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FORMULATION DEVELOPMENT OF SUSTAINED RELEASE ANTIULCER DRUG AND STUDY OF PRE-FORMULATION PARAMETERS AND ITS CHARACTERIZATION

Satbir Singh[*1], Dr. Gaikwad Dushyant Dadabhau[2], Kehar Singh[3]

[1,3]Research Scholar, Department of Pharmacy, Sunrise University, Alwar, Rajasthan
[2]Professor, Department of Pharmacy, Sunrise University, Alwar, Rajasthan

***Corresponding Author:**Satbir Singh
*Research Scholar, Department of Pharmacy, Sunrise University, Alwar, Rajasthan
Email: satbirpharma89@gmail.com.Mobile: 8708977210

Abstract
The aim of present study was to formulate and developed sustained release tablets of Nizatidine (220 mg) by varying concentration of polymers like chitosan, Kollidon SR and HPMC K100M by wet granulation technique. The pre-formulation parameters were studied like melting point of drug, FTIR study and DSC analysis of drug. Various pre-compression parameters were evaluated like Bulk density, Tapped Density, Carr' Index, Angle of repose. This study revealed the idea about how the concentration of polymers affects pre-compression parameters of the drug formulation.

Keywords: Sustained Release, Antiulcer, Nizatidine, Pre-formulation, characterization

Introduction

The drug release time or rate of medications in modified-release dosage forms can be altered. The most popular method of administration is oral drug delivery, out of all the channels that have been investigated for systemic drug delivery via pharmaceutical products of various dose forms: ophthalmic, rectal, nasal, transdermal, and parentral.[1]

There have been medication items on the market for a long time that is intended to lower dosage frequency by accelerating drug absorption. Drug release from controlled-release drug delivery systems (CRDDS) is regulated, predictable, and occurs at a predetermined rate. In order to guarantee continued absorption of the released drug, as illustrated in figure 1 below, it is imperative that the drug have good absorption throughout the gastrointestinal tract, preferably by passive-diffusion. [2,3]

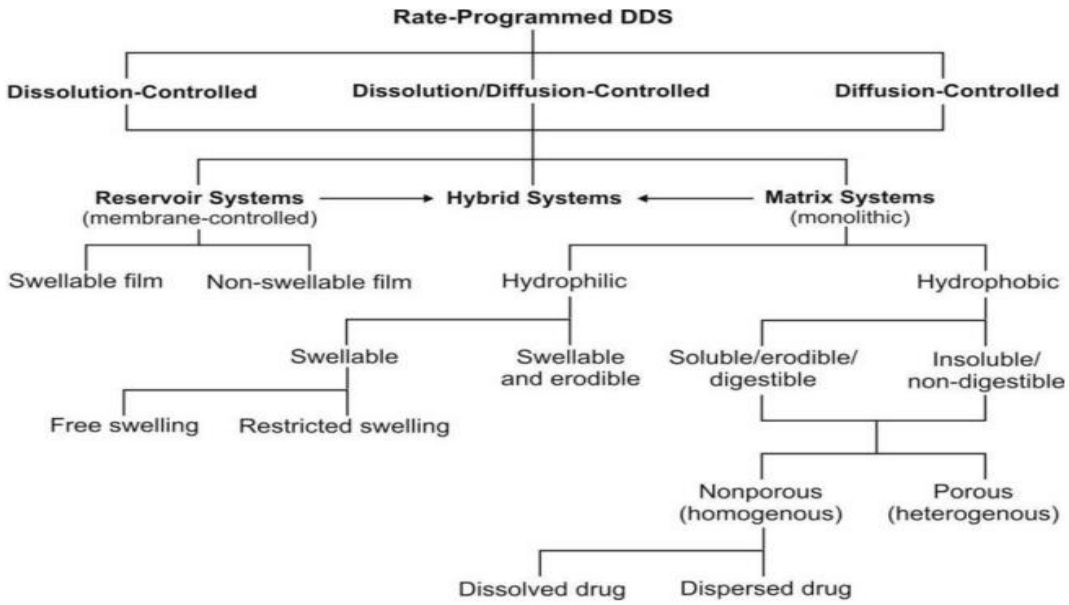

Figure 1: Classification of CRDDS

The oral route of administration, which substitutes sustain release drug delivery for traditional drug administration by delivery system, is said to be the most frequently recognized method due to its ease of self-administration, compactness, and ease of manufacture. Controlling the rate and/or site of drug release from oral formulations has received more attention recently. These goals include enhancing patient compliance and treatment efficacy, resolving issues with drug targeting to particular organs or tissues, and regulating the rate of drug delivery to the target site.[4]There has been a lot of buzz about hydrophilic polymers being used as controlled-release and sustained-release delivery systems for chemicals that are soluble or insoluble in water. The addition of dry PVP made the wet material ready for use. To assess the impact of binders, tests were conducted to measure weight variation tolerance, drug content uniformity, hardness, tensile strength, friability, disintegration time, and dissolution. The hydrated gel layer's thickness dictates the drug molecules' diffusion route into the diffusion medium from the polymer bulk. [5]

Material and Methods

The Drug Nizatidine was received a gift sample from Ind Swift Laboratories Ltd. The other excipients HPMC and Kollidon SR was purchased from the Yarrow chem. Products, Mumbai, Talc and Chitosan was purchased from Central Drug house, (P)Ltd, New Delhi. All ingredients are of analytical grade.

1. Pre-formulation Studies

Characterization of nizatidine Drug Sample

1.1 Organoleptic properties of Drug Sample

The organoleptic characteristics of the nizatidine sample, including color, odor, and appearance, were examined.

1.2 Melting point (M.P) of Drug Sample

Melting point equipment was used to determine the melting point of nizatidine. The medication was placed in a glass capillary with one end flame-sealed in order to determine the m.p.[6]

1.3 FTIR Spectroscopy of Drug

A FT-IR spectrometer (Shimadzu 8400s) was used to study drug sample. In this a 1:100 ratio, the dried nizatidine sample was combined with IR grade potassium Bromide. Using a hydraulic press and 10 tons of pressure, this mixture was compacted into the shape of a pellet. The wave number range of 4000 to 400 cm-1 was used to scan the pellets.[7]

1.4 Differential scanning calorimetry studies of Drug with Excipients

Thermal analysis was performed using DSC-60 Shimadzu Japan with a differential scanning calorimeter equipped with a computerized data station. The drug was processed in sealed aluminum pans at a scanning rate of 20°C/min from 50 and 300°C and 30 ml/min flow. The differential scanning calorimetry analysis gives an idea about the interaction of various materials at different temperature.[8]

1.5 Determination of solubility

A number of standard solvents were used of different pH like 7.5, pH 4.75 and pH 1.2 to determine the solubility of nizatidine hydrochloride. Ten milligram (10 mg) of the medication were taken and added to a series of 25 milliliter volumetric flasks along with ten milliliters of each solvent. After clamping and shaking the flasks in a vortex shaker for six hours at room temperature, equilibrium was reached. Visual inspection was done to check for drug particles that were insoluble in the flasks. We removed and filtered the supernatant. After an appropriate dilution, Nizatidine hydrochloride was quantitatively determined using a UV/Visible spectrophotometer. Absorbances were measured in the 200–400 nm range, and solubility calculations were performed.[9,10]

1.6 Calibration curve of nizatidine in 0.1 N HCl

Nizatidine (30 mg) was accurately weighed and transferred to 100 ml volumetric flask. It was then dissolved in 25 ml 0.1 N HCl and diluted up to 100 ml with same. The above made solution was further diluted to obtain concentration ranging from 30-210 µg/ml. The absorbance of the resulting solutions was recorded at 313 nm using UV Visible Spectrophotometer. HCl (0.1N) was taken as a blank. Calibration plots were constructed and the linearity was established.

2. Formulation and Development

2.1 Calculation of theoretical drug release profile and fixation of dose

Based on the Drug pharmacokinetic properties, a theoretical sustained release drug profile was computed. Using the following formula, the immediate release doses (IRD) of the medicine (drug release at the first hour) was determined as follows:

$$\mathbf{IRD} = \frac{\mathbf{Css \times Vd}}{\mathbf{F}}$$

Where,
Vd-volume of distribution
F-Bioavability
Css represents steady state concentration which is calculated by the following formula given below:

$$\mathbf{Css} = \frac{\mathbf{F \times D}}{\mathbf{CL \times \tau}}$$

Where,
CL= clearance (liter/kg)
D = conventional single dose (150 mg)

τ = dosing interval (150 mg OD = 12 h)
Maintenance dose/total dose (MD) represents drug fraction required to maintain sustained delivery of drug from formulation for required time (t) and it was calculated using the following formula as shown below:

Total Dose/MD = IRD {1 + (0.693 * t/t1/2)}
Where,
IRD-immediate release dose
t- Predetermined time up to which sustained action is needed (12 h)
$t_{1/2}$- half life
Theoretical drug release profile and drug dose for sustained delivery was fixed using values of IRD, MD for predetermined time t (12 h).[11,12]

2. Method for preparation of Sustained Release Tablet
Different tablet formulations were prepared by wet granulation method. All the powders passed through sieve no 40 the required quantity of drug, various polymers and other ingredients were mixed thoroughly, and a sufficient volume of granulating agent (iso-propyl alcohol) was added slowly. After enough cohesiveness was obtained, the wet mass was sieved through sieve no.8 the granules were dried at 60^0C for 30 minutes and then dried granules were passed through sieve no.16. Talc and magnesium stearate were finally added as a glidant and lubricant respectively the granules were directly compressed using a single punch tablet compression machine. Each tablet contained 220 mg of Nizatidine.[13]

Table 1: Formulation of Sustained Release Tablet of Nizatidine

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Nizatidine	220	220	220	220	220	220	220	220
Chitosan	40	80	-	-	-	-	40	80
Kollidon-SR	-	-	40	80	-	-	-	-
HPMC K100M	-	-	-	-	40	80	40	20
Lactose	85	45	85	45	85	45	45	25
Mg Streate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	350	350	350	350	350	350	350	350

Characterization of Sustained Release Tablet of Nizatidine

I.Pre-compression Parameter Study

Angle of Repose

The largest angle that the powder plane forms with the horizontal surface while it rotates is known as the angle of repose. Angle of repose is useful in evaluating the flow characteristics of particles, which may be further connected to the mechanical configurations and packing densities of the particles.
The funnel method was utilized to ascertain the granules' angle of repose. The finely measured grains were placed in a funnel. The funnel's height was modified so that the tip of the funnel just brushed the top of the granule pile. Granules were free to pour onto the surface through the funnel. The following formula was used to determine the angle of repose and estimate the diameter of the powder cone.[14]
$\tan\theta = h/r$
where h =height of the powder heapr=radius of
the powder heap
θ=angle of repose

Table 2: SignificanceofAngleofRepose

S.No.	Angleofrepose	Flowproperty
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Poor

Bulk Density and Tapped Density Determination

The graduated cylinder was carefully filled with a precisely weighed quantity of grains or powder (W), and the volume (V0) was measured. Subsequently, the graduated cylinder was placed inside the tap density tester (USP) and covered with a lid. After setting the density apparatus for 100 tabs, the volume (Vf) was measured, and the process was repeated until the two successive readings were equal.[15]

The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0 Tapped density=W/V_f

Where, W=Weight of the powder V_0 = Initial volume

V_f= final volume

CompressibilityIndex(Carr's Index)

One significant metric that may be derived from the bulk and tapped densities is the Carr's index (CI). Theoretically, a material becomes more flowable the less compressible.

CI=(TD-BD) x100/TD

where, TD is the tapped density and BD is the bulk density.[16]

Table 3: Carr'sIndexValues

S.No.	Carr'sIndex	Properties
1	5-12	Freeflowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner's Ratio

It is the tapped density divided by the bulk density. Hausner discovered that this ratio could be used to predict the parameters of powder flow because it was associated with interparticle friction. Good flow qualities are generally indicated by a value less than 1.25, which is equal to 20% of Carr's index.[17]

Hausener's Ratio=Tapped density/Bulk Density

Table 4: Significance of Hausener's Ratio

S.No	Hausner'sRatio	Property
1	0-1.2	Freeflowing
2	1.2-1.6	Cohesivepowder

PREFORMULATION PARAMETERS CHARACTERIZATION

Characterization of Nizatidine Drug Sample

Organoleptic properties of Drug Sample

The organoleptic characteristics of the nizatidine was found

Color: off white to buff crystalline solid in appearance

Odor: Mild sulphur like odor

Taste: Bitter taste

Melting Point

Table 5: Melting point of Drug

Parameters	Reference Value	Experimental Value
Melting point	**127-130ºC**	**128±0.6ºC**

FTIR SPECTROSCOPY

Research was done to determine whether nizatidine and polymers such chitosan, Kollidon-SR-SR, and hydroxyl propyl methylcellulose (HPMCK100M) were compatible. Drug, polymer, and physical mixtures of the two were created as samples.For the functional group bands, the resultant spectra were compared and analyzed. Using a frequency range of 4000-400 cm-1, the Shimadzu 8400s FTIR spectrometer examined the sample.

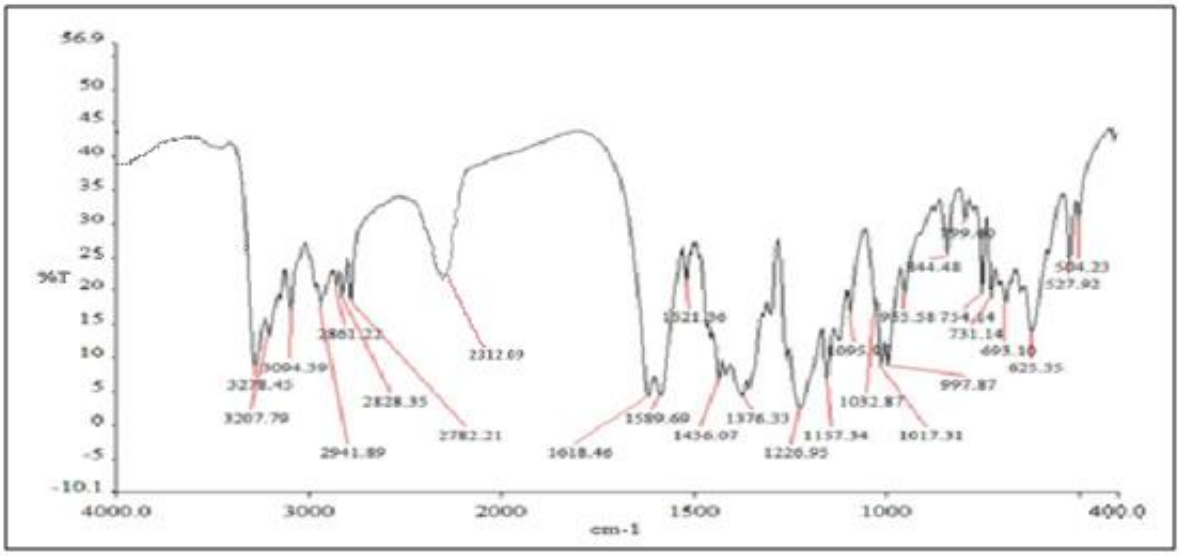

Figure2: FTIR Spectra of Drug Sample (Nizatidine)

Differential scanning calorimetry studies of Drug Nizatidine

Nizatidine and the excipients do not interact, according to the DSC thermogram obtained from thermal analysis using the DSC-60 Shimadzu Japan. Drug melting caused a sharp peak to be detected at 130.1°C.

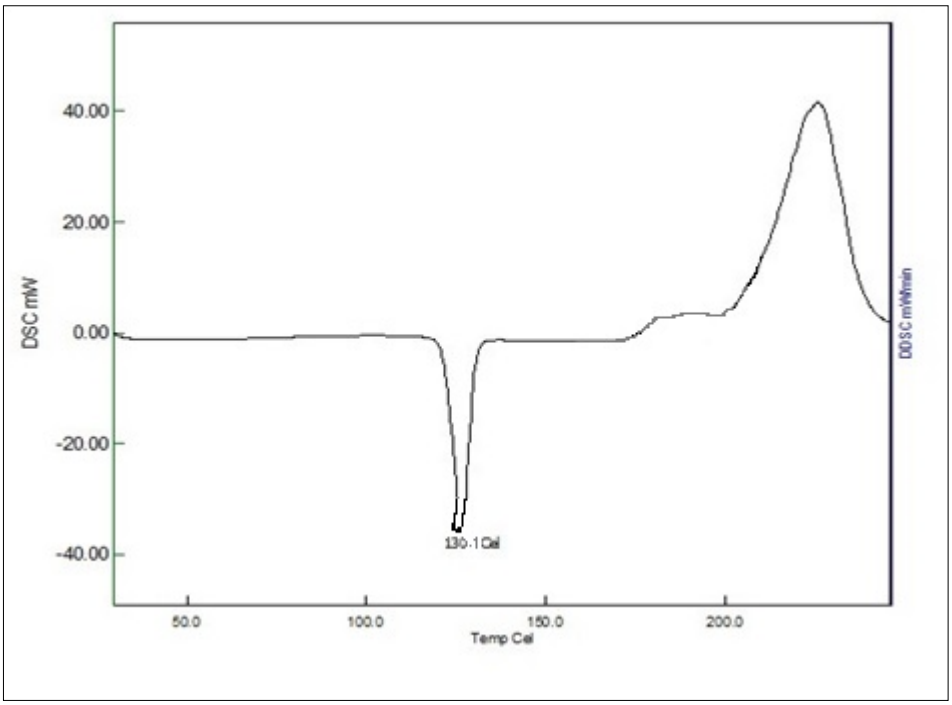

Figure3: DSC Thermogram of Drug Nizatidine

Determination of solubility

After testing the drug's solubility in several pH buffer solutions, it was determined that the drug's solubility was pH dependant, decreasing as pH increased, as seen in the figure below.

Table 6: Solubility Profile of Drug Nizatidine

Sr. No	Solvent of Different pH	Solubility (mg/ml)
1	pH 7.5 Buffer	14.8
2	pH 4.75 Buffer	38.2
3	pH 1.2 HCL 0.1 N Solution	56.3

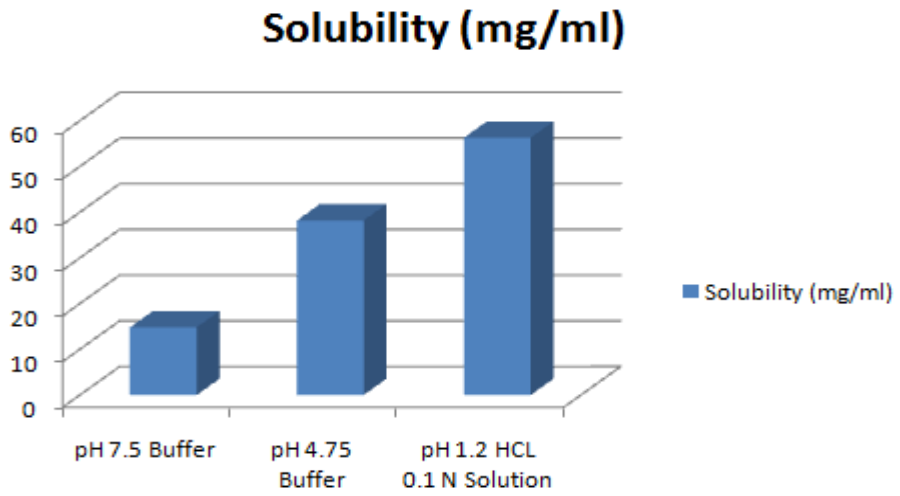

Figure4: Solubility Profile of Drug Nizatidine

Calibration curve of Nizatidine:

Nizatidine's calibration plot was made at 255 nm in 0.1 N HCl. It was discovered that the drug's plot of various concentrations against absorbance was linear within the concentration range of 0 µg/ml to 25 µg/ml. Table 7 displays the findings, which are also depicted in below Figure.

Table 7: Calibration curve of Nizatidine of 0.1N HCL

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.124
3	10	0.244
4	15	0.3
5	20	0.5
6	25	0.65

Average of three determinants

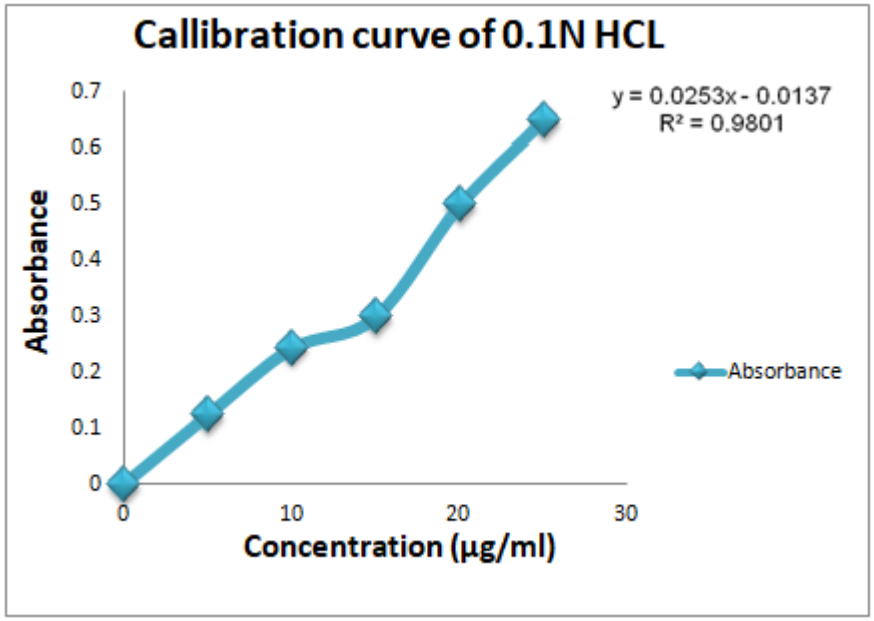

Figure5: Calibration Plot of Nizatidine in 0.1N HCl at 255nm

A straight line (y=mx+c) was generated to facilitate the calculation for amount of drug and R^2value was found to be 0.9801. The equation obtained is: Absorbance (y) =0.0253x+0.0137.

Calibration curve of Nizatidine of pH 6.8 Phosphate buffer:

Table 7: Calibration curve of Nizatidine of pH 6.8 Phosphate buffer:

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.124
3	10	0.267
4	15	0.342
5	20	0.432
6	25	0.578

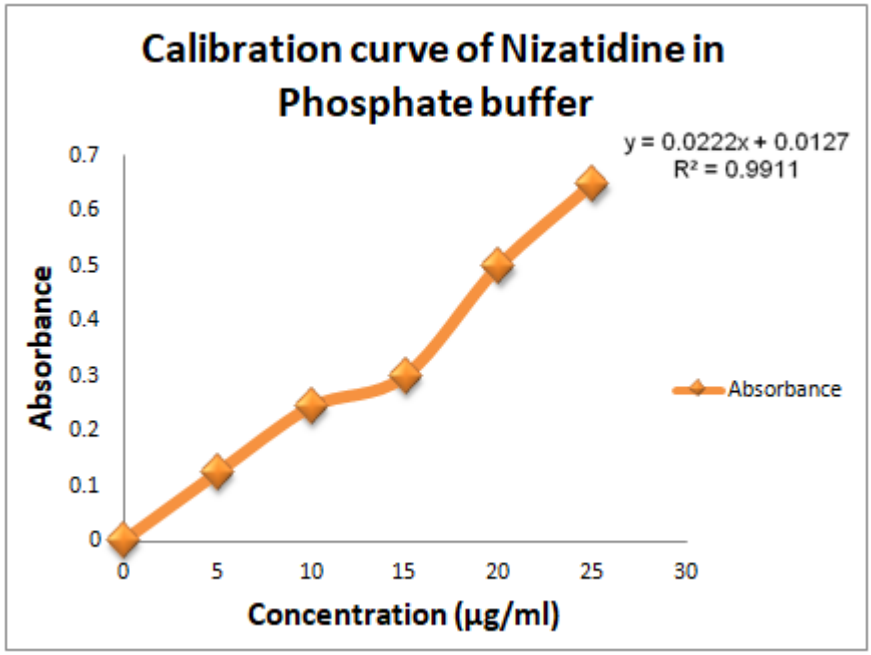

Figure 6: Calibration curve of Nizatidine of pH Phosphate buffer

A straight line (y=mx+c) was generated to facilitate the calculation for amount of drug and R^2value was found to be 0.9911.The equation obtained is: Absorbance(y) =0.0222x+0.0127.

Formulation and Development

1. Calculation of theoretical drug release profile and fixation of dose

One possible sustained release medication profile was calculated using the drug's pharmacokinetic parameters. This method was used to calculate the medicine's immediate release doses (IRD) (drug release during the first hour):

IRD = Css × Vd
F

Where,
F-Bioavability
Vd-volume of distribution
Css represents steady state concentration which is calculated by the following formula given below:

Css = F × D
CL × τ

Where,
CL= clearance (liter/kg)
τ = dosing interval (150 mg BD = 10 hrs)
D = conventional single dose (150 mg)

Css = 65X150
42X10
= 23.21 mg/litre

IRD = 120X23.21
65
= 42.85 mg ~50 mg

The method below was used to compute the maintenance dose/total dosage (MD), which is the drug fraction needed to ensure sustained drug delivery from the formulation for the necessary amount of time (12 hours). By entering the aforementioned numbers into the calculation, we obtain

Total Dose/MD = IRD {1 + (0.693 * t/t1/2)}

Where,

IRD-immediate release dose

$t_{1/2}$- half life

t- Predetermined time up to which sustained action is needed (24 h)

Theoretical drug release profile and drug dose for sustained delivery was fixed using values of IRD, MD for predetermined time t (24 h). [99,100]

Total Dose/MD = 40{1 + (0.693 * 24/2)}
= 221 mg ~ 220 mg
% Drug Release within 1 hr
$\%D_{1hr}$ = 50 X 100
220
= 22.7272 %
% Drug Release within 11 hrs
$\%D_{11hrs}$ = 170 X 100
220
= 77.2727%
% Drug Release Every hr
77.2727
11
=7.0247%

Therefore, the dose for formulations was determined at 220 mg based on the calculations above. The immediate release dose of 50 mg is divided into two parts: 22.72% will release within the first hour of administration, and the remaining 170 mg will release over the course of 11 hours at a rate of 7.0247% per hour. The calculated cumulative percentage release is displayed in Table No. 8 below, along with the theoretical drug release depicted in the picture below.

Table 8: Theoretical Release Profile of Drug

Sr. No	Time (hr)	% Theoretical Drug Release	% Cumulative Drug release
1	1	22.72	22.72
2	2	7.02	29.74
3	3	7.02	36.76
4	4	7.02	43.78
5	5	7.02	50.8
6	6	7.02	57.82
7	7	7.02	64.84
8	8	7.02	71.86
9	9	7.02	78.88
10	10	7.02	85.9
11	11	7.02	92.92
12	12	7.02	99.94

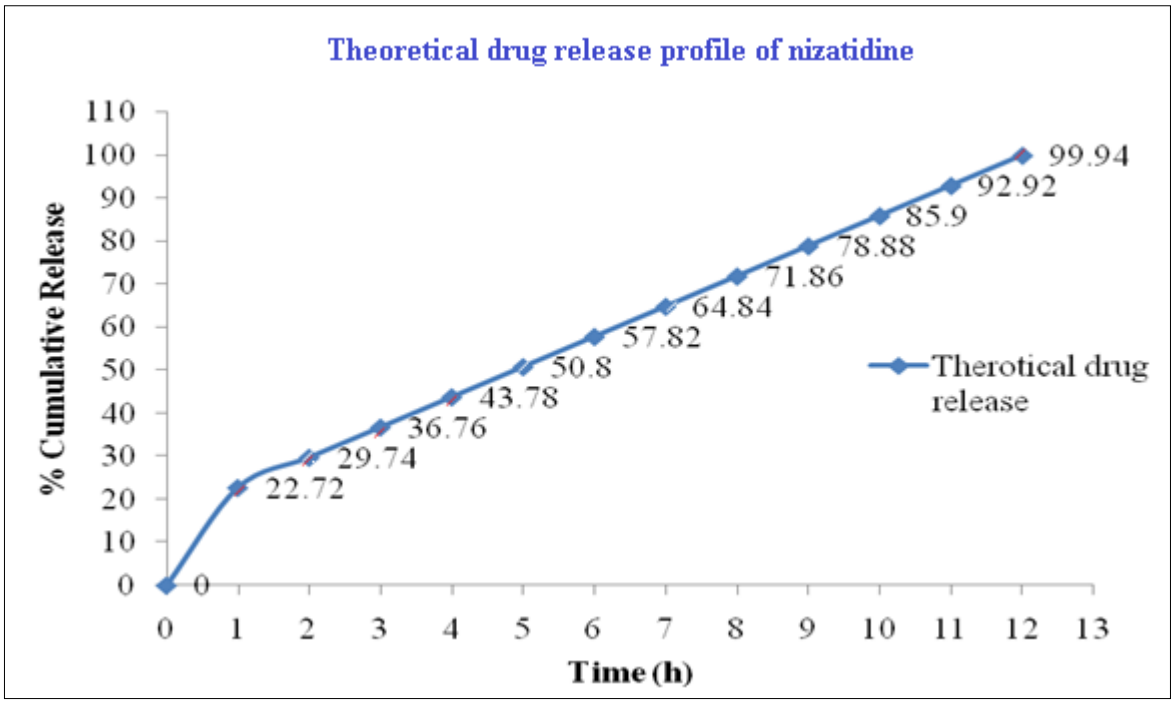

Figure7: Theoretical drug release profile of nizatidine

EVALUATION:

Pre-compression parameter:

Various pre-compression parameters were evaluated eg. Bulk density, Tapped Density, Carr' Index, Angle of repose as shown in table no 9.

Table 9: Pre-compression parameter

Formulation Code	Bulk density (gm/ml) ±SD	Tapped density (gm/ml) ±SD	Carr's Index (%)±SD	Angle of Respose (0)±SD
F1	0.36±0.81	0.43±0.52	16.27±0.24	25.54±0.33
F2	0.36±0.01	0.46±0.45	21.73±0.13	28.23±0.12
F3	0.39±0.54	0.45±0.02	13.33±0.48	27.12±0.55
F4	0.37±0.11	0.42±0.59	11.90±0.87	24.23±0.79
F5	0.38±0.02	0.45±0.77	15.54±0.19	25.33±0.12
F6	0.39±0.98	0.46±0.15	15.21±0.14	22.15±0.18
F7	0.38±0.61	0.45±0.21	15.55±0.74	23.18±0.48
F8	0.36±0.11	0.45±0.14	20.00±0.19	25.01±0.41

Conclusion

After successful pre-formulation studies of drug Nizatidine it was conclude that drug is off white to buff crystalline with sulphur like odor with bitter taste and the melting point of sample was found 128±0.6°C while the DSC thermogram was observed at 130.1°C. during solubility profile study it was found that solubility is pH dependent which means as the pH of the liquid (pH 7.5, pH 4.75 & pH 1.2) increases solubility start decreases.In the calibration plot of Nizatidine in 0.1N HCL at 255 nm R^2 value was found 0.9801 with (y) =0.0253x+0.0137. In the phosphate buffer R^2value was found to be 0.9911 with (y) =0.0222x+0.0127. The bulk density lie between 0.36±0.01- 0.39±0.98 gm/ml and the tapped density was 0.42±0.59 - 0.46±0.45 gm/ml. The Carr's index value lie between 11.90±0.87 - 21.73±0.13

and the Angle of Repose value lie between 22.15±0.18 - 28.23±0.12. The formulation F7 showed promising results.

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Conflict of Interest
The authors declare that they have no conflict of interest.

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