ahmedabad and Gelucire 44/14, Gelucire 43/01 Gifted by Gattefosse Pvt. Ltd, Mumbai, Empty Hard gelatine capsules gifted from Astron Research Ltd., Ahmedabad. All other chemicals and reagents used are of analytical grade.

Methods

Preliminary investigation indicated that when lower amount of gelucire 44/14 used drug not dissolve and when higher amount of gelucire 44/14 used, granules disperse quickly. Concentration of gelucire 44/14 and gelucire 43/01 was optimized in prepared multipurpose granules. Dose of 200 mg ibuprofen divided in to two Parts: 50 mg and 150 mg. In 50 mg drug, excess amount of gelucire 44/14 (350 mg) used as solubility enhancing carrier so drug dissolve quickly (requirement of loading dose is fulfill) and above granules dissolve quickly in Dissolution Medium (0.1 N HCl) and above solution help to dissolve remaining 150 mg of drugs because larger amount of gelucire 44/14 in dissolution medium gave surfactant like action.

In remaining 150 mg drug, concentration of gelucire 43/01 and gelucire 44/14 optimize by applying factorial design. Small amount of gelucire 44/14 was added to disperse whole granules within targeted time (3 hrs)

Formulation Design

This study investigated utility of a 2-factor, 3-level central composite design and optimization process for floating granules of ibuprofen. Amount of gelucire 44/14 (A) and amount of gelucire 43/01 (B) were selected as the independent variables whereas floating time (Y_1) and t_{100}% (time require to dissolve 100% drug) Y_2 were selected as dependent variables.

The prepared granules of ibuprofen were evaluated for dissolution study. The responses were analyzed using ANOVA and the individual response parameters were evaluated using F test and polynomial equation was generated for each response using MLRA.

Preparation of Ibuprofen Granules

Floating ibuprofen granules were prepared by fusion method. 200 mg ibuprofen divided in to 50 mg and 150 mg, 350 mg gelucire 44/14 melted and 50 mg ibuprofen added, disperse with glass road for uniform distribution of drug in to molted carrier, remaining 150 mg ibuprofen added in to molted Gelucire 44/14*, this whole dispersion added in to molted gelucire 43/01*.
* Amount mentioned in following Table. 3

In Vitro Dissolution of Prepared Formulations

Dissolution of prepared formulations equivalent to 200 mg of ibuprofen was performed in 900 ml 0.1 N HCl (pH 1.2) in USP type-II Dissolution apparatus at 50

Table 1: Independed Factor

Independent variable	Levels		
	Low	Middle	High
	-1	0	1
A (amt of gelucire 44/14)	0 mg	25 mg	50 mg
B (amt of gelucire 43/01)	75 mg	187.5 mg	300 mg

Table 2: Central Composite Design

Formulation code	Coded value		Actual value	
	A	B	A	B
I1	-1	-1	0	75
I2	-1	0	0	187.5
I3	-1	1	0	300
I4	0	-1	25	75
I5	0	0	25	187.5
I6	0	1	25	300
I7	1	-1	50	75
I8	1	0	50	187.5
I9	1	1	50	300

Table 3: Design Data

Formulation code	Amt. of gelucire 44/14	Amt. of gelucire 43/01
I1	0	0
I2	0	187.5
I3	0	300
I4	25	0
I5	25	187.5
I6	25	300
I7	50	0
I8	50	187.5
I9	50	300

RPM. Dissolution medium was kept at 37 ± 0.5^0C. 5 ml sample were collected at different time interval and filtered through a whatman filter paper (0.45 µm). The same amount of fresh dissolution medium was added to maintain sink condition. The absorbance was measured at 220.5 nm using UV-visible spectrophotometer. The concentration of ibuprofen was calculated by using standard curve equation.

Data Analysis

The response surface methodology is a collection of mathematical and statistical techniques used for modeling and analysis of problems in which a response of interest is influenced by several variable and the objectives is to optimize this response.

The run or formulation, which are designed based on central composite design are evaluated for the response. The response values are subjected to multiple regressions analysis to find out the relationship between the factor used and the response value obtained. The response values subjected for this analysis are floating time & T100%

The multiple regression analysis was done using DESIGN EXPERT 7.1.6 (STAT-EASE) demo version software, which specially meant for this optimization process.

Analysis of data was carried out using ANOVA and the individual parameter was evaluated with F-test. Using the regression coefficient of factor, the polynomial equation for the each response is generated (Prakobvaitayaki & Vimmannit, 2003).

Formulations Optimization

The computation for optimized formulation was carried using software, DESIGN EXPERT 7.1.6 (STAT-EASE). The response variable considered for optimization were floating time and T1000%

The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors). Constraints for responses and factors are shown in Table 4.

various preparations were recorded at room temperature on Bruker's D8 Advance diffractometer (Karlsruhe, West Germany) Cu Kα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter with divergence slit (0.5°), antiscattering slit (0.5°), and receiving slit (1 mm). The diffractometer was equipped with a 2θ compensating slit, and was calibrated for accuracy of peak positions with silicon pellet. Samples were subjected to X-ray powder diffraction analysis in continuous mode with a step size of 0.01° and step time of 1 sec over an angular range of 3 to 40 °2θ. Samples were loaded on zero background sample holder.

Release Kinetic Determination of optimized formulation by applying Model-Dependent Approaches

Release kinetics is an integral part of formulation development because if the kinetics of drug release is known, one can also advance for the establishment of in vivo in vitro (IVIVC) correlation. Mathematical approach is one of scientific methods to optimize and evaluate the error in terms of deviation in AUC to the release profiles of formulated products during the formulation development stage. Mathematical model approach important in research and development because of its simplicity and their inter-relationships may minimize the number of trials in final optimization, thereby improving the formulation development

Table 4: Constraints for optimization

Name	Goal	Lower Limit	Upper Limit
Amt. of gelucire 44/14	In range	0 mg	50 mg
Amt. of gelucire 43/01	In range	75 mg	300 mg
T100% (min)	Target = 150 min.	30	180
Floating time (hr)	Target = 3 hr.	0	8

By utilizing DESIGN EXPERT 7.1.6 (STAT-EASE) demo version software, we got one solution for optimized formulation. The optimized formulation is prepared and evaluated for floating time and T100%. Observe response value of the optimized formulation is compared with predicted value.

Physical Characterization of Optimize Formulation

Differential Scanning Calorimetry (DSC) Analysis

DSC scans of all powdered samples were recorded using Shimadzu DSC-60 with TDA trend line software. All samples were weighed accurately in crimped aluminum pans (8–10 mg) and heated at a scanning rate of 10 °C/min under dry nitrogen flow (100 mL/min) between 50 and 300 °C. Aluminum pans and lids were used for all samples. Pure water and indium as primary standard were used to calibrate the DSC temperature scale and enthalpic response.

Powder X-ray Diffraction (PXRD) Analysis

The X-ray diffraction study was carried out to characterize the physical form of ibuprofen in samples of selected batches. The physical state of Ibuprofen in the

process.

In vitro drug release data were fitted to kinetic models such as zero-order (Brazel & Peppas, 2000), first-order (Lapidus & Lordi, 1966), Higuchi equation (Higuchi, 1963), Korsemeyer–Peppas equation (Korsmeyer et al.), Hixson–Crowell equation (Hixson & Crowell, 1931).

Qt versus t (zero order)
log Qt versus t (first order)
Qt versus square root of t (Higuchi)
log %Qt versus log %t (Korsmeymer-Peppas)
Qt versus cube root of t (Hixson–Crowell)
log Qt versus log t (Weibull)

Where Qt is the amount of drug released at time t.

The criteria for selecting the most appropriate model are lowest sum of square of residuals (SSR) and highest R^2 value (Thakkar et al., 2009).

Lowest sum of square of residuals (SSR) indicate the minimum variance between the predicted and observed dissolution data. Highest R^2 value indicates linearity of dissolution data.

Table 5: The design and response summary data

Formulation code	Factors		Response	
	Amt. of gelucire 44/14	Amt. of gelucire 43/01	T100% (min)	Floating time (hr)
I1	0	0	75	0
I2	0	187.5	390	7.3
I3	0	300	480	8. 3
I4	25	0	45	0
I5	25	187.5	150	3
I6	25	300	210	4
I7	50	0	30	0
I8	50	187.5	90	2
I9	50	300	105	2.15

Residual values between predicted and observed data were used to calculate the sum of squares of residuals, The entire dissolution profile was compared by taking the absolute difference (residual) between the predicted and observed calculated AUC data.

RESULTS AND DISCUSSION

In Vitro Dissolution study
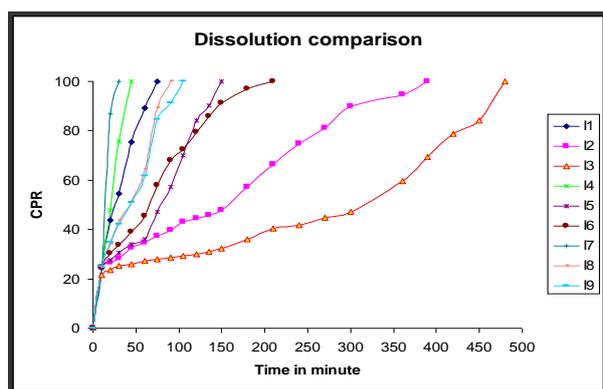
Fig. 1: Dissolution comparison of Batch I1-I9

fen dispersed in excess amount of molted gelucire 44/14 (350 mg) and granules was prepared. Above granules in 0.1 N HCl dissolve quickly and that solution help to dissolve remaining 150 mg of drugs because larger amount of gelucire 44/14 in dissolution medium gave surfactant like action.

Formulation I1, I4, I7, I8 and I9 gave 100 % drug soluble in 75 minutes, 45 minutes, 30 minutes, 90 minutes and 105 minutes but after some time drug was reprecipitated from solution (hazy solution formed) that was due to supersaturated solution formed due to fast release of poorly soluble high dose of ibuprofen hence drug release retarded in batch I2, I3, I5, and I6 then it was better solubilizes as compare to precipitation observed in formulation I1, I4, I7, I8 and I9.

In formulation I2 and I3, gelucire 44/14 was absent hence drug release was retarded. It indicated gelucire 44/14 was responsible for giving fast release. As compare to formulation I2, I3 gave more sustained effect and higher floating time due to more amount of gelucire 43/01 was present.
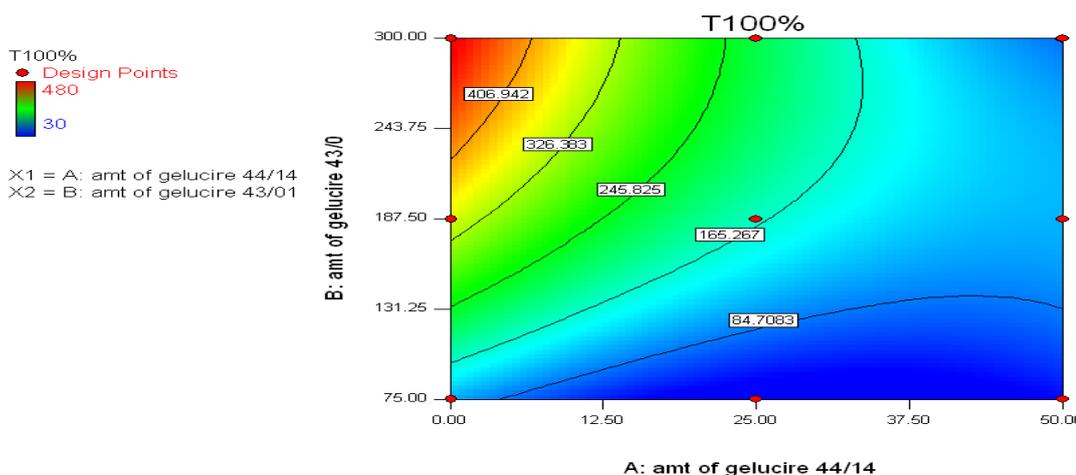

Fig. 2: Contour plot showing the effect of amount of gelucire 44/14 and amount of gelucire 43/01 on T100%

Dissolution of Batch I1 to I9 showed in above fig. 1. Initial 25% ibuprofen release in 10 minutes in all batches. These burst release was due to 50 mg ibupro-

DATA ANALYSIS

The responses were recorded and analysis of data was carried out using ANOVA in (STAT-EASE). The individual

parameter was evaluated using F-test and a polynomial equation for each response was generated using MLRA. The design and response summary data are represented in Table 5.

Response: T100% (Y$_1$)

In ANOVA table, values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, AB are significant model terms.

Final Equation in Terms of Coded Factors:

T100% = +170.00 -120.00 A +107.50B -82.50 AB + 60.00 A^2 -52.50 B^2

Response: Floating time (Y$_2$)

In ANOVA table, Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms.

Final Equation in Terms of Coded Factors:

Floating time = +3.49 -1.86 A +2.36 B -1.46 AB +0.91A^2 -1.74 B^2

creased due to hydrophilic and solubilizing nature of gelucire 44/14 so when amount of gelucire 44/14 increase formulation dissolve quickly but as the amount of gelucire 43/01 increases, T100% increase because of hydrophobic and release retarding nature of gelucire 43/01 itself so presence of both gelucire 44/14 and gelucire 43/01 is important in achieving desired floating time.

The relationship between the dependent and independent variables was further elucidated using contour plots. Here, logically predecided to obtain the values of the T100% time 150 minutes from the formulated products. In contour plot only formulation I5 showed T100% near to desired T100% (Fig. 2 indicated by light blue). The final selection of the optimized batch would be done after considering the other requirements of the dosage form i.e, floating time.

It was logically decided to obtain the values of the floating time 150 minutes from the formulated products. Values of "Prob > F" less than 0.0500
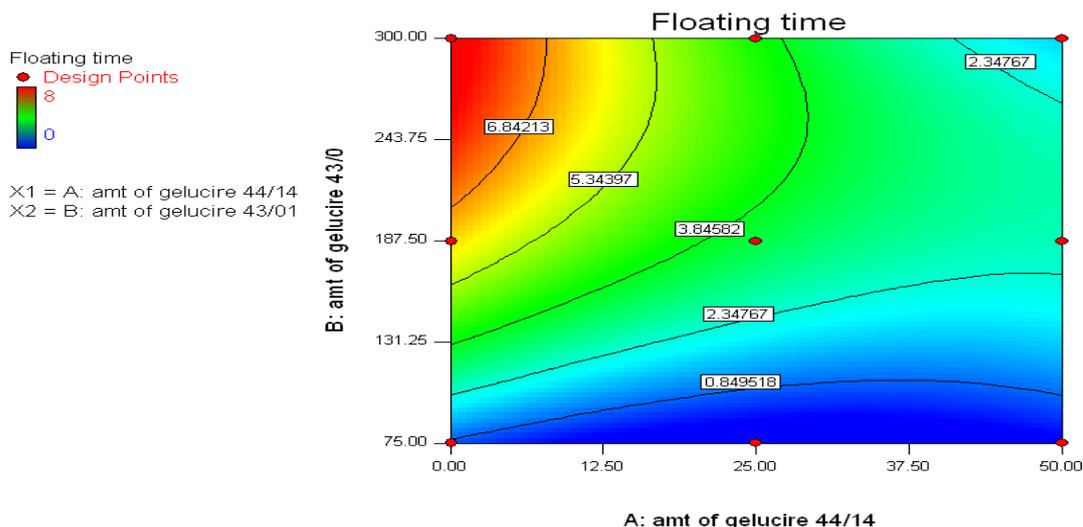

Fig. 3: Contour plot showing the effect of amount of gelucire 44/14 and amt of gelucire 43/01 on floating time

A 3^2 central composite design was adopted, using the amount of gelucire 44/14 and amount of gelucire 43/01 as independent variables. The response values subjected for this analysis were T100% and floating time.

It was logically decided to obtain the values of the T100% was 150 minutes from the formulated products. The results for dependent variables floating time of the batches are shown in Table 26. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case A, B, AB are significant model terms (Table 27). As the amount of gelucire 44/14 increased, T100% de-

indicate model terms are significant, in this case A, B had significant effect on floating time. Floating was not observed in Batch I4 and I7 due to absence of gelucire 43/01 while batch I2 and I3 having more floating time due to only presence of gelucire 43/01. Batch I1 also show zero floating time due to both absence of gelucire 44/14 and gelucire 43/01.

As the amount of gelucire 44/14 increased, floating time decreased due to gelucire 44/14 is hydrophilic and solubilizing excipients so when amount of gelucire 44/14 increase formulation disintegrate quickly but as the amount of gelucire
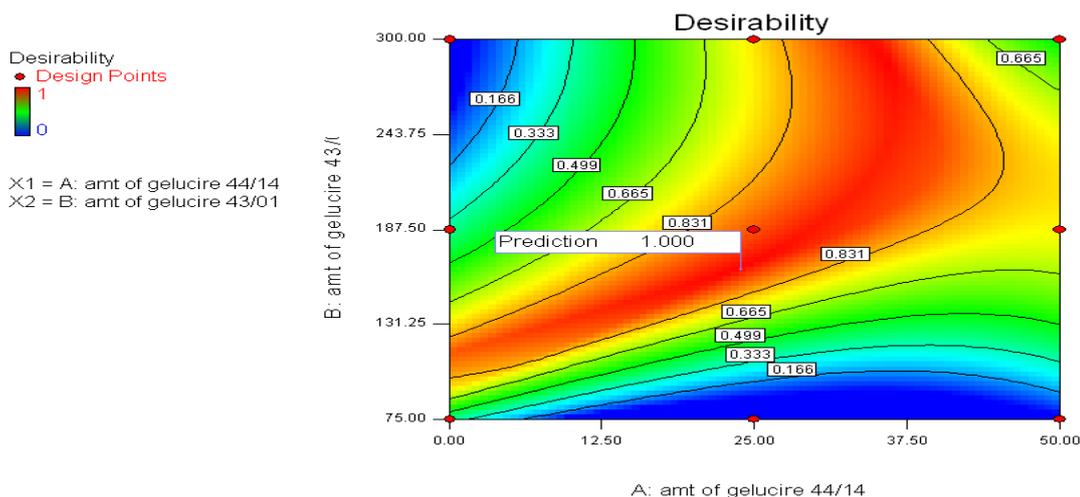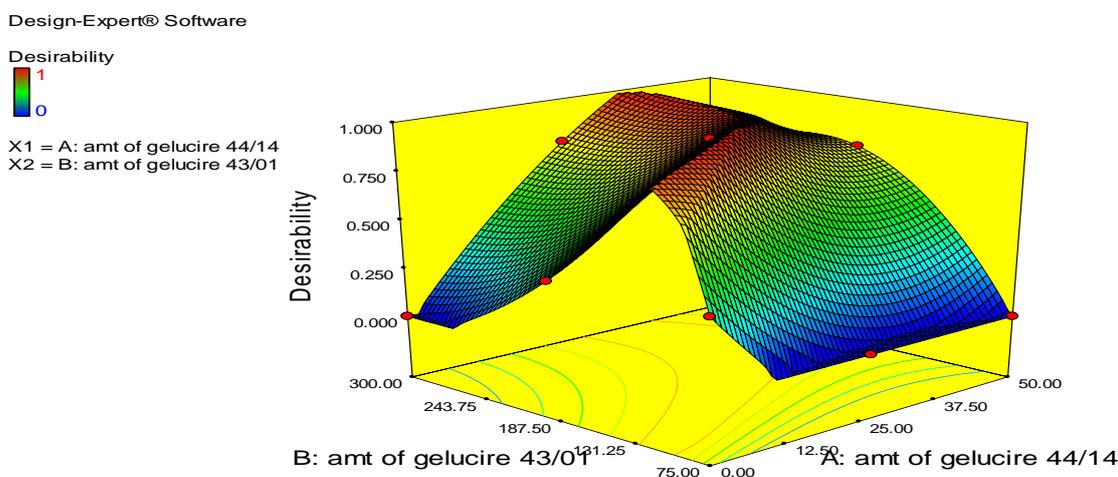
Fig. 4: Contour Plot for optimization

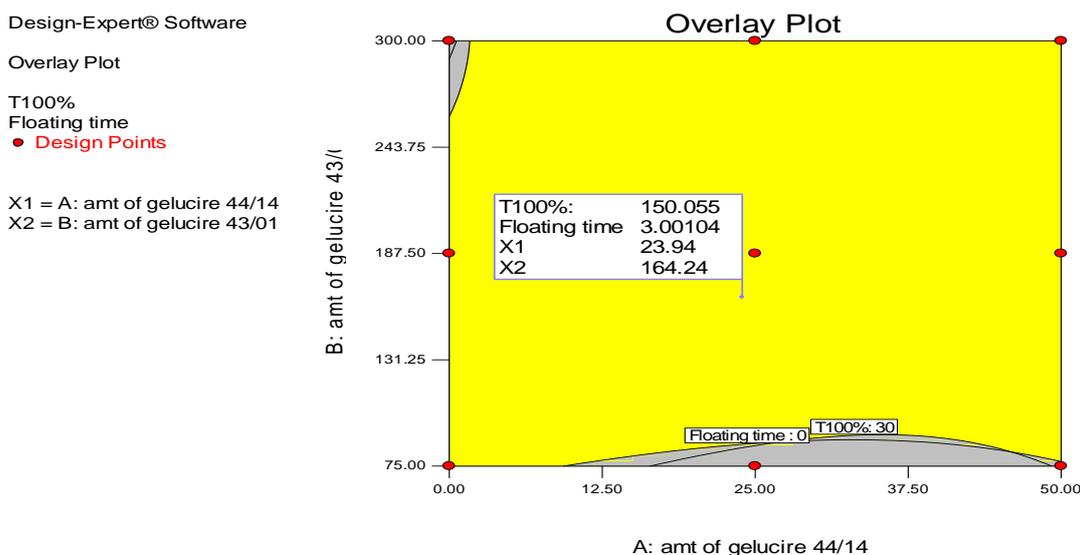

Fig. 5: Response Plot for optimization

Fig. 6: Overlay plot for optimization

43/01 increases, floating time increase because of hydrophobic and floating nature of gelucire 43/01 itself so presence of both gelucire 44/14 and gelucire 43/01 is important in achieving desired floating time.

The relationship between the dependent and independent variables was further elucidated using contour plots. Here, logically predecided to obtain the values of the floating time 180 minutes from the formulated products. In contour plot only

formulation I5 showed floating time near to desired floating time (Fig. 3, Indicated by green color). Exact amount of gelucire 44/14 and gelucire 43/01 for achieving desired response was found out from optimization.

FORMULATION OPTIMIZATION

For the optimization of floating granules of ibuprofen constraints was fixed for all factors and response (Table 4). Constraints were set according to formulation of floating granules using minimum amt of excipients, which would give desired response values. In the present study our aim was floating time should be 180 min. and T100% should be 150 minutes. In optimization (Fig. 6) desirability 1.0 indicated optimum formulation was achieved at 23. 94 mg of gelucire 44/14 and 164.24 mg of gelucire 43/01 mg. Validation of optimization technique done by preparing checkpoint batch and response were evaluated. The responses value observed in checkpoint batch was very near to optimized batch.

PHYSICAL CHARACTERIZATION OF OPTIMIZED FORMULATION

Differential Scanning Calorimetry (DSC) Analysis

The DSC thermograms for plain ibuprofen and optimized batch are shown in fig. 7 & 8. In DSC scan of ibuprofen sharp endothermic peak observed at 79.86 that is the characteristic peak of ibuprofen while in the DSC scan of solid dispersion absence of ibuprofen peak at 79.86 indicates furosemide solubilizes in gelucire 44/14.
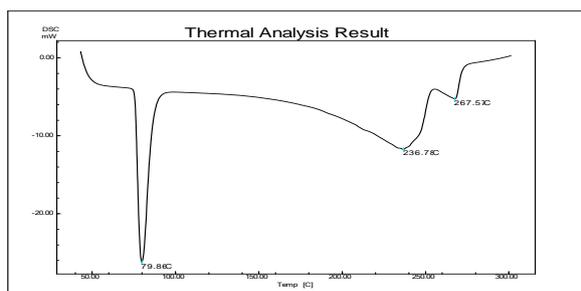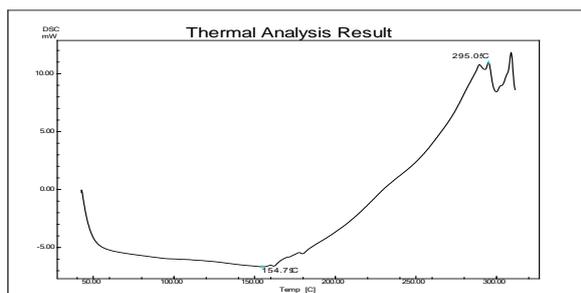

Fig. 7: DSC spectra of Ibuprofen

Fig. 8: DSC spectra of optimized batch
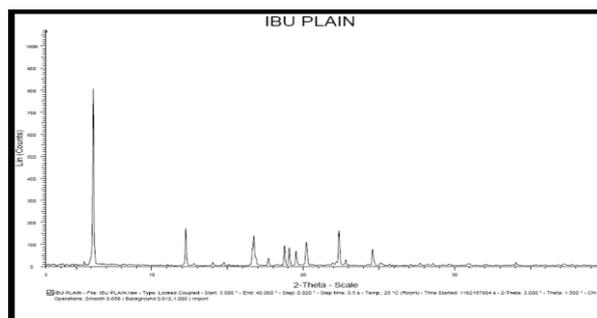
Powder X-ray Diffraction (PXRD) Analysis

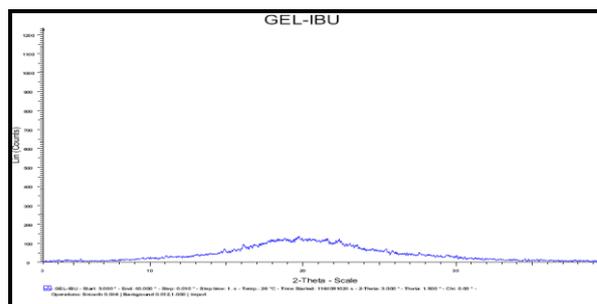**Fig. 9: XRD spectra of Ibuprofen**

Fig. 10: XRD spectra of optimized batch

The XRD spectra for plain ibuprofen and optimized batch are shown in fig. 9 & 10.

The presence of numerous distinct peaks in the PXRD spectrum of ibuprofen indicated that ibuprofen was present as a crystalline material with major characteristic diffraction peaks appearing at a diffraction angle of 2θ at 6, 13, 17, 20, and 22. These are characteristic peaks of crystalline ibuprofen.

The diffraction patterns of optimized formulation show helo shape spectrum with complete absence of diffraction peaks. An absence of diffraction peaks corresponding to Ibuprofen indicating ibuprofen was present as amorphous material inside the lipidic excipients (Gelucire 44/14 and Gelucire 43/01).

Table 6: Result of model fitting for optimized batch

Model	R^2	SSR	Slope	Intercept
Zero-order	0.9949	733213.76	0.6728	-0.813
First-order	0.7801	1042.31	0.0108	0.6528
Higuchi	0.914	14374.69	8.4741	-16.12
Korsmey-mer-peppas	0.9724	0.75	1.0297	-0.159
Hixson-crowell	0.9252	3950.79	30.63	-70.32
Weibull	0.9956	0.033	0.93	-0.048

Table 7: Percentage deviation in release profile for the optimized batch from the weibull

Log t	Predicted weibull release profile		Observed weibull release profile		Absolute difference in AUC
	Log Q t	AUC	Log Q t	AUC	
1	0.89	0.445	0.8	0.4	0.045
1.477	1.35	0.57	1.35	0.681	0.112
1.778	1.61	0.423	1.555	0.334	0.089
1.875	1.7	0.164	1.672	0.213	0.049
1.954	1.78	0.153	1.757	0.162	0.009
2.021	1.85	0.139	1.845	0.176	0.036
2.079	1.9	0.103	1.926	0.166	0.063
2.13	1.955	0.116	1.955	0.061	0.055
2.176	2	0.097	2	0.097	0

RELEASE KINETIC DETERMINATION OF OPTIMIZE FORMULATION BY APPLYING DIFFERENT MATHEMATICAL MODELS

The criteria for selecting the most appropriate model are lowest sum of square of residuals (SSR) and highest R^2 value.

Lowest sum of square of residuals (SSR) indicate the minimum variance between the predicted and observed dissolution data. Highest R^2 value indicates linearity of dissolution data.

Residual values between predicted and observed data were used to calculate the sum of squares of residuals, The entire dissolution profile was compared by taking the absolute difference (residual) between the predicted and observed calculated AUC data

Highest R^2 and lowest Sum of square residual (calculated from AUC) was observed in Weibull model (Table 6).

CONCLUSION

From above research work it was concluded that for improving dissolution of weakly acidic and those drugs which are mostly absorb through stomach, floating approach is require if drugs remain insoluble in gastric fluid . Academicians and researchers may adopt this method because of its simplicity and their inter-relationships may minimize the number of trials in final optimization, thereby improving the formulation development process.

ACKNOWLEDGMENTS

REFERENCES

Brahma NS, Kwon HK, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, Journal of Controlled Release, 63, 2000, 235–259

Brazel CS., Peppas NA, Modeling of drug release from swellable polymers. Eur. J. Pharm. Biopharm, 49, 2000, 47–58.

Higuchi T, Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 1963, 52, 1145–1148.

Hixson AW, Crowell JH, Dependence of reaction velocity upon surface and agitation: theoretical considerations. Ind. Eng. Chem. 1931, 23, 923–931. The regression analysis was performed.

Korsmeyer RW, Gurny R., Doelker E, Buri P, Peppas NA, Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 1983, 15 (1), 25–35.

Lapidus H, Lordi NG, Some factors affecting the release of a water-soluble drug from a compressed hydrophilic matrix. J. Pharm. Sci. 1966, 55, 840–843.

Prakobvaitayaki M, Vimmannit V. Optimisation of poly-lactic-co-glycolic acid nanoparicles containing itraconazole using 3^2 factorial design, AAPS Pharm Sci Tech 2003, 4(4), 1-9.

Swarbrick JM, Boylan JC, Encyclopedia of Pharmaceutical Technology second edition, volume-I, Marcel Dekker series, 717-728.

Thakkar VT, Shah PA, Soni TG, Parmar MY., Gohel MC. and Gandhi TR, Goodness-of-Fit Model-Dependent Approach for Release Kinetics of Levofloxacin Hemihydrates Floating Tablet, Dissolution technology, 1, 2009, 35-39.