RESEARCH PAPER

Formulation and Evaluation of Gastroretentive Drug Delivery System (GRDDS) of Aspirin Using Quality by Design and In-silico Study

Mr.Anand J.Purohit*[1], Sheelpriya Walde[2], Shakshi G. channe[3], Suhas Padmane[4], Raksha A. Purohit[5]

[1,3]Researcher , Gurunanak College of pharmacy, Nagpur

[2]Professor , Gurunanak College of pharmacy, Nagpur

[4]Associate Professor , Gurunanak College of Pharmacy , Nagpur

[5] Researcher, Department of pharmaceutical sciences -RTMNU nagpur

Abstract

The present study aimed to develop and evaluate a gastroretentive drug delivery system (GRDDS) of aspirin using a Quality by Design (QbD) approach, supported by in-silico molecular docking studies. Floating tablets were formulated to enhance gastric residence time and improve the bioavailability of aspirin. Critical material attributes and process parameters were optimized through a systematic QbD framework. The in-vitro evaluation included buoyancy, dissolution, and drug release studies. The optimized formulation showed a floating lag time of less than 1 minute, total buoyancy over 12 hours, and sustained drug release of 99.98% within 6 hours in 0.1N HCl at 37 °C. In-silico docking of aspirin with PDE7B protein revealed favorable binding interactions with residues H186, K190, and G113, suggesting possible neurotherapeutic potential. These findings highlight the feasibility of using QbD-driven formulation design and computational tools to improve aspirin's therapeutic performance through GRDDS.

Keywords

Aspirin, Gastroretentive Drug Delivery System (GRDDS), Floating tablets, Quality by Design (QbD), In-silico docking, PDE7B

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Introduction

Oral drug delivery remains the most common and patient-preferred route due to ease of administration, low cost, and wide patient compliance. However, rapid gastric emptying limits the bioavailability of drugs such as aspirin that are primarily absorbed in the stomach and upper intestine. Gastroretentive drug delivery systems (GRDDS) have been designed to prolong gastric residence, improving solubility, absorption, and therapeutic effectiveness. Floating drug delivery systems (FDDS) are among the most widely explored GRDDS as they remain buoyant in gastric fluids while releasing the drug in a

controlled manner. Aspirin, a commonly used NSAID, is an ideal candidate for GRDDS due to its narrow absorption window. This study applies QbD principles to optimize aspirin GRDDS tablets and further supports the study with in-silico molecular docking against PDE7B to explore potential neurotherapeutic benefits.

Materials and Methods

1. Determination of absorption maxima

A solution containing the concentration 10ug/ml drug was prepared in 0.IN HCL UV spectrum was taken using double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200-400nm

2. Preparation of calibration curve

100 mg of aspirin pure drug was dissolved in 100 ml of 0.1N HCL then take 10 ml on this solution volume make up to 100 ml using 0.1N HCL The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 2,4,6,8,10 µg/ml of per ml of solution. The absorbance of the above dilutions was measured at 272 nm by using UV- Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R2) which determined by least- square linear regression analysis.

3. Physiochemical interaction[61]

To determine the compatibility of aspirin with different excipient FTIR spectroscopy and DSC thermal analysis were performed. FTIR spectra were obtained using a KBr pellet in FTIR spectrophotometer (Shimadzu-8400S, Kyoto, Japan). Transmittance (%T) was recorded in the spectral region of 500–4500 cm1 using a resolution of 4 cm1 and 40 scans. DSC analysis was used to characterize the drug by examining endothermal transitions from the thermogram obtained. It involved the heating signal to a sample and a reference. DSC (TA Instruments, New Castle, DE) analyses were carried out on a nitrogen flow of 50 mL/min and a heating rate 10 C/min from 20 to 300 C.

4. Preformulation parameters

a.Bulk density

It is a ratio of the mass of untapped powder to tapped powder. It is expressed in gram per milliliter (g/ml). It may also be expressed in grams per cubic centimeter (g/cm3). It can be determined by the volume of sieved powder sample into a graduated cylinder.

b.Tapped density

It is increased bulk density acquired after mechanically tapping a cylinder containing the powder sample. Practically, it is done by using bulk density apparatus in which graduated cylinder containing powder sample is tapped mechanically after noting the initial mass or volume. Then after 100 taps, volume or mass is noted down and then after 50 taps, volume or mass is observed until volume gets constant. The mechanical tapping is established by raising the graduated cylinder and let it drop by its own mass.

c.Angle of repose

It is a parameter used to evaluate interparticle force. Practically, it is measured by using funnel with wide mouth open is placed at distance of minimum 10cm above the platform and a piece of paper is placed under the funnel. Then pour the powder sample in funnel and let it flow through and gets collected on the paper. And outline the boundary where powder sample is present and measured the height of peak and diameter obtained with ruler. Then by applying following formula, angle of repose (Ɵ) can be estimated.

$\theta = \tan{-1}\ h/\ r$

When angle of repose is less than 25 degree, then flow is said to be excellent and if angle of repose is more than 40 degree, then flow is said to be poor.

Table : Angle of Repose values (as per USP)

Sr. No.	Angle of repose (degree)	Flow Character
1	<25	Excellent
2	25-30	Good
3	31-38	Passable
4	>38	Poor

a. Carr's index:

Carr's index evaluates the capability of powder to combine or unite. It can be calculated by following formula:

$$Carr'\ s\ index = \frac{Tapped\ volume - Bulk\ volume}{Tapped\ volume}$$

Bulk volume is a volume of powder having no direct contact whereas tapped volume can be obtained by tapping in bulk density apparatus. A Carr's index less than 20% meant to have better flow.

Table 6: Carr's index values (as per USP)

Sr. No.	Carr's Index (%)	Flow Character
1	0-10	Excellent
2	11-15	Good
3	16-20	Fair
4	21-25	Passable
5	26-31	Poor
6	32-37	Very poor
7	>38	Extremely poor

b.Hausner's ratio

It is a ratio between the tapped density and bulk density. It is used to measure cohesiveness between particles. It can be calculated by following formula:

$$Hausner's\ ratio = Tapped\ density / Bulk\ density$$

Ratio lower than 1.25 .

Table 7: Hausner's ratio values (as per USP)

Sr. No.	Hausner Ratio	Flow Character
1	1.00-1.11	Excellent
2	1.12-1.18	Good
3	1.19-1.25	Fair
4	1.26-1.34	Passable
5	1.35-1.45	Poor
6	1.46-1.59	Very Poor
7	>1.60	No flow

2.Formulation of tablet by Direct Compression:

Aspirin floating tablets were prepared by direct compression method using excipients and polymers to release the drug sustainably after administration. Accurately weighed quantities of excipients were placed in a mortar and gradually mixed with pestle for constant kneading to ensure homogeneous mass. The powder was passed through sieve no. 40 and mixed with the drug blend which was also passed through sieve no. 40. Then the powder was lubricated with magnesium stearate and talc. Then the mixture equivalent to 300mg was directly compressed into tablets with punch no. 13 on a Tablet punching machine.

a. Weight Variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

1.Plackett-Burman Design

Design Summary

Factors:	4	Replicates:	1
Base runs:	13	Total runs:	13
Base blocks:	1	Total blocks:	1

Center points: 1

Quality by Design (QbD)

Std	Run	PtT	Blo	HPM	Sodium	Cit	MCC	Floa	%Dru

Order	**Order**	**ype**	**cks**	**CK100**	**bicarbonate**	**ricacid**		**ting time (min)**	**grelease**
9	1	1	1	150	20	20	150	250	78
6	2	1	1	200	30	40	100	270	80
13	3	0	1	175	25	30	125	340	99
10	4	1	1	200	20	20	100	290	82
12	5	1	1	150	20	20	100	240	70
5	6	1	1	200	30	20	150	300	90
3	7	1	1	150	30	40	100	260	85
1	8	1	1	200	20	40	100	320	92
7	9	1	1	150	30	40	150	290	87
11	10	1	1	150	30	20	100	250	78
2	11	1	1	200	30	20	150	310	92

8	12	1	1	150	20	40	150	280	85
4	13	1	1	200	20	40	150	300	97

Formulation of Trial batches by QbD

Figure 9: Formulation of Trial batches by QbD

Figure : Formulation of floating tablet

1.1Evaluation of post compression parameters for prepared tablets:

Average weight of tablets (mg) (IP)	Average weight of tablets (mg) (USP)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than 250	More than 324	5

Tablel: Pharmacopoeial specifications for tablet weight variation

a. Thickness

The thickness of the ten tablets was measured in mm by using Vernier calipers.[65]

b. Hardness:

The hardness of 10 tablets was measured using Monsanto Hardness tester.[66] for four minutes. After four minutes the tablets were weighed again.[67]

c. Friability:

The % friability of the tablets was determined using Roche friabilator. 10 tablets were initially weighed and transferred to the friabilator. The friabilator was operated at 25 rpm.

F= Winitial- Wfinal/Winitial× 100

d. In-vitro Buoyancy studies

The tablets were placed in a beaker containing 0.1N hydrochloride solution (200 ml). The time required for the tablet to rise to the surface was determined as floating lag time and time period for which tablet remains at surface was determined as total floating time.[68]

e. Swelling Index of tablets

The swelling of floating tablets were determined by swelling the tablets in 0.1 N HCl at the room temperature. Swollen weight of the tablet determined then swelling index was calculated by following equation. [69-70]

Swelling Index = WT - WO/WO Where, W0= initial weight of tablet

WT= final weight of tablet

f. In vitro Buoyancy study

The in vitro buoyancy was determined by floating lag time, and total floating time.

g. Floating lag time (FLT)

The NA tablets were placed in a beaker containing 250ml of 0.1N HCl and the time (sec) required to float the tablet was observed and recorded as FLT.

h. Total floating time (TFT)

The time (hr) up to which the NA tablet remains buoyant was noted and recorded as TFT.

i. In vitro drug release study

Dissolution test parameters:

Apparatus: USP-II, Paddle Method Dissolution medium: 900 ml of 0.1 N HCl Rotation speed: 50 rpm

Temperature: 37 0.5° C Sampling volume: 5 ml

Sampling intervals (hrs): 1, 2, 3, 4, 5, 6 hrs

Procedure

900ml of 0.1 HCL was placed in vessel and the USP apparatus -II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 6 hours and then the medium 0.1 N HCL was taken and process was continued from 0 to 6 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with media and analyzed by spectrophotometric ally at 272 nm using UV-spectrophotometer.

Kinetic model fitting

An appropriate drug release test is required to characterize the drug product and ensure batch to batch reproducibility and consistent pharmacological/biological activity and to evaluate scale up and post approval changes such as manufacturing site changes, component and composition changes. The release of drug from a sustained release formulation is controlled by various factors through different mechanism such as diffusion, erosion or osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems. In order to characterize the kinetics of drug release from dosage forms several model dependent methods are reported by various researchers. The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modelling. Linear models include Zero order, Higuchi, Hixon - Crowell, Quadratic and Polynomials, where as the nonlinear models include First order, Weibull, KorsMeyer - Peppas, Logistic etc.

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and Reference dissolution profiles are as follows:

- Zero order kinetics
- First order kinetics
- Korsmeyer-Peppas model
- Higuchi model

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation:

$$W0 – Wt = K0t$$

Where, W0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant. Dividing this equation by W0 and simplifying:

$$ft = k0t$$

Where ft = 1 – (Wt /) and ft represents the fraction of drug dissolved in time t and k0 the apparent dissolution rate constant or zero order release constant in this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled. In this way a graphical relationship between ft versus time is established to get the Zero order constant from the slope. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of transdermal systems as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

A. First order kinetics

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$Log\ Qt = Log\ Q0 - K1t/2.303$$

Where Qt is the amount of drug released in time t, Q0 is initial amount of drug in the solution and K1 is the first order release rate constant. In this way a graphical relationship is established between log percent drug remaining versus time to get the First order constant from the slope. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices release the

drug in a way that is proportional to the amount of drug remaining in its interior, in such a way, that the amount of drug released by unit of time diminishes.

B. Korsmeyer Peppas model:

Korsmeyer et al., (1983) developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t). Qt/Qα = Kkt n Where Kk is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism. For matrix tablets, an n value of ~0.5 indicates diffusion – controlled mechanism while an n value of ~1.0 indicates erosion. Hariharan et al., 1997 a suggested that if the value of n is 0.5, it indicates Fickian transport, a value of 0.5 and 1.0 non-Fickian transport, and the values close to 1.0 indicate that the system is releasing drug in a zero-order manner regardless of the actual mechanism of release (Table 9).

C. Higuchi Model:

$Qt = KHt^{½}$

Where Qt = the amount of drug released at time t and KH = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time and the concentration indicates that the drug release follows strictly Fickian diffusion. For purpose of data treatment, the above equation is usually reduced to:

$Q = Kt^{½}$

Therefore a plot of amount of drug released versus the square root of time should be linear, if drug release from the matrix is diffusion controlled. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time. An important advantage of the above equation is its simplicity.

(a) Ligand and Protein preparation:

The drug molecule aspirin was betrieved from Auto cad 4.0 software. The energy minimization was done by PRODRG Server [76]. The protein PDE7B (cAMP-specific 3',5'-cyclic phosphodiesterase 7B) is a crucial regulator of many critical physiological processes and didn't have the three-dimensional X-ray structure. This protein has a theoretical model which was old and removed from the PDB entries (1LXW) in 2002 (https://www.modelarchive.org/doi/10.5452/ma-ca9f6). Hence, a swiss model technique was used to develop a three dimensional modelled structure [77]. The sequence of protein PDE7B (UniprotKB ID:Q9NP56) was retrieved and used to identify the template structure from the PDB source. The best-fit template (69.62%) for the protein sequence was identified using BLAST

search and its PDB entry is 3G3N. The possible ligand binding sites of the modelled target receptor was explored by Computer Atlas of Surface Topology of proteins (CASTp) server.

(b) Docking analysis:

The docking analysis was carried out using Auto cad 4.0[79]. The searching grid extended above the preferred target protein and the grid box was set as 80*80*80 in the XYZ angle; hydrogens were added to the ligand moieties. Kollman charges were assigned and atomic salvation parameters were added to the protein atoms. Polar hydrogen charges of the Gasteiger-sort were allocated and the nonpolar hydrogens were combined with the carbons and the internal degrees of flexibility and torsions were set to the protein molecule. The compound aspirin was docked to target modelled protein PDE7B with the molecule considered as a rigid body and the ligands being flexible. Evaluation of the results was done by sorting the different complexes concerning the predicted binding energy. All the images and protein-ligand interactions were visualized using PyMOL, (http://www.pymol.org).

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Table 10: Drug transport mechanism at various release exponent (n) values

Release exponent (n)	Drug transport mechanism	Rate as function of time
0.5	Fickian diffusion	t-0.5
0.5< n<1.0	Anomalous transport (nonfickian)	t n-1
1.0	Case-II transport	Zero-order release

Higher than 1.0	Super Case-II transport	tn-1

This type of analysis of release behaviour is valuable to the formulator for comparative purposes (Hariharan et al., 1997). The release exponent can be obtained from the slope and the Constant (Kk) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

G.Higuchi Model: [75]

$Qt = KHt^{1/2}$

Where Qt = the amount of drug released at time t and KH = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time and the concentration indicates that the drug release follows strictly Fickian diffusion. For purpose of data treatment, the above equation is usually reduced.

RESULTS AND DISCUSSION

1.Construction of Standard calibration curve of Aspirin in 0.1N HCL

An UV- Visible Spectrophotometric method was used for estimation of Aspirin. A solution of Aspirin (10 µg/mL) was scanned in the wavelength range of 200-400 nm and found to have maximum absorption (λ max) at 272 nm. Standard stock solutions of pure drug containing 100mg of Aspirin/100mL were prepared and making up the volume with 0.1N HCl solution. The working standard solutions were obtained by dilution of the stock solution in 0.1N HCl. The standard curve for Aspirin was prepared in the concentration range of 2- 10 µg/mL at the selected wavelength of 272 nm. Their absorptivity values were used to determine the linearity (Table 10). Solutions were scanned and Beer Lamberts law limit was obeyed in concentration range of 2- 10µg/ml.

Table 11: Standard Calibration graph values of Aspirin in 0.1N HCl at λ max 272 nm

Sr. no.	Concentrations(µg/ml)	Absorbance
0	0	0
1	2	0.128
2	4	0.242
3	6	0.349
4	8	0.474
5	10	0.603

Standard plot of Aspirin plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown figure

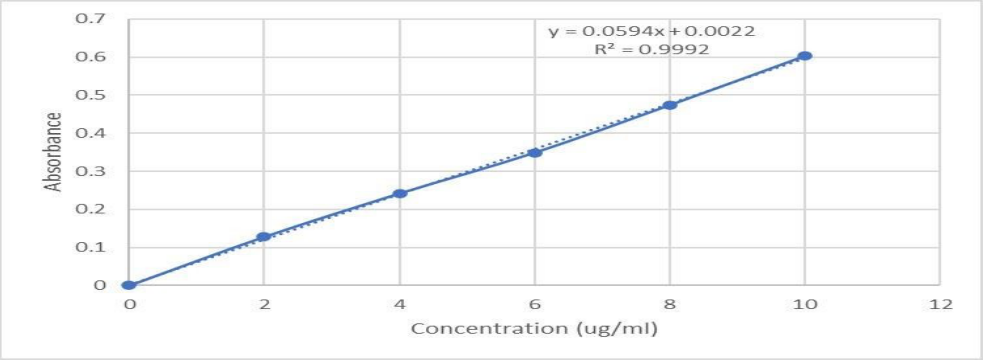


Figure 11: Standard calibration curve of Aspirin in 0.1N HCl

Solubility of aspirin

Excess amount of Aspirin was placed in 0.1 N HCl in order to determine its solubility. The sample was shaken for 24 hrs at 37 °C in a horizontal shaker. Aspirin is freely soluble in 0.1N HCL and Distilled water is observed.

Acetylsalicylic acid is slightly soluble in water, with a limit of solubility reported as approximately 3 mg/ml at 25 Deg C.

Quality by design

a. Factorial Regression: Floating time (min) versus HPMC K100, Sodium bicarbonate, Citric acid, MCC, PtType

Coded Coefficients

Term	Effect	Coef	SE Coef	T-Value	P-Value	VIF
Constant		280.00	4.88	57.38	0.000	
HPMC K100	36.67	18.33	4.88	3.76	0.007	1.00
Sodium bicarbonate	0.00	0.00	4.88	0.00	1.0000	1.00
Citric acid	13.33	6.67	4.88	1.37	0.214	1.00

MCC	16.67	8.33	4.88	1.71	0.131	1.000
Ct Pt		60.0	17.6	3.41	0.011	1.000

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
16.9031	81.35%	68.03%	*

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	5	8723.1	1744.62	6.11	0.017
Linear	4	5	1	4	0

		4000.0	3500.000	.72	.036
HPMC K100	1	4033.3	4033.333	14.12	0.007
Sodium bicarbonate	1	0.0	0.000	0.000	1.000
Citric acid	1	533.3	533.333	1.87	0.214
MCC	1	833.3	833.333	2.92	0.131
Curvature	1	3323.1	3323.108	11.63	0.011
Error	7	2000.0	285.71		
Lack-of-Fit	6	19	32	6.	0.

		50.0	5.00	50	292
Pure Error	1	50.0	50.00		
Total	12	1072323.1			

Regression Equation in Uncoded Units

Floating time (min) = 90.0 + 0.733 HPMC K100 - 0.000 Sodium bicarbonate + 0.667 Citric acid + 0.333 MCC + 60.0 Ct Pt

Fits and Diagnostics for Unusual Observations

Obs	Floating time (m	Fit	Resid	Std Resid

	i n)					
2	270.0	296.7	-26.7	-26.07	R	
3	340.0	340.0	0.0	*		X

Alias Structure

Factor	Name
A	HPMC K100
B	Sodium bicarbonate
C	Citric acid

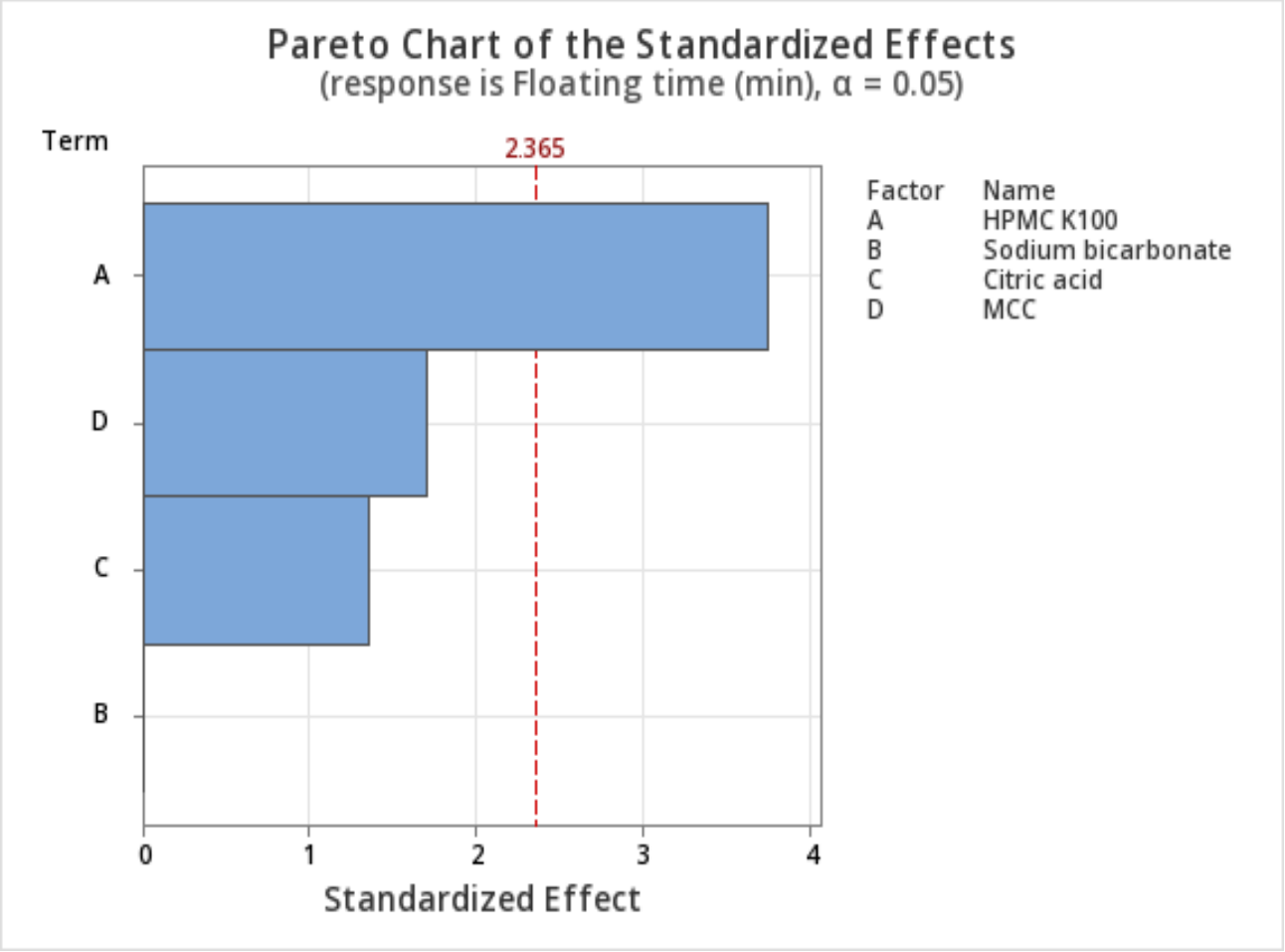
Aliases

I - 0.33 ABC + 0.33 ABD - 0.33 ACD - 0.33 BCD - 0.33 ABCD

A - 0.33 BC + 0.33 BD - 0.33 CD - 0.33 BCD - 0.33 ABCD

B - 0.33 AC + 0.33 AD - 0.33 CD - 0.33 ACD - 0.33 ABCD

C - 0.33 AB - 0.33 AD - 0.33 BD - 0.33 ABD + 0.33 ABCD



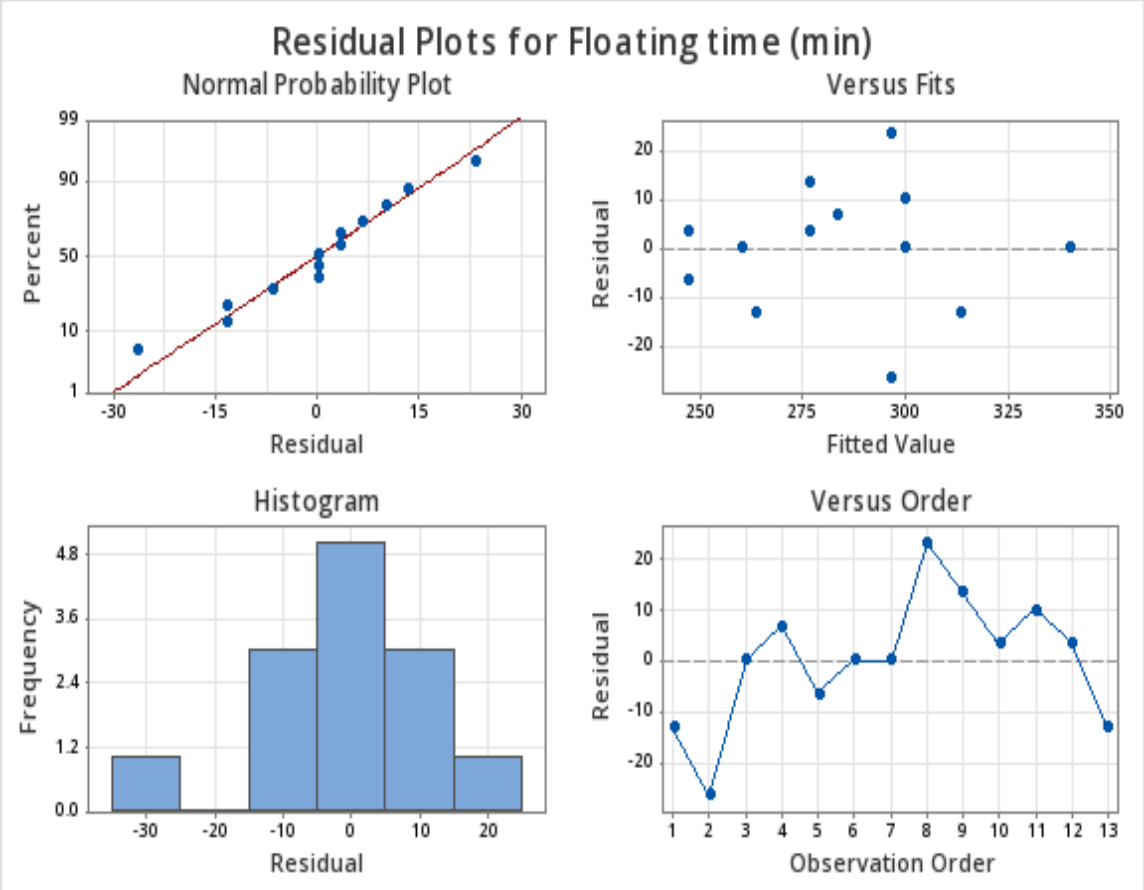


Figure 12: Pareto chart of the standardized effects and Residual plots for floating time(min)

b. Factorial Regression: % Drug release versus HPMC K100, Sodium bicarbonate, Citric acid, MCC, PtType

Coded Coefficients

Term	Effect	Coef	SE Coef	T-Value	P-Value	VIF
Constant		84.67	1.37	61.73	0.000	
HPMC K100	8.3	4.1	1.3	3.0	0.0	1.0

	3	7	7	4	19	0
Sodium bicarbonate	1.33	0.67	1.37	0.49	0.642	1.00
Citric acid	6.00	3.00	1.37	2.19	0.065	1.00
MCC	7.00	3.50	1.37	2.55	0.038	1.00
Ct Pt		14.33	4.94	2.90	0.023	1.00

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
4.75094	80.64%	66.82%	*

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	5	658.308	131.662	5.83	0.019
Linear	4	468.667	117.167	5.19	0.029
HPMC K100	1	208	208	9.2	0.0

		.3333	.3333	3	19
Sodium bicarbonate	1	5.333	5.333	0.24	0.642
Citric acid	1	108.000	108.000	4.78	0.065
MCC	1	147.000	147.000	6.51	0.038
Curvature	1	189.641	189.641	8.40	0.023
Error	7	158.000	22.571		
Lack-of-Fit	6	156.000	26.000	13.00	0.209
Pure Error	1	2.0	2.0		

		0 0	0 0
Total	1 2	8 1 6 . 3 0 8	

Regression Equation in Uncoded Units

% Drug release	=	25.7 + 0.1667 HPMC K100 + 0.133 Sodium bicarbonate + 0.300 Citric acid + 0.1400 MCC + 14.33 Ct Pt

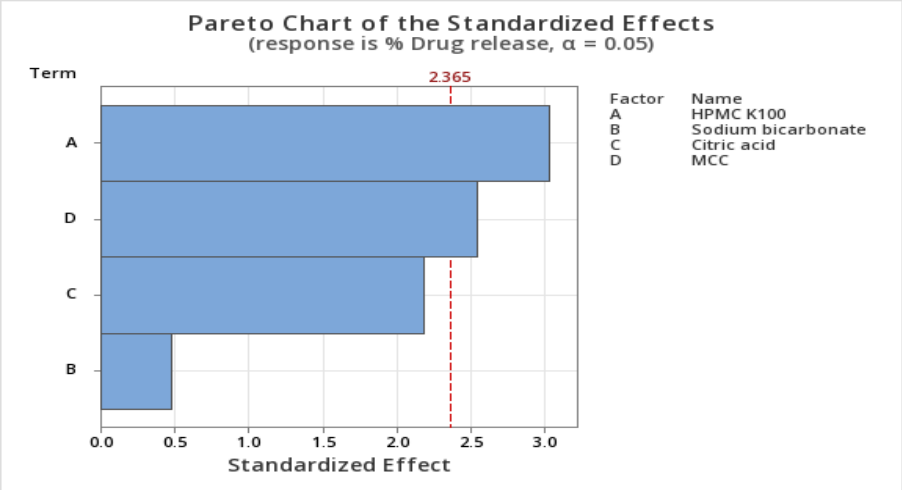
Fits and Diagnostics for Unusual Observations

Obs	% Drug release	Fit	Resid	Std Resid		
2	80.000	89.000	-9.000	-2.48	R	
3	99.000	99.000	-0.000	*		X

Alias Structure

Factor	**Name**
A	HPMC K100
B	Sodium bicarbonate
C	Citric acid
D	MCC

Aliases
I - 0.33 ABC + 0.33 ABD - 0.33 ACD - 0.33 BCD - 0.33 ABCD
A - 0.33 BC + 0.33 BD - 0.33 CD - 0.33 BCD - 0.33 ABCD
B - 0.33 AC + 0.33 AD - 0.33 CD - 0.33 ACD - 0.33 ABCD
C - 0.33 AB - 0.33 AD - 0.33 BD - 0.33 ABD + 0.33 ABCD
D + 0.33 AB - 0.33 AC - 0.33 BC - 0.33 ABC - 0.33 ABCD



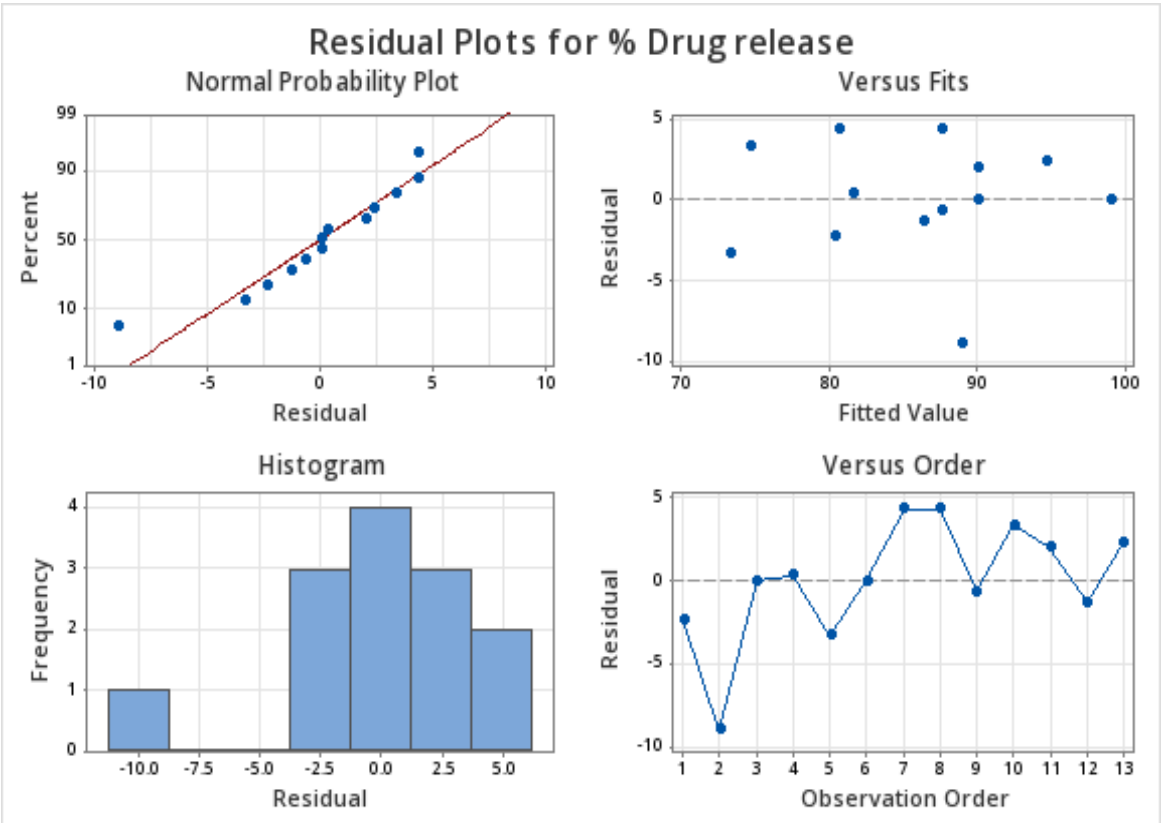


Figure 13: Pareto chart of the standardized effects and Residual plots for % drug release

a. Response Optimization: % Drug release, Floating time (min)

Parameters

Response	Goal	Lower	Target	Upper	Weight	Importance
% Drug release	Target	70	100	110	1	1
Floating time (min)	Target	240	360	396	1	1

Solution

Solution	HPMCK100	Sodium bicarbonate	Citric acid	MCC	% Drug release	Floating time	Composite Desirability

		e			s e F i t	(m i n) F it	si ra bi lit y
1	175	25	30	125	99	340	0.897527

Multiple Response Prediction

Variable	Setting
HPMC K100	175
Sodium bicarbonate	25
Citric acid	30
MCC	125

Response	Fit	SE Fit	95% CI	95% PI
% Drug release	99.00	4.75	(87.77, 110.23)	(83.11, 114.89)

Floating time (min)	340.0	16.9	(300.0, 380.0)	(283.5, 396.5)

Final Optimized Batch

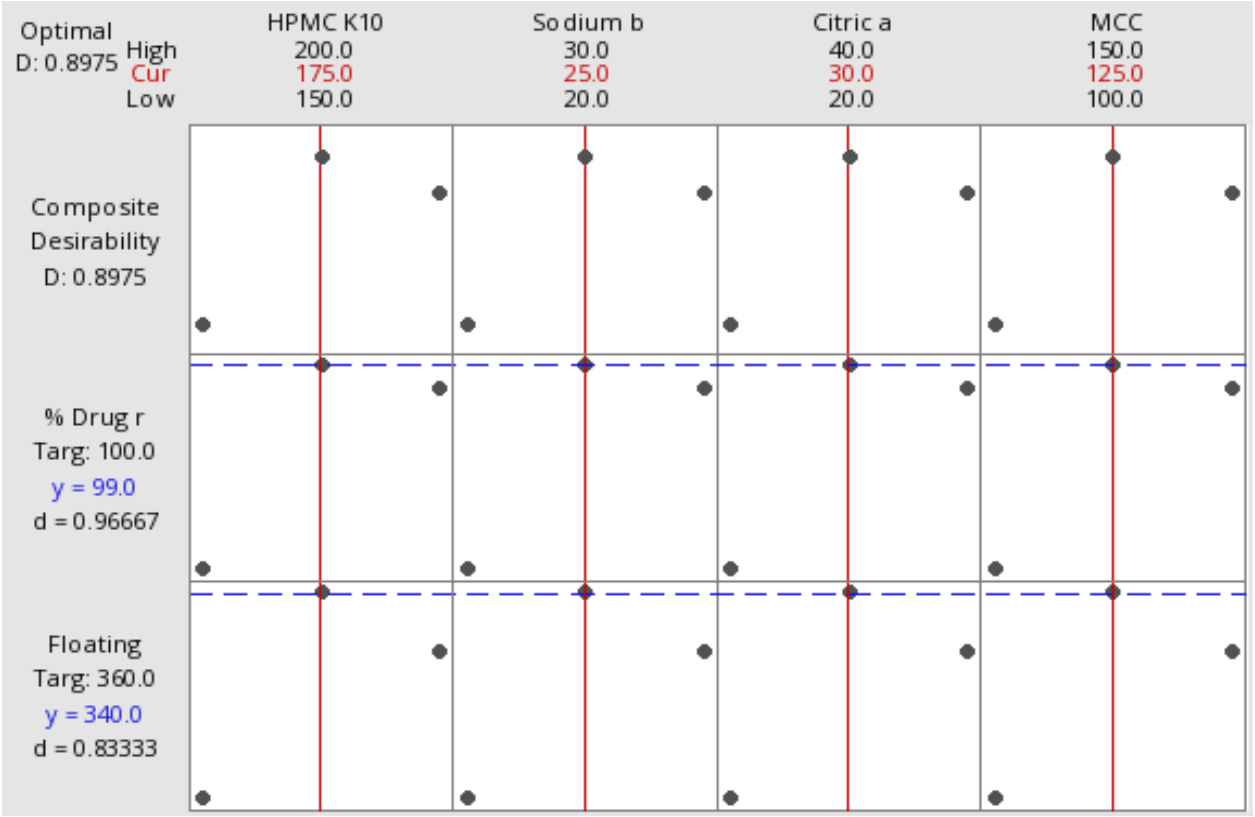


Figure 14: Optimized batch by QbD

1.1 Drug-excipient compatibility studies

A. Fourier transform infrared (ft-ir) spectroscopy

The thermal behavior of pure drug and the respective excipients and the binary mixture of drug and excipients are compared in the FT-IR thermograms.

The infrared (FT-IR) spectra were obtained in KBr pellet method using a perkinelmer FT-IR spectrometer spectrum from 4000 to 400 cm^{-1}. Typical FT-IR spectra of pure citric acid (Figure 15) showed absorption at the following wave number in cm^{-1} 1561.44, 1529.62,1427.39, 1388.81, & 1052.21.

Typical FT-IR spectra of pure HPMC K100 (Figure 16) showed absorption at the following wave number in cm^{-1} 1589.41,1561.44,1529.62,1388.81,1424.49,1242.21 & 1291.40

Typical FT-IR spectra of pure Sodium bicarbonate (Figure 17) showed absorption at the following wave number in cm^{-1} 2455,2360.11,1932.76,1691,1607,1450,1410,1249,1047,1032.

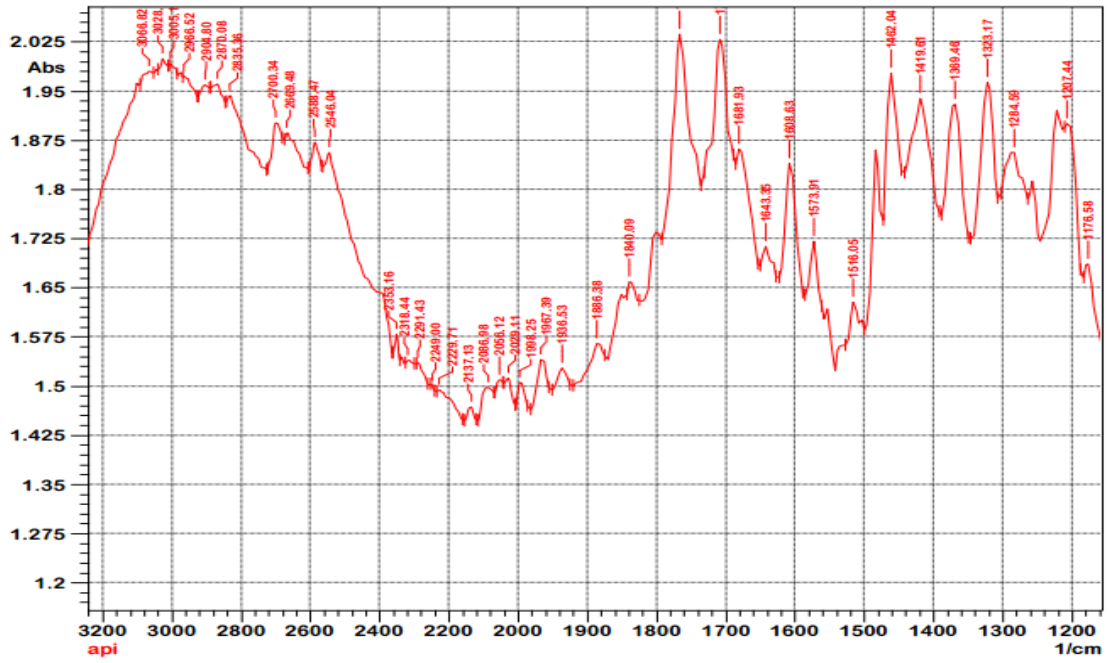


Figure : FTIR spectrum of Aspirin

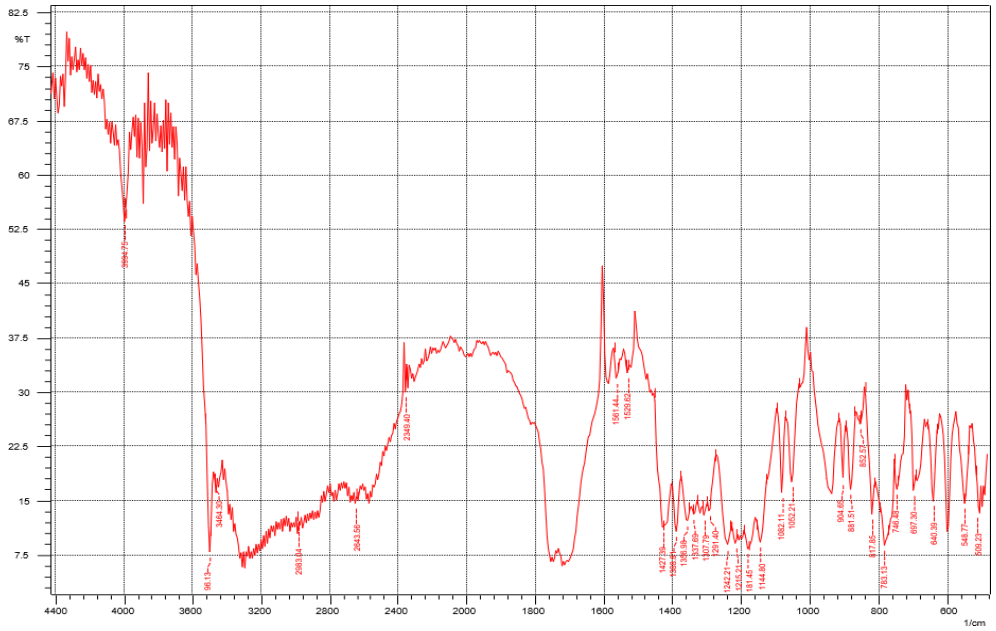


Figure: FTIR spectrum of Citric acid

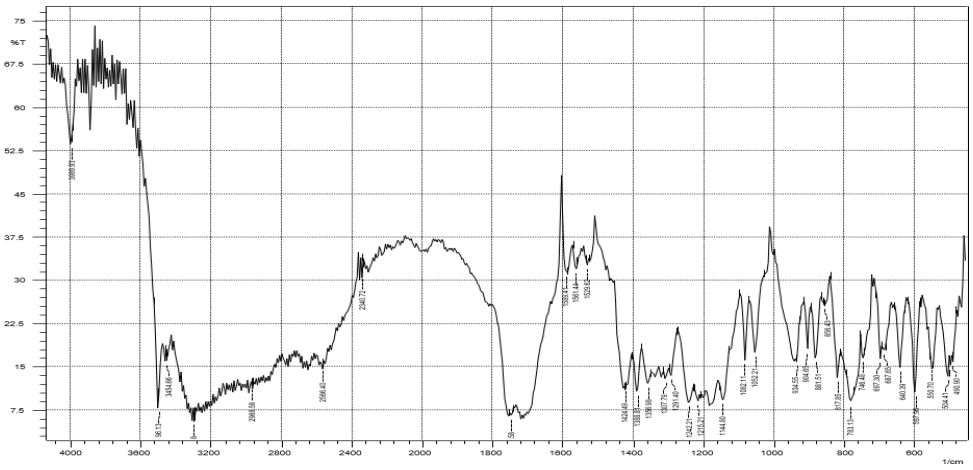


Figure : FTIR spectrum of HPMC K100

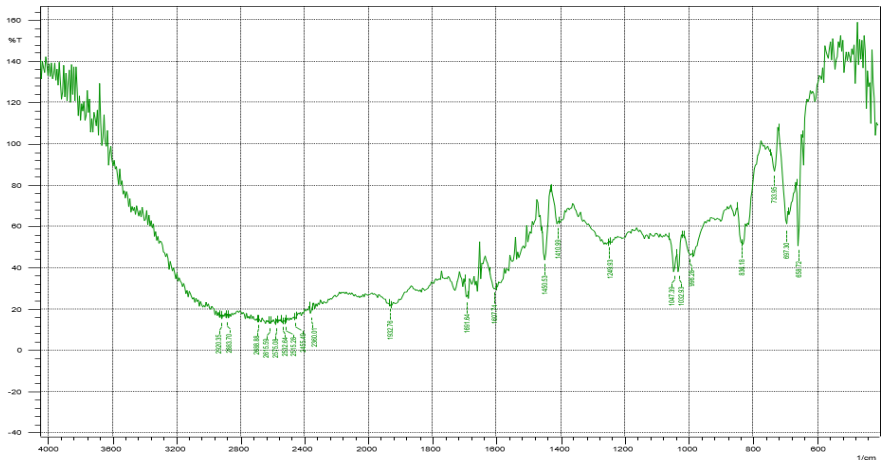


Figure: FTIR spectrum of Sodium bicarbonate

FTIR were used to investigate the compatibility between Aspirin with excipients. The results demonstrate that there is no interaction between drug and excipients (HPMC K100M, Sodium bicarbonate, Citric acid). Hence Aspirin with these excipients could be used to formulate the floating tablets.

B. Differential Scanning Calorimetry (DSC)

Module: DSC

Data Name: Aspirin

Measurement Date: 28-05-2024

Temperature Program: Comment: Cel/min min

Sample Name: Aspirin

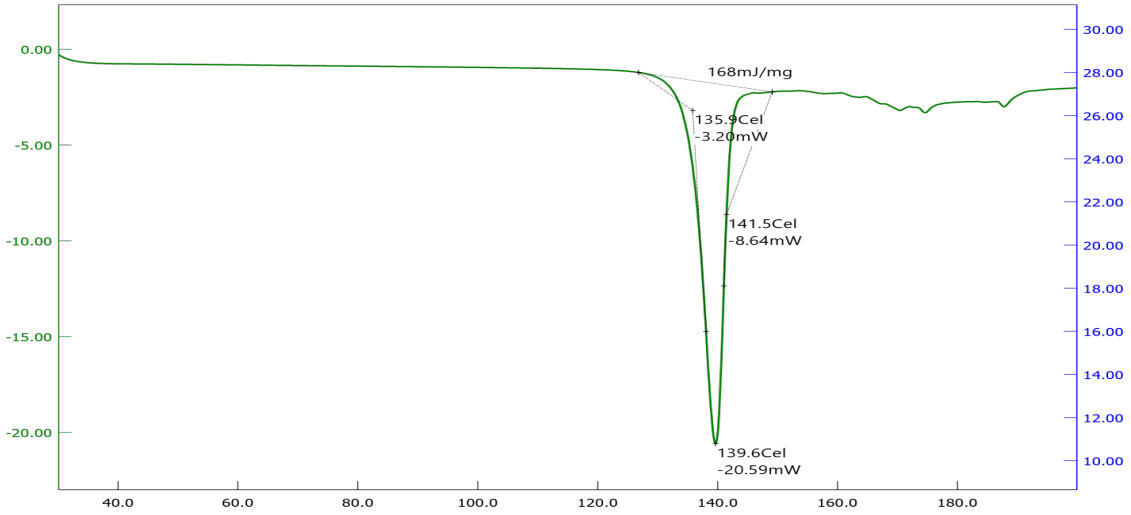


Figure : DSC of Aspirin

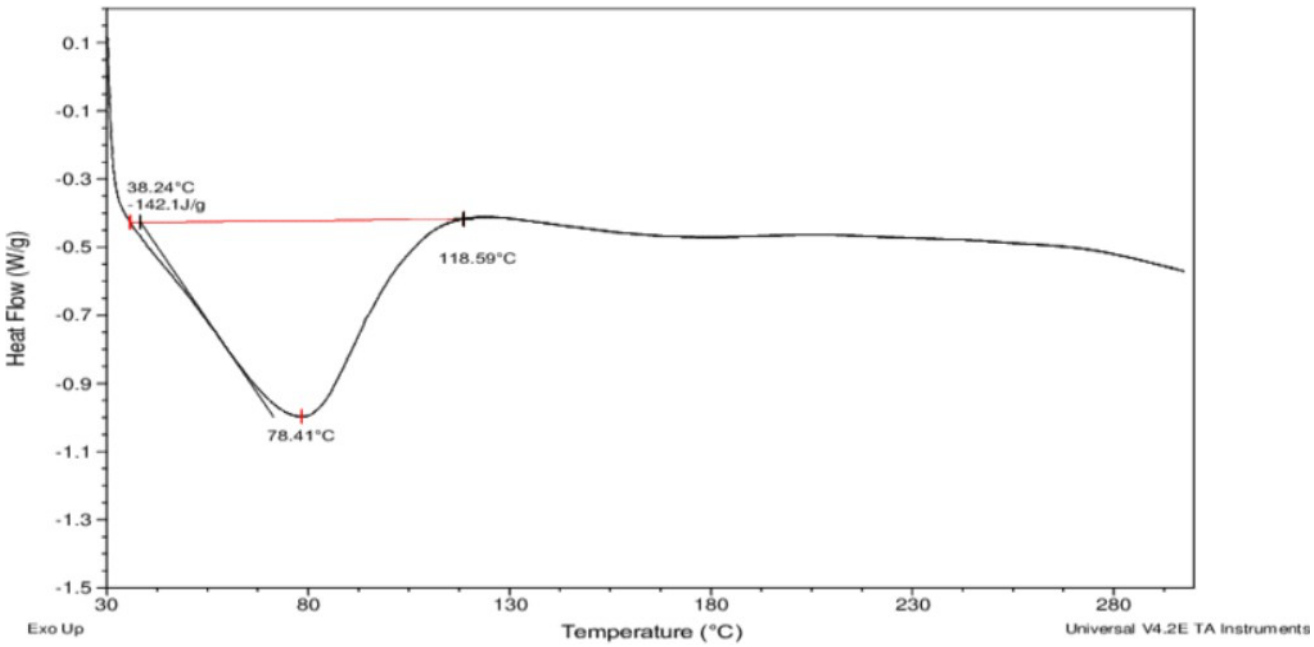


Figure : DSC of HPMC K100

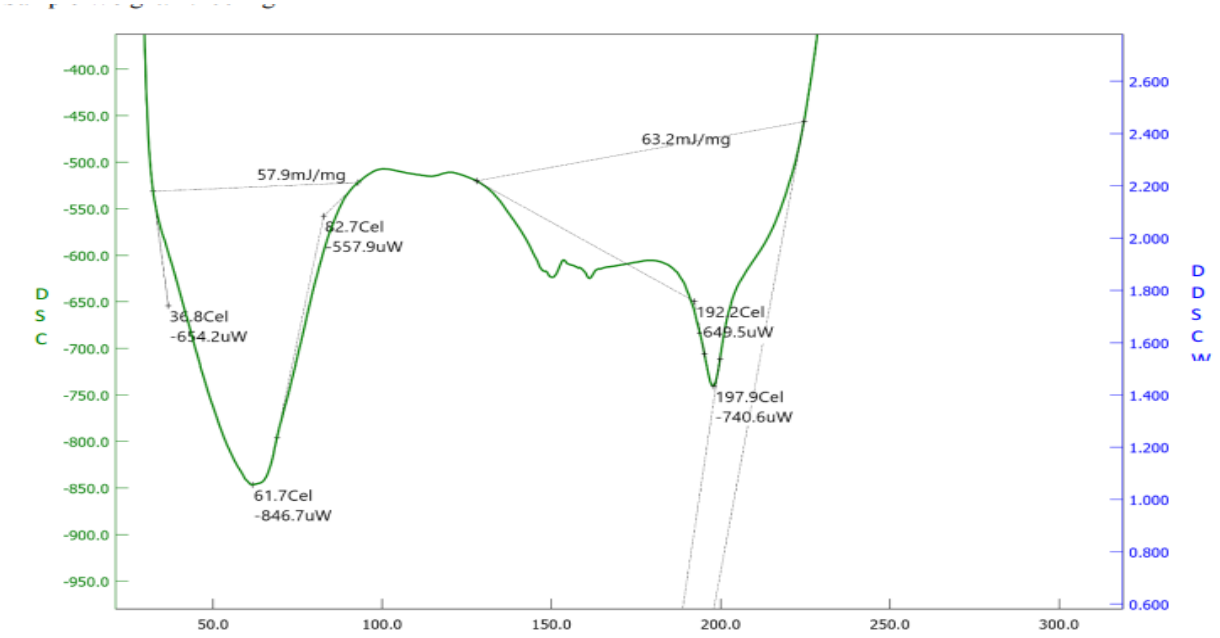


Figure : DSC of Aspirin tablet formulation

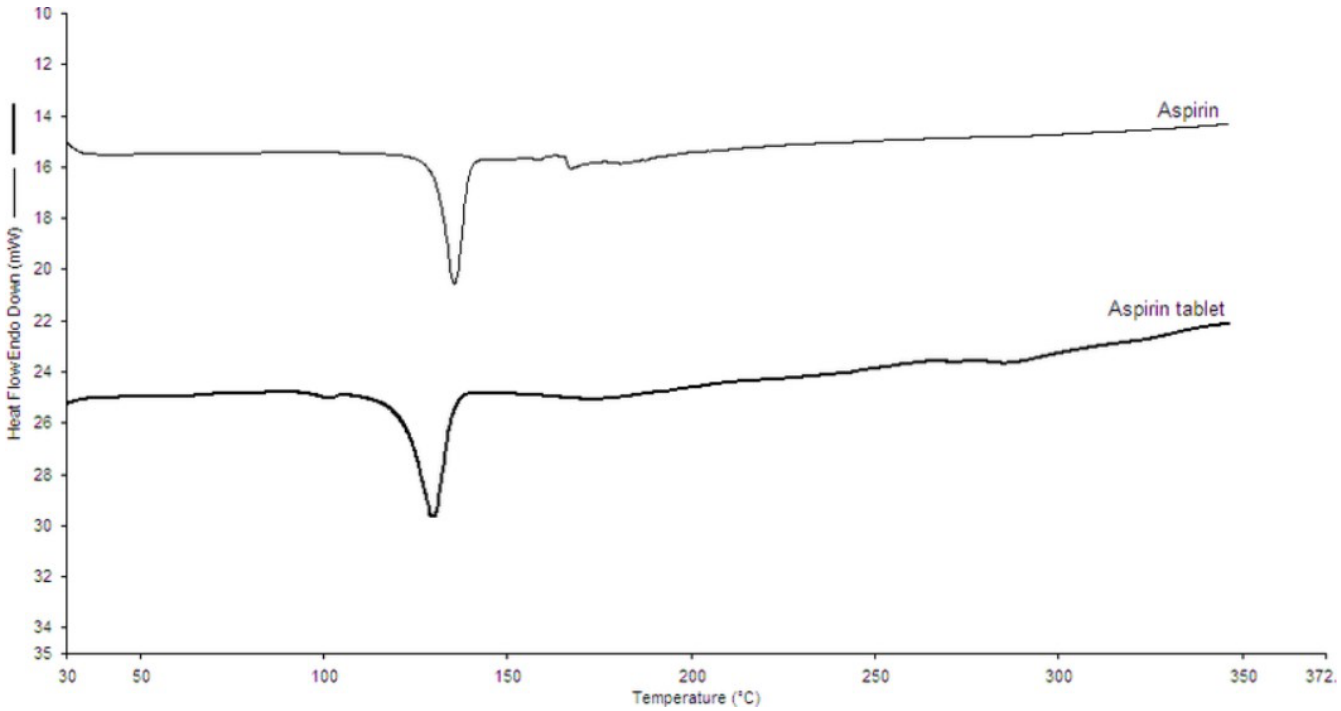


Figure : DSC of Aspirin and Aspirin formulation

In-silico study

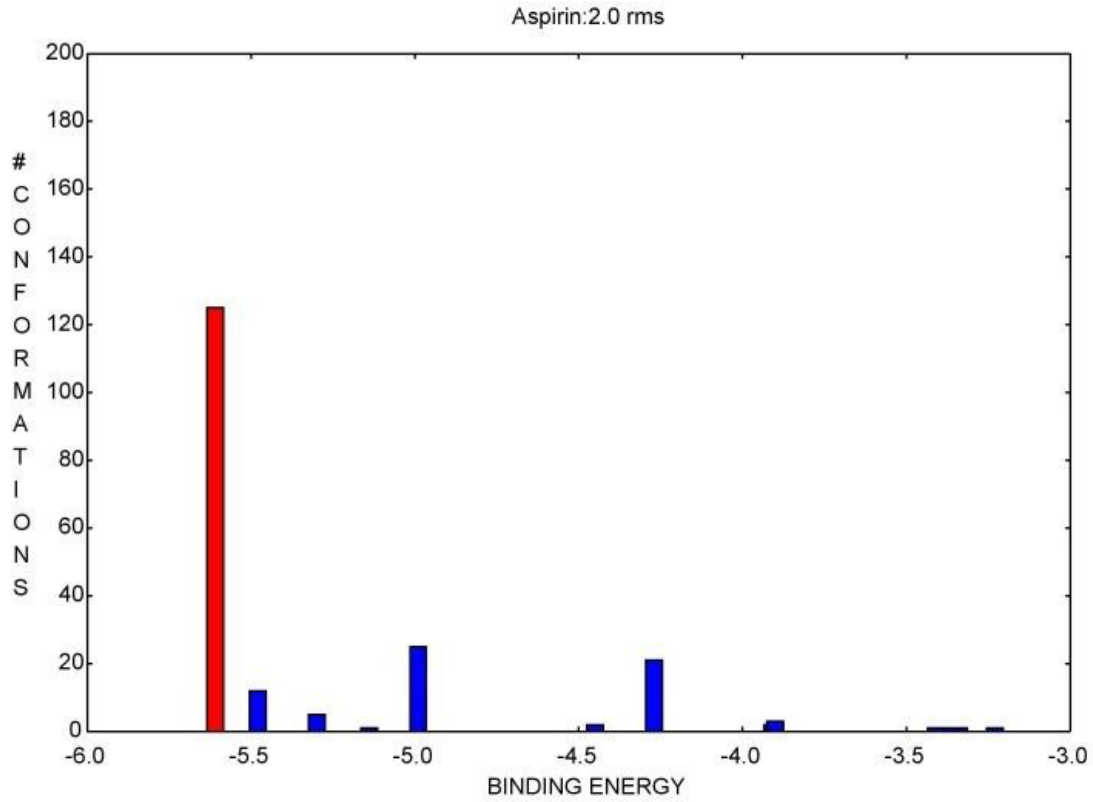
The structure of aspirin retrieved from Auto cad 4.0 is elucidated in The protein structure obtained in homology modelling is described in The best docked conformation of aspirin was located near the N-terminal region of the protein The residues such as H186, K190, and G113 made crucial contacts with aspirin. The carboxylic group of aspirin formed two salt bridges with K190 (1.937 Å, 2.150 Å). It was also observed that H186 forming a stronger salt bridge with -COOH group of aspirin (1.646 Å). The Oxy group of acetyl formed a hydrogen bond with the backbone NH group of G113 (1.871). The aromatic ring of aspirin was in close proximity to V112. Unlike forskolin and vasicine, the interaction of aspirin was mainly modulated by salt bridges and hydrogen bonding rather than hydrophobic interactions. Also the binding site of Aspirin was ~30 Å away from Forskolin/Vasicine's binding sites. The calculated binding energy was ~5.61 KCal/mol.

Aspirin showed binding to H186, K190, and G113 amino acid residues of PDE7B. Previous studies have revealed that H173 is the active binding site of PDE7B protein which is located in the catalytic region of this protein. Contradictory results have been shown with aspirin and its effects on cognitive functions.

Protein-Ligand docking scores

Ligand	Protein PDB ID	Binding energy	Binding energy	Inhibition Constant	vdW_HB (kcal/mol)	Ligand efficiency

		dRes idues	calc/mol)	antmM		
Aspirin	PDE7B_HUMAN_cAMP_Modelled	His186, Lys190, Gly113	-5.61	1.72	-5.13	0.29



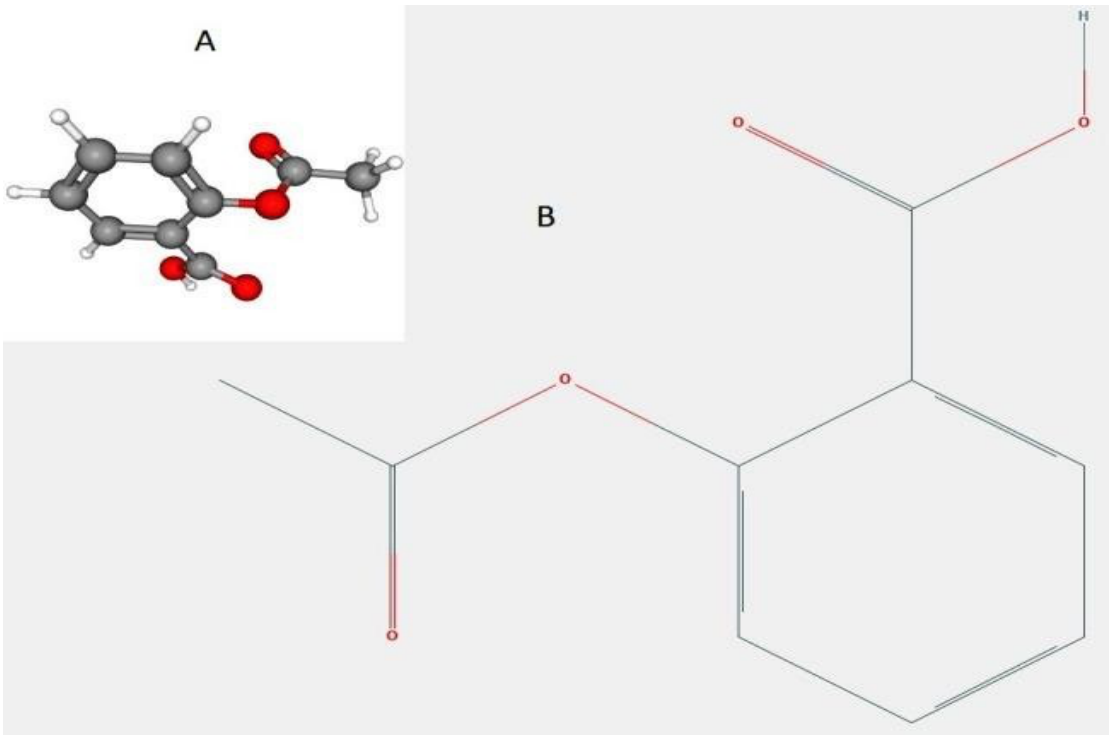
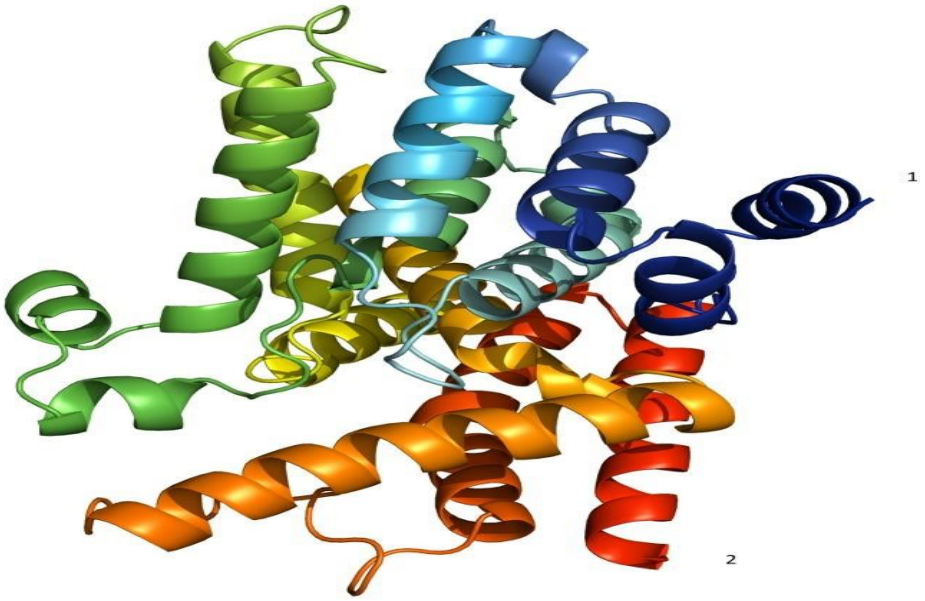
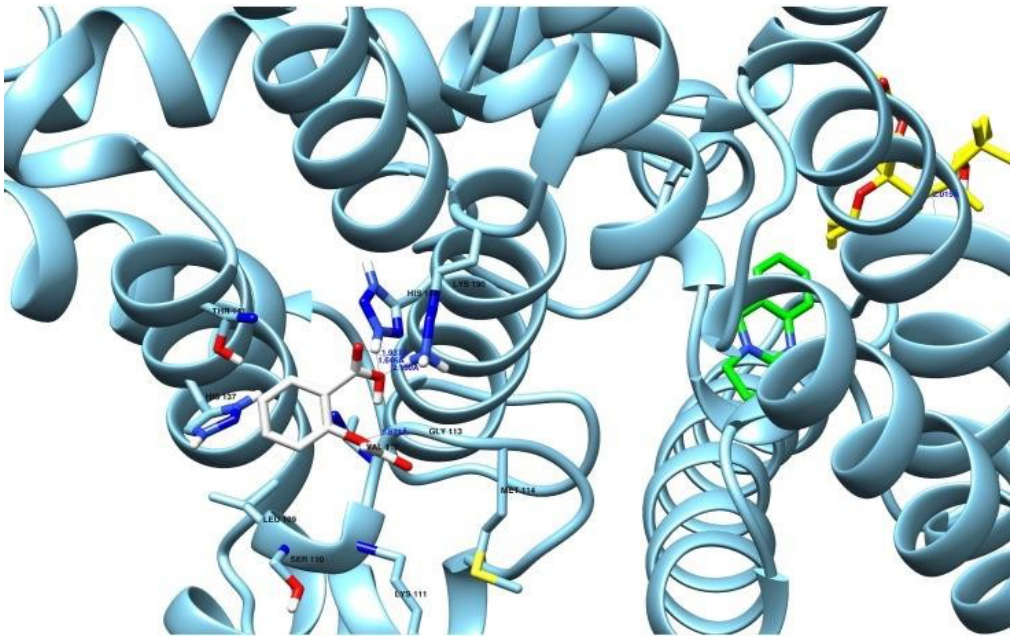


Figure :Binding energy and conformations of PDE7B. Red colour indicates maximum number of conformations.

Chemical structure of aspirin, retrieved from Autocad 4.0. A- 3d view, B-2d view



PDE7B structure obtained in homology modelling. 1-N terminus; 2-C terminus



Physical properties of prepared powder blends

Various properties of granules such as Carr's Index, Hausner's Ratio , Bulk density, Tapped density and Angle of repose were determined and the results are:

Table : Physical properties of prepared formulations

Formulation	**Angle of repose**	**Bulk density (gm/ml)**	**Tapped density (gm/ml)**	**Carr's index (%)**	**Hausner's ratio**
F1	30.51 ±1.01	0.58 ±0.007	0.71±0.011	17.64±2.16	1.21 ±0.025
F2	29.36 ±0.58	0.58 ±0.010	0.69±0.0057	16.08±0.84	1.26 ±0.01
F3	34.05 ±0.93	0.56 ±0.014	0.66±0.0068	15.76±1.85	1.18 ±0.02
F4	34.60 ±0.55	0.56 ±0.007	0.69±0.0095	12.88±2.20	1.14 ±0.03
F5	31.30 ±0.92	0.58 ±0.075	0.71±0.015	20.31±2.81	1.25 ±0.041
F6	30.09 ±0.	0.56 ±0.017	0.70±0.0052	17.95±1.64	1.21 ±0.026

	21				
F7	30.74 ±0.83	0.56 ±0.065	0.64±0.012	14.83±0.70	1.17 ±0.011
F8	34.20 ±0.74	0.56 ±0.080	0.70±0.0072	14.71±0.70	1.24 ±0.05
F9	35.58 ±0.08	0.58 ±0.065	0.67±0.011	18.15±0.74	1.22 ±0.01

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.56 ±0.007 to 0.58 ±0.075 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.64 ±0.012 to 0.71 ±0.015 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 18 which shows that the powder has good flow properties. All the formulations has shown the Hausners ratio ranging between 1.14 ±0.03 to 1.26±0.01 indicating the powder has good flow properties.

Evaluation of post compression parameters of floating tablets of aspirin

Table 14: Evaluation of formulations

Formulation	**Weight variation (mg)**	**Hardness (kg/cm2)**	**Friability (% los**	**Thickness (mm)**	**Assay/ Drug content**

			s)		(%)
F1	288.61	3.48	0.63	1.52	99.19
F2	289.48	3.59	0.79	1.78	98.62
F3	288.22	3.48	0.64	1.59	99.27
F4	305.73	3.74	0.68	1.65	99.86
F5	301.55	3.88	0.74	1.77	97.37
F6	300.92	3.67	0.66	1.55	98.56
F7	289.44	3.49	0.71	1.64	99.47
F8	301.30	3.62	0.85	1.72	98.12
F9	287.32	3.45	0.88	1.47	97.76

The results of the physical tests of the formulations were within the limits and comply with the standards. The weights of the tablets ranged from 287mg to320 mg; the weights being with ±5% of the average weight. The thickness was found to be in the range 1.52mm to 1.78mm. Hardness of the tablets was in the range of

3.45 to 3.88 g/cm2 and friability was in the range 0.63to 0.88 %, indicating that the tablets are hard enough to withstand the external mechanical stresses. The drug content on an average was found to be 99.27%. All these parameters were within acceptable limits. The results of the physical tests of many of the formulations were in the limits and comply with the standards.

Floating properties of aspirin floating tablets

All the formulations were tested for floating properties like floating lag time and total floating time. All the batches showed good *in vitro* buoyancy.

Table : In vitro buoyancy studies:

Formulation	Total Floating Time (hrs)	Floating Lag Time (sec)
F1	<6	10
F2	<6	12
F3	<6	10
F4	<6	11
F5	<6	13
F6	<6	10
F7	<6	14
F8	<6	15
F9	<6	11

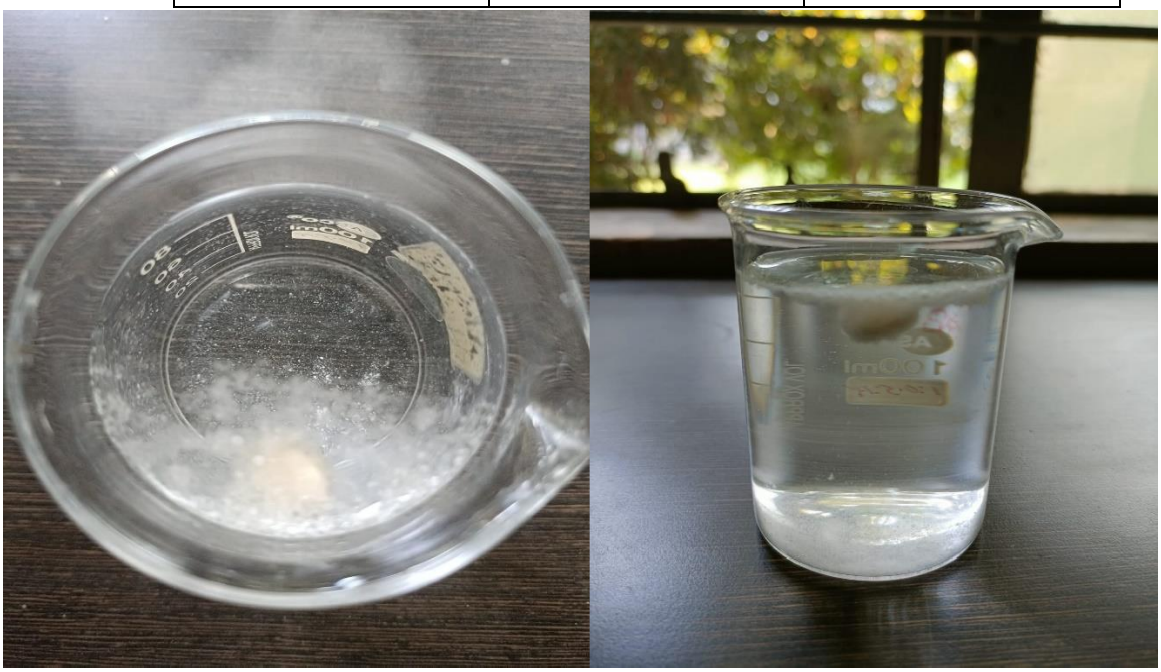


Figure : Formulated floating tablet

Table : % Cumulative Drug Release

TIME (hrs)	F3 Batch
0	0
1	21.97
2	36.75
3	57.24
4	66.78
5	84.80
6	99.27

Summary and conclusion

Floating drug delivery systems prolongs the gastric residence time which in turn produces increased drug bioavailability. Due to its less density than the aqueous medium, it floats in the gastric fluid. These drug delivery systems are suitable in the stomach or in upper small intestine due to its narrow absorption window.

In this present project, aspirin was used as a model drug for the floating tablets. Aspirin is used antiplateletic drug, aspirin prevents blood from clotting by inhibiting cyclooxygenase, the enzyme responsible for the formation of thromboxane A2, which is a mediator of platelet aggregation.

Aspirin has a low bioavailability due to first pass effect and hydrolysis to salicylate metabolism in the gut wall. Aspirin is rapidly absorbed in the upper gastrointestinal tract, especially in the portion of the small intestine therefore, formulation of floating drug delivery system are designed to improve the bioavailability of aspirin.Floating tablets of aspirin were developed to prolong gastric residence time and increase its bioavailability.Floating tablets of aspirin were prepared using individual and combination of excipient. The excipient HPMC, sodium bicarbonate, citric acid were used in different ratios. Totally nine formulations (AF1-AF9) were designed and formulated. The flow properties bulk density, tap density, angle of repose were determined and the results were found to be within the limit for all the formulations. The aspirin

floating tablets were prepared by direct compression method. The direct compression method is easy, simple and time consuming. These formulations (AF1- AF9) were evaluated for various tests like weight variation, content uniformity, friability, hardness and dissolution studies.The hardness and friability of the tablets were within the limits for all the formulations. The weight variation of the tablets was found to be within the limits.

The content uniformities of the prepared tablets were found to be within the limits.

The floating lag time for the prepared formulation was ideal for the floating drug delivery systems.

The percentage drug release of the formulations AF1, AF2, AF3, AF4 and AF5, AF6, AF7, AF8, AF9 was 73.28, 82.37, 99.27, 95.44, 84.63, 91.45, 92.35, 79.45, and 79.51 up to 6 hrs.

The formulation (AF3) was found to be best formulation with floating time of 6 hrs and drug release of about 99.27%.

This present research work focuses on the floating tablets of aspirin, and succeeded in the formulation.

QbD: By Plackett-Burman Design we concluded, Factorial Regression: Floating time (min) versus HPMC K100, Sodium bicarbonate, Citric acid, MCC, PtType and Factorial Regression: % Drug release versus HPMC K100, Sodium bicarbonate, Citric acid, MCC, PtType and finally we get the optimized batch. The current study claimed as an ideal tool for the development of product as per outline of QbD including specified limits of excipients in ranges within the designed acceptance space for product's optimum performance.

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