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DEVELOPMENT AND EVALUATION OF MICROBALLOONS OF IBUPROFEN

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ABSTRACT

In present study an attempt was made to prepare microballoons of ibuprofen by emulsion solvent diffusion technique for sustained delivery by using polymers like Ethyl cellulose to extend the drug release for about 12 hours in the upper GIT, which may result in enhanced absorption and there by improved bioavailability. Development of ibuprofen loaded microballoons was carried out by using different concentration of Polyvinyl alcohol (PVA) and Ethyl cellulose. Total four batches were formulated. All four batches were evaluated for Yield and entrapment efficiency Among all batches F2 shows maximum Yield and entrapment efficiency and was considered as optimized formulation. Optimized batch F2 was evaluated for Zeta Potential, Particle Size Distribution SEM and stability study.

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INTRODUCTION

Microballoons are gastro-retentive drug delivery systems based on non-effervescent approach. Microballoons are in strict sense, spherical empty particles. These microballoons are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer. Gastro-retentive Microballoons are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[1, 2] Microballoons improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved.[3] Ibuprofen is commonly used to treat anti-inflammatory drug. Ibuprofen is BCS class II drug having low solubility and high permeability. It is well absorbed from upper gastro intestinal track, absorption is decreases with increase in pH so absorption of drug decreases in the intestinal portion of the gastro intestinal tack. Ibuprofen shows higher absorption at upper part of gastro intestinal track and thus was selected for the study.[4]

MATERIALS AND METHOD

Ibuprofen, Ethyl cellulose, Tween 80, Poly Vinyl Alcohol (PVA), Methanol, Dichlor methane (DCM) were procured from Sulab Laboratory, Vadodara.

Method of Preparation of Microballoons

Emulsion Solvent Diffusion Technique is a new approach to prepare microballoons. In this technique, the drug and polymer was dissolved in organic solvent [i.e. methanol: DCM (1 : 2)]. Then, the dispersion solution was added drop-by-drop into 1 % PVA solution containing 0.3% Tween 20. Resultant emulsion was stirred at 1400 rpm using a propeller-type agitator for 2 hour. The microballoons were separated by filteration, washed with water and dried at room temperature in a desiccator for 24 hr.[1, 5]

CHARACTERIZATION OF MICROBALLOONS

Fourier Transform Infrared Spectroscopy (FTIR)

The microballoons were subjected to Fourier Transform Inferred Spectroscopy (FTIR) studies using (Shimadzu 8400 s). The potassium bromide (KBr) disk method was used for preparation of sample. The spectrum was compared with the infrared spectra of plain drug and polymer and checked for the drug-polymer interaction.[1, 5]

Percentage Practical Yield

The prepared microballoons were collected and weighed. The measured weight was devided by total amount of all non-volatile components which were used for preparation of microballoons.[1, 2]

$$\% \text{ Practical Yield} = \frac{\text{Weight of dried microballoons}}{\text{Weight of solid used (excipients + drug)}} \times 100$$

Drug Entrapment Efficiency

Separation of free drug: Analysis of Ibuprofen from microballoons was done by separating free drug from the microballoons dispersion. The separation was done by filtration (Whatmann filter paper) of microballoons. Then, the microballoons and filtrate were separated out.[5]

Indirect method

In this method, analysis of drug from microballoons was done by appropriately diluting filtrate in distilled water and absorbance was taken at 296 nm against distilled water as a blank on UV-Visible Spectrophotometer. To find out % entrapment following equation was used.[5]

$$\% \text{ EE} = \frac{\text{Weight of total drug} - \text{Weight of free drug in filtrate}}{\text{Weight of total drug}}$$

Drug Loading Efficiency

Drug loading was calculated using following equation[5]

$$\%\text{Drug Loading efficiency} = \frac{\text{Weight of Drug loaded in microballoons}}{\text{Total weight of powdered microballoons}} \times 100$$

Scanning Electron Microscopy

SEM is an instrument that produces largely magnified image by using electrons instead of light to form an image. The morphology of optimized formulation of Ibuprofen loaded microballoons was determined using scanning electron microscopy (SEM).[5]

Measurement of particle size and zeta potential

Zeta potential of a microballoons reflects the electric potential of particles and is used to characterize the surface charge properties and to determine whether the charged particle is encapsulated within the centre or adsorbed on to the surface of microballoons. The Particle size and Zeta potential of microballoons was recorded using Zetasizer. The optimized formulation was subjected to particle size and zeta potential analysis.[5]

In vitro diffusion studies:

In-vitro drug diffusion of microballoons in present research work is carried out by Dialysis Bag diffusion method. A 4–5 cm long portion of the dialysis tubing was made into a dialysis sac by folding and tying up one end of the tubing with thread. It was then filled up with simulated gastric fluid (pH 1.2) containing 0.02 w/v % tween 20 and examined for the leaks. The sac was then emptied and 100 mg of the microballoons was accurately transferred into sacs, which served as the donor compartments. The sacs were once again examined for leak and then suspended in the glass beakers containing 200 ml simulated gastric fluid (pH 1.2) containing 0.02 w/v % tween 20 , which become the receptor compartment, and maintained at 37± 0.5°C at a rotation speed of 100 rpm. At predetermined time intervals, 5 ml samples were withdrawn from the receptor compartment and analyzed spectrophotometrically. Fresh simulated gastric fluid was used to replenish the receptor compartment at each time point.[1, 2]

Stability Study

The stability study was carried out for optimized formulation of Ibuprofen loaded microballoons as per ICH guidelines. The microballoons of the best formulation were placed in glass vials and stored at ICH storage condition (2°C - 4°C Refrigeration condition, 30± 2°C / 60% ± 5% RH and 40 ± 2°C / 75% ± 5% RH) for a period of 30 days. The samples were analyzed for physical appearance, Entrapment Efficiency and for the drug release after 30 days.[1, 2]

RESULTS AND CONCLUSION

FT-IR Studies

The compatibility of the drug with various excipients was checked by FTIR spectrophotometric analysis using FTIR instrument. The spectra of all the drugs and excipients were taken which are as follows.

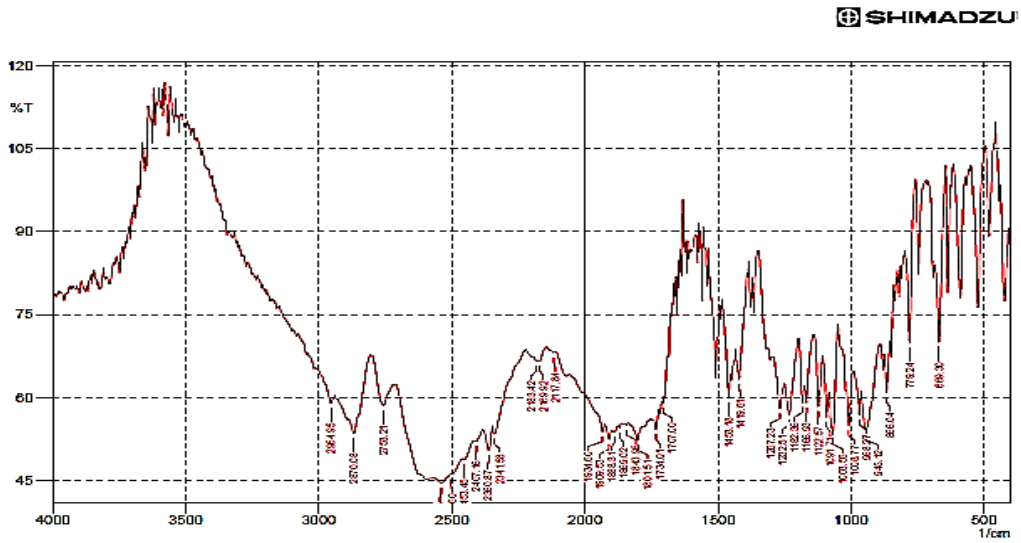

Figure 1 : FT-IR spectrum of pure drug ibuprofen in range of 4000 to 400nm^{-1}

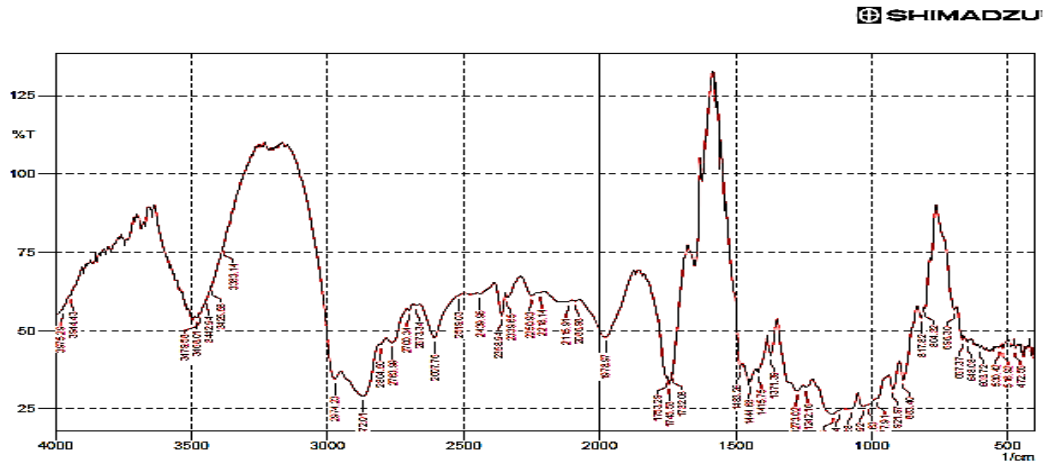

Figure 2: FT-IR Spectrum of Ethyl cellulose in range of 4000 to 400nm^{-1}

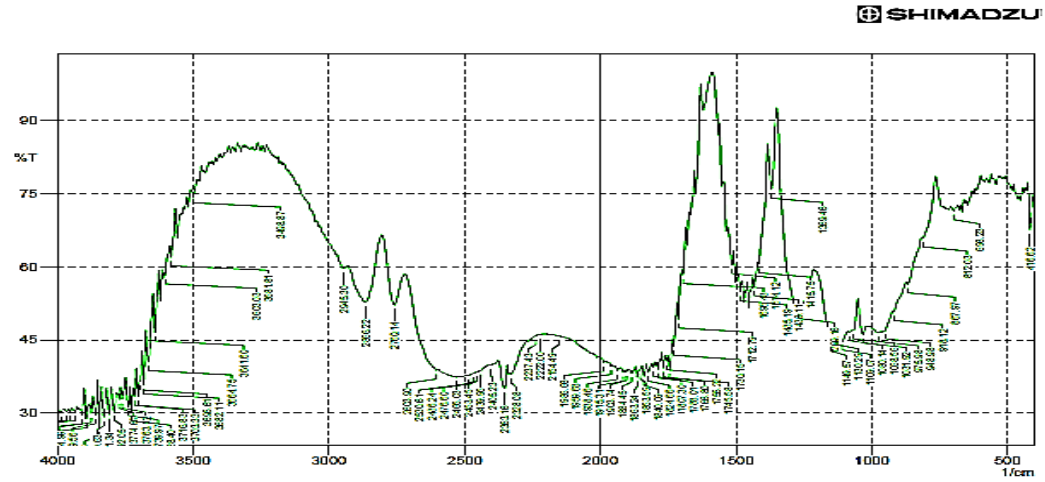

Figure 3: FT-IR Spectrum of Polyvinyl Alcohol (PVA) in range of 4000-400 cm^{-1}

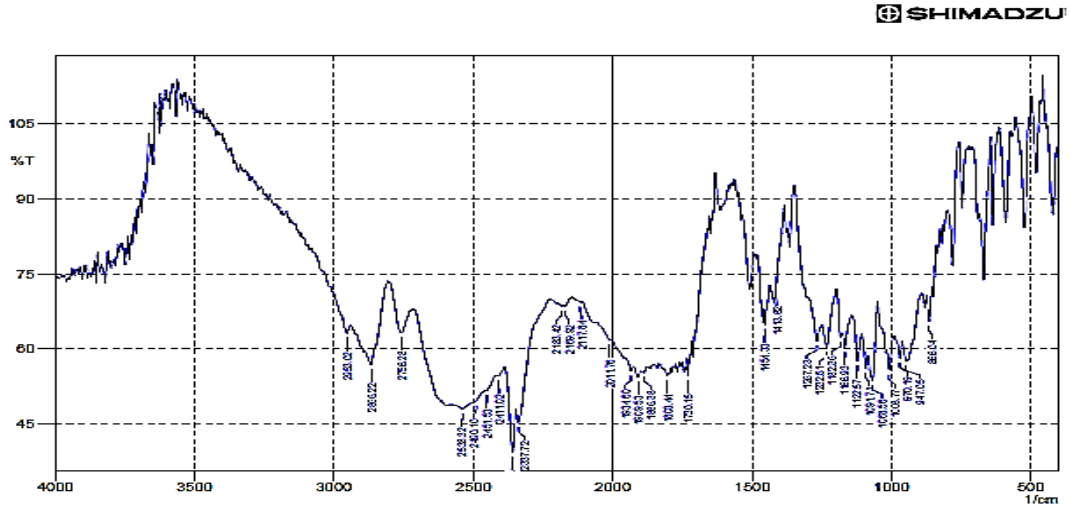

Figure 4: FT-IR Spectrum of ibuprofen+Ethyl cellulose in range of 4000-400 cm^{-1}

EXPERIMENTAL DESIGN

Table 1: Detail of code for experimental design.

Sr.no	Batch code	Polymer(ethyl cellulose)	PVA(%w/v)
1	F1	150mg	1%
2	F2	300mg	1%
3	F3	600mg	1%
4	F4	1200mg	1%

Practical Yield

Table 2: Practical yield of ibuprofen microballoons.

Formulation Code	%Practical yield
F1	44.73
F2	52.38
F2	56.66
F4	57.22

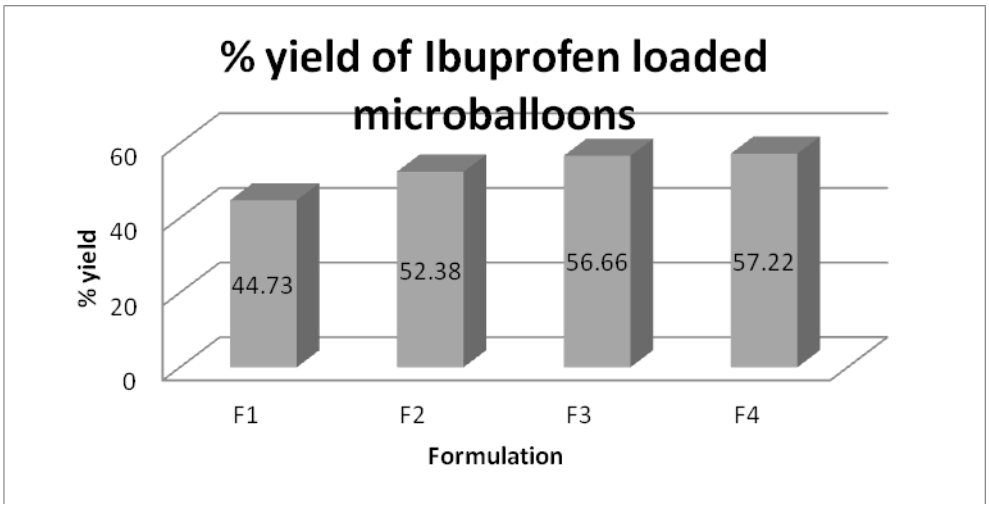

Figure 5: Column diagram for % Practical Yield.

Entrapment Efficiency

Table 3: % Entrapment Efficiency.

Batch	Entrapment Efficiency
F1	11.54
F2	96.66
F3	95.16
F4	95.87

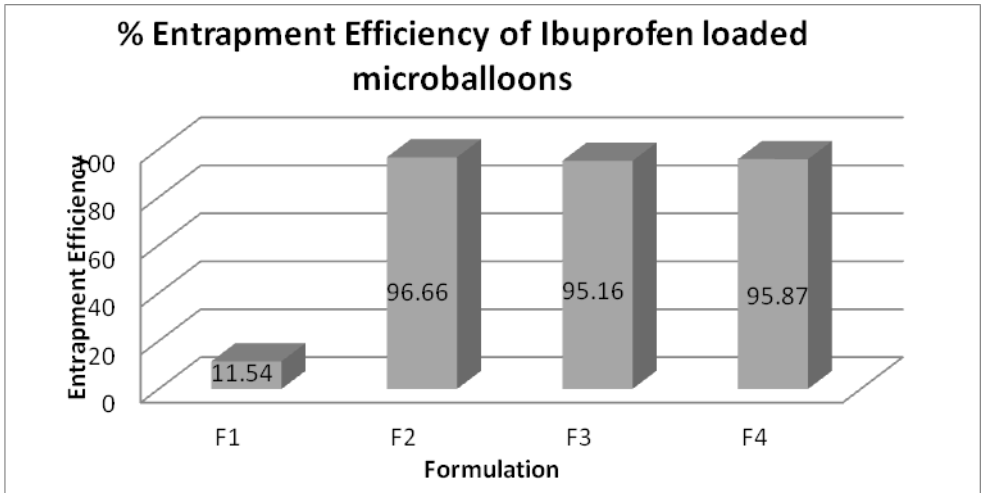

Figure 6: column diagram of % Entrapment efficiency.

Drug Loading Efficiency

Table 4: % Drug loading efficiency.

Batch	% Drug Loading Efficiency
F1	95.55
F2	90.6
F2	83.96
F4	55.84

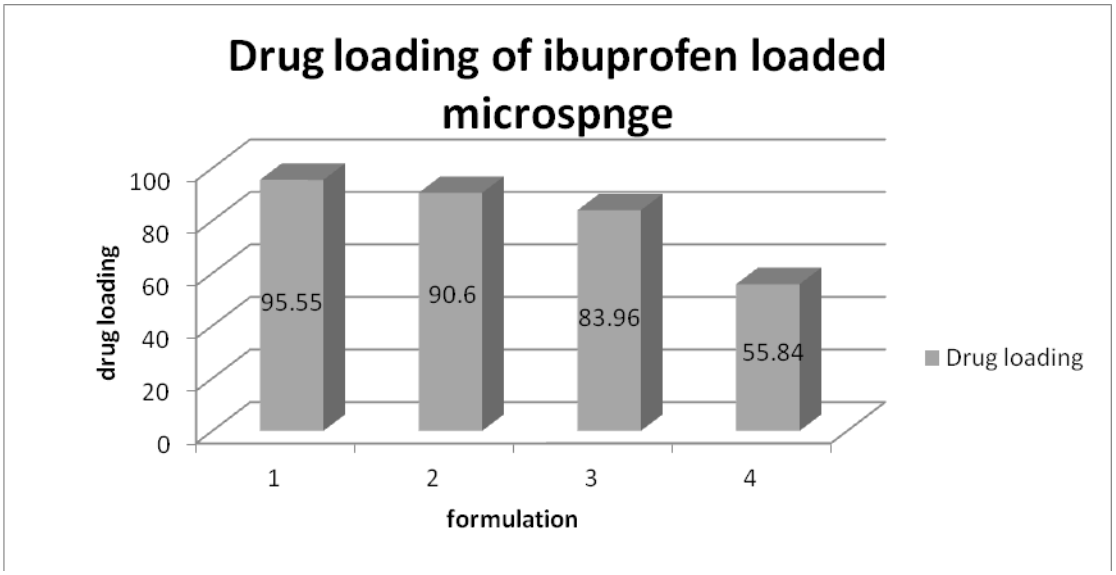

Figure 7: Column diagram for %Drug Loading Efficiency.

Contour Plots

Contour plots are diagrammatic representation of the values of the response

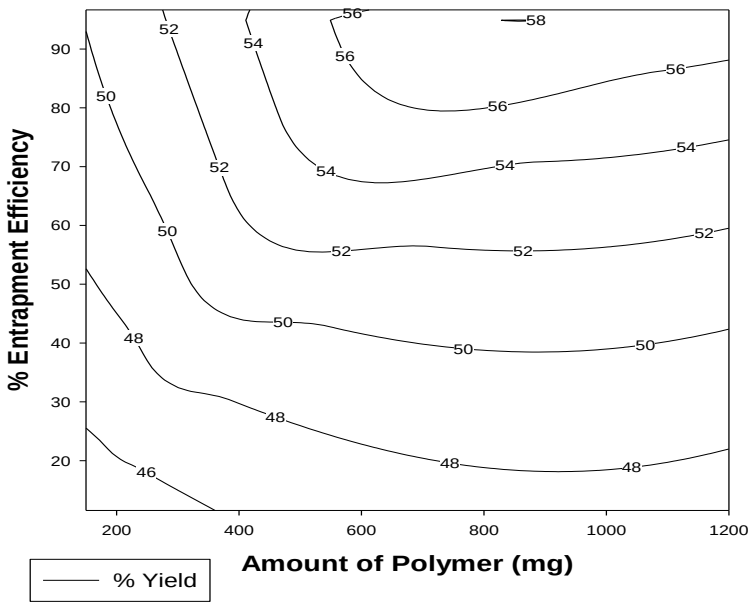

Figure 8: Contour plot showing the effect of polymer (ethyl cellulose) on %entrapment efficiency (Y1) and % yield(Y2).

Response Surface Plots

Response surface plots are very helpful in learning about both the main and interaction effects of the independent variables.

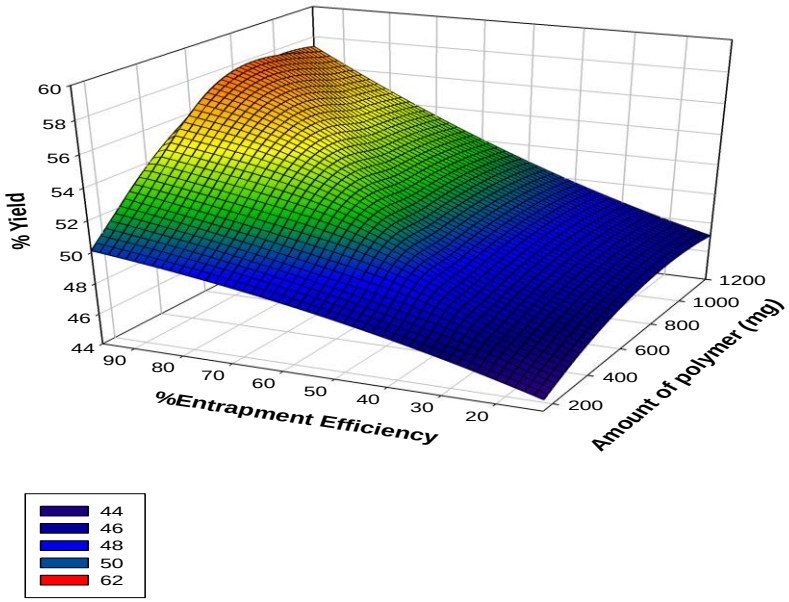

Figure 9: Response curve plot showing the effect of polymer (ethyl cellulose) on %entrapment efficiency (Y1) and % yield(Y2).

Floating Time: Floating time for all batches in 0.1 N HCL remains above 24hr.

In Vitro Release Study

Table 5: The in vitro release study carried out for a period of 1 to 12 hrs.

Time(hr)	%CDR
1	7.95
2	12.69
3	18.88
4	32.18
5	44.61
6	55.40
7	62.79
8	81.92
9	90.30
10	91.90
11	96.30
12	96.72

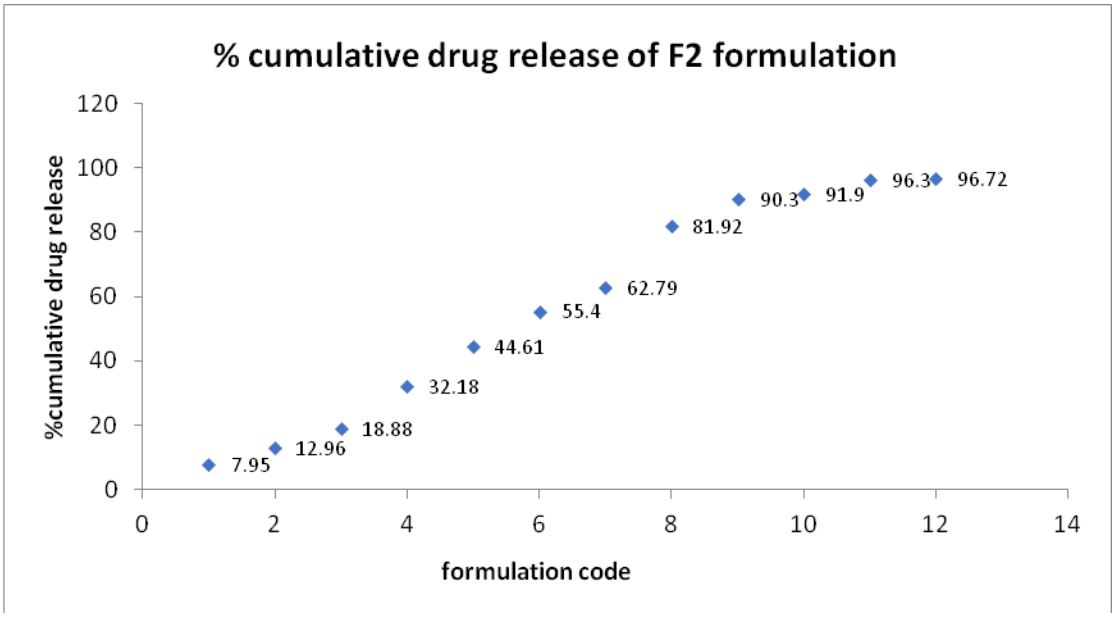

Figure 10: In vitro diffusion profile of F2.

Morphological Appearance

Figure 11: Flakes Shaped Morphological Appearance of F3 Formulation.

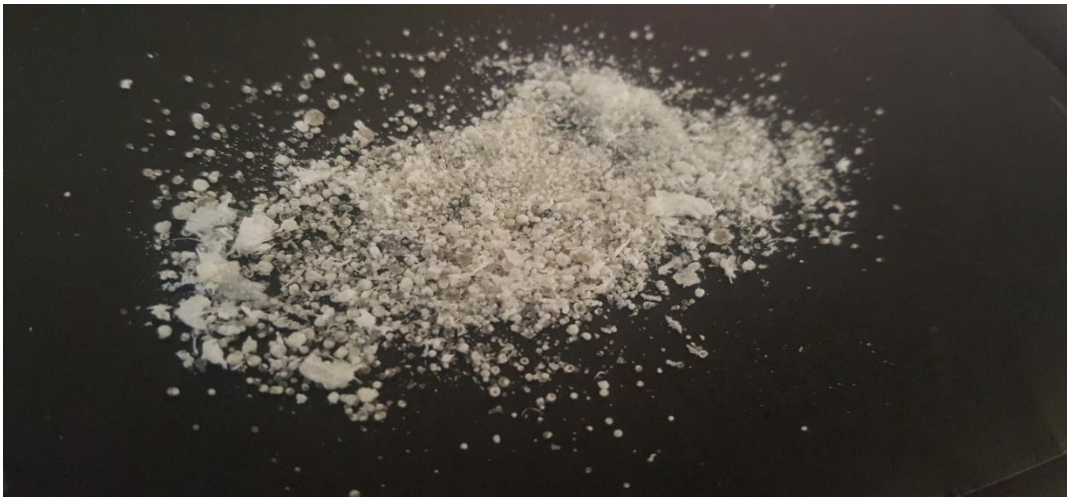

Figure 12: Spherical Shaped Morphological Appearance of F2 Formulation (Optimized Formulation).

Scanning Electron Microscopy

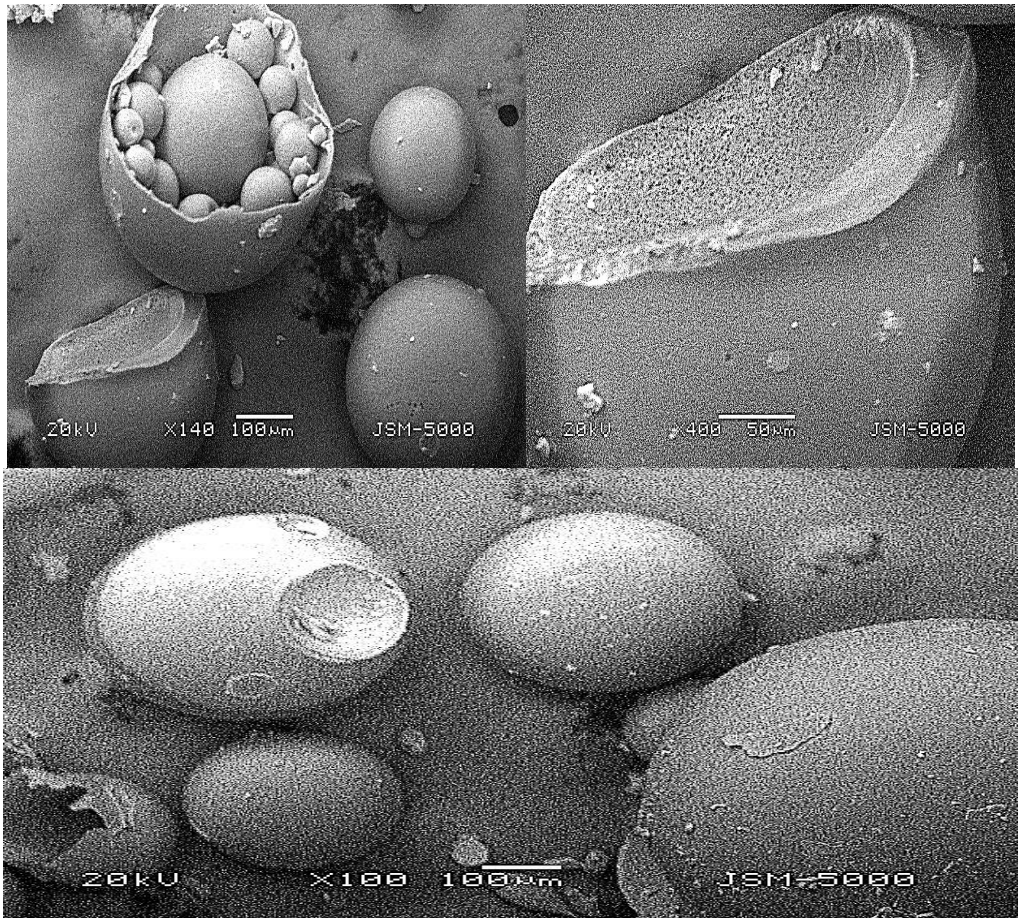

Figure 13: SEM Analysis of F2 Formulation.

Zeta Potential and Particle Size Distribution

Optimized Formulation F2 was evaluated for Zeta Potential and Particle Size Distribution which was obtained as -31.8mV and 1.44 µm respectively.

Stability Study

On the basis of this study it was considered that there was no significant change in the formulation F2 and so we can conclude that formulation was stable after 1-month study at accelerated stability study.

Table 6: Stability study data.

Sr. No.	Parameter	Before storage	After 1 month storage
1	Morphological Appearance	Buff White	Buff White
2	%Entrapment efficiency	96.66	95.16
3	% Drug release (12 hours)	96.72	95.35

DISCUSSION

The basic objective was to improve solubility rate by decreasing particle size and increase entrapment efficiency of Ibuprofen loaded microballoons. The preformulation study was performed and found good properties of Ibuprofen comparing with standard. The compatibility parameter was characterized by using FT-IR and found no interaction between drug and excipients. Formulation of Ibuprofen loaded microballoons were prepared by using different concentration of Polyvinyl alcohol (PVA) and Ethyl cellulose by using emulsion solvent evaporation technique. Total 4 batches were formulated. All 4 batches were evaluated for entrapment efficiency and practical yield. F3 and F4 batch though exhibit high yield and entrapment but are having Flakes formation and thus are not considered as optimized. Among all batches F2 shows maximum entrapment efficiency and practical yield was considered as optimized formulation. Optimized batch F2 was evaluated for Zeta Potential and Particle Size Distribution whose values are -31.8mV and 1.44 µm respectively. Batch F2 was charged for stability. After 1 months of accelerated study, samples were withdrawn and microballoons showed no significant changes in physical appearances, Entrapment Efficiency and drug release which indicate that the microballoons were stable.

CONCLUSION

The present research work concludes that the solubility of BCS class II drugs can be enhanced if delivered in the form of microballoons. The microballoons, also known as the hollow microspheres also facilitates better absorption of the drug from the upper GIT by remaining buoyant. In this work Ibuprofen was selected to treat inflammation effectively by formulating microballoons. This drug belongs to BCS class II in which solubility of the drug is a limiting factor for better absorption. An effort was made to formulate microballoons of Ibuprofen for improving the solubility and for gastroretention. The research work further concludes that the concentration of polymer ethyl cellulose 600mg and stabilizer PVA 1%w/v play a key role in the optimization of the formula. The % drug entrapment efficiency and practical vary with the different concentration of the polymer and the stabilizing agent. The microballoons of the Ibuprofen showed high % entrapment efficiency i.e. 96.66 and maximum drug loading 95.55. The process of optimization showed that the microballoons of Ibuprofen showed high entrapment at 1300 rpm. The work further concludes that the microballoons of the Ibuprofen can be a better drug delivery system for the treatment of inflammation.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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ABBREVIATIONS

GIT : Gastrointestinal tract
PVA : Poly Vinyl Alcohol
DCM : Dichloromethane
FTIR : Fourier Transform Infrared Spectroscopy
Rpm : rotation per minute
Ml : millilitres
Cm : centimetres
Hr : hour
SEM : scanning electron microscopy

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