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Formulation and *In-vitro* Evaluation of Diltiazem Hydrochloride Non Effervescent Floating Tablets

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Abstract: ***In the present research work non effervescent floating formulation of Diltiazem hydrochloride by using various polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations.. Then the formulation was developed by using different concentrations of polymers of various polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulation F7 prepared by using Chitosan 10 mg produced maximum drug release compared to other formulations hence it was considered as the optimized formulation. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order kinetics of drug release.***

Keywords: Diltiazem hydrochloride, Chitosan, non effervescent floating Tablets

1. Introduction

The floating drug delivery system (FDDS) also called Hydro dynamically Balanced Drug Delivery System (HBS). FDDS is an oral dosage forms (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. Drug dissolution and release from dosage retained in the stomach fluids occur at the pH of the stomach under fairly controlled condition.

The gastro retentive dosage form can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Diltiazem, a benzothiazepine calcium channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina. Diltiazem is a non-dihydropyridine (DHP) member of the calcium channel blocker class, along with Verapamil. Diltiazem is similar to other peripheral vasodilators. The elimination half-life of Diltiazem is 3 to 4.5 h.Diltiazem is well absorbed from the gastrointestinal tract but undergoes substantial hepatic first-pass effect.

2. Materials

Diltiazem, Methocel K 4M, Chitosan, Methocel K 15M, Accurel@MP100, MCC pH 102
Magnesium stearate, Talc all the chemicals used were laboratory grade.

3. Methodology

Optimization of Accural concentration:
Accural was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of Accural were employed; floating lag time and floating duration were observed. Based on that the concentration of Accural was finalised and preceded for further formulations.

Table 1: Optimization Accural concentration

S.No	Excipient Name	EF1	EF2	EF3
1	Diltiazem hydrochloride	30	30	30
2	Methocel K 4M	10	10	10
3	Accural	10	20	30
4	Mg.Stearate	3	3	3
5	Talc	3	3	3
6	MCC pH 102	Q.S	Q.S	Q.S

Based on the floating lag time and floating duration the concentration of Accural was optimized.

Table 2: Composition of Floating Tablets of Diltiazem hydrochloride by Using Different Concentrations of Polymers

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem hydrochloride (mg)	30	30	30	30	30	30	30	30	30
Methocel K4M (mg)	10	20	30	-	-	-	-	-	-
Methocel K15M (mg)	-	-	-	10	20	30	-	-	-
Chitosan (mg)	-	-	-	-	-	-	10	20	30
Accural (mg)	20	20	20	20	20	20	20	20	20
Magnesium Stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH 102 (mg)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	150	150	150	150	150	150	150	150	150

Method of Preparation:

In this work, direct compression method has been employed to prepare floating matrix tablets of Diltiazem hydrochloride with Methocel K15M, Methocel K4M & Chitosan. All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes then , Micro crystalline cellulose, Accural, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 40mesh. Tablets were compressed by direct compression method on a multi punch12 station Rotary tablet compression machine) using 7mm flat round punches.

Evaluation of post compression parameters for prepared Tablets

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

4. Results & Discussion

The present study was aimed to developing non effervescent floating tablets of Diltiazem hydrochloride using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method

Graphs of Diltiazem hydrochloride was taken in Simulated Gastric fluid(pH 1.2) at 225 nm.

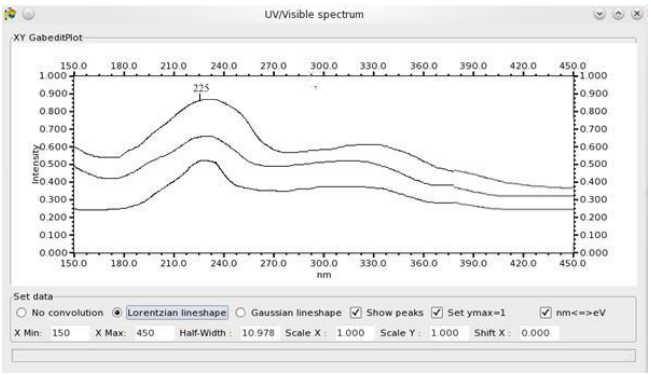

Figure 1: UV spectrum graph of pure drug

Table 3: Observations for graph of Diltiazem hydrochloride in 0.1N HCl (225 nm)

Concentration (µg/ml)	Absorbance
2	0.154
4	0.286
6	0.428
8	0.535
10	0.685

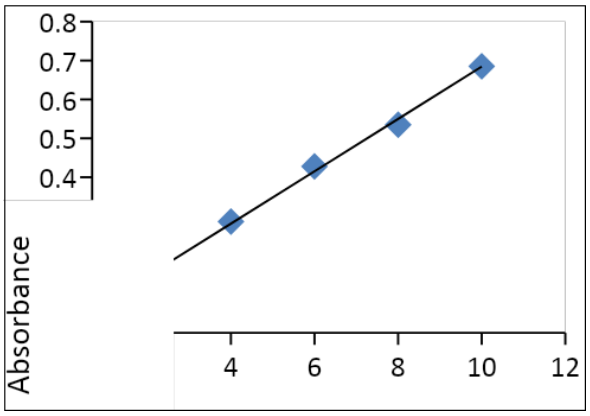

Figure 2: Standard graph of Diltiazem hydrochloride in 0.1N HCl ndard graph of Diltiazem hydrochloride in 0.1N HCl

Fourier Transform-Infrared Spectroscopy:

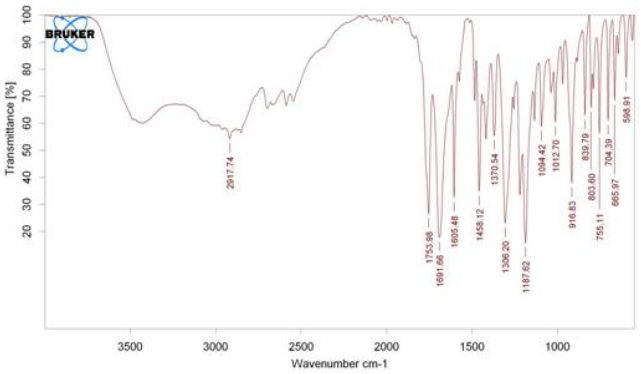

Figure 3: FT-TR Spectrum of Diltiazem hydrochloride pure drug

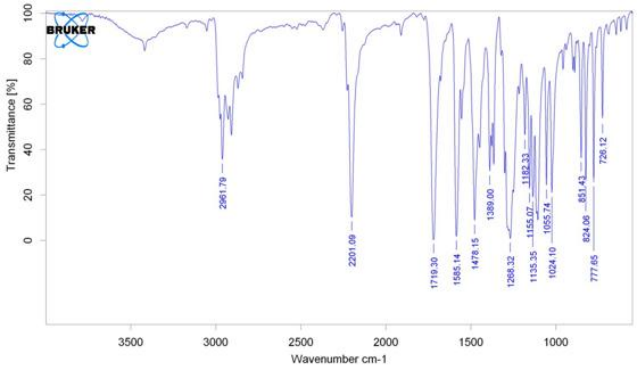

Figure 4: FT-IR Spectrum of Optimized Formulation

Table 4: Pre-formulation parameters of blend

Formulation Code	Bulk density	Tapped density	Compressibility Index	Hausner's ratio
F1	0.49±0.09	0.57±0.03	16.21±0.22	0.86±0.02
F2	0.56±0.19	0.62±0.29	16.87±0.29	0.98±0.28
F3	0.52±0.22	0.68±0.67	17.11±0.18	0.64±0.33
F4	0.54±0.29	0.64±0.98	17.67±0.13	1.12±0.74
F5	0.53±0.48	0.67±0.84	16.92±0.29	1.2±0.28
F6	0.56±0.29	0.66±0.45	17.65±0.22	1.06±0.28
F7	0.58±0.33	0.69±0.34	16.43±0.43	0.76±0.19
F8	0.48±0.45	0.57±0.48	17.97±0.82	1.15±0.22
F9	0.54±0.39	0.62±0.48	17.54±0.19	1.17±0.19

The powder blends were prepared by mixing of various ingredients mentioned and used for characterization of various flow properties of powder.

Bulk density:
The bulk density of all the formulations was found to be in the range of 0.49 ±0.09 to 0.58±0.33 (gm/cm3) showing that the powder has good flow properties.

Tapped density:
The tapped density of all the formulations was found to be in the range of 0.57±0.03to 0.69±0.34showing the powder has good flow properties.

Compressibility index
The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties.

Hausner ratio
All the formulations has shown the hausner ratio ranging between 0.6 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets:
Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets.

Table 5: Quality control parameters for tablets

Formulation Code	Weight variation (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	Buoyancy lag time (sec)	Duration of buoyancy(hrs)	Swelling Index(%)
F1	148±0.54	3.4±0.45	2.1±0.07	0.48±0.02	100.8±0.08	98±0.98	>12±0.03	2.2±0.93
F2	154±0.32	3.25±0.46	2.1±0.34	0.38±0.28	97.8±0.12	112±0.18	10±0.19	2.4±0.28
F3	150±0.34	3.5±0.65	2.2±0.38	0.46±0.18	99.99±0.11	108±0.34	11±0.11	2.3±0.16
F4	152±0.54	3.1±0.45	2.3±0.37	0.40±0.28	101.33±0.87	99±0.11	8±0.38	1.9±0.45
F5	154±0.46	3.4±0.37	2.3±0.35	0.60±0.45	100.07±0.15	99±0.22	9±0.29	1.9±0.33
F6	152±0.56	3.5±0.36	2.2±0.76	0.43±0.65	95.61±0.18	105±0.58	>12±0.11	2.1±0.27
F7	149±0.44	3.2±0.88	2.3±0.71	0.45±0.76	98.91±0.83	97±0.19	>12±0.13	1.8±0.18
F8	154±0.35	2.9±0.87	2.3±0.32	0.52±0.87	100.12±0.28	99±0.55	10±0.12	2.2±0.22
F9	151±0.35	3.2±0.36	2.3±0.82	0.45±0.38	99.08±0.18	105±0.65	11±0.54	2.3±0.15

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Appearance
The tablets were observed visually and did not show any effect such as capping, chipping and lamination.

Physical characteristics
The physical characteristics of Diltiazem hydrochloride floating tablets (F1 to F9) such as weight variation, thickness, hardness, friability and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

Hardness
A difference in tablet hardness reflects difference in tablet density and porosity. The hardness of tablets was found to be in the range of 2.9±0.87 Kg/cm^2 to 3.5±0.65 Kg/cm^2

Percentage friability
Percentage friability of all formulations was found to be in the range of 0.38±0.28% to 0.60±0.45%.This indicates good handling property of the prepared tablets.

Thickness
The thickness of the prepared formulations were found to be in the range of 2.1±0.07mm to 2.3±0.82

Weight variation
The average weight of the tablet is 100mg. The pharmacopoeial limit for percentage deviation is ±5%. The weights of all tablets were ranged from 148±0.54mg to 154±0.35mg.

Drug content
All the floating tablet formulations shown good uniformity in drug content and they contain 97.8±0.12 to 101.33±0.87% of Diltiazem hydrochloride which is within the specified limit.

***In-Vitro* Drug Release Studies**

Table 6: Dissolution Data of F1, F2, F3 Formulations

Time (hrs)	F1	F2	F3
0	0	0	0
0.5	2.13±0.51	5.05±0.45	3.82±0.69
1	8.91±0.64	11.61±0.72	8.09±0.78
2	16.85±0.49	19.54±0.63	13.11±0.46
3	22.18±0.81	24.57±0.51	22.72±0.57
4	31.19±0.57	32.29±0.46	31.51±0.49
5	39.27±0.46	41.73±0.78	43.26±0.81
6	47.05±0.78	49.62±0.57	52.83±0.64
7	53.28±0.63	58.91±0.49	61.21±0.51
8	61.24±0.72	64.07±0.81	65.36±0.63
9	66.53±0.45	72.16±0.64	71.21±0.45
10	73.29±0.39	79.61±0.49	75.29±0.62
11	77.41±0.57	85.72±0.78	81.51±0.39
12	82.25±0.43	91.2±0.39	84.71±0.51

Table 7: Dissolution Data of F4, F5, F6

Time (hrs)	F4	F5	F6
0	0	0	0
0.5	4.41±0.71	4.02±0.45	2.03±0.39
1	9.34±0.49	10.17±0.51	8.36±0.72
2	11.41±0.57	17.32±0.78	12.52±0.63
3	19.82±0.51	23.75±0.63	20.94±0.64
4	23.11±0.81	29.38±0.49	27.51±0.57
5	31.86±0.46	36.18±0.81	35.85±0.78
6	39.01±0.63	45.27±0.64	46.24±0.81
7	45.36±0.78	56.26±0.57	54.06±0.46
8	56.24±0.57	64.17±0.46	65.12±0.51
9	63.91±0.72	69.42±0.39	73.67±0.45

10	69.15±0.51	73.36±0.78	79.82±0.49
11	72.08±0.45	79.19±0.72	86.27±0.39
12	79.54±0.56	85.04±0.64	92.72±0.54

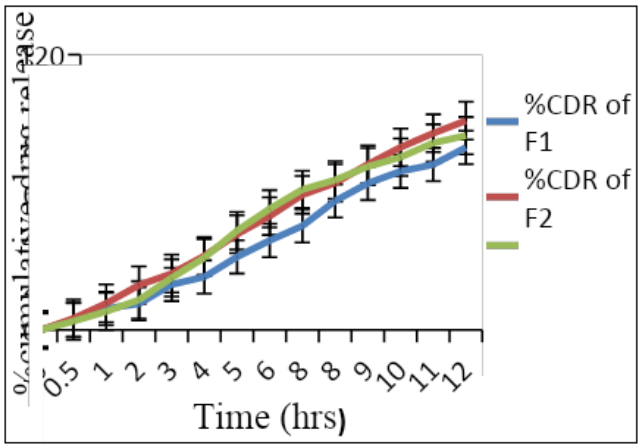

Figure 5: Dissolution profile of F1, F2, F3 formulations

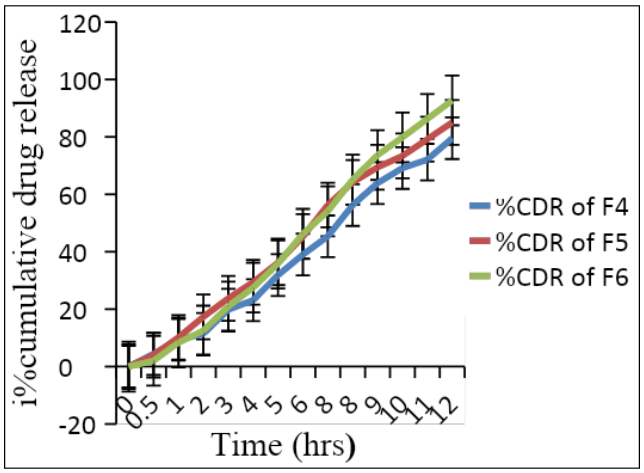

Figure 6: Dissolution profile of F4, F5, F6 formulations.

Table 8: Dissolution Data of F7, F8, F9 Formulations

Time (hrs)	F7	F8	F9
0	0	0	0
0.5	3.51±0.47	3.19±0.72	4.54±0.45
1	10.23±0.46	8.42±0.78	9.82±0.64
2	18.54±0.49	16.63±0.63	13.55±0.81
3	25.85±0.81	27.25±0.46	21.37±0.57
4	34.13±0.51	36.14±0.64	27.23±0.46
5	46.84±0.57	45.12±0.81	36.96±0.63
6	54.47±0.78	54.16±0.57	44.37±0.51
7	63.23±0.63	63.74±0.49	53.91±0.72
8	72.99±0.72	68.29±0.73	61.53±0.78
9	79.22±0.64	74.16±0.45	69.73±0.48
10	85.31±0.52	79.03±0.51	73.86±0.49
11	93.08±0.67	84.25±0.39	79.06±0.57
12	97.19±0.39	92.98±0.37	86.09±0.72

From the above dissolution results, it was observed that all the formulations drug release is sustained

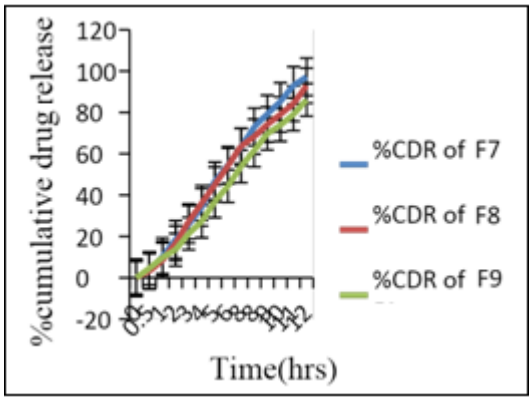

Figure 7: Dissolution profiles of F7, F8, F9 formulations

for up to 12 hours. In case of formulations prepared with Methocel K4M (F1-F3), percentage of drug release is not more than 92.0% within 12 hours. In case of formulations prepared with Methocel K15M (F4-F6), percentage of release was not more than 93.0%. And whereas, in case of formulations prepared with chitosan (F7-F9), percentage of release was more than 95%. In case of formulation F7, percentage of drug release was extended up to 97.0%. Hence, F7 formulation is the optimized.

Table 9: Release kinetics data for optimised formulation

Cumulative (%) Release Q	Time (T)	ROOT (T)	LOG (%) Release	LOG (T)	LOG (%) Remain
0	0	0			2
3.51	0.5	0.458	0.545	1.987	1.984
10.23	1	1	1.01	0	1.953
18.54	2	1.414	1.268	0.301	1.911
25.85	3	1.732	1.412	0.477	1.87
34.13	4	2	1.533	0.699	1.819
54.47	6	2.449	1.736	0.778	1.658
63.23	7	2.646	1.801	0.845	1.565
72.99	8	2.828	1.863	0.903	1.432
79.22	9	3	1.899	0.954	1.318
85.31	10	3.162	1.931	1	1.167
93.08	11	3.317	1.969	1.041	0.84
97.19	12	3.464	1.988	1.079	0.449

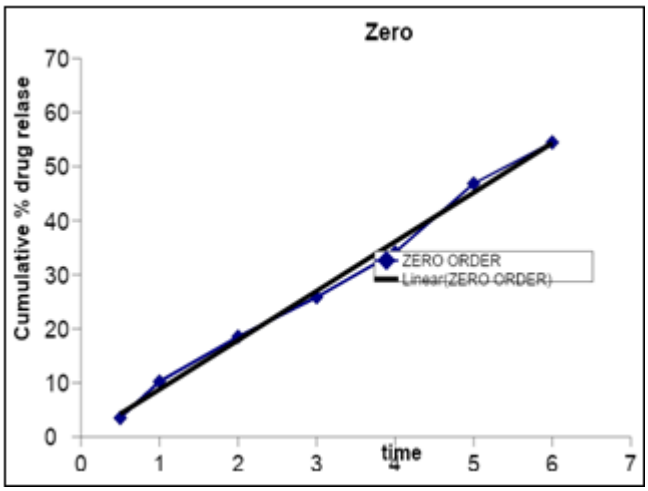

Figure 8: Zero order release kinetics graph

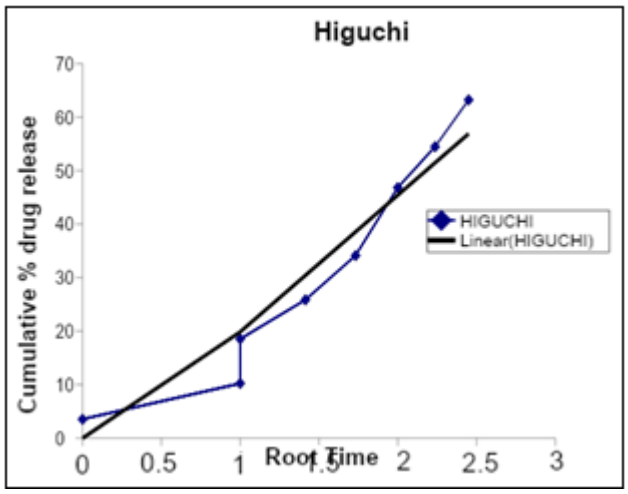

Figure 9: Higuchi release kinetics graph

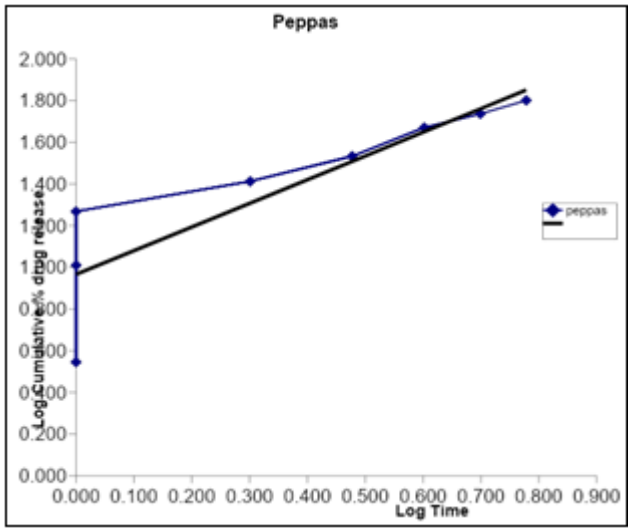

Figure 10: Kars mayer peppas graph

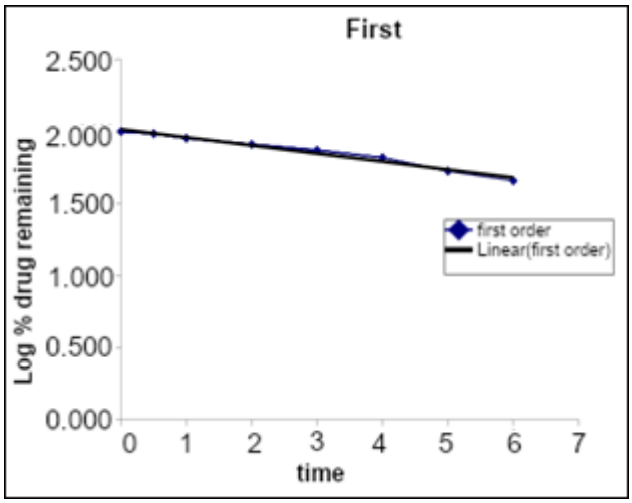

Figure 11: First order release kinetics graph

From the above graphs it was evident that the formulation F7 was followed Zero order release mechanism.

5. Conclusion

In the present research work non effervescent floating formulation of Diltiazem hydrochloride by using various polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations.. Then the formulation was developed by using different concentrations of polymers of various polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulation F7 prepared by using Chitosan 10 mg produced maximum drug release compared to other formulations hence it was considered as the optimized formulation. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed zero order kinetics of drug release.

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