Formulation, Development and Investigation of Matrix Type Sustained Release Tablet of Antiulcer Drug by Using Soluble Polymer as a Drug Release Retarding Agent

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Abstract: The main goals of sustained release drug delivery are to modify the medication's biopharmaceutical, pharmacokinetic, and pharmacodynamic properties in order to lessen adverse effects, increase patient compliance, and treat the illness. The current work set out to create sustained release tablets of nizatidine (220 mg) using a wet granulation process and different concentrations of polymers such as chitosan, Kollidon SR, and HPMC K100M. Pre-formulation characteristics were examined, including medication DSC analysis and FTIR research. We assessed a number of post-compression characteristics, including content homogeneity, thickness, hardness, friability, and weight uniformity. This study demonstrated how the post-compression characteristics of the drug formulation are influenced by the concentration of polymers.

Keywords: Sustained Release, Drug Release, Nizatidine, Pre-formulation, characterization, post compression parameters

Introduction

Any method of administering medication that causes a slow, continuous release of the drug is referred to as sustained release. In order to accomplish the intended therapeutic effect, the majority of sustained release formulations are formulated to release a first dose of drug upon intake. Then, in order to maintain the therapeutic impact, they deliver more medication gradually and consistently over an extended period of time, typically eight to twelve hours.[1]

The most widely used type of drug administration is the oral route, which replaces traditional drug administration via delivery system with sustained release drug delivery. This is because it is simple to manufacture, easy to self-administer, and compact. More focus has recently been placed on regulating the pace and/or site of medication release from oral formulations. Resolving medication targeting challenges to specific organs or tissues, controlling the pace of drug delivery to the target site, and improving patient compliance and treatment efficacy are some of these objectives.[2]

The interactions of chitosan and its derivatives with metal ions have garnered increasing attention due to their efficient binding properties. Furthermore, simple, cost-effective methods have been devised for the synthesis of derivatives with increased sorption capacity and selectivity. These studies have greatly broadened the range of applications for chitosan as a polymer ligand.[3]

Material and Methods

Ind Swift Laboratories Ltd. provided a gift sample of the drug nizatidine. Kollidon SR and HPMC, the two excipients, were bought from Yarrow Chem. Products from Central Drug House, (P) Ltd, New Delhi were purchased, including talc and chitosan, in Mumbai. Every component is of analytical quality.

FTIR Spectroscopy of Drug

To examine the drug sample, an FT-IR spectrometer (Shimadzu 8400s) was employed. The dried nizatidine sample was mixed with potassium bromide of IR grade in a ratio of 1:100. This combination was compressed into the form of a pellet using a hydraulic press and ten tons of pressure. The pellets were scanned within the wave number range of 4000 to 400 cm-1.[4]

Differential scanning calorimetry studies of Drug with Excipients

Using a differential scanning calorimeter with a computerized data station, Shimadzu Japan's DSC-60 was used for thermal analysis. In sealed aluminum pans, the medication was treated at a scanning rate of 20°C/min from 50 to 300°C and a flow rate of 30 ml/min. A concept of how different materials interact at different temperatures can be obtained from the differential scanning calorimetry analysis.[5]

Method for preparation of Sustained Release Tablet

Using the wet granulation process, several tablet formulations were created. Following a thorough mixing of the various polymers and other materials, all of the powders passed through filter number 40. A suitable amount of granulating agent (iso-propyl alcohol) was then gradually added. Following the achievement of a sufficient level of cohesiveness, the wet material was sieved through sieve No. 8. The granules were then dried for 30 minutes at 600C before being again sieved through No. 16. After adding talc and magnesium stearate as lubricants and glidants, respectively, the granules were compressed directly in a single punch tablet compression machine. There were 220 mg of nizatidine in each tablet.[6]

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

Post Compression Parameter Study

Thickness

A digital vernier caliper was used to measure the thickness of each of the twenty tablets that were randomly selected from the representative sample. The standard deviation and average thickness data were calculated.[6]

Hardness

The tablets' hardness was assessed using the Monsanto hardness tester. Each batch of tablets had six of its hardness evaluated; the standard deviations and average of the six measurements were noted.[6]

Friability Test

Each batch of ten pills was carefully weighed before being added to the Roche friabilator, a tool for determining friability. During the four minutes while the device ran at 25 rpm, tablets were detected. The tablets were taken out, dusted, and weighed once more following 100 spins. The friability was calculated using the percentage of weight lost.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% friability was calculated as follows

% Friability = $(W_1 – W_2) \times 100/W_1$ where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.[7]

Weight Variation Test

To research variations in weight using an electronic balance, the individual weights (WI) of 20 tablets from each formulation were recorded. We computed their average weight (WA). This is how the percent weight variance was computed. The tablets' average weights and standard deviation values were computed.[7]

% weight variation = $(W_A–W_I) \times 100/ W_A$

Drug Content Uniformity (Assay)

If the amount of the active ingredient in each of the ten tested tablets falls between 90% and 110% of the standard amount, then the drug content of the matrix tablets, as assessed by internal standards, satisfies the requirements.[8]

Stability Study of optimized Formulation

If a pharmaceutical product can retain its therapeutic, toxicological, chemical, and physical characteristics over its shelf life, it is considered stable. The ICH specifies the length of the investigation and the amount of storage needed.[9]

Long term testing: $25^0C±2^0C$/75%RH±5% for 12 months duration

Accelerated testing: $40^0C±2^0C$/75%RH±5% for 6 months duration

In Vitro Drug Release Study

Dissolution test apparatus : USP II

Speed : 100±0.1 rpm

Stirrer : paddle type

Volume of medium : 500 ml

Time interval : 0,1h,2h,3h,4h,5h,6h,7h,8h,9h,10h,11h,and 12h

: 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours

Temperature: 37 ± 0.5 ^0C

Using a Whatman filter paper, the extracted samples were filtered and diluted ten times. Following a UV spectrophotometer analysis of the diluted filtrate at a wavelength of 255 nm, the % release values were computed.

Data Release Kinetic Study

A number of kinectic equations, including the zero order, first order, Higuchoi model, and Korsmeyer–Peppas model, were fitted to the data from the in vitro release investigations.

Zero order equation

$Q=Q_0-K_0t$

First order equation

$In\ Q=In\ Q_0-K_1t$

Higuchi equation

$Q=K_2t^{1/2}$

Korsmeryer–Peppas equation

$Q/Q_0=K\ t^n$

Where, K_0 to K_2 were release rate constants, Q/Q_0 was fraction of drug released at time t , K was a constant and n was diffusion constant that indicates general operating release mechanism.[10]

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.

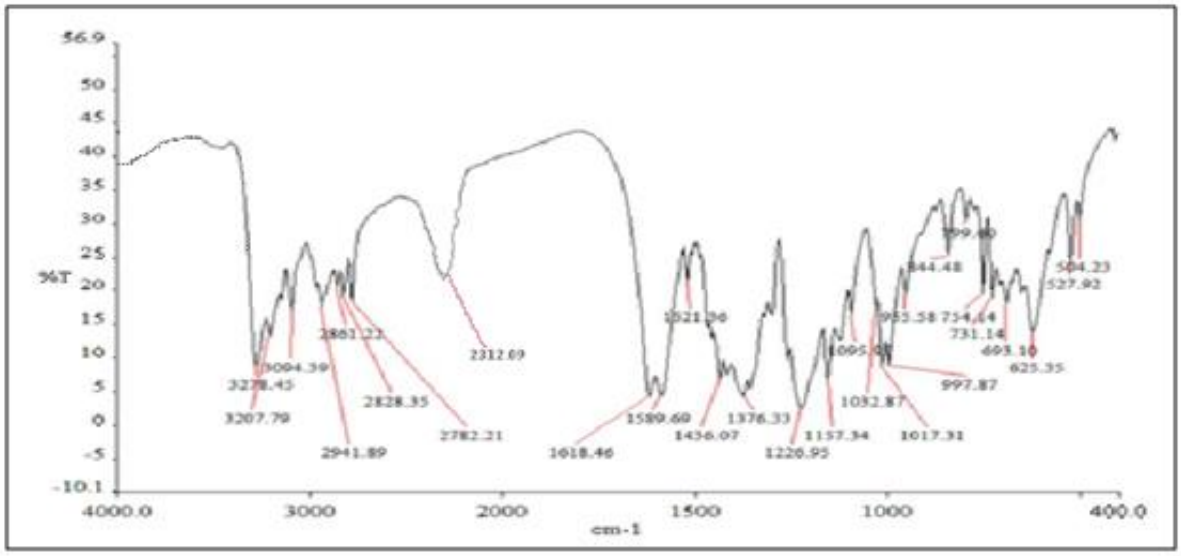

Figure 1: FTIR Spectra of Drug Sample (Nizatidine)

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.

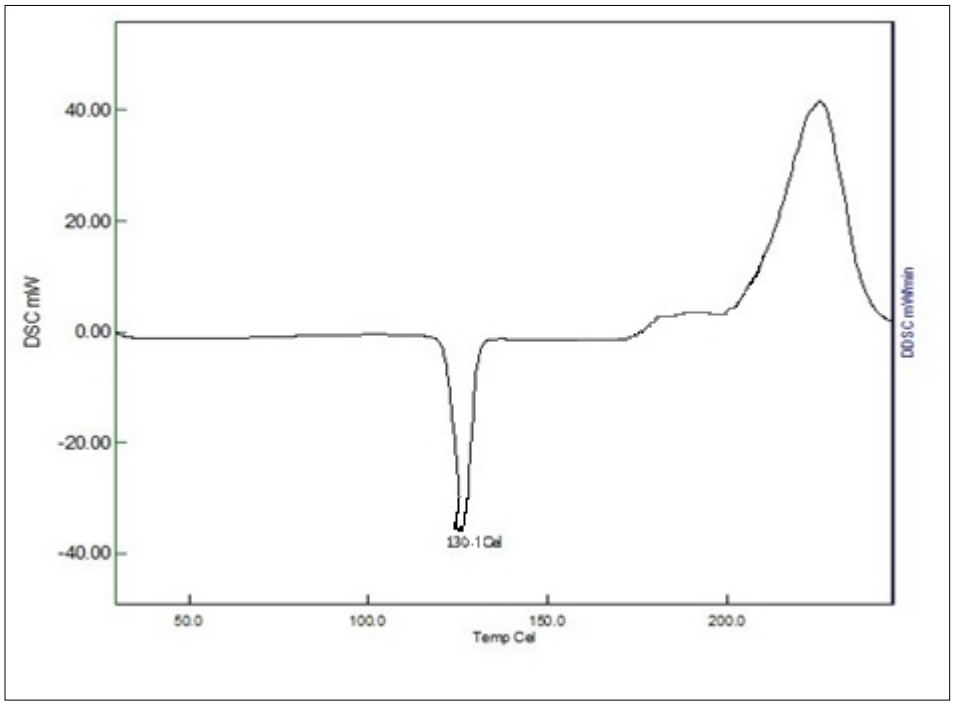

Figure 2: DSC Thermogram of Drug Nizatidine

Post-compression parameter:

Various post-compression parameters were evaluated eg. Thickness, Hardness, Friability, Weight uniformity, Content Uniformity as shown in table no 13.

Table 2: Post-compression parameter

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Uniformity	Content Uniformity
F1	3.90±0.02	6.2±0.23	0.81±0.21	349.10±0.12	98.35±0.56
F2	3.96±0.98	6.9±0.13	0.91±0.11	348.16±0.50	99.44±0.96
F3	4.10±0.12	6.1±0.56	0.86±0.33	350.31±0.49	100.93±0.55
F4	4.99±0.36	6.6±0.90	0.89±0.12	349.23±0.12	101.13±0.44
F5	4.52±0.20	6.12±0.55	0.88±0.89	351.81±0.96	97.39±0.56
F6	3.96±0.56	6.0±0.33	0.90±0.63	347.24±0.45	98.66±0.20
F7	4.25±0.31	6.5±0.52	0.80±0.97	349.22±0.20	99.93±0.49
F8	4.23±0.12	6.8±0.45	0.81±0.22	350.33±0.96	101.75±0.96

Stability study:

There was no significant difference in physical appearance, thickness, friability, hardness, weight variation and drug content of optimized tablet formulations.

Table 3: Stability Study Data

Table for Stability study of optimized formulation (F7) for 45 days

Parameters	Initial	After 15 days	After 30 days	After 45 days
Physical appearance	White to off white	No change	No change	No change
Weight variation (mg)	349.22±0.20	347±2.34	347±1.51	346±1.23
Thickness (mm)	4.25±0.31	4.18±1.87	4.18±1.01	4.18±0.98
Hardness (kg/cm2)	6.5±0.52	6.1±0.99	6.1±0.64	6.1±0.21
Friability (%)	0.80±0.97	0.71±0.05	0.70±0.08	0.78±0.06
Drug content(%/tablet)	99.93±0.49	99.63±0.34	99.10±0.34	99.01±0.87

Average of three determinations.

DATA OF IN VITRO DRUG RELEASE STUDIES

The kind and preparation of matrix-forming polymers affected the release of nizatidine from sustained release tablets. To maintain an effective drug plasma concentration, sustained release tablets should ideally release the necessary amount of drug. Based on the Nizatidine SR tablet's in vitro drug dissolution profile, it was discovered that the F7 formulation, which contains Kollidon-SR-SR, chitosan, and HPMCK100M in a 1:1 ratio, released 99.36% of the medication in 12 hours. In formulation F8, where the ratio of chitoson to HPMCK100M was 1:2, the release rate falls as the excipients concentration rises. The rate of medication release reduces as the excipient amount is increased.

Table 4: In vitro release of Nizatidine from formulation of F1 TO F8:

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	8.7±0.23	6.26±0.11	7.06±0.12	7.82±0.55	8.21±063	7.24±0.23	8.71±0.54	8.06±036
2	17.1±0.73	12.28±0.2	17.82±0.22	13.26±0.38	17.26±0.97	14.36±0.55	17.02±0.22	20.02±0.39
3	28.35±0.56	20.02±0.68	20.26±0.35	24.86±1.2	24.36±0.31	25.96±0.56	21.62±1.56	26.96±1.14
4	36.45±0.90	29.36±0.59	29.28±0.93	36.01±0.99	39.28±0.56	39.01±0.96	32.02±0.66	29.01±0.56
5	46.59±0.80	38.45±0.25	35.86±0.86	45.26±0.96	43.88±1.02	44.24±0.92	40.75±0.36	45.57±1.6
6	57.17±0.83	46.21±0.44	46.96±0.77	54.26±0.33	24.14±0.86	56.56±0.71	49.13±1.67	51.31±1.45
7	67.21±0.94	53.21±0.86	59.23±0.88	66.86±0.61	68.21±0.75	66.86±0.89	54.52±0.45	65.02±0.68
8	76.26±0.55	60.06±0.59	63.45±0.31	74.26±0.98	77.26±0.91	71.36±1.36	63.25±0.99	74.25±0.93
9	83.21±0.86	73.21±0.98	72.6±0.66	82.29±0.3	83.410.22±	84.23±0.12	70.01±0.58	80.05±0.96
10	92.26±0.96	80.06±0.33	90.36±0.96	88.26±0.12	91.86±0.3	89.25±0.23	77.91±0.86	85.34±1.02
11		89.26±0.53		93.02±0.96		91.01±0.36	88.36±0.39	91.3±0.73
12							99.93±1.01	90.06±0.51

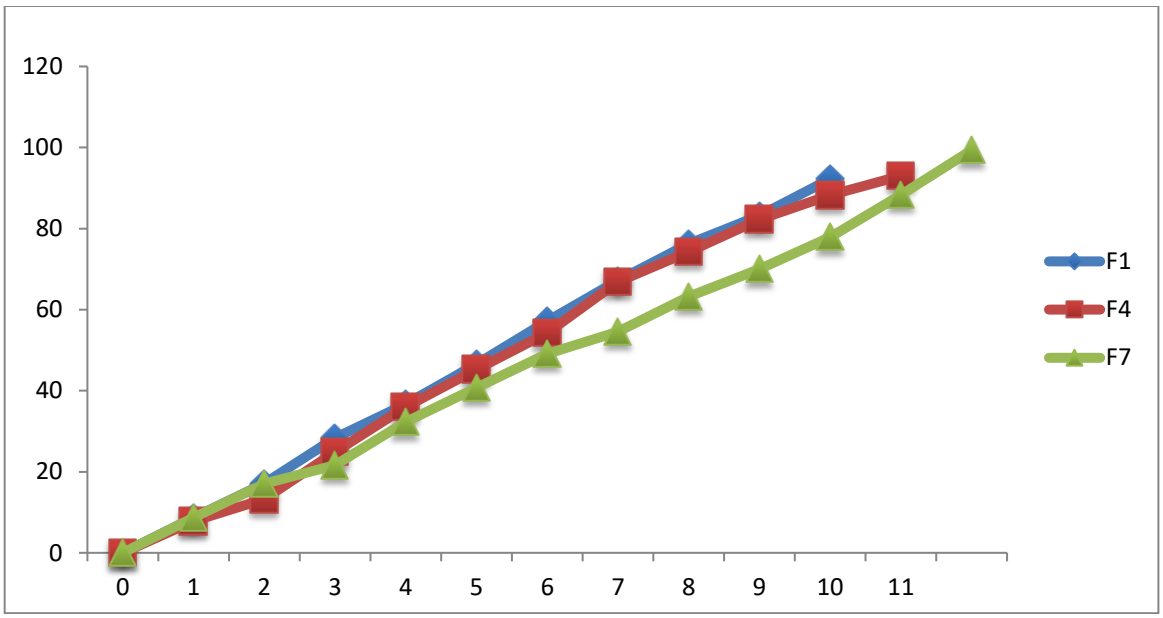

Figure 3: Mean values of dissolution parameters of Nizatidine tablet formulation F1, F4 & F7

Table 5: Percent Drug Release

Time (h)	Percent Drug Released	Log % CPR	Log T	Square root of Time
	Mean±S.D.			
0	0	0	-	0
0.5	11.090±2.439	1.045	-0.301	0.707
1	17.532±1.430	1.244	0	1
2	27.574±0.741	1.44	0.301	1.414
3	35.420±1.907	1.549	0.477	1.732
4	48.688±2.122	1.687	0.602	2
5	66.594±2.574	1.823	0.699	2.236
6	74.654±1.683	1.873	0.778	2.449
8	83.444±2.053	1.921	0.903	2.828
10	89.653±1.056	1.953	1	3.162
12	95.582±1.549	1.98	1.079	3.464
14	101.165±1.748	2.005	1.146	3.742

Table 6: R^2 Values

Model	Slope	R2 value
Zero order	7.285	0.912
First order	0.092	0.559
Higuchi	30.4	0.969
Korsmeyer-Peppas	0.702	0.982

DATA RELEASE KINETICS STUDY

1. **Zero order Release Kinetics of F7 Formulation**

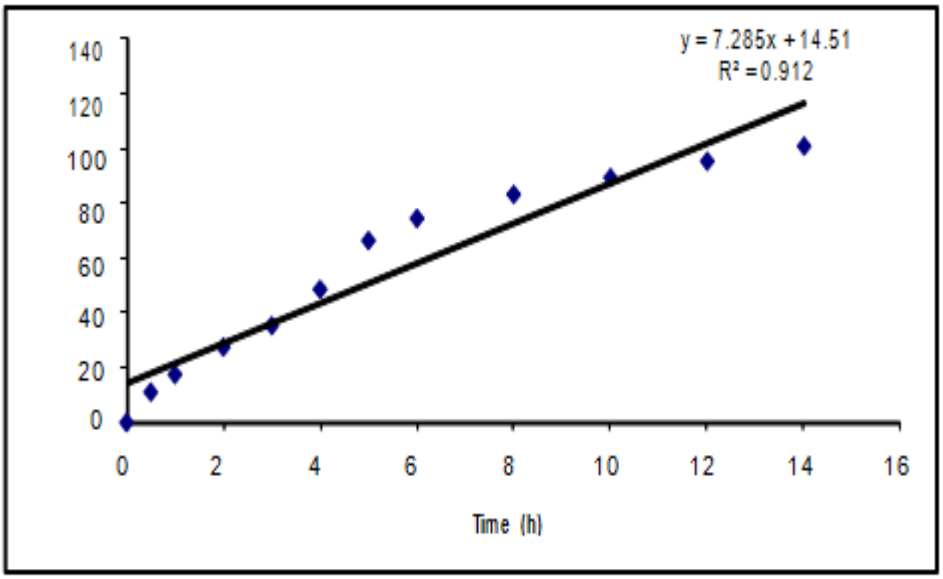

Figure 4: Zero order Plot of F7

2. **First order Release Kinetics of F7 Formulation**

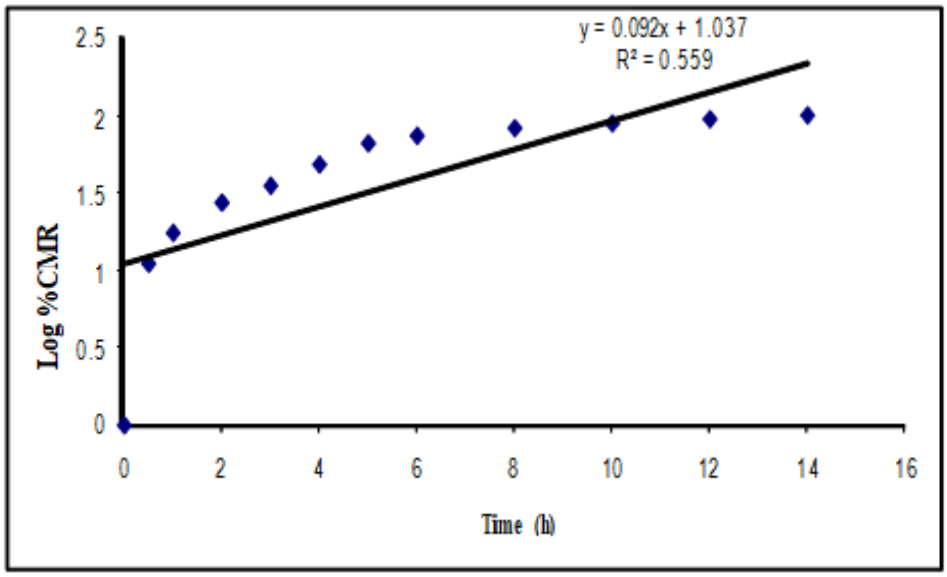

Figure 5: First order Plot of F7

3. **Higuchi order Release Model of F7 Formulation**

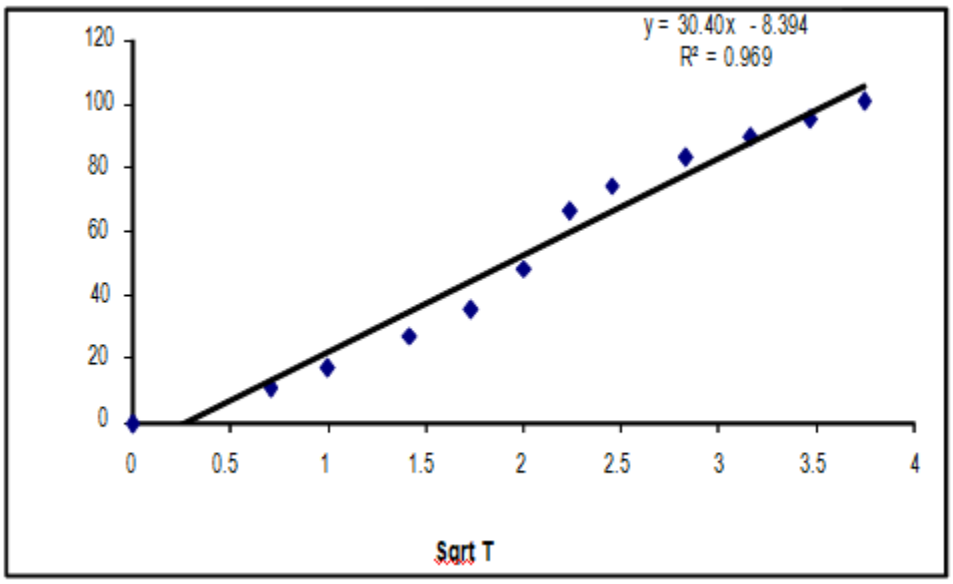

Figure 6: Higuchi Plot of F7

4. Korsemeyer & Peppas Model of F7 Formulation

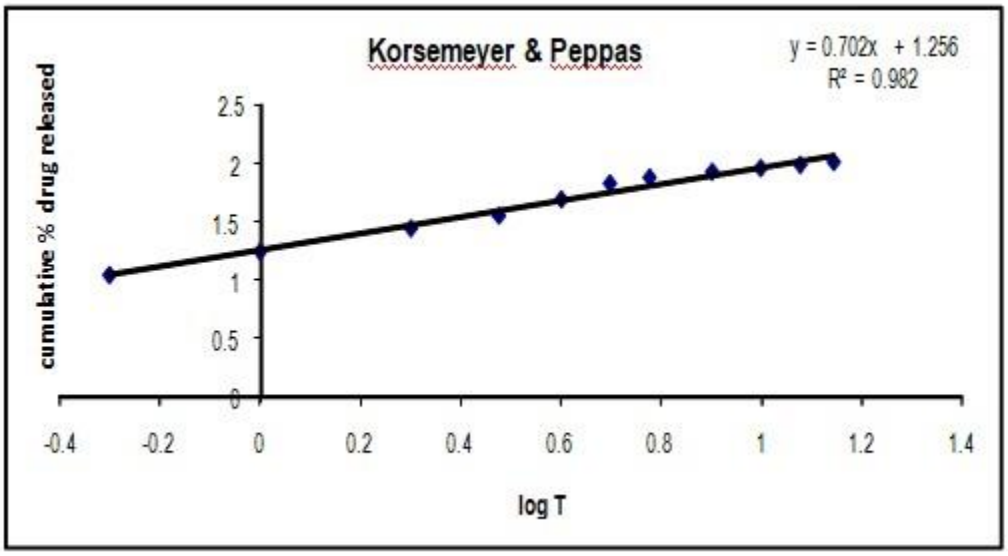

Figure 7: Korsemeyer & Peppas Plot of F7

Conclusion

For the determination whether the chosen medication, nizatidine, could interact with the polymers HPMCK100M and chitosan, kollidon-SR, a FT-IR analysis was conducted. According to the study's findings, there was no interaction between the polymers and the drug of choice. Wet granulation was used to create the sustained release matrix tablets containing nizatidine. Various drug-polymer ratios were used to investigate the impact of polymer concentration. HPMC K100M, Chitosan, lactose and Kollidon-SR as binding agents. Talc was utilized as a lubricant and magnesium stearate as a glidant. The tablets were assessed for hardness, weight fluctuation, content uniformity, and friability. Nizatidine in vitro release from the produced tablets was observed in 0.1 N HCL for two hours and in phosphate buffer pH 6.8 for ten hours. The drug release from the tablets was seen to be slowed by the polymers HPMC K 100M, Chitosan and Kollidon-SR-SR. Based on in vitro release experiments and physicochemical attributes, the optimal formulation (F7) was chosen among all of the developed formulations. We tested release kinetics on the optimal formulations. Zero order diffusion controlled medication release was seen from the formulation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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