

Original Article

Formulation & In Vitro Evaluation of Effect of Polymer in Gastro-Retentive Drug Delivery System Using Ciprofloxacin Hydrochloride as A Model Drug

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Abstract: Gastro-retentive dosage form offer many advantages having absorption from upper gastrointestinal tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new gastro-retentive floating drug delivery system was developed for ciprofloxacin preferably once daily. The design of the delivery system was based on the sustained release formulation with floating and swelling features in order to prolong the gastric retention time of the drug delivery system. Final formulations were prepared and optimized by Box-Behnken design by using HPMC K100M and Carbopol 934 as a polymers and sodium bicarbonate as a gas generating agent. The tablets were prepared by wet granulation method. The prepared formulations were evaluated for hardness, weight variations, thickness, swelling index, in-vitro buoyancy, drug content and drug release study. The effect of polymer (HPMC K100M and Carbopol 934) concentration on drug release profile and swelling index was evaluated. The in-vitro dissolution study showed that the drug release profile could be sustained by increasing the concentration of polymers (HPMC K100M and Carbopol 934). Result of swelling index showed that increasing the concentration of polymers, increases the swelling index of tablet. The optimized formulations containing 12.36 % of HPMC K100M, 7.47 % of Carbopol 934 and 18.66% of Sodium bicarbonate with citric acid in the ratio of 2:1 sustained the drug release upto 12 hours, following Higuchi model of drug release and drug release mechanism was non-fickian diffusion. This study proves that using HPMC K100M and Carbopol 934 as a matrix polymer in combination with Sodium Bicarbonate as a gas generating agent can be used to develop sustained release floating tablets of Ciprofloxacin.

Keywords: gastro-retentive floating drug delivery, HPMC, Ciprofloxacin HCl

1. INTRODUCTION

Despite the significant progress in drug delivery, oral administration is still the most popular method for systemic circulation due to its ease of use, low cost, patient compliance, and formulation flexibility [1]. Approximately 90% of all drugs used to produce systemic effects are administered orally. Among the drugs that are administered orally, solid oral dosage forms are the most preferred class of products [2]. The most prevalent type of solid dosage form in current use is tablets, and they have different classifications depending on the drug release pattern, for example, conventional immediate release or modified release

[3]. Conventional drug delivery systems including normal tablets, capsules, or sterile drug preparations, are associated with limitations, including low site-specific accumulation of drugs, unfavorable body distribution, adverse side effects, etc [4]. Drug release from dosage forms, the stomach emptying process, the gastrointestinal transit time of dosage forms, and the site of drug absorption are only a few of the many variables that affect the highly variable process of drug absorption in the gastrointestinal tract [5]. Drugs that are quickly absorbed from the digestive system and have short durations of action are rapidly cleared from the blood stream [6]. Gastro-retentive systems can persist in the stomach area for long periods and thus considerably increase the time that drugs stay in the stomach. Longer gastric retention enhances drug absorption, reduces drug loss, and improves the dissolvability of drugs that are less soluble in alkaline conditions [7]. Gastric retention can offer new treatment options and significant advantages for patients. The regulated gastric retention of solid dosage forms can be achieved by the methods of muco-adhesion, floating, settling, swelling, altered shape systems, or by the use of pharmacological agents that slow down stomach emptying [8]. GRDDS are beneficial for such drugs by improving their absorption, efficacy, and dosage reduction [9]. Besides these benefits, these systems also offer other pharmacokinetic advantages such as keeping stable therapeutic levels for a long time and thus lowering the therapeutic dose [10]. Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made up of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions [11]. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours [12]. This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases [13]. After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern [14]. The gastric residence time of a dosage form is primarily influenced by its density, buoyant dosage forms, with a density lower than that of gastric fluids, float in the stomach [15]. This buoyancy keeps the dosage unit away from the pyloric sphincter, resulting in prolonged retention in the stomach. Reports indicate densities below 1.0 g/ml, which is less than that of gastric contents [16]. The drug release and floating characteristics of Floating Drug Delivery Systems (FDDS) are significantly impacted by the viscosity of polymers and their interactions [17]. It was noted that low viscosity polymers offer greater advantages in enhancing floating properties compared to high viscosity polymers [18]. Hollow microspheres (Microballoons), loaded with drug in their outer polymer shells, and are prepared by emulsion-solvent diffusion method [19]. The Microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours [20]. In this approach formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulfate, zinc oxide and titanium oxide so that the density of the formulation exceeds the density of the normal gastric content [21].

2. MATERIALS & METHODS

Ciprofloxacin Hydrochloride and all other materials except HPMC K 100M was received as a gift sample from Pharmaco Industries Pvt. Ltd. HPMC K 100M was received as a gift sample from Apex Pharmaceuticals Pvt. Ltd., Birgunj, Nepal. All the materials and chemicals used were of either pharmaceutical or analytical grade. The list of material along with the name of the supplier is listed in Table below.

Table 01: Materials and their suppliers

S.no.	Materials	Supplied by
1	Ciprofloxacin Hydrochloride	Aarti Drugs Ltd.
2	Carbopol 934	Shree Chemical Pvt. Ltd.
3	Sodium Bicarbonate	Life science
4	Citric Acid	Life science
5	Microcrystalline cellulose 102	Accent Microcell Pvt. Ltd.
6	Polyvinyl Pyrrolidone K30	Alenit Chemicals LLP
7	Isopropyl Alcohol	
8	Magnesium Stearate	Accent Microcell Pvt. Ltd.
9	Talc	A.S.T Pvt. Ltd
10	Colloidal Silicon Dioxide	K Kumar & Co
11	Hydrochloric acid	Balkumari International

The list of Instrument and Equipment used in the project along with model number and manufacturer is listed in Table.

Table 02: Equipment and their manufacturer

S.no.	Instruments name	Model no.	Manufacturer
1	Electronic weighing balance	AR1530	Ohaus
2	Tapped Density Apparatus		Aastha International
3	Moisture Balance	MB27	Ohaus Corporation, USA
4	Tray Drier		Aastha International
5	20 Stations tablet compression machine	Cip3 RY-20 STN, GMP Newlook	Cip machineries Pvt. Ltd.
6	Tablet hardness tester	EH01P	Electrolab
7	Friability test apparatus	EF-2 (USP)	Electrolab
8	Sonicator	3.5L 100H	PCI Analytics
9	pH meter	Multipara MP-8	Spectralab Instrument Pvt. Ltd.
10	Tablet dissolution test Apparatus	DS 8000	Lab India Pvt. Ltd.
11	UV-Visible Spectrophotometer	Cary 60 UV-Vis	Agilent Cary 60
12	FTIR spectrophotometer		Thermoscientific

Pre-formulation studies can therefore be defined as; Laboratory studies to determine the characteristics of active substance and excipients that may influence formulation and process design and performance. A small quantity of pure ciprofloxacin hydrochloride powder was taken in a butter paper and viewed in well illuminated place. Very less quantity of ciprofloxacin hydrochloride was used to get taste with the help of tongue as well as smelled to get the odor. Solubility is important pre-formulation parameter because it affects the dissolution of drug bio availability of drug. Solubility of ciprofloxacin hydrochloride was determined in methanol, ethanol and 0.1N hydrochloric acid. Solubility studies were performed by taking excess amount of ciprofloxacin hydrochloride in different beakers containing the solvent. The melting point of ciprofloxacin hydrochloride was determined by capillary method, using small quantity of ciprofloxacin hydrochloride was taken and placed in apparatus and determined the melting point and matched with standards. The tablets each containing 500mg Ciprofloxacin Hydrochloride were prepared by wet

granulation method. At first, Ciprofloxacin Hydrochloride, MCCP 102, Carbopol 934, HPMC, Sodium bicarbonate and citric acid was passed through #60 mesh sieve. The API, excipients and polymers were mixed for 2 minutes in polybag. PVPK 30 was used as a binder and was dissolved in 30 ml of IPA. Then the granulating fluid was poured into mixed powder and kneaded manually. The granules were first passed through #12 mesh sieve. Granules were blow dried for 10 minutes and heat dried at 50°C for about 10 minutes and dried granules were again passed through #12 mesh. All other excipients like Aerosol, Talc and Magnesium stearate were passed through #100 mesh sieves. These sieved excipients were mixed with dried granules in a polybag for around 2 minutes. Final granules are subjected for compression in single hopper 20th station rotary compression machine (Eliza-Press, EP-200L) using 19mm oblong biconcave punch. Compression weight was set to 1190mg, weigh accurately about 50 mg of Ciprofloxacin HCl RS. Transfer to the volumetric flask, dissolve and make up the volume to 1000 ml with 0.1N HCl. Take 1 ml of solution and make up the volume to 100 ml with 0.1N HCl. Powder 20 tablets, weigh accurately the powder equivalent to about 50 mg of Ciprofloxacin HCl and make dilution similarly as standard. Centrifuge the solution before making second dilution. Take the reading of standard and sample solution at the maximum at about 275 nm in a suitable UV-spectrophotometer taking 0.1N HCl as a blank. Calculate the content of Ciprofloxacin from the declared content in Ciprofloxacin HCl RS. The tablets were placed in a 200 ml beaker containing 0.1 N HCl. The time between introduction of dosage form and its buoyancy on 0.1 N HCl, and the time during which the dosage form remains buoyant were measured. The time taken for the dosage form to emerge on surface of medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time during which the dosage form remains buoyant is called Total Floating Time (TFT). A 50mg of Ciprofloxacin Hydrochloride RS was weighed and transferred to 100ml volumetric flask. About 20ml of dissolution medium was added to flask and sonicated for 10 minutes to dissolve. It was then allowed to cool down to room temperature and volume was made up by dissolution medium. One milliliter of this solution was diluted to 100ml using dissolution medium to prepare solution containing 0.01mg/ml of Ciprofloxacin Hydrochloride RS. Method validation can be defined as the process of proving that a particular developed analytical method is acceptable for its intended use. Method validation is a continuous process, and the final goal of validation of an analytical method is to ensure that every future measurement in routine analysis will be close enough to the unknown true value for the content of the analyte in the sample. System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated.

3. RESULTS & DISCUSSION

3.1 Organoleptic Properties

These tests were performed as per procedure given and results were illustrated in table below.

Table 03: Observation of organoleptic properties:

Test	Specification	Observation
Color	Pale Yellow	Pale Yellow
Odour	Odourless	Unpleasant
Taste	Tasteless	Bitter

Ciprofloxacin hydrochloride samples are examined and it was found to be soluble in water and slightly soluble in methanol, soluble in dimethyl formamide. It also dissolves in dilute alkali and in dilute acids. Melting point of ciprofloxacin hydrochloride was found to be 290°C. Melting point compared with USP standards that showed that drug is pure.

3.2 Compatibility Study

IR spectroscopic studies were conducted to determine possible drug-polymer interactions. IR spectra of pure drug Ciprofloxacin HCl and polymers HPMC K100M, Carbopol 934, Sodium Bicarbonate and Citric acid and their physical mixture in the ratio of 1:1 (Drug : Polymer) were observed after storing at 40°C in hot air oven for 4 weeks. Ciprofloxacin, HPMC K100M, Carbopol 934, Sodium Bicarbonate and Citric Acid when scanned individually showed peaks at different frequencies as in figure which can be interpreted as shown in table.

3.3 Standard calibration curve of Ciprofloxacin HCL

The λ_{max} of Ciprofloxacin HCl in 0.1 N HCl was found to be 275 nm by scanning the spectrum between 200 to 400 nm using UV-visible spectrophotometer.

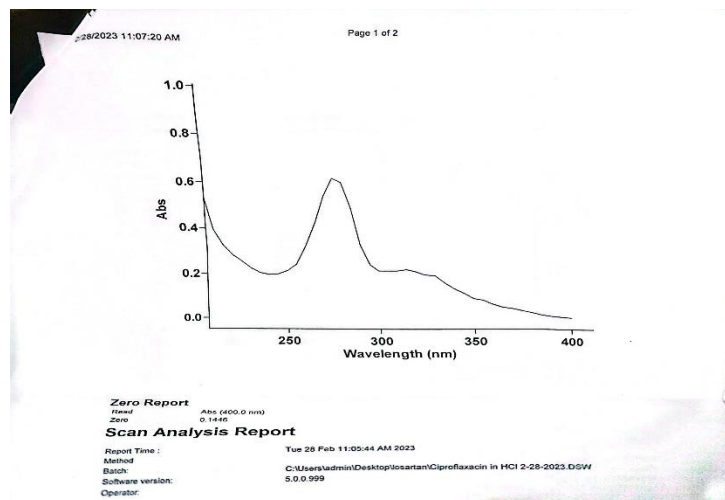


Figure 01: Scan of Ciprofloxacin HCl in 0.1 N HCl using UV Spectrophotometer

The absorbance values are tabulated in Table. Ciprofloxacin HCl obeyed Beer's law in the concentration range of 2-10 $\mu\text{g/ml}$ with regression coefficient of 0.9953. The correlation coefficient (R^2) values of ciprofloxacin hydrochloride reference standard in 0.1N HCl was found to be 0.9953 which justified that solvents have no interference on absorbance readings. The standard calibration curve of Ciprofloxacin HCl.

Table 04: Absorbance of standard solutions of Ciprofloxacin Hcl

S.No.	Concentration ($\mu\text{g/ml}$)	Absorbance (276nm)
1	2	0.2238
2	4	0.4474
3	6	0.6592
4	8	0.9188
5	10	1.0709

3.4 Box Behnken Design

Significant factors HPMC K100M, Carbopol 934, Sodium Bicarbonate and Citric Acid were further optimized by response surface methodology using Minitab 20.4. Box Behnken Design resulting in a total 15 experiments were used to optimize the chosen key factors that affects drug release and floating time.

3.5 Experimental Design

A preliminary study was performed to find out the effect of HPMC K100M, Carbopol 934, Sodium bicarbonate and Citric acid in dissolution profile of Ciprofloxacin Hydrochloride. For this initially, four formulations were prepared using HPMC K100M. The result showed decreasing drug sustaining effect of HPMC K100M (from C1 to C4) with decrease in percentage of HPMC K100M in the tablet formulation. The formulation C2 to C4, containing HPMC K100M from 15 to 25% respectively, did not meet the desired drug release profile. Hence, we decreased the amount of HPMC in C1 to 10%. Decreasing amount of HPMC in C4 gave the drugs release profile as of desired drug release profile but the drug release at 8th hour was relatively higher.

Table 05: Composition of Trial batches from C1 to C4

Formulations	%HPMC K100M	1	2	4	8	12	24
C1	10	19.18	27.77	41.32	61.35	86.33	101.97
2	15	11.59	19.18	28.94	49.99	80.89	96.64
C3	20	9.579	12.506	19.838	34.36	73.76	89.04
C4	25	6.581	11.788	18.009	23.903	67.59	78.89

Table 06: Cumulative Drug Release of Trial using HPMC K100M only.

Formulations	%HPMC K100M	1	2	4	8	12	24
C1	10	19.18	27.77	41.32	61.35	86.33	101.97
2	15	11.59	19.18	28.94	49.99	80.89	96.64
C3	20	9.579	12.506	19.838	34.36	73.76	89.04
C4	25	6.581	11.788	18.009	23.903	67.59	78.89

Table 07: Composition of Trial batches from C5 to C10

Ingredients	C5	C6	C7	C8	C9	C10
Ciprofloxacin HCl	582	582	582	582	582	582
HPMC K100M	109 (10%)	109 (10%)	109 (10%)	109 (10%)	109(10%)	109(10%)
Carbopol 934	54.5 (5%)	54.5 (5%)	54.5 (5%)	85.35 (7.83%)	23.67 (2.17%)	76.3 (7%)
Sod. Bicarbonate	57.62 (7.93%)	109 (15%)	159.87 (22%)	109 (15%)	109 (15%)	72.67 (10%)
Citric Acid	28.82	54.5	79.93	54.5	54.5	36.33
MCC PH 102	127.26	50.2	6.6	19.35	81.03	82.9
PVP K30	109	109	76.3	109	109	109

Talc	10.9	10.9	10.9	10.9	10.9	10.9
Aerosil	5.45	5.45	5.45	5.45	5.45	5.45
Magnesium Stearate	5.45	5.45	5.45	5.45	5.45	5.45
Total Weight	1100	1100	1100	1145	1100	1100

Table 08: Cumulative % Drug Release of Trial batches using HPMC K100M, Carbopol 934 and Effervescent agent.

Formulations	1	2	4	6	8	10	12	24
C5	32.09	41.44	45.43	54.44	67.86	78.19	81.28	102.33
C6	52.96	62.58	74.24	84.275	86.93	90.78	94.82	99.97
C7	99.95							
C8	23.38	34.49	45.43	55.27	66.4	78.15	89.07	98.95
C9	91.47							
C10	40.89	52.89	64.46	71.4	81.715	89.77	95.9	

The formulation from preliminary trial was optimized statistically by Box-Behnken design using three independent factors HPMC K100M content (A), Carbopol 934 content (B) and Effervescent agent (Sodium bicarbonate + Citric Acid) content (C) with three level. The level of independent variables was set based on preliminary trials. The detail study of effect of individual independent variables on dependent variables i.e. Drug release at 1st hour, Drug release at 2nd hour, Drug release at 4th hour, drug release at 6th hour, drug release at 8th hour, Drug release at 10th hour and drug release at 12th hour was done using statistical tool.

Table 09: Variables in Box Behnken Design

Independent variable					Level		
					Low	Medium	High
					(-1)	0	(+1)
(A) Amount of HPMC K100M					9	12	15
(B) Amount of Carbopol 934					7	9.5	12
(C) Amount of Effervescent agent					15	20	25
Response Variable					Constraints		
X1=cumulative % drug dissolved in 1sthour					NLT 10 %		
X2=cumulative % drug dissolved in 2ndhour					20 - 30 %		
X3=cumulative % drug dissolved in 4thhour					30 - 50 %		
X4=cumulative % drug dissolved in 6thhour					NLT 50 %		
X5=cumulative % drug dissolved in 8thhour					55 - 75 %		
X6=cumulative % drug dissolved in 10thhour						NLT 75 %	
X7=cumulative % drug dissolved in 12thhour					NLT 85 %		

Fifth teen batches (S-01 to S-15) were prepared according to experimental design for optimization of HPMC K 100M, Carbopol 934 and Effervescent agent concentration to obtain the desired drug release profile. Compositions of the factorial batches are shown in Table.

Table 10: Factorial Batches obtained from Minitab 20.4

	Std Order	Run Order	Pt Type	Blocks	HPMC K100M	Carbopol 934	SB+CA
1	8	1	2	1	15	9.5	25
2	15	2	0	1	12	9.5	20
3	12	3	2	1	12	12.0	25
4	5	4	2	1	9	9.5	15
5	3	5	2	1	9	12.0	20
6	6	6	2	1	15	9.5	15
7	7	7	2	1	9	9.5	25
8	9	8	2	1	12	7.0	15
9	11	9	2	1	12	7.0	25
10	2	10	2	1	15	7.0	20
11	10	11	2	1	12	12.0	15
12	13	12	0	1	12	9.5	20
13	4	13	2	1	15	12.0	20
14	1	14	2	1	9	7.0	20
15	14	15	0	1	12	9.5	20

3.6 Pre-Compression Parameters

Formulation of granules is the key factors in the production of tablet dosage form involving floating sustained release of drug from matrix type. The formulated granules blends of different formulations S-1 to S-15 and S-OP were evaluated for Angle of Repose, Bulk Density, Tapped Density, Carr's Index and Hausner's Ratio. The angle of repose for all formulation ranged below 30 and indicated excellent and good flow properties of the entire formulated granules. The bulk density of powder depends primarily on particle size distribution, particle shape and the tendency of particle to adhere together. The value of bulk density and tapped density were found to be in range of 0.4615 gm/ml to 0.668 gm/ml and 0.545 gm/ml to 0.769 gm/ml. Compressibility Index and Hausner's Ration predict the flow properties of the powder. Car's Index ranged from 11.20 to 20.37 %, shows powder blend has required flow property for compression. Hausner Ratio ranged from 1.13 to 1.26, considered to have good flow property for the compression. Overall all the results indicates that the formulated granules blend possessed satisfactory flow properties when the batches were fabricated by wet granulation method.

3.7 Tablet weight variation, hardness, thickness, friability and drug content

The tablets of different formulations S-01 to S-15 and drug content were evaluated for various parameters viz. thickness, hardness, friability, weight variation and drug content. The average weight of the tablets varied from 1243.02±0.46 mg. The weight variation of all formulations passed the pharmacopeial requirements. The tablets prepared were oblong shaped having diameter varied from 19.49 to 19.63 mm. All the formulations showed uniform thickness. The thickness varied from 7.06 to 7.58 mm. The hardness varied from 11.64 to 23.04 kg/cm². This ensure good handling characteristics of all formulations. The friability of formulations varied from 0.12 to 0.36 %. The percentage friability for all the formulations was below 1% ensuring that the tablets were mechanically stable. Drug content was found to be uniform among different formulations of tablets and percentage of drug content was varied from 96.25 to 102.115 %.

3.8 In-Vitro Buoyancy Study

The tablets were evaluated for floating lag time, matrix integrity and total floating time. Sodium bicarbonate was used as a gas generating agent in order to float the tablet and citric acid used to maintain the

dissolution medium in acidic. The sodium bicarbonate induces CO₂ generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1gm/ml and the tablets become buoyant.

Regression Equation in Uncoded Units

FLT = -810 + 106.2 HPMC K100M + 19.1 Carbopol + 14.2 SB+CA - 3.77 HPMC K100M*HPMC K100M - 0.67 Carbopol*Carbopol - 0.188 SB+CA*SB+CA - 0.40 HPMC K100M*Carbopol - 0.700 HPMC K100M*SB+CA + 0.180 Carbopol*SB+CA

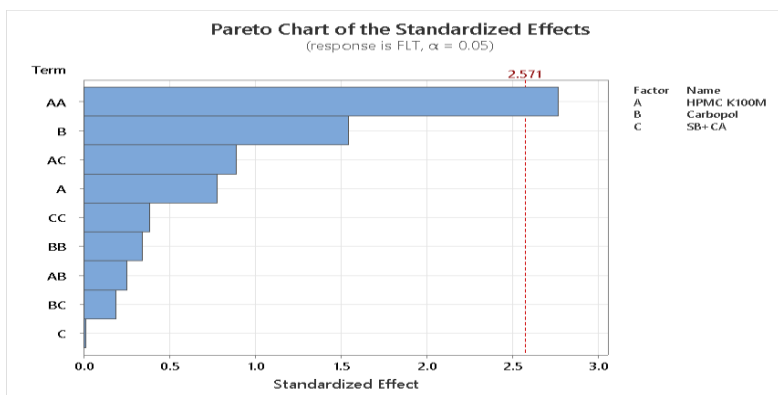


Figure 02: Pareto Chart of Floating Lag Time

Response Surface Method (RSM) was used with 3 factors (HPMC, Carbopol & Sodium Bicarbonate) in which Citric acid was used concentration dependent on Sod. Bicarbonate with 2%. By analyzing in Pareto Chart, the results showed that there was significant effect on floating lag time by HPMC K100M but not by Carbopol and Sodium Bicarbonate.

3.9 Swelling Index

Intake of water determined the swelling of HPMC K100M and Carbopol 934 polymers at varied concentrations. Swelling index was measured at a specified frequency for 6 hours. To test swelling, HPMC K100M and Carbopol 934 were in tablets at 9, 12, and 15% HPMC and 7, 9.5, and 12% Carbopol. Because polymer hydrates and swells and gel barrier forms at the outer surface, swelling index increases over time. The hydration swelling release process continues to new exposed surfaces while the gelatinous layer dissolves and/or disperses, retaining dosage form integrity. Citric acid content was sod-dependent in Response Surface Method (RSM) with HPMC, Carbopol, and Sod. Bicarbonate. Two-percent bicarbonate. Pareto Chart analysis showed no significant effect on swelling index HPMC, Carbopol, and Sodium Bicarbonate. Tablet swelling may take many hours. Citric acid content was sod-dependent in Response Surface Method (RSM) with HPMC, Carbopol, and Sod. Bicarbonate. Two-percent bicarbonate. Pareto Chart analysis showed no significant effect on swelling index HPMC, Carbopol, and Sodium Bicarbonate. Tablet swelling may take many hours. Citric acid content was sod-dependent in Response Surface Method (RSM) with HPMC, Carbopol, and Sod. Bicarbonate. Two-percent bicarbonate. Pareto Chart analysis showed no significant effect on swelling index HPMC, Carbopol, and Sodium Bicarbonate. Tablet swelling may take many hours. Citric acid content was sod-dependent in Response Surface Method (RSM) with HPMC, Carbopol, and Sod. Bicarbonate. Pareto Chart analysis showed that Carbopol and Sodium bicarbonate significantly reduced swelling index. HPMC had no significant effect on swelling index, citric acid content was sod-dependent in Response Surface Method (RSM) with HPMC, Carbopol, and Sod. Pareto Chart analysis showed that Carbopol and Sodium bicarbonate significantly reduced swelling index. HPMC had no

significant effect on swelling index. Citric acid content was sod-dependent in Response Surface Method (RSM) with HPMC, Carbopol, and Sod. Pareto Chart analysis showed that Carbopol and Sodium bicarbonate significantly reduced swelling index. HPMC had no significant effect on swelling index.

3.10 In-Vitro Dissolution Study

To evaluate the effect of the polymer concentration over drug release, HPMC K100M and Carbopol 934 were used in combination at 3 different levels-9, 12 and 15% and 7, 9.5 and 12 %. In formulation S-14, Ciprofloxacin HCl tablet was prepared with 16% polymers. The tablet showed poor matrix integrity; moreover 45.62 % of drug was released within 1 hours at this low concentration of polymers. Formulation S-13 with 27% polymers showed good matrix integrity; moreover 10.8 % drug release at first hours and 84.80 % drug release at the end of 12 hours. There must be sufficient polymer content in a matrix system to form a uniform barrier. This barrier protects the drug from immediately releasing into the dissolution medium. If the polymers level is too low, a complete gel layer may not form resulting into higher amount of drug release. Formulation S-14 with 16% polymers showed 96.42 % of drug release at 10 hour. Formulation S-04 and S-05 with 18.5% and 21 % of polymers showed further reduction of drug release viz. 97.72 % and 92.25 % at 12 hours. The effect of polymer concentration on t_{50%} and t_{80%} release of the formulation was also evaluated. Upon increasing the concentration of the polymers from 16 % to 18.5 % per tablet, t_{50%} of the formulation increased from 1.24 hr to 3.83 hrs and t_{80%} prolonged from 5.73 to 7.87 hrs. Similarly, upon increasing the concentration of the polymers from 19 % to 21.5 % per tablet, t_{50%} of the formulation increased from 3.55 to 5.94 hrs and t_{80%} prolonged from 7.40 to 10.12 hrs. Likewise, upon increasing the concentration of the polymers from 24.5 % to 27 % per tablet, t_{50%} of the formulation increased from 6.02 to 7.38 hrs and t_{80%} prolonged from 10.21 to 11.39 hrs.

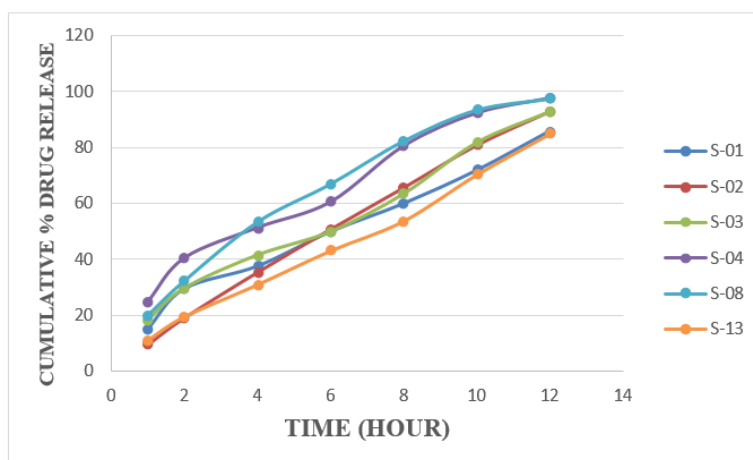


Figure 03: Effect of polymers over drug release

Effect of polymers in t_{50%} and t_{80%} (by Pareto chart, Contour Plot & Surface Plot) as shown in below:

At t_{50%}:

$$T_{50\%} \text{ (hr)} = -41.5 + 1.99 \text{ HPMC K100M} + 4.03 \text{ Carbopol} + 1.12 \text{ SB+CA} - 0.0089 \text{ HPMC K100M} \times \text{HPMC K100M}$$

$$- 0.1357 \text{ Carbopol} \times \text{Carbopol} - 0.0209 \text{ SB+CA} \times \text{SB+CA} - 0.0913 \text{ HPMC K100M} \times \text{Carbopol} - 0.0193 \text{ HPMC K100M} \times \text{SB+CA} - 0.0007 \text{ Carbopol} \times \text{SB+CA}$$

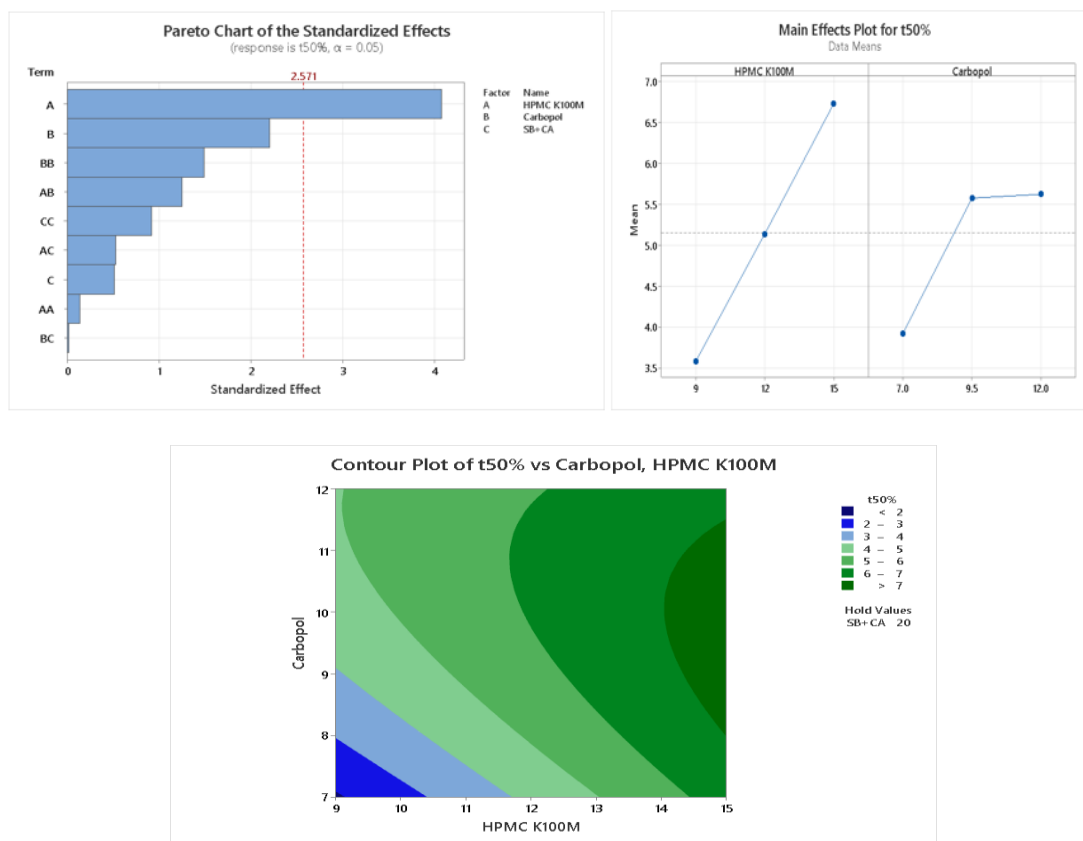
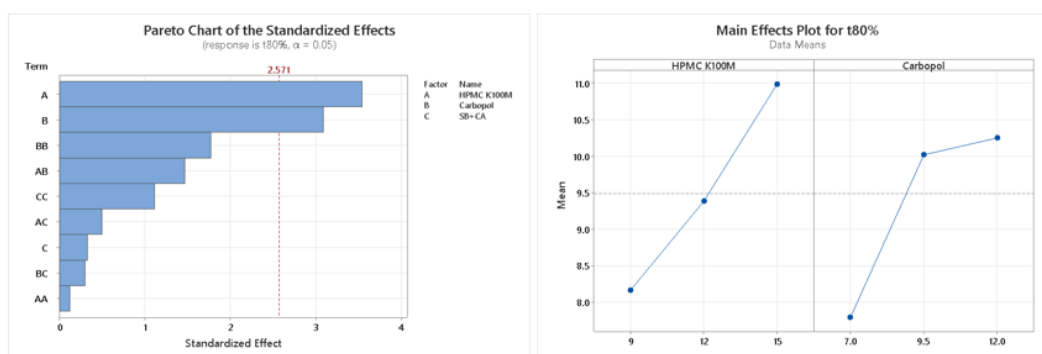


Figure 04: Pareto chart, Main effect plot and Contour Plot of t50% Release.

Response Surface Method (RSM) was used with 3 factors (HPMC, Carbopol & Sod. Bicarbonate) in which Citric acid was used concentration dependent on sod. Bicarbonate with 2%. By analyzing in Pareto Chart, Main effect plot and Contour plot, the results showed that there was significant effect on t50% by HPMC. But the result showed that there was not significant effect on t50% by Carbopol and Sodium Bicarbonate.

At t80%:

$T80\% \text{ (hr)} = -44.4 + 1.70 \text{ HPMC K100M} + 5.24 \text{ Carbopol} + 1.43 \text{ SB+CA} + 0.0080 \text{ HPMC K100M} * \text{HPMC K100M}$
 $- 0.1661 \text{ Carbopol} * \text{Carbopol} - 0.0261 \text{ SB+CA} * \text{SB+CA} - 0.1101 \text{ HPMC K100M} * \text{Carbopol} - 0.0188 \text{ HPMC K100M} * \text{SB+CA} - 0.0135 \text{ Carbopol} * \text{SB+CA}$



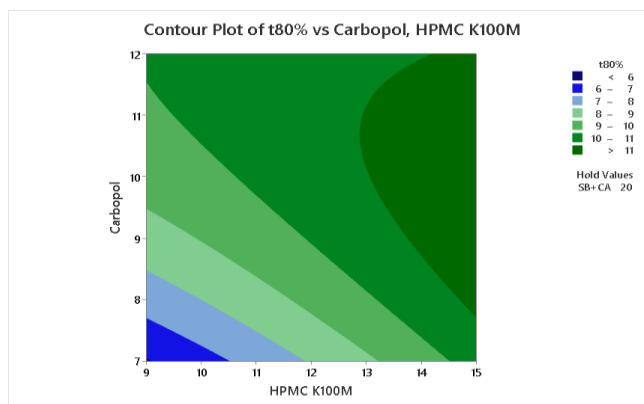


Figure 05: Pareto chart, Main effect plot and Contour Plot of t50% Release.

Response Surface Method (RSM) was used with 3 factors (HPMC, Carbopol & Sod. Bicarbonate) in which Citric acid was used concentration dependent on sod. Bicarbonate with 2%. By analyzing in Pareto Chart, Main effect plot and Contour plot, the results showed that there was significant effect on t80% by HPMC and Carbopol. But the result showed that there was not significant effect on t80% by Sodium Bicarbonate.

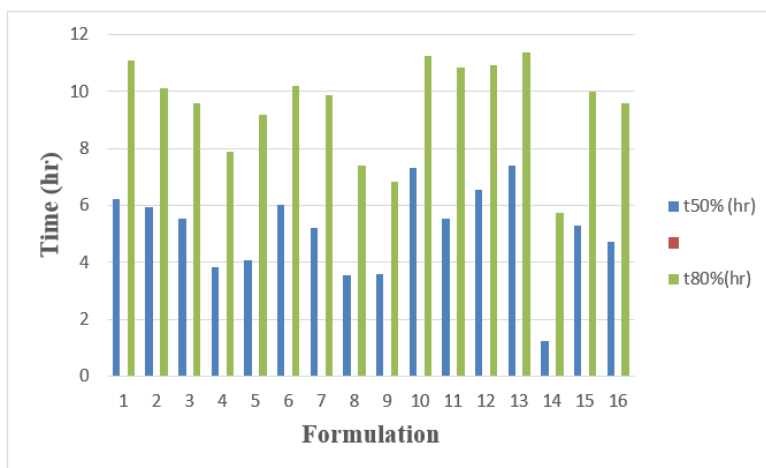


Figure 06: t50% and t80% of different formulations

The hydrophilic polymer HPMC rapidly hydrates to produce a gelatinous coating on the exterior of the tablet skin when it comes into contact with water. To stop the interior from becoming wet and the tablet core from disintegrating, a gelatinous coating must quickly develop. Additional water cannot penetrate into the tablet after the protective gel layer has developed. A new inner gel layer that is cohesive and continuous enough to prevent water from entering the system and regulate drug diffusion must replace the outer gel layer as it completely hydrates and dissolves. The effect of sodium bicarbonate and citric acid over drug release was evaluated by using sodium bicarbonate at 3 different levels (125 mg, 166.67 mg and 208.34 mg) and citric acid at 3 different levels (62.5 mg, 83.33 mg and 104.16 mg). Upon contact with the dissolution medium, sodium bicarbonate generates carbon dioxide gas, which expands the matrix volume, thereby accelerating the drug release rate. However, the dispersion of carbon dioxide bubbles within the matrix may partially obstruct the diffusion path. Consequently, the presence of these gas bubbles hinders water transport within the matrix and the movement of dissolved Ciprofloxacin HCl outwards. Furthermore, due to its hydrophobic nature, citric acid impedes water penetration into the matrix,

potentially leading to a decrease in drug dissolution. Hence, sodium bicarbonate and citric acid in combination may not have any overall effect on drug release.

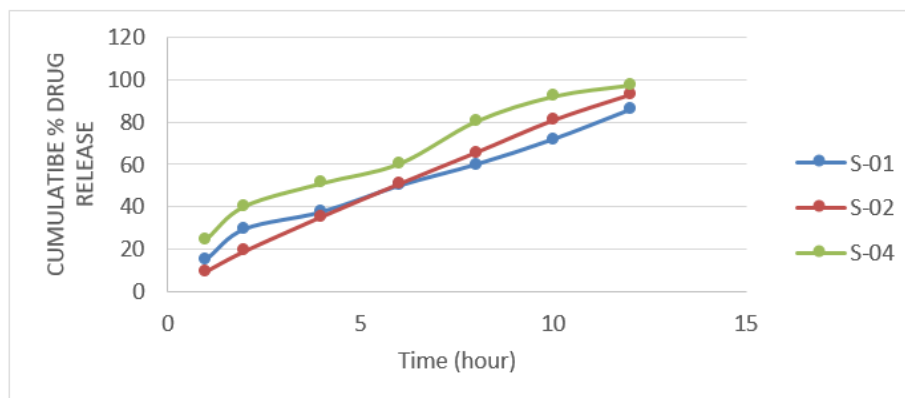


Figure 07: Effect of sodium bicarbonate and citric acid over drug release

By analyzing in Pareto Chart, the results showed that there was no significant difference upon changing the concentration of sodium bicarbonate.

3.11 Drug Release Kinetics

The values of in-vitro release were attempted to fit into various mathematical models-zero order, first order, Higuchi model, Hixson & Crowell model and Korsmeyer-Peppas model. The drug release data were explored for the types of release mechanism followed. The best fit with the highest determination R^2 coefficients was shown by Higuchi models. Higuchi model have a good fit to all dissolution profiles of all tablets as shown by R^2 values ($0.94 < R^2 < 1$). The values were ranged from 0.9448 to 0.9992, Higuchi square root kinetic model describes, release drug from the insoluble matrix as square root of time dependent process. It describes release of drug by simple diffusion mechanism. For zero order kinetics, R^2 values were obtained from 0.9434 to 0.9974. Zero order release describes the release rate independent of drug concentration. For first order release kinetics, R^2 values were obtained from 0.854 to 0.9721. The final optimized formulation showed good fit to Higuchi and Korsmeyer Peppas model with a value 0.9798 and 0.992 respectively. The value of n was 0.6428 showing non-fickian drug release.

3.12 Optimization

From the data of dissolution parameters, for Box-Behnken formulation S-01 to S-15, regression equation for dissolution in predetermined interval have been derived by using Minitab 20.4. Regression models including interaction and quadratic terms were generated for all the response variable using multiple linear regression analysis approach. Regression equation in general form is

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2$$

Where, Y is dependent variable, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 15 runs; β_1 to β_5 are the coefficients computed from the observed experimental values of Y ; and X_1 and X_2 are the coded levels of the independent variable(s). The terms $X_1 X_2$ and X_i^2 ($i = 1$ to 2) represent the interaction and quadratic terms, respectively. The interaction term ($X_1 X_2$) shows how the response changes when two factors are simultaneously changed. The regression terms (X_1^2 and X_2^2) are included to investigate non-linearity. Response surface methodology (RSM) was used with 3 factors (HPMC, Carbopol and Sod. Bicarbonate) in which Citric acid was used concentration dependent on Sod. Bicarbonate with 2%.

The equation for 1st hour is:

$$1 \text{ hr} = 388.3 - 26.63 \text{ HPMC K100M} - 29.60 \text{ Carbopol} - 5.58 \text{ SB+CA} + 0.652 \text{ HPMC K100M} * \text{HPMC K100M} + 1.055 \text{ Carbopol} * \text{Carbopol} + 0.152 \text{ SB+CA} * \text{SB+CA} + 0.805 \text{ HPMC K100M} * \text{Carbopol} + 0.029 \text{ HPMC K100M} * \text{SB+CA} - 0.079 \text{ Carbopol} * \text{SB+CA}$$

From the estimated coefficient, it was found that significant factors are HPMC K100M ($P=0.005$) while Carbopol 934 ($P=0.088$), Sodium Bicarbonate ($P=0.798$), interaction between HPMC K100M ($P=0.072$), Interaction between Carbopol 934 ($P=0.051$), interaction between Sodium Bicarbonate ($P=0.201$), interaction between HPMC K100M and Carbopol 934 ($P=0.059$), interaction between HPMC K100M and Sodium Bicarbonate ($P=0.867$) and interaction between Carbopol 934 and Sodium Bicarbonate ($P=0.706$). The value of HPMC K100M and interaction of Carbopol 934 are largest as the coefficient which indicates the main influence factor on the drug release from the tablet. Here, interaction between HPMC K100M, Carbopol 934, Sodium Bicarbonate, interaction between HPMC K100M, interaction between Sodium Bicarbonate, interaction between HPMC K100M and Carbopol 934, interaction between HPMC K100M and Sodium Bicarbonate and interaction between Carbopol 934 and Sodium Bicarbonate have antagonistic effect on drug release.

The equation for 2nd hour is:

$$2 \text{ hr} = 410 - 26.52 \text{ HPMC K100M} - 25.1 \text{ Carbopol} - 8.61 \text{ SB+CA} + 0.580 \text{ HPMC K100M} * \text{HPMC K100M} + 1.010 \text{ Carbopol} * \text{Carbopol} + 0.167 \text{ SB+CA} * \text{SB+CA} + 0.522 \text{ HPMC K100M} * \text{Carbopol} + 0.247 \text{ HPMC K100M} * \text{SB+CA} - 0.106 \text{ Carbopol} * \text{SB+CA}$$

The same result was seen as shown in release in first hour.

The equation for 4th hour is:

$$4 \text{ hr} = 365 - 13.8 \text{ HPMC K100M} - 28.5 \text{ Carbopol} - 7.92 \text{ SB+CA} + 0.103 \text{ HPMC K100M} * \text{HPMC K100M} + 1.104 \text{ Carbopol} * \text{Carbopol} + 0.148 \text{ SB+CA} * \text{SB+CA} + 0.507 \text{ HPMC K100M} * \text{Carbopol} + 0.171 \text{ HPMC K100M} * \text{SB+CA} - 0.029 \text{ Carbopol} * \text{SB+CA}$$

The same result was seen as shown in release in first hour.

The equation for 6th hour is:

$$6 \text{ hr} = 356 - 13.9 \text{ HPMC K100M} - 30.5 \text{ Carbopol} - 4.51 \text{ SB+CA} + 0.100 \text{ HPMC K100M} * \text{HPMC K100M} + 1.195 \text{ Carbopol} * \text{Carbopol} + 0.064 \text{ SB+CA} * \text{SB+CA} + 0.509 \text{ HPMC K100M} * \text{Carbopol} + 0.183 \text{ HPMC K100M} * \text{SB+CA} - 0.044 \text{ Carbopol} * \text{SB+CA}$$

The same result was seen as shown in release in first hour. Except that the effect of Carbopol 934 have significant effect on drug release.

The equation for 8th hour is:

$$8 \text{ hr} = 394 - 12.6 \text{ HPMC K100M} - 25.3 \text{ Carbopol} - 9.75 \text{ SB+CA} + 0.029 \text{ HPMC K100M} * \text{HPMC K100M} + 0.812 \text{ Carbopol} * \text{Carbopol} + 0.182 \text{ SB+CA} * \text{SB+CA} + 0.548 \text{ HPMC K100M} * \text{Carbopol} + 0.161 \text{ HPMC K100M} * \text{SB+CA} + 0.021 \text{ Carbopol} * \text{SB+CA}$$

The same result was seen as shown in release in first hour.

The equation for 10th hour is:

10 hr=301 - 3.8 HPMC K100M - 18.6 Carbopol - 8.28 SB+CA - 0.150 HPMC K100M*HPMC K100M + 0.405 Carbopol*Carbopol + 0.138 SB+CA*SB+CA + 0.394 HPMC K100M*Carbopol + 0.054 HPMC K100M*SB+CA + 0.194 Carbopol*SB+CA

The same result was seen as shown in release in first hour.

The equation for 12th hour is:

12 hr=148.3 + 1.91 HPMC K100M - 3.72 Carbopol - 3.53 SB+CA - 0.140 HPMC K100M*HPMC K100M - 0.085 Carbopol*Carbopol + 0.0758 SB+CA*SB+CA + 0.151 HPMC K100M*Carbopol - 0.069 HPMC K100M*SB+CA + 0.125 Carbopol*SB+CA

The same result was seen as shown in release in first hour.

The dissolution parameter predicted from the response optimizer and equations of 1st, 2nd, 4th, 6th, 8th, 10th, and 12th hour equation derived and those observed from the experimental results are summarized in the table below:

Table 11: Release profile for Predicted value and Observed Value

Formulation	Predicted Values (% release)							Observed Values (% release)						
	1st	2nd	4th	6th	8th	10th	12th	1st	2nd	4th	6th	8th	10th	12th
S-OP	18.73	31.23	48.44	62.75	75	87.80	94.65	19.53	28.015	45.96	53.94	69.12	85.25	96.78

3.13 Overlaid Contour Plot

An overlaid contour plot was drawn in order to obtain the range of formulations which provides the desired release of Ciprofloxacin HCl floating tablet. The limit for every hour was set on the basis of dissolution study done using Box-Behnken Design formulation. For 12 hours of drug release provides the desired dissolution of Ciprofloxacin HCl floating tablet. The white area shown in the overlaid contour plot of 1st, 2nd, 4th, 6th, 8th, 10th and 12th hours, gives the required range of concentration of HPMC K100M, Carbopol 934 and Sodium Bicarbonate that can be used for obtaining the desired release of Ciprofloxacin HCl floating tablets.

3.14 Method Validation

To verify that the analytical system is working properly and can give accurate and precise results, the system suitability test was performed. Test was performed using 5 replicates of standard solution of ciprofloxacin hydrochloride and the data were recorded.

Table 12: Observed data for system suitability test

S. No.	Concentration (PPM)	Absorbance (275 nm)	Limit	% RSD
1	100	0.7138	RSD ≤3.0%	1.1107
2	100	0.7003		
3	100	0.7139		
4	100	0.7020		
5	100	0.6954		
6	100	0.6995		

It is observed from the data tabulated above that the method complies with the system suitability parameters. Hence, it can be concluded that the system suitability test meets the requirements of method validation. The spectrums of specificity are shown below.

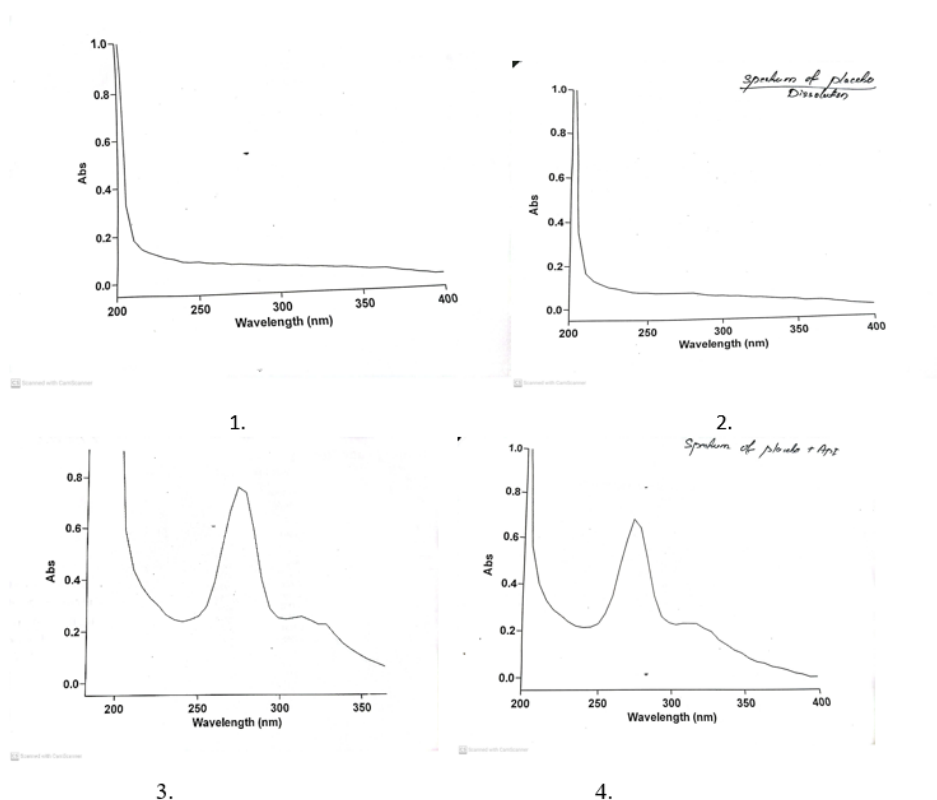


Figure 08: 1 (Blank 0.1N HCl), 2 (Placebo), 3 (Standard Solution), 4 (Sample Solution)

In order to demonstrate the analytical procedure is specific for analyte, firstly positive result was carried out by scanning 5 PPM solution of reference standard of Ciprofloxacin HCl in 0.1 N HCl in UV range, in UV spectrophotometer. Then, 5 PPM solution of placebo (without ciprofloxacin HCl) in 0.1N HCl was also scanned in the same range. During the run of spectrum, a prominent peak was observed at 275 nm in 0.1N HCl at the range of 200-400 nm for the first ciprofloxacin solution whereas a flat line as observed by the placebo and blank (0.1 N HCl) in the same range of wavelength. There was no interference from the blank and placebo, so the method was found to be specific for Ciprofloxacin HCl floating tablet.

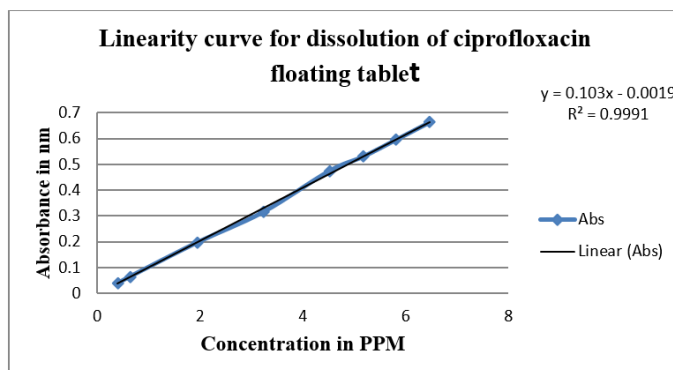


Figure 09: Calibration Curve for Area under curve versus concentration in percentage of ciprofloxacin HCl.

The calibration curve shows the linear relationship between Ciprofloxacin HCl concentration and its Absorbance. The R² value was found to be 0.999 which is greater than the limit 0.98.

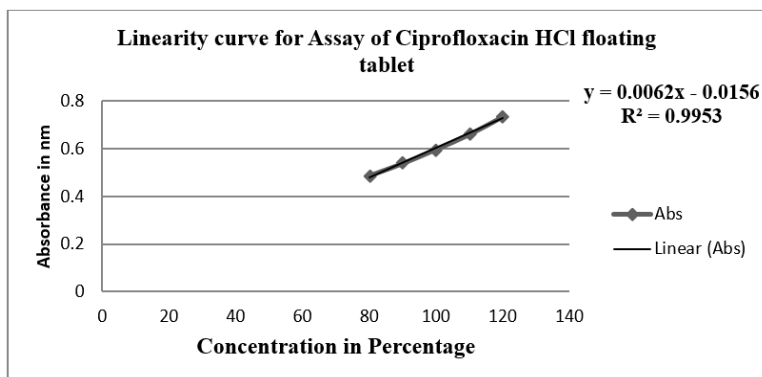


Figure 10: Calibration Curve for Area under curve versus concentration in percentage of ciprofloxacin HCl.

The calibration curve shows the linear relationship between Ciprofloxacin HCl concentration and its Absorbance. The R² value was found to be 0.9953 which is greater than the limit 0.98.

4. CONCLUSIONS

The gastro-retentive floating tablet of Ciprofloxacin HCl was prepared successfully using various polymer such as HPMC K100M, Carbopol 934 as rate retarding agent and a combination of Sodium Bicarbonate and citric acid as a gas generating agent. The concept of floating drug delivery system was used to retain the drug in the stomach for a prolong time. The attempt was made to design and optimize GRDDS of Ciprofloxacin HCl using HPMC K100M, Carbopol 934, Sodium Bicarbonate and Citric acid. The formulations were obtained as per Box-Behnken Design. A response surface method was used for final optimization of Ciprofloxacin HCl GRDDS, and all the designed 15 batches of formulations were evaluated for diameter, thickness, hardness, friability, weight variation, assay, swelling index and in-vitro drug release. All the prepared tablets exhibited satisfactory physico-chemical properties. The in-vitro dissolution was performed using USP dissolution apparatus II (paddle) at 37±0.50C and 50 RPM in 900 ml 0.1N HCl. HPMC K100M when used at the concentration of 9%, 12% and 15%, t_{50%} was found to be 3.83, 5.53 and 6.23 hr whereas t_{80%} was found to be 7.87, 9.58 and 11.10 hr respectively. By using similarity and dissimilarity factor, the observed values obtained from the optimized formulation were compared with predicted values. From the result of similarity and dissimilarity factor, it was shown that the cumulative drug release obtained from the optimized formulations was similar to the predicted cumulative drug release. The study proves that Polymers like HPMC K100M, Carbopol 934 as rate retarding agent and a combination of Sodium Bicarbonate and Citric acid as a gas generating agent in appropriate amount can be used to formulate GRDDS of Ciprofloxacin HCl. Such system can remain buoyant for more than 12 hours along with the sustained drug release at the region of stomach and thus possible enhancement of medication at targeted site and reduce systemic adverse effect.

REFERENCES

- [1] Bagherwal, A., Patidar, D. K., & Sharma, P. (2010). Studies on formulation and evaluation of floating tablets of ciprofloxacin HCl. *Pharmacie Globale (IJCP)*, 5(02), 1-4.

- [2] Dr. Sangam Pokharel, Dr. Rajesh Yadav, Dr. Anima Pradhan & Dr. Ashmita Paudel (2024). Comparative Study of Bupivacaine 0.5% and Ropivacaine 0.75% Epidurally In Lower Limb Orthopedic Surgeries. *Dinkum Journal of Medical Innovations*, 3(02):165-173.
- [3] Dehghan, M., & Kha, F. (2009). Gastroretentive drug delivery systems: A patent perspective. *International Journal of Health Research*, 2(1).
- [4] Newton, A. M. J., Maheshbabu, C., Kumar, N., & Sachdeva, R. K. (2014). Effect of carbopol 940 on drug release profile and floating characteristics of floating drug delivery system of amoxicillin trihydrate using HPMC different grades. *J. Appl. Biopharm. Pharmacokinet*, 2, 29-39.
- [5] Manish, J., & Hardik, P. (2013). Gastro retentive floating drug delivery system: a review. *IJPRBs*, 2(2), 358-77.
- [6] Abdul Mumin, Abdullah Al Amin, A.K.M. Shahriar Kabir, Rifat Ara Noor & Urmi Rahman (2024). Role of C- Reactive Protein (CRP) and Neutrophil Lymphocyte Ratio (NLR) in detecting severity & Predicting outcome of Acute Pancreatitis patients. *Dinkum Journal of Medical Innovations*, 3(01):01-12.
- [7] Jayaselvi, S. (2012). Formulation and Evaluation of Floating Tablet formulation and Evaluation of Floating Tablets of Ciprofloxacin HCL (Doctoral dissertation, JKK Munirajah Medical Research Foundation College of Pharmacy, Komarapalayam).
- [8] Sharma, N., Agarwal, D., Gupta, M. K., & Khinchi, M. (2011). A comprehensive review on floating drug delivery system. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2(2), 428-441.
- [9] Karthi, R. (2017). Formulation and Evaluation of Ciprofloxacin Hydrochloride Floating Tablets using Natural Polymers (Doctoral dissertation, JKK Nattraja College of Pharmacy, Kumarapalayam).
- [10] Govindaraj, S. (2019). Formulation and Invitro Evaluation of Norfloxacin Gastric Floating Drug Delivery System (Doctoral dissertation, JKK Nattraja College of Pharmacy, Kumarapalayam).
- [11] Waqar, M. A., Mubarak, N., Khan, A. M., Khan, R., Shaheen, F., & Shabbir, A. (2024). Advanced polymers and recent advancements on gastroretentive drug delivery system; a comprehensive review. *Journal of Drug Targeting*, 1-17.
- [12] Dr. Prabin Kumar Jha, Dr. Bindu Laxmi Shah, Dr. Shruti Kumari Thakur & Dr. Avinash Thakur (2024). Effectiveness of Dexamethasone as an Adjuvant to Bupivacaine in Supraclavicular Brachial Plexus Block. *Dinkum Journal of Medical Innovations*, 3(01):13-25.
- [13] Rathor, M., & Garg, A. (2024). Gastroretentive drug delivery system: An overview.
- [14] Sanjanwala, D., Mehta, N. V., & Patravale, V. (2024). Pharmaceutical polymers for modified drug delivery and controlled release. In *Polymers for Pharmaceutical and Biomedical Applications* (pp. 199-260). Elsevier.
- [15] Kumar, V., Somkuwar, S., & Singhai, A. K. (2024). A recent update on gastro retentive drug delivery systems. *GSC Biological and Pharmaceutical Sciences*, 27(1), 125-144.
- [16] Wafa, A., Raihan, R., & Tyagi, S. (2024). Recent Advances in Gastro Retentive Drug Delivery Systems. *European Journal of Theoretical and Applied Sciences*, 2(2), 702-710.
- [17] Hansan, M., Mathew, S. E., & Irene, A. M. (2024). Advances in gastroretentive drug delivery systems: Formulation strategy and therapeutic applications. *International Journal of Science and Research Archive*, 11(1), 1078-1088.
- [18] Maheer Jamil, Mubashir Anwar, Jaweria Awan & Naila Alam (2023). Initiatives for the Prevention and Management of Psychoactive Drug Utilization among Asian Undergraduates. *Dinkum Journal of Medical Innovations*, 2(12):508-514.
- [19] Dey, A., Singh, A., Kurmi, B. D., & Singh, D. (2024). A Complete Sojourn of Current Trends in Gastro-retentive Drug Delivery System: Recent Advances and Patent Survey. *Recent Patents on Nanotechnology*, 18(2), 190-206.

- [20] Dhiman, S., Philip, N., Gurjeet Singh, T., Babbar, R., Garg, N., Diwan, V., & Singh, P. (2023). An insight on novel approaches & perspectives for gastro-retentive drug delivery systems. *Current Drug Delivery*, 20(6), 708-729.
- [21] Jain, S., & Srinivasan, B. An Insight on the Strategical Approach of Gastro-retentive Drug Delivery System.
- [22] Rathor, M., & Garg, A. (2024). Gastroretentive drug delivery system: An overview.
- [23] Vasave, V. S. (2023). A REVIEW ON: FLOATING DRUG DELIVERY SYSTEM. *World Journal of Pharmaceutical Research*, 12(2), 641-669.
- [24] Sen, O., Manna, S., Nandi, G., Jana, S., & Jana, S. (2023). Recent advances in alginate based gastroretentive technologies for drug delivery applications. *Medicine in Novel Technology and Devices*, 100236.
- [25] Anand Gopal & Nandita Shetty (2023). Literature Review on Comparison of Efficacy and Safety of Mometasone Furoate 0.1% Gel Versus Mometasone Furoate 0.1% Cream and Adapalene Gel 0.1%. *Dinkum Journal of Medical Innovations*, 2(02):57-71.
- [26] Sanjanwala, D., Mehta, N. V., & Patravale, V. (2024). Pharmaceutical polymers for modified drug delivery and controlled release. In *Polymers for Pharmaceutical and Biomedical Applications* (pp. 199-260). Elsevier.
- [27] Kumar, V., Somkuwar, S., & Singhai, A. K. (2024). A recent update on gastro retentive drug delivery systems. *GSC Biological and Pharmaceutical Sciences*, 27(1), 125-144.
- [28] Ebraheem, A. S., & El Naggar, E. E. (2023). Gastroretentive drug delivery systems: A summarized overview. *Octahedron Drug Research*.
- [29] Tafish, A. M., Ebraheem, A. S., El Naggar, E. E., Elfar, N., & Yasser, M. (2023). Gastroretentive drug delivery systems: A summarized overview. *Octahedron Drug Research*, 3(1), 40-56.
- [30] Singh, P. K. (2023). DEVELOPMENT AND EVALUATION OF FLOATING TABLETS BEARING MODEL ANTIULCER DRUG FOR THE TREATMENT OF PEPTIC ULCER.
- [31] Landge, P., Lavande, J., Swami, A., & Dharashive, V. (2023). A Review on Gastroretentive Drug Delivery System.
- [32] Singh, B., Sharma, V., Mohan, M., Sharma, P., & Ram, K. (2023). Design of ciprofloxacin impregnated dietary fiber psyllium-moringa gum-alginate network hydrogels via green approach for use in gastro-retentive drug delivery system. *Bioactive Carbohydrates and Dietary Fibre*, 29, 100345.
- [33] Ahmad, S., Khan, J. A., Kausar, T. N., Mahnashi, M. H., Alasiri, A., Alqahtani, A. A., ... & Sadiq, A. (2023). Preparation, characterization and evaluation of flavonolignan silymarin effervescent floating matrix tablets for enhanced oral bioavailability. *Molecules*, 28(6), 2606.
- [34] Rai, S., & Sultana, S. (2023). Gastric Retentive Drug Delivery system and its recent insights: A.
- [35] Sabei, F. Y., Safhi, A. Y., Alsalhi, A., Khan, K. A., Bakkari, M. A., Fatease, A. A., & Madkhali, O. A. (2023). Preparation and In Vitro Evaluation of Levofloxacin-Loaded Floating Tables Using Various Rate-Controlling Agents. *ACS omega*, 8(45), 42659-42666.