Gastroretentive Formulation and Characterization of Carvedilol Floating Tablets

Krishnagiri Krishnababu[1], Gururaj S Kulkarni[2*], A Muthu kumar[3], Yuktha H J[4], Padmaa M Paarakh[5]

[1,2,4] Department of Pharmaceutics, The Oxford College of Pharmacy, Bengaluru, Karnataka, India,
[3] Department of Pharmacology, The Oxford College of Pharmacy, Bengaluru, Karnataka, India,
[5] Department of Pharmacognosy, The Oxford College of Pharmacy, Bengaluru, Karnataka, India.
[1]k.krishnababu2020@gmail.com, [2]skguru2006@gmail.com,
[3]drmkresearch14@gmail.com, [4]yukthajagadish07508@gmail.com,
[5]padmaampaarakh@gmail.com

Corresponding author
Dr. Gururaj S Kulkarni[2*]
Professor & Head, Department of Pharmaceutics, The Oxford College of Pharmacy, Bengaluru, Karnataka, India,
Ph. No: +91 9886564346
E-Mail id: skguru2006@gmail.com

Abstract

Objective:
The main objective of this current study is to formulate gastroretentive tablets of carvedilol using different concentrations of polymers and excipients for retaining the medication in the stomach, as solubility is higher at an acidic pH.

Methods:
The direct compression method was used for preparing GRDDS with varying concentrations of polymers. The drug-excipient compatibility study was conducted. A total of nine formulation batches were developed and evaluated for pre and post compression parameters. The buoyancy behaviour and swelling index were conducted for all formulation batches. The optimized formulation batch studied the impact of the pH on floating and drug release.

Results:

In the prepared formulations F1-F9, hardness was in the range of 4-6kg/cm^2, friability was <1%, and drug content ranged from 98.48 to 99.87%. The buoyancy lag time showed a range of 45 to 78 seconds, and the total floating time was found to be >7 hours. Formulation batch nine reports the highest swelling index of 61.04% and a better drug release of 46.47% for 6 hours. The impact of pH on floating behaviour and drug release results shows there was no impact on the properties.

Conclusion:

All formulation batches pre- and post-formulation results are within the specifications, and F9 was the finest formulation to treat hypertension. The floating tablets of Carvedilol maintain drug delivery, which improves bioavailability, therapeutic efficacy, and patient compliance.

Keywords: *Carvedilol, Floating, Gastroretentive dosage form, Direct compression method, Buoyancy.*

1. Introduction

For decades, the oral route of drug delivery has been recognized as the most promising and convenient route of administration among all other routes of systemic drug delivery[1]. In contrast to conventional drug delivery, oral sustained or controlled drug delivery provides continuous, predictable, and reproducible kinetics that help to reach the maximum achievable therapeutic plasma concentration. The modified dosage forms give better patient compliance[2, 3]. These dosage forms are not intended to deal with issues related to physiological conditions of the stomach and gastric emptying, which have the potential to impact the bioavailability and therapeutic efficacy of the medication. The gastroretentive dosage forms were aimed at retaining the medication in the upper part of the stomach; gastric emptying is delayed, and the dose form is concentrated in the GIT [4]. These GRDDS will stay in the stomach for a longer period, prolong the GRT of the dosage form, and improve bioavailability while minimizing drug degradation owing to enzymatic metabolism in the intestinal environment. As a result, there is less drug waste, and medications that are less soluble in alkaline pH are more soluble[5].

Carvedilol, a nonselective adrenergic blocking medication with 1-blocking efficacy, lowers blood pressure and is a common treatment for symptomatic heart failure[6]. Carvedilol pH-influenced solubility requires increasing the drug's absorption profile in the upper part of the stomach, expanding the absorption, and making it a candidate for the GRDDS. Due to high first-pass metabolism, carvedilol has a bioavailability of 25–35% and a half-life of 6–9 hours. The rate of absorption is delayed when given with meals, put off in the time it takes to reach peak plasma levels, with no discernible variation in the amount of bioavailability[7, 8]. Research work was conducted to formulate and evaluate the gastroretentive tablet to prolong the drug release. The development of the gastroretentive dosage form relies on drug and polymer interaction studies, evaluation parameters, buoyancy behaviour.

2. Materials and Methods:

A free sample of carvedilol was received from Sun Pharma, Pvt. Ltd, India. Sodium alginate (Thomas baker chemicals Pvt ltd, Mumbai), Carboxy methyl cellulose- Sodium (Rolex chemical industries, Mumbai), Guar gum (Loba chemie Pvt. Ltd, Mumbai), Microcrystalline cellulose (MCC)and Citric acid (S.D. fine-Chem Ltd, Mumbai), Sodium bicarbonate (Nice chemicals, Kerala), Magnesium stearate (Loba chemie Pvt. Ltd, Mumbai). Other materials and solvents used were of analytical grade. All the studies were conducted using double distilled water.

Methods:

Determination of calibration curve

Carvedilol 100mg was dissolved in a few ml of methanol in a 100 ml volumetric flask. The solution was then made up to the required concentration using 0.1N HCl to give 1000 mcg/mL (stock I). To make a solution with a concentration of 100 mcg/ml (stock II), 10 ml of this solution is dispersed into 100 ml with 0.1 N HCl. Using 0.1 N HCl, the volume of stock solution-2 was raised from 10 ml to 100 ml in order to achieve concentrations of 10 g/ml. Pipette 2, 4, 6, 8, or 10 ml of solution into a 10 ml volumetric flask, and then add 0.1N HCl to the solution to bring the volume up to 10 ml to get 2, 4, 6, 8, or 10 g/ml concentrations[8, 9].

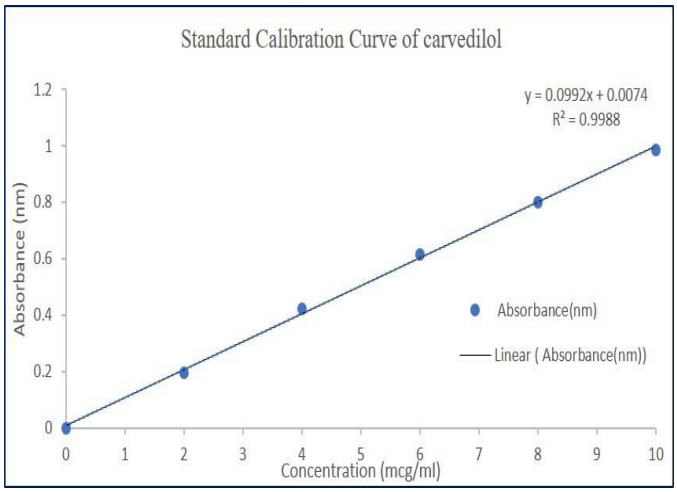

Figure No. 1 Calibration curve of Carvedilol

Drug excipient compatibility studies by FTIR:

FTIR spectroscopy determines the functional groups in the drug molecule. The electromagnetic radiation passes through the sample range of 400 cm-1 and 4000 cm-1. The molecules present in drug and polymers have their bonds occupied by electromagnetic radiation, causing them to spin. The wavelength of the radiation absorbed is a property of the bond that absorbs it[10].

Formulation of floating tablets

The direct compression technique was used to develop CVD gastroretentive tablets, and the formula is shown in Table I. The key ingredients for twenty tablets were accurately weighed and properly mixed after passing through sieve no. 22 to achieve uniformity. Initially, the exact amounts of the active ingredient, carvedilol, and the polymer were blended in the powder mixture in opposition to the precise amounts of the effervescent agents, NaHCO3 and citric acid, which were added separately. The blend was uniformly blended with microcrystalline cellulose (MCC), and the tablet mixture was lubricated with magnesium stearate. Using circular tablet punches with a diameter of 6.0 mm, tablets containing 15.5 mg of carvedilol were compressed using a tablet machine[11,12].

Table I: Master formula for Gastric floating tablets

S.NO	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Carvedilol	15.5	15.5	15.5	15.5	15.5	15.5	15.5	15.5	15.5
2	Guar gum	10	-	-	15	-	-	20	-	-
3	Sodium alginate	-	10	-	-	15	-	-	20	-
4	Sodium CMC	-	-	10	-	-	15	-	-	20
5	Microcrystalline cellulose	47.5	47.5	47.5	42.5	42.5	42.5	37.5	37.5	37.5
6	Sodium bicarbonate	20	20	20	20	20	20	20	20	20
7	Citric acid	5	5	5	5	5	5	5	5	5
8	Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight of each tablet 100 (mg)										

Pre-compression parameters

Bulk density (BD):

The total weight of the powder divided by the bulk volume is the bulk density. Particle form has a significant impact on bulk density; as particles got more spherical in shape, bulk density rose. A measuring cylinder was filled with five grams of powder after it was weighed. The bulk volume and weight of the powder were obtained[13]. The BD was calculated using the formula.

$$\rho b = M / V_0 \quad (1)$$

Where, ρb = BD, M = weight of sample

V_0 = apparent unstirred volume

Tapped density (TD):

To measure BD, it was configured for 150 tapings, and the final volume was calculated utilizing the formula [14]:

$$\rho t = M / V_f \quad (2)$$

Where, ρt = Tapped density
M = weight of sample
V_f = final Tap volume

Angle of repose (Ɵ)

The angle of repose is calculated using the fixed-funnel method used to complete the test. An angle of powder was created on the paper by allowing the powder mass to fall through the funnel hole that was fastened vertically to the plain paper that was moving over the horizontal surface. The following equation can be used to get the angle of repose by dividing the pile's height (h) by its radius (r)[12,15].

$$\Theta = tan^{-1}(h/r) \quad (3)$$

Where, h = height of the pile of powder (cm), r = radius of the pile (cm).

Compressibility Index

The TD and the BD are used to calculate the compressibility index. The formula was used to calculate the compressibility index[16].

Compressibility Index (%) = [(TBD – LBD) × 100]/TBD **(4)**

Where, TBD is the total bulk density and LBD is the loose bulk density.

Hausner's ratio

By dividing the ratio of the tapped density by the ratio of the poured density, one can get Hausner's ratio using the formula below.

$$\text{Hausner's ratio} = V_0/V_f \quad (5)$$

Where, Vf = final tapped volume, Vo = initial untapped volume.

Post-compression parameters

The formulated gastroretentive dosage form was evaluated for thickness, hardness, friability, drug content, and weight variation. Tablet hardness was evaluated using a Pfizer hardness tester, while tablet friability was assessed using a Roche friabilator. A Vernier caliper was used to measure the thickness of the tablets. The weight variation test was conducted using the recommended methodology. By measuring the sample's absorbance at 240 nm with a Shimadzu UV spectrophotometer and comparing the content with the calibration curve of the sample, the drug content of carvedilol was determined[15,16].

***In vitro* buoyancy determination**

The GRDDS depends significantly on its floating properties, and it has an impact on the DDSs' in-vitro performances. The time length of floating and lag time was measured using the in vitro buoyancy that was achieved. 100 ml of pH 1.2 buffer was taken. Both the total floating time and the FLT the amount of time it takes for the tablet to rise from the water[17].

Determination of swelling behaviour

Tablet swelling behaviour was examined at room temperature in buffer pH 1.2 of 0.1N HCl. The tablet's increased dimensions were calculated at predetermined intervals[10,18].

$$\% \text{ Increase in Diameter} = \frac{\text{Diameter final} - \text{Diameter initial}}{\text{Diameter initial}} \times 100 \quad (6)$$

$$\% \text{ Increase in Thickness} = \frac{\text{Thickness final} - \text{Thickness initial}}{\text{Thickness initial}} \times 100 \quad (7)$$

In vitro dissolution studies

Tablet dissolution assays were performed to investigate in vitro medication release. Dissolution was accomplished using a USP XIII dissolving device type II (paddle type). 900 ml of buffer pH1.2 maintained at 37 °C served as the dissolution medium. 50 rpm was the continuous paddle speed. At intervals of 0, 1, 2, 3, 4, 5, 6, and 5 ml, samples were withdrawn and returned in the same buffer. Readings were taken at 240 nm by using a UV spectrophotometer [19,20].

Drug excipients compatibility studies by DSC:

Conducting the thermal analysis using DSC investigations, the potential for any interactions between Carvedilol and the excipients in floating tablets was evaluated. For DSC studies, pure drug (Carvedilol) and tablets of optimized formulation F9 were taken, and the thermal behaviour of samples was determined using DSC at a heating rate of 10 C/min. The measurements were performed at a heating range of 30 to 200^0C under a nitrogen atmosphere[20,21].

Impact of pH on floating behaviour

The optimized batch formulation was subjected to an evaluation of the floating behaviour of tablets at different pH. To examine the impact of pH on buoyancy, pH buffer solutions of 1.2, 2, and 3 pH, each 100 ml, were made of hydrochloric acid[22,23].

Impact of pH on drug release

The test was conducted on the improved formulation to determine the impact of pH and stomach contents on medication release. Different pH levels were investigated, and a dissolution profile was found. pH 1.2, 2, and 3 are buffered by hydrochloric acid[24,25].

3. Results and discussion:

With the intention of extending the GRT of a poorly soluble BCS Class II drug, gastroretentive tablets were made employing several polymers (Na CMC, sodium alginate, and guar gum), MCC, citric acid, and sodium bicarbonate as gas-producing agents.

Calibration curve:

Carvedilol calibration curves were constructed at a maximum recorded wavelength of 240 nm in 0.1N HCL buffer solutions with a pH of 1.2. The calibration curve was created using Beer's law with concentrations between 2 and 10 g/ml. Following the technique, the linearity of the carvedilol standard graph was plotted. With an R^2 of 0.998, the carvedilol standard graph displayed (Fig. 1) excellent linearity and complied with "Beer-Lambert's" law.

Pre-compression parameters:

All formulation batches, their pre-compression parameters, and evaluated results are shown in Table II. The bulk and tapped densities for all formulations of powder blends range from 0.39 to 0.47 and 0.54 to 0.62. The manufactured powder blend for direct compression has a tolerable Carr's index and angle of repose value range of 15.33±0.8 to 26.57±1.1 and 31.80.44 to 35.5±0.82, respectively. As shown in Table II, the powder flow attribute is once again connected with Hausner's ratio, with values set between 1.16 and 1.34 signifying a moderate flow.

Table No II: Pre-compression parameters of powder blend

S. No	Formulation	Angle of repose (±SD)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's ratio (± SD)
1	Fl	26.21±0.04	0.34±0.01	0.52±0.02	18.65±0.06	1.18±0.05
2	F2	27.16±0.01	0.387±0.03	0.62±0.04	15.31±0.07	1.11±0.04
3	F3	26.24±0.03	0.47±0.06	0.55±0.01	20.63±0.04	1.09±0.02
4	F4	29.11±0.07	0.41±0.04	0.51±0.07	19.52±0.01	1.29±0.06
5	F5	26.37±0.09	0.42±0.03	0.56±0.03	24.12±0.03	1.06±0.03
6	F6	25.51±0.06	0.45±0.01	0.52±0.01	18.57±0.01	1.05±0.01
7	F 7	26.26±0.03	0.41±0.04	0.62±0.02	22.56±0.04	1.26±0.03
8	F8	27.41±0.09	0.39±0.05	0.58±0.03	23.61±0.07	1.05±0.05
9	F9	26.56±0.04	0.47±0.02	0.54±0.01	26.24±0.05	1.28±0.04

Drug excipients compatibility studies:

FTIR tests were conducted using the pure drug carvedilol and excipients. A physical mixture of the medication and polymers was obtained, and its IR spectra were examined. The principal peaks are at 3342.71 cm-1 due to N-H stretching, 2989.98 cm-1 due to O-H stretching, 2919.57 cm-1 characteristic of C-H stretching, 1250.73 cm-1 due to the C-O group, 1502.89 cm-1 characteristic of aromatic C=C stretching, and 1099.15 cm-1 characteristic of C- The FTIR characteristics of carvedilol with polymers are almost identical to the spectra of real carvedilol samples. According to the investigations, there is no compatibility issue between drugs and polymers. The peaks are shown in figures 2,3,4 and 5.

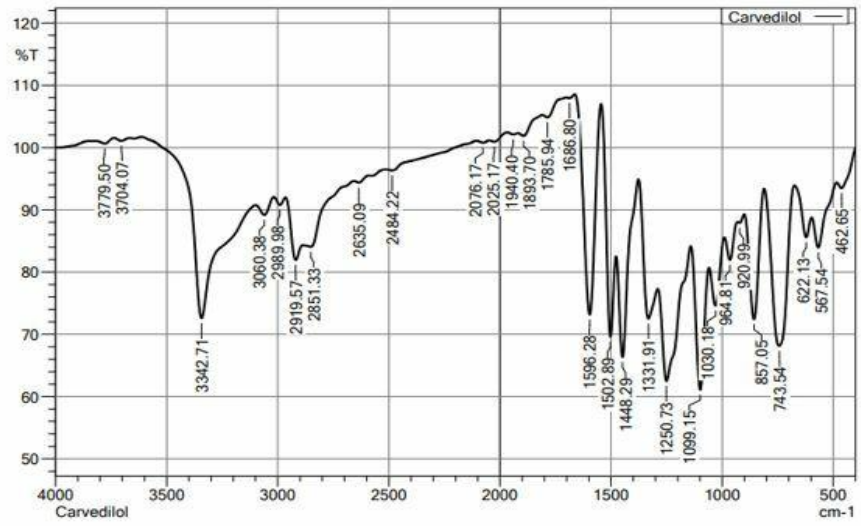

Figure No. 2: FTIR spectrum of carvedilol standard

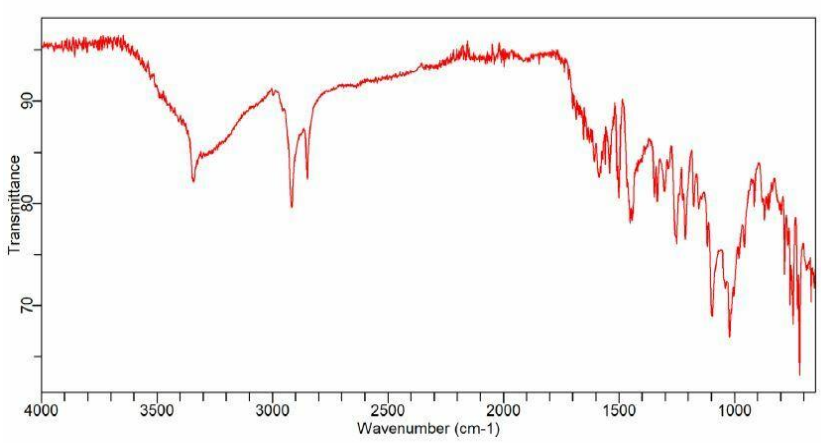

Figure No: 3: FTIR Spectrum of carvedilol, polymers, and excipients (Physical Mixture 1)

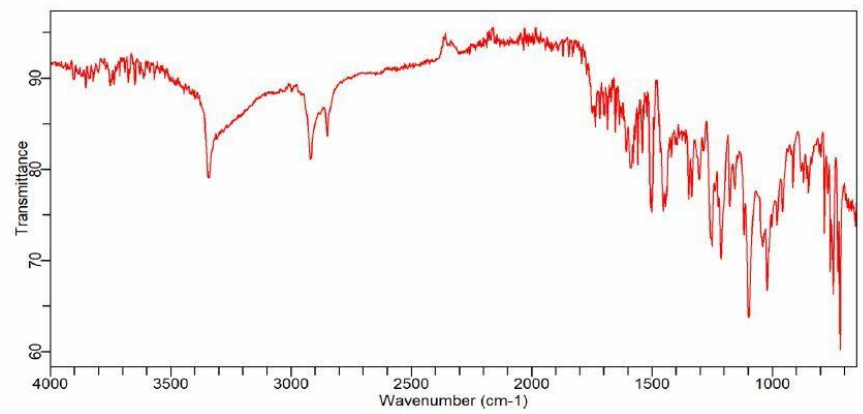

Figure No: 4: FTIR Spectrum of carvedilol, polymers, and excipients (Physical Mixture 2)

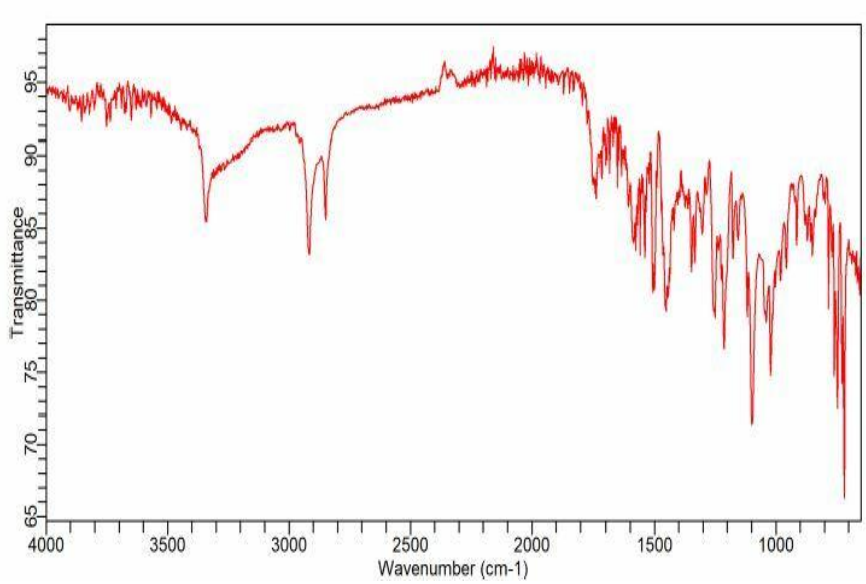

Figure No: 5: FTIR Spectrum of carvedilol, polymers, and excipients (Physical Mixture 3)

Drug polymer compatibility studies using DSC:

DSC investigations on the potential physical interactions between the excipients and the pure carvedilol were conducted. The melting point of the substance was indicated by the sharp endothermic peak that the pure drug produced at 116.17 °C. The optimized formulation F9 is taken, and the thermal behaviour of the sample is determined using a differential scanning calorimeter. The endothermic peak obtained after stability studies is 113.39^0 °C. There is no significant change in the endotherm peak of the drug observed in optimized floating tablets. This led to the conclusion that, even after stability testing, there was no interaction between the API and excipients. The graphs are shown in Fig. 6a, 6b.

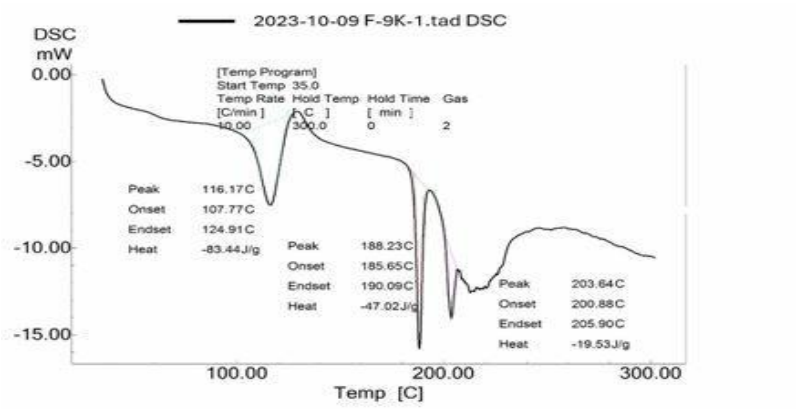

Figure No. 6 a. DSC thermogram of pure Carvedilol

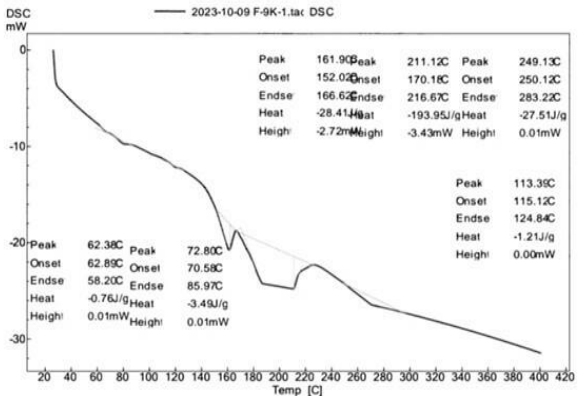

Figure No. 6 b. DSC thermogram of formulation F9

Post compression parameters*:* The mean values of thickness ranges from 2.7±0.9, diameter 3.3±0.98 mm, hardness ranges from 4.6±0.42 to 5.5±0.56, Friability 0.57 - 0.78%, weight variation 99±1.6 to 101.14±2.06 and drug content ranges from 97.55 to 104.05% of prepared gastric floating tablets and shown in Table III along with S.D. The pharmacopeia limit was found to be fulfilled for weight variation and percentage friability across all formulations of all batches.

Table-III: Evaluation of Physical parameters for formulated tablets

Formulation	Thickness in mm (±SD)	Hardness in kg/cm^2	Friability	Weight variation	Drug Content
Fl	1.3±0.12	5.2±0.34	0.340	100±1.99	99.5±0.19
F2	1.2±021	5.4±0.73	0.115	101±1.98	98.85±0.27
F3	1.3±0.53	5.2± 1.92	0.263	100±2.7	104.05±0.11
F4	1.3±0.16	4.8+0.44	0.290	99±2.5	97.55±0.21
F5	1.3±0.42	4.9±0.28	0.463	101±1.3	98.85±0.26
F6	1.2±0.53	4.7±0.37	0.528	100±1.59	99.5±0.17
F7	1.3±0.24	5.3±0.89	0.409	99±1.6	97.55±0.32
F8	1.2±0.16	4.6±0.42	0.232	101±2.06	98.2±0.33
F9	1.2±0.29	5.5±0.56	0.288	100±2.5	99.5±0.16

In vitro* buoyancy determination*:

The lag time duration ranged from 45 to 78 s in all formulations. All formulations were produced with the same gas-producing agent concentration, but the floating lag time varied since it relied on the quantity and density of the polymer employed. All results are compared in Table IV and Fig.7.

Table-IV: Floating study report

Formulation	Floating lag time (FLT)	Total Floatation time (TFT)
Fl	65	>6
F2	59	5.5
F3	78	6
F4	55	>6
F5	71	>6
F6	45	>6
F7	50	>6
F8	45	>7
F9	47	>7

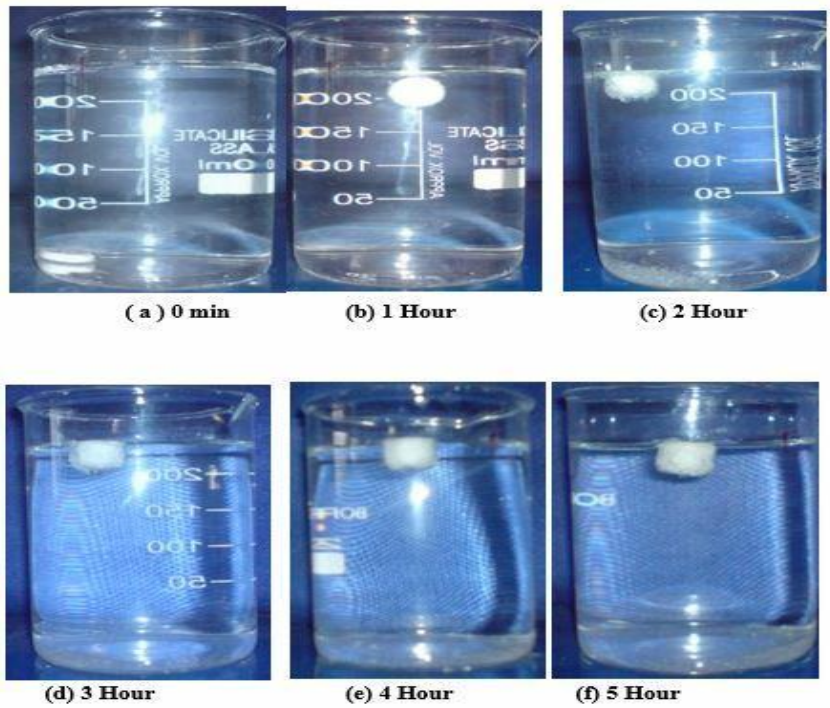

Figure No. 7: In vitro buoyancy study of carvedilol floating tablets

Swelling Index*:*

The measurement of swelling as a percentage was based on formulation studies of water uptake. The variation in tablet swelling was caused by the change in polymer concentration. At the conclusion of the four hours, the swelling had fully developed, after which diffusion and erosion started. In comparison to formulations containing sodium CMC, those containing sodium carboxymethyl cellulose exhibit increased swelling. With a higher polymer concentration, the tablets' swelling index is shown in Table V and Figure 8.

Table No: V: % Swelling index of formulated floating tablets F1-F9

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1hr	19.27	26.43	19.21	18.48	20.11	17.64	10.24	9.25	29.06
2hr	26.09	44.6	34.12	30.12	33.16	28.72	19.19	16.37	32.18
3hr	39.02	40.57	49.56	47.23	48.32	46.16	28.12	24.43	48.7
4hr	52.47	56.22	51.89	51.42	53.06	36.45	39.21	52.09	61.04

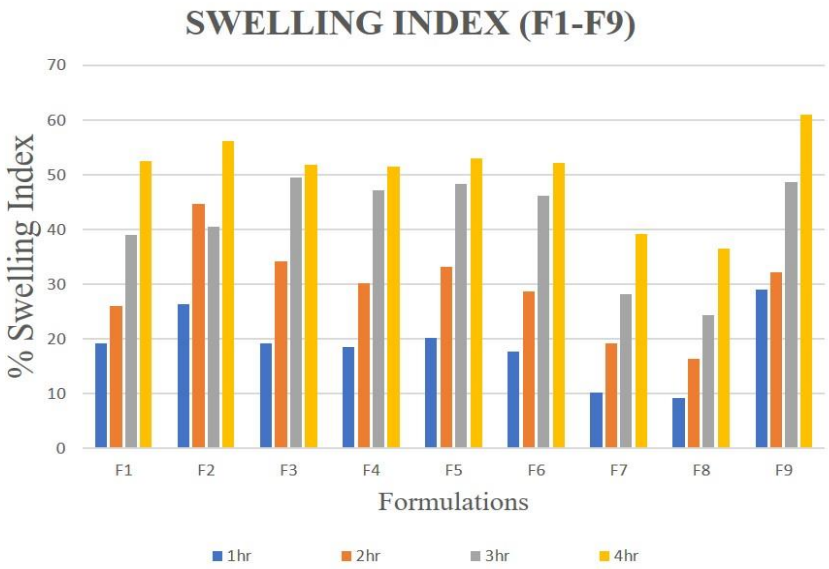

Figure No :8 Swelling index comparison graph F1-F9

In- vitro* dissolution study*: The nature and concentration of the polymer affect the dissolving study's conclusions. The formulation of the sustained-release floating tablets is evaluated for drug release in an in vitro dissolution procedure. The USP XIII paddle-type device was used to conduct the in vitro dissolution test in 900 ml of 0.1 N HCL at 50 rpm and 37.5^{o}C. The kind and concentration of the polymer affects the dissolving study's conclusions. polymer-containing formulations (API, carboxymethyl cellulose, sodium salt, sodium alginate, guar gum, MCC, sodium bicarbonate, citric acid, and magnesium stearate (F1-F9)). The drug release from formulation F9 with sodium carboxymethyl cellulose was 46.47% in 6 hours. The drug release from the formulation incorporating sodium alginate (F8) was 49.85% in 6 hours. The drug release from the Guar Gum (F7) containing formulation was 65.09% in 6 hours. When compared to formulations comprising sodium alginate and guar gum, formulation F9 with sodium carboxymethyl cellulose has a better release profile. All the results are shown in Table VI and Figure 9.

Table No: VI: Cumulative Drug Release F1-F9

TIME (HRS)	% CUMULATIVE DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.48	8.77	12.37	28.68	20.03	25.16	30.63	22.38	8.77
2	32.306	18.19	24.81	32.93	28.97	26.47	37.04	26.63	18.19
3	46.41	28.78	34.306	41.21	34.32	34.09	42.209	34.90	28.78
4	57.61	38.205	39.66	52.32	42.607	38.23	50.54	37.89	38.2
5	60.607	41.76	45.58	65.26	50.31	41.76	53.41	44.39	41.76
6	75.84	57.59	52.68	71.18	52.71	50.56	65.09	49.85	46.47

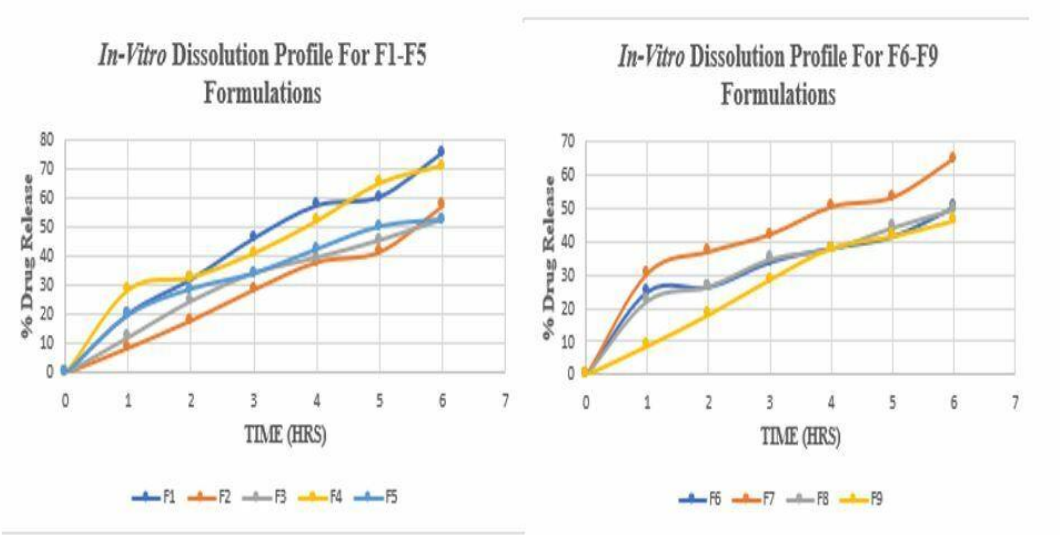

Figure No: 9 In-vitro Dissolution profile for F1-F9 Formulations

Impact of pH on floating behaviour:

The impact of a pH shift on the FLT and FT of the improved formulation (F9) was assessed. The findings demonstrated that the formulation's FLT and FT were not impacted by pH changes, as shown in Table VII. Thus, it may be deduced that changes in the pH of the gastric content may not have an impact on the floating behaviour of the dosage form.

Table: No: VII: Effect of pH on floating behaviour for optimised formulation

pH Medium	Optimised Formulation (F9)	
	FLT (secs)	TFT (hrs)
pH 1.2	45.25	>7
pH 2	46.64	>7
pH 3	46.25	>6

Impact of pH on drug release:

On release of the drug, the impact of pH variation on the optimized formulation (F9) was assessed. Variations in the gastric contents may not alter the floating lag time (FLT) of the tablets, according to in vitro buoyancy tests. It is also possible that the drug release may not be impacted. The impact of varying pH levels on medication release leads to the conclusion that pH changes brought on by variations in the stomach environment may not have a substantial impact on drug release, as shown in Fig. 10 and Table VIII.

Table. No: VIII: Effect of pH on drug release

Time (hrs)	% CDR (pH 1.2)	% CDR (pH 2)	% CDR (pH 3)
0	0	0	0
1	8.77	9.25	15.47
2	18.19	15.67	21.89
3	28.78	29.48	28.88
4	38.2	40.22	35.72
5	41.76	43.68	39.98
6	46.47	47.19	45.93

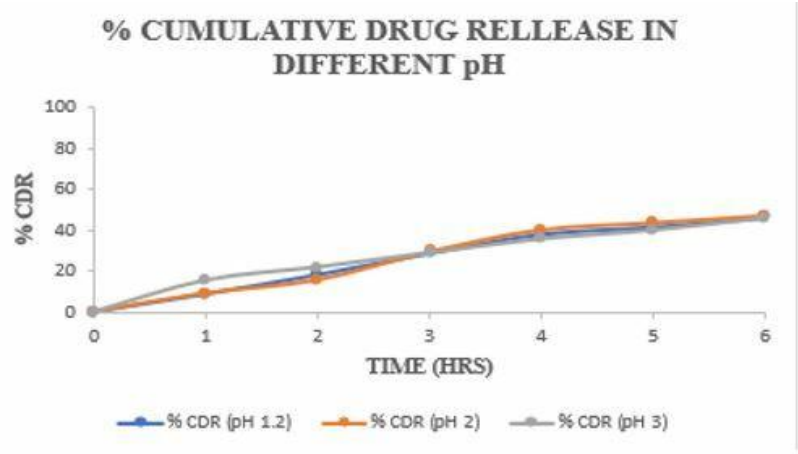

Figure. No :10: Effect of pH on % CDR

4. CONCLUSION:

The aim of the present study was to prepare floating tablets of carvedilol. For this study, various polymers like guar gum, sodium alginate, and sodium carboxymethyl cellulose were used. The Preformulation and post formulation results were within the limits of the standard. Among all the formulations (F1-F9) F9 showed the best floating lag time of 45 seconds & total floating time was more than six hours. F9 containing sodium carboxymethyl cellulose showed the highest swelling index of 61.04% and the percentage drug release at 6hrs was 46.47%. The effect of pH on floating and drug release was carried out for the optimized formulation, and it showed that there was no impact on the pH. Thus, it can be concluded that the gastroretentive tablets of Carvedilol can be formulated by using the hydrophilic polymer (Na CMC) in various concentrations.

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References

[1] *Laffleur F, Keckeis V. Advances in drug delivery systems: Work in progress still needed? International journal of pharmaceutics. 2020 Nov 30; 590:119912. PMID: 32577616; PMCID: PMC7305387.*

[2] *Lou J, Duan H, Qin Q, Teng Z, Gan F, Zhou X, Zhou X. Advances in oral drug delivery systems: Challenges and opportunities. Pharmaceutics. 2023 Feb 1;15(2):484.*

[3] *Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastro retentive drug delivery systems for improving drug bioavailability. International journal of pharmaceutics. 2016 Aug 20;510(1):144-58.*

[4] *Tripathi J, Thapa P, Maharjan R, Jeong SH. Current state, and future perspectives on gastro retentive drug delivery systems. Pharmaceutics. 2019 Apr 20;11(4):193.*

[5] *Vinchurkar K, Sainy J, Khan MA, Sheetal MA, Mishra DK, Dixit P. Features and Facts of a Gastro retentive Drug Delivery System-A Review. Turkish Journal of Pharmaceutical Sciences. 2022 Aug;19(4):476.*

[6] *Sponer G, Bartsch W, Strein K, Müller-Beckmann B, Böhm E. Pharmacological profile of carvedilol as a beta-blocking agent with vasodilating and hypotensive properties. J Cardiovasc Pharmacol. 1987 Mar;9(3):317-27.*

[7] *Hamed R, Awadallah A, Sunoqrot S, Tarawneh O, Nazzal S, AlBaraghthi T, Al Sayyad J, Abbas A. pH-Dependent Solubility and Dissolution Behavior of Carvedilol--Case Example of a Weakly Basic BCS Class II Drug. AAPS PharmSciTech. 2016 Apr;17(2):418-26.*

[8] *Mohapatra PK, Satyavani CH, Sahoo SA. Design and development of carvedilol gastroretentive floating drug delivery systems using hydrophilic polymers and in vitro characterization. Int J Pharm Pharm Sci. 2020 Jul 1;12(7):66-73.*

[9] *Srikanth Meka V, Wee Liang VA, Dharmalingham SR, Sheshala R, Gorajana A. Preparation, and in vitro characterization of non-effervescent floating drug delivery system of poorly soluble drug, carvedilol phosphate. Acta Pharm. 2014 Dec;64(4):485-94.*

[10] *Gunda RK, Kumar JN, Satyanarayana V, Satyprasad B. Formulation development and evaluation of carvedilol phosphate gastro retentive floating tablets. Int Res J Pharm. 2016;7(1):44-51.*

[11] *Aulton ME. Handbook of Pharmaceutics, second edition, published by: Vallabh prakashan,2007; 347-352.*

[12] *Willard, merit. Instrumental method of analysis, sixth edition, published by: CBS Distributors, 1948; 201-209.*

[13] *Nama M, Gonugunta CS, Reddy Veerareddy P. Formulation and evaluation of gastroretentive dosage forms of clarithromycin. Aaps PharmSciTech. 2008 Mar; 9:231-7.*

[14] *Sharma YR, Vig OP. Elementary organic and spectroscopy, third edition, published by: S. Chand &company.2010; 132-133.*

[15] *Zaya KS, Nayak MJ, Mishra JN. Formulation and evaluation of floating tablet of atenolol for the treatment of hypertension. Journal of Population Therapeutics and Clinical Pharmacology. 2023 Mar 16;30(4):765-76.*

[16] *Gunda RK, Kumar JN, Brahma CK, Satynarayana V, Prashant NK. Design, formulation, and evaluation of atenolol gastro retentive floating tablets. Asian Journal of Pharmaceutics. 2015;9(4). S34.*

[17] *Getyala A, V Gangadharappa H, Sarat Chandra Prasad M, Praveen Kumar Reddy M, M Pramod Kumar T. Formulation, and evaluation of non-effervescent floating tablets of losartan potassium. Current drug delivery. 2013 Oct 1;10(5):620-9.*

[18] *Damien T, Rao BS, Kumar PA, Yadav AS, Kuikarni SV. Formulation and Evaluation Theophylline Floating Tablets and the Effect of Citric Acid on Release. Research Journal of Pharmacy and Technology. 2010;3(4):1066-71.*

[19] *Salunkhe AK, Dias RJ, Mali KK, Mahajan NS, Ghorpade VS. Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate. Der Pharmacia Letter. 2011;3(3):147-60.*

[20] *Sagar K, Vivek S, Avinash D, Rakesh W. Formulation and Evaluation of Fast Disintegrating Tablet of Carvedilol. International journal of pharmacy and pharmaceutical research. 2018: 13(1); 196-212.*

[21] *Kesarla RS, Vora PA, Sridhar BK, Patel G, Omri A. Formulation and evaluation of floating tablet of H2-receptor antagonist. Drug development and industrial pharmacy. 2015 Sep 2;41(9):1499-1511.*

[22] *Garse H, Vij M, Yamgar M, Kadam V, Hirlekar R. Formulation and evaluation of a gastro retentive dosage form of labetalol hydrochloride. Arch Pharm Res. 2010 Mar;33(3):405-10.*

[23] *Metta S, Maddukuri S, Nagadani SL, Meegada B, Kandukuri S. Formulation and evaluation of gastro retentive tablets of losartan potassium. International journal of research in pharmacy and chemistry. 2017, 7(3); 327-337.*

[24] *Swati C. Jagdale, Amit J. Agavekar, Sudhir V. Pandya, Bhanudas S. Kuchekar, and Aniruddha R. Chabukswar. Formulation and Evaluation of Gastro retentive Drug Delivery System of Propranolol Hydrochloride. AAPS PharmSciTech, 2009; 10(3); 1071-79.*

[25] *Panda S, Kumari CH, Puniya G. Formulation and evaluation of compression coating floating tablets of carvedilol phosphate once daily dose. International journal of pharmacy and pharmaceutical sciences. 2018; 10(6); 82-89.*